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*“Giraffes! A people
Who live between the earth and skies,
Each in his own religious steeple,
Keeping a light-house with his eyes.”*

In: ‘Dreaming spires’
Roy Campbell (1901 – 57)
South African Poet

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Achieving Deep Remission in Crohn's Disease: Treating Beyond Symptoms

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease which is progressively destructive in nature. Persistent inflammation often leads to bowel damage over time, with the development of strictures, fistulae and abscesses. Current standard therapeutic strategies have not modified the course of CD. The focus of effective management of CD has shifted from short-term symptom control to long-term modification of disease course and complications. Traditionally, clinical remission was regarded as a therapeutic endpoint, however mucosal healing (MH) has emerged as a major therapeutic goal in CD. It is associated with lower relapse and hospitalisation rates, less bowel damage and reduced need for surgery. Growing evidence indicates that we have to look beyond clinical symptoms. Hence, achieving deep remission (clinical remission and mucosal healing) may be the way to alter the natural course of CD.

Mucosal Healing

MH is broadly defined as the absence of inflammation on endoscopic assessment. There is no consensus on what truly defines MH and the different grades of inflammation between MH and severe mucosal inflammation. Furthermore, endoscopic remission differs from histological remission.¹ Histological remission is impractical in CD as inflammation in CD tends to be patchy resulting in the need for multiple biopsies for evaluation.

Endoscopic remission to assess for MH is the most well studied method of evaluation. Largely driven by trials with biologic agents, it gained more traction in recent years as a desirable and realistic outcome of treatment. However, a universally accepted system for grading mucosal inflammation is lacking, with various trials using different classifications to measure MH.

MH is important as CD is a progressive disease with a relapsing and remitting course. Most patients will initially present with inflammatory CD without penetrating features and longitudinal studies have shown that chronic inflammation alters the behaviour of disease, eventually leading to fistulae and strictures. The number of surgical interventions a patient will have adds to the disease burden

as most CD patients will undergo surgery at some point in their lives.^{2,3}

The theory behind MH as an efficacy endpoint is the belief that halting tissue injury promptly and controlling mucosal inflammation over the course of disease will alter the course of disease, and prevent complications of penetration and stricture formation. There is a growing body of evidence from numerous trials that MH translates into higher rates of steroid free remission, less CD-related hospitalisations, lower surgical rates ultimately culminating in better quality of life.

Surrogate Markers for MH

As ileocolonoscopy is an invasive and costly procedure, there is a need for tests that would be accurate surrogates for MH. The time-tested C-reactive protein (CRP) is the most commonly used method for assessing severity of CD but it lacks sensitivity for patients with minimal symptoms. Moreover, it does not predict long-term prognosis.⁴

Cross-sectional imaging like magnetic resonance imaging (MRI) and computed tomography (CT) allow for evaluation of the gastrointestinal tract beyond the ileocolonoscopy, give better detail for the anatomy of strictures, fistulae and deep tissue healing. An MRI activity index (MRAI) for CD has been developed and has good correlation with Crohn's disease endoscopy index of severity (CDEIS).^{5,6} CT is also comparable to MRI but carries the added risks of radiation for patients who are already at higher risk for malignancies due to disease and treatment.⁷

Faecal calprotectin and lactoferrin remain the most promising candidate biomarkers for MH. Calprotectin is a protein that comprises about 40% of neutrophil's cytosol and is easily measured in faeces. It is fairly resistant to degradation. Faecal lactoferrin is a glycoprotein expressed by activated neutrophil. When raised levels are detected in faeces, they suggest active luminal inflammation. Both faecal calprotectin and lactoferrin correlate well with CDEIS, with falling levels paralleling treatment response and normal levels reflecting MH.^{8,9}

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CDEIS is considered to be the gold standard scale, requiring the assessment of ileocolonic segments, area of mucosa involved and ulcer size and depth. There is minimal interobserver variability but does require training and experience. Its complexity restricts its application in clinical practice, and limits its usage to trials.¹⁰

Rutgeert's scale is a postoperative score used to assess the neoterminal ileum to predict clinical recurrence of disease. Grades i0 to i4 are determined by the number of aphthous ulcers, presence of ileitis, nodules and narrowings. This scale's obvious limitation is its applicability to post-surgical patients.¹¹

Therapeutic Choice for Achieving Complete MH

Induction of MH can be attained with thiopurines and anti-TNF α agents. Methotrexate, steroids, 5-aminosalicylate compounds do not have strong data to support its use in MH, but are still useful in inducing clinical remission.

Azathioprine (AZA) has been studied and is superior to placebo in inducing and maintaining mucosal healing. In a study involving patients with ileocolitis, 54% to 70% achieved MH at 24 months.¹² Mantzaris et al demonstrated that patients with steroid dependent ileocolitis were more likely to achieve histologic remission at 1 year with AZA than budesonide (83% vs 24%).¹³ A Cochrane review also showed that AZA was more effective than 5-aminosalicylate compounds in reducing the recurrence of postoperative CD.¹⁴

Anti-TNF α agents initially sparked interest in MH and since then led to a large body of literature demonstrating efficacy over placebo in their respective trials. Infliximab has been proven to induce and maintain MH in ACCENT 1 trial, adalimumab in EXTEND trials. In ACCENT 1, patients who received infliximab and achieved MH at week 54 after induction and maintenance therapy, there was a longer median time to clinical relapse as well as lower hospitalisation rates when followed up beyond that.¹⁵ SONIC (infliximab vs azathioprine vs combination of both) showed that up to 43.9% of patients achieve MH at 26 weeks if infliximab and azathioprine combination treatment is introduced early in disease, compared to infliximab alone (30.1%) and azathioprine alone (16.5%).¹⁶

Step-up vs top-down study which compared patients who underwent early induction therapy with infliximab and azathioprine vs patients who were gradually progressed from steroids to ultimately infliximab, showed 73% vs 30% MH at 2 years respectively.¹⁷ Schnitzler demonstrated that patients who received infliximab and managed to achieve mucosal healing, had a higher rate of remaining in clinical remission at 5 years (65% (83/128) vs 40% (34/86)).¹⁸

EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing (EXTEND) study compared induction and maintenance therapy with adalimumab (ADA) to

induction with ADA followed by placebo. Complete mucosal healing was achieved at 12 weeks in 27.4% of patients in the group receiving continuous ADA and 13.1% of patients in the induction-only group. At 52 weeks, rates of complete MH were 0% and 24.2% in the 2 groups, respectively.¹⁹

In addition, post-hoc analysis revealed that MH at 12 weeks predicted lower CDAI scores at 1 year. Higher Simple Endoscopic Index for Crohn's Disease (SES-CD) scores were associated with higher CDAI score and lower chance of clinical remission.²⁰

Prior to EXTEND, Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) evaluated adalimumab with clinical remission as an endpoint. Treatment with ADA translated into a 56% reduction for all cause hospitalisations at 1 year.²¹ Once healing is achieved with a biologic, continuous therapy appears to be appropriate. This was shown in the CHARM study. Data from this study showed that ADA maintenance therapy conferred better Health Related Quality of Life scores for patients up to 56 weeks. It can be inferred that this culminates from decreased CD-related hospitalisations, fewer symptoms and less surgeries.²²

Deep Remission

Deep remission has been discussed extensively in recent years and is defined as CDAI of <150 and complete MH by some. This concept arose from observations that patients with MH can remain symptomatic. Possible explanations for this phenomenon include the presence of irritable bowel syndrome (IBS) in this group of patients, presence of histological remission that was not documented due to sampling error, submucosal inflammation not visible macroscopically and inflammation that occurs at a cellular level, not seen microscopically. It seems logical that complete absence of inflammation would result in a combination of both symptom control and MH.²³ The EXTEND trial involving ADA showed that regular dosing was superior to placebo in inducing and maintaining deep remission (DR) at 12 (16.1% vs 9.8%) and 52 (19.4% vs 0%) weeks, with lower hospitalisations, surgeries and better quality of life. Also, patients with DR fared better than patients with MH only.^{24,25}

Downside of Biologics

As a potent immunosuppressant, opportunistic infections are a cause for concern, especially intra-cellular pathogens. Inhibition of TNF α affects the ability to form granulomas, therefore increasing the risk of tuberculosis infection. TNF α is also required for immune response against viral pathogens. Patients will need to be screened for tuberculosis, hepatitis B and human immunodeficiency virus (HIV) prior to starting treatment.²⁶

More worryingly, there is a small but significant risk of developing non-Hodgkin's lymphoma (NHL) and the highly lethal hepatosplenic T-cell lymphoma (HSTL). Due to the low absolute numbers, it is difficult to quantify the exact risk, however we know that concurrent immunomodulator use, duration of use, age and male gender are risk factors for lymphoma.²⁷

Thus, even as anti-TNF α are useful drugs for the management of CD, a clear benefit should be expected before initiating therapy, more so in patients at higher risk of developing them.²⁶

Conclusion

In the coming years, the paradigm shift in clinical trials should translate into clinical practice on the ground as potent designer agents become more available. We must not forget that CD has numerous phenotypes affecting people from various backgrounds. Management plans and goals should be discussed with the patient and decision on the course of action undertaken should be jointly made. Deep remission will increasingly become a viable goal for patients who seek to reduce debilitating complications and have a decent quality of life with lower disease burden.

REFERENCES

- Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002;122:512-30.
- Olaion G, Smedh K, Sjö Dahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. *Gut* 1992;33:331-5.
- Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;8:244-50.
- Jones J, Loftus EV Jr, Panaccione R, Chen LS, Peterson S, McConnell J, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008;6:1218-24.
- Rimola J, Rodriguez S, Garcia-Bosch O, Ordás I, Ayala E, Aceituno M, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. *Gut* 2009;58:1113-20.
- Rimola J, Ordás I, Rodriguez S, Panes J. Colonic Crohn's disease: value of magnetic resonance colonography for detection and quantification of disease activity. *Abdom Imaging* 2010;35:422-7.
- Panés J, Bouzas R, Chaparro M, García-Sánchez V, Gisbert JP, Martínez de Guereñu B, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011;34:125-45.
- Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Farkkila M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008;14:40-46.
- Jones J, Loftus EV Jr, Panaccione R, Chen LS, Peterson S, McConnell J, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008;6:1218-24.
- Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989;30:983-9.
- Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. *Gut* 1984;25:665-72.
- D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. *Gastrointest Endosc* 1999;50:667-71.
- Mantzaris GJ, Christidou A, Sfakianakis M, Roussos A, Koilakou S, Petraki K, et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. *Inflamm Bowel Dis* 2009;15:375-82.
- Doherty G, Bennett G, Patil S, Cheifetz A, Moss AC. Interventions for prevention of post-operative recurrence of Crohn's disease. *Cochrane Database Syst Rev* (Online) 2009;CD006873.
- Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541-9.
- Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383-95.
- D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;371:660-7. [PMID: 18295023 DOI: 10.1016/S0140-6736(08)60304-9]
- Schnitzler F, Fidler H, Ferrante M, Noman M, Arijis I, Van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009;15:1295-301.
- Rutgeerts P, D'Haens GR, Van Assche GA, Sandborn WJ, Wolf DC, Colombel J, et al. Adalimumab induces and maintains mucosal healing in patients with moderate to severe ileocolonic Crohn's disease—first results of the Extend trial. *Gastroenterology* 2009;136:A-116.
- Feagan BG, Panaccione R, Sandborn WJ, D'haens GR, Schreiber S, Rutgeerts PJ, et al. (2007b) An evaluation of adalimumab on the risk of hospitalization in patients with Crohn's disease, data from CHARM. *Gastroenterology* 132:T1312.
- Loftus EV, Feagan BG, Colombel JF, Rubin DT, Wu EQ, Yu AP, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008;103:3132-41.
- Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995;30:699-706.
- Colombel JF, Louis E, Peyrin-Biroulet L, Sandborn WJ, Panaccione R. Deep remission: a new concept? *Dig Dis* 2012;30(suppl 3):107-11.
- Colombel JF, Rutgeerts PJ, Sandborn WJ, Yang M, Camez A, Pollack PF, et al. Adalimumab induces deep remission in patients with Crohn's Disease. *Clin Gastroenterol Hepatol* 2014;12:414-22.
- Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab treatment results in deep remission for patients with moderate to severe ileocolonic Crohn's disease: results from EXTEND. *Gastroenterology* 2010;138:S518.
- Laura E Targownik, Charles N Bernstein. Infectious and Malignant Complications of TNF Inhibitor Therapy in IBD. *Am J Gastroenterol* 2013;108:1835-42; doi:10.1038/ajg.2013.294.
- Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;9:36-41.e1.

Spectrum and Burden of Movement Disorder Conditions in a Tertiary Movement Disorders Centre—A 10-Year Trend

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Abstract

Introduction: The precise burden of movement disorder conditions in our movement disorders centre is unclear. This study investigated the clinical burden of the Movement Disorders Clinic (MDC) in National Neuroscience Institute (NNI) over 10 years, aiming to identify the burden and spectrum of movement disorders conditions, to facilitate future resource allocation. **Materials and Methods:** We identified all patient visits from January 2002 to December 2011 at MDC from the Movement Disorders (MD) database using a standardised data collection form. **Results:** There was a linear increase in the clinical burden of MDC during this period. Parkinsonism comprised 71.6% of this clinical burden of which 84.8% were Parkinson's disease (PD) patients. Dividing the incident cases of MD conditions into two 5 years' blocks, the proportion of PD cases had not changed. There was significant increase in time to diagnosis for PD, hemifacial spasm and dystonia. **Conclusion:** There was nearly 4-fold increase in the burden of movement disorders conditions in our tertiary condition within a decade. However, we did not find increasing proportion of PD cases which would be in line with an ageing population. This could be due to the fact that we are still in the early stages of an ageing population and we postulate that this proportion will go up in the future. The increased time to diagnosis may indicate increasing waiting time to see a movement disorders specialist and that current outreach effort to promote awareness may not be reaching its target audience. The upward trend of clinical burden indicates a need for increased resource allocation to cope with demand for movement disorders services.

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Key words: Clinical burden, Movement disorder, Parkinson Disease, Tremor

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Introduction

Movement disorders refer to a group of neurological conditions that cause either hyperkinetic or hypokinetic movements. Movement disorders are common. As an example, the prevalence of Parkinson's disease (PD) exceeds 1% in individuals aged 60 and above with increasing rates found amongst older individuals.¹ The prevalence rate of essential tremor is 4% in individuals over the age of 40 and the rate increases to 14% in those over the age of 65.^{2,3} These conditions largely afflict the elderly and their occurrence is expected to increase in Singapore as a result of our ageing population.

Although the prevalence and incidence rates of PD⁴ and hemifacial spasm⁵ in Singapore had been published previously, the burden of movement disorders as a whole is

unclear. Furthermore, the spectrum of movement disorders conditions seen in our tertiary centre has not been analysed. A better understanding of the burden and spectrum of movement disorders will facilitate more accurate manpower projections and resource allocations in this field. Hence, we undertook this study to understand the burden, trends and spectrum of patients with movement disorders in Singapore.

Materials and Methods

Study Population

We used the Movement Disorders (MD) database to identify all patient visits to the Movement Disorders Clinic (MDC) of National Neuroscience Institute (NNI) from January 2002 to December 2011. The MD database was

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started in 2002 and since then, clinical and demographic information of all patients attending the MDC has been captured onto it, at each clinic visit, using a standardised data collection system. The database and study received approval from the institutional ethics committee. In our centre, PD was diagnosed based on the NINDS diagnostic criteria for PD,⁶ multiple system atrophy was diagnosed based on the consensus statement on the diagnosis of multiple system atrophy⁷ and progressive supranuclear palsy was diagnosed based on NINDS-SPSP clinical criteria.⁸ A standardised data collection form was used to retrieve demographic information for movement disorders conditions such as parkinsonism, tremor, myoclonus, and dystonia from the MD database. We examined the clinical burden, which is defined as the number of clinic visits over 10 years. We had used this definition as we felt that it was appropriate to tag clinical burden to the clinic visits as this would reflect the subvention that our institution received from the Ministry of Health in Singapore and therefore our capability to increase manpower. The number of incident cases or first patient visits were also tabulated and classified according to diagnosis. The age of onset and time to diagnosis (duration from symptom onset to diagnosis) were also analysed.

Data Analysis

Descriptive statistics, t-test, chi-square test and Mann-Whitney test were performed where appropriate using SPSS version 2.0.

Results

Clinical Burden

There was an upward trend in the clinical burden over the past 10 years, with increases observed almost every year (Fig. 1). The clinical burden had increased nearly 4-folds from 2002 (1238 clinic visits) to 2011 (4697 clinic visits). Parkinsonism had the highest clinical burden (71.64%), followed by myoclonus (9.43%), tremors (6.47%)

and dystonias (5.32%) respectively. These 3 disorders represented 87.54% of the clinical burden. Looking into clinical burden per physician ratio, we noted that there was an increase from a ratio of 619 clinic visits per physician in 2002 to 1371 clinic visits per physician in 2011. Among the common neurological diseases in our institution, clinical burden in the movement disorders subspecialty was the highest compared to stroke and dementia services. There were 4697 clinic visits for the MD subspecialty compared to 2711 clinical visits and 1241 clinical visits for stroke and dementia services respectively. We further compared clinical burden per physician among these 3 conditions as this will reflect the workload more accurately. Clinical burden per physician in the movement disorders, stroke and dementia subspecialty were 1371, 677 and 1241 clinic visits respectively in the year 2011. This difference is statistically significant ($P < 0.001$). To better quantify manpower needs, we also looked into the differences between numbers of visits per patient per year for early PD compared to advanced PD. We defined early PD as Hoehn and Yahr stage 2.5 and below, and advanced PD as Hoehn and Yahr stage 3 and above. We used this definition because in our opinion, patients with postural instability with a tendency to fall tend to prefer spaced out clinical visits due to the inconveniences of transportation to the hospital. Comparing clinical visits per year for early and advanced PD patients, we noted no differences in their frequency (2.40 vs 2.52; $P = 0.47$).

PD had the highest clinical burden (19,494 clinic visits in 10 years), comprising 84.8% of the clinic burden among patients diagnosed to have parkinsonism. This was followed by multiple system atrophy (940 visits) and progressive supranuclear palsy (854 visits), comprising 4.1% and 3.7% of the parkinsonism clinical burden respectively. The proportions of clinical burden of the different parkinsonian syndromes had remained fairly constant over the last 10 years.

Essential tremor was the most common condition among those who were diagnosed with a tremor syndrome

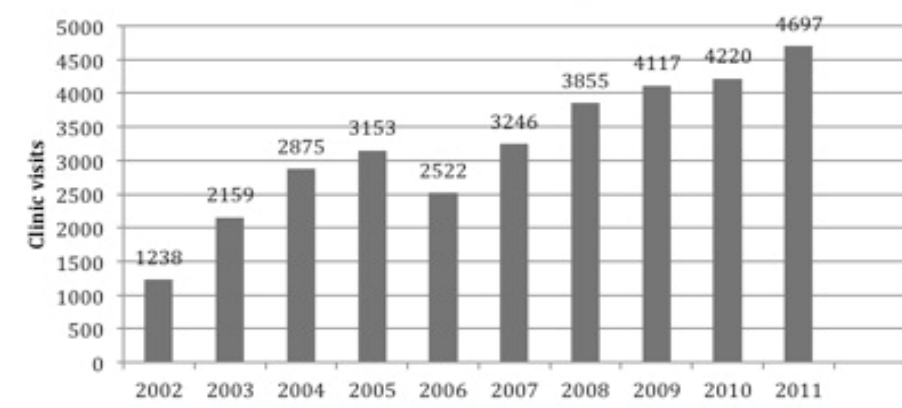


Fig. 1. Chart showing the clinical burden of movement disorders over 10 years.

