BRUNEI DARUSSALAM JOURNAL OF HEALTH

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THE SULTAN HAJI HASSANAL BOLKIAH FOUNDATION

The Sultan Haji Hassanal Bolkiah Foundation was established on 12th October 1992 to be:

• the channel of charitable endowment of His Majesty Sultan Haji Hassanal Bolkiah Mu'izzaddin Waddaulah and Members of His Majesty's Royal Family

• a symbol of the care and affection of His Majesty Sultan Haji Hassanal Bolkiah Mu'izzaddin Waddaulah towards His Majesty's subjects who are always loyal and faithful to His Majesty and His Majesty's Government

• the symbol of the creation and unity of the society and the nation, Brunei Darussalam which is peaceful and prosperous, as well as for the harmony of people of all other countries according to the circumstances and appropriateness blessed by Allah The Almighty.

These concepts are rooted in Faith, Charity and Good Deeds. Faith is the channel, Charity is the care and Good Deed is the creation of society and harmony. Since its establishment, the Foundation has implemented several projects and activities in accordance with the principles and objectives of the establishment of the Foundation in the areas of religion, welfare, education, development and finance.

Religion

Generally all projects and activities carried out by the Foundation in the field of religion has focused towards efforts in enhancing the propagation and preeminence of Islam in the country.

The Sultan Haji Hassanal Bolkiah Foundation has also extended financial assistance for promoting religious education of the subjects of His Majesty The Sultan and Yang Di-Pertuan of Brunei Darussalam. Qualified students without funding or scholarship from either the Government or other agencies have been given the opportunity to pursue their religious studies at universities and institution of higher learning overseas.

New Muslim converts are provided with housing assistance under the Foundation Housing Scheme to care for the welfare of the new converts so that they are able to practise life as a Muslim properly. This includes providing comfortable abodes for converts living in rural areas so that they can carry out their obligations to Allah The Almighty in a comfortable and harmonious environment.

The Foundation also gives annual financial donations to a number of mosques and other places of Islamic worship throughout the country in order to cover the cost of construction and maintenance of mosques, 'suraus' and prayer halls. Donations of appropriate materials such as religious books, praying mats and public address system to mosques are 'suraus' are also carried out periodically as required.

A contribution from the Foundation to the welfare of the community

Welfare

The Foundation are also involved in an effort to enhance the welfare and well-being as well as to stimulate the social, cultural and economic development of the citizens and residents of Brunei Darussalam.

The contributions in the form of cash, food items and other requirements to the unfortunates and poor comes at times of natural disasters and fire. Families with low income are also given appropriate assistance to improve their standard of living. The Foundation also gives support and provides sponsorship to non-government bodies (NGOs) in implementing programmes designed to encourage the needy to be self-reliant .

The welfare of people with special needs in the country also gets the attention of the Foundation whereby financial support is extended to the development and rehabilitation programmes for the people with special needs through non-government bodies involved in organising these programmes.

Other recipients of financial support from the Foundation are various youth development projects carried out by non-government bodies in this country such as basic training programmes for school leavers seeking employment, youth camp and youth workshops, competition in the field of writings, literatures, cultures and sports.

The Foundation has two huge housing projects in the country implemented under the Foundation Housing Scheme:

a) Housing assistance project for the poor and destitute people and whose houses are not safe to be inhabited. The housing assistance is hoped to provide a house which is comfortable and clean thus creating a peaceful family living environment and further develop a harmonious society.

b) The construction of the well-arranged housing project in Kampong Ayer (Brunei Darussalam Water Village) known as the Sultan Haji Hassanal Bolkiah Housing of Kampong Bolkiah 'A' and Kampong Bolkiah 'B'. The aim is to provide housing for the Kampong Ayer residents who were involved in a fire incident in 1993 which rendered approximately 1,000 people losing their homes and belongings. A total number of 476 houses were built under this housing project.

The Foundation also gives assistance to the disaster stricken communities and war victims in other countries as collaboration with Government and private agencies. The biggest of this is the Humanitarian Relief Initiative for The Tsunami and Earthquake Victims in Aceh, Republic of Indonesia. This project was implemented in two phases. The first phase was the emergency relief, which is the disseminating of food, clothing and medical help to the victims. The second phase involved helping in the re-construction of houses, mosques, schools and orphanages.

Sultan Haji Hassanal Bolkiah Housing of Kampong Bolkiah 'A' and Kampong Bolkiah 'B'

Education

Projects and activities implemented by the Foundation in the field of education focus on the provision of the educational assistance and research as well as educational services and infrastructure. This assistance is in the form of monthly subsistence allowance and given to students who do not receive any form of scholarship or grant and who are the subjects of His Majesty. The opportunity allows them to further their studies in various fields at overseas universities and institutions of higher learning. There are two important areas in education that the Foundation are involved in:

(i) The "Sultan's Scholar" scholarship is a prestigious scholarship offered by the Foundation with the aim of producing individuals who are knowledgeable, skillful, disciplined and well-mannered for the long-term benefit towards the Religion, Monarch and Country. The recipients are students who are recognised by the Foundation and the Ministry of Education as excellent students who have obtained excellent results in their GCE Advanced (A) Level or its equivalent and are engaged in extracurricular activities.

(ii) The establishment of the Sultan Haji Hassanal Bolkiah Foundation Schools comprising the Foundation Nursery School, the Foundation Primary School and the Foundation Secondary School represents the Foundation's involvement in offering educational services as a contribution to the development of education and human resources in Brunei Darussalam.

The Sultan Haji Hassanal Bolkiah Foundation School is located at Simpang 336-71, Jalan Kebangsaan, Berakas, situated in a peaceful environment and attractive surroundings. The school complex has been designed with distinctive features, integrating modern technology and equipped with modern and suitable facilities to provide a conducive teaching and learning environment.

Other periodic activities by the Foundation are to give assistance in the form of books, stationery and other study materials to students who need them so that they can continue their education properly. The Foundation also gives contributions in the form of teaching equipment such as computers and printers, photocopy machine, projector and reading materials to schools which require such assistance. Another important area that the Foundation gives suppot and financial contribution is in Research and Development Projects to institutions of higher learning in Brunei Darussalam for the benefits of scientific, technological and community development.

Development and Finance

The foundation also participates in development activities in the field of finance. Amongst the projects is participation in commercial enterprise and industrial activities; to purchase, guarantee or otherwise acquire any stocks and shares; and to establish a company or corporation to operate or manage any project, scheme or enterprise. A significant development and financial project undertaken by the Foundation is the establishment of The Sultan Haji Hassanal Bolkiah Foundation complex.

Situated splendidly between the Water Village at the Brunei River and the Omar ‘Ali Saifuddien Mosque, the Sultan Haji Hassanal Bolkiah Foundation Complex (the Foundation Complex) is an investment project in real property undertaken by the Foundation whereby income derived from this investment is used to finance charitable projects initiated by the Foundation. The Foundation Complex is one of the biggest and prominent commercial buildings in the heart of Bandar Seri Begawan. With a total floor plan area of about 110,305 square meters, the Complex provides a wide range of commercial activities under one roof such as shops, boutiques, supermarket, restaurants, offices, clinics, telecommunications and banks.

Personal Gifts from His Majesty Sultan Haji Hassanal Bolkiah Mu’izzaddin Waddaulah, The Sultan and Yang Di-Pertuan of Brunei Darussalam

The Foundation has two other important roles in the community of Brunei Darussalam. These are the management and distribution of personal gifts from His Majesty Sultan Haji Hassanal Bolkiah Mu’izzaddin Waddaulah, The Sultan and Yang Di-Pertuan of Brunei Darussalam namely dates which are given with the intention that they are to be consumed in breaking the fast and they are donated every fasting month of Ramadhan to all Muslim citizens and residents of Brunei Darussalam. The second is the annual distribution carried out since 1995, exclusively for Brunei Darussalam’s intending pilgrims given every haj season. These comprise of ‘ihram’ clothes (2 pieces of unsewn white clothes worn by men during a certain part of the pilgrimage in the holy city of Mecca) and ‘telekong’ (women prayer cloaks).

BOARD OF EDITORS

Promoting national and international collaborations at the Institute of Medicine, Universiti Brunei Darussalam

Mas Rina Wati Haji Abdul Hamid
Institute of Medicine, Universiti Brunei Darussalam

1. Landmarks in international scientific collaborations

Notable recent international collaborative research projects that have had a major impact on science include the Word Climate Research Programme (WCRP). The results from the WCRP led to the recommendations of the Inter-Governmental Panel on Climate Change (IPCC) that in turn led to international agreements on limiting greenhouse gas emissions. Their significance was recognised by the IPCC being jointly awarded the Nobel prize for peace in 2007 [1].

More directly concerning human health, the human genome project (HGP) was a large international, laboratory–based, collaborative effort [2]. Commencing in October 1990, the international DNA sequencing consortium was made up of laboratories in the following countries: China, France, Germany, Japan, the UK and the USA. The HGP was completed in April 2003. The HGP has helped characterize genes associated with many human diseases and led to the invention of the high-end tools including computers and sophisticated techniques. A large number of scientists and technicians enhanced their skills in advanced DNA techniques as a result of the HGP. New issues concerning ethics, law and society pertaining to the information obtained from the sequencing the human genome have led to the universal adoption of new codes in bioethics. An important message from programs such as the HGP and WCRP is that collaborative efforts benefit not just one individual, organization or country, but have multiple benefits for many organizations, societies and countries.

Correspondence
Mas Rina Wati Haji Abdul Hamid
Institute of Medicine, Universiti Brunei Darussalam,
Jalan Tungku Link, Gadong BE 1410, Brunei Darussalam
Tel +673-2463001 ext 1997
Email: masrw@im.ubd.edu.bn

2. Research in health care

Health care can be seen as becoming more complex as different health professionals are involved in the diagnosis, treatment and overall care of a patient. Recently there has been a move to include more inter-professional learning in medical curriculum across the globe [3]. Consequently some aspects of medical and health care research also requires that interdisciplinary teams work together in the planning of the research work. This process helps to develop links between health professionals. It has been reported that success and continuity of collaboration depends on social features of the relationship and not just the cognitive products, sufficient meetings or equal status [4].

3. Collaborations in teaching and learning at the Institute of Medicine

Medical and health care education in Brunei Darussalam started with the establishment of the Institute of Medicine in 2000. IM has a mission to support the vision of UBD in becoming a world class international University with a distinctive national identity. To perform this mission, and being a young and developing faculty, IM promotes collaborations in the delivery of its teaching, research and professional development. IM collaborates with Ministry of Health, Brunei Darussalam in the delivery of the MSc in Primary Health Care. The undergraduate programme, Bachelor of Health Science/Medicine was developed with a major support from St George's, University of London formerly known as St George's School of Medicine, University of London. A great deal of clinical teachings in this programme is also undertaken by clinicians and general practitioners from the Ministry of Health. The programme is a three-year ordinary degree after which students will transfer to a partner medical school in Australia, Canada or the United Kingdom. The students will graduate with a medical degree from the respective partner school.

The Institute of Medicine has also established collaboration with Faculty of Medicine, Kagawa University, Japan, in the areas of student and staff exchange. The international summer medical school attended each year by eight medical students from Kagawa University has run for two years, and is very popular with the Japanese students. Students from the Institute of Medicine have also visited and undertaken academic activities at the Faculty of Medicine, Kagawa University through an international winter exchange programme. This program is funded by Japanese Student Services Organisation (JSSO) and the Brunei government.

4. Collaborations in research at the Institute of Medicine

Staff from Institute of Medicine, Universiti of Brunei Darussalam and Faculty of Medicine, Kagawa University have exchanged visits, and young Bruneian faculty at IM have explored possible research collaborations, with Faculty of Medicine, Kagawa University. One Bruneian tutor is currently researching for a PhD at the Department of Pharmacology, Kagawa University.

Collaborations to establish research in other areas of health sciences are actively pursued. A memorandum of understanding is being developed with University of Montpellier, France. Specific interests have been expressed in the fields of immunology, Islamic medicine, natural products and oncology.

Research projects are also undertaken collaboratively with clinicians and public health professionals from the Ministry of Health. Some involve student projects with joint supervision coming from faculty at the Institute of Medicine and staff at the Ministry of Health.

At present the Institute of Medicine staff are also engaged in collaborative research projects in biomedical sciences, neuroscience, epidemiology and public health, and medical and health profession education with counterparts in many countries including Bangladesh, Canada, Iran, Japan, France, Germany, Malaysia, Nigeria, Russia, Saudi Arabia, Spain, Sri Lanka, Switzerland and the United Kingdom. Such collaborations enhance the international profile of the Institute of Medicine and UBD

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Potential biotechnological applications of a *Lactococcus lactis* strain lacking cell wall hydrolase that persists in the gastrointestinal tract

R. Ramasamy [1]* and S.A.V. Moorthy [2]
[1] *Institute of Medicine, Universiti Brunei Darussalam, Gadong, Brunei Darussalam*
[2] *National Science Foundation, Colombo, Sri Lanka*
* *corresponding author*

Abstract

Lactococcus lactis has a long use in traditional biotechnology for making fermented dairy and other food products. A *L. lactis* mutant lacking the cell wall hydrolase acmA, and growing in long chains, is shown to survive in the normal mice for several weeks, unlike wild type *L. lactis*. Persistent *L. lactis* has greater potential for safe, long term delivery of vaccines and therapeutics.

Introduction

Lactococcus lactis is a Gram positive coccus that has been used for thousands of years in traditional biotechnology for making cheese, buttermilk and other fermented food products. It is typically ovoid with a diameter of 0.5-1µm, grows best at 30°C in pairs or short chains, is not invasive and does not colonise the gastrointestinal tract (GIT) except in germ-free mice [1-3]. Because *L. lactis* is generally regarded as safe for ingestion, it is being developed for use in modern biotechnology as a carrier or vector for eliciting systemic and mucosal immunity against pathogens through oral immunisation [3, 4] and for delivering therapeutics to the GIT, e.g. IL-10 in colitis [5]. However the transitory nature of the organism in the GIT limits exposure to antigen or therapeutic, and often requires that the foreign protein expression is induced *in vitro* before feeding.

Correspondence:
R. Ramasamy
Institute of Medicine,
University Brunei Darussalam,
Jalan Tungku Link,
Gadong BE1410,
Brunei Darussalam
Tel: +673-2463001 ext 1965
Fax: +673 2461081
Email: ramasamy@im.ubd.edu.bn

A mutant form of *L. lactis* strain NZ9000 that lacks the cell wall hydrolase AcmA (*L. lactis*-Δ*acmA*) grows as very long chains in culture because the cells fail to separate properly after division [6]. We examined the survival of *L. lactis*-Δ*acmA* in mice in the context of the use of *L. lactis* expressing heterologous proteins for mucosal immunisation.

Materials and Methods

Wild type *L. lactis*-NZ9000 expressing the malaria protein MSA2 [4] and mutant *L. lactis*-Δ*acmA* were from the Department of Genetics, University of Groningen, Groningen, The Netherlands. Balb/c mice were from the Medical Research Institute, Colombo, Sri Lanka and were age-matched for each experiment. The bacteria were grown in M17 medium (Difco, MD, USA) containing 1% glucose at 30°C as standing cultures and stocks were stored frozen in a viable state at -80°C in glycerol as described [4].

Mice were fed orally with 4.5 x 10^9 bacteria in 20% sucrose through a plastic micropipette, while 0.5 x 10^9 bacteria were introduced into the nasal cavities with a plastic pipette at the same time. This procedure was adopted because of a concomitant investigation of the immune response to MSA2. The procedure was repeated for two

consecutive days (delivery on days 0-2) and then again after 3 weeks (days 20-22) and finally after a further 4 weeks (days 49-51). Faecal pellets were freshly collected, beginning with the day after the first feeding, from two groups of two marked mice fed the mutant and wild type *L. lactis* respectively. The pellets were weighed, homogenised in sterile PBS (1 ml per 100mg wet weight of faeces) and 50µl aliquots of serial ten-fold dilutions in PBS plated on M17 agar. Chloramphenicol (5 $\Delta g.ml^{-1}$) was added to the plates for selecting wild type *L. lactis*, since this strain carried a resistance gene (5). The extracts from mice fed *L. lactis*-Δ*acmA* were plated without the antibiotic as the mutant lacked the resistance gene. The plates were incubated for 16h at 30°C and the colonies counted. The colonies were examined under the microscope to determine the morphology of the cells. The cells were also Gram-stained to confirm identity.

Results

The plates from faeces of wild type *L. lactis* contained a small proportion of unrelated colonies of a single, clearly distinguishable morphotype, probably a yeast. However such contaminants were rare in plates of faecal extracts from mice fed of *L. lactis*-Δ*acmA*, probably because of the higher numbers of *L. lactis*-Δ*acmA* excreted. No lactococcal colonies were obtained from faeces of control mice not fed *L. lactis*. The *L. lactis* colony forming units (cfu) in the faecal pellets of one representative mouse from each group are shown in Fig 1. Similar results were obtained from the other mice fed the mutant and wild type *L. lactis*. The mouse fed wild type *L. lactis* excreted viable bacteria for 2-5 days after commencement of feeding with peaks reaching approximately 10^4-10^5 cfu per 100mg faeces on the second and third days of feeding. The mouse fed *L. lactis*-Δ*acmA* showed continuous excretion of bacteria at approximately 10^5 cfu/100mg faeces over the 62 days of observation, with peaks reaching approximately 10^9 cfu/100mg faeces on the second and third days of feeding. It was estimated that the average wet weight of faeces produced by this cohort of Balb/c was 100mg per day.

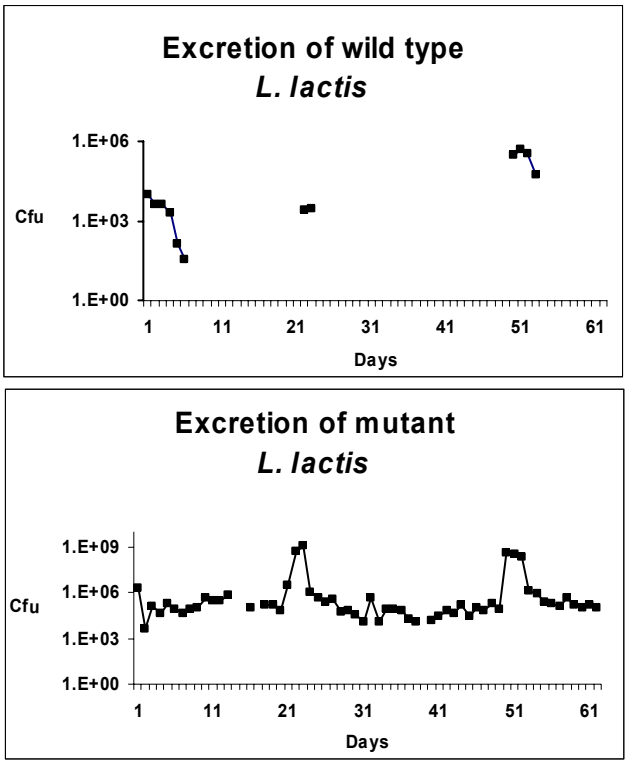
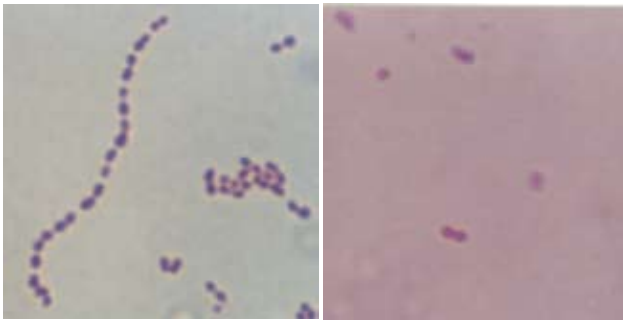


Figure 1. Graphs showing the excretion of wild type and Δ*acmA*-*L. lactis* from one mouse of each group. The results are expressed as colony forming units (cfu) of *L. lactis* per 100 mg of faecal pellet which were collected and analyzed every day for 62 days. When no *L. lactis* was detected this is shown without a data point in the graph except for days 14,15 & 17 for the mouse fed Δ*acmA*-*L. lactis* when the faecal pellets were not collected for analysis.

Gram staining confirmed that the colonies enumerated were typical of wild type *L. lactis* and *L. lactis*-Δ*acmA* (Fig 2). The mice were sacrificed on day 63 and their spleens, mesenteric lymph nodes and GIT examined. These were normal morphologically and histologically, except for a tendency for larger mesenteric lymph nodes and more prominent Peyer's patches in mice fed either strain of *L. lactis*, compared to unfed controls. We also examined serum antibody production to lactococcal antigens in mice similarly fed wild type and mutant *L. lactis*. Antibody levels increased with each set of feedings, but were not significantly different between the two *L. lactis* strains (data not shown).



ΔacmA *L. lactis* wild type *L. lactis*

Figure 2. Photomicrographs of Gram-stained samples of Δ*acmA*-*L.* lactis and wild type *L. lactis* colonies from plated faecal extracts, viewed at x 1000 magnification. The morphology is characteristic of the mutant and wild type strains described previously [6].

Discussion

It has been reported that *L. lactis* is quite resistant to gastric acidity but susceptible to trypsin and other factors in the duodenum, and relatively less affected in the lower GIT of rats [7]. *L. lactis* colonisation in germ-free mice predominantly occurs in the caecum [9]. *L. lactis* does not colonise normal mouse GIT [8] and does not translocate to the mesenteric lymph nodes and spleen, unlike endogenous gut bacteria [9]. Experimental findings on feeding wild type *L. lactis* to humans are compatible with the rodent findings, and show that the bacterium is killed and lysed in the GIT with <2% of the ingested bacteria being excreted live in faeces [2]. Our findings confirm that wild type *L lactis* is eliminated from normal mice within a few days and only a very small proportion, estimated in the order of 0.002%, is detectable as live bacteria in faeces. In contrast, *L. lactis*-Δ*acmA* persists and is shed from the GIT continuously for at least 3 weeks after introduction, with approximately 10% of ingested bacteria detected in faeces as live bacteria. The actual numbers of live bacteria in the faeces may be greater, and dependent on the sensitivity of the extraction and detection procedure.

The constant rate of excretion of live *L. lactis*-Δ*acmA* is consistent with the hypothesis that mutant persists in the lower GIT and is able to multiply there. The long chains of *L. lactis*-Δ*acmA* may facilitate trapping in the GIT. However the possibility that the bacterium survives in the nasal cavity and is then shed into the GIT, although unlikely, cannot be entirely excluded on the present data. Our results also suggest that *L. lactis*-Δ*acmA*, despite its enhanced persistence, does not produce more changes in host animals than wild type *L. lactis*.

We anticipate that *L. lactis*-Δ*acmA*, and similar mutants of other food grade bacteria, will be useful for safely improving the delivery of probiotics, therapeutics and vaccines to man and animals.

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Patterns and Trends of Religious Edicts (Fatwa Mufti Kerajaan & Irsyad Hukum) on Medical Matters in Brunei Darussalam 1962-2005

Omar Hasan K. Kasule Sr.
Institute of Medicine, Universiti Brunei Darussalam

Abstract

This paper reports analysis of published religious edicts relating to medicine in Brunei for the period 1962-1995 showing the patterns and trends of medically-related fatwa. In The most popular types of medical fatwa in descending order of frequency were medicines, modern (new) medical issues, physical acts of worship, surgery, normal conditions and ethico-legal issues.

Introduction

The objective of this study is to identify medico-legal issues that are of importance from an Islamic perspective in the Bruneian society. This information will be used in designing educational and training curricula for health care givers in Brunei to make sure they can communicate effectively with their Muslim patients and can give them quality care based on comprehensive understanding of the Bruneian socio-religious context. The study covered religious edicts on medical matters issued by the Mufti Kerajaan in the period 1962-2005.

The Mufti of Brunei gave religious edicts, *fatwas*, on a wide range of questions addressed to him. These were published in an annual volume called *Fatwa Mufti Kerajaan*. A fatwa is issued if a specific question is addressed to the Mufti by an individual or an organization. Government departments often seek guidance from the Mufti on matters concerning their field of activity. In addition to fatwas, the office of the Mufti took the initiative to write about issues that needed clarification and these writings are published as *Irsyad Hukum* on an annual basis. Medical issues take a significant portion of both publications and are put under sections titled *Perubatan* or *Rawatan & Kesihatan* [1-24]. There were however other matters of implicitly medical importance found scattered in other parts of the publications. The scope of the study is limited to identification and classification of the edits as explicitly medical or implicitly medical and then to further classify them according to general medical diagnostic categories that also correspond to specific sections of the medical curriculum.

Correspondence
Omar Hasan Kasule,
Institute of Medicine,
Universiti Brunei Darussalam,
Tungku Link, Gadong BE1410,
Brunei Darussalam

Methods

The following official publications were bought from the publication unit of the Mufti's office: Fatwa Mufti Kerajaan 1994-2003 in Bahasa Melayu [1-9], Fatwas of the State Mufti 1994-1995 in English [10], Fatawa Mufti al Dawlat 1994-1995 in Arabic [11], Fatwa Mufti Kerajaan: Rawatan & Kesihatan 1962-2005 in Bahasa Melayu[12], Ibadat Korban [13], Hukum Rokok & Merokok in Bahasa Melayu[14], and Irsyad Hukum 1995-2002 in Bahasa Melayu [15-24]. The questions and answers were read carefully and essential information on each edict was abstracted using a uniform and pre-tested data abstraction form. Each edict was classified in one of 3 ways: non-medical, implicitly medical, or explicitly medical. Edicts of medical nature were classified as either normal physiological conditions or disease conditions. Both categories were then classified further according to the organ system and the physiological or pathological process.