(excluding tremor associated with parkinsonism syndromes), with 1783 clinic visits, or 85.9% of the tremor clinical burden. This was followed by enhanced physiological tremor (5.4%). Hemifacial spasm was the predominant diagnosis in the myoclonus group of movement disorders with 2921 visits, or 96.6% of the myoclonus clinical burden (Table 1, Fig. 2).

Incident Parkinsonism Cases

There were 3748 incident cases, or new cases, seen at the NNI MDC from 2002 to 2011. Patients with parkinsonism contributed the largest portion, with 2084 (55.60%) new cases. This was followed by tremors, with 610 cases

(16.28%), myoclonus with 347 cases (9.26%) and dystonia with 222 cases (5.92%).

There were 1503 new PD cases from 2002 to 2011, accounting for 72.12% of new parkinsonism cases. This was followed by drug-induced parkinsonism (111 cases), multiple systems atrophy (111 cases) and vascular parkinsonism (105 cases) (Table 2). We further divided the incident parkinsonism cases into 2 blocks of 5 years' period to compare if there were any differences between causes of parkinsonism. We observed an upward trend in the proportion of newly identified drug-induced parkinsonism cases nearing statistical significance (3.89% vs 6.53%, $P = 0.054$) (Table 2). The other causes of parkinsonism were not significantly different between the two 5 years' period.

Age of Onset

The median age of onset of PD among our patients was 65.8 years. Among 1459 PD patients with known age of onset, 156 (10.70%) patients had an age of onset of less than 50 years (young onset PD). There was no significant

Table 1. Clinical Burden of Movement Disorders

Disease	n (% of Disease Clinical Burden in Disorder Category)
Parkinsonism (22,985 clinic visits)	
Parkinson's disease	19,494 (84.8)
Multiple system atrophy	940 (4.1)
Progressive supranuclear palsy	854 (3.7)
Tremors (2075 clinic visits)	
Essential tremor	1783 (85.9)
Myoclonus (3024 clinic visits)	
Hemifacial spasm	2921 (96.6)

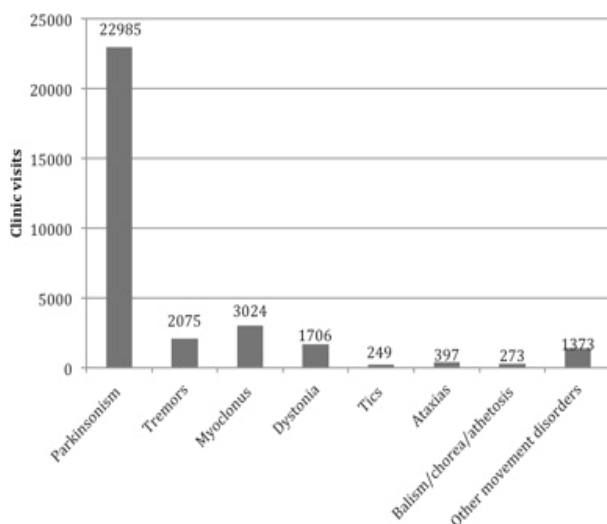


Fig. 2. Chart showing the clinical burden of movement disorders categories over 10 years.

Table 2. Incident Cases of Parkinsonism Cases over 10 Years

Disease	2002 to 2006, n (%)	2007 to 2011, n (%)	Total in 10 year, n (%)
Parkinson's disease	709 (74.6)	794 (70.0)	1503 (72.1)
Drug-induced parkinsonism	37 (3.9)	74 (6.5)	111 (5.3)
Multiple systems atrophy	59 (6.2)	52 (4.6)	111 (5.3)
Vascular parkinsonism	44 (4.6)	61 (5.4)	105 (5.0)
Atypical parkinsonism	28 (2.9)	74 (6.5)	102 (4.9)
Progressive supranuclear palsy	38 (4.0)	42 (3.7)	80 (3.8)
Cortico-basal-ganglia	21 (2.2)	16 (1.4)	37 (1.8)
Normal pressure hydrocephalus	10 (1.1)	10 (0.9)	20 (1.0)
Diffuse Lewy body disease	2 (0.2)	9 (0.8)	11 (0.5)
Post-encephalitic parkinsonism	2 (0.2)	1 (0.1)	3 (0.1)
Toxicant-induced parkinsonism	1 (0.1)	0 (0)	1 (0.1)
Total	951	1133	2084

difference in the proportion of incident cases of young-onset PD patients in the first half of the study decade compared to the second half ($P = 0.524$). The median age of onset for the other major parkinsonism syndromes were progressive supranuclear palsy (65.3 years), corticobasal syndrome (66.9 years) and diffuse dementia with Lewy bodies (73.1 years).

The median age of onset for the other common movement disorders such as essential tremor, dystonia and hemifacial spasm were 47.4, 47.2 and 51.3 years respectively (Fig. 3). We did not find any change in the average age of onset for these disorders over the 10 years of data.

Gender and Racial Distribution

There were more males than females with PD and essential tremor ($P = 0.0007$). We also observed significantly more females with hemifacial spasm ($P = 0.0154$) (Fig. 4).

Singapore is a multiethnic country, comprising 74.1% Chinese, 13.4% Malays, 9.2% Indians according to the 2010 population census. In our MDC, Chinese patients were over-represented and Malays and Indians were under-represented for PD, essential tremor, dystonia and hemifacial spasm.

Time to Diagnosis

We also studied the time to diagnosis as this could reflect the degree of disability from the symptoms of various movement syndromes, as experienced by the local population. PD had the shortest time to diagnosis, with patients presenting at a median of 11 months after the onset of disease. Hemifacial spasm and dystonia had similar time to diagnosis, at 12 months and 12.5 months

respectively. Patients with essential tremor had the longest time to diagnosis, with a median of 42.8 months. The median time to diagnosis in 2007 to 2011 was significantly higher than the median time of diagnosis in 2002 to 2006 for PD ($P = 0.0221$), hemifacial spasm ($P < 0.0001$) and dystonia ($P = 0.0210$).

Discussion

Our study showed an ever-increasing clinical burden at the NNI MDC, with a 4-fold increase from 2002 to 2011. We postulated that this could be due to an increase in population in Singapore in the last decade. We also postulate that with an ageing population in Singapore, diseases that mostly affect the elderly such as PD, will see an increasing trend over other movement disorders patients. This is similar to a worldwide trend, a study projected that the number of individuals with PD will double from 4.1 – 4.6 million in 2005 to 8.7 – 9.3 million by 2030 in Europe's 5 most populous nations and the world's 10 most populous nations.⁹ However, we noted that the clinical burden of parkinsonian disorders had not grown in proportion relative to the clinical burden of all movement disorders in our study. This could be due to the fact that we are still in the early stages of an ageing population and incidence has yet to peak. Hence, we would expect the clinical burden of parkinsonian disorders to have an absolute increase, as well as an increase relative to the other movement disorders in an ageing population in the years to come.

Parkinsonism disorders comprised the highest number of incident cases. As expected, PD comprised the most number of incident cases consistent with other studies.^{10,11}

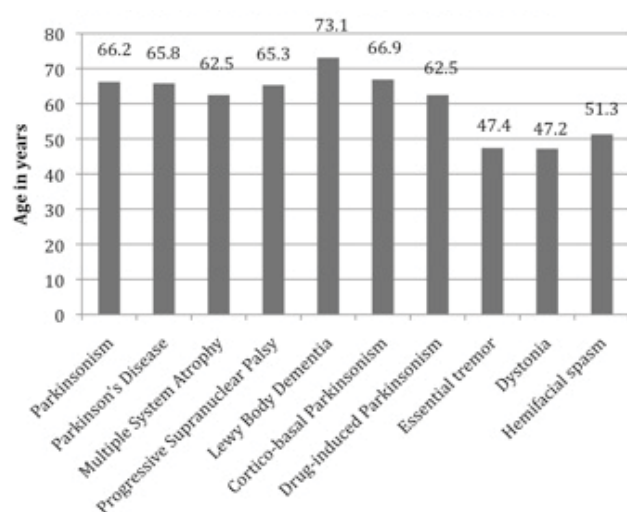


Fig. 3. Chart showing the age of onset of common movement disorders conditions.

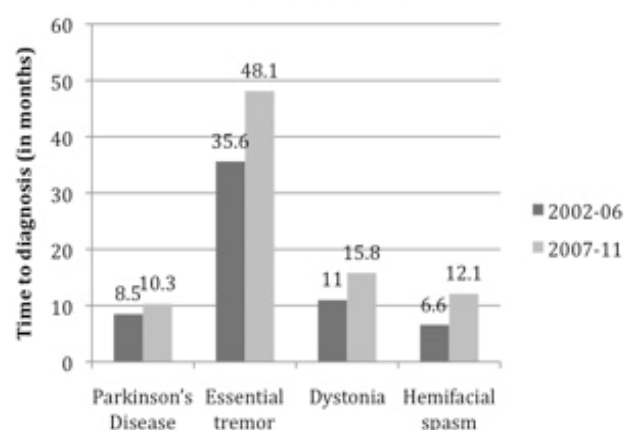


Fig. 4. Chart showing the median time to diagnosis for common movement disorders conditions.

In a study done by Tan et al, it was estimated the age and sex-adjusted (US 1990 population) incidence rate to be 32 per 100,000 person years for individuals aged 50 years and above.⁴ The actual incidence rate in the local population is likely to be slightly higher as individuals younger than 50 years were not included in that study. In our study population, 10.70% of incident PD cases had an age of onset of less than 50 years.

As mentioned previously, PD was the most common parkinsonian disorder, with incident cases comprising 72.1% of all incident parkinsonism cases in our centre. This was followed by drug-induced parkinsonism (5.33%), and multiple systems atrophy (5.33%). The proportion of progressive supranuclear palsy and cortico-basal-ganglia is 3.84% and 1.78% respectively. This differed from the proportions observed in other studies. In a prospective cohort study performed in the Netherlands, the proportion of PD was 51%, parkinsonism associated with dementia 18%, drug-induced parkinsonism 12%, cerebrovascular disease 5%, multiple system atrophy or progressive nuclear palsy 2% and parkinsonism unspecified 12%.⁷ In a retrospective study performed in the States, the proportion of PD was 42%, drug-induced parkinsonism 20%, parkinsonism in dementia 14%, and 7% with other causes.¹¹ Looking into the differences, we noted that PD carried a higher than expected proportion of our parkinsonism patients while dementia with Lewy bodies was rarely seen in our movement disorders centre. We postulated that the differences observed may be due to racial differences, differences in exposure to environmental risk factors, or differences in study methodology.¹² Another possible explanation is that a large number of dementia with Lewy bodies patients in our institution received treatment at the memory clinic, hence data for these patients were not captured in the MD database. Hence, further studies need to be done to evaluate the exact incidence and prevalence of various parkinsonian disorders in our local population.

We observed an increasing trend in the percentage of drug-induced parkinsonism cases over 2002 to 2011 that almost reached significance ($P = 0.054$). The percentage of drug-induced parkinsonism cases among parkinsonism cases was 3.89% (2.7% to 5.1%, 95% SI) between 2002 and 2006, and increased to 6.53% from 2007 to 2011 (5.1% to 8.0%, 95% SI). This may be due to better recognition of drug-induced parkinsonism from the use of antipsychotic, thus causing a spike in incident cases. Another explanation may be due to an increased use of drugs that induces parkinsonism such as antipsychotics and other antidopaminergic medications (e.g. metoclopramide and prochlorperazine), which were frequently used in the treatment of dizziness in Singapore. There may be a benefit to increase awareness of drug-induced parkinsonism among healthcare providers who will be prescribing these drugs in order to reverse this trend.

We observed a statistically significant increase in the time to diagnosis for PD, essential tremor, and dystonia in 2007 to 2011 as compared to 2002 to 2006. This was unexpected, as we postulated that there would be a decrease in the time taken due to the following reasons—an increasingly educated and affluent society that would in turn lead to increased health literacy, and outreach efforts to promote awareness of movement disorders such as PD. There were several reasons that could explain this increase in the time to diagnosis for the conditions above. Diagnosis of PD and dystonia in Singapore are usually made in the specialised movement disorders clinic. Referral to these clinics from the general practitioners were limited by the availability of slots in a physician's clinic. Our data showed that clinic visits per physician ratio had increased from 619 clinic visits in 2002 to 1371 clinic visits in 2011 and thus the increase in the waiting time to see a movement disorders specialist and the delay in making a definitive diagnosis. Another explanation for this increase in the time to diagnosis was that existing outreach efforts may be reaching out to those who were already aware of PD, rather than a wide swathe of the population. Future outreach efforts should be geared to increase awareness in those who would otherwise not be aware of this disease. There can also be initiatives to improve knowledge of movement disorder conditions among primary care practitioners, who are first line in patient care. A previous survey of Singapore general practitioners found that there is poor level of awareness in the identification and presence of alternative parkinsonian conditions.¹³ The early detection of movement disorders such as PD is important as it may lead to a reduction of severe cases at presentation and mortality.^{14,15}

Our study has several limitations. Singapore has other tertiary hospitals with neurology departments that also care for movement disorder patients. Hence, trends observed in NNI may not be representative countrywide. However, NNI is an institute dedicated to neurological conditions that sees a substantial portion of patients with neurological patients from the central part of Singapore, and so the trends observed are likely to be representative of the general population. This is a retrospective study based on data in the MD database. It was not practicable to review the medical records of all our patients to confirm the findings in the database. However, the information has been prospectively entered after each clinic visit and previous audits on the database have found the information collected to be accurate.

Conclusion

Despite these limitations, this is a comprehensive review of the cases seen in a movement disorders clinic over a period of 10 years. It is the first to describe the clinical burden of movement disorders in Singapore. Our study revealed a

trend of increasing burden of movement disorders, and is likely to increase further in coming years. This indicates a need for more resources to be allocated in order to cope with an increasing demand for movement disorders services.

REFERENCES

1. von Campenhausen S, Bornschein B, Wick R, Botzel K, Sampaio C, Poewe W, et al. Prevalence and incidence of Parkinson's disease in Europe. *Eur Neuropsychopharmacol* 2005;15:473-90.
2. Dogu O, Sevim S, Camdeviren H, Sasmaz T, Bugdayci R, Aral M, et al. Prevalence of essential tremor: door-to-door neurologic exams in Mersin Province, Turkey. *Neurology* 2003;61:1804-6.
3. Moghal S, Rajput AH, D'Arcy C, Rajput R. Prevalence of movement disorders in elderly community residents. *Neuroepidemiology* 1994;13:175-8.
4. Tan LC, Venketasubramanian N, Jamora RD, Heng D. Incidence of Parkinson's disease in Singapore. *Parkinsonism Relat Disord* 2007;13:40-3.
5. Au WL, Tan LC, Tan AK. Hemifacial spasm in Singapore: clinical characteristics and patients' perceptions. *Ann Acad Med Singapore* 2004;33:324-8.
6. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999;56:33-9.
7. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. Consensus statement on the diagnosis of multiple system atrophy. *J Auton Nerv Syst* 1998;11:189-92.
8. Litvan I, Agid Y, Jankovic J, Goetz C, Brandel JP, Lai EC, et al. Accuracy of clinical criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *Neurology* 1996;46:922-30.
9. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 2007;68:384-6.
10. de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. *Neurology* 2004;63:1240-4.
11. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. *Neurology* 1999;52:1214-20.
12. Lang AE, Lozano AM. Parkinson's disease. First of two parts. *New Engl J Med* 1998;339:1044-53.
13. Tan JH. Singapore general practitioners' awareness of atypical features in early Parkinson's disease. *Singapore Med J* 2007;48:338-41.
14. Liou HH, Wu CY, Chiu YH, Yen AM, Chen RC, Chen TF, et al. Mortality of Parkinson's disease by Hoehn-Yahr stage from community-based and clinic series [Keelung Community-based Integrated Screening (KCIS) no. 17]. *J Eval Clin Pract* 2009;15:587-91. PubMed PMID: 19674213. Epub 2009/08/14. eng.
15. Liou HH, Wu CY, Chiu YH, Yen AM, Chen RC, Chen TF, et al. Natural history and effectiveness of early detection of Parkinson's disease: results from two community-based programmes in Taiwan (KCIS no. 11). *J Eval Clin Pract* 2008;14:198-202.

Postoperated Hip Fracture Rehabilitation Effectiveness and Efficiency in a Community Hospital

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Abstract

Introduction: This study aims to determine the inpatient rehabilitation effectiveness (REs) and rehabilitation efficiency (REy) of hip fracture in a Singapore community hospital (CH), its association with socio-demographic variables, medical comorbidities and admission Shah-modified Barthel Index (BI) score as well as change in independent ambulation from discharge to 4 months later. **Materials and Methods:** A retrospective cohort study using data manually extracted from medical records of all patients who had hip fracture within 90 days and admitted to a CH after the operation for rehabilitation. Multiple linear regressions are used to identify independent predictors of REs and REy. **Results:** The mean REs was 40.4% (95% Confidence Interval (CI), 36.7 to 44.0). The independent predictors of poorer REs on multivariate analysis were older age, Malay (vs non-Malay) patients, fewer numbers of rehabilitative therapy sessions and dementia. The mean REy was 0.41 units per day [CI, 0.36 to 0.46]. The independent predictors of poorer REy on multivariate analysis were higher admission BI and being non-hypertensive patient. The prevalence of independent ambulation improved from 78.9% at the discharge to 88.3% 4 months later. **Conclusion:** CH inpatient rehabilitative therapy showed REs 40.4% and REy of 0.41 units per day and the optimum number of rehabilitative therapy session was from 28 to 41 in terms of rehabilitation effectiveness and the maximum rehabilitation efficiency was seen in those doing 14 to 27 sessions of rehabilitative therapy. The study also showed improvement in BI at discharge and improvement in the independent ambulation 4 months after discharge from the CH.

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Key words: Modified Barthel Index, Length of stay, Length of weight bearing

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Introduction

Individuals who sustained hip fracture may exhibit high mortality and often demonstrate permanent disability and dependency despite successful surgical repair.¹⁻³ One in 5 persons dies in the first year after sustaining hip fracture. Of those who survive past one year, only 40% can perform all routine activities of daily living and only 54% can walk without aid.^{1,4,5} Disability from hip fracture is prevalent among the older population and rehabilitation is essential after hip fracture to maximise recovery and function, re-integrate them into society and regain self-dignity.^{6,7} Some studies suggest that intense physical therapy (twice-daily therapy sessions) may help improve long-term functional outcomes.^{8,9} Ideally, they should follow a gradual progressive exercise regime prescribed from the first day

postoperation.¹⁰

Functional status of the patients can be assessed by using the 100-point Shah-modified Barthel Index (BI) score.¹¹ It ranges from 0 to 100, with 5 subcategories for each of the activities of daily living (ADL) and 100 possible discrete values with higher scores indicating greater independence ADLs. A score of 0 indicates total dependency and a score of 100 indicates full independence in ADL. The ADL includes personal hygiene, bathing, dressing, feeding, toileting, bowel control, bladder control, transferring, ambulation and stair climbing. The Shah-Modified Barthel Index is used by all rehabilitative community hospitals (CHs) in Singapore to quantify functional impairment, as recommended by the Ministry of Health Elderly and Continuing Care Division (2004).¹²

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With increasing elderly population in the country, there will be increased need for rehabilitative services including admission to the rehabilitative centre due to the various disabling conditions in the near future. Knowing the final outcome of rehabilitation for hip fracture or for any other disease, like mortality, discharge BI, or absolute function gain (AFG) at the discharge may not be enough as this does not consider the length of the stay and number of therapy sessions in the calculations as well as the speed of recovery with the rehabilitative therapy. As the need for bed and rehabilitative services increases, it is important that rehabilitative services should be most efficient for maximum gain to the patient as well as in terms of the length of stay. Reducing the length of stay is aimed by many healthcare systems and is thought to indicate the efficiency of the system.¹³⁻¹⁵ Thus, there is a need for more effective measures that show how efficient a rehabilitative method is, taking into account the length of stay (time factor) or number of rehabilitative sessions (intervention factor) in the rehabilitation centre. Rehabilitation effectiveness (REs) and efficiency (REy) are such measures which have been used as early as 1987 in many studies for many disabling diseases.¹⁶⁻²⁶ Rehabilitative impact index like AFG does not consider the potential maximal functional improvement like REs. It also does not take into the account the rate of functional improvement per unit time like REy. A study also found that REs was associated with cognitive impairment while AFG did not have any such association, supporting the superiority of REs over AFG.²⁷

Heinemann¹⁹ and Shah¹⁶ and colleagues defined measures of REs as the percentage of potential functional improvement actually achieved. It is calculated as follows:

$$\text{REs} = \frac{(\text{Final BI score} - \text{initial BI score})}{(\text{Maximum possible BI score} \{ \text{i.e. 100 points} \} - \text{initial BI score})} \times 100\%$$

REy is the rate of functional recovery during the rehabilitation^{16,19} and is calculated as follows:

$$\text{REy} = \frac{(\text{Final BI score} - \text{initial BI score})}{(\text{Duration between dates of initial and final BI scoring in days})}$$

The value of REy per day is usually less than one unit per day so it can be multiplied by 30 days to obtain the REy over a month.