Results

Tables 1-2 show the results of data analysis. There was no significant increase in medical fatwas as a percentage of the total fatwas for the two periods 1962-1999 and 2000-2004. The proportion of medically-related irsyad hukum increased between the 1995-1999 and the 2000-2004. The most popular types of medical fatwa in

descending order of frequency were medicines, modern (new) medical issues, physical acts of worship, surgery, normal conditions and ethico-legal issues. Fatwas on medicines addressed questions on therapeutic drugs and spiritual approaches to disease treatment. Fatwas on modern issues addressed questions on abortion, AIDS, blood transfusion, contraception, cosmetic surgery, drug abuse, artificial life support and transplantation. Fatwas on physical acts of worship were about fasting (*puasa*), ablution (*taharat*) and pilgrimage (*hajj & umrah*). Fatwas on surgery addressed use of artificial teeth, blood transfusion, contact lenses and dental fillings. Fatwas on normal physiological conditions covered menstruation, pregnancy, and the postnatal period. There was only one fatwa that could have been classified as ethico-legal.

Table 1 Fatwa mufti kerajaan edicts by time period

	Explicitly Medical	Implicitly Medical	Non-Medical	Total
1995-1999	1(0.6%)	17(9.7%)	158(89.8%)	176(100%)
2000-2004	5(2.2%)	17(7.5%)	204(90.3%)	226(100%)
Total	6(1.5%)	34(8.5%)	362(90.0%)	402(100%)

Table 2 Irshad hukum edicts by time period

	Explicitly Medical	Implicitly Medical	Non-Medical	Total
1995-1999	1(1.1%)	12(13.6%)	75(85.2%)	88(100%)
2000-2004	6(5.7%)	17(16.0%)	83(78.3%)	106(100%)
Total	7(3.6%)	29(14.9%)	158(81.4%)	194(100%)

Discussion and recommendations

The paper has identified the most frequent issues that Bruneians seek answers to and that religious officials address. The range of medical fatwas was diverse indicating sophistication of medical services and preparedness of the religious authorities to venture into the area of medicine. Religious authorities played a commendable role in tobacco control by issuing a whole book about it instead of issuing one fatwa. This indicated their preparedness to keep pace with modern trends in public health and their role in disease control. The fatwas on medical matters appear to be well researched with a good understanding of the underlying medical issues. It is recommended that these issues be included in educational curricula of medical, nursing and allied health students as well as continuing medical education programs for practicing physicians and nurses. This will improve communication between caregivers and Muslim patients and result in more patient compliance and cooperation. Compilations of fatwas of medical relevance are made in many Muslim countries and are published as books or online. No statistical analysis of patterns of medically related *fatwas* has, to the best of the author's knowledge, been carried out in any other Muslim country.

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Hepatitis C virus infection in Brunei Darussalam: A genotypic study

Vui Heng Chong, Aza Zetty Feorena Jamaludin, Anand Jalihal
Gastroenterology Unit, Department of Medicine
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital

Abstract

Hepatitis C virus (HCV) infection is one of the major causes of complicated liver disease. Viral genotypes have been shown to significantly affect treatment outcomes and may be a factor in disease progression. The aim of this study was to assess the genotypes in our local setting. Patients with HCV infection and had undergone genotypic testing were retrospectively reviewed. There were 75 patients (61 male, mean age 40.8 ± 9.8 years) who had genotypic testing. Four genotypes were detected; genotype 1 (n = 26, 34.7%), genotype 2 (n = 4, 5.3%), genotype 3 (n = 45, 60%) and genotype 4 (n = 2, 2.7%). Two patients were infected with dual genotypes (1 & 4 and 2 & 4 respectively). Both these patients had blood transfusion more than 20 years ago, one had transfusion in Egypt. The median viral load was 2.74 x 10^6 copies (range, 2,490 to 39 x 10^6). Between the favourable (genotypes 2 & 3) and non-favourable (genotypes 1 & 4) genotypes, there were no significant differences in the age ($p = 0.314$), between gender ($p = 0.226$), the mode of acquisition (intravenous drug injections vs. others, $p = 0.223$), viral load (< or ≥ 2 x 10^6 copies, $p = 0.763$) and the baseline serum alanine aminotransferase activity ($p = 0.403$). In conclusion, our study showed that the commonest genotype is genotype 3 followed by genotype 1. There were no significant differences between the favourable and non-favourable genotypes in the patients' demographics, mode of acquisition and necro-inflammatory activities and viral load.

Introduction

Chronic liver disease (CLD) is an important cause of morbidity and mortality. In the Asian Pacific region, Hepatitis B virus infection represents a major aetiology whereas in the United States, Europe and Japan, Hepatitis C virus (HCV) infection is the main aetiology [1, 2]. In the West and Japan, HCV has been estimated to account for 80% of chronic hepatitis, 40% of cirrhosis, 70% of hepatocellular carcinoma and 30% of transplant indications [3]. An estimated 150 to 200 million individuals are affected by this infection worldwide with 3 to 4 million new infections annually. HCV infection is now the leading cause of end stage liver disease and the leading indication for liver transplantation in Europe and North America. Overall, the incidence of HCV infection has decreased since its discovery in 1989. However, it is still common in a subset of the population, particularly among those in correctional and institutional facilities, intravenous drug users (IVDU), homeless, and patients with end stage renal failure (ESRF) undergoing haemodialysis [2, 4, 5].

HCV is a positive-stranded RNA virus of approximately 9,400 nucleotides that belong to the Flaviviridae family. HCV accounts for the majority of the non-A non-B chronic hepatitis [6]. Sequence analysis and comparisons of variants isolated from different geographical areas have led to the identifications and classifications of at least six genotypes (designated 1-6) [7]. Some of these genotypes contain a number of closely related, yet distinct subtypes of the virus (designated a, b, c, etc...). There are currently more than 50 subtypes [2]. These differences in nucleotides sequences identified may be as much as 20 to 23%.

Treatments for HCV infection are now better defined with the combination of interferon and ribavarin. Viral characteristics such as viral load and genotypes have been shown to be important factors that predict treatment outcome [2].

Correspondence:
VH Chong
Gastroenterology Unit, Department of Medicine
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital
Bandar Seri Begawan BA 1710,
Brunei Darussalam
Fax: 673 2242690
Tel: 673 2232111 Ext 3303
Email: chongvuih@yahoo.co.uk

Favourable genotypes were those shown to have favourable responses to standard therapy, consisting of mainly genotypes 2 and 3. Genotypes 1 and 4 have less favorable responses. There is currently limited information on the other remaining genotypes. Genotype has also shown to affect the natural history of HCV infection [8]. There are currently six distinct genotypes identified and different genotypes are more prevalent in different regions (Table 1) [9]. There is no published data regarding HCV infection in Brunei Darussalam. This study assesses the genotypic distributions among HCV infected patients, including the favourable and non-favourable genotypes, in patients in Brunei.

Table 1. Hepatitis C virus genotypes and their distributions

Genotypes	Distributions
1	Europe, North America, Japan
2	Southern Europe
3	Southeast Asia
4	Middle East, Egypt, Central Africa
5	South Africa
6	Indochina

Methods

Patients who were detected to have a positive HCV IgG serology are those that are routinely referred to the Hepatology Clinic for further evaluation including: HCV IgG, liver function test, detection of chronic liver disease, routine screening of blood donors, patients with ESRF undergoing haemodialysis and incarcerated inmates for suspected or confirmed drug offences. These patients were also routinely checked for co-infections particularly with hepatitis B virus or HIV virus. Intra-venous drug users (IVDU) were also checked for syphilis infection. Such patients were routinely followed up and evaluated for the need of treatment using the current standard pegylated interferon and ribavarin. Routine HCV RNA detection by PCR and genotyping with specific probes was performed through the contracting laboratories of the Ministry of Health (National University Hospital laboratory, Singapore and Gribbles Pathology, Kuala Lumpur and Melbourne).

Presences of risk factors (IVDU, haemodialysis or HD, previous operations, blood transfusion, other percutaneous procedures or positive sexual contacts) were regularly checked. Modes of HCV acquisitions were determined according to the risk factors. In patients with multiple risk factors, the most likely risk factor to be strongly associated with HCV transmission was considered to be the underlying aetiology.

Patients with HCV infection were identified from the clinics (Hepatology Clinic, RIPAS Hospital, Bandar Seri Begawan) and laboratory registries and retrospectively reviewed. Only patients followed in the Hepatology clinic in RIPAS hospital was included in the study. The Hepatology Clinics in RIPAS Hospital receive all referrals and follow up patients with chronic HCV infection. RIPAS Hospital serves three of the four districts with population catchments of approximately 320,000 (Economic Planning Unit, Ministry of Finance, projected population 2005). The other hospital, Suri Seri Begawan Hospital located in Kuala Belait, also sees and manages a smaller number of patients. The central laboratory handles all the blood testings for HCV and receives all the results for viral load and genotype testings.

At the time of the study (up till October 2005), there were a total of 185 patients under the follow up of the Hepatology Clinics and of this, 75 patients had undergone genotype testing. Blood samples were collected and send to the overseas centre for PCR and genotyping. Demographic data (age, gender and race), mode of acquisition (IVDU, transfusion related, haemodialysis related or others) and laboratory investigations (liver function test, viral load and viral genotype) were retrieved from case notes and computer results where available.

All data were coded and entered into the SPSS package (Version 10.0, Chicago, IL, USA) for analysis. The *Student's t-test, Chi-squared* and *Fisher's* exact tests were used when appropriate. The modes of acquisition were grouped into IVDU and others as in the comparison between favoruable (genotypes 2 and 3) and non-favourable (genotypes 1 and 4) genotypes. The results were considered to be statistically significant when p value is < 0.05 (2-tailed).

Results

The mean age of the patients was 40.8 ± 9.8 years old, consisted mainly male (81.3%) and predominantly Malay (80%). The most common mode of acquisition of HCV was through IVDU (63.5%). Two patients were co-infected with hepatitis B virus and none were positive for HIV infection. The demographics of patients and mode of acquisition of HCV infection are shown in Table 2.

Table 2: Baseline demographic data, mode of acquisition and baseline liver function test of patients with genotypic testings

Age (years)	40.8 ± 9.8
Gender	
Male	61 (81.3%)
Female	14 (18.7%)
Race	
Malay	60 (80%)
Chinese	8 (10.7%)
Indigenous	6 (8%)
Others	1 (1.3%)
Mode of acquisitions *	
Intravenous drug use	33 (63.5%)
Haemodialysis	6 (11.5%)
Transfusion/operation	6 (11.5%)
Sexual contact	3 (5.8%)
Unknown	7 (7.7%)
Baseline Liver function test	
Protein (gm/L)	79.4 ± 5.2
Albumin (gm/L)	39.0 ± 3.9
Bilirubin (mmol/L)	17.2 ± 8.9
Alkaline phosphatase (U/L)	78.7 ± 24.9
Gammaglutamyl transpeptidase (U/L)	68.7 ± 83.5
Alanine aminotransferase (U/L)	91.6 ± 63.9

* Based on 52 patients (23 patients did not have this data recorded)

There were four genotypes detected and the commonest genotypes were genotypes 3 and 1, accounting for 58% and 34% respectively. Genotype 2 accounted for 5%. Figure 1 show the distribution of genotypes. Two patients were infected with dual genotypes (1 & 4 and 2 & 4 respectively). Both these patients had blood transfusion more than 20 years ago, and one had it in Egypt.

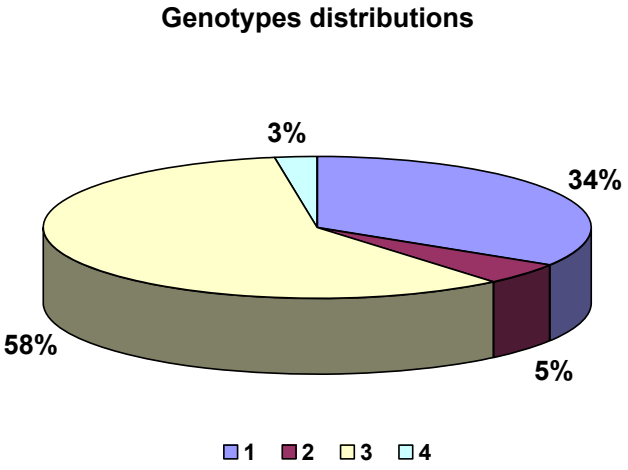

Figure 1. Genotypes distribution of hepatitis C virus

The median viral load was 2.74 x 10^6 copies (range, 2,490 to 39 x 10^6).

There were no significant differences between the favourable (genotypes 2 & 3) and non-favourable (genotypes 1 & 4) genotypes. Although those with favourable genotypes were younger, this was not statistically significant (p = 0.314). Similarly, there were no difference between genders (p = 0.226), the mode of acquisition (IVDU vs. others, p = 0.223), viral load (< or ≥ 2 x 10^6 copies, p = 0.763) and the baseline liver function test including the baseline serum alanine aminotransferase activity (p = 0.403), necroinflammatory and the fibrosis stages between the favourable and non-favourable genotypes. This is shown in Table 3.

Table 3. Comparison between patients with favourable (genotypes 2 and 3) and non-favourable (genotypes 1 and 4) hepatitis C virus genotypes

Parameters	Favourable	Non-Favourable	*p* value
Demographics			
Age (yrs)	39.9 ± 8.4	42.4 ± 11.8	0.314
Gender (male)	85.4%	74.1%	0.226
Mode of acquisition			
IVDU	69.7%	52.6%	0.223
Others	30.3%	47.4%	
Blood investigations			
Alanine aminotransferase (U/L)			
Baseline	96.8 ± 61.9	82.6 ± 67.5	0.403
Highest level	117 ± 70.9	118 ± 116.2	0.967
Albumin (gm/L)	39.3 ± 3.9	38.6 ± 4.3	0.633
Alkaline phosphatase (U/L)	73.5 ± 25.4	87.6 ± 22.2	0.107
Gammaglutamyl transpeptidase (U/L)	61.2 ± 37.2	82.5 ± 133.9	0.466
Protein (gm/L)	79.5 ± 5.4	79.2 ± 4.9	0.832
Viral load (≥ 2 x 106 copies)	48.4%	52.9%	0.763
Overall Cirrhosis	0.0%	11.1%	0.180
Histology			
Grade of inflammation	1.6 ± 1.0	2.0 ± 0.7	0.478
Stage of fibrosis	1.8 ± 0.9	1.4 ± 0.9	0.450

IVDU: Intravenous drug users

Discussion

Our study showed that four genotypes exist in Brunei Darussalam with the commonest genotype being genotype 3. Genotype 2, the other favourable genotype accounted for only 5%. Overall, favourable genotypes accounted for 63%. This finding is consistent with published data. These genotypes have been shown to have more favourable responses to treatment. Genotypes 1, 2 and 3 have a worldwide distribution with type 1 (especially subtypes a and b) being commonest, accounting for about 60% of global infections. In our setting, genotype 1 accounted for a third of our cases. Interestingly, we also found two patients with genotype 4, most probably acquired outside of the country. This genotype is uncommon outside of the Middle East, Egypt and Central Africa. Both of our patients had co-infections with other genotypes (1 and 2 respectively) and one had a history of blood transfusion more than twenty years before in Egypt. The other patient only had a history of blood transfusion more than twenty years ago. Whether both genotypes were acquired simultaneously is possible. However it is more likely than the different genotypes were acquired at different times. Currently it is not known whether co-infections with multiple genotypes have any impact on the natural progression. However, treatment is usually targeted at the less favourable genotype. We did not find any genotypes 5 and 6 among our patients. This is an expected finding as these genotypes are found only in Indochina and South Africa.

Reports from Europe and North America show that co-infections of HCV with other viruses, especially with HIV are not uncommon [10, 11]. This is particularly true in those with history of IVDU [12]. Similarly, co infections with HBV also occur [13, 14]. Currently, there are very little data from the South East Asia regions. Fortunately, in our setting, the incidence of HIV infections remains low and none of our patients had HIV infection. Only two had co-infections with HBV. Co infections with HBV can be managed concurrently as interferon used for HCV treatment is also a standard treatment for HBV.

Studies have shown that genotypes may influence the natural history and be associated with disease progression. Genotype 1, especially subtype b has been shown to be associated with higher risk of hepatic decompensation by three fold in patient with established liver cirrhosis [8]. Presence of steatosis may be associated with disease progression [15] and genotype 3 has been shown to be strongly associated with hepatic steatosis. However this is reversible with successful treatment. [16] Unfortunately, we were not able to assess this correlation as the number of patients having had liver biopsies was too small. However, there no significant differences when we compared between the favourable and unfavourable genotypes in the patients' characteristics, necro-inflammatory activities and viral load.

The commonest mode of acquisition among our patients was through IVDU followed by HD. With the implementation and improvement of infection control measures (designated HD machines and points), infection through HD is becoming less and IVDU is now becoming a major source of HCV infection in our local setting. A local study looking at patients with HCV undergoing HD in Suri Seri Begawan Hospital showed that the infection rate had declined significantly through these infection control measures [17]. Among those patients who acquired HCV after starting HD, the median time for HCV IgG to become positive was 45 months (range, 20 to 70). It is more difficult to estimate time of infection among IVDU as most were detected later once they were incarcerated. Furthermore, most were not very forth coming or cannot remember the exact time of starting IVDU. Furthermore, time of HCV acquisition is not necessary correlated to the first time of IVDU use. Among the different modes of acquisition, the favourable genotypes were more common among our IVDU group; however this did not reach statistical significance. This is important as this has cost saving as treatment duration for favourable genotypes is shorter.

Current treatment guidelines recommend six month of therapy for favourable genotypes (genotypes 2 and 3) regardless of viral loads and non-favourable genotypes with low viral load ($< 2 \times 10^6$ copies). However, 12 months of therapy have been recommended for non-favourable genotypes with high viral load ($\geq 2 \times 10^6$ copies). [2] More importantly, there are studies now showing that even shorter duration of treatment may be adequate for the favourable genotypes. [18, 19] Success rate in term of sustained viral response (absence of RNA detected six months post completion of treatment) have been shown to be as high as 76 to 82% for genotypes 2 and 3 compared to 42 to 46% for genotype 1 [2] Overall, this has cost implications as the treatment is costly and associated with significant side effects that can severely impair quality of life.

The main weaknesses of our study are the small sample size of patients having been tested for genotype and being a single centre study. This is mainly because at the time of the study, a proportion of patients already had been treated and some patients were still waiting for their results. Results from single center study may not be generalisable due to referral biases of tertiary centers. However, in our case, our clinics have a large population catchment of more than 75% of the overall population. Hence our results obtained are quite generalisable in our local contact.

In conclusion, our study showed that the commonest genotype is genotype 3 which is a favourable genotype. However, non-favourable genotypes are also common in particular genotype 1. Co infections are fortunately uncommon. There were no significant differences between the favourable and non-favourable genotypes in the patients' demographics, mode of acquisition, necro-inflammatory activities and viral load.

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Breast cancer in Brunei Darussalam – Differential community distribution and an analysis of common molecular tumour markers

Foo Ren Kang[1], PU Telesinghe[2], Syaffiq bin Abdallah[3], and R. Ramasamy[1]
[1]Institute of Medicine, Universiti Brunei Darussalam, [2]Department of Pathology, RIPAS hospital, [3]Department of Oncology, RIPAS hospital, Brunei Darussalam

Abstract

The distribution of breast cancer among women of Chinese and Malay origin of different ages presenting at RIPAS hospital, Brunei Darussalam and its relative incidence in the Chinese and Malay populations of the country were determined for the years 2004 and 2005. While the incidence rate for Chinese in Brunei is comparable to that seen in Singapore, the incidence rate for Malays in Brunei is significantly lower than in Singapore. The differences are consistent with genetic or culture associated behavioral factors or both playing a role in the development of breast cancer.

The findings also indicate that breast cancer arises more in a slightly younger age group in the South East Asian populations, including Brunei Darussalam when compared to the USA. The difference may be related to genetic, cultural, behavioural, and environmental factors

The presence of the molecular markers, estrogen and progesterone receptors (ER and PR), pS2 protein, HER-2/Neu receptor, Bcl-2, p53 and Ki67 in ductal carcinomas in situ and invasive ductal carcinomas was investigated by immunohistochemistry. While no relationship was observed between tumour stage and the expression of the different molecular markers, the results suggest that the expression of both ER and PR, although not statistically significant, tend to be inversely related to grade of the tumour, consistent with observations made elsewhere. Only 3 of 35 tumours were positive for the Ki67 marker of cell division and all these were of tumour grade 3. The findings did not demonstrate a relationship between p53, Bcl-2 or Her 2 and tumour grade. However the detection of Her 2 in the tumours is important for considering Herceptin therapy.

These findings help establish a baseline for more detailed investigations on factors influencing the incidence of breast cancer, and the use of molecular markers in clinical oncology, in Brunei Darussalam.

1. Introduction

Breast cancer is the most common malignancy among women in many countries [1]. The majority of breast cancers are adenocarcinomas. They are classified into *in situ* carcinomas which are neoplasms that are restricted within the ducts or lobules by the basement membrane, and invasive carcinomas that are able penetrate the basement membrane and invade surrounding lymphatic and blood vasculature and are also able to metastasize to distant regions [2]. *In situ* carcinomas are classified into intraduct carcinomas (accounting for about 5% of all breast cancers) and lobular carcinoma (accounting for about 6% of breast cancers). Invasive carcinomas are classified into several types, of which invasive ductal carcinoma is the most common, accounting for about 70% of all breast cancers [3]. We examined the distribution of breast cancer among women of Chinese and Malay origin of different ages presenting at RIPAS hospital, Brunei Darussalam and estimated its relative incidence in the Chinese and Malay populations of the country.

Molecular markers characteristic of breast cancer cells, that can be detected by commercially available antibodies using immunohistochemical techniques, have been found

Correspondence:
R. Ramasamy, Institute of Medicine,
Universiti Brunei Darussalam,
Jalan Tungku Link,
Gadong, BE 1410,
Brunei Darussalam.

to be useful in prognosis and for devising suitable treatments. Prognostic factors assess the patient's risk of relapse based on intrinsic biological characteristics of the tumour and the disease stage at diagnosis. They help to identify the need for adjuvant therapy [4]. Predictive factors are helpful in assessing the responsiveness of the tumour to particular treatment [5]. Several molecular markers exhibit both prognostic and predictive values; e.g. estrogen and the HER2/neu (c-erb-2) receptors. The predictive and prognostic values of different molecular markers in breast cancer have been extensively reviewed elsewhere [4-9]. In our study we attempt to relate the presence or absence of the estrogen receptor (ER), the progesterone receptor (PR), pS2, HER2/neu (Her2), p53, Bcl2 and Ki67 to the stage and grade of invasive ductal carcinomas and in situ intraduct breast carcinomas seen in the years 2004-5 at RIPAS hospital, Brunei Darussalam.

The estrogen receptor (ER) and the progesterone receptor (PR) are steroid hormone-activated transcription factors. Estrogens mediate their effects through two specific intracellular ER receptor subtypes, ER α and ER β. Both receptors are expressed form different genes and have similar but not identical ligand binding characteristics [6]. In clinical practice only ER α is currently measured [5]. In terms of its clinical use in breast cancer, overexpression of ER α has been shown to have valuable prognostic and predictive properties [6]. Patients with ER positive tumour have shown to have prolonged disease survival rates compared to those with ER negative tumours regardless of the involvement of nodes [7]. They can also be treated with selective ER modulators such as Tamoxifen. The PR is produced when the estrogen-ER pathway is active. It has similar prognostic value as the ER. The pS2 protein is an estrogen regulated secretory protein that is expressed predominantly in ER-positive tumours [9]. The exact function of the protein is uncertain though it seems to be involved in growth regulation, and act as indicator for an intact cellular estrogen-processing mechanism [7, 9].

Her2-neu (*Her2*) proto-oncogene, located on chromosome 17q21-q22 [8], codes for a transmembrane tyrosine kinase growth factor receptor. It is a one of a family of epidermal growth factor receptors. This gene has been found to be amplified in 15 – 20% of invasive human carcinomas. Her2 overexpression has been associated with poor prognosis of in both primary operable and advanced breast cancer patients [8]. However, Her2 is the target for treatment of breast cancer with a humanised monoclonal antibody, Herceptin.

p53 is a tumour suppressor gene found on the chromosome 17p13 that acts as a negative regulator of cell proliferation. It does so by binding to DNA and inducing the transcription of *p21* protein which goes on to block the entry of the cell into the S phase of the cell cycle [10]. Mutant p53 is the most common genetic deficit in human cancers, including breast cancer [9]. There is a strong relationship between an abnormal p53 phenotype and poor clinical outcome.