Singapore has invested large amounts in upgrading the skills of members of the rehabilitation team in the past decade. However, REs and REy in hip fractures have not been studied much locally. This study aimed at finding overall REs and REy of patients in a CH in Singapore, the factors independently associated with REs and REy and the proportion of postoperative hip fracture patients who became independent between discharge and 4 months later.

Materials and Methods

The study included a retrospective cohort of all patients admitted to a CH from 1 May 2008 to 31 August 2009. This CH uses the 100-point BI to measure functional status of all patients upon admission and before discharge. BI scoring is performed by trained healthcare professionals, usually the rehabilitation therapists in the CH. All patients who had hip fracture within 90 days (day 90th inclusive) upon admission to the CH and were operated on for the fracture management were included in the study. Our aim was to study those patients who have had recent fracture and were operated on for the fracture. We excluded those who did not have hip fracture within the 90 days period upon admission to the CH. We excluded these patients because those who had fractures long time ago would have already plateaued in the functional recovery. Also, those patients with hip fracture but were not operated upon were excluded from the study. For rehabilitation to have an effect, it should be provided for a sustained and sufficient duration. We have included only those patients in the study who were admitted and underwent rehabilitation therapy for at least 14 days. This is an arbitrary cut off for number of days of rehabilitation we have taken, as we wanted to give adequate time frame for rehabilitation. The standard practice in a Singapore CH is to provide the standard 45 minutes inpatient rehabilitative therapy during each session for 2 sessions in a day. These comprise active ranging exercises for hip joints, strengthening exercises for hip musculature and a walking programme with the appropriate walking aids if they are allowed weight bearing activities.

We followed the ambulation status with scores from the BI. In subset of ambulation, a score of 0 represents totally dependent person in ambulation and highest score of 15 represents independent ambulation with or without walking aid and able to walk 50 metres without help or supervision. In the current study, we include those with BI score of 12 or more as walking independently with or without the walking aid. A BI score of 12 is defined as those individuals who are independent in ambulation but unable to walk 50 metres without help, or require supervision for confidence or safety in hazardous situations. This score would correspond to all patients with independent ambulation at home with or without ambulation aid.

Data were manually extracted from medical records by research assistants not involved in the study using a standardised data collection format. Comorbidity burden data was obtained using Charlson Co-Morbidity Index (CCMI). The CCMI is the most extensively studied comorbidity index (Charlson et al, 1987).²⁸ CCMI is recognised as a valid and reliable clinical research tool with high construct validity and predictive validity for mortality, disability, readmissions and length of stay.²⁹ It

has 19 categories of comorbidity. Each category has an associated weight which is based on the adjusted risk of one-year mortality. The overall CCMI score is the sum of the weighted scores and it reflects the cumulative disease burden: the higher the score, the greater the burden of comorbidity. We also obtained data for hypertension and ischaemic heart disease (with or without previous myocardial infarction), which are not included in CCMI. Four months post discharge from the CH, patients' ambulation status was again reviewed.

Statistical Package for Social Sciences (SPSS) software version 18 was used for statistical analysis, *P* values are reported in 2-tailed and the level of statistical significance (α) was taken at 0.05. Confidence intervals are reported at 95%. The study was approved by the National University of Singapore Institutional Review Board.

Results

There were 201 admissions during the 16-month study period. Only 166 admissions were eligible for the study (5 patients stayed less than 14 days and 30 patients were not operated on). The ethnicity division comprised 145 (87.3%) Chinese, 18 (10.8%) Malays and 3 (1.8%) Indian. The admission primary diagnosis was fracture neck of femur 101 (60.8%) and inter-trochanteric fracture 65 (39.2%). The demographic profile of the study population is shown in Table 1.

The mean number of days after operation to the CH was 10.9 days. The mean length of stay in CH was 50.4 days (CI, 46.9 to 53.4). The mean length of weight bearing days in inpatient CH stay was 39.9 days. The mean number of 45-minute rehabilitative therapy sessions was 34.3 (standard error mean 1.4) while the mode and median was 30. The BI shows improvement with the rehabilitative therapy. The mean admission BI was 54.1 and the discharge mean BI was 72.2. The mean abbreviated mental test (AMT) was 7.42 out of the maximum score of 10.

Ambulation Status and Mortality 4 Months After Discharge

Three patients died after discharge thus, the mortality rate at 4 months after discharge was 1.8%. Majority of patients who were discharged were ambulating independently with or without walking aid (78.9%). This improved significantly ($P = 0.0046$) to 88.3% at 4 months post discharge review (Fig. 1).

Overall Rehabilitation Effectiveness (REs)

The mean REs score was 40.4% (CI, 36.7 to 44.0). The median REs score was 39.0% and the inter-quartile range (IQR) was 23.2% to 58.3%. None of the subjects had negative REs scores i.e. no declines in REs. Eight (4.8%) subjects had REs score of zero, indicating their functional

Table 1. Demographic Profile of Study Population

Demographic Variable	All (N = 166) n (%)
Age (years)	
50 to 59	4 (2.4)
60 to 69	16 (9.6)
70 to 79	69 (41.6)
80 to 89	61 (36.7)
90 to 99	16 (9.6)
Mean age	78.9 (SD 7.9)
Gender	
Male	26 (15.7)
Female	140 (84.3)
Charlson Co-Morbidity Index	
Mean	2.89 (SD 0.168)
Admission BI score (units)	
0 – 33	21 (12.7)
34 – 66	96 (57.8)
67 – 100	49 (29.5)
Mean Admission BI	54.1 (SD 16.9)
0 – 33	21 (12.7)
34 – 66	96 (57.8)
67 – 100	49 (29.5)
Mean Admission BI	54.1 (SD 16.9)

BI: Barthel Index; SD: Standard Deviation

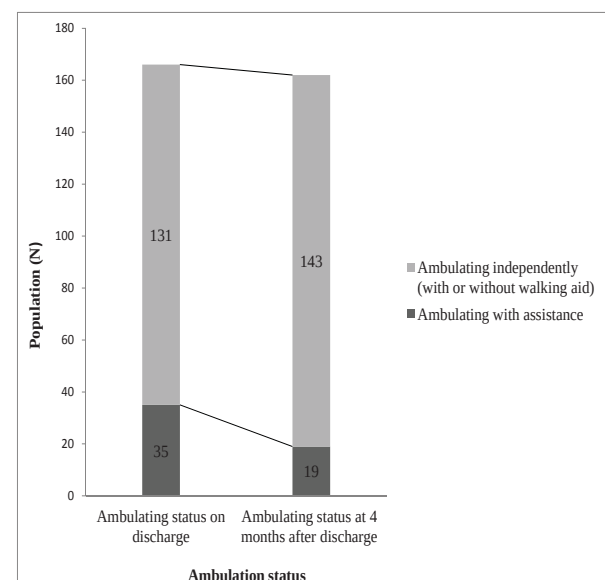


Fig. 1. Ambulating status on discharge and 4 months after discharge.

Note: Of those ambulating independently on discharge, 3 died (1.9%) and 1 (0.6%) was not contactable. McNemar's test for independent ambulation at discharge and 4 months after discharge is significant with $P = 0.0046$.

status did not change during their admission. There was no significant difference of mean REs with gender ($P=0.26$) or primary diagnosis at admission i.e. neck or inter-trochanteric fracture of femur ($P=0.934$). The relationships of REs to the other variables are shown in Table 2. On bivariate analysis with specific comorbidities, the mean REs of patients with dementia were significantly ($P=0.004$) worse than those who did not have dementia. The rest of the comorbidities did not have individual significant differences in REs. From

multivariate analysis, factors that are significantly associated with the poorer REs are older age, Malay (vs non-Malay ethnicity), having dementia, non-hypertensive and those doing 27 or less sessions of the 45-minute rehabilitative therapy sessions (all $P<0.05$) (Table 3, Part A).

Rehabilitation Efficiency (REy)

The mean REy score of all subjects was 0.41 units (CI,

Table 2. Relationship between the Rehabilitation Effectiveness and the Various Variables

Age groups (years) (n)	Mean REs (%)	CI	P value (comparing with the mean of the last group)
Overall	40.4 (SD $\pm$ 26.3)	36.7 – 44.0	
50 – 59 (4)	33.46	- 4.73 – 71.65	0.788
60 – 79 (85)	44.90	38.71 – 49.29	0.048*
80 – 99 (77)	36.68	31.6 – 41.68	-
Ethnicity			
Indian	36.29	- 8.87 – 81.44	0.677
Malay	28.07	19.22 – 36.91	0.018*
Chinese	41.96	38.04 – 45.89	-
Charlson Co-Morbidity Index Score (n)			
0 (22)	37.02	26.05 – 47.99	0.842
1 – 3 (88)	44.05	38.87 – 49.22	0.042*
≥ 4 (56)	37.11	30.24 – 30.24	-
Admission BI Score (units)			
0 – 33	35.47	25.82 – 45.12	0.325
34 – 66	41.08	36.13 – 46.04	0.369
67 – 100	41.01	34.43 – 47.59	-
Length of stay (days)			
14 – 27	28.57	16.95 – 40.19	0.003*
28 – 55	40.05	35.08 – 45.02	0.05*
56 – 83	42.54	36.23 – 48.84	0.127
≥ 84	54.04	38.97 – 69.11	-
Length of weight bearing (days)			
0 – 27	31.76	24.66 – 38.86	0.019*
28 – 55	42.66	37.78 – 47.53	0.157
56 – 83	42.66	34.60 – 50.72	0.181
≥ 84	57.72	18.35 – 97.09	-
No. of rehabilitative therapy sessions			
0 – 13	18.74	1.85 – 35.64	0.014*
14 – 27	35.72	30.54 – 40.91	0.019*
28 – 41	46.11	39.04 – 53.17	0.990
≥ 42	46.17	39.76 – 52.57	-

*Significant at $P<0.05$.

BI: Barthel Index; CI: 95% Confidence Interval of mean; SD: Standard Deviation

0.36 to 0.46 units) per day. The median REy score was 0.38 units per day. There was no statistically significant differences between the REy of all the demographic variables i.e. no differences in REy between the different age groups, gender, ethnicity, whether the fracture was neck of femur or intertrochanteric or those with different CCMI score. On bivariate analysis of the various morbidities, those in CCMI as well as with hypertension and ischaemic heart disease, only patients with hypertension had higher rehabilitation efficiency than those who did not have hypertension ($P = 0.019$). From multivariate analysis, significantly lower REy ($P < 0.05$) was seen with those with higher admission BI and being non-hypertensive patient (Table 3, Part B).

REy decreases with regard to higher admission modified BI. There was a significant difference in the mean of REy with increasing admission BI. The REy also decreases with increasing length of stay beyond 83 days. There was an increase in rehabilitation efficiency with more rehabilitative therapy sessions up to 27 sessions. However, there was a decrease in rehabilitation efficiency with 28 or more rehabilitative therapy sessions. Thus, an inverted 'U-shaped' relationship between the number of rehabilitative therapy sessions with rehabilitation efficiency and the maximum in

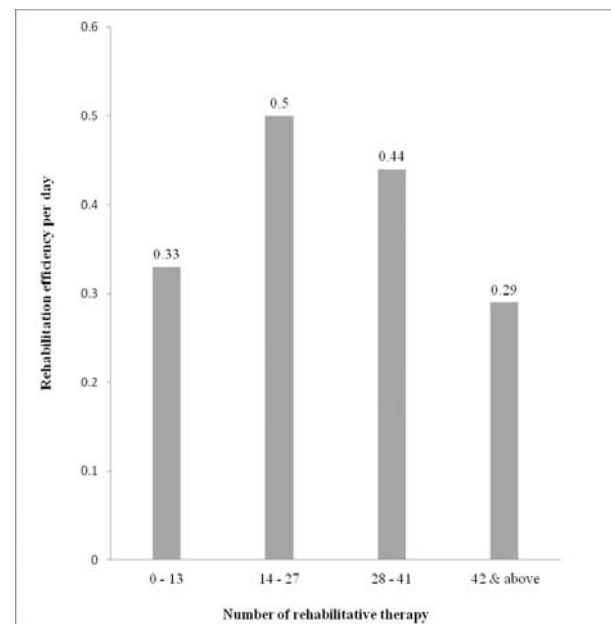


Fig. 2. Relationship between rehabilitation efficiency and number of rehabilitative therapy sessions.

Table 3. Multivariate Analysis of Rehabilitation Effectiveness and Rehabilitation Efficiency

Variable	Unstandardised β coefficient	P value
(A) Rehabilitation Effectiveness		
Age (old vs young)	6.812	0.046*
Ethnicity (Malay vs non-Malay)	14.38	0.008*
Charlson Co-Morbidity Index (low vs high)	-1.661	0.733
Hypertension (no vs yes)	8.695	0.022*
Dementia (no vs yes)	-26.107	0.002*
Diabetics mellitus with end organ disease (no vs yes)	-8.389	0.112
Length of stay (days) (short vs long)	4.409	0.527
Duration of weight bearing in days (short vs long)	4.094	0.423
No. of rehabilitative sessions (≤ 27 vs > 27)	11.038	0.003*
(B) Rehabilitation Efficiency		
Hypertension (no vs yes)	0.108	0.031*
Visual impairment (no vs yes)	0.100	0.086
No. of rehabilitative therapy session (≤ 27 vs > 27)	-0.097	0.055
Admission BI score (≤ 33 vs > 33)	-0.157	0.003*
Length of weight bearing days (≤ 27 vs > 27)	-0.075	0.189

*Significant at $P < 0.05$

BI: Barthel Index

efficiency was seen in the 14 to 27 sessions group (Fig. 2).

There was no significant social issue in regard to the discharge destination of the patients. From the total of 166 patients included in the study, 155 patients were discharged home with some form of day rehabilitation or daycare. Only 7 patients were discharged to nursing home and 1 patient to the sheltered home. Remaining 3 patients' discharge destinations were not traceable. Analysis of mean REy for those who were discharged home and those to sheltered or nursing home did not show any statistical significance ($P = 0.707$).

Discussion

The current study shows that the profile of the hip fracture population in a CH setting in Singapore is usually elderly Chinese females with fracture neck of femur. The mean age was 78.9 years with 2.4% of patients below 60 years. Three patients died within 4 months after discharge thus, mortality rate of 1.8 % was similar to a study by Shyu et al with the mortality rate at 0.8% after 3 months of discharge following rehabilitations.³⁰ Studies done in Singapore have shown all-cause mortality from hip fracture to be as high as 27.1% for all patients, and 26% for those older than 60 years of age over 1 year follow-up period.^{5,31} Studies have shown that functional independence was the main predictor of the mortality following the hip fracture.^{31,32} The low mortality rate in the current study may be a reflection of significant improvement of the BI with rehabilitative therapy at discharge. Majority of patients were able to ambulate

at the discharge with or without walking aid, as well as exhibit subsequent significant ($P = 0.0046$) improvement in independent walking from 78.9% to 88.3% at 4 months following the discharge. This was comparatively more than the intervention trial in Taiwan.³⁰ Studies have shown that early ambulation following the hip fracture surgery is associated with lower mortality and better functional independence.^{2,31,32} There was significant longer mean length of stay of 50.4 days (CI, 46.9 to 53.4) in the current study as compared to similar study by Huusko et al with an average total hospital length of stay of 34 days, which perhaps translate into better BI in the current study at the discharge.³³

There are a few published studies on REs and REy in Singapore. The recent study by Chen et al has REs and REy for all-cause fractures in 4 CHs in Singapore but not for hip fracture alone.¹⁷ Comparing with this study, the current study has slightly older age patients (78.9 years vs 76.2 years, respectively) and more female patients (84.3% vs 73%, respectively). The mean admission and discharge BI were better in the current study (49.1 & 65.1 vs 54.1 & 72.2, respectively). Length of stay (LOS) was also longer in current study with median LOS of 46.5 vs 33 days, respectively.

The median REs of 39% (IQR, 23.2% to 58.3%) in the current study was better than the previous study's¹⁷ median REs of 34.2% (IQR, 10.1 to 58.1) in spite of more females and older age in the current study. This may point to the fact that REs of hip fracture may be better compared to all cases of fractures combined together. But, it may also be better due to the fact that the current study's mean admission BI was much higher and had longer days of rehabilitation in CH (46.5 days vs 33 days). The current study median REy was 11.4 for 30 days compared to 14.3 for 30 days in the recent study.¹⁷ The maximum REy was seen with those who had 14 to 27 sessions of rehabilitative therapy and REy declined as the number of sessions increased. However, the REy for those who had 28 to 41 sessions showed a lesser drop (REy 0.44/day or 13.2/30 days) as compared to those who had stayed beyond 41 sessions (REy 0.29/day or 8.7/30 days).

Comparing the independent and associated predictors of REs and REy (Table 4), the current study also showed that short length stay in CH for rehabilitations and higher score in CCMI was associated with poorer outcome on REs in bivariate analysis. Older age, dementia, fewer numbers of rehabilitative therapy sessions, Malay (vs non-Malay ethnicity) and non-hypertensive patients are the independent predictors of poorer REs in our study. Previous studies^{21,22} have found that lower admission ADL scores, age above 80 years and greater comorbidity burden are independent predictors of poorer REy. In this study, the other independent

Table 4. Summary of Predictors of Poorer Rehabilitation Effectiveness and Rehabilitation Efficiency

	Factors associated with poor Rehabilitation Effectiveness (REs)	Factors associated with poor Rehabilitation Efficiency (REy)
Associated Predictors (Bivariate analysis)	1. Short length of stay 2. Dementia* 3. Fewer rehabilitative therapy sessions* 4. Malay* 5. Higher Charlson Co-Morbidity Index 6. Older age*	1. Higher admission BI score* 2. Few or too many no. of rehabilitative therapy sessions 3. Longer weight bearing to discharge 4. Non-hypertensive*
Independent Predictors (Multivariate analysis)	1. Dementia* 2. Fewer rehabilitative therapy sessions* 3. Malay* 4. Non-hypertensive† 5. Older age* 6. Non-hypertensive*†	1. Higher admission BI score*† 2. Non-hypertensive†

*Predictors common to both bivariate and multivariate analysis;

†Predictors common to both REs and REy.

BI: Barthel Score

predictors associated with poorer REy were high admission BI (REy less sensitive to change at high Barthel index) and being non-hypertensive.

Limitations

The current findings are limited to a short period of 16 months and one CH only, therefore, the results cannot be fairly extrapolated to other CHs or other inpatient rehabilitation settings. It would be good to know how the rehabilitation was with those who were discharged home or to a nursing home directly from the acute hospital as well as those who were not operated upon or unable to do at least 14 days of rehabilitative therapy at the CH. We also did not have the data regarding the nutritional status of the patients and prior rehabilitation status before the admission to the CH. Other conditions like depression and bone mineral density (not enough data in the records) would have been good to study with relation to REs and REy in the operated hip fracture patients.

Conclusion

Current study has shown that a CH stay was associated with a positive rehabilitation effectiveness and efficiency for patients after an operated hip fracture. The optimum number of rehabilitative therapy sessions was between

28 and 41 in terms of rehabilitation effectiveness. So an estimated length of stay of postoperative hip fracture patient who is weight bearing should correspond to 28 to 41 sessions of rehabilitative therapy in the CH. There is an inverted 'U-shaped' relationship between the number of rehabilitative therapy sessions with rehabilitation efficiency and the maximum efficiency seen in the 14 to 27 therapy sessions group. The independent predictors of REs and REy can be used by healthcare professionals in inpatient elderly rehabilitation settings to gauge the rehabilitation potential and speed of functional recovery in their hip fracture patients.

REFERENCES

- Wolinsky FD, Fitzgerald JF, Stump TE. The effect of hip fracture on mortality, hospitalization and functional status: a prospective study. *Am J Public Health* 1997;87:398-403.
- Siu AL, Penrod JD, Boockvar KS, Koval K, Strauss E, Morrison RS. Early ambulation after hip fracture: effects on function and mortality. *Arch Intern Med* 2006;166:766-71.
- Koh GC, Tai BC, Ang LW, Heng D, Yuan JM, Koh WP. All-cause and cause-specific mortality after hip fracture among Chinese women and men: The Singapore Chinese Health Study. *Osteoporos Int* 2013;24:1981-9.
- Huddleston JM, Whitford KJ. Medical care of elderly patients with hip fractures. *Mayo Clin Proc* 2001;76:295-8.
- Lee AY, Chua BS, Howe TS. One-year outcome of hip fracture patients admitted to a Singapore hospital: quality of life post-treatment. *Singapore Med J* 2007;48:996-9.
- Halbert J, Crotty M, Whitehead C, Cameron I, Kurrle S, Graham S, et al. Hip Fracture Rehabilitation Trial Collaborative Group. Multi-disciplinary rehabilitation after hip fracture is associated with improved outcome: A systematic review. *J Rehabil Med* 2007;39:507-12.
- Chudyk AM, Jutai JW, Petrella RJ, Speechley M. Systematic review of hip fracture rehabilitation practices in the elderly. *Arch Phys Med Rehabil* 2009;90:246-62.
- Morrison RS, Chassin MR, Siu AL. The medical consultant's role in caring for patients with hip fracture. *Ann Intern Med* 1998;128:1010-20.
- Guccione AA, Fageron TL, Anderson JJ. Regaining functional independence in the acute care setting following hip fracture. *Phys Ther* 1996;76:818-26.
- Brummel-smith K. Rehabilitation. In: Cassel CK, editor. *Geriatric Medicine: an evidence-based approach*. 4th ed. New York: Springer; 2003:259-76.
- Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol* 1989;42:703-9.
- Elderly and Continuing Care Division, Ministry of Health, Singapore. *Healthcare Services for the Elderly. An information booklet for healthcare professionals*. Singapore: Ministry of Health, 2004.
- Clarke A. Why are we trying to reduce length of stay? Evaluation of the costs and benefits of reducing time in hospital must start from the objectives that govern change. *Qual Health Care* 1996;5:172-9.
- Clarke A, Rosen R. Length of stay. How short should hospital care be? *Eur J Public Health* 2001;11:166-70.
- Larsen K, Hansen TB, Thomsen PB, Christiansen T, Søballe K. Cost-effectiveness of accelerated perioperative care and rehabilitation after total hip and knee arthroplasty. *J Bone Joint Surg Am* 2009;91:761-72.
- Shah S, Vanclay F, Cooper B. Efficiency, effectiveness, and duration of stroke rehabilitation. *Stroke* 1990;21:241-6.
- Chen C, Koh GC, Naidoo N, Cheong A, Fong NP, Tan YV, et al. Trends in length of stay, functional outcomes, and discharge destination stratified by disease type for inpatient rehabilitation in Singapore community hospitals from 1996 to 2005. *Arch Phys Med Rehabil* 2013;94:1342-51.
- Koh GC, Chen C, Cheong A, Choo TB, Pui CK, Phoon FN, et al. Trade-offs between effectiveness and efficiency in stroke rehabilitation. *Int J Stroke* 2012;7:606-14.
- Heinemann A, Roth EJ, Cichowski K, Betts HB. Multivariate analysis of improvement and outcome following stroke rehabilitation. *Arch Neurol* 1987;44:1167-72.
- Lin JH, Chang CM, Liu CK, Huang MH, Lin YT. Efficiency and effectiveness of stroke rehabilitation after first stroke. *J Formos Med Assoc* 2000;99:483-90.
- Patrick L, Knoefel F, Gaskowski P, Rexroth D. Medical comorbidity and rehabilitation efficiency in geriatric inpatients. *J Am Geriatr Soc* 2001;49:1471-7.
- Yu F, Richmond T. Factors affecting outpatient rehabilitation outcomes in elders. *J Nurs Scholarsh* 2005;37:229-36.
- Lin JH. Influence of admission functional status on functional gain and efficiency of rehabilitation in first time stroke patients. *Kaohsiung J Med Sci* 2001;17:312-8.
- Lin JH, Hsiao SF, Liu CK, Lin YT. Rehabilitation fees, length of stay and efficiency for hospitalized stroke patients: a preliminary study based on function-related groups. *Kaohsiung J Med Sci* 2001;17:475-83.
- Kortebein P, Bopp MM, Granger CV, Sullivan DH. Outcomes of inpatient rehabilitation for older adults with debility. *Am J Phys Med Rehabil* 2008;87:118-25.
- Yu F, Evans LK, Sullivan-Marx EM. Functional outcomes for older adults with cognitive impairment in a comprehensive outpatient rehabilitation facility. *J Am Geriatr Soc* 2005;53:1599-606.
- Heruti RJ, Lusky A, Barell V, Ohry A, Adunsky A. Cognitive status at admission: does it affect the rehabilitation outcome of elderly patients with hip fracture? *Arch Phys Med Rehabil* 1999;80:432-6.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic co-morbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;40:373-83.
- De Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: A critical review of available methods. *J Clin Epidemiol* 2003;56:221-9.
- Shyu YIL, Liang J, Wu CC, Su JY, Cheng HS, Chou SW, et al. A pilot investigation of the short-term effects of an interdisciplinary intervention program on elderly patients with hip fracture in Taiwan. *J Am Geriatr Soc* 2005;53:811-8.
- Wong MK, Arjandas, Ching LK, Lim SL, Lo NN. Osteoporotic hip fractures in Singapore-costs and patient's outcome. *Ann Acad Med Singapore* 2002;31:3-7.
- Dubljanin-Raspopović E, Marković-Denić L, Marinković J, Nedeljković U, Bumbaširević M. Does early functional outcome predict 1-year mortality in elderly patients with hip fracture? *Clin Orthop Relat Res* 2013;471:2703-10.
- Huusko TM, Karppi P, Avikainen V, Kautiainen H, Sulkava R. Intensive geriatric rehabilitation of hip fracture patients. A randomized, controlled trial. *Acta Orthop Scand* 2002;73:425-31.

The Relationship Between Gamma-Glutamyltransferase (GGT), Bilirubin (Bil) and Small Dense Low-Density Lipoprotein (sdLDL) in Asymptomatic Subjects Attending a Clinic for Screening Dyslipidaemias

Kazuhiko Kotani, ^{1,2}MD, PhD, Kokoro Tsuzaki, ¹BSc, Naoki Sakane, ¹MD, PhD

Abstract

Introduction: Gamma-glutamyltransferase (GGT), bilirubin (Bil) and small dense low-density lipoprotein (sdLDL) particles are each known to be risk markers for cardiometabolic diseases which are characterised by oxidative stress conditions. These markers are connected with the oxidative milieu; however, the association between GGT, Bil, and sdLDL has been hardly examined. This hospital-based study investigated the association between GGT and sdLDL, as well as the association between Bil and sdLDL, in asymptomatic subjects. **Materials and Methods:** Cardiometabolic variables, GGT, Bil and the mean LDL particle size were measured in 100 asymptomatic subjects attending a clinic for screening dyslipidaemias (36 men and 64 women, mean age 64 years). Correlation analyses of the association between the mean LDL particle size and other variables, such as GGT and Bil, were performed. **Results:** The mean (standard deviation) levels of GGT, Bil, and the mean LDL particle size were found to be 21.7 (8.3) IU/L, 14.0 (4.3) μ mol/L, and 26.7 (0.6) nm, respectively. An univariate correlation test showed both a significant inverse correlation between the mean LDL particle size and GGT ($r = -0.33$, $P < 0.01$) and a significant positive correlation between the mean LDL particle size and Bil ($r = 0.32$, $P < 0.01$). A multiple regression analysis revealed similarly significant results of their correlations, independent of the other cardiometabolic variables. **Conclusion:** These results suggest that the correlation of GGT and sdLDL, as well as that of Bil and sdLDL, may be cooperatively associated with cardiometabolic processes. Further research is warranted in order to confirm the observed association.

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Key words: Atherosclerosis, LDL particle size, Oxidative stress, γ GT, Total bilirubin

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Introduction

Oxidative stress, which is caused by an oxidant-antioxidant imbalance, is an emerging risk factor for the development of cardiovascular disease (CVD), a crucial health problem in Western countries, Asia and other developing countries.¹ Therefore, understanding oxidative stress conditions and developing a therapeutic approach to limit the effects of oxidative stress are crucial for the prevention of CVD.^{2,3} Recently, 2 serum markers, gamma-glutamyltransferase (GGT) and bilirubin (Bil), which are reflective of hepatic function in general, have been recognised as oxidative stress and antioxidative markers.⁴⁻¹⁰ In fact, GGT and Bil levels are shown to be associated with the development of cardiometabolic diseases,⁴⁻¹⁰ while the underlying mechanisms of the association between GGT and CVD,

as well as the underlying mechanisms of the association between Bil and CVD, are not yet sufficiently established.

The presence of small, dense low-density lipoprotein (sdLDL) particles, which exhibit both a small LDL particle size and a greater susceptibility to oxidation, in the blood is considered to be a risk marker of CVD.^{11,12} We have noted that subjects with insulin resistance and metabolic syndrome (oxidative stress conditions that are often concomitantly accompanied by hepatic dysfunction) display an atherogenic lipoprotein profile that includes the presence of sdLDL particles.¹³⁻¹⁵ Subjects with metabolic syndrome can have high GGT levels and low Bil levels.^{6,7,10} Circulating GGT is also thought to bind to lipoproteins, including LDL particles.⁷ In addition, a few studies indicate that the blood

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work of subjects with Gilbert's syndrome (having a total Bil level $>34.2 \mu\text{mol/L}$ ⁶) displays fewer sdLDL particles and shows an inverse correlation between Bil and sdLDL.^{16,17}

The associations among GGT, Bil, and sdLDL may explain a possible link between these markers and CVD; however, these associations have yet to be examined. Given this background, the present study is intended to investigate the association between GGT and sdLDL, as well as the association between Bil and sdLDL, in asymptomatic subjects.

Materials and Methods

A total of 100 asymptomatic subjects attending a clinic for screening dyslipidaemias (36 men and 64 women with a mean age of 64 years) were enrolled in this hospital-based study. The inclusion criteria were as follows: subjects who were non-smokers, abstainers from alcohol, and subjects who were not taking any medications. The exclusion criteria excluded subjects who were pregnant, subjects with acute infections, subjects with a history of diabetes and subjects with a history of cardio/cerebrovascular, thyroid, collagen, severe kidney, or viral liver disease. Subjects with serum levels of alanine transaminase and aspartate transaminase $<39 \text{ IU/L}$ and GGT $<40 \text{ IU/L}$ were recruited in consideration of an approximate upper limit of their reference values, based on the pertinent literature and our experience.^{7,18} The clinical characteristics of the studied subjects are listed in Table 1. The study was approved by the institutional ethics committee and all subjects gave their informed consent.

Both the systolic blood pressure (SBP) and the diastolic

blood pressure (DBP) were measured on the subject's right arm using a sphygmomanometer while the subject was in a seated position and after the subject had rested for 5 minutes. The body mass index (BMI) was calculated as the weight divided by the square of the height while wearing light clothes. Blood was sampled after a 10-hour overnight fast. The subjects' plasma glucose levels and serum lipid panels, including LDL-cholesterol (LDL-C), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), were measured enzymatically (reagents: Kyowa Medex Co. Ltd., Tokyo, Japan). Bil (reagent: Kainos Laboratory Inc., Tokyo, Japan) and GGT (reagent: Kyowa Medex Co. Ltd., Tokyo, Japan) were both measured with enzyme methods that were implemented in an autoanalyser (AU5800 system; Beckman Coulter Co. Ltd., Tokyo, Japan). The intra- and inter-assay coefficients of variation (CV) were found to be 1.0% and 1.0% in Bil and 1.2% and 1.1% in GGT, respectively. The mean LDL particle size was measured using a high-resolution, non-gradient polyacrylamide gel electrophoresis system (Lipoprint system; Quantimetrix, Redondo Beach, CA, USA)¹⁹ that was validated using the gold standard method of nuclear magnetic resonance spectroscopy. After the serum samples (25 μL) were photopolymerised, the samples and loading gels were briefly applied to gel tubes and then electrophoresed. The scanning system then calculated the mean LDL particle size based on the fractionalisation of the lipoproteins.¹⁹

The data are expressed as either the mean $\pm$ standard deviation or the median plus interquartile ranges. A Pearson's correlation test with a simple univariate analysis and a multiple regression analysis that was adjusted for all of the measured variables were utilised to observe the correlation between the mean LDL particle size and the other atherosclerotic risk variables, including GGT and Bil. Only the SBP was entered into the multiple regression analysis as a result of a close colineality of the SBP and the DBP. The TG values were log-transformed for all of the analyses because of their skewed distribution. A *P* value of <0.05 was considered to be statistically significant.

Results

The correlations between the mean LDL particle size and the other atherosclerotic risk variables, such as GGT and Bil, are listed in Table 2. A univariate correlation test showed that the mean LDL particle size was significantly and positively correlated with both HDL-C and Bil, while the mean LDL particle size was significantly and inversely correlated with age, BMI, SBP, TG, glucose and GGT.

A subsequent multiple regression analysis revealed both an independent, significant, and inverse correlation between the mean LDL particle size and GGT and an independent, significant, and positive correlation between the mean LDL

Table 1. Clinical Characteristics of Study Subjects

Variables	Levels*
Age, years	59 $\pm$ 11
Men/women, number	36/64
Body mass index, kg/m^2	23.1 $\pm$ 3.1
Systolic blood pressure, mmHg	135 $\pm$ 20
Diastolic blood pressure, mmHg	77 $\pm$ 10
LDL-cholesterol, mmol/L	4.28 $\pm$ 0.91
HDL-cholesterol, mmol/L	1.76 $\pm$ 0.50
Triglycerides, mmol/L	1.20 (0.84 – 1.73)
Plasma glucose, mmol/L	5.97 $\pm$ 1.57
Mean LDL particle size, nm	26.7 $\pm$ 0.6
GGT, IU/L	21.7 $\pm$ 8.3
Bilirubin, $\mu\text{mol/L}$	14.0 $\pm$ 4.3

GGT: Gamma-glutamyltransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein

*Values are expressed as the mean $\pm$ standard deviation, median (interquartile range) or number

Table 2. Correlation of the Mean LDL Particle Size (Outcome Variable) with Other Atherosclerotic Risk Variables, such as GGT and Bilirubin

Variables	r (P value)*	For GGT	For Bilirubin
		β (P value)*	β (P value)*
Age, years	– 0.22 (0.03)†	– 0.12 (0.19)	– 0.08 (0.34)
Gender, male	– 0.14 (0.17)	0.12 (0.19)	0.09 (0.32)
Body mass index, kg/m ²	– 0.42 (<0.01)‡	– 0.08 (0.37)	– 0.10 (0.29)
Systolic blood pressure, mmHg	– 0.28 (<0.01)‡	– 0.04 (0.65)	– 0.04 (0.67)
Diastolic blood pressure, mmHg	– 0.19 (0.07)	–	–
LDL-cholesterol, mmol/L	– 0.03 (0.77)	– 0.11 (0.17)	– 0.11 (0.19)
HDL-cholesterol, mmol/L	0.41 (<0.01)‡	0.24 (0.01)†	0.21 (0.03)†
Triglycerides, mmol/L	– 0.64 (<0.01)‡	– 0.43 (<0.01)‡	– 0.44 (<0.01)‡
Plasma glucose, mmol/L	– 0.27 (<0.01)‡	– 0.12 (0.18)	– 0.13 (0.13)
GGT, IU/L	– 0.33 (<0.01)‡	– 0.17 (0.048)†	–
Bilirubin, μ mol/L	0.32 (<0.01)‡	–	0.15 (0.049)†

GGT: Gamma-glutamyltransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein

*Values are expressed as r (Pearson's correlation coefficient) and β (coefficient by multiple regression analysis, adjusted for age, gender, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides and glucose).

†P < 0.05

‡P < 0.01

particle size and Bil. In addition, both an independent, significant, and inverse correlation between the mean LDL particle size and TG and an independent, significant, and positive correlation between the mean LDL particle size and HDL-C were commonly seen in the multiple regression analyses that were done to examine the correlation between the LDL particle size and GGT or Bil.

Discussion

This study showed that, in asymptomatic subjects, GGT was independently, significantly and inversely correlated with the mean LDL particle size, while Bil was independently, significantly and positively correlated with the mean LDL particle size. A significant correlation between sdLDL and TG or HDL-C is an expected result, based on the prior literature.^{11,12} The findings of a significant association between GGT, Bil and the mean LDL particle size suggest that GGT and sdLDL, as well as Bil and sdLDL, may be cooperatively involved in atherogenesis. While the clinical relevance of these findings should be further confirmed with future studies, our present findings of significant relationships of GGT and Bil with sdLDL may provide new insights into the association between GGT and CVD, as well as the association between Bil and CVD. As a result, these findings are meaningful as both GGT and Bil are recently attractive markers of CVD that are measurable in daily practice, as well as the underlying mechanisms of the association between GGT and Bil on incident CVD remain to be explored.⁴⁻¹⁰ In addition, the result of an inverse correlation between Bil and sdLDL appears to be similar to findings in subjects with Gilbert's

syndrome (who differ from our study population).^{16,17} Thus, of note, our present study will extend the knowledge currently available regarding Bil and sdLDL.

Although we do not fully know whether GGT is an innocent bystander or a causal contributor to the development of CVD,⁷ we do know that GGT participates in glutathione metabolism and in the extracellular degradation of the antioxidant glutathione GSH, thereby triggering a pro-oxidant action.⁷ Bil is the major product of heme metabolism and plays a role in cellular protection by scavenging for peroxyl radicals (this antioxidant capacity is attributable to any of the Bil forms).⁴ GGT (having an oxidative property) and Bil (having an antioxidant property) are both inversely associated with oxidative stress conditions.⁷ Oxidative stress can potentially induce regional and/or systemic insulin resistance,²⁰ while insulin resistance can also induce oxidative stress.²¹ Oxidative stress and insulin resistance are associated with the overproduction of VLDL in the liver and the bloodstream, thereby producing sdLDL (in part by modulating the activities of lipoprotein lipase and hepatic lipase).¹¹⁻¹⁵ Existing sdLDL can be involved in vascular atherogenesis, which causes further oxidative stress in the atherosclerotic lesions.^{11,12} Subsequently, GGT and Bil may also respond to the oxidative stress states. Thus, these interrelationships highlight a vicious cycle of the oxidative milieu that may partly explain the results of our present study.