Bcl-2 is an anti-apoptotic protein that suppresses the function of Bax, an apoptosis-inducing protein which forms mitochondrial pores. Opening of such pores releases mitochondrial cytochrome c which then activates caspases to induce apoptosis [11]. Surprisingly, the loss of Bcl 2 expression correlates with the loss of endocrine sensitivity, unfavourable tumour biology and poor prognosis [3, 7]. The reason for this is not known at present.

The Ki67 marker is a monoclonal antibody reactive nuclear antigen, detected in dividing cells [7]. High levels of Ki67 are associated with poor histologic differentiation and with metastasis to the lymph nodes, and are capable of predicting 4 year survivability irrespective of the ER and nodal status.

2. Methods and Materials

2.1 Patient details

All breast cancer patients in Brunei are referred to the RIPAS hospital, Bandar Seri Begawan for treatment. Details of breast cancer patients for the years 2004 and 2005 were obtained from the Cancer Registry of the RIPAS Hospital. Female patients with complete records in 2004 and 2005 that were used in this study numbered 45 and 41 respectively. The one male patient seen during this period was excluded from the study. The records were in the form of case summaries originating from the Oncology Department, RIPAS hospital. Histopathological reports were obtained from the State Pathology Laboratory, RIPAS

hospital. Incomplete or missing patient records due to deferred follow-ups, etc, were excluded from the analysis. For determination of breast cancer incidence and age on diagnosis, the entire set of patients from 2004-5, totalling 86, were used.

2.2 Statistics

The incidence of breast cancer among females in the population or ethnic group, and 95% confidence limits, were calculated as follows using the exact binomial test [12]:

$$\frac{\text{No. of patients with breast cancer}}{\text{Total mid year female population (country or ethnic group) / 100 000 persons}}$$

The significance of differing proportions among tumour molecular markers in the varying grades or stages of tumours was determined by the Fisher's exact test.

2.3 Classification of tumours

From the macroscopic and microscopic results, the size of the tumour (T), the number nodes exhibiting metastasis (N) and the pathological grading were obtained. With these and the metastasis status (M) of patients obtained from the case summaries, the TNM staging of the tumour was determined according to established procedures [13]. The grading of the tumour was based on the microscopic examination of the tumour to assess the level of differentiation of the tumour. G1 indicated a well differentiated tumour cells, G2 indicated moderate or poorly differentiated tumour cells and G3 indicated undifferentiated tumour cells [1].

2.4 Immunohistochemical staining data for markers and their relationship to stage and grade of invasive ductal and intraductal carcinomas

Immunohistochemical staining was performed routinely by the Pathology Department of RIPAS hospital, on the biopsy specimens, using standard procedures. These showed levels of ER , PR , Her 2, Ki-67, p53, Bcl-2 and pS2 proteins. A typical slide of a medullary carcinoma showing the brown immuno-peroxidase reaction for for Her 2 is shown in Figure 1. The specificity of the reaction is shown by the absence of staining in adjacent non-tumour cells that serve as an internal negative control.

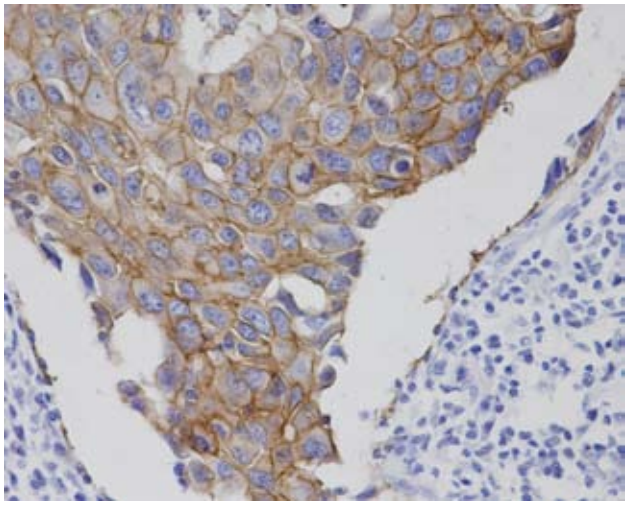

Figure 1. Immuno-peroxidase staining for Her2 in medullary carcinoma of the breast

The units for expression levels of the molecular markers were presented in the form: +1, +2 and +3. The interpretation of these units were based on the microscopic examination of the pathologist as follows:

Units	Proportion of cells that were seen to be positive
-	<25%
1+	25-50%
2+	50-75%
3+	>75%

Table1. Interpretation of immunohistochemistry units

The expression levels of each of the molecular markers were compared with the staging and grading of each of the tumors. In this study, only invasive ductal carcinomas and intraduct carcinomas were analyzed due to the relatively small number of other types of breast carcinomas.

3. Results

3.1 Incidence of breast cancer in the population and among ethnic groups

The incidence rates of breast cancer in the country for the female population of Brunei Darussalam for the period 2004-2005 are shown in Table 2. The results show that the incidence of breast cancer is higher in the Chinese female population than in the Malay female population in Brunei Darussalam. There were seven cases of breast cancer among patients who could not be classified as ethnic Chinese or Malay.

Ethnicity	n[a]	Incidence[b]	95% CI
Malay	51	22.0	16.4, 28.9
Chinese	28	74.5	49.5, 107.6
Total	86	24.9	19.9, 30.8

[a] number of breast cancer patients
[b] number of cases per 100,000 population per year in the period 2004-2005

CI – confidence interval

Table 2 Incidence of Breast Cancer (BC) for 2004-2005

3.2 Age at diagnosis of the breast cancer

The age at which cancer was first diagnosed in all of the female breast cancer patients is shown in Figure 1. There were more patients diagnosed in the 40-49 and 50-59 age groups than in other age groups in the period 2004-2005, with equal numbers in both the 40-49 and 50-59 age (33.7% of all cases each)

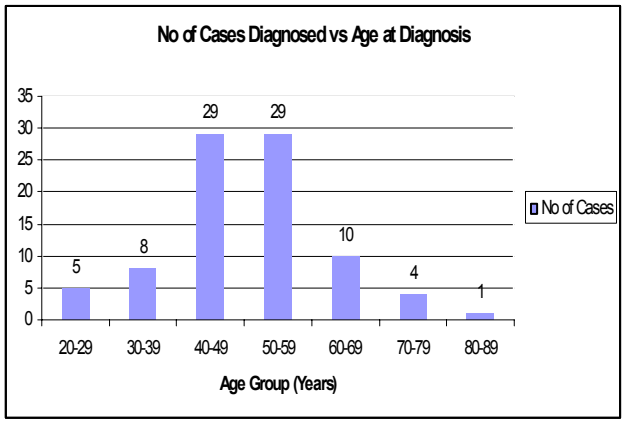

Figure 1. Number of cases diagnosed by age group in 2004-2005. The numbers in each group are indicated above the bars in the figure.

3.3 Proportions of tumours with different molecular markers

Because this was a retrospective analysis, results from the determination of molecular markers in tumours were only available for a proportion of the tumours. Of those where results were available, the proportions of stained tumours that gave a positive reaction for the different markers is shown in Table 2.

Marker	No. of Tumours Examined	No. Positive	Percent Positive
ER	59	25	42%
PR	58	25	43%
Her2	56	36	64%
p53	36	15	42%
Ki67	35	03	09%
Bcl2	36	12	33%
pS2	35	10	29%

Table 2. Proportions of positive tumours among those examined for different molecular markers, 2004-2005

3.3. Relationship between the level of markers and tumour stage

No clear trends or statistically significant relationships could be discerned between the level of expression of the different tumour molecular markers and tumour stage in the patients at diagnosis. Hence the details of these data are not presented.

3.4 Relationship between the level of markers and tumour grade

The relationship between the grade of tumour and the different tumour markers was also examined. Figure 2 shows the relationship between the level of detection of ER and the grade of the tumour. This relationship was statistically analysed by comparing the proportions of tumours expressing the marker at any level, and marker-negative tumours, in tumours of different grades. The pooling of the tumours that expressed markers at any level for each grade of tumour was done to increase the numbers in a given category for statistical analysis. Although the relationship did not reach acceptable statistical significance, there appeared to be a tendency for the higher grade tumours to be ER negative (Fisher's exact test p=0.097).

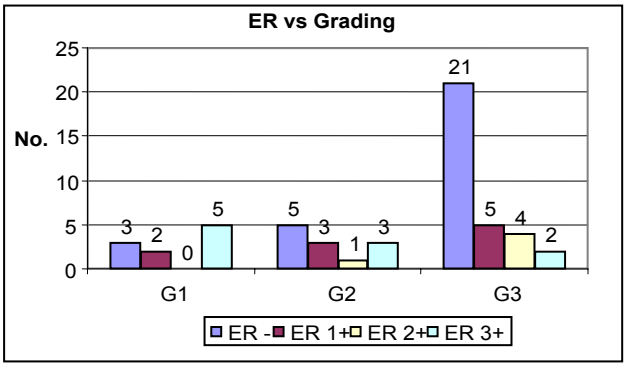

Figure 2. Relationship between ER expression levels and the grade of tumour. The numbers in each group are indicated above the bars in the figure.

A tendency for a similar relationship between the detection of PR and the grade of the tumour, although not reaching statistical significance, was also observed (Figure 3, p=0.112 by Fisher's exact test).

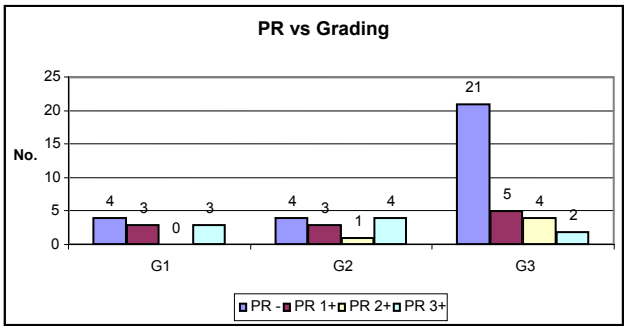

Figure 3. Relationship between PR expression levels and the grade of tumour. The numbers in each group are indicated above the bars in the figure.

For p53 the proportions of positive and negative marker reactions in tumours of different grades were not significant by the Fisher's exact test (p=0.889) and no obvious trend could be discerned (Figure 4). Although a large proportion of G3 stage tumours were p53 negative, this was also the case for G1 stage tumours.

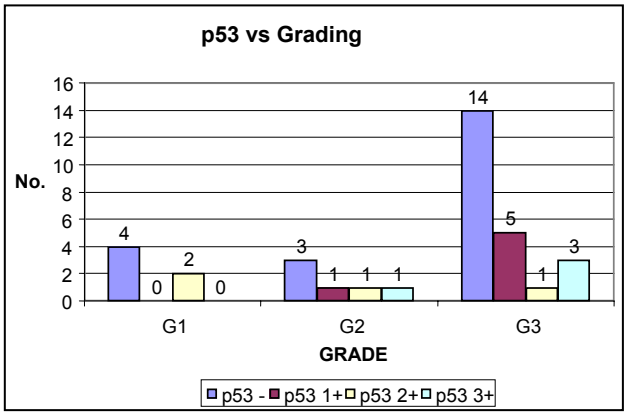

Figure 4. Relationship between p53 expression levels and the grade of tumour. The numbers in each group are indicated above the bars in the figure.

Additionally, no clear trend could be discerned, or statistically significant relationship established, between the expression of Bcl2 or Her2 and the grade of the tumour (Figures 5 & 6). With Ki67, the three tumours where the antigen was detected (two at the 3+ level and one at the 2+ level) were all of tumour grade 3.

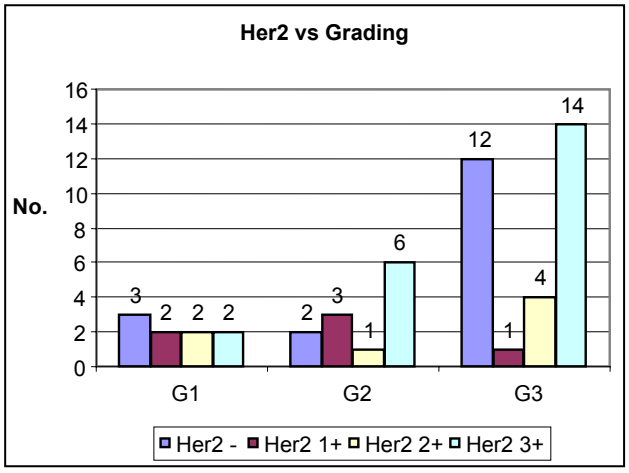

Figure 5. Relationship between Her2 expression levels and the grade of tumour. The numbers in each group are indicated above the bars in the figure.

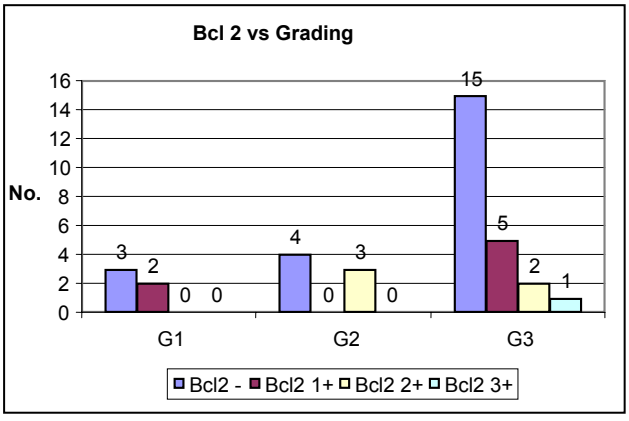

Figure 6. Relationship between Bcl2 levels and the grade of tumour. The numbers in each group are indicated above the bars in the figure.

3.5 Relationship between ER and pS2 expression in the tumours

Because pS2 is expressed after ER mediated estrogen signalling, a correlation between its expression and that of ER would be expected. It was observed that of 13 ER +ve tumours, 5 were pS2 +ve and of 22 ER –ve tumours, only 5 were pS2 +ve. The relationship between pS2 and ER expression was not statistically significant by Fisher's exact test (p=0.44). However, 49% of the tumours were both pS2 and ER –ve, while only 14% were pS2 +ve and ER –ve.

4. Discussion

4.1 Incidence of breast cancer in Brunei

Data from Singapore also show a higher incidence rate in Chinese females compared to Malay females [14]. For the 1998-2002 period in Singapore, the incidence rate for the Chinese female population was 72.7 per 100,000 per year with a 95% CI of 70.64 to 74.8 compared to an incidence rate for the Malay female population of 46.4 per 100,000 per year with a 95% CI between 42.5 and 50.4. While the incidence rates for Chinese in Singapore is comparable to that seen in Brunei in our study, the incidence rate for Malays in Singapore in significantly higher than in Brunei. While this may possibly be due to sociological differences related to seeking medical treatment for breast cancer in the two countries, it may also reflect geographical and other socio-economic factors that are reported to affect the incidence of breast cancer [2, 15]. The differential factors that tend to reduce the incidence of breast cancer among Bruneian Malays merit further investigation.

The differences between the Chinese and Malay populations observed in this study is consistent with genetic or culture associated behavioral factors or both playing a role in the development of breast cancer [3]. It is reported for example that the incidence of breast cancer in the USA greater for Caucasians than for African Americans and is least for the Asian/Pacific Islanders/Amerindians [16]. More detailed studies are needed to determine the ethnicity-related factors affecting breast cancer incidence in Brunei.

4.2 Age at diagnosis

The Second Report of the National Cancer Registry of Malaysia also reported a similar pattern of age-dependence for breast cancer incidence in Malaysia in 2003, as we find in Brunei in 2004/5. About 33 % of cases were diagnosed in the 40-49 age group and 31% in the 50-59 age group in Malaysia in 2003 [17]. In Singapore, the Singapore Cancer Registry report no.6 (2004) reported that over 54% of all breast cancer cases was diagnosed at 50 years of age or later [14]. On the other hand, the median age of diagnosis of breast cancer in the USA is 61 years [16].

The findings therefore suggest that breast cancer arises more in a slightly younger age group in the South East Asian populations, including Brunei Darussalam, than in the USA. The difference may be related to genetic, cultural, behavioural, and environmental factors and merits further investigation.

4.3 Relationship between the molecular markers and staging and grading

The prognosis is poorer for the more highly staged tumours [13] and for tumours of a higher grade (less differentiated tumours) [7]. The present study could not establish a clear relationship between the staging and any of the molecular markers. On the other hand, the results suggest that the expression of both ER and PR may tend to be inversely related to grade of the tumour which is consistent with other observations [9]. Analysis of a larger number of samples in Brunei for ER and PR will be needed to demonstrate a statistically significant relationship between the expression levels of these two markers and tumour grade. Such a finding would assist prognosis.

Mutation in the p53 gene leads to an accumulation of dysfunctional p53 protein that is detectable immunohistochemically [18]. Therefore it might be expected that more aggressive tumours of higher grade and stage might have more p53 detectable by immunohistochemistry. However there are conflicting reports in the literature with either a positive [19] or no [20] correlation of p53 detection with grade/stage of breast cancers.
The detection of Ki67 only in the G3 tumours is consistent with it being a marker for dividing cells. It has been reported that the expression of Ki67 in >20% of nuclei (approximately > Grade 1 according to the classification used in the present study) correlates significantly with histological grade and the absence of ER and PR, and that it is a simple, inexpensive and reliable measure of proliferation rate in breast cancer compared to flow cytometric measurement of DNA content [21].

Our findings did not demonstrate a relationship between Bcl-2 or Her 2 and tumour grade or stage. However the detection of Her 2 in the tumours is important for considering Herceptin therapy.

While not statistically significant, there was a tendency for the absence of the pS2 marker to be correlated with the absence of ER, consistent with pS2 being expressed downstream of estrogen signalling. However 5/22 ER negative tumours showed detectable pS2, and this may be due to the sensitivity of ER detection or the dysregulation of gene expression associated with malignant transformation. The pS2 positive fraction of ER positive tumours has been reported to have a better prognosis [9].

The expression of molecular markers in tumour cells is confounded by the gross genomic instability of tumours, which can result in highly dysregulated expression of proteins. Variable sensitivity of detection in immunocytochemistry is also possible. Gene expression profiling using nucleic acid hybridisation techniques is considered to be potentially of great value clinically in predicting sensitivity of tumours to new and established drugs. The findings reported here provide a baseline for more detailed investigations, and investigations using more sensitive techniques, on the use of molecular tumour markers in improving the treatment of breast cancer.

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Clinical presentations and outcomes of patients with non-variceal upper gastrointestinal bleeding requiring endoscopic therapy

Alexander Philip Jacob, Vui Heng Chong, Aza Zetty Feroena Jamaludin,
Anand Jalihal, Maliackal John Alexander
Gastroenterology Unit, Department of Medicine,
Raja Isteri Pengiran Anak Saleha Hospital

Abstract

Gastrointestinal bleeding is a common medical emergency that requires urgent endoscopy and treatment. Rebleeding is an important complication that can lead to death. Scoring systems such as the Rockall score and Forrest endoscopic criteria can predict rebleed and poor outcomes. We investigated the clinical presentation and outcome of patients with non-variceal upper gastrointestinal (GI) bleeding who required endoscopic therapy. Patients presenting with non variceal upper GI bleed over a one year period (Jan to Dec 2004) were identified from the endoscopy register and retrospectively reviewed. There were 61 patients (male 77%) with a mean age of 54.6 years (range 3-92). The commonest presentation was with melena (77%). 49.2% were on medications associated with increased risk for GI bleed and 46% had significant comorbid illnesses. Peptic ulcer was the most common cause of bleeding (78.7%). The prevalence of *Helicobacter pylori* was 31%. Blood transfusion was required in 44 patients (72.1%) with a mean requirement of 3.3 units per patient (range 0-21). Rebleeding occurred in 25% and 3.3% were referred for surgery. The overall mortality was 18%. However, majority died from other significant illnesses. Two deaths (3.3%) occurred as result of bleeding. Older age ($p < 0.05$), higher admission INR ($p < 0.05$), longer hospital stay ($p < 0.05$) and higher blood transfusion requirements ($p < 0.05$) were predictive of mortality. The Rockall score correlated with rebleed and death but not the Forrest endoscopic criteria. In conclusion, ulcer disease account for the major proportion of non-variceal upper GI bleed and half of these patients were taking medications associated with increased risk for bleeding. Certain factors are predictive of mortality.

Introduction

Upper gastrointestinal (GI) bleed is defined as GI blood loss proximal to the ligament of Treitz. [1] It may be variceal or non-variceal. Acute non-variceal upper GI bleed is a common emergency with a reported incidence of 50-100 cases/100,000 population/year [2, 3] and a mortality of 5-14% [3, 4] Peptic ulcer is the most common cause of acute non-variceal upper GI bleed [4] Over the past three decades there have been advances in the management of this condition. Endoscopy has become an important tool and has changed from a purely diagnostic procedure to a first line therapeutic tool in the management of GI bleeding. In additions, prognostic scores such as the endoscopic Forrest criteria and Rockall score [5, 6] have been developed to predict risk of rebleed and poor outcomes. This study aimed to evaluate the clinical, endoscopic features and outcome of our patients in Brunei Darussalam undergoing endoscopic therapy for non-variceal upper GI bleeding

Correspondence:
Vui Heng Chong
Gastroenterology Unit, Department of Medicine,
Raja Isteri Pengiran Anak Saleha Hospital
E-mail: chongvuih@yahoo.co.uk

Methods

All patients admitted with suspected upper GI bleeding had full blood count, urea and electrolytes, clotting and cross match done. Liver function test was done if underlying liver disease was suspected. All patients were assessed for severity of blood loss and resuscitated with volume expander. Patients were monitored closely and kept nil per orally until bleeding settled. They were given acid suppression with either omeprazole or ranitidine. Patients who developed GI bleeding as in-patient were routinely referred to the gastroenterologist on duty. Decision for either urgent or elective endoscopy depends on the time of admission or referral. Generally, cases referred during office hours have their endoscopy done during the same day. Otherwise, patients have their endoscopy in the next available endoscopy list.

There are five endoscopists working in the unit during the period of the study, consisting of three specialists and two senior medical officers. Overall four endoscopists had experience with over 1,000 procedures and one trainee with less than 1,000 procedures carrying out procedures under supervision. Treatment modalities available for treatment of bleeding lesions included; i) adrenaline injection mono-therapy (1 mg in 1/10,000 dilution with water); b) heater probe coagulation mono-therapy; c) combination of adrenaline and heater probe coagulation; d) haemoclip. Treatment modalities used were at the discretion of the endoscopists.

Rebleeding was defined as new onset of hematemesis, coffee ground vomitus, malena and drop in hemoglobin level of 2 or more grams after a successful initial endoscopic treatment over the next 48 to 72 hours. Failure of treatment is defined as failed endoscopic therapy to achieve haemostasis or ongoing evidence of blood loss with 24 hours of first endoscopy. Repeat endoscopies with further attempt at achieving haemostasis were often carried out before considering alternative interventions. The modalities available for repeat endoscopic therapies were the same as the index endoscopy. Decisions for surgical intervention were made if there was failure to achieve haemostasis at the index endoscopy or if there was rebleed after two previous endoscopic interventions.

Patients with non-variceal upper GI bleed requiring endoscopic therapy over a one year period (Jan-Dec 2004) were identified from the endoscopy register. Their charts were reviewed retrospectively. Clinical data, endoscopic findings, laboratory data & outcome measures (blood transfusion requirements, rebleed, surgery and death) were retrieved and coded in preset proforma. The endoscopic findings for the bleeding lesions were extracted from the endoscopic record and the Forrest grade and Rockall scores of patients were assigned as per criteria given in Tables 1 and 2. The data was entered into the SPSS program (SPSS, Version 10.0, Chicago, IL, USA) for analysis. The Mann-Whitney U test was used for continuous variables and the Fischer's Exact or Chi-squared tests were used for categorical variables. Significance was taken when $p < 0.05$.

Table 1: Forrest classification of bleeding peptic ulcers

Results

Forrest classification	Endoscopic findings
1a	Spurting
1b	Oozing
2a	Non-bleeding vessel
2b	Ulcer with surface clot
2c	Ulcer with haematenic spot at base (Red spot, blue or black spot)
3	Ulcer with clean base

Risk of rebleed: 100%, 50% and <3% (for types 1a, 2a & 3 ulcers respectively) [1]
Risk of death: 11%, 11% and 2% (for types1a, 2a & 3 ulcers respectively) [7]

Table 2: Rockall risk scoring system [6]

Variables	0	1	2	3
Age (yrs)	< 60	60 to 80	> 80	
Shock	Systolic BP >100 mmHg Pulse rate <100 No Major comorbidity	SBP > 100 mmHg Pulse rate > 100	SBP < 100 mmHg Pulse rate > 100	Renal failure Liver disease Disseminated malignancy
Co morbidity			Cardiac failure Ischemic heart disease Any major co-morbidity	
Diagnosis	Mallory-weiss tear No lesion identified No SRH*	All other diagnosis	Malignancy of upper gastrointestinal tract	
Major SRH	None Dark spot sign		Blood in upper GI tract Adherent clot Visible or spurting vessel	

SRH: Stigmata of recent haemorrhage
Risk of rebleed: 5% (if score is ≤2) and 40% (if score ≥ 8)
Risk of death: <1% (if score is ≤2) and 41% (if score ≥ 8)

RESULTS

There were a total of 61 patients identified and their demographic is shown in Table 3. Forty one patients (67.2%) presented with GI bleed and in the remainder (32.8%) bleed occurred when hospitalized for other illnesses. The most common presentation was malena (77%) followed by haemetemesis (47.5% - fresh blood 26.2% and coffee ground 21.3%). Haemotochezia occurred in 6.6%. 37.7% presented with various combinations of the above symptoms. Bleeding following endoscopic procedures occurred in 8.2%. Fifty-eight patients (95.1%) received medical treatment in addition to endoscopic treatment. Omeprazole was used intravenously in 49 (80.3%) patients and orally in 7 (11.5%). Two patients (3.3%) were treated with intravenous ranitidine.