The limitations of this study included a small sample size and a cross-sectional design. Our study setting (i.e. hospital-based screening for specific conditions such as dyslipidaemias) might restrict generalisation of the results.

In addition, data on CVD-related outcomes were not available. These issues must be addressed in future studies in order to generalise the results of this study.

Conclusion

In conclusion, among asymptomatic subjects attending a clinic for screening dyslipidaemias, the mean LDL particle size was both independently, significantly, and inversely correlated with GGT and independently, significantly, and positively correlated with Bil. This suggests that GGT and sdLDL, as well as Bil, may be cooperatively involved in atherogenesis. Further research is needed to confirm these findings.

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REFERENCES

1. Moe KT, Wong P. Current trends in diagnostic biomarkers of acute coronary syndrome. *Ann Acad Med Singapore* 2010;39:210-5.
2. Galassetti PR, Nemet D, Pescatello A, Rose-Gottron C, Larson J, Cooper DM. Exercise, caloric restriction, and systemic oxidative stress. *J Invest Med* 2006;54:67-75.
3. Sugamura K, Keaney JF Jr. Reactive oxygen species in cardiovascular disease. *Free Radic Biol Med* 2011;51:978-92.
4. Mayer M. Association of serum bilirubin concentration with risk of coronary artery disease. *Clin Chem* 2000;46:1723-7.
5. Kazemi-Shirazi L, Endler G, Winkler S, Schickbauer T, Wagner O, Marsik C. Gamma glutamyltransferase and long-term survival: is it just the liver? *Clin Chem* 2007;53:940-6.
6. Lin LY, Kuo HK, Hwang JJ, Lai LP, Chiang FT, Tseng CD, et al. Serum bilirubin is inversely associated with insulin resistance and metabolic syndrome among children and adolescents. *Atherosclerosis* 2009;203:563-8.
7. Giral P, Ratzu V, Couvert P, Carrié A, Kontush A, Girerd X, et al. Plasma bilirubin and gamma-glutamyltransferase activity are inversely related in dyslipidemic subjects with metabolic syndrome: relevance to oxidative stress. *Atherosclerosis* 2010;210:607-13.
8. Lin JP, Vitek L, Schwertner HA. Serum bilirubin and genes controlling bilirubin concentrations as biomarkers for cardiovascular disease. *Clin Chem* 2010;56:1535-43.
9. Turgut O, Tandogan I. Gamma-glutamyltransferase to determine cardiovascular risk: shifting the paradigm forward. *J Atheroscler Thromb* 2011;18:177-81.
10. Onat A, Can G, Ornek E, Çiçek G, Ayhan E, Doğan Y. Serum γ -glutamyltransferase: independent predictor of risk of diabetes, hypertension, metabolic syndrome, and coronary disease. *Obesity (Silver Spring)* 2012;20:842-8.
11. Kwiterovich PO Jr. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol* 2002;90:i30-47.
12. Rizzo M, Kotur-Stevuljevic J, Berneis K, Spinaz G, Rini GB, Jelic-Ivanovic Z, et al. Atherogenic dyslipidemia and oxidative stress: a new look. *Transl Res* 2009;153:217-23.
13. Reaven GM, Chen YD, Jeppesen J, Maheux P, Krauss RM. Insulin resistance and hyperinsulinemia in individuals with small, dense low-density lipoprotein particles. *J Clin Invest* 1993;92:141-6.
14. Howard BV. Insulin resistance and lipid metabolism. *Am J Cardiol* 1999;84:J28-32.
15. Raal FJ. Pathogenesis and management of the dyslipidemia of the metabolic syndrome. *Metab Syndr Relat Disord* 2009;7:83-8.
16. Tapan S, Karadurmus N, Dogru T, Ercin CN, Tasci I, Bilgi C, et al. Decreased small dense LDL levels in Gilbert's syndrome. *Clin Biochem* 2011;44:300-3.
17. Očadlík I, Hliněšáková S, Oravec S. Relationship between unconjugated hyperbilirubinemia and lipoprotein spectrum. *Neuro Endocrinol Lett* 2011;32:360-4.
18. Shimoyama R, Muramatsu T, Kato T, Sekiguchi S. Set-up of standard value by sex and age of biochemical tests derived from blood donors (in Japanese with English abstract). *Rinsho Byori* 1999;47:790-4.
19. Tsuzaki K, Kotani K, Fujiwara S, Sano Y, Matsuoka Y, Domichi M, et al. The Trp64Arg polymorphism of the beta3-adrenergic receptor gene is associated with increased small dense low-density lipoprotein in a rural Japanese population: the Mima study. *Metabolism* 2007;56:1689-93.
20. Ando K, Fujita T. Metabolic syndrome and oxidative stress. *Free Radic Biol Med* 2009;47:213-8.
21. Wright E Jr, Scism-Bacon JL, Glass LC. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. *Int J Clin Pract* 2006;60:308-14.

Mid-term Outcomes of Laparoscopic Versus Open Choledochal Cyst Excision in a Tertiary Paediatric Hospital

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Abstract

Introduction: Paediatric laparoscopic choledochal cyst excision has increasingly gained acceptance as an alternative to open excision. Laparoscopic excision is feasible and safe in the short term, but long-term outcomes are not as well established. KK Women's and Children's Hospital started performing laparoscopic choledochal cyst excision in children since 2007. In this paper, we report our experience with the laparoscopic approach, and the early and mid-term outcomes in comparison with the conventional open approach. **Materials and Methods:** Thirty-five consecutive cases by a single surgeon between May 2006 and April 2012 were retrospectively reviewed. Patient characteristics and surgical outcomes were analysed. **Results:** There were 13 laparoscopic and 22 open cases. Baseline patient characteristics were similar. Operative time was longer in the laparoscopic group. Three cases in the laparoscopic group were converted to open in our early experience. There were no differences in time to feeds or length of hospitalisation. One laparoscopic case developed minor bile leak that resolved on conservative management. There were no complications in the laparoscopic group on median follow-up of 35 months. In the open group, there was 1 case of pancreatitis, cholangitis, and hypertrophic scarring respectively. There were 3 cases of suspected adhesive colic that resolved without surgery. **Conclusion:** Laparoscopic choledochal cyst excision enjoys excellent early and mid-term outcomes compared to open excision, even in centres with smaller patient volume. It should be the approach of choice where technical expertise is available.

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Key words: Hepaticojejunostomy, Minimally invasive, Postoperative outcomes

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Introduction

Paediatric choledochal cyst is an uncommon benign cystic dilatation of the biliary tree, and is more prevalent in Asia than in the West. Accepted treatment consists of complete excision of the cyst with bilio-enteric reconstruction. Left untreated, choledochal cysts can lead to significant morbidity and mortality, including spontaneous rupture, pancreatitis, cholangitis, biliary cirrhosis, and an increased risk of developing cholangiocarcinoma.

With the advent of minimally invasive surgery in children, the laparoscopic approach has increasingly gained acceptance since its first description by Farelo in 1995.¹ Although laparoscopic excision of choledochal cyst is technically demanding, several authors have since reported on its feasibility and short-term safety. However, the mid-term and long-term outcomes have yet to be established.

The KK Women's and Children's Hospital is one of two tertiary paediatric hospitals in Singapore. Since 2007, we have been performing the laparoscopic procedure on children. This is the first local series of laparoscopic choledochal cyst excision reported in Singapore.

Materials and Methods

Thirty-five consecutive choledochal cyst excisions performed by a single surgeon between May 2006 and April 2012 were retrospectively reviewed. The decision between laparoscopic and open surgery was based on surgeon and parental preference. Excluded from review were 2 cases performed by another surgeon, and 2 cases performed in an emergency setting for perforated choledochal cysts.

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The data retrospectively collected from inpatient and outpatient electronic, and written medical records included patient age, gender, clinical presentation, cyst size, operative time, time to commencement of feeds, time to discharge and all postoperative complications. Cyst size was represented by maximum measured dimension on preoperative imaging, either on ultrasonography, computed tomographic scans or magnetic resonance cholangiopancreatography (MRCP).

Roux-en-Y hepatico-jejunostomy (HJ) was the preferred bilio-enteric reconstruction for all cases. Among the laparoscopic cases, an epigastric port was used for liver retraction for the first 3 cases. Subsequent operations were done via a 4-port technique, with liver retraction effected by hitch stitches on the falciform ligament and gallbladder. A combination of 3 mm and 5 mm instruments were used. Laparoscopic dissection was largely carried out with the monopolar hook. Proximally, the duct was transected just below the level of the hepatic bifurcation. Distally, the intrapancreatic portion of the cyst was followed until it tapered to the calibre of the normal common bile duct, as shown in Figure 1. This was followed by extra-corporeal transumbilical jejunostomy and intra-corporeal HJ. Open excision was performed through a right subcostal incision, with subsequent cyst excision and enteral reconstruction performed in a manner similar to the laparoscopic approach.

Postoperative management of all patients followed standard guidelines, with commencement of feeds on return of bowel function, and discharge from hospital after establishing full feeding. Follow-up was at 2 weeks post-discharge with clinical, biochemical and ultrasound

assessments, repeated at 3 months and thereafter, annually if well.

Patient characteristics and surgical outcomes were analysed using SPSS 19.0 (Chicago). Mann-Whitney U tests were used for statistical analysis. A level of $P < 0.05$ was considered to be statistically significant. The review had obtained approval by the hospital ethics board.

Results

Of the 35 cases, there were 13 laparoscopic cases and 22 open cases. The demographic data of the patients in both groups are summarised in Table 1. There were no significant differences between patients' age at the time of surgery or preoperative cyst size. One patient in each group was antenatally diagnosed and asymptomatic before surgery. All other patients were symptomatic and presented variably with recurrent abdominal pain, cholangitis, pancreatitis or obstructive jaundice. Table 2 shows details of the clinical presentations in each group.

Table 1. Patient Characteristics

	Laparoscopic (n = 13)	Open (n = 22)	P value
Median age at operation (months)	36.5	36.5	0.824
Gender ratio (Female : Male)	8 : 5	19 : 3	
Type of choledochal cyst (based on Todani Classification ¹⁴)	Type 1 (100%)	Type 1 (90.9%) Type 4 (9.09%)	
Median cyst Dimension (cm) (on preoperative imaging)	4.4 (Range, 1.7 – 15.1)	2.45 (Range, 0.7 – 10.7)	0.091

Table 2. Clinical Preoperative Presentation of Patients

Clinical Presentation	Laparoscopic (n = 13)	Open (n = 22)
Asymptomatic	1	1
Cholangitis	8	5
Obstructive jaundice	1	3
Pancreatitis	0	8
Recurrent abdominal pain	3	5



Fig. 1. Site of distal common bile duct transection beyond choledochal cyst.

Median operative time was longer in the laparoscopic group compared to the open group (536 vs 300 minutes, $P < 0.01$). There were no intraoperative complications in either group. Postoperatively, there were no significant differences in time to commencement of feeds ($P = 0.473$, Table 3), or total length of hospitalisation ($P = 0.184$, Table 3). The median follow-up period was 35 months in the laparoscopic group, and 41 months in the open group. No patient was lost to follow-up.

In the early postoperative period, a patient in the laparoscopic group developed minor bile leak. This resolved conservatively with intravenous antibiotics, and the child remained asymptomatic with normal liver biochemistry and ultrasound imaging on follow-up of 11 months. There were no early complications in the open group. On subsequent outpatient follow-up, there were no complications in the laparoscopic group. In the open group, there was 1 case of postoperative pancreatitis, 1 case of postoperative cholangitis that resolved with intravenous antibiotics, and 1 case of asymptomatic intra-hepatic biliary dilatation that resolved spontaneously after 62 months of follow-up. There was also 1 case of hypertrophic scar formation at the subcostal incision, and 3 cases of non-obstructive abdominal colic. These were possibly adhesive in nature, but did not require re-operation.

Three cases in the laparoscopic group which were performed early in our experience necessitated conversion to open surgery. Two were for bleeding due to dense adhesions from previous inflammation; and one was for difficult anatomy requiring open ductoplasty. However, a subsequent case with cyst extension into the proximal ducts requiring extensive duct reconstruction was completed laparoscopically with good early results.

Discussion

The role of laparoscopic surgery in infants and children is now widely accepted. Minimal access and lesser tissue handling accelerates recovery with reduced postoperative pain, ileus and adhesions formation. Wound complications

are reduced and cosmesis is improved.² Magnification allows improved visualisation of deep-seated anatomical structures, resulting in a decreased risk of bleeding and inadvertent injury.³ These advantages are amplified when the open surgery necessitates a sizeable incision, and when the incision is in the upper abdomen, impacting postoperative respiratory rehabilitation. These conditions apply particularly to the surgical excision of choledochal cyst, where a large muscle-dividing right subcostal incision is required to access the deep hepatic hilum for accurate anastomosis at the hepatic bifurcation.

Despite these benefits, laparoscopic excision of choledochal cyst is not widely practised. For many surgeons, it remains a technically demanding operation. The condition is rare, and bilio-enteric anastomosis demands the advanced skillset of intra-corporeal laparoscopic suturing. The notorious variability of the hepatobiliary vascular anatomy, added to the difficult surgical planes from recurrent episodes of inflammation in most patients, contribute significantly to the surgical challenge. This is particularly so in centres with lower patient volumes.

Notwithstanding these challenges, authors in small case series have demonstrated early to mid-term safety of laparoscopic choledochal cyst excision in children.⁴⁻⁹ Larger series from a few major centres in China and Vietnam (Table 4) show similar or improved long-term outcomes when compared to historical data from the open method.^{3,10-12} A key shortcoming in drawing conclusions from historical data is that factors other than the surgical approach, such as changes in perioperative practices or improved equipment, may introduce bias. Our report compares outcomes between the laparoscopic and open group performed within the same study period, with patients from both groups subject to similar perioperative practice guidelines, thus eliminating this bias. Limitations of this study are its small study population, and lack of randomisation with resultant potential selection bias. Nonetheless, both patient groups were found to be evenly matched in terms of cyst size and age—the 2 factors most likely to influence procedural difficulty and outcomes.

Table 3. Postoperative Outcomes for Laparoscopic and Open Choledochal Cyst Excision

Sample size	Hospital stay (days)	Postoperative feeding (median, days)	Overall complications (%)	Bile leak	Pancreatitis	Cholangitis	Anastomotic stenosis	Adhesive ileus or obstruction	Roux loop obstruction
Lap: 13	6 (4–25)	3 (3–4)	7.7	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Open: 22	5 (5–7)	3 (2–5)	31.8	0 (0.0%)	1 (4.5%)	1 (4.5%)	0 (0.0%)	3 (13.6%)	0 (0.0%)

Table 4. Summary of Literature Comparing Outcomes for Laparoscopic and Open Choledochal Cyst Excision

Author/ Year	Sample size	Hospital stay (mean ± SD) (days)	Postoperative feeding (mean ±SD) (days)	Overall complications (%)	Bile leak (%)	Pancreatitis (%)	Cholangitis (%)	Anastomotic stenosis (%)	Adhesive ileus or obstruction (%)	Roux loop obstruction (%)
She 2009 ¹⁰	Lap: 10			20.0		1.5	1.5	10.0	0.0	
	Open: 65	NA	NA	30.0	NA	0.0	0.0	1.5	1.5	NA
Liuming 2011 ¹¹	Lap: 39	5.5 ± 0.9	3.5 ± 0.7	20.5	2.6	0.0			0.0	2.6
	Open: 38	7.0 ± 1.4	4.9 ± 0.9	15.8	2.6	2.6	NA	NA	2.6	0.0
Diao 2011 ³	Lap: 218	7.4 ± 2.4	2.86 ± 1.23	2.7	0.9	0.0	0.0	0.0	0.0	0.9
	Open: 200	9.9 ± 3.5	3.78 ± 1.52	41.0	5.5	2.5	4.5	6.0	4.0	0.0
Liem 2011 ¹²	Lap: 309	7.0 ± 0.2	2.5 ± 0.1	3.9	2.3	0.6				
	Open: 307	9.1 ± 0.2	3.7 ± 0.1	5.5	2.0	0.0	NA	NA	NA	NA

We used time to commencement of feeds and length of hospitalisation as measures of recovery time, and showed that the laparoscopic approach was comparable to the open. Our small study population is the likely reason why we were unable to demonstrate any clear benefits, though other larger series have shown shorter recovery times in the laparoscopic group.^{3,11,12}

One patient in the laparoscopic group developed early bile leak that was minor and resolved on conservative management. Bile leak is a potentially serious complication that may necessitate re-operation or result in late strictures and its sequelae. However, reported rates of bile leak from laparoscopic series worldwide, ranging from 0.9% to 8.1%,^{3,5,7,12} compares favourably with that of 2.0% to 7.3% in the open series.^{3,11-13}

All patients in the laparoscopic group were complication-free on longer term follow-up. In contrast, 2 patients in the open group developed significant postoperative events: 1 with cholangitis and 1 with pancreatitis. Both cholangitis and pancreatitis are known complications following cyst excision. Postoperative cholangitis can be caused by bilio-enteric anastomotic strictures or the formation of intrahepatic stones, especially in Type 4a cysts with multiple intra-hepatic and extra-hepatic biliary tree dilatations.^{14,15} Pancreatitis can be due to protein plug or calculi formation obstructing the pancreatic duct. This reflects the importance of ensuring complete cyst excision, particularly the intra-pancreatic portion of the cyst.¹⁶ In this series, however, there were no biliary abnormalities on imaging surveillance to account for these occurrences. Both patients were conservatively treated and respectively remained asymptomatic for 5 to 6 years thereafter. Three patients in the open group also experienced adhesive colic, and 1 patient developed a complication directly related to the means of surgical access—a hypertrophic subcostal scar. Diao et al³ similarly reported significantly decreased

early and mid-term morbidity from anastomotic strictures, pancreatitis, cholangitis and adhesive obstruction in laparoscopic excisions. The authors attributed this to the better visualisation and improved precision of the bilio-enteric anastomosis with laparoscopy.

In our early experience, 1 case was converted to open surgery due to hepatic duct stricture and the need for ductoplasty. With increased experience, laparoscopic hilar ductoplasty was performed in a subsequent case with proximal cyst extension. Other authors have recently demonstrated that similar laparoscopic hilar ductoplasty can be performed safely for strictures near the hepatic duct confluence.¹⁷ Complex ductal anatomy need not necessitates open conversion with careful preoperative planning and meticulous technique.

Two patients in our laparoscopic series were infants, at 5 and 6 months of age. One was asymptomatic, while the other had obstructive jaundice. In both cases, operative times were shorter than the median operative times. It has been the authors' experience that in infants, surgical planes were easier. A shorter history associated with fewer prior inflammatory episodes is the likely reason. Others have similarly reported that in experienced hands, laparoscopic excision and reconstruction can be achieved even in the very young.³

One key disadvantage shown by our study was that laparoscopic excision entailed significantly longer operative times. Despite the potentially increased risks of prolonged anaesthesia and carbon dioxide pneumoperitoneum, we observed no adverse outcomes. There is a steep learning curve for choledochal cyst excisions, with some authors reporting an improvement of operative times only after the initial 30 to 35 procedures, and more recent cases with operative times not inferior to that of open surgery.³ Centres with smaller patient volumes may thus take longer to achieve equivalent operating times to the open approach. But it is

our contention that where appropriate paediatric anaesthetic support is available, meticulous operative technique should not be traded off for shorter operative times if surgical outcomes are not to be compromised.

Longer operative times in laparoscopic choledochal cyst excision have triggered a revival of interest in hepaticoduodenostomy (HD) as an alternative to HJ. Without the Roux-en-Y jejuno-jejunostomy, HD can be completed in a shorter time, whether open or laparoscopically.^{18,19} Santore et al reported shorter operative times, faster recovery and fewer complications with HD, and argued that HD was the more physiological option.¹⁸ However, the increased rates and implications of asymptomatic bile gastritis and the potential long-term carcinogenic risk of HD have yet to be ascertained.¹⁹⁻²¹ For an infant or child undergoing surgery early in life, this is an important consideration. We contend that until data concerning long-term safety of HD is available, HJ, in spite of longer operative times, remains the proven option.

Robotic surgery, with articulating arms allowing for greater dexterity to aid intracorporeal suturing, is a new frontier in minimally-invasive surgery. Several authors in scattered case series have begun exploring robotic choledochal cyst surgery in a bid to reduce operating time.²² However, its benefits will perhaps be truly realised when robotic equipment become sufficiently miniaturised for use in infants and small children, made more widely available, and more cost-friendly.

Conclusion

In conclusion, our study shows that laparoscopic surgery is feasible, safe and enjoys excellent short- and mid-term outcomes in comparison with the open technique. This is achievable even in centres with low patient volumes. Young age and complex ductal anatomy need not be deterrents with careful preoperative planning and meticulous technique.

REFERENCES

1. Fareello GA, Cerofolini A, Rebonato M, Bergamaschi G, Ferrari C, Chiappetta A. Congenital choledochal cyst: video-guided laparoscopic treatment. *Surg Laparosc Endosc* 1995;5:354-8.
2. Najmaldin A. Minimal access surgery in paediatrics. *Arch Dis Child* 1995;72:107-9.
3. Diao M, Li L, Cheng W. Laparoscopic versus Open Roux-en-Y hepatojejunostomy for children with choledochal cysts: intermediate-term follow-up results. *Surg Endosc* 2011;25:1567-73.
4. Ure BM, Nustede R, Becker H. Laparoscopic resection of congenital choledochal cyst, hepatojejunostomy, and externally made Roux-en-Y anastomosis. *J Pediatr Surg* 2005;40:728-30.
5. Nguyen Thanh L, Hien DP, Dung le A, Son TN. Laparoscopic repair of choledochal cyst: lessons learned from 190 cases. *J Pediatr Surg* 2010;45:540-4.
6. Le DM, Woo RK, Sylvester K, Krummel TM, Albanese CT. Laparoscopic resection of type 1 choledochal cysts in pediatric patients. *Surg Endosc* 2006;20:249-51.
7. Hong L, Wu Y, Yan Z, Xu M, Chu J, Chen QM. Laparoscopic surgery for choledochal cyst in children: a case review of 31 patients. *Eur J Pediatr Surg* 2008;18:67-71.
8. Liem NT, Pham HD, Dung le A, Son TN, Vu HM. Early and intermediate outcomes of laparoscopic surgery for choledochal cysts with 400 patients. *J Laparoendosc Adv Surg Tech A* 2012;22:599-603.
9. Lee KH, Tam YH, Yeung CK, Chan KW, Sihoe JD, Cheung ST, et al. Laparoscopic excision of choledochal cysts in children: an intermediate-term report. *Pediatr Surg Int* 2009;25:355-60.
10. She WH, Chung HY, Lan LC, Wong KK, Saing H, Tam PK. Management of choledochal cyst: 30 years of experience and results in a single center. *J Pediatr Surg* 2009;44:2307-11.
11. Liuming H, Hongwu Z, Gang L, Jun J, Wenying H, Wong KK, et al. The effect of laparoscopic excision vs open excision in children with choledochal cyst: a midterm follow-up study. *J Pediatr Surg* 2011;46:662-5.
12. Liem NT, Pham HD, Vu HM. Is the laparoscopic operation as safe as open operation for choledochal cyst in children? *J Laparoendosc Adv Surg Tech A* 2011;21:367-70.
13. Saing H, Han H, Chan KL, Lam W, Chan FL, Cheng W, et al. Early and late results of excision of choledochal cysts. *J Pediatr Surg* 1997;32:1563-6.
14. Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K. Congenital bile duct cysts: Classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. *Am J Surg* 1977;134:263-9.
15. Urushihara N, Fukumoto K, Fukuzawa H, Mitsunaga M, Watanabe K, Aoba T, et al. Long-term outcomes after excision of choledochal cyst in a single institution: operative procedures and late complications. *J Pediatr Surg* 2012;47:2169-74.
16. Koshinaga T, Hoshino M, Inoue M, Gotoh H, Sugito K, Ikeda T, et al. Pancreatitis complicated with dilated choledochal remnant after congenital choledochal cyst excision. *Pediatr Surg Int* 2005;21:936-8.
17. Urushihara N, Fukuzawa H, Fukumoto K, Sugiyama A, Nagae H, Watanabe K, et al. Totally laparoscopic management of choledochal cyst: Roux-en-Y jejunojejunostomy and wide hepaticojejunostomy with hilar ductoplasty. *J Laparoendosc Adv Surg Tech A* 2011;21:361-6.
18. Santore MT, Behar BJ, Blinman TA, Doolin EJ, Hedrick HL, Mattei P, et al. Hepaticoduodenostomy vs hepatojejunostomy for reconstruction after resection of choledochal cyst. *J Pediatr Surg* 2011;46:209-13.
19. Shimotakahara A, Yamataka A, Yanai T, Kobayashi H, Okazaki T, Lane GJ, et al. Roux-en-Y hepatojejunostomy or hepaticoduodenostomy for biliary reconstruction during the surgical treatment of choledochal cyst: which is better? *Pediatr Surg Int* 2005;21:5-7.
20. Maeda A, Yokoi S, Kunou T, Saeki S, Murata T, Niinomi N, et al. Bile duct cancer developing 21 years after choledochoduodenostomy. *Dig Surg* 2003;20:331-4.
21. Takada K, Hamada Y, Watanabe K, Tanano A, Tokuhara K, Kamiyama Y. Duodenogastric reflux following biliary reconstruction after excision of choledochal cyst. *Pediatr Surg Int* 2005;21:1-4.
22. Akaraviputh T, Trakarnsanga A, Suksamanapun N. Robot-assisted complete excision of choledochal cyst type I, hepatojejunostomy and extracorporeal Roux-en-y anastomosis: a case report and review literature. *World J Surg Oncol* 2010;8:87.

Younger Women with Ovulation Disorders and Unexplained Infertility Predict a Higher Success Rate in Superovulation (SO) Intrauterine Insemination (IUI)

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Abstract

Introduction: Superovulation-intrauterine insemination (SO-IUI) is the most common assisted reproductive technique (ART) in the world, with good evidence of efficacy and cost-effectiveness. However, parameters affecting its success have not been consistently reported. So in this study, we aim at determining the parameters influencing the success rate of SO-IUI. **Materials and Methods:** We conducted a retrospective cohort study of 797 SO-IUI cycles from 606 patients, performed between 2007 and 2009 in a single centre. These women received clomiphene citrate (CC), recombinant FSH (rFSH) or both. **Results:** There were 127 clinical pregnancies with a pregnancy rate (PR) of 15.9% (127/797) per treatment cycle. Factors associated with higher PR included maternal age <38 ($P = 0.02$), subfertility diagnoses of ovulatory disorders, unexplained infertility, sexual dysfunction and unilateral tubal obstruction ($P = 0.02$), an endometrial thickness ≥ 8 mm ($P = 0.03$), total number motile spermatozoa (TNMS) of ≥ 1 million ($P = 0.03$), and spermatozoa normal forms (NF) $\geq 4\%$ ($P < 0.01$) on bivariate analysis. When CC is used, the endometrial thickness is more likely to be suboptimal (<8 mm). All the above parameters remained significant except the subfertility diagnoses on multivariate analysis. **Conclusion:** Patients' selection with women <38 years old and preferably with ovulation disorders and unexplained infertility is associated with the highest PR in SO-IUI. Cycle parameters such as the use of rFSH alone, with the avoidance of CC, TNMS ≥ 1 million and NF $\geq 4\%$ is likely to result in the best outcomes and reduce the high order multiple pregnancy risk.

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Younger Women with Ovulation Disorders and Unexplained Infertility Predict a Higher Success Rate in Superovulation (SO) Intrauterine Insemination (IUI)

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Abstract

Introduction: Superovulation-intrauterine insemination (SO-IUI) is the most common assisted reproductive technique (ART) in the world, with good evidence of efficacy and cost-effectiveness. However, parameters affecting its success have not been consistently reported. So in this study, we aim at determining the parameters influencing the success rate of SO-IUI. **Materials and Methods:** We conducted a retrospective cohort study of 797 SO-IUI cycles from 606 patients, performed between 2007 and 2009 in a single centre. These women received clomiphene citrate (CC), recombinant FSH (rFSH) or both. **Results:** There were 127 clinical pregnancies with a pregnancy rate (PR) of 15.9% (127/797) per treatment cycle. Factors associated with higher PR included maternal age <38 ($P = 0.02$), subfertility diagnoses of ovulatory disorders, unexplained infertility, sexual dysfunction and unilateral tubal obstruction ($P = 0.02$), an endometrial thickness ≥ 8 mm ($P = 0.03$), total number motile spermatozoa (TNMS) of ≥ 1 million ($P = 0.03$), and spermatozoa normal forms (NF) $\geq 4\%$ ($P < 0.01$) on bivariate analysis. When CC is used, the endometrial thickness is more likely to be suboptimal (<8 mm). All the above parameters remained significant except the subfertility diagnoses on multivariate analysis. **Conclusion:** Patients' selection with women <38 years old and preferably with ovulation disorders and unexplained infertility is associated with the highest PR in SO-IUI. Cycle parameters such as the use of rFSH alone, with the avoidance of CC, TNMS ≥ 1 million and NF $\geq 4\%$ is likely to result in the best outcomes and reduce the high order multiple pregnancy risk.

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Key words: Assisted reproductive technique, Fertility, Ovulation disorder, Predictive factors

Introduction

Intrauterine insemination (IUI) with or without stimulation is the most common assisted reproductive technique (ART) in the world. Currently, IUI is widely used for treating infertility as a cheaper, simpler and less invasive method compared to in vitro fertilisation (IVF) techniques. While there is good evidence of the efficacy and cost-effectiveness of stimulated IUI (SO-IUI),¹ the pregnancy rates (PR) of an unselected infertile population following homologous SO-IUI can vary from 8.2% to 16.9%.¹⁻⁶ Accordingly, the ESHRE Capri Workshop Group attempted, to clarify the role of individual parameters such as maternal age, aetiology of infertility, the ovulation induction drug utilised,

number of preovulatory follicles available and semen parameters. However, the results were either conflicting or non-informative.⁷ Thus, we conducted a retrospective study in a cohort of Southeast Asian patients undergoing SO-IUI in our centre with the aim of examining factors that influence the PR.

Materials and Methods

This is a single centre cohort study. Out of 907 treatment cycles started between 2007 and 2009, we excluded cycles which were not stimulated, cancelled due to under- or over-

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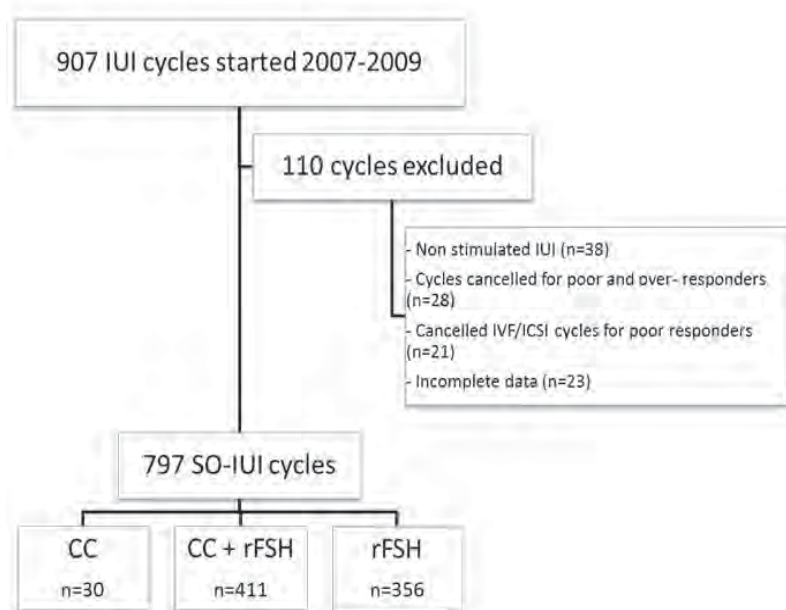


Fig. 1. Study flowchart.

response, and those where data were incomplete (Fig. 1). Only homologous cycles using patient's spermatozoa were included. The primary outcome was a clinical pregnancy, where a fetal cardiac activity is seen at 6 weeks of amenorrhea. The other parameters analysed were maternal age, aetiology of infertility, type of stimulation, number of mature follicles achieved, spermatozoa normal forms (NF) and total number of motile spermatozoa (TNMS) inseminated. This study was approved by the Institutional Review Board.

Ovarian stimulation was initiated on Day 2 of the menstrual cycle with either clomiphene citrate (CC), recombinant follicle stimulating hormone (rFSH) (Puregon, Organon, France) or a combination of CC and rFSH. CC was given at 50 mg per day from Day 2 to 6 of the menstrual cycle, while rFSH was given either from Day 7 in a mixed cycle with CC, or from Day 2 in a rFSH-alone cycle (50 to 75 IU), and the dose altered accordingly from Day 8 of stimulation.

Follicular sizes were determined by the average of the 2 maximum diameters measured by transvaginal ultrasound. Human chorionic gonadotropin (5000 units of Pregnyl, Organon, France) was administered when at least 1 mature follicle (≥ 16 mm) was achieved, followed by IUI 36 hours later in the absence of endogenous luteinizing hormone (LH) surge. When an endogenous LH surge has occurred with a mid-size follicle (14 to 16 mm), hCG was administered and the IUI performed 24 hours later. Cycles where the endogenous LH surge occurred where follicle size was < 14 mm were excluded.

Semen was processed by the swim-up method,⁸ concentrated with HTF medium (Irvine Scientific, USA) and supplemented with human serum albumin (Baxter, USA). Density and motility of the spermatozoa were assessed following WHO criteria⁸ and morphology following strict Kruger criteria.⁹ IUI was done with a Tomcat catheter (Cottman SBA, Australia). Luteal phase support through 400 mg cyclogest pessaries for 17 days post IUI were given for the rFSH-alone group only (Dumex-AlphaPharmaApS, Denmark), and clinical pregnancies determined at 6 weeks of amenorrhea.

Statistical Analysis

Bivariate association between clinical pregnancy and baseline characteristics of patients such as age, body mass index (BMI), parity, basal early follicular serum FSH and subfertility diagnosis were evaluated using the Fisher's exact test. To take into account the possible intrasubject correlation in outcome where multiple cycles were involved, the mixed effect logistic regression model was used to evaluate the effect of risk factors such as number of mature follicles ≥ 16 mm, endometrial thickness, stimulation protocol, TNMS and NF.

Significant risk factors in the bivariate analyses were further considered for inclusion in the multivariable mixed-effects logistic regression model to identify predictors of clinical pregnancy. The variable selection was made via the likelihood ratio test. All statistical analyses were generated using STATA v.12, assuming a 2-sided test at the 5% level of significance.

Results

A total of 907 cycles were started during the study period, of which 797 cycles from 606 patients were analysed after excluding non-stimulated cycles ($n = 38$), cancelled cycles from under and over-responders ($n = 28$), cancelled IVF cycles ($n = 21$), and where data was incomplete ($n = 23$) (Fig. 1). Fifty-seven percent were ethnic Chinese, 25% were Indians, 7% were Malays and 10% were composed of Caucasians and others, reflecting a typical South East Asian population (Table 1).

Seventy-two percent of the patients were aged below 35 years, 17% of them were between 35 and 38 years and 11% of them were 38 years and above. Sixty-seven percent had normal body mass index (BMI), with 24% being overweight and 9% obese. Eighty-one percent are nulligest and 96% of them have a normal ovarian reserve (Day 2/3 FSH <10 mIU/L). The most prevalent subfertility diagnoses were male factor (35%), combination of male factor and ovulatory disorder (23%), and multiple factors (21%). Seventy-two percent of patients had undergone a single cycle, 24% and

Table 1. Characteristics of 606 Patients Undergoing SO-IUI and Bivariate Analysis of Clinical Pregnancy Rates (PR) According to Patients' Characteristics

Patients' Characteristics	n	%	PR	OR (95% CI)	P value
Age (years)					0.022
<35	434	71.6	21.4	1.00	
35 to <38	105	17.3	20.0	0.92 (0.51 – 1.59)	
38 to <40	40	6.6	5.0	0.19 (0.02 – 0.77)	
≥ 40	27	4.5	7.4	0.29 (0.03 – 1.22)	
Ethnicity					0.203
Chinese	349	57.6	20.3	1.00	
Malay	40	6.6	15.0	0.69 (0.23 – 1.75)	
Indian	152	25.1	19.1	0.92 (0.55 – 1.53)	
Caucasian	5	0.8	60.0	5.87 (0.66 – 71.1)	
Others	60	9.9	15.0	0.69 (0.29 – 1.51)	
BMI (kg/m²)					0.825
<25	344	66.5	19.8	1.00	
25 to <30	125	24.2	17.6	0.87 (0.48 – 1.51)	
≥ 30	48	9.3	20.8	1.07 (0.45 – 2.32)	
Parity (live birth)					0.581
0	456	81.4	18.6	1.00	
≥ 1	104	18.6	21.2	1.17 (0.66 – 2.02)	
FSH_{D2-3} – mIU/L					0.099
<10	536	95.9	19.8	1.00	
≥ 10	23	4.1	4.3	0.18 (0.01 – 1.17)	
Subfertility diagnosis					0.021
Male factor	210	34.7	17.1	1.00	
Ovulatory disorders	44	7.3	31.8	2.26 (1.00 – 4.90)	
Male factor + Ovulatory disorders	137	22.6	19.7	1.19 (0.65 – 2.13)	
Tubal factor	8	1.3	25.0	1.61 (0.15 – 9.46)	
Ovarian failure	8	1.3	12.5	0.69 (0.01 – 5.66)	
Sexual dysfunction	6	0.99	66.7	9.67 (1.31 – 108.91)	
Unexplained	56	9.2	26.8	1.77 (0.82 – 3.68)	
Multiple factors	126	20.8	13.5	0.75 (0.38 – 1.46)	
Others	11	1.8	18.2	1.07 (0.11 – 5.51)	

Note: Bivariate analysis based on mixed effects logistic regression model

BMI: Body Mass Index

3% proceeded to 2 or more cycles respectively. A total of 127 pregnancies were achieved over 797 cycles (PR = 15.9% per cycle). In this bivariate analysis, the highest PR was achieved within the second cycle with a PR of 12.9% (78/606) compared to 9.7% (16/169) and 9.4% (2/22) respectively in cycle 1 and 3, although the results did not reach statistical significance ($P = 0.53$) possibly due to the small numbers involved (Table 2). Of the 127 patients with clinical pregnancy, 14 (11.0%) had a multiple pregnancy, of which 4 (3.1%) were high-order multiple pregnancies.

Patients younger than 35 years old have a 4-fold higher chance in conceiving compared to those 38 years or older, while ethnicity, BMI, parity and baseline FSH levels had no significant impact on PR. The bivariate analysis also showed subfertility diagnosis to be a predictive factor for clinical pregnancy ($P = 0.02$), with diagnoses of sexual dysfunction, ovulation disorder and unexplained infertility resulting in better PR compared to other diagnoses (Tables 1 and 2).