Table 3: Patients demographic, co-morbidities and medications used

Mean age (yrs)	54.6 (range, 3-92)
Genders (male / female)	47 (77%)/ 14 (23%)
Race	
Malay	47 (77%)
Chinese	5 (8.2%)
Indigenous	6 (9.8%)
Others	3 (4.9%)
Co morbidities	
Renal disease	12 (19.7%)
Gastrointestinal disease	12 (19.7%)
Cardiovascular disease	12 (19.7%)
Malignancy	4 (6.6%)
Cerebrovascular disease	3 (4.9%)
Respiratory	6 (9.8%)
Medications associated with GI bleeding	30 (49.2%)
NSAIDs	14 (23%)
Aspirin	13 (21.3%)
Clopidogrel	9 (14.8%)
Warfarin	3 (5%)
Heparin	2 (3.3%)
History of dyspepsia	25 (41%)
History of previous upper GI bleeds	21 (34.4%)

NSAIDs: non-steroidal anti-inflammatory drugs
GI: gastrointestinal

Endoscopy was carried out as emergency procedure (≤ 24 hrs) in 16 patients (26.2%) and as elective procedure (> 24 hrs) in the remaining 45 (73.8%).Endoscopy was carried out as emergency procedure (≤ 24 hrs) in 42 patients (85.7%) and as elective procedure (> 24 hrs) in the remaining 7 (14.3%). Findings at endoscopy are shown in Table 4. All patients were treated with submucosal adrenaline injection. Heater probe coagulation was used in 15 patients (25%) in addition to the adrenaline injection. *H. pylori* was tested in 29 patients (47.5%) and was positive in 9, giving a prevalence of 31%. The mean duration of hospital stay was 13.8 days (range 1-92).

Table 4: Causes of GI bleed at endoscopy

Findings	n (%)
Oesophagus	
Oesophageal ulcer	2 (3.3)
Mallory Weiss tear	1 (1.6)
Stomach	
Gastric ulcers (GU)	18 (29.5)
Malignancy	2 (3.3)
Haemorrhagic gastritis	2 (3.3)
Post procedure bleeding	
Biopsy	2 (3.3)
Polypectomy	2 (3.3)
Duodenum	
Duodenal ulcers (DU)	30 (49.2)
Malignancy	1 (1.6)
Post sphincterotomy	1 (1.6)

Multiple GUs: 5(8.2%); Multiple DUs: 4(6.6%); Combined GU and DU: 5(8.2%)

Outcome measures are summarized in Table 5. Forty-four patients (72.1%) needed blood transfusion. The bulk of the patients who rebled were old (age ≥ 60 - 86.7%) and had significant comorbidities (93.3%). Rebleed occurred early in 46.7% of patients (within 24 hrs in 20% and between 24 to 72 hrs in 26.7%) and was delayed beyond 72 hours in the remainder. Nine (60%) patients' rebleeding settled, five spontaneously and four after a second endoscopic therapy session. The overall mortality rate was 18% (n = 11). Eight of the patients who had rebleeding died giving mortality among rebleeders of 53.3%. However, in 7 of the 11 patients who died in this series, GI bleed had already settled and the patients died as results of severe underlying illness. In the remaining 4 patients, there was evidence of

on going bleeding; metastatic gastric carcinoma (n = 1), carcinoma of the gallbladder with biliary/systemic sepsis (n = 1), proximal oesophageal ulcer/hepatobiliary tuberculosis and polyarthritis/PUD (n = 1). Both patients with malignancies were at terminal stages. When deaths due to severe underlying illnesses and malignancies were excluded, there were only two deaths (3.3%) directly attributable to bleeding. One patient had an oesophageal ulcer that was believed to be an aortoesophageal fistula. The other patients had significant com morbid conditions. Older age ($p < 0.05$), higher admission INR ($p < 0.05$), longer hospital stay ($p < 0.05$) & higher blood transfusion requirements ($p < 0.05$) were predictors of mortality.

Table 5: Outcome measures

Mean blood transfusion requirement (range 0-21)	3.3 units
Incidence of rebleeding	15 (24.6%)
Number referred for surgery	2 (3.3%)
Overall mortality	11 (18%)

The Rockall score (Fig. 1) correlated with risk of rebleed and mortality ($p < 0.05$). However, there was no correlation with the Forrest grade [Fig. 2: risk of rebleed ($p = 0.59$) and mortality ($p = 0.83$)].

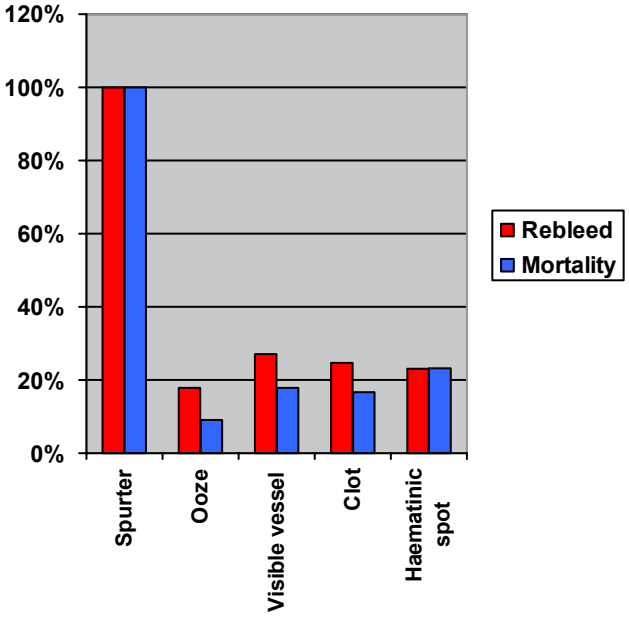

Figure 1: Correlation of the Forrest grade with rebleed and mortality

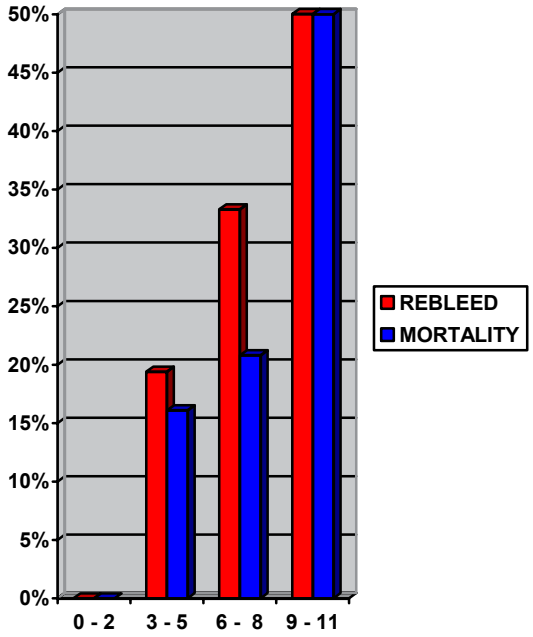

Figure 2: Correlation of the Rockall score with rebleeding and mortality.

Discussion

Our study shows that patients undergoing endoscopic therapy for non-variceal upper GI bleeding were elderly, predominantly male with malena as their most common presenting symptom. They have a high prevalence of co-morbid illnesses and a large proportion were taking medications associated with increased risk for bleeding. This is consistent with published findings reporting older age and male gender to be at higher risk. [3, 8] However, our patients were slightly younger with a mean age of 54.6 years compared to 66 years reported in the West. [9] Male preponderance in our series is higher than corresponding figures from the West [9] (M: F ratio of 3:1 vs. 1.6:1). Medications especially non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are well known risk factors for the development of peptic ulcer and bleeding. [10, 11] Nearly 44% of patients in our series were on either aspirin or NSAIDs which could have contributed to ulcer formation and bleeding in this group. Up to a third of our patients had history of upper GI bleed and this may be accounted by the higher prevalence of use of medications associated with risk of bleeding. As reported in other studies, peptic ulcer was the most common cause of bleeding in our series. [4, 12]

It is interesting to note that there were five patients (8.2%) with endoscopic procedure related bleeding that required endoscopic therapy in our study. Two were post polypectomy, two post biopsy and one post sphincterotomy bleed after endoscopic retrograde cholangiopancreatograpy. Bleeding post sphincterotomy and polypectomy are well recognized complications with prevalence of 1-2% and 5-6% respectively. [13, 14] Biopsy related bleeding is less common but have also been reported. [14] This probably reflects the growing role of endoscopy in management of various GI illnesses. Most of our patients had endoscopy within 24 hours of admission. There were some delay with the remaining patients for reasons that included; late referral, delay in patients or family giving consent for endoscopy or admission over weekend with patients being hemodynamically stable.

H. pylori is an important association with PUD. In our series, only 47.5% of patients were tested for *H. pylori* and approximately a third tested were positive. Despite lower than expected, this is still higher than the overall prevalence of *H. pylori* among patients referred for endoscopy in our local setting (25%). [16] The low number of patients tested is due to the fact that in the setting of GI bleeding the main goal of endoscopy is to control bleeding. Callicutt *et al.* reported that only 2 out of their 42 patients had assessment for *H. pylori* prior to undergoing surgery for acute non-variceal upper GI bleeding although all of them had upper GI endoscopy. [17] Prevalence of *H. pylori* in their series was 68.7% for duodenal ulcer and 39.1% for gastric ulcer. Prevalence was reduced in those over 60 years of age (28.6%). In our study, *H. pylori* was assessed mainly by rapid urease test. Our previous finding showed that rapid urease test has a low sensitivity (57.1%) when compared to histology. [18] Therefore, the prevalence rate may be higher if histology was used instead of rapid urease test. More diligent testing for *H. pylori* will increase the detection and subsequent eradication rate and hence the risk of rebleeding.

Mean blood transfusion requirement in our series (3.3 units) was slightly higher than that reported by Barkun *et. al* (2.9 units). [4] The rebleeding rate in our study was 24.6%. This is in agreement with other studies which reported rebleeding rates varying from 14.1% to 36%. [4, 19] Our surgical referral rate (3.3%) was comparable to other studies (4.5 to 6.5%). [2, 4] The low surgical referral rate is probably due to the increasingly successful use of endoscopy as a first line tool in the management of this condition. The overall mortality in our study was 18%. This is higher than the 5-14% reported in literature. [3, 9] However, majority of our patients who died had significant illnesses and did not have bleeding as cause of death. This is in agreement with a study done in Singapore. Most of patients who died were due to worsening of co morbid conditions and none of the patients who had rebleed died. [20] Only two deaths (3.3%) were directly attributable to bleeding. These two patients also had significant co illness and had evidence of on going blood loss when these patients died. Older age, higher admission INR, longer hospital stay and higher blood transfusion requirements were predictive of mortality in our series. This is also comparable to published data. [1]

In our study, the Forrest Criteria did not correlate with either rebleeding rates or mortality. However, the Rockall scores showed good correlations. Forrest Criteria is widely accepted to be predictive of rebleed based on the endoscopic findings. The discrepancy of the Forrest Criteria in our study is probably due to the overall small number of patients in our study. In fact, there was only one patient with Forrest type 1a ulcer. This patient had a poor outcome. Moreover our study is a retrospective and factors like inter-observer disagreement on Forrest classification [21], endoscopic technique used to treat different Forrest class ulcers [22] were not controlled for and these could account for the observed discrepancy. However in our unit, the endoscopic findings were routinely recorded down with any assignment of any criteria. The Forrest criteria were retrospectively assigned based on the most advanced lesions recorded. In contrast, the Rockall score correlated well with outcome of patients as assessed both in terms of rebleed and mortality rates. The risk of rebleed and death increased as the scores increased. Rockall *et al*. in their original study [6] had suggested that patients with a low score could be candidates for early discharge with considerable savings to the health care system. Our study is in agreement with theirs. Patients with Rockall score of equal or less than 2 had no rebleed and mortality rates in our study could possibly be considered for early discharge.

There are few limitations with our study. Firstly, this is a retrospective study and this is inherently associated with limitations such as incomplete data and lack of essential data. Secondly, the sample size is small and results obtained may not be very accurate. Thirdly, the reporting and the criteria for choosing the type of endoscopic treatment were not standardized and depended on the individual endoscopists. However, almost all endoscopists are experienced and have been involved with therapeutic works. The modalities available in our centre are standard and comparable what is commonly used in many endoscopic centers, internationally and regionally. [12] Overall, our results are comparable to published reports.

In conclusion, the findings in our study are generally in agreement with that reported in literature with some exceptions as discussed above. Ulcer disease accounted for the major proportion of non-variceal upper GI bleed. Importantly, almost half of our patients were taking medications associated with increased risk for bleeding. Certain factors are predictive of mortality. Despite the small sample size, our study provides useful information on clinical and endoscopic features and outcomes of patients undergoing endoscopic therapy in our local setting. These findings however need to be validated by bigger sample in a prospective study. In the meantime the findings reported could serve as a benchmark for audit purposes in future.

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Spectrum of endoscopic findings in patients referred for suspected upper gastrointestinal bleeding

Aza Zetty Fereona Jamaludin, Vui Heng Chong
Gastroenterology Unit,
Department of Medicine,
Raja Isteri Pengiran Anak Saleha Hospital.

Abstract

Upper gastrointestinal bleeding (UGIB) is a common emergency for referral for endoscopy. However, endoscopy may not reveal any findings that may account for the suspected UGIB. We present a review of the findings among patients suspected to have UGIB referred for endoscopy in our local setting. All upper gastrointestinal procedures (n = 4,640) done between the periods January 2001 to December 2004 were reviewed. Significant findings were any ulcer diseases, portal hypertension related, malignancies, significant reflux diseases, polyps, vascular formations and any bleeding sources. Suspected UGIB accounted for 8.8% (n = 373) of the overall indications. The mean age of patients was 49.5 ± 20.8 years old, significantly older than patients with other indications (45.5 ± 16.2 years old). The findings consisted of peptic ulcer disease (47.5%), significant reflux oesophagitis (3.5%), varices (1.1%), Mallory-Weiss tears (1.1%) and malignancy (0.5%). The ulcerative disorders consisted of duodenal ulcers only (n = 100, 56.5%), gastric ulcers only (n = 44, 24.9%) and both (n = 33, 18.6%). 49.6% of procedures did not reveal any significant findings that may account for UGIB. The overall prevalence of *Helicobacter pylori* was 20.6%. Male and older patients (>50 years) were more likely to have significant findings on endoscopy (p values < 0.05). In conclusion, peptic ulcer disease is the main significant finding among patient with suspected UGIB. Male and older patients were more likely to have significant findings. Importantly, half of the patients with suspected UGIB did not have any significant findings.

Introduction

Upper gastrointestinal bleeding (UGIB) is a common medical emergency that requires urgent treatment. Untreated, it is associated with significant morbidity and despite effective treatment, mortality associated with UGIB remains around 5 to 14% [1, 2]. Confirmed or suspected UGIB is a common indication for admission and referral for endoscopy either as an emergency or elective procedure. The modes of presentations depend on the severity of bleeding with haemodynamic status being the main factor influencing timing of endoscopy. Both international and regional guidelines for non-variceal and variceal UGIB recommend rapid assessment and resuscitation as the initial step in management of these patients. Oesophagogastroduodenoscopy (OGD) should be performed once patients are stable and this should be carried out as soon as possible [3, 4]. Data in the local setting are lacking. We report our experience in patients referred for endoscopy for suspected UGIB over a three years period.

Correspondence
VH Chong
Gastroenterology Unit,
Department of Medicine,
Raja Isteri Pengiran Anak Saleha Hospital
Bandar Seri Begawan BA 1710,
Brunei Darussalam.
E-mail: chongvuih@yahoo.co.uk

Methods

The Endoscopic Unit, RIPAS Hospital is the largest endoscopic unit in the country serving three of the four districts for all endoscopic works. The unit receives referrals from the various clinics (RIPAS hospital clinics, government peripheral clinic and private clinics), Tutong Hospital, Temburong Hospital and the various wards in RIPAS Hospital. This Unit has an open access policy for upper endoscopic procedures; referrals are accepted via phone and appointments given at the earliest depending on urgency of the situations. Endoscopic retrograde cholangiopancreatography (ERCP) and lower gastrointestinal endoscopy are referred to the gastroenterologists for consultation prior to giving appointments. Upper gastrointestinal procedures are carried out daily in the morning. All patients admitted for suspected UGIB are given acid suppression therapy either *per os* or via the intravenous route, depending on the clinical parameters. Emergency procedures can

be arranged at any time by the attending gastroenterologist. Patients were required to fast for a minimum of four hours before procedure. Topical anesthesia was used and conscious sedation provided was required at the patient's request. *Helicobacter pylori (H. pylori)* testing was routinely done by rapid urease test (*CLOtest*, Delta West Ltd, Bentley, West Australia) or histology if there was no contraindication. After the procedure, patients were reviewed by the endoscopist with the result of the *CLOtest* and appropriate treatment or advice was prescribed. A repeat endoscopy at six to eight weeks was performed in cases of positive for *H. pylori* or for documentation of ulcer healing, in particularly gastric ulcers.

The endoscopic therapeutic modalities available for the treatment of bleeding lesions included adrenaline injection (1 mg in 1:10,000 dilution), heater probe, haemoclip, sclerotherapy or rubber band ligations for bleeding varices. These various modalities may be used in combinations. Data were collected from endoscopic records.

Demographic details (age, gender, and race), indications and endoscopic findings were collected from the endoscopic sheet. Significant findings were taken as findings that included ulcer diseases, portal hypertension related, malignancies, significant reflux diseases, polyps, vascular formations and any bleeding sources. Data were coded and entered in the SPSS program (Version 10.0, Chicago, IL, USA) for analysis. Level of significance was taken when P values were less than 0.05 (two- tailed).

Results

During this period, a total of 4,640 upper gastrointestinal procedures were performed. Complete records were available for 4,329 cases and formed the study cases. Procedures with suspected or confirmed UGIB as the indication for endoscopy accounted for 8.6% (n = 373) of cases. The indication for endoscopies over this period is shown in Table 1. Among this various indications, there were more males in the suspected UGIB group (60.3%) and they were also significantly older compared to patients with other indications (49.5 ± 20.8 vs. 45.5 ± 16.2 years old, $p<0.001$).

Table 1: Overall indications over the three years period

Indications	N (%)
Dyspepsia	2,164 (50.0)
Anaemia	481 (11.1)
Gastrointestinal bleeding	373 (8.6)
Gastroesophageal reflux	287 (6.6)
Helicobacter pylori positive	619 (14.3)
Loss of appetite/loss of weight	85 (2.0)
Vomiting	88 (2.0)
Dysphagia/odynophagia	59 (1.4)
Others	173 (4.0)

The racial breakdown of the patients was similar to the national breakdown with the Malays predominating. The demographic of patients is shown in Table 2.

Table 2: Demographic characteristics of patients with UGIB (N = 373)

Mean age (yrs)	49.5 ± 20.8
Sex	
Male	225 (60.3)
Female	148 (39.7)
Racial groups	
Malays	287 (76.9)
Chinese	44 (11.8)
Indigenous	20 (5.4)
Others	22 (5.9)

Age presented as mean ± standard deviation
Gender and race presented as absolute number and percentages in bracket

Overall, significant findings (findings that were likely to explain bleeding) were seen in 50.4%. The remainders consisted of mild oesophagitis, gastritis, duodenitis or normal findings. Patients with significant findings were more likely to be male (58.2% vs. 38.5%, $p<0.001$) and older (>50 years old) (63.4% vs. 36.3%, $p<0.001$). Peptic ulcer disease (PUD) was the most common finding, accounting for 47.5% of cases. The significant findings are shown in Table 3.

Table 3: Overall findings of endoscopic evaluations

Findings	N (%)
Significant oesophageal findings	
Reflux oesophagitis (grade C/D)	13 (3.5) ‡
Mallory Weiss tear	4 (1.2)
Varices	3 (0.9)
Candidiasis	2 (0.6)
Oesophageal ulcers	5 (1.4)
Significant gastric findings	
Gastric ulcer (GU)	77 (20.6) *
Varices	1 (0.3)
Arterio-venous malformation	1 (0.3)
Malignancy	2 (0.6)
Polyps	2 (0.6)
Significant duodenal findings	
Duodenal ulcer (DU)	133 (36.7) *

‡ Overall reflux oesophagitis was seen in 19%
* Concomitant GU and DU occurred in 33 patients

Older patients (>50 years) were more likely to have significant gastric findings (30.9% vs. 15.6%, $p<0.05$). Significant duodenal findings were seen among male patients (45.3% vs. 21.6%, $p<0.001$) and older patients (41.8% vs. 29.6%, $p<0.05$).

The overall prevalence of *H. pylori* was 20.6%. This was higher in males compared to females (23.1% vs. 16.9%, $p = 0.147$) and the younger (<50 years) age group (24.6% vs. 17.0%, $p = 0.071$), although these did not reach statistical significance.

Discussion

Our study showed that only half of patients referred with suspected UGIB have findings that may account for blood loss. This suggests that some of the indications were likely to be wrong diagnosis or bleeding beyond the second part of the duodenum. During upper GI endoscopy, it is routine to inspect up to proximal second part of the duodenum. Examination beyond this point can be difficult and can cause unnecessary discomfort. Furthermore, significant findings beyond this point are uncommon. Other causes of suspected blood loss or anaemia such marrow dysfunction, anaemia of chronic diseases, intravascular haemolysis or non gastrointestinal blood loss should be considered [5,6]. Excess venesections for blood investigations have been reported to be a factor [7,8,9].

Peptic ulcer disease was the most common finding in our study. Other causes such as severe oesophagitis, portal hypertension related disorders or malignancies were less common. Significant findings were more common among the elderly, both significant gastric and duodenal findings. Male patients were more likely to have significant duodenal findings. This is not unexpected considering older patients were more likely to have significant co-morbid conditions and to use medications associated with increased risk for ulcerations. Portal hypertension related disorders have been reported to account for approximately 10% of all UGIB. However, in our study, this only accounted for 1.2% of cases. This most likely reflects the low prevalence of variceal bleeding in our local setting.

Since its discovery, *H. pylori* has emerged as the most important aetiological factor in peptic ulcer disease [10]. It was reported to be responsible for over 95% of duodenal ulcers and 70-80% of gastric ulcers. However, there have been few recent studies that showed declining prevalence [11,12]. Our own data also showed a decline in the prevalence of *H. pylori* from 32.3% to 25.6% over a five years period (2000 to 2004) [13]. Our own study showed that the overall prevalence was 20.6% among patients with suspected UGIB. The prevalence among those with findings of ulcer diseases was 40%. This is lower than previously reported. Reasons that may account for this included predominant use of rapid urease test for *H. pylori* detection which have low sensitivity and presence of blood in the

stomach may produce false negative results [14,15]. Unfortunately we do not have information on non-steroidal anti-inflammatory drugs (NSAIDs) use as this was not reliably documented. NSAID use either overt or occult is now becoming an important factor for *H. pylori* negative ulcers [16].

There are several limitations with our study. Firstly, this was a retrospective study and this is inherently associated with many limitations. Secondly only the main indication for endoscopy was routinely recorded and it is likely that some patients in the other indications groups may have gastrointestinal bleeding and not included in the study group. Thirdly, data on NSAID use were not available. However, despite this our results would be a useful guide for health care worker managing patients with suspected UGIB.

In conclusion, peptic ulcer disease is the main significant finding among patient with suspected UGIB. Male and older patients were more likely to have significant findings. Importantly, half of the patients with suspected UGIB did not have any significant findings.

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Renal cell carcinoma in Brunei Darussalam

[1]L.N. Teo, [2]P.U. Telesinghe
1Division of Haemato-oncology, Department of Internal Medicine,
[2]Department of Pathology
RIPAS Hospital

Abstract

The incidence of renal cell carcinoma in Brunei Darussalam in the period 1996 to 2005, the some characteristics of presentation and tumour histology are analysed with a view of developing a better understanding of the disease in the country.

1. Introduction

Renal cell carcinoma (RCC) accounts for 1-2 % of cancer diagnosed in Brunei Darussalam [1]. RCC is not a single cancer but made of different subtypes, each with different histology, clinical course and different genetic changes [2]. Histological classification categorizes renal cell carcinomas into clear cell, papillary, chromophobe, oncocytoma, collecting duct, and unclassified RCC subtypes [3]. RCC occurs in both sporadic (nonhereditary) and hereditary forms. About 5% of tumours are hereditary, and a better understanding of their molecular basis has led to development of novel therapeutic interventions [2, 4].