A mono-follicular response (single follicle of ≥ 16 mm diameter) was seen in 54% of cycles, while multi-follicular responses (2 follicle or ≥ 3 follicles recruited), were represented in 25% and 7% of the cycles respectively. There was a trend towards an increase in the PR with increasing number of mature follicles, from a PR of 10.3% with a single follicle ≥ 16 mm in diameter, to 15.5% for 3 or more follicles ($P = 0.3$). Even in cycles where no mature follicle was observed (14%), the PR achieved was 8.6%. In this particular group of patients contributing to 112 cycles, at least one mid-size follicle (14 to 16 mm) was observed in 91% of cycles (102/112), with a PR of 10.8% ($n = 11/102$). There were no pregnancies achieved where all follicles were < 14 mm diameter. Endometrial thickness ≥ 8 mm at the time of hCG trigger was associated with a higher PR compared with < 7 mm (OR 3.01, 95% CI 1.10 to 8.23, $P = 0.03$). An endometrial thickness of ≥ 8 mm was achieved in 3%, 41% and 56% of CC, CC+rFSH and rFSH alone groups respectively.

Table 2. Bivariate Analysis of Clinical Pregnancy Rate (PR) According to Cycle Parameters

Cycle Parameters	N Cycles	PR (%)	OR (95% CI)	P value
Number of mature follicle ≥ 16 mm				0.303
0	112	8.6	1.00	-
1	429	10.3	1.22 (0.60 – 2.51)	0.582
2	198	14.2	1.78 (0.82 – 3.86)	0.147
≥ 3	57	15.5	1.95 (0.72 – 5.32)	0.190
Endometrial thickness (mm)				0.090
< 7	84	4.2	1.00	-
7	133	9.2	2.33 (0.77 – 7.09)	0.135
≥ 8	576	11.6	3.01 (1.10 – 8.23)	0.032
Stimulation protocol				0.548
Clomid	30	6.3	1.00	-
Clomid + rFSH	411	10.3	1.71 (0.41 – 7.16)	0.460
rFSH	356	11.9	2.03 (0.48 – 8.55)	0.336
TNMS (millions)				
< 1	42	1.0	1.00	-
≥ 1	753	11.2	12.19 (1.36 – 109.54)	0.026
NF (millions) before preparation				
< 4	507	9.2	1.00	-
≥ 4	289	16.2	1.90 (1.20 – 3.00)	0.006
Number of cycles				0.527
1	606	9.7	1.00	-
2	169	12.9	1.38 (0.78 – 2.42)	0.262
≥ 3	22	9.4	0.96 (0.24 – 3.75)	0.949

Note: Bivariate analysis based on mixed effects logistic regression model.

NF: Normal forms; rFSH: Recombinant follicle stimulating hormone; TNMS: Total number motile spermatozoa

In terms of the modality of superovulation, rFSH alone yielded a higher PR of 11.9% ($n = 356$ cycles) as compared to 10.3% when combined with CC ($n = 411$) and 6.3% for CC ($n = 30$) alone, although results were not statistically significant. Of the 14 patients with multiple pregnancies, 10 received CC+rFSH ($n = 10/411$, 2.4%), while the other 4 received rFSH only ($n = 4/356$, 1.1%). All four cases of higher order multiple pregnancies occurred in the CC+rFSH group. PR was significantly higher when TNMS was ≥ 1 million (11.2% vs 1.0%, $P = 0.03$) and NF $\geq 4\%$ (16.2% vs 9.2%, $P < 0.01$).

The following variables which were significant at the 10% level in the bivariate analysis were further considered for inclusion in the multivariable mixed effect logistic regression model, taking into account the effects of potential confounders: age, subfertility diagnosis, basal early follicular serum FSH, endometrial thickness, TNMS and NF. Based on the likelihood ratio test, only age, TNMS, endometrial thickness and NF were eventually found to be important predictors of clinical pregnancy outcome (Table 3). Consistent with the bivariate analysis, the odds of clinical pregnancy were reduced for women between 38 and 40 years (adjusted OR = 0.18, 95% CI, 0.03 to 0.97, $P < 0.05$) and above 40 years (adjusted OR = 0.21, 95% CI, 0.04 to 1.18, $P = 0.076$). Conversely, endometrial thickness of at least 8 mm conferred a beneficial effect on PR (adjusted

OR = 3.13; 95% CI, 1.13 to 8.69, $P = 0.03$) as did TNMS ≥ 1 million (adjusted OR = 9.96; 95% CI, 1.07 to 92.55, $P < 0.05$) and NF $\geq 4\%$ (adjusted OR = 1.88, 95% CI, 1.13 to 3.11, $P = 0.02$). A multivariable mixed-effects logistic regression model involving age, endometrial thickness, TNMS and NF did not improve on the predictive value (AUC 0.6439).

Discussion

Over the past decade, success rates with IVF treatment has improved substantially, with live-birth rates reaching more than 30% in Europe and North America.^{1,10} In this context, the role of SO-IUI has to be redefined. In particular, the critical factors governing success rates needs to be determined to better select the group of patients who can benefit the most from it. Until now, there is only but one published study in an Asian population for IUI, but not for stimulated IUI.¹¹ Our retrospective analysis of 606 Asian couples who had undergone 797 SO-IUI cycles over a period of 3 years resulted in an overall PR of 15.9% per cycle. This is comparable to other published studies reporting PR between 8.2% and 16.9%.^{2,4-6}

In our study, the woman's age was a strong predictor of success with an almost 4-fold higher pregnancy rates achieved in women younger than 38 years old, as reported by several other groups.^{2,4,6,12-14}

The most prevalent diagnoses in our cohort were isolated male factor, a combination of male factor and ovulation disorder and multiple factors. In our study, we had 6 couples suffering from sexual dysfunction, with 4 of them conceiving (PR = 67%). Only one article from Denil and colleagues in 1996, described the outcome of SO-IUI and IVF/ICSI cycles in young adults ($n = 37$) suffering from ejaculatory disorders, where PR of 14% per IVF cycle was achieved, with no success noted with the use of SO-IUI.¹⁵ We obtained good PR with ovulation disorders and unexplained infertility (PR of 32% and 27% respectively), which is similar to the 33% PR reported by Guzick and colleagues' randomised controlled trial on SO-IUI in a population of unexplained infertility.¹⁶

We observed a trend towards an improved PR with increasing number of mature follicles, in keeping with the reports from a few other groups,^{3,5,17} although there had been other groups which did not demonstrate this correlation.¹⁸⁻²⁰ This could be due to the differences in defining the size of a mature follicle. Both Steures and Merviel have used a follicular size of ≥ 16 mm,^{2,13} while others have defined it as ≥ 18 mm.^{3,5} Although there is no definitive study on what constitutes a mature follicle, study by Gleicher et al on 3347 SO-IUI cycles concluded that the number of follicles 16 mm or larger was not significantly associated with the

Table 3. Predictors of Clinical Pregnancy Outcome

Characteristics/Cycle Parameters	Adjusted OR (95% CI)	P value
Age (years)		0.02
<35	1.00	-
35 to <38	1.07 (0.56 – 2.03)	0.834
38 to <40	0.18 (0.03 – 0.97)	0.045
≥ 40	0.21 (0.04 – 1.18)	0.076
Endometrial thickness (mm)		0.038
<7	1.00	-
7	2.25 (0.74 – 6.88)	0.155
≥ 8	3.13 (1.13 – 8.69)	0.028
TNMS (millions)		
<1	1.00	-
≥ 1	9.96 (1.07 – 92.55)	0.043
NF (millions) before preparation		
<4	1.00	-
≥ 4	1.88 (1.13 – 3.11)	0.015

Note: Multivariate mixed-effects logistic regression model
NF: Normal forms; TNMS: Total number motile spermatozoa

incidence of pregnancy neither with high-order multiple pregnancy while the total number of follicles was.²¹ This was later confirmed by Tur et al, in a large series of 1878 consecutive pregnancies demonstrating that the number of growing follicle (≥ 10 mm) on the day of hCG was a better predictor of high-order multiple implantation than the number of mature follicles.²² These studies suggest that, besides the number of mature follicles, the total number of follicles in the cohort, especially the mid-size ones, is correlated with the risk of high-order multiple pregnancies. In our cohort, pregnancies were also observed in the absence of a mature follicle, although all of them have at least one mid-sized (14 to 16 mm diameter) follicle.

In spite of similar PR in the CC-rFSH and rFSH treatment groups, we observed a 2-fold higher multiple pregnancy rates in the CC-rFSH group, with all 4 higher order pregnancies (triplets) occurring in this group. However, because of the small number of the CC group ($n = 30$), its outcome cannot be meaningfully compared to the other 2 stimulation protocols.

The probability of achieving a pregnancy for an endometrial thickness ≥ 8 mm was thrice that of those < 7 mm. We find that the addition of CC into the superovulation protocol (CC alone and CC-rFSH) had a detrimental effect on the endometrium results with an 18-fold increase in the likelihood of having an endometrial thickness (ET) ($ET < 7$ mm in 18.4% versus 0.8% in the rFSH group). This was in keeping with findings by Dickey et al in 474 SO-IUI cycles.²³

Patients with normal sperm morphologies ($NF \geq 4\%$) had a 2-fold higher PR in our cohort. This was similar to van Waart et al's meta-analysis of 6 SO-IUI studies.²⁴ However, Wainer et al failed to find a correlation between morphology and pregnancies.²⁵ This could be due to the differences in the method employed, and the evolving cut-off values over the past few decades.^{8,26-29} With respect to the TNMS, the probability of conceiving was 11-fold higher when TNMS was 1 million and above, in broad agreement with most published studies.^{4,5,30}

Conclusion

In this first study of SO-IUI in an Asian population, we have shown that SO-IUI is most effective in women < 38 years old, when the indication is sexual dysfunction, unexplained infertility, ovulation disorder, when the endometrial thickness ≥ 8 mm, when TNMS is at least 1 million and the normal morphology $\geq 4\%$. To optimise the success rate and reduce the high order multiple pregnancy risk, the use of rFSH alone, with the avoidance of CC is likely to result in the best outcomes. Furthermore, both the number of mid-size and mature follicles should be monitored closely to avoid higher order multiple pregnancies.

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REFERENCES

1. Nyboe Andersen A, Goossens V, Bhattacharya S, Ferraretti AP, Kupka MS, de Mouzon J, et al. Assisted reproductive technology and intrauterine inseminations in Europe, 2005: results generated from European registers by ESHRE: ESHRE. The European IVF Monitoring Programme (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). *Hum Reprod* 2009;24:1267-87.
2. Steures P, van der Steeg JW, Mol BW, Eijkemans MJ, van der Veen F, Habbema JD, et al. Prediction of an ongoing pregnancy after intrauterine insemination. *Fertil Steril* 2004;82:45-51.
3. Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Effect of diagnosis, age, sperm quality, and number of preovulatory follicles on the outcome of multiple cycles of clomiphene citrate-intrauterine insemination. *Fertil Steril* 2002;78:1088-95.
4. Stone BA, Vargyas JM, Ringler GE, Stein AL, Marrs RP. Determinants of the outcome of intrauterine insemination: analysis of outcomes of 9963 consecutive cycles. *Am J Obstet and Gynecol* 1999;180:1522-34.
5. Khalil MR, Rasmussen PE, Erb K, Laursen SB, Rex S, Westergaard LG. Homologous intrauterine insemination. An evaluation of prognostic factors based on a review of 2473 cycles. *Acta Obstet Scand* 2001;80:74-81.
6. Tay PY, Raj VR, Kulenthiran A, Sitizawiah O. Prognostic factors influencing pregnancy rate after stimulated intrauterine insemination. *Med J Malaysia* 2007;62:286-9.
7. The ESHRE Capri Workshop Group. Intrauterine insemination. *Hum Reprod Update* 2009;15:265-77.
8. World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 4th ed. Cambridge: Cambridge University Press;1999.
9. Kruger TF, Menkveld R, Stander FS, Lombard CJ, Van der Merwe JP, van Zyl JA, et al. Sperm morphologic features as a prognostic factor in in vitro fertilization. *Fertil Steril* 1986;46:1118-23.
10. Stern JE, Brown MB, Luke B, Wantman E, Lederman A, Missmer SA, et al. Calculating cumulative live-birth rates from linked cycles of assisted reproductive technology (ART): data from the Massachusetts SART CORS. *Fertil Steril* 2010;94:1334-40.
11. Azantee YW, Murad ZA, Roszaman R, Hayati MY, Norsina MA. Associated factors affecting the successful pregnancy rate of intrauterine insemination at International Islamic University Malaysia (IIUM) Fertility Centre. *Med J Malaysia* 2011;66:195-8.
12. Sahakyan M, Harlow BL, Hornstein MD. Influence of age, diagnosis, and cycle number on pregnancy rates with gonadotropin-induced controlled ovarian hyperstimulation and intrauterine insemination. *Fertil Steril* 1999;72:500-4.
13. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. *Fertil Steril* 2010;93:79-88.
14. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. *Hum Reprod* 1999;14:698-703.
15. Denil J, Kuczyk MA, Schultheiss D, Jibril S, Kupker W, Fischer R, et al. Use of assisted reproductive techniques for treatment of ejaculatory disorders. *Andrologia* 1996;28 Suppl 1:43-51.

16. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. *N Engl J Med* 1999;340:177-83.
17. Iberico G, Vioque J, Ariza N, Lozano JM, Roca M, Llacer J, et al. Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. *Fertil Steril* 2004;81:1308-13.
18. Goverde AJ, Lambalk CB, McDonnell J, Schats R, Homburg R, Vermeiden JP. Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: effects on pregnancy and multiple pregnancy rates. *Hum Reprod* 2005;20:3141-6.
19. van Rumste MM, Custers IM, van der Veen F, van Wely M, Evers JL, Mol BW. The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis. *Hum Reprod Update* 2008;14:563-70.
20. Gulumser C, Narvekar N, Conway G, Saridogan E, Davies M. Limiting multiple pregnancies in 4242 cycles of IUI: increase in follicle numbers increases multiple pregnancy but not clinical pregnancy rate. *Hum Reprod* 2008;23(Suppl 1):i63.
21. Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A, Karande V. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. *N Engl J Med* 2000;343:2-7.
22. Tur R, Barri PN, Coroleu B, Buxaderas R, Martinez F, Balasch J. Risk factors for high-order multiple implantation after ovarian stimulation with gonadotrophins: evidence from a large series of 1878 consecutive pregnancies in a single centre. *Hum Reprod* 2001;16:2124-9.
23. Dickey RP, Olar TT, Taylor SN, Cuore DN, Matulich EM. Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. *Fertil Steril* 1993;59:756-60.
24. Van Waart J, Kruger TF, Lombard CJ, Ombelet W. Predictive value of normal sperm morphology in intrauterine insemination (IUI): a structured literature review. *Hum Reprod Update* 2001;7:495-500.
25. Wainer R, Albert M, Dorion A, Bailly M, Bergere M, Lombroso R, et al. Influence of the number of motile spermatozoa inseminated and of their morphology on the success of intrauterine insemination. *Hum Reprod* 2004;19:2060-5.
26. Macleod J, Gold RZ. The male factor in fertility and infertility. 7. Semen quality in relation to age and sexual activity. *Fertil Steril* 1953;4:194-209.
27. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update* 2010;16:231-45.
28. Eggert-Kruse W, Schwarz H, Rohr G, Demirakca T, Tilgen W, Runnebaum B. Sperm morphology assessment using strict criteria and male fertility under in-vivo conditions of conception. *Hum Reprod* 1996;11:139-46.
29. Menkveld R, Wong WY, Lombard CJ, Wetzels AM, Thomas CM, Merkus HM, et al. Semen parameters, including WHO and strict criteria morphology, in a fertile and subfertile population: an effort towards standardization of in-vivo thresholds. *Hum Reprod* 2001;16:1165-71.
30. Ombelet W, Deblaere K, Bosmans E, Cox A, Jacobs P, Janssen M, et al. Semen quality and intrauterine insemination. *Reprod Biomed Online* 2003;7:485-92.

Advances in Bariatric and Metabolic Surgery

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Bariatric surgery is the euphemistic name for the surgical treatment of severe or morbid obesity.¹ Weight loss is induced by 2 main mechanisms. The first mechanism is restriction of the stomach, effected either by placement of a band to narrow the gastric inlet (think of a choker necklace) or by removing part of the stomach to limit its capacity. The second mechanism is reduced nutrient absorption; a gastro-intestinal bypass is created such that there is less surface area and contact time between food and intestine. These mechanisms are represented today in the 3 most widely accepted procedures—laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB).

Emerging in the post-world war II economic boom, bariatric surgery was largely unregulated and very much a fringe discipline in the early years. However, recognition of truncal obesity as a contributor to a conglomeration of risk factors leading to increased cardiovascular risk (now called the metabolic syndrome) put obesity on the radar of health authorities.² The availability of standardised operative procedures which produced significant and long-term weight loss led the National Institutes of Health (NIH) to publish guidelines on the indications for bariatric surgery in 1991.³ Several events soon converged to allow bariatric surgery to grow into an independent specialty.

The first was the advent of laparoscopy. In 1993, the first laparoscopic gastric bypass was performed by Alan Wittgrove in the USA.⁴ At the same time, the first gastric bands were placed by laparoscopy in both Europe and Australia.^{5,6} The laparoscopic approach was shown to be safer than open surgery.⁷ Hospital length of stay and major complication rates were consistently lower after laparoscopic surgery. However, there was an important caveat. Surgeons needed training in this new type of surgery to be good at it. The concept of the “learning curve” was born.⁸ It was important to acquire good skills, and spend enough time to gain adequate experience before one could operate independently with consistently good results.

The second was the recognition that obesity-related medical conditions improved dramatically after bariatric

surgery. In particular, type 2 diabetes mellitus (T2DM) appeared to be “cured” after gastric bypass up to 80% of the time.⁹ Improvement was also noted in the control of blood pressure and cholesterol. These results were momentous and provided real medical (and survival) benefit to many obese patients who otherwise had a dismal future and limited treatment options. In the USA, the national society eventually changed its name to the American Society of Metabolic and Bariatric Surgery (ASMBS) to fully describe the new spectrum of weight loss surgery.

The third was the change in obesity patterns worldwide: no more is obesity a problem of the Western world. With developing countries registering rapidly rising obesity rates, over-nutrition overtook under-nutrition in terms of health impact.¹⁰ Obesity is today well and truly a pandemic. In tandem with the rise in obesity comes the demand for its treatment. However as with all diseases, there is a wide variation in patterns of obesity and the medical implications thereof in different ethnic groups and different environments. For example, for each kilogramme of body weight, Asians have more body fat—and visceral fat in particular—compared to Caucasians.¹¹

The last but most significant transformation of recent times is that both society at large and medical professionals, who in general are rather conservative, acknowledge that obesity requires serious attention. Much debate has sprung up in the past year after the American Medical Association declared obesity to be a disease.¹² Whether the ‘disease’ label is appropriate or not, there is little doubt that leaving obesity untreated in individuals with serious obesity-related conditions such as T2DM, is tantamount to disregarding the ‘elephant in the room’. Perhaps the perceived reluctance on the part of endocrinologists and internists to address this obvious target has emboldened bariatric surgeons to enter the war on diabetes.¹³

Safety and Weight-loss Outcomes

The largest meta-analysis addressing the risks of bariatric surgery to date including 161,756 patients reported

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perioperative morbidity of 10% to 17% and 30-day mortality rates of 0.08% to 0.35%.¹⁴ Re-operation rates ranged from 3% to 12%. The lowest number of early complications, but also highest re-operation rates, were noted after LAGB. Many physicians are concerned about referring patients for bariatric surgery because of the risks involved, but analysis of data from the prospective matched cohort Swedish obese subjects study points towards a long-term reduction in overall mortality with an adjusted hazard ratio of 0.71, associated with a significant reduction in cardiovascular and cancer related deaths in the surgical cohort compared to matched obese control subjects receiving usual care.¹⁵

The multi-centre LABS-2 study group recently published detailed post-surgery weight loss outcomes up to 3 years, demonstrating a wide variation in individuals undergoing the same procedure.¹⁶ Although median weight loss at 3 years was 15.9% following LAGB and 31.5% after RYGB, closer examination of subjects' individual data points demonstrated a marked heterogeneity. The majority of subjects in the LAGB group (62%) experienced initial rapid weight loss in the first 6 months, then a gradual weight loss until 2 years, after which the curve remains rather flat. This is in contrast to 76% of RYGB subjects who experienced rapid weight loss in the first 1 year, gradual weight loss in the second year and then small weight regain between years 2 and 3. Interestingly, the Look AHEAD study which compared standard diabetes support and education with intensive lifestyle intervention (ILI) in 5145 overweight/obese adults with T2DM reported similar weight loss trajectories in the ILI arm. Mean weight loss was 4.7% at the 8-year time point, but analysis of the data revealed that 26% of the cohort did not lose any weight (and possibly gained some), whilst 27% of subjects lost more than 10% of their initial weight.¹⁷

Such a diverse spread of results might prompt one to ask the question: does the patient fail the treatment or the treatment fail the patient? The answer is not immediately obvious, but the take home message is that weight-loss interventions must be appropriately individualised or potentially be doomed from early on.