Early stage RCC is cured with surgical resection, but up to 50% of patients either have metastatic disease at diagnosis or have recurrence resection. Chemotherapy regimens have only minimal activity and immunotherapy agents such as interferon alpha and interleukin-2 results in 10-20% response in patients with metastatic disease [5]. There is no proven treatment benefit for patients with progressive disease.

Several new agents that targets the vascular endothelial growth factor receptor, and signaling pathways downstream from the von Hippel-Lindau gene product defect, have clinical activity in patients with metastatic RCC as shown in phase II trials [6, 7]. These may be introduced for treatment of RCC in Brunei in the near future.

This study analyses the occurrence, histological subtypes and clinical presentation of RCC in Brunei Darussalam from 1996 to 2005. The data provide baseline information for developing better treatment procedures, including the use of more specifically targeted chemotherapeutics.

2. Methods

2.1 Patients

This is a retrospective review of a total of 33 patients diagnosed with RCC presenting from January 1996 to December 2005 at RIPAS hospital. Clinical data, surgical notes, pathologic findings, and summaries of treatment details were analysed.

2.2 Pathology

Tumors were classified as either conventional (nonpapillary) or papillary. Conventional tumors were further sub classified as clear-cell, chromophobe, and collecting duct carcinoma. A standard staining procedure with haematoxylin and eosin was employed. Cytologic grading was assigned according to the criteria proposed by Fuhrman et al [8]. This system uses nuclear grades that are based on size, irregularity of the membrane and nucleolar prominence.

Correspondence
LN Teo
Division of Haemato-oncology,
Department of Medicine,
RIPAS Hospital,
Bandar Seri Begawan, Brunei Darussalam

2.3 Staging and clinical data

Tumor stage was determined according to the 1997 TNM (AJCC) classification of renal tumors.

Stage I - tumour 7cm or smaller confined to kidney (T1a-<4cm T1b>4cm)

Stage II - tumour> 7cm confined to kidney (T2,N0,M0)

Stage III - T3a:Tumour invades adrenal gland or perinephric tissues but not beyond Gerota's fascia.
- T3b:Tumour extends into renal vein or vena cava
- T3c:Tumour extends into vena cava above diaphragm or Metastasis to single node

Stage IV -Tumour invading beyond Gerota's fascia (T4) or multiple lymph node metastases or distant metastatic disease.

3. Results

3.1 Occurrence of RCC and age distribution

The annual detection of RCC in Brunei Darussalam for the period 1996 to 2005 is shown in Figure 1. Thirty three patients (26 males and 7 females) were diagnosed with RCC during this period (Figure 2).The age of patients ranged from 28 to 90 years (53.8median).

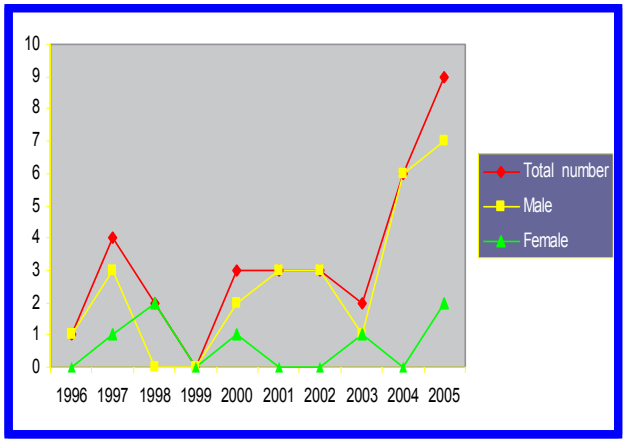

Figure 1. Renal cell carcinoma in Brunei Darussalam 1996-2005

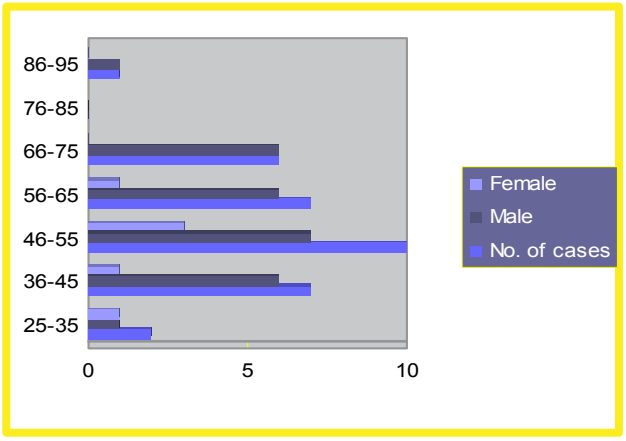

Figure 2. Age distribution of renal cell carcinoma in Brunei 1996-2005

3.2 Histological characteristics

Twenty seven patients (81.8%) had clear cell RCC, four patients (12.2%) papillary histotype, one (3%) chromphobe cell type and one (3%) collecting duct type (Table 1).Of the twenty seven patients with RCC, three patients (9%) had sarcomatoid stroma which carries a worse prognosis [9].

Histology	Patients %
Clear cell	81.8
Papillary	12.2
Chromophobe	3
Collecting Duct	3

Table 1. Histological characteristics of RCC in Brunei 1996-2005 (N=33)

3.3. Staging of tumours

Thirty one patients were staged. Five patients (16.1%) classified as stage I, nine (29%) stage II, seven (22.6%) stage III, (T3a-4 patients, T3b-3 patients) and ten (32.3%) stage IV (Table 2). Two patients were diagnosed with bilateral tumor.

Stage	Patients %
I	16.1
II	29
III	22.6
IV	32.3

Table 2. Presenting stage of RCC in Brunei 1996-2005 (N=31)

Fuhrman grading was assigned to 16 patients (48%); five (31.3%) classified as grade 1; four (25%) grade 2; three (18.7%) grade 3; and four (25%) grade 4 (Table 3).

Fuhrman Grade	Patients %
1	31.3
2	25
3	18.7
4	25

Table 3. Fuhrman Grading of RCC in Brunei 1996-2005 (N=16)

3.4 Tumour size

Tumor size, examined in 27 patients, was 4 -7cm in 29.6%), > 7- 10cm in 33.3% and more than 10 cm in 22.2% [Figure 3].

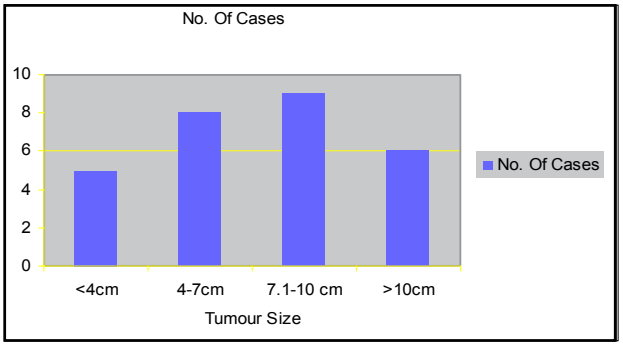

Figure 3. Tumour size distribution of RCC in Brunei 1996-2005

3.5 Clinical presentation

Majority of patients presented with haematuria though there were a few cases where the diagnosis was made on radiological imaging done for other reasons (Figure 4)

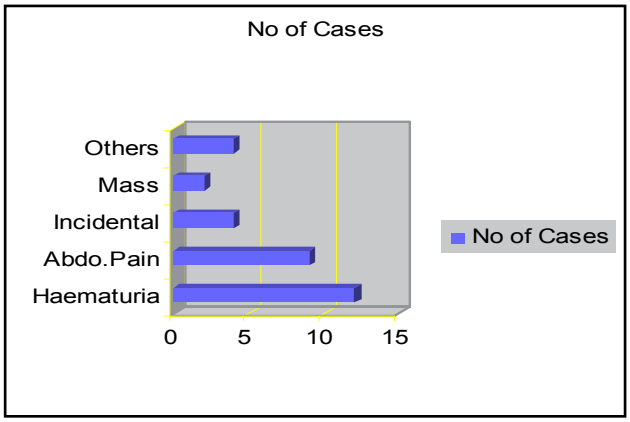

Figure 4. Clinical presentation of RCC in Brunei 1996-2005

4. Discussion

RCC is three times more common in males than females in Brunei which is similar to that observed in Singapore [10]. RCC is also more common among males in the USA, where its overall incidence is on the increase [11]. A relatively higher number of RCC were detected in 2005 in Brunei and the trend needs to be studied over a longer period to determine whether the incidence of RCC is increasing in Brunei. RCC is most commonly detected in the 4th and 6th decades of life in the USA [11], and this also is the case in Brunei.

The majority of patients with RCC in Brunei Darussalam have a clear cell histology which is comparable to that reported in western countries [4]. The analysis shows that patients also tended to present with stage IV disease (32.3%) and tumour size > 7 cm (53.5%). TNM stage and Fuhrman grade are widely recognized prognostic factors in RCC [12]. Some patients are diagnosed by radiological imaging done for reasons other than suspected cancer and this causes stage migration due to earlier diagnosis. It is anticipated that the data analysed here will lead to a better understanding of RCC in Brunei and contribute to developing more effective treatment procedures in the future.

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Well-being of the elderly: linking objective and subjective dimensions in a wellness index

Haliza Mohd Riji*, S Tajuddin S Hasan
Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia

Abstract

In cognisance of the world's increase in elderly people, researchers in Malaysia are concerned with knowing what the needs of the elderly are and how can these be recognised. A wellness index is deemed timely and appropriate for measuring the improvement of an elderly person's well-being. This paper describes a process of understanding quality of life in older persons with the final goal of developing a wellness index for Malaysians aged 40 years and over. The rationale was to identify possible contributing factors to well-being, to consider models for discovering the relationships between factors and quality of life, and to suggest that both quantitative and qualitative research on the objective and subjective dimensions be performed for developing a wellness index. Over several months, internet searches for keywords conveying meaning of wellness, well-being, quality of life, life satisfaction, and terms to denote the aging population, such as "older persons, aging, elderly, old age, older people, midlife, and later life" were carried out. The entire process was guided by three research questions: 1) in which areas of health and social aspects of life are the term 'quality of life' used; 2) what objective and subjective dimensions are considered; 3) what possible models could be adopted and adapted for understanding a holistic approach to wellness. Over 80 articles (57 ScienceDirect; 23 Springerlink; seven BioMed Central; two PubMed), 21 books, and 14 internet sites were used as resources in this paper. Of the models reviewed, three were selected for further consideration. The authors note that the broad topics of wellness and well-being have drawn so much interest from varied and diverse fields, including: culture, health, gerontology, geriatric medicine, sports, society, economics, nursing, medicine (cancers, cardiology), psychology, ethics, morality, history, environment and occupation. The few related articles on the Malaysian situation were more concerned with characterization of wellness rather than its deliberation. The authors conclude that quality of life is a dynamic concept that contains a myriad meanings and interpretations. Objective and subjective dimensions interact forcefully or subtly in the process. The range and context have to be explored and understood before a holistic wellness index can be formulated.

Good health is only a part of what individuals can experience; they also can experience "wellness". Wellness can only be experienced by individuals, however, if they actively pattern their behavior and life style to suit their circumstances [1]

1. Viewing global and local concerns of elderly person's well-being

Over the last few decades the world's population has been marked by a gradual increase in the proportion of elderly. This has partly been due to the dramatic swing, from high birth and high death rates to low birth and low death rates. This transformation is spurred by social and community systems enhancement, cultural changes, and economic progress, and also by innovations in medical and health technology. In 10 years, persons aged 80 years or more are expected to be proportionally higher than today's total population [2].

Although having a disease appears to be less disabling than in the past, the aged faces continuing burden as most diseases occur in late life [3]. Malaysia emulates closely the global changing trend in the USA where the top five diseases for males 60 years and over are cardiovascular diseases, chronic respiratory diseases, cancer, infectious diseases, and digestive system disorders; for females they are cardiovascular diseases, infectious diseases, chronic respiratory diseases, cancer, and sense organ disorder

Corresponding author:
Assoc. Prof. Dr Haliza Mohd. Riji
Department of Community Health
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia 43400 UPM Serdang
Email: liza.riji@gmail.com

[4]. While developed nations enjoy the gain of longevity among their people, and have put in place effective preventive measures, yet no matter how successful they can be, chronic diseases are inevitable among the elderly [5]. For a developing country like Malaysia the disease burden will undoubtedly exert more demands for economic, health and social life betterment [6].

Wealthy nations have the means and resources to ensure their citizens become healthier, but can money buy them happiness? Evidence [7] suggests that while economic growth has been achieved in the UK and other developed countries, people's satisfaction with their lives have not been concomitantly and correspondingly enhanced. Consequently, a well-being manifesto that focuses 'upon creating an economy based on social justice, environmental sustainability, and well-being' came into being in September 2004. In fact, wealthy nations are moving toward making their money more worthy of their existence. The New Economic Foundation (nef), in the UK has established a well-being programme that aims to find 'ways to promote policies and practical solutions that help people live more fulfilled lives.'

Another global trend is the paradigm change towards making people appreciate a more successful, productive, or active life as they age, hence the use of 'the new aging' terminology as the catch word [8]. As people are able to physically, mentally, spiritually and psychologically cope with chronic health problems and declining cognitive skills, they are encouraged to maximize desired outcomes and minimize undesired ones [9]. Hence governments and governing authorities rhetorically posit that the secret of healthy individuals and society is through empowering people, including the elderly, to take charge of their own life and health. As illustrated by Katz and Marshall [10], aging does not necessarily connote sexual decline; a newer meaning has been culturally created through market and consumer activities, hence promoting sexually active senior citizens. Obviously, this is easier said than done, especially so in many developing and poor countries [11].

It is also recognized that in defining, enumerating and assessing the criteria and parameters of successful aging, it is imperative to include the major domains of physical, cognitive, social, psychological and environmental functions; and within each domain the relevant array of determinants [12]. Having advanced knowledge and enlightened understanding of the mental, cognitive, and psychological faculties, it has been possible for the developed countries to transform knowledge fora into drivers of human learning process [13]. Their generally better research-enabled society is always enriched by newly-generated information, hence knowledge. Research and learning become an integral part of their society.

Malaysia is fortunate in many domains of its existence and development. It has in many ways keeps in tandem with and satisfies the 'modern goals and demands' of society and cultural setting [14]. Economically, it has moved itself from being greatly dependent on agricultural commodities to becoming a more diversified-economy-based nation, with particular strength in manufacturing and downstream plantation and agro-based industries. Hence its gross national income is derived not only from the agricultural sector but also from manufacturing, trading, and commercial activities. Politically, it has gained complete independence from British rule in 1957, which subsequently enables Malaysians to govern the country according to their own vision, capacity and capability. Culturally, the peaceful and dynamically adaptive coexistence of various ethnic groups has led to a harmonious relationship among the people [15]

On the health front, the country has overall been able to control communicable diseases such as those caused by mosquito-borne infections; for examples malaria, filariasis, and dengue, and nutrition-deficiency related diseases such as stunting and underweight disorder [16]. Such achievement has been made possible through well-organized disease control programs and health promotion strategies. Yet, despite obvious milestones in overall health improvement, there remain critical issues that relate to the health and well-being of the elderly. Malaysia would be hard pressed to sustain being a welfare-oriented state in view of rising medical costs. Living alone and weakening family support can add serious problems to the elderly if they are deficient in financial support. At the individual level, the elderly are experiencing biological problems due to indigestion, constipation, poor nutrition and gastritis. These can result from deteriorating oral health, lack of physical activity and bacterial infections [17]. These issues need to be addressed immediately.

In 1990, the Malaysian National Social Welfare Policy was introduced. Through this instrument the government hoped to safeguard the care of the aged by encouraging their family and the community to lend their support. Changing socio-economic situations in the years that follow led to the formulation and adoption in 1995 of the National Policy for the Elderlys. The policy mission statement contained within it was 'to develop a society of elderly people who are contented, with dignity and possess a high sense of self-worth by optimizing their self-potential and ensuring that they enjoy every opportunity as well as care and protection as members of their family, society and nation'.

In attempting to assess and contrast the variables and context of quality of life and their relationship to aging between developed, developing and poor countries, and their relevance to Malaysia, reference to selected articles was deemed necessary. Streib's [18] *Old Age in Sociocultural Context: China and the United States* critically looks at three main areas, i.e. economic development, traditional cultural patterns, and the polity. The two countries differ significantly in their ways of responding to their older members. Within the cultural context, gender difference is an important factor to consider. The issue of mobility impairment has also been examined [19]. Men perceived their impairment more negatively; thus their higher levels of distress. Religion (Islam) was a likely reason for viewing their physical impairment as limitations since Muslim men had to attend the Friday prayers at the mosque. In poor countries such as Cambodia, the major influencing factor is very much related to the economic and social status of the people [20]. For rural Cambodians, the economic status of the household is indicative of their well being than income. In a society much affected by civil strife and unfavorable living conditions, including poor health care facilities, there is marked association between wealth and health.

2. Framing well-being, quality of life, and healthy living

The term 'well-being' is often used interchangeably with 'quality of life' and 'wellness'. The term 'Quality of Life' can mean anything depending on the value and context a person or group is in. In its general context, it can refer to one's overall life satisfaction. The plethora of definitions is because "it is a problematic concept as different people value different things" [21]. According to Utian [22], the phrase "Quality of Life" (QOL) "is both an enigma and a cliché." It seems that people understand what it refers to yet there is always confusion about its meanings and how the domains can be measured. Interest in the subject of happiness and life satisfaction has grown internationally. Developed countries such as Denmark and Canada have funded national research to look at the quality of life of their citizens. Denmark set up a Quality of Life Research Centre in 1994, and in the UK there were projects supported by the Economic and Social Research Council to examine quality of life of elderly [23]. These researches examine comprehensive knowledge and skill domains, including those for generic assessment, disease-specific characterization, disease- specific measures, domain-specific evaluation, activities of daily living (ADL), and disability measuring tools [24].

Although generally, the term well-being connotes the physical, mental and psychological domains of life, the meaning appears to be more definitive within the health context. The health of women, for example, often make people think of their reproductive functions, hence their quality of life is determined by their ability to reproduce and to care for their children. Feminist researchers regard such biological perspective as only part of the women's overall functional ability across her life cycle. Well-being or the quality of life for the women increasingly takes account of their mental health issues as more women suffer from psychological stress due to their burden and responsibilities associated to their gender status [25].

It is increasingly evident that the concept of 'quality of life' entails both easily observable characteristics and those that require theoretical and empirical considerations. How do researchers differentiate questions like "how does quality of life affect old age?" and "how does old age affect quality of life?" and "how are the two affected by living in socially deprived areas?" [26]. Thus both tangible and intangible entities are intertwined in a life's wellness index.

Within the context of the Malaysian society, the term can mean everything desired by an old person – physi-

cal health, spiritual enlightenment, intellectual alertness, life satisfaction, well-being, happiness, family support, financial security, independence, self-worth, dignity, and so forth. While ageing is a natural biological process, being contented and feeling good about old age is the outcome of many objective and subjective interrelated factors. The nature and nurture elements are of central importance and the person's quality of life are bounded by his/her and society's spatial and temporal continuum [27]. Admittedly, there are factors outside of the individual self – the external factors that directly or indirectly influence and shape the person's behavior and existence. These include the physical structures (build) and facilities, resources and their accessibility (including health and other information), laws and policy, and the larger cultural environment matrix [28].

One meaning of well-being can be obtained from a look at historical development of the concept. Burns [29] notes that well-being can be explained in terms of adaptation of people and their environment. This is a very ecological approach in which life is framed in a dynamic and evolving interactive process of action and interaction [30]. Traditional views of shamans or medicine men have maintained that for achieving health the physical, emotional and spiritual well-being should form a holistic entity. Hence, the oneness or connectedness between person, ecology and cosmology should result in the right balance or well-being. This is the philosophy of Buddhism and of Tibetan medicine which stipulates 'a system of pscho-cosmo-physical healing'. Subsequently, Rene Descartes philosophized that mind and matter are vital constituents of well-being through a reductionistic approach, followed by Sigmund Freud's theory on the inner workings of the mind – the id, ego, and superego. The focus on the mind and its inner processes put a limit to the larger understanding of well-being. Theorists such as Burn are proposing that well-being is best understood if all information from both traditional and research laboratories are used together for the betterment of wellness of mankind [31].

Health is understood as a normal condition characterized by the absence of disease or disability affecting the body and mind. As many as there are factors that affect health, so are there factors that contribute to ill-health or disease. The term holistic health is more meaningful, hence the term wellness is reflective of the multidimensional nature of health to include the whole person's relation to the total environment and toward attaining optimal health. In fact, it is everything from visible correlates to cognitive processes. 'Wellness is the active, lifelong process of becoming aware of the different dimensions of your life and health, identifying the dimensions that need improvement, and making changes in lifestyle behaviors that help you attain the highest level of health and well-being possible for you' [32].

Both men and women enjoy a wide variety of life-sustaining and life-enhancing resources. Longevity does not necessarily follow a healthier life. Aging can be psychologically and socially fulfilling, yet it does increase the likelihood of having chronic diseases. The context of aging is gender-related. Women, in particular are more likely to spend their last years in poverty and loneliness. The media's images of the elderly more often than not portray women more than men as frail individuals, who are besieged with many problems. Ruta et al [33] have shown that using a definition on quality of life for patients with back pain through such terms as narrowing "the gap between a patient's hopes and expectations and what actually happens", has more "meaning and relevance in the context of their daily lives". There have been a number of attempts, usually theoretical, to formulate, conceptualize, and model well-being as a continuum of dynamic universe, comprising interacting and transacting-processes' life domains and constructs (physically, spiritually, mentally-cognitively-neurologically, behaviour-psychologically), and the bounding-frames of socio-economic-cultures [34;35].

Despite its inherent meaning, there are no universally accepted definition and no standard indicator of well-being. One suggestion is that [36], well-being can fall into three categories; subjective, psychological and objective well-being. While subjective well-being is concerned with how happy and how satisfied a person is with his/her life, the psychological well-being has to do with attitudinal or mental aspect of a person toward his/her life goal. The objective well-being can be determined by the measurement of physical characteristics or material parameters such as ownership of property or income.

Aging is a natural biological process. However, it carries different meanings to different cultures. Generally, however, aging is negatively perceived by society at large. So important is the issue related to bad image of old age that the year 1999 was named the International Year of Older Persons. The then UN Secretary-General, Kofi Annan, urged the world to promote "a society for all ages is one that does not caricature older persons as patients and pensioners" [37]. "Culturally, age is depicted as a dreaded and undesirable state. This is due to a number of factors - a youth oriented culture in a society that is given over to the "administration of life and consequently pathologizes age as a time of physical decline and ultimately death." [38].

Given the above precepts and the importance of understanding what is meant by well-being, initial conceptual framework was considered and discussed. The suitable model which needs to be developed would stipulate well-being as 'satisfaction with different aspects of life'; and incorporates sense of meaning as 'a sense of purpose in life' [39]. Such a view of life having a predetermined purpose aligns well with the philosophy of human life as predesigned entity [40]. It is expected that the model has to be refined or changed in due course as better understanding of the key concepts accrues. Nevertheless, it is visualised that this simple model encapsulates the fundamental elements of natural progression from input (external conditions) to output (sense of), through the processing entities (intraindividual conditions).

3. Some factors influencing well-being or quality of life

3.1 External conditions – environmental, sociocultural, biophysical

The traditional culture and social systems provide family-based and communal safety nets which enable elderly to cope with challenges and vagaries of life. Unfortunately there is a definite erosion of those traditional societal pillars of strength. In contrast, elderly people in developed countries are presented with many resources to enhance and maintain their well-being. It is common knowledge that the reading, writing, and inquisitive culture of developed countries, as compared with developing and poor countries, propel many enhanced researches, generate more new knowledge, and empowers more people including elderly to be more independent and take charge of their lives, hence their well-being [41]. As examples, there are books on various aspects of self-help and self-implement; self-improvement and self-implement e.g. on foods which can alleviate and even helps to obviate pain [42], on meanings of grief and grieving [43], and on understanding of head injury experience [44]. In line with optimizing of life's satisfaction and self empowerment, using knowledge and learning resources, our research project intends to measure the extent of using knowledge resources by elderly in their everyday life, which may enhance their well-being.

It is well acknowledged that a literate and a learned society produce well-informed communities. Governmental authorities and governing bodies always dream of empowering the people, including the elderly group, to manage and maintain their own health requirement, hence their well-being. It is logically expected that as a person's intellectual faculty increases, the domain of his or her well-being ecosystem expands to include "enlightened and luxury" constructs such as liberty, equality and fraternity entities [45]. In a fast developing country such as Malaysia, the broad-knowledge-based reading culture is still at a low level, especially among rural-based elderly. Nevertheless urban influences, especially ones with negative impacts e.g. smoking and low-imbalanced nutrient food regime, gain foothold easily, including among elderly.

The influence of culture on health and well-being is best observed in communities comprising ethnically, socio-economically, and culturally diverse and heterogeneous people. People's judgments are essentially their perceptions of what they regard as acceptable or unacceptable in their culture. For instance, in the case of mental illness, each culture has provided ways of determining whether one is mentally ill or not. In non-western societies, mental illness can be linked to factors, distinguishably different from western societies. It is usually linked to spirit possession and breaking of religious taboos [46]. Moreover cultural influences can also be observed across continents.

Changing cultural matrix with globalisation is due to a large extent on technology revolution which on wellness through health care and health promotion. Knowledge and information access and acquisition become spatially and

temporally borderless [47]. This mass democratization of knowledge, including health and well-being information, transforms decision making from being monopolised by the expert few to a larger community organization. This is a definitive trend across continents, with clear emphasis on prevention, rehabilitation, and chronic illness care [48]. Online knowledge gateways and repositories, e.g. URLs of the Communication Initiative, Global Knowledge Partnership, and the Global Alliance of Information Communication Technology for Development, enable free access to a wide domain of global information at anytime from anywhere. Consequently there emerged a global shared vision of building health and well-being communities culminating in the formation of for examples, the Healthy People 2010 documented project of the USA [49], which preliminarily defines generic wellness indicators [50]. It is common knowledge that in essence, the community decision-making culture is actually the traditional indigenous culture of many people across the world. Nevertheless, despite the evidently positive trend of community-based participation, in many aspects of socio-economy-health domain, an increasingly large gap exists between rich and poor nations [51]. Hence, domains of wellness for developed countries are not necessarily directly applicable to developing countries. Such scenario portends increasing disparity in achievement of health and well-being between rich and poor nations.

3.2 Intra-individual conditions – health, functional ability, coping mechanisms, personality

Within the health care system, concerns with the quality of life of elderly people are frequently drawn to aspects of their physical health status. Health care facilities are more particularly needed by the elderly since the group is prone to illnesses and disability due to old age and susceptibility to infections. For example, gut flora populations within the intestinal tract, are phenomenon which result from physiological changes among elderly [52]. Cardiovascular diseases are commonly suffered by the aged [53]. Apart from that impaired vision occurs most frequently among the elderly. In an early study by Chen in Malaysia [54], the rates of disabilities were 3.5 per 100,000 persons for those aged 60 to 64 years; the rate increased to 5.2 for those 65 to 69 years and 6.1 for those 70 years and above. Research findings have shown that decreasing quality of life is associated with increasing age, and its related factors; disability, discomfort, pain and immobility. Gender is one determining factor. More women are believed to report ill-health than do men. In a study to explain whether worse health-related quality of life scores among women were due to differential reporting patterns, it was concluded that the tendency for women to report worse health condition was really due their worse health status than men on the basis of higher prevalence of disability and chronic conditions [55]. Losing one's physical strength and overall fitness is associated with advancing age. Among many elderly, living with some kind of debilitating illness seems unavoidable [56]. Pain and long-term care can decrease the persons' quality of life. Having to experience rheumatoid arthritis and osteoarthritis, for example, often lead to changes in the individual's life [57].

Associated with the functional status of the elderly is their mental health status. Mental health is understood as the ability of the individual to deal with his total well-being and with others around him. In this regard, it is assumed that he or she should possess a sound mind to know what is good or bad for him or her respectively. In contrast a person is said to be having a mental health problem when he or she is not able to cope with life's situations, such as those caused by loss of loved one, or failures to accomplish something that is desired. Women particularly those in developing countries are faced with adverse life situations such as poverty, child-rearing responsibility and also caring for family members. Mental health disorders due to changes in brain function are more common among elderly people than young ones [58]. As women aged into later life, they then need carers to look after their physical and psychological needs. Lately, there has been evidence to indicate that the elderly, especially women, have been neglected by their children and left to fend for themselves. Nevertheless, there still exists evidence of the caring attitude among the extended families as shown in studies done by Universiti Utara Malaysia [59].

Aging is widely perceived with the loss of independence due to physiological changes and this can include one's mental alertness. As such life's activities will in time become imperatively reduced due to those changes. Nevertheless, in the USA, elderly are still allowed to drive and to travel in airplanes, provided they are healthy [60].

While on the one hand, the term 'quality of life' can apply to both the physical, mental and psychological domains of life; the meaning appears to be more definitive within the health context. The health of women, for example, often make people think of their reproductive functions, hence their quality of life is determined by their ability to reproduce and to care for their children. Feminist researchers regard such biological perspective as only partial of the women's overall functional ability across the life cycle. Well-being or the quality of life for the women has to take account of their mental health issues as more women suffer from psychological distress to their gender status.

It is increasingly evident that the concept 'quality of life' entails both easily observable characteristics and those that require theoretical and empirical considerations. How do researchers differentiate questions like "how does quality of life affect old age?" and "how does old age affect quality of life?" and "how are the two affected by living in socially deprived areas?" [61].

3.3 Sense of well-being: meaning, value

What do the elderly value in the remaining years of their life? An article by Chin Mui Yoon in the Star [62], lamented on one 68 year old woman's travel experience she had three years earlier. She felt special when people in New Zealand offered so much help when she fell down while crossing the road there. This could mean that she did not have the chance to 'feel like somebody special back in Malaysia.' The same article highlighted statements on the general population's attitudes toward aging. Evidently quality of life for the elderly has a lot to do with their psychological well-being – having enough money to maintain their livelihood, avoiding sickness, having comfortable housing, able to travel, and enjoying leisure.

Pain and long term care for disabled individuals [63] is a real central concern for elderly people. Associated with issues of caring, provision and achievement of structural target [64], e.g. caring environment and society, are of central and critical importance in elderly perceptions about wellness. In order to achieve a meaningful mental mechanism of coping psychologically with traumas and tribulation of life, the conceptual and operational meanings [65] of wellness and purpose of life take a central pivotal role. Once an individual, including an elderly, is able to mentally inculcate and mindfully acculturate the 'secret' purpose of life, positive outcome of negative circumstances can be achieved [66].

Embedded in the positive outlook of life is the feeling of happiness. Happiness may be an obvious outward indication or a consequence of life satisfaction. Contemporary measurement of happiness emphasizes very subjective aspects such as emotion, role, social and cognitive functioning [69]. As such, both intrinsic and extrinsic structures and processes are involved, and therefore these have to be included in the proposed study. Happiness, feeling of life's satisfaction, and emotive sense of good self-worth, are abstract constructs or concepts or domains. Measuring and evaluation are subjectively contextual within specified societal-environmental continuum. Individual's expectation and inclination, and societal norms and acculturation, permeate and design these domains. Every human being aims to be within spatial and temporal coordinates of these domains. Essentially these domains comprise the state of well-being. Consequently, the researchers/authors of this paper focused on intrinsic and intrinsic health factors in their deliberation to design the wellness research project. As individual ages, there will be accompanying changes in morphology, physiology, and psychology. It is a general norm that as one ages, say above 50 years, there will be a general decline in bodily functions and body metabolism. Nevertheless, authors of this paper are cognizant of intrinsic and extrinsic ageing [70]. Hence intrinsic and extrinsic components comprise essential entities in our study's conceptual frame.

4. Issues relating to validity, reliability, sensitivity and responsiveness of instruments

In order to ensure future applicability of the wellness index matrices, issues relating to validity, reliability, and sensitivity have to be addressed. The instruments to be used should be tested judiciously so that they correlate with other pertinent observable behavior. Local cultural context shall determine the morphology and taxonomy of the contents of measuring tools. The instruments should really measure the intended constructs. It is necessary to delineate and ensure acceptable levels of content validity, criterion validity, construct validity (convergent and discrimi-

nant validity) [71]. Possible flaws regarding reliability and its connection to validity and minimization also have to be considered. Potential significant differences which may arise and due change that could occur are mainly attributed to the sensitivity and responsiveness of respondents in a study. To address these crucial issues, a pilot study is deemed necessary.

As time progressed, it then became clear that the proposed research should adopt a model which would encompass both objective and subjective domains affecting both the individual's as well as group's quality of life. A wellness index is a measure which represents the degree of 'wellness' of a person. After viewing all available literature the authors chose to focus on an approach or model proposed by Costanza et al [72].

The key advantage of this model is that it provides the connections between opportunities that are provided to meet human needs and the available policy and culture which can be utilized for enhancing the opportunities. Four types of capital need to be in place – social capital, human capital, built capital, and natural capital. Deficiency of investment in these capitals needs to be addressed by nations, especially the third world countries. Failure to do so will definitely lead to an increasing larger divide in socio-economy and human wellness between developed and developing countries [73]. An important feature of this model is the integration of the objective dimensions and their measurements of QOL with the subjective dimensions and their indicators. Costanza et al. [74] believed that the above model of QOL is conceptualized as "the extent to which objective human needs are fulfilled in relation to personal or group perceptions of subjective well-being… The relation between specific human needs and perceived satisfaction with each of them can be affected by mental capacity, cultural context, information, education, temperament, and the like, often in quite complex ways". It is only through such integration that 'health' and 'non-health' determinants can be linked quantitatively in order to develop population health indicators [75], including those of the elderly [76). Thus, the broader enveloping frame of community-based approach and policy-driven imperative on wellness achievement portends a brighter prospect to an overall wellness of a nation [77].

5. Conclusions

In essence this paper conjures visioning ideas, actions, and tribulation; comprising initial preparations, planning of strategies - brainstorming on conceptual blueprint, concept papers, concept analysis [78], content analysis [79], stakeholders buy-in, conscripting players and soothsayers, and tackling bureaucracy. We had mapped out structurally [80] the imperatives and drivers for actioning the research processes. We emphasized the need for sampling the broadest range of healthy, disabled, and morbid old persons, including patients and carers of cognitively-impaired condition [81].

Indices are measurable indicators of a phenomenon. Hence, wellness index is a measure of indicator of wellness of people, community, and a nation. Quantitative measures are essential for many utilitarian purposes, including future quality improvement, aid in policy decision-making, comparative analysis for strategic social-health management, and in-built content package for an e-Health [82] delivery collaborative and distributive knowledge and information system [83]. The authors therefore posit a synthesis of a time-based and spatially-coordinated measured entity which can indicate the health of a nation.

Suitable and appropriate instruments for local cultural context are to be selected. All activities are planned to ensure a reasonably seamless process in transforming data into information, subsequently into knowledge-base and skill-base, and ultimately into a strategic and critical application. The central underlying premise to this project is an integrated approach to ensure that researchers can untangle and define the meaning of life, within the context of enhancing and augmenting wellness in the elderly. Given current knowledge relating to the topic, the researchers believe that a holistic approach is the only meaningful way of understanding wellness, hence enabling the elderly to achieve a dignified and fruitful productive life. A firm conviction - one that will not succumb to reticence is upheld, and the approach to be adopted is holistic and synthetic as a measure to unravel the meaning of the concept of well-being as precondition to formulating the wellness index.

The authors' review of more than 80 articles (57 ScienceDirect; 23 Springerlink; 2 BioMed Central), 21 books, and 14 internet sites reveal that the topic on quality of life in the elderly spread over many disciplines and interests - culture, gerontology, geriatric, sports, social, economics, nursing, medicine (cancers, cardiology), psychology, ethics and moral, history, environment, occupation. The bulk of studies are from European (including Russia) countries, the USA, Japan, Korea and Hong Kong. The few related articles from Malaysia [84;85;86] dealt mainly with characteristics such prevalence of diseases, and none was found on wellness index. Of the models reviewed, three were selected for further consideration; Perry [87] Sarvimaki & Stenbock-Hult, and Costanza et al. However, the model by Felce and Perry, though intricate, would pose greater challenge if adopted, hence avoided. The two latter models are considered most appropriate as they contain essential objective and subjective dimensions. The pertinent breadth and depth of context, within both global and local perspectives, have to be explored and understood before a holistic wellness index can be formulated. Designed models would conform to local context and contents. Studies, especially in developed countries, strengthen our conviction that measurement of wellness index is essential to gauge the overall health of a nation. The authors conclude that quality of life is a dynamic concept that contains a myriad of meaning and interpretations. Both objective and subjective dimensions interact forcefully and subtly in the process.

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Vaccine development against Dengue and Shigellosis and implications for control of the two diseases in Brunei Darussalam

Lim Chun[1], Lakshmi Devi Telisinghe[2], Mohammad Moshadeque Hossain[1], Ranjan Ramasamy[1]
[1] Institute of Medicine, Universiti Brunei Darussalam and [2] Ministry of Health, Brunei Darussalam

Abstract

Dengue and shigellosis are common in the Asia-Pacific region. There are constraints on effective treatment of the two diseases that can pose a health risk to Brunei Darussalam. Vaccines against other flaviviral and enteric bacterial pathogens are currently available but not yet against the dengue virus or *Shigella* bacteria. The state of vaccine development against the two diseases and the prevalence of the diseases in Brunei Darussalam and neighbouring countries are reviewed. For dengue, live attenuated viral strains and chimaeric viruses based on a yellow fever virus backbone are in clinical trials. Shigellosis vaccines based on O antigen – protein conjugates, and O antigen incorporated into hydrophobic proteosomes, have undergone clinical trials. It is concluded that vaccines against the two diseases are not needed for routine or mass vaccination in the country, but that they will be useful in protecting travelers to endemic countries and in controlling potential epidemics.

1. Introduction

Dengue and shigellosis are two infectious diseases found in the Asia-Pacific region associated with high morbidity and mortality. Dengue is endemic in Brunei Darussalam and outbreaks occur from time to time in the country. Although shigellosis is not endemic in Brunei Darussalam, there is always a risk of infection spreading from neighboring countries to Brunei. There is no specific anti-viral drug available for the treatment of dengue infection. There are four serotypes of dengue viruses that circulate globally and this and other factors have restricted vaccine development. *Shigella* is gaining resistance to many antibiotics used in its treatment and several infective species are prevalent worldwide. However vaccines against dengue and Shigellosis are now in clinical trials. This article examines the current state of vaccine development against the two pathogens and the potential use of such vaccines in Brunei Darussalam.

Correspondence:
Lim Chun
c/o Institute of Medicine,
Universiti Brunei Darussalam,
Jalan Tungku Link,
Gadong BE 1410,
Brunei Darussalam
E-mail: limchun2186@hotmail.com

1.1 Dengue

Dengue is a global health problem accounting for 50-100 million cases of febrile illness annually, including more than 500,000 cases of dengue hemorrhagic fever and dengue shock syndrome (DHF/DSS) with an approximate case fatality rate of 20%. The disease is endemic in more than 100 countries in different parts of the tropical developing world, placing more than two billion people at risk of infection [1].

Dengue is caused by an arbovirus and the virus belongs to the family Flaviviridae, genus Flavivirus. The dengue viruses consist of four antigenically distinct serotypes (DV1, DV2, DV3 and DV4). Infection with one serotype confers immunity for several years against that serotype but only short-lasting protection against other serotypes. Infection with one serotype may also increase the risk of developing DHF/DSS on subsequent infection with another serotype.

Dengue virus is transmitted to humans by the bite of infected female *Aedes aegypti* (the primary vector) and Ae. *albopictus* (a subsidiary vector) mosquitoes. The *Aedes* mosquito species have adapted well to human habitation and urbanisation. They often breed in stagnant water collections in domestic water storage containers, blocked drains, roof gutters, flower pots and rubbish deposits (Fig 1). Currently there is no specific antiviral drug to treat dengue infections leading to an urgent need to develop a vaccine.

Figure 1. Potential breeding sites for *Aedes* mosquitoes, Kampong Ayer, Brunei Darussalam

1.2 Shigellosis

Shigellosis is also of major health concern in many countries. There are approximately 164.7 million cases of shigellosis worldwide, of which 163.2 million occur in developing countries and 1.5 million in industrialized countries [2]. Each year approximately 1.1 million people die of shigellosis. There are also 580 000 cases of shigellosis reported among travelers from industrialized countries. Sixty-nine percent of all the infections and 61% of all deaths attributable to shigellosis involve children less than 5 years of age.

Shigellosis is caused by a group of bacteria belonging to the genus *Shigella* [3]. Shiga, a Japanese scientist, first discovered the causative agent over 100 years ago. Shigella was adopted as a genus in the 1950s and grouped into four species: *Shigella dysenteriae, Shigella flexneri, Shigella boydii*, and *Shigella sonnei*. *S dysenteriae* serotype 1 is responsible for deadly epidemics and *S. boydii* is restricted to the Indian subcontinent. *S flexneri* and *S. sonnei* are prevalent in developing and developed countries, respectively. *S. flexneri*, an enteroinvasive gram-negative bacterium, is responsible for the worldwide endemic form of bacillary dysentery [4].

Shigellosis is particularly prevalent in developing countries with poor sanitation [5]. The fecal-oral route is most common method of transmission of the disease. Ingestion of contaminated food or water, contact with a contaminated inorganic object and sexual contact are other modes of transmission. Vectors like the housefly can spread shigellosis by physically transporting infected faeces.

In recent decades, *Shigella* has gained resistance to the antibiotics that were initially effective in treating the infection. Shigella acquired resistance to sulfonamides in the 1940s, tetracycline and chloramphenicol in the 1950s, ampicillin in the 1970s and trimethoprim/ sulfamethaxazole in the late 1980s. A vaccine against shigellosis would therefore be extremely useful. The Lanzhou Vaccine Institute's vaccine is the only available vaccine today but it is not licensed outside China [6].

2. Targets molecules for vaccine development.

2.1 Dengue

Dengue virus envelope surface projections are made up of dimers of the viral envelope (E) glycoprotein and membrane (M) protein [7]. The capsid (C) protein is the only other protein constituent in the virion. The E glycoprotein is responsible for attaching the virus to receptor on target cell membrane and fusing the virus envelope with the cell membrane. It also bears the virus neutralization epitopes. In native virions, the elongated three-domain molecule lies tangentially to the virus envelope in a head-to-tail homodimeric conformation. The E dimers are changed to stable target cell membrane-inserted homotrimers that realign themselves vertically to promote virus-cell fusion upon penetration of the virion into the target cell endosome.

The 10.5 kb-long genomic RNA is a single stranded mRNA which is translated into a precursor polypeptide. The individual viral proteins derive from this polypeptide by cleavage, staring with the C, prM and E proteins followed by nonstructural proteins NS1 to NS5. NS3 is a protease and a helicase, whereas NS5 is an RNA polymerase. In addition to the glycoprotein, only NS1 had been associated with a role in protective immunity. This glycoprotein is not present on the virion but is found on the surface of infected cells. Immunization with NS1 has been shown to elicit protective immunity in animal models. NS3 contains the largest number of T cell epitopes.

Various vaccines under development have focused on the dengue virus E protein for the following reasons:

- It binds host cell surface receptor
- It is a target of neutralizing antibodies
- It elicits the first antibody response with the longest lasting activity
- Several monoclonal antibodies specific to receptor binding domain of the E protein block virus adsorption and infectivity
- Purified E protein can induce neutralizing anti bodies and protective immunity

Most vaccine designs also include the prM protein, implicated in the maintenance of the structural/antigenic integrity of the E protein.

2.2 Shigellosis

Natural and experimental exposure to *Shigella* antigens has been observed to induce clinical immunity [8]. For example, monkeys experimentally infected with *S. flexneri 2a* were unaffected when rechallenged with the same strain but became ill when rechallenged with *S. sonnei* or *S. flexneri*. Israeli soldiers, with pre-existing serum anti-lipopolysaccharide [LPS] antibodies, deployed to a field area were significantly less likely to become ill upon exposure to homologous *Shigella* serotype than seronegative soldiers. From this and other observations, immunity was found to be serotype-specific leading to the recognition that the O antigen of LPS as a crucial moiety to be included in a *Shigella* vaccine.

3. Vaccines under development against dengue and shigellosis

3.1 Dengue vaccines

Currently there is no vaccine against dengue approved for clinical use [9]. However there are two promising approaches to vaccines in the late stages of development viz. one involving the use of live attenuated dengue virus strains and the other using chimeric viruses. Other forms of experimental vaccines are also under development but these may be less immunogenic and therefore require more immunizations to be effective, which is a disadvantage for controlling epidemics. All dengue vaccines have to take into consideration that non-neutralising anti-viral antibodies may promote the development of DHS/DSS and that more than one serotype of dengue virus may be circulating in any one locality. Therefore for a vaccine to be effective it must elicit protection against all four strains, or at least all the strains occurring in a particular locality, and should not promote the subsequent development of DHS/DSS upon infection.

3.1.1 Live attenuated dengue virus strains

The first of these vaccines was developed at Mahidol University, Thailand [10]. The vaccines were made by serially culturing the wild type-virus in animal kidney cells.

DV1, 2 and 4 were grown in primary dog kidney (PDK) cells, and DV3 in African green monkey cells. The vaccine underwent laboratory studies and later clinical trials in Thailand in the mono and polyvalent forms.

The vaccine was licensed to Sanofi-Pasteur, France, for commercial development. In a phase 1 clinical trial, tetravalent neutralizing antibody seroconversion rates of 80-90% was achieved in children aged 3-14 years and antiviral activity remained stable for at least a year. DV3 was the most immunogenic. Various formulations of the tetravalent vaccine were tested in an attempt to obtain a similar immune response for each serotype. The Mahidol University developed vaccine strains have a lower infection, dissemination rates and transmissibility in *Aedes aegypti* than those of parent viruses [11]. Apart from this property, the passage in humans and mosquitoes did not change the characteristics of the vaccine strains. More recently, it has been reported that the Mahidol vaccine, while being immunogenic, has high reactogenicity in adults and children and that Sanofi-Pasteur have withdrawn their interest in the vaccine [12].

Another live, attenuated vaccine is being developed at the Walter Reed Army Institute of Research, USA in cooperation with GlaxoSmithKline (GSK) [9]. The vaccine is also made by serially culturing the wild type virus in PDK cells and a final passage in fetal lung cells of rhesus monkey. All four monovalent formulations induced neutralizing antibodies production and were well tolerated in humans. Tetravalent formulations prepared were evaluated in rhesus monkeys and were shown to cause seroconversion after two doses of the vaccine. Pilot studies in humans using three doses of the most promising vaccine combination managed to induce 90% neutralizing antibody formation to DV-1, 60% to DV-2, 3 and 25% to DV-4. A small-scale Phase 1 study involving children of age 6-9 years in Thailand produced acceptable immunogenicity and reactogenicity profiles. These attenuated virus strains were also poorly transmitted by mosquitoes, like the Mahidol strains, and are therefore considered unlikely to be transmitted under natural conditions [13].

3.1.2 Chimeric vaccines strains

Acambis, Cambridge, USA has applied the ChimeriVax system, which was originally developed to modify a Japanese Encephalitis vaccine, into a dengue vaccine [7]. The vaccine, Chimeri Vax-DV, was prepared by substituting the prM and E genes of an attenuated 17D strain of yellow fever virus with those from the dengue viruses. The chimeric viruses were shown to be attenuated, including after intracerebral injection of monkeys, and showed 92% efficacy at protecting monkeys from homologous DV challenge. The viruses did not show any replication in mosquitoes after blood virus mixtures oral feeding. A monovalent ChimeriVax-DV-2 vaccine formulation tested on 56 human volunteers in a Phase 1 clinical trial in USA showed 100% neutralizing responses to DV-2. In 2005, a Phase 1 trial of the tetravalent combination in collaboration with Sanofi-Pasteur showed seroconversion to all four dengue serotypes. Sanofi Pasteur has progressed this vaccine into Phase 2 trial.

Groups in three other institutions have used modified dengue viruses as the basis for a multivalent vaccine [14]. The National Institutes of Health, USA developed a DV4 mutant containing a 30bp deletion in the 3' non-coding region of the DNA as a genetic background for the construction of chimeric viruses. Phase 1 clinical trials of the mutant carried out in 20 adult volunteers exhibited only minor symptoms with 100% neutralizing antibody formation. The mutated virus was then used as the backbone for the construction viruses with DV1, 2 and 3 envelope glycoproteins by insertion of DV1, 2, 3 prM and E genes. Alternatively the deletion mutation was induced in DV1, 2 and 3.

The Centers for Disease Control, USA carried out a similar work by using an attenuated DV2 vaccine mutant (strain 16681, PDK-53) as a backbone to construct chimeric attenuated viruses by changing the prM and E genes with those from DV1, 3 and 4.

The US Food and Drug Administration has also created a chimeric vaccine by replacing 3 nucleotides in the terminal 3' stem structure of DV1 and inserting DV2-4 prM and E genes into the DV1 backbone. The candidate vaccines were found to be highly immunogenic in susceptible rhesus monkey.

3.1.3 DNA vaccines

A DNA vaccine expressing prM and E proteins of DV1 tested on *Aotus* monkeys showed that there was induction of a protective immune response [15]. More extensive preclinical and clinical trials are required before the DNA vaccine is acceptable for practical use as the general problem with DNA vaccines has been the requirement for multiple boosting immunisations to generate sufficient immunogenicity [16].

3.1.4 Inactivated and subunit vaccines

Successes in development of inactivated flavivirus vaccines against Japanese encephalitis and tick-borne encephalitis have triggered attempts to develop an inactivated dengue vaccine. DV2 grown in Vero cells was inactivated, purified, concentrated and tested in laboratory animals. Trials in monkeys have shown production of a protective level of antibodies [9].

Subunit vaccines have been developed by several researchers using the recombinant DNA techniques. In recombinant DNA techniques, specific genes encoding for protective antigens are cloned and expressed in other host cells including *E.coli*, yeast and insect cell systems. Recombinant E protein of DV2 produced using a baculovirus vector-insect cell system was able to induce neutralizing antibody production and provide partial protection to immunized monkeys [17].

A major drawback with inactivated or recombinant vaccines is the need for more effective adjuvants suitable for human use, to increase immunogenicity, thereby reducing the number of immunisations needed to achieve protection.

3.1.5 Vaccinia virus as vector for dengue vaccine

The Modified Vaccinia Ankara (MVA) vector with a restricted host range has been used for the construction of dengue recombinants. Trials whereby monkeys having repeatedly immunized with MVA recombinant expressing DV2 E protein were shown to produce virus neutralizing antibodies [18]. Construction of MVA recombinants expressing immunogenic E protein of other dengue virus serotypes is being planned. However pre-immunity to *Vaccinia* may limit its replication in immunized persons, as has been shown in trials with antigens from other pathogens, thereby similarly limiting efficacy against dengue in multiple immunizations. Pre-immunity to *Vaccinia* may be overcome by using a different viral vector, such as recombinant fowl pox virus, for boosting.

3.2 Shigella vaccines

The main approaches in *Shigella* vaccine development are the use of live attenuated bacteria vaccines and subunit vaccines [8]. The subunits vaccines consist of the conjugate vaccines, proteosome vaccines and the ribosomal vaccines.

3.2.1 Live attenuated oral vaccines

Two strategies to attenuate the bacteria are being used. The first approach is to create deletions in genes controlling metabolic processes, such as those involved in the biosynthesis of essential metabolites or transport of nutrients. The other approach is to mutate genes that encode specific virulence factors. These approaches are bedeviled by the fact that attenuated bacteria may cause serious infections in immunosuppressed and immunodeficient vaccinees in *Shigella*-endemic countries

3.2.2 Parenteral conjugate vaccines

The National Institutes of Health has developed several vaccines by conjugating the O antigen of *S. sonnei, S. flexneri* or *S. dysenteriae* to *Pseudomonas aeroginosa* recombinant exoprotein A (rEPA). In one trial, the *S. sonnei* vaccine was shown to be immunogenic in 90%, and the *S. flexneri* vaccine in 73%, of adult Israelis. A phase 3 efficacy field trial involving Israeli soldiers showed that a single intramuscular injection of *S. sonneri*-rEPA conferred 74% efficacy against shigellosis [19]. A vaccine containing a several specific O antigens conjugated to a protein carrier may however be expensive for production.

3.2.3 Nasal proteosome vaccines

Another approach for developing the vaccine is by delivering *Shigella* LPS in proteosomes. LPS is non-covalently

complexed by hydrophobic interactions into proteosomes, or multimolecular vesicular structures, which are made from purified meningococcal outer membrane proteins. Proteosomes are also believed to generate mucosal adjuvanticity. A phase 1 trial of *S. flexneri 2a* LPS vaccine showed no efficacy against the primary endpoint (diarrhoea, dysentery, fever and early treatment) but apparently diminished the severity of illness [20].

3.2.4 Ribosomal vaccine

The International Vaccine Institute (IVI) in Korea has used a different approach to develop a *Shigella* vaccine. Researchers at IVI had discovered that ribosomes from the *Shigella* bacteria have specific O antigen non-covalently bound to their surface and free of the lipid A associated with O antigen in LPS. Preliminary results in mice have shown good antibody responses both in serum and faeces following parenteral injection with the purified ribosomes [6].

3.3 Dengue in Brunei and the region

Brunei Darussalam on the north-west part of Borneo Island is surrounded by the South China Sea to the north and the Malaysian State of Sarawak on all the other sides. Also located on the Borneo Island are the Malaysian State of Sabah and Indonesian State of Kalimantan.

Brunei consists of four districts: Brunei Muara, Tutong, Belait and Temburong. Brunei has an equatorial climate characterized by a consistent high temperature, high humidity and heavy rainfall. Rainfall varies from 2,500 mm on the coast to 7,500 mm in the interior annually. There is no specific wet season.

Figure 2 below shows the number of dengue cases notified in Brunei for the past 5 years[23]. Before this period (1995-2001), the annual number of reported cases was less than 10. The notified number of dengue cases has been on the rise since 2002. In the year 2003, there was a localised outbreak of dengue. The predominant infecting serotype is DV2 followed by DV1 as shown recently [22]. The Breteau Index, which estimates percentage of containers infested with Aedes larvae per number of inspected houses, has since remained low in the country. However this is not a definite indicator of the vector density.

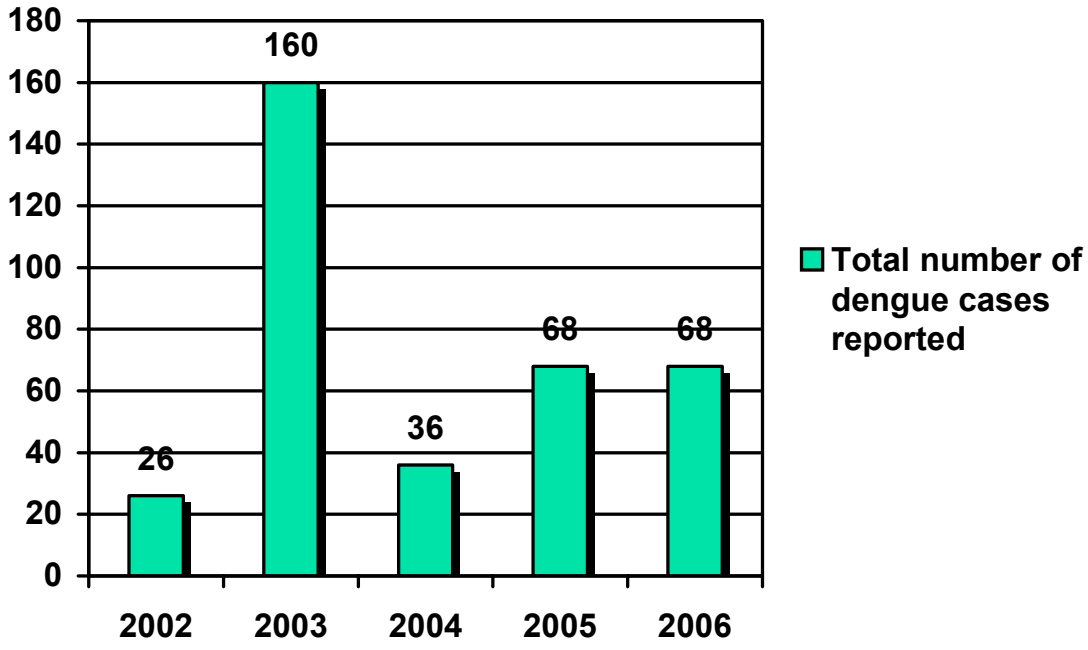

Figure 2. Total number of dengue cases reported in Brunei from year 2002 to 2006

Figure 3. shows the distribution of dengue cases in the four districts of Brunei Darussalam [23]. The dengue cases reported were usually sporadic cases. Prior to 2005, there were no outbreaks in the Temburong district. However in 2005, there were an appreciable number of cases reported from this district.

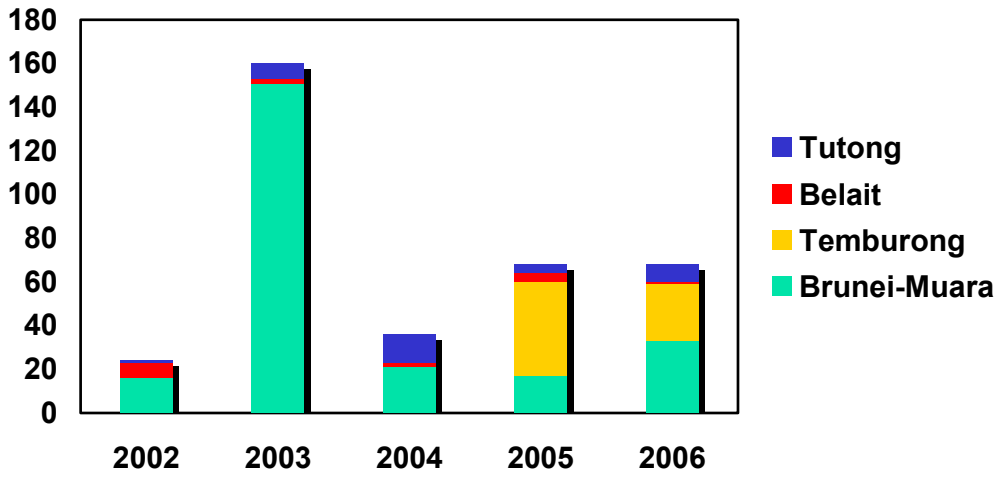

Figure 3. Dengue cases reported in four districts of Brunei from 2002 to 2006 [23]**.**

The outbreak of dengue which started in Kampong Ayer in 2003 mainly involved the Brunei Muara district where there was a definite local transmission. The disease spread to the neighbouring villages. The control of the outbreak was successfully carried out by adopting the following:

• Eradication and control of the *Aedes* larva, which was found breeding abundantly in and around houses of all the kampongs affected, by treating with the chemical larvicide Abate, and destroying all potential breeding places.

• Emergency spraying of insecticides carried out in all affected kampongs.

• The assistance of the penghulus and ketua kampungs and the community in enhancing the coverage of all control operations.

• Education of public on the nature of the disease and vector, and their positive involvement in control of vectors.

• Investigations of positive cases and serological testing of close contacts was used to assess the extent of the outbreak. The ability to rapidly report results by the State Laboratory in RIPAS was invaluable in this regard.

The outbreak in Brunei-Muara district was brought under control in two months through the efforts of the staff of the Environmental Health Division in the district, supported by the State Laboratory at RIPAS hospital. Following the 2003 outbreak, the Environmental Health Services continue to play a proactive role in the control of dengue in the country.

The following remain ongoing dengue control actions of the Environmental Health Services [Figure 4]:

• Source reduction

• Entomological survey of vector breeding and control of adults and larvae.

• Epidemiological surveillance with laboratory support

• Control of vectors by destroying breeding places by larviciding and adulticiding

• Involving the community in assisting Environmental Health services staff in controlling of vectors.

• Educating the community, including schoolchildren, on a healthy environment (‘healthy village’, sanitation of villages)

(a) Suspected breeding site identified.

(b) Larva samples collected.

(c) Larva samples placed in container.

(d) Abate 1% sand granule (insecticide)

(e) Abate 1% sand granule added.

(f) Larva samples identified in laboratory.

Figure 4. Aspects of *Aedes* vectors survey and control in Brunei Darussalam

The incidence rate of dengue per 100,000 population in some of the countries in South East Asia is shown in Figure 5. Sarawak had 1799 cases of DF and 22 cases of DHF reported with an incidence rate of 78.7 cases per 100,000 population in the year 2006 (61.0 cases per 100,000 population in 2005) [24]. The incidence rate in 2006 is calculated based on the most updated 2005 population census available. In Sabah, 1,865 cases of DF and 36 cases of DHF were reported with an incidence rate of 64.8 cases per 100,000 population in year 2005 [25].

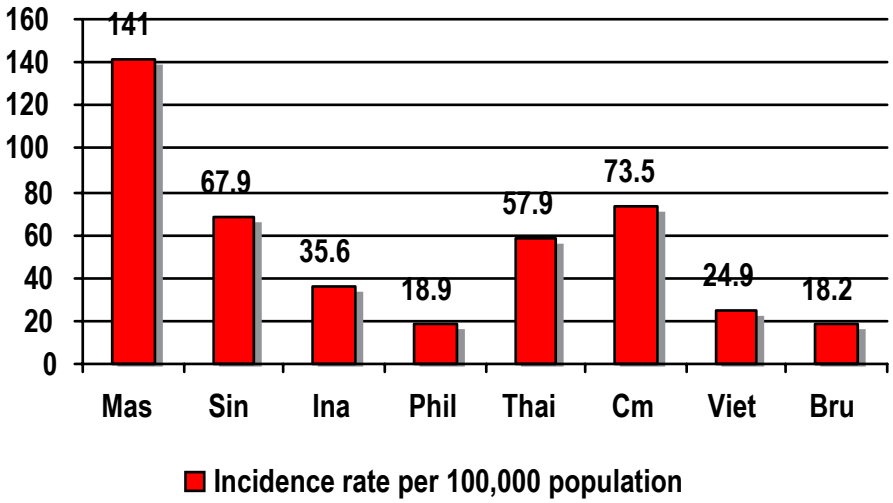

Figure 5. Dengue incidence rate in Southeast Asian countries [26].

3.5 Shigellosis in Brunei and the region

In Brunei Darussalam, shigellosis is an uncommon but notifiable infectious disease under the Infectious Disease Order 2003 of Brunei. All health practitioners and laboratory personnel are obliged to report to the Ministry of Health upon identification of shigellosis cases. Shigellosis is classified as gastroenteritis or dysentery case. The Ministry of Health follows the guidelines of management of Shigellosis in the Control of Communicable Diseases Manual of the World Health Organization.

The high standard of living, with proper housing, good water supply and sanitation, strict commercial food safety regulations, and health screening of immigrant workers before entry are all factors that contribute to the better record of Brunei in limiting shigellosis compared to many Asian countries. However there is still a considerable risk of travelers carrying the disease into the country from the now frequent travel to endemic areas.

A recent study to obtain more accurate and current estimates of shigellosis in the Asian region has been carried out due to the belief that current estimates of shigellosis are under detected and inaccurate [5]. Three rural or semi rural sites (in China, Vietnam and Thailand) and three urban slum sites (in Bangladesh, Pakistan and Indonesia) were chosen. The study involved approximately 600,000 participants over a 1-3 year period. Sixty thousand cases of diarrhoea were detected and 5% were shigellosis.

The overall incidence of shigellosis was 2.1 cases per 1,000 residents per year in all ages and 13.2 cases per 1000 residents per year for children under 60 months old. The incidence of shigellosis increases after the age of 40 years old. During the study, several reasons possible for under detection of shigellosis were identified. Culture of stool samples is normally the diagnostic tool for *Shigella* detection in clinical settings. However evidence shows that a more sensitive detection method based on polymerase chain reaction (PCR) analysis detected *Shigella* DNA in one-third of culture-negative stool specimens. Another reason is that less than one-third of culture proven shigellosis cases presented with dysentery, which is a frequently used clinical case definition in government data collection. Shigellosis cases can present with other signs and symptoms such as fever, vomiting and others stated.

Shigellosis is endemic in Malaysian cities with a high prevalence of *S. flexneri*, and resistance to common antibiotics [27].

4. Discussion

No matter how advanced or effective is the existing treatment for infectious diseases, the ideal way to protect people from contracting the disease is by immunizing them with vaccines because this prevents morbidity and consequent mortality and saves on treatment costs. An ideal vaccine has to be free of adverse effects, easy to administer and provide long-term immunity. Such effective vaccines will greatly help control dengue and shigellosis in nearby Asian countries where the diseases are endemic.

Brunei Darussalam is surrounded by or close to countries where incidences of dengue and shigellosis are reportedly high and the diseases are endemic. This increases the risk of both diseases spreading to Brunei as there is constant and rapid movement of population to and fro across the border. The present modes of rapid transportation by air and land can introduce virulent forms of the diseases into Brunei through visitors or migrant workers entering Brunei and the return of Bruneian residents who contract the diseases abroad. DHF/DSS and antibiotic resistant strains of *Shigella* have not been reported in the recent past in Brunei. With urbanisation, dengue has found a foothold in Brunei and may cause outbreaks in the future, if not properly controlled.

Cost is another important factor. The Paediatric Dengue Vaccine Initiative estimates that a dose of dengue vaccine to the public sector will cost US$0.50 [28]. Assuming that the whole population of Brunei is vaccinated in the public sector, requiring one dose to provide lifelong immunity, mass vaccination will reduce the costs of treating patients with dengue in hospital, and vector control operations. It will also diminish economic loss due to reduced morbidity. However, additional manpower and equipment needed for vaccination, the costs of multiple doses of vaccine required to provide immunity, management of adverse events after vaccination, etc are other factors that have to be considered in the equation.

The two diseases are not a major threat to the public health at present. The strategies adopted by the Ministry of Health have therefore been very effective in controlling these two diseases in Brunei. However it is notable that the incidence rate of dengue in Brunei for the year 2006 is comparable to that in neighboring Southeast Asian countries. Although the available data indicates the total burden of these two diseases in Brunei is low, a continuous and comprehensive epidemiologic profile of these two diseases in the country is required.

Brunei has a national immunisation program for children [29], similar to that in neighbouring countries. Also available in Brunei are optional vaccines such as those for influenza and yellow fever. The efficacy of the current available experimental vaccines against dengue and shigellosis have yet to be perfected. Even if these vaccines were developed free from known adverse effects, there is always the possibility of unforeseen adverse effects, when additional immunizations to the current routine vaccinations are introduced.

Given the current burden of dengue and shigellosis, we may conclude that vaccines against these two pathogens are not needed for routine vaccination of the entire population of Brunei. However, increased travel between Brunei and neighboring countries and urbanization increase the risk of dengue and shigellosis outbreaks. Therefore if appropriately effective, safe and affordable vaccines become available, the possibility of implementing vaccinations to protect travelers may be considered. An appropriately polyvalent dengue vaccine may in particular be useful in helping to control localized outbreaks of the disease. Furthermore such effective vaccines may be stockpiled for use in preventing possible epidemics in neighboring countries from spreading to Brunei in the future. The use of vaccines in epidemics that spread across national boundaries will require close coordination among neighbouring countries.

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Epidemiological research based on large data analysis: study characteristics

Omar Hasan Kasule Sr and Lin Naing
Institute of Medicine, Universiti Brunei Darussalam, Tungku Link, Gadong BE1410, Brunei Darussalam

Abstract

Analysis of studies published in one volume of each of 3 major epidemiological studies revealed median study sizes above 1000 for all types of study design, data collection, and study population. Cross sectional and follow up studies had the highest median study sizes when they were based on previously and routinely collected data. The paper discusses some of the problems associated with large studies.

Introduction

This study was motivated by the observation that recent epidemiological research is based on existing large databases or defined cohorts and that 100% sampling was the usual practice. This is a reversal of the traditional epidemiological practice of selecting a small probability sample from a study population in order to reach conclusion about the target population [1].

Developments in information technology and mass access to the internet opened up new fields of endeavor for the epidemiologist. For example data could be collected from a large number of people using internet-based questionnaires [2]

The objective of the research was to survey epidemiological research published in 2006 in three high-impact journals to make a statistical description of the characteristics of these studies. The three journals selected for study were the American Journal of Epidemiology 2006 Volume 169 Nos. 1-12, The International Journal of Epidemiology 2006 Volume 35 Nos. 1-4, and The European Journal of Epidemiology 2006 Volume 21 Nos. 1-9.

Correspondence:
Omar Hasan Kasule
Institute of Medicine,
Universiti Brunei Darussalam,
Tungku Link, Gadong BE1410,
Brunei Darussalam

Methods

The study included only original papers that involved raw data. Reviews, meta-analyses, and analyses based on published data were excluded. A pre-tested data abstract form was used to abstract the following essential information from each original research article: title, authors, issue and volume number, date of publication, type of study (cross sectional, case control, cohort, randomized community control, randomized clinical), Study population (general population, defined population, ongoing study), type of data collection (routinely collected data, newly collected data, previously collected data or a combination among the above) and total number of study subjects (number recruited before any exclusions). Defined populations were hospitals, health insurance of health maintenance organizations, clinics, schools, factories, and ongoing studies. For case control studies cases and controls were added up. For ongoing studies it was assumed that data collection was new unless a special mention was made of using previously collected data. The data was keyed into an SPSS data base for categorical analysis using the chi-square test statistic to test for association. The Kruskall-Wallis non-parametric test statistic was used to compare study size by various study designs and types of data collection.

Results

A total of 137 studies were analyzed. Table 1 shows a significant variation in journal preference for study designs and methods of data collection. There was however no significant variation among journals in the choice between defined and general study populations.

Table 1 Classifications of articles by journal

Study Characteristics		IJE	EJE	AJE	Total	$X^2(df)$	*P* value[a]
		n (%)	*n* (%)	*n* (%)			
Study design	Cross sectional	16 (39.0)	33 (60.0)	13 (31.7)	62	10.10 (4)	0.039
	Case control	9 (22.0)	9 (16.4)	7 (17.1)	25		
	Follow up	16 (39.0)	13 (23.6)	21 (51.2)	50		
Study population	Defined population	12 (29.3)	23 (41.8)	22 (53.7)	57	5.02 (2)	.081
	General population	29 (70.7)	32 (58.2)	19 (46.3)	80		
Data Collection	Newly & routinely	6 (14.6)	5 (9.1)	3 (7.3)	14		0.030[b]
	Newly	13 (31.7)	28 (50.9)	25 (61.0)	66		
	Previously	0 (0.0)	1 (1.8)	3 (7.3)	4		
	Routinely	22 (53.7)	21 (38.2)	10 (24.4)	53		

[a] Chi-square test; [b] Fisher's exact test;
IJE = International Journal of Epidemiology
EJE = European Journal of Epidemiology
AJE = American Journal of Epidemiology

Table 2 shows that the median study side was over 1000 for all journals and types of study design. Its variation among journals was significant for follow up studies and not cross sectional and case control studies. The median study size did not vary significantly among the 3 journals for different study populations and methods of data collection.

Table 2 Number of research subjects by study characteristics and journal

Study characteristics	Journal	*n*	Number of research subjects			$X^2.(df)$	*P* value[a]
			Median	Min.	Max.		
Study design							
Cross sectional	IJE	16	7,183	107	212,467,094	0.63 (2)	.730
	EJE	33	4,599	112	36,000,000		
	AJE	13	2,255	139	212,467,094		
Case control	IJE	9	1,263	288	166,310	1.61 (2)	.446
	EJE	9	1,051	372	2,222,404		
	AJE	7	1,875	730	212,467,094		
Follow up	IJE	16	60,925	1,016	60,000,000	7.80 (2)	.020
	EJE	13	9,778	34	11,000,000		
	AJE	21	2,446	209	212,467,094		
Study population							
Defined population	IJE	12	6,381	726	246,146	2.47 (2)	.291
	EJE	23	1,272	34	6,240,130		
	AJE	22	2,102	299	1,299,177		
General population	IJE	29	14,495	107	212,467,094	1.36 (2)	.506
	EJE	32	7,404	188	36,000,000		
	AJE	19	10,932	139	212,467,094		

Data Collection							
	IJE	6	2,380	274	246,146		
Newly & routinely	EJE	5	11,081	1,051	2,222,404	0.75 (2) 0	.686
	AJE	3	11,234	1,068	212,467,094		
	IJE	13	3,290	288	14,495		
Newly	EJE	28	937	34	6,240,130	3.90 (2)	0.142
	AJE	25	2,010	139	21,610		
	IJE	-	-	-	-		
Previously	EJE	1	56,214	56,214	56,214	0.20 (1) 0	.655
	AJE	3	1,516	619	212,467,094		
	IJE	22	180,155	107	212,467,094		
Routinely	EJE	21	19,801	212	36,000,000	2.43 (2) 0	.296
	AJE	10	399,910	1,832	212,467,094		

[a] Kruskal-Wallis Test
IJE = International Journal of Epidemiology
EJE = European Journal of Epidemiology
AJE = American Journal of Epidemiology

Table 3 shows that cross sectional and follow up studies had significantly higher median study size in general populations than in defined populations. No such significant variation was seen in case control studies.

Table 3 Number of research subjects by study design and study population

Study design S	tudy pop.	*n*	Number of research subjects			*Z*	*P* value[a]
			Median	Min	Max		
Cross sectional	Defined pop.	22	2,222	112	6,240,130	-2.28	0.023
	General pop.	40	10,832	107	212,467,094		
Case control	Defined pop.	10	1,552	726	2,222,404	-1.00	0.318
	General pop.	15	1,083	288	212,467,094		
Follow up	Defined pop.	25	2,311	34	1,299,177	-3.77	<0.001
	General pop.	25	83,875	188	212,467,094		

[a] Mann-Whitney test

Table 4 shows that follow up studies had higher median study size if based on previously and routinely collected data. No such significant variation was observed for cross sectional and case control study designs.

Table 4 Number of research subjects by study design and type of data collection

Study design	Data collection	*n*	Number of research subjects			X^2.(*df*)	*P* value[a]
			Median	Min	Max		
Cross sectional	New & routine	3	7,000	274	11,193	7.49 (3)	0.058
	Newly	33	2,650	112	6,240,130		
	Previously	3	1,516	619	212,467,094		
	Routinely	23	95,000	107	212,467,094		
Case control	New & routine	7	1,678	1,051	212,467,094	2.86 (2) 0	.240
	Newly	13	909	288	4,778		
	Previously	-	-	-	-		
	Routinely	5	1,272	828	166,310		
Follow up	New & routine	40	15,127	11,081	246,146	29.53 (3)	<0.001
	Newly	20	995	34	11,267		
	Previously	1	56,214	56,214	56,214		
	Routinely	25	87,922	212	212,467,094		

[a] Kruskal-Wallis Test

Table 5 shows significant variation of median study size with the type of data collection. Study size in defined populations was highest for newly and routinely collected data whereas in the general population median study size was highest for previously and routinely collected data.

Table 5 Number of research subjects by study population and method of data collection

Study population	Data collection	*n*	Number of research subjects			X^2 (*df*)	*P* value[a]
			Median	Min	Max		
Defined population	New & routine	7	11,234	7,000	2,222,404	12.10 (2)	0.002
	Newly	39	2,010	34	6,240,130		
	Previously	-	-	-	-		
	Routinely	11	1,272	212	1,299,177		
General population	New & routine	7	1,263	274	212,467,094	27.47 (3)	<0.001
	Newly	27	1,653	139	47,859		
	Previously	4	28,865	619	212,467,094		
	Routinely	42	187,530	107	212,467,094		

[a] Kruskal-Wallis Test

Discussion

Median study sizes were highest for cross sectional and follow up studies and when based on previously or routinely collected data. This is due to availability of large data bases with routinely or previously collected information. The availability of large data bases and high speed computers has encouraged epidemiologists to analyze data without probability sampling. A large data set gives very stable parameters but the same degree of precision could have been obtained from a smaller sample. What is lost is the ability of the epidemiologist to inspect a small manageable data set, internalize it, and let his intuition act before the data is analyzed. The more intimate contact of the epidemiologist with the data traditionally accounted for deep understanding and discussion which are missed in the new trend. Easy availability of large databases also encouraged epidemiologists to plunge into data analysis before serious thought about the research questions. In some cases the research questions can be prompted by preliminary analysis which can lead to numerous biases. Use of large data sets has the advantage of external validity which had never been the primary objective of epidemiological research. Epidemiologists have traditionally aimed at carrying out a small study based on probability sampling so that they can easily identify and control confounding and other sources of bias with the ultimate aim of internal validity. They knew that external validity (generalization) would be attained inductively by consideration of several studies that are internally valid. Use of large sets of routinely collected data also raises the issue of the quality of the data which is collected with service and administrative and not research considerations in mind.

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Are cell phones safe? - A pilot meta-analysis of case control studies linking cellphone use to acoustic neuroma

Omar Hasan Kasule Sr
Institute of Medicine, Universiti Brunei Darussalam

Abstract

This pilot meta-analysis based on few reports has suggested a weak association between cellphone use and the risk of acoustic neuroma. These findings will need confirmation by analysis of more research reports. The results of the expanded study will be used as the basis for planning a long-term prospective study of the risk of cancer among long-term users of cell phones.

Introduction

Acoustic neuroma is a benign, slow growing tumor of the 8th cranial nerve. It presents with otological symptoms (tinnitus, vertigo, and hearing loss) and signs (abnormal hearing tests, facial numbness and weakness, and papilledema). Larger tumors can cause symptoms and signs due to compression of the brain stem and involvement of the facial and trigeminal nerves. Men are affected more than women. Presentation is above 30 years. Elderly patients without serious symptoms and signs are left untreated but are followed up for complications. Micro surgery, radio surgery or a combination of the two may be used in treatment.

Electromagnetic radiation is a known cause of cancer. The localized radio frequency microwave energy emitted by cell phones has been suspected as a cause of brain malignancies. This is an issue of public concern because cell-phone use is increasing very rapidly in Brunei and other countries. Evidence indicates that the incidence of brain tumors has been rising in the recent past when cell-phone use became very popular. Hardell et al found a significant increase of +0.80% in the incidence of all brain tumors taken together for the 1960-1998 [1]. The risk of cancer in association with cell-phone use has also been observed to rise in the same period. Hardell et al 2003 in a computation of annual risk increase by treating exposure as a continuous variable showed increase of risk with time the annual risk increase being 1.04 (1.01 – 1.08) [2].

Evidence of the relation between radio frequency electromagnetic fields and brain tumors has been contradictory. Some authors found no relation while others found the evidence to be weak and unconvincing [3-5]. The studies reviewed below show weak or insignificant association. Considering all brain tumors together, Hardell et al. 2002 in a study of 588 cases and 581 controls found the following odds ratios with 95% confidence intervals for analog cell-phones 1.13 (0.86 – 1.48); for cordless phones 1.13 (0.85 – 1.50); and for digital cell-phones OR = 1.59 (1.05 – 2.41). Ipsilateral use increased the risk [6]. Hardell et al 2002 in a study of 1617 cases and 1617 controls found the risk for short term exposure to analog telephones to be OR = 1.3 (1.02 – 1.6) and for long term exposure OR = 1.8 (1.1 – 2.9). The risk was higher on the same side. There was no significant risk from cordless or digital cell-phones[7]. Hardell at al 2004 reported the overall risk of using analog telephones to be OR = 1.31 (1.04-1.64). The risk increased to OR = 1.65 (1.19 – 2.30) for ipsilateral use. Risk was highest among the 20-29 age group with the ipsilateral risk being OR = 5.91 (0.63 – 55). This age group experienced a raised ipsilateral risk if the latency period was over 5 years with OR = 8.17 (0.94-71) for analog phones[8]. Lonn et al 2004 in a study of 148 cases and 604 controls found the risk of acoustic neuroma from mobile phone use to be OR = 1.0 (0.6 – 1.5) for short term use and OR = 1.9 (0.9 – 4.1) for long term use. The risk was increased on the same side [9]. Hardell et al 2006 in a study of 317 cases and 692 con-

Correspondence:
Omar Hasan Kasule
Institute of Medicine,
Universiti Brunei Darussalam,
Jalan Tungku Link,
Gadong BE 1410,
Brunei Darussalam

trols found the following risks for various cell-phones and durations of use. The risk for analog cell-phones was OR = 2.6 (1.5-4.3) for short term use and OR = 3.5 (2.0 – 6.4) for long term use. The respective risks for digital cell phones were OR=1.9 (1.3-2.7 and OR=3.6 (1.7-7.5) and for cordless phones OR=2.1 (1.4-3.0) and OR= 2.9 (1.6-5.2). Multivariate analysis showed all three phone types to be associated with increased risk[10].

This article reviews case control studies relating cell-phone use to acoustic neuroma. Hardell et al 2003 in a study of 1429 cases and 1470 controls found the risk of acoustic neuroma among analog telephone users to be OR = 4.4 (2.1-9.2)[2]. Hardell et al 2005 in a case control study of 84 acoustic neuroma cases found the risk from analog phones to be OR = 4.2 (1.8 -10) for the short term and OR = 8.4 (1.6-45) for long term exposure. The risk for digital phones was OR = 2.0 (1.05 – 3.8). Cordless phones did not show increased risk. Multivariate analysis showed analog phones to be an independent risk factor for acoustic neuroma [11]. Schoemaker et al 2005 in a study of 678 cases and 3553 controls found no increased risk of acoustic neuroma from regular cell-phone use. This applied even if the analysis was carried out separately for analog and digital cell-phones. Risk was increased for the same side and for long term exposure OR 1.8 (1.1 – 3.1)[12]. Takebayashi et al 2006 in a study of 101 cases and 339 matched controls found no association between cell-phone use and acoustic neuroma. There was no association between risk and cumulative years of cell-phone use[13]. Hardell et al 2006 in an analysis of 2 pooled case control studies with 1254 cases and 2162 controls found the risk of acoustic neuroma to be OR = 2.9 (2.0 – 4.3) for analog cell-phones, OR = 1.5 (1.1 – 2.1) for digital cellphones, and OR = 3.8 (1.4 – 10) for cordless phones. The risk for analog cell-phones increased if exposure was >15 years to OR = 3.8 (1.4 – 10). Multivariate analysis showed use of analog cell-phones to be an independent risk factor for acoustic neuroma[14]. Schlehofer et al 2007 in a study of 97 cases and 194 matched controls found the risk of acoustic neuroma from regular mobile phone use to be OR = 0.67 (0.38-1.19)[15].

We can conclude from the literature survey above that studies relating cell-phone use and brain cancers in general are either negative or show a weak association but the trend to increasing risk with longer duration of cell-phone use is very clear. This indicates that the risk may exist but is not detected due to 3 methodological defects explain the results: duration of follow up not sufficient, inaccurate measurement of the level of exposure and biases of response and recall [16].

The present study is a review of recent studies on cell phone use and acoustic neuroma. The objective of this preliminary study is to derive an estimate of acoustic neuroma risk by combining data from a few case control epidemiological studies. This is a pilot study that will be extended to include more studies as soon facilities for extensive literature search are available. All these efforts will culminate in the design and execution of a long-term prospective study in Brunei of the relation between cell-phone use and risk of various malignancies. Brunei has an advantage for such a study because of ease of follow up in a small population.

Methods

Five case control studies from the Interphone international collaborative study of the association between cell-phone use and cancer were identified with the help of PUBMED. The studies were all carried out using the same protocol so they had similar design and analytic methods. Tables 1 and 2 summarize the salient features of each research report. The odds ratio with 95% confidence intervals was abstracted from each report. Other essential data abstracted were: type of cell phone used, years of cellphone use <10=short, >10= long), and number of study subjects. The inverse variance meta analytic method was used compute a pooled odds ratio over several studies by summation of the odds ratios of individual studies each being weighted by the inverse of its variance. $OR_p = \sum w_i OR_i / \sum w_i$ where OR_p = pooled odds ratio, w_i = weighting which is the inverse of the variance of the odds ratio. The 95% Confidence Intervals were computed using the standard error $S(OR_p) = 1/\text{sqrt}\{\sum w_i\}$. Heterogeneity was tested using $\chi = \sum w_i (OR_i - OR_p)^2$ where $w_i = 1/S_i^2$. All computations were carried out using log-transformed data.

TABLE 1: STUDIES WITH NO MENTION OF THE TYPE OF PHONE

Author and type of phone	Country anddates	Study subjects	OR (95% CI)
Takebayashi et al. 2006	Japan 2000-2004	101 cases; 339 controls	Short term OR = 0.73 (0.43, 1.23) Long term OR = 1.09 (0.58, 2.06)
Schoemaker MJ, et al. 2005	UK, Sweden, Norway, Denmark, Funland	678 cases 3553 controls	Short term OR = 0.9 (0.7, 1.0) Long term OR = 1.8 (1.1-3.1)
Lonn et al. 2004	Sweden 1999-2002	148 cases 604 controls	Short term OR = 1.0 (0.6,1.5) Long term OR = 1.9 (0.9 – 4.1)
Schlehofer et al. 2007	Germany.	97 cases 194 controls	Short term OR = 0.67 (0.38, 1.19)

TABLE 2: STUDIES THAT GAVE SEPARATE DATA FOR ANALOG AND DIGITAL CELLPHONES

Author	Country	Study subjects	Odds Ratio (95% CI)
Hardell L et al 2005.	Sweden	84 cases 692 controls	Short term analog OR = 4.2 (1.8,10) Long term analog OR = 8.4 (1.6,45) Short term digital OR = 2.0 (1.05,3.8)
Hardell L, et al. 2006	Sweden	1254 Cases 2162 controls.	Short term analog OR = 2.9 (2.0, 4.3) Long term analog OR = 3.8 (1.4, 10) Short term digital OR = 1.5 (1.1, 2.1)

Results

Tests for heterogeneity were negative so pooled effect measures were computed. There was no strong, consistent, and significant association between cell phone use and acoustic neuroma in the short term (less than 10 years of use). The data did however suggest increasing risk with long-term use, use of analog cell phones as compared to digital phones, and disease on the same side of the head as the cell phone is usually held. For research reports without specification of the type of cell-phone, the pooled effect estimates (95% confidence limits) were OR_p = 0.9 (0.7, 1.0) for short term use and OR_p = 1.6 (1.1, 2.2) for long term cell-phone use. The pooled effect measures for analog cell-phones were OR_p = 3.1 (2.2, 4.4) for short term use and OR_p = 4.3 (2.2, 8.1) for long term use. The pooled effect measure for digital cell-phone use in the short term was 1.6 (0.51, 4.9). Data was not available for long term digital cell-phone use.

Discussion

The data suggests association between use of analog cell-phones with acoustic neuroma. The association is significant for analog cell-phone short term follow up. It is stronger for long term analog cell-phones on longer term follow up but does not reach significance due to the large variance based on few research reports. Analysis of more research reports is needed to confirm these findings.

The data quality was high being collected under a uniform INTERPHONE protocol. The studies were also similar in design and data collection because they largely used the same protocol. Lack of detailed raw data prevented use of the Mantel-Haenszel method and sparsity of the data prevented control for confounding. Use of self-reported questionnaires had limitations in accurate measurement of the total duration of use, frequency of use every day, position in which the cell phone is used, type and power of the phone used. More accurate exposure information can be obtained from the billing records of cell phone subscriber companies which have detailed automated data on times of calls, duration of the calls, type of phone and strength

of the radiation energy emitted. It is however doubtful that these companies will cooperate because of business self-interest. A study in Denmark found that there was a fair agreement between self-reported cell-phone use and subscriber data. Risk measures based on the two exposure measurements were not very different from one another. Each of the 2 methods has its limitations[17]. The fair agreement between the 2 methods is good news because we can rely on self-reported use that we can get easily instead of trying to obtain subscriber information that is not easily accessible. Exposure assessment is the weak link in studies of the association between cell-phone use and cancer. Self reported use of cell-phones is unreliable for duration of exposure. The relationship between duration of use and strength of the electromagnetic field is not known. In view of these limitations prospective studies will be needed to settle the questions under study [18].

The current analysis has not showed a strong, consistent, or conclusive evidence of a link between cell phone use and acoustic neuroma although the data suggests such a link. Definitive answers will be obtained from studies of longer-term prospective studies because cancer has a long induction period.

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Perceptions, attitudes, knowledge and practice of traditional medicine among Bruneians – a pilot study

Dk Nurolaini Pg Haji Muhd Kifli[1*], Zaw Wint[1], Linda Lim[2]

[1] *Institute of Medicine, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong, BE 1410*
[2] *Outpatient Pharmacy, Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, Bandar Seri Begawan, Brunei Darussalam*

Abstract

The use of Traditional Medicine (TM) has become very popular especially in the Asian regions however published comprehensive data on use of TM not available for Brunei. The aims of the study were: to investigate the extent of TM use in Brunei; to study Bruneians' perceptions of, attitudes to, and use of TM; to compare use of TM with that of prescription medicines; and to support future studies. The questionnaire was designed and was pre-tested. The study sample was selected using the snow balling method. Two hundred and fifty self-administered questionnaires were distributed to patients at Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, university staff, friends and families. The SPSS package was used for data management and analysis. The response rate was 60%. The proportion of Bruneians who had used some form of TM in their life was 68.5%. The use of Traditional Chinese Medicine (TCM) was significantly higher among the Chinese ethnic group compared to other ethnicities, 88.2% $p<0.05$. The proportions among Malays were 40% for local herbs and 38.8% for TCM. The use of TM was highest in the 31-45 years age group ($p<0.05$). There was no significant difference in TM use by gender. Seventy percent of the respondents indicated that TM was readily available. Fourteen percent of users of prescribed medicines (common cold remedies, antipyretics and antibiotics) reported using TM as well. More than 70% of respondents did not report their use of TM to their doctors. Seventy seven percent of the respondents claimed that there were no adverse effects accompanying use of TM; 30% reported minor side effects such as weight loss, weight gain, abdominal pain, nausea and vomiting. We concluded that TM is widely used among Bruneians due to its availability and belief in its efficacy. More than 50% of users did not know the effectiveness and safety of TM. The perception was that TM was safe because it had been used for generations and because it is from natural sources.

Introduction

The World Health Organisation[1] (WHO) defines traditional medicine as including diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness. Traditional Medicine (TM) is a comprehensive term used to refer both to Traditional Medicine systems such as Traditional Chinese Medicine, Indian Ayurveda and Arabic Unani medicine, and to various forms of indigenous medicine. The use of traditional medicine (including local and Indonesian herbal remedies (Jamu), Traditional Chinese Medicines, Indian Traditional Medicines (Ayurveda), and others) has become very popular especially in the Asian regions.[2,3] Use of TM in Brunei is also likely to be high but data is not available. Currently TM is not regulated and can be freely purchased from outlets ranging from health and local food stores to internet sites. This has led to concerns about their safety and quality. There is also the potential for interactions with conventional drugs.[4]

This preliminary questionnaire study investigated the extent, perceptions of, attitudes to and practices of traditional medicine usage in Brunei Darussalam. This study had several aims: (i) to investigate the extent of traditional medi-

Correspondence:
Dk Dr Nurolaini Pg Haji Muhd Kifli
Institute of Medicine, Universiti Brunei Darussalam
Jalan Tungku Link, Gadong, BE 1410
Brunei Darussalam
Tel: +673 2463001 ext 1780
Fax: +673 2461051
Email: nurol@im.ubd.edu.bn

cine usage in Brunei; (ii) to study Bruneian's perception, attitude and practices on the use of traditional medicine; (iii) to quantify the usage of traditional medicine against prescriptive medicines; and (iv) to support future study in this area.

Methods

The questionnaire was designed by the researchers and was available in English and in Malay. Questionnaire items required a yes/no/not sure response. It consists of 28 item-structured questions comprising demographic data (gender, age, races, identity card (i/c) number, occupation), history of use of traditional medicine, sources and expenditure of traditional medicines per month, and concurrent use with prescribed medicines and safety of TM. Bruneians were defined as local respondents who possess a yellow i/c (98%) and permanent residents with a red i/c (2%). As a result of the pre-test, modifications were made to produce a final version. The study was conducted over a period of 3 months, i.e. from December 2006 until February 2007. The snow balling method was used. Two hundred and fifty survey forms were distributed to patients at a tertiary referral hospital (RIPAS Hospital) located in Bandar Seri Begawan, University staff members and students, friends and families. Participants received an information sheet about the aims of the study.

The questionnaire included a definition of traditional medicine used in ASEAN as 'any medicinal product for human use consisting of active ingredients derived from natural sources (plants, animals and/or minerals) used in the system of traditional practice'. This definition covered botanical and herbal medicines used traditionally for therapeutic purposes over an undefined period of time. It also covered any remedies prepared using traditional recipes or purchased as commercialised products from dispensaries, supermarkets or others. Specific enquiries were made into the types of the traditional medicines used, duration of use, frequency of use, period and reasons of use. Opinions about traditional medicine were also asked from the respondents. Questions were also included about minor adverse effects such as weight loss, weight gain, abdominal pain, nausea and vomiting. In order to compare the use of traditional medicine with prescription medicines, participants were asked the names of prescribed medications taken together with the traditional medicine.

The data were coded and analyzed using the SPSS (version 15.0 software). Univariate and bivariate analyses were carried out using a significance level of α=0.05.

Results

Overall, the response rate was 60%. The data showed that 68.5% of Bruneians had used some form of traditional medicine in their life. By ethnicity, 88.2% of the Chinese had used Traditional Chinese Medicine (TCM); 40% of the Malay had used local herbs and 38.8% had used TCM. Other ethic groups (Dusun, Iban, Murut and Kedayan) although selected in the sampling were too few in number for a meaningful analysis. Figure 1 shows that use of traditional medicines was highest among the 31-45 years age group (82%, $p < 0.05$). The ratio of male to female users was 1:1. The majority, 90%, of the users were either working with the government or were students.

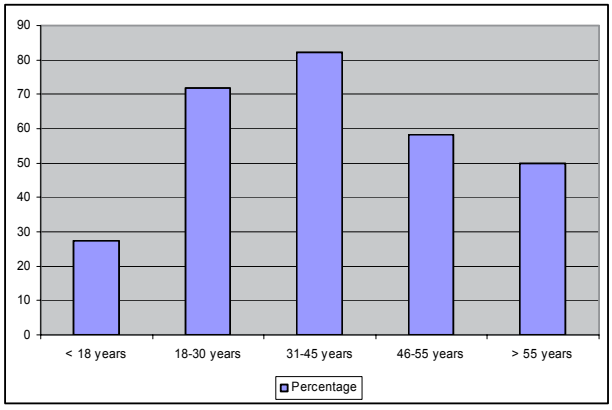

Figure 1. Self reported TM use by respondents by age group.

A majority of the respondents stated that they used multiple types of traditional medicine. Figure 2 shows reasons for using TM. Most respondents agreed that they used TM as recommended by friends and families. Other reasons reported were minor conditions, chronic conditions, infectious diseases, and any abnormality.

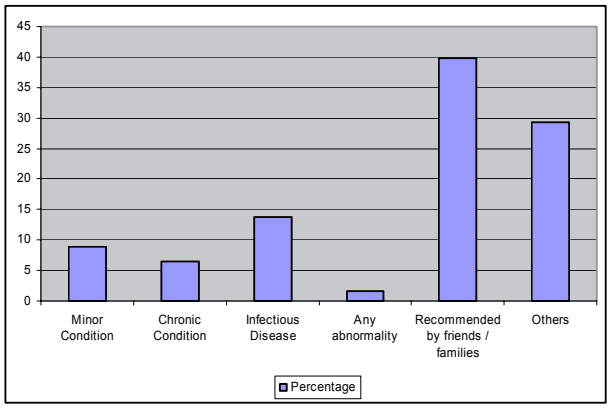

Figure 2. The reasons of taking traditional medicines among Bruneians.

It was found that 14% of those using prescribed medicine also used TM. The types of prescribed medicines used with TM were common cold remedies, antipyretics, and antibiotics. More than 70% of respondents mentioned that they would not inform their doctors about use of TM. Regarding adverse effects, 77% reported no adverse effects with TM while 23% reported that TM use was associated with minor side effects such as weight loss, weight gain, abdominal pain, nausea and vomiting. Figure 3 shows that more than 60% of respondents were unsure of the efficacy of TM when compared to the conventional medicines.

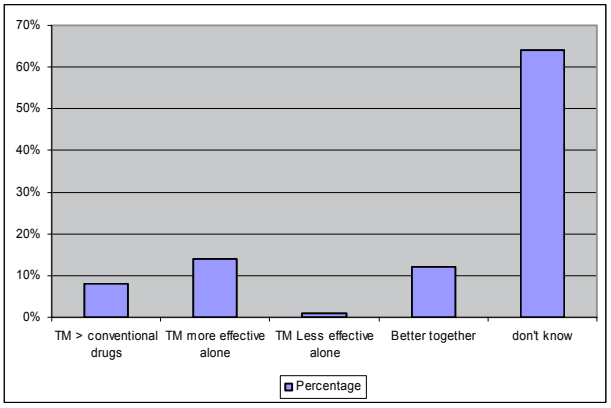

Figure 3. Opinion regarding the effectiveness of traditional medicine versus conventional medicines.

Figure 4 shows that most respondents were still unsure of the safety of TM. Respondents who were sure that TM was safe based their opinion on 3 reasons: lack of adverse effects, natural origin of TM, and cultural beliefs.

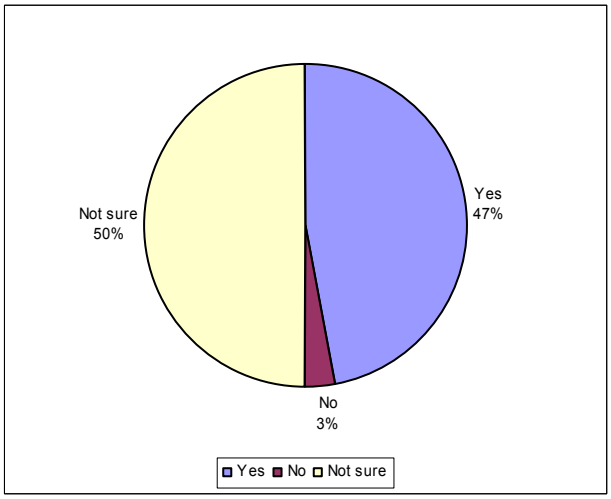

Figure 4. Opinion on the safety of traditional medicines.

Seventy percent of the respondents indicated that TM was readily available from Chinese dispensaries, local supermarkets, family and friends.

Discussions and conclusions

This study showed that TM use is common among the Bruneian community with nearly 70% reported ever using traditional medicine in their lifetime. This figure is comparable to other studies done in other communities within the Asian countries. TM is widely practiced among Bruneian Chinese communities due to the availability and beliefs that family and friends have used them before. Another local study of the prevalence and predictive factors for complementary and alternative medicines (CAM) use among patients and relatives at RIPAS Hospital (*n*=568) has documented similar findings where Chinese communities are the highest users of CAM with the highest prevalence of CAM user being in the 30-39 year age group. Besides TM, that study included health supplements such as vitamins and minerals.[5]

Fourteen percent of users of TM reported also using prescription medicines concurrently. This could result into adverse side effects due to interaction between conven-

tional medicine and herbal products. Most of the conventional medications reported were common cold remedies, antipyretics and antibiotics which are used for minor ailments. Many respondents could not remember the names of the prescription medicines that they took. This is an alarming observation because it could indicate that they are not well informed about the interactions between conventional medicines and TM or that they perceive that the interaction is safe. More than 50% of the users did not know how effective and safe TM products were.

In conclusion, the data from this study will benefit a larger ongoing study. We will also need to extend this study to rural areas and the elderly. In all these studies, clarification to the respondents of what is meant by traditional medicine will be essential.

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