Metabolic Benefits

Earlier sensational reports regarding the reversal and cure of diabetes following bariatric surgery have been somewhat mollified by the solid evidence from several carefully designed prospective studies and randomised controlled trials. Clearly bariatric surgery is a powerful addition to the therapeutic armamentarium for T2DM. Even in poorly controlled T2DM, 42% to 75% of patients may achieve normo-glycaemia in the 12 months following gastric bypass, without any additional medical therapy.¹⁸⁻²⁰ Reduction

in (visceral?) fat mass and the consequent improvement in insulin resistance is the presently accepted rationale, although alterations in incretin hormones, bile acids and microbiota provide exciting avenues for research.

These stunning results have drawn the attention of physicians to now seriously consider a surgical option for their obese diabetic patients.²¹ On the other hand, overzealous surgeons clamouring for a surgery-first approach for "diabesity" may be putting the cart before the horse.²² The importance of eating correctly and increasing physical activity in obese individuals cannot be overemphasized. Remarkable as the improvement in glycaemic control is, a cure for T2DM is terribly elusive and such claims may be potentially misleading. A significant proportion of patients are likely to relapse in the long term,¹⁵ thereby necessitating the involvement of a diabetes physician and lifelong follow-up for all patients.

Bariatric and metabolic surgery today is in primetime. Recent data has shown clearly the benefits and dangers of this radical treatment. Much research is currently underway to delineate the weight-related and weight-independent effects of bariatric surgery. Physiological alterations induced by bariatric surgery mirror the effect of incretin-based therapies for T2DM. Perhaps in the coming years more effective drug treatments may mimic the drastic power of bariatric surgery and obviate the need to unsheathe the knife. Till then, bariatric surgery remains a vital treatment for obesity.

REFERENCES

1. DeMaria EJ. Bariatric surgery for morbid obesity. *N Engl J Med* 2007;356:2176-83.
2. Reaven G. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. *Circulation* 2002;106:286-8.
3. Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. *Am J Clin Nutr* 1992;55(2 Suppl):615S-9S.
4. Wittgrove AC, Clark GW, Tremblay LJ. Laparoscopic gastric bypass, Roux-en-Y: Preliminary report of five cases. *Obes Surg* 1994;4:353-7.
5. Favretti F, Cadiere GB, Segato G, Bruyns G, De Marchi F, Himpens J, et al. Laparoscopic adjustable silicone gastric banding: Technique and results. *Obes Surg* 1995;5:364-71.
6. O'Brien PE, MacDonald L, Anderson M, Brennan L, Brown WA. Long-term outcomes after bariatric surgery: fifteen-year follow-up of adjustable gastric banding and a systematic review of the bariatric surgical literature. *Ann Surg* 2013;257:87-94.
7. Hutter MM, Randall S, Khuri SF, Henderson WG, Abbott WM, Warshaw AL. Laparoscopic versus open gastric bypass for morbid obesity: a multicenter, prospective, risk-adjusted analysis from the National Surgical Quality Improvement Program. *Ann Surg* 2006;243:657-62.

8. Shikora SA, Kim JJ, Tarnoff ME, Raskin E, Shore R. Laparoscopic Roux-en-Y gastric bypass: results and learning curve of a high-volume academic program. *Arch Surg* 2005;140:362-7.
9. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 1995;222:339-50.
10. Prentice AM. The emerging epidemic of obesity in developing countries. *Int J Epidemiol* 2006;35:93-9.
11. Deurenberg-Yap M, Chew SK, Deurenberg P. Elevated body fat percentage and cardiovascular risks at low body mass index levels among Singaporean Chinese, Malays and Indians. *Obes Rev* 2002;3:209-15.
12. American Medical Association House of Delegates. Available at: <http://media.npr.org/documents/2013/jun/ama-resolution-obesity.pdf>. Accessed 6 March 2014.
13. Buchwald H, Scopinaro N. An invitation to our medical colleagues: Work with us. *Obesity Surgery* 2010 (20):1465-67.
14. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: An updated systematic review and meta-analysis, 2003-2012. *JAMA Surg* 2013 Dec 18. doi: 10.1001/jamasurg.2013.3654. [Epub ahead of print].
15. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al; Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683-93.
16. Courcoulas AP, Christian NJ, Belle SH, Berk PD, Flum DR, Garcia L, et al; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *JAMA* 2013;310:2416-25.
17. LookAHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: The look AHEAD study. *Obesity (Silver Spring)* 2014;22:5-13.
18. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012;366:1567-76.
19. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577-85.
20. Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet WB, Billington CJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 2013;309:2240-9.
21. Dixon JB, Zimmet P, Alberti KG, Rubino F; International Diabetes Federation Taskforce on Epidemiology and Prevention. Bariatric surgery: an IDF statement for obese Type 2 diabetes. *Diabet Med* 2011;28:628-42.
22. Brethauer SA, Aminian A, Romero-Talamás H, Batayyah E, Mackey J, Kennedy L, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. *Ann Surg* 2013;258:628-36.

Informing the Design of a Discrete Choice Experiment for Evaluating Warfarin Pharmacogenetic Testing Among Mandarin-speaking Chinese Warfarin Patients in Singapore: A Mixed Methods Analysis

Dear Editor,

Specific genetic variants have a substantial effect on warfarin dose response but warfarin pharmacogenetic testing (WPGT) is still not routine clinical practice. Apart from clinical validity, economics, social, ethical and legal implications are also important aspects in the implementation of WPGT. Several studies have revealed high interest in pharmacogenetic testing (PGT) but also concerns over privacy, confidentiality and cost.^{1,2} However, these studies were all conducted in non-Asian populations, whom may have different perceptions and attitudes towards PGT from Asians due to cultural differences. On the economic front, the cost-effectiveness of WPGT is inconclusive³ and no cost-benefit analyses, where willingness-to-pay (WTP) is used to value health benefits in monetary terms,⁴ have been done. The discrete choice experiment (DCE) methodology is an increasingly popular method not just for generating health preferences in healthcare decision-making, but also to elicit WTP.⁵ In a DCE, individuals are asked to state their preferences between alternative choice sets with each choice set defined by a number of attributes, which may include cost and efficacy in the context of WPGT. To the best of our knowledge, there has been no preference study for WPGT in any population internationally.

Although the DCE is relatively intuitive, this methodology is unfamiliar to the Asian population, especially in the field of healthcare. We hereby report the results of a developmental study aimed specifically to (i) determine the effectiveness of WPGT educational materials, (ii) identify concerns about WPGT, (iii) identify the most relevant efficacy attribute(s) for the DCE, and (iv) determine participants' ability to understand and complete the DCE.

Mandarin-speaking Chinese warfarin patients of age ≥ 21 years were recruited from the anticoagulation clinics at the National University Hospital between April to May 2011 using convenience sampling. Patients with signs of cognitive function problems, as perceived by the interviewer, were excluded. Individual voice-recorded, face-to-face interviews were conducted in Mandarin, using a semi-structured interview protocol with the aid of show cards. The interview was divided into several sections: (i) education on WPGT and post-education evaluation, (ii) selection of 1 to 2 (from 5 shortlisted) efficacy attributes important to WPGT, (iii) a trial DCE (using attributes 3 and 4 (Table 1), and cost), and (iv) post-DCE evaluation.

The ability to understand WPGT after education was assessed based on the patients' ability to explain it in their

Table 1. Combinations of Efficacy Attributes Chosen by Patients, n (%)

Most important attribute*	Second most important attribute*						Total
	1	2	3	4	5	NIL	
1	-	1 (2.3)	0	0	0	2 (4.7)	3 (7.0)
2	1 (2.3)	-	1 (2.3)	0	1 (2.3)	1 (2.3)	4 (9.3)
3	2 (4.7)	3 (7.0)	-	1 (2.3)	4 (9.3)	6 (14.0)	16 (37.2)
4	4 (9.3)	4 (9.3)	1 (2.3)	-	1 (2.3)	1 (2.3)	11 (25.6)
5	0	1 (2.3)	1 (2.3)	5 (11.6)	-	2 (4.7)	9 (20.9)
Total	7 (16.3)	9 (20.9)	3 (7.0)	6 (14.0)	6 (14.0)	12 (27.9)	43 (100)

Patients were asked to choose up to 2 attributes that they found most important. The numbers choosing the various combinations of attributes are tabulated.

*Attribute 1: Chance of having accurate starting dose; Attribute 2: Time to stable dose; Attribute 3: No. of INR (International Normalized Ratio) tests until stabilisation; Attribute 4: Risk of serious ADR (Adverse Drug Reaction) in first 3 months; Attribute 5: Risk of hospitalisation due to serious ADR in first 6 months.

own words, state at least 1 potential benefit and interviewer rating patients at least 4 points (out of 5) with regard to their understanding. The ability to understand and complete the DCE was assessed based on the post-DCE evaluation (whether any problems were encountered, ability to verbalise thought process or make comments that indicate their understanding) and the ability to complete all choice sets offered. The DCE was designed in an iterative manner, with the trial DCE introduced only after the 5th patient and administered to 44 patients with 5 using 5 choice sets and 39 using 7 choice sets.

Of 174 patients approached, 43 were ineligible, 81 refused and 50 agreed to participate, giving a response rate of 38.2%. Of those who refused participation, 47 (58%) were males. One patient was dropped due to perceived poor cognitive function, resulting in a final sample size of 49.

Overall, 65% of them were deemed able to understand the WPGT. Those who could understand WPGT were younger (mean age: 52.1 vs 64.8 years, t -test $P = 0.0029$) and more educated ($\chi^2 P = 0.007$). Those who did not know their time to stable dose also tended not to understand WPGT, compared to those who were able to state a duration ($\chi^2 P = 0.002$). Overall, 30 patients (68.2%) were able to understand the DCE, and most could handle all the choice sets presented. A large majority (93.3%) of those who could understand WPGT also understood the DCE.

Of 43 patients who completed the section on choice of efficacy attributes, number of International Normalized Ratio (INR) tests until stabilisation and risk of serious adverse drug reactions (ADR) in the first 3 months were most commonly chosen (Table 1). Three patients (6.3%) had some concerns about WPGT prior to being told the possible risks. One was concerned about what was actually tested (e.g. unintended tests) and another stated anxiety as a concern. The third patient was opposed to genetic testing but could not verbalise her exact concerns. After being shown the possible risks of WPGT, 7 patients (14.6%), including the 3 who expressed prior concerns, said they would be concerned about at least one of the risks. The most commonly cited concerns were the possibility of other disease risks being revealed from the WPGT results, and being labeled, thus affecting self-perception and causing anxiety.

This semi-qualitative study focused on targeted aspects of WPGT and DCE methodology in preparation for a larger survey. The relationship between understanding of WPGT with age and educational status, coupled with the fact that few patients offered any constructive criticisms about the show cards suggest that it was their inherent characteristics rather than inadequacy of the show cards or explanation that affected their ability to understand it. There are several limitations in this study. Firstly, sampling was non-random so generalisability of the results may be limited. Secondly,

there may be some non-response bias. Males were over-represented but since gender was not associated with any of the outcomes, this is unlikely to have biased the results. Thirdly, understanding of the DCE was based on the interviewer's perception, which may be subjective. However, interviewer bias is likely to be minimal given that explicit criteria were used and the same interviewer conducted all the interviews. Lastly, in this exercise, we assumed that patients' view alone is sufficient in the choice of DCE attributes, which is not necessarily so.

Conclusion

In conclusion, the educational materials on WPGT were effective and the DCE is feasible when accompanied with good explanation. Patients are concerned over potential WPGT risks, highlighting the need to communicate these risks clearly. Finally, the 2 most relevant efficacy attributes that should be used in the DCE were number of INR tests until stabilisation and risk of serious ADR in the first 3 months.

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REFERENCES

1. Rogausch A, Prause D, Schallenberg A, Brockmöller J, Himmel W. Patients' and physicians' perspectives on pharmacogenetic testing. *Pharmacogenomics* 2006;7:49-59.
 2. O'Daniel J, Lucas J, Deverka P, Ermentrout D, Silvey G, Lobach DF, et al. Factors influencing uptake of pharmacogenetic testing in a diverse patient population. *Public health genomics* 2010;13:48-54.
 3. Verhoef T, Redekop W, Darba J, Geitona M, Hughes D, Siebert U, et al. A systematic review of cost-effectiveness analyses of pharmacogenetic-guided dosing in treatment with coumarin derivatives. *Pharmacogenomics* 2010;11:989-1002.
 4. Brent R. Cost-benefit analysis and willingness to pay. In: Brent R, editor. *Cost-Benefit Analysis and Health Care Evaluations*. UK: Edward Elgar Publishing Limited, 2003.
 5. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. *Pharmacoeconomics* 2008;26:661-77.
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Feasibility of Endobronchial Ultrasound in Mechanically Ventilated Patients

Dear Editor,

The safety profile and diagnostic utility of endobronchial ultrasound (EBUS) for the diagnosis and staging of lung cancer,¹ centrally located tumours, unknown hilar and/or mediastinal lymphadenopathy have been well established in elective diagnostic bronchoscopy; however, their safety and utility in intensive care units (ICU) has not been described before. We have found a new utility for both linear and radial EBUS in mechanically intubated patients in the ICU with undiagnosed mediastinal lymphadenopathy and unresolved pneumonia.

Materials and Methods

Between January 2009 and December 2012, we performed 480 EBUS-transbronchial needle aspiration (TBNA) and 121 EBUS-transbronchial lung biopsies. Amongst these cases, EBUS was performed in 6 ICU patients with diagnostic dilemma. Computed tomography scanning revealed either mediastinal/ hilar lymphadenopathy or central masses adjacent to the major airways, which were subsequently targeted for needle biopsy.

All patients were intubated with an endotracheal tube of at least 7.5 mm (preferably 8 or 8.5 mm) and ventilated with assist control ventilation that was pressure targeted; positive end-expiratory pressure (PEEP) being 5 cm water. Patients were deeply sedated to a sedation agitation scale score of 3 with intravenous propofol. Morphine was used as an analgesic. Supplemental oxygen was increased to 100% prior to bronchoscopy as per our standard practice; and 5 ml of lidocaine 2% solution was also instilled via the endotracheal tube before the procedure.

EBUS-TBNA was performed for all 6 patients using a bronchoscope with an integrated linear ultrasound transducer (BF-UC260F-OL8; Olympus, Tokyo, Japan) and EU-C2000; Olympus processor. This bronchoscope has an external diameter of 6.9 mm and an oblique endoscopic view. EBUS balloon tip was utilised for all cases. A22-gauge needle was used to obtain at least 2 core specimens from each lymph node station. Core specimens were fixed in formaldehyde; needle aspirates were smeared on slides and sent in an alcohol fixative to the cytopathology laboratory. Rapid on-site cytopathology was utilised for all patients except Patient no. 3.

Additionally, transbronchial lung biopsy was performed in 2 patients (Patients 1 and 2). Radial EBUS probe (MAJ-935; with 20 MHz radial probe UM-S20-20R; Olympus, Tokyo, Japan) was passed through the working channel of a standard flexible bronchoscope to identify lesions. A guide sheath was used so that once the lesion was identified, the radial probe could be replaced with forceps to biopsy the visualised region. A chest radiograph was performed after the procedure to exclude any iatrogenic pneumothorax.

Results

Patient Characteristics

The median age of the 6 patients was 71.0 years. Three patients (Patients 1 to 3) presented with hypoxic respiratory failure and radiological suggestion of severe community acquired pneumonia (CAP). There was no response to standard antibiotic therapy, and all microbiological cultures including bronchoalveolar lavage were unyielding. They were subsequently diagnosed to have advanced lung cancer (2 adenocarcinoma and 1 poorly differentiated carcinoma). Two patients (Patients 4 and 5) presented with hypercapnic respiratory failure with obstructions in tracheal and right upper lobe and diagnoses of small cell lung cancer and anaplastic large cell lymphoma were made. Patient no. 6 presented with large right upper lobe mass compressing the superior vena cava and right main pulmonary artery. Aggressive lung malignancy was suspected. She underwent 2 previous procedures which were unyielding (1st EBUS-TBNA from subcarinal lymph node revealed mainly blood and transthoracic needle aspiration of the right upper lobe mass revealed mainly inflammatory cells). Computed tomography one month later revealed increasing size of mass with new cavitation, occlusion of superior vena cava and severe narrowing of the right main pulmonary artery, right upper lobe pulmonary artery and right upper lobe bronchus. She was electively intubated for EBUS-TBNA in the ICU. EBUS-TBNA of the right upper lobe mass extending to the right paratracheal region was performed (7 passes) revealing high grade dysplasia, but no carcinoma. Right upper lobe endobronchial biopsies revealed the same finding. Microbiological samples were sent for bacteria (including modified acid fast for nocardia), mycobacteria,

Table 1. Clinical Presentation, Findings, Diagnostic Results and Outcome of Patients who Had EBUS Guided Biopsy in the ICU

Age/Gender/ Smoking history (pack-years)	Clinical Presentation	EBUS Findings (size)	EBUS Results	Clinical Outcome
1. 75/female/ Non-smoker	Severe community acquired pneumonia	EBUS-TBNA of subcarinal lymph node Radial EBUS – Right lower lobe consolidation	Adenocarcinoma histological T3N2M0 stage 3A Adenocarcinoma	Palliative care and withdrawal of ventilator support after refusal of chemotherapy
2. 70/male/ Smoker (40)	Adult respiratory distress syndrome and shock	EBUS-TBNA–of left hilar lymph node (15 mm) Radial EBUS–Right lower lobe consolidation	Adenocarcinoma histological T1N3M1 stage 4 Adenocarcinoma	Palliative care and withdrawal of ventilator support
3. 64/male/ Smoker (40)	Severe community acquired pneumonia	EBUS-TBNA of lower right paratracheal lymph node (30 mm)	Poorly differentiated carcinoma T3N2M1 stage 4	Palliative care and withdrawal of ventilator support
4. 75/male/ Smoker (40)	Stridor	EBUS-TBNA–Anterior mediastinal mass with obstruction of superior vena cava (>40 mm)	Small cell lung cancer (limited disease)	Etoposide and cisplatin chemotherapy. Extubated 2 days after EBUS
5. 43/male/ Smoker (20)	Right upper lobe collapse	Extrinsic compression of right upper lobe bronchus by lymph nodes at right lower paratracheal lymph node and subcarinal lymph node (>40 mm)	Anaplastic large cell lymphoma (ALK positive)	Chemotherapy with cyclophosphamide, vincristine, doxorubicin and prednisolone and extubated 4 days after EBUS
6. 72/female/ Non-smoker	Right upper lobe mass	EBUS-TBNA of subcarinal Lymph node EBUS-TBNA of right upper lobe/ paratracheal mass	Mainly blood Atypical squamous cells	Palliative radiotherapy and demise without definitive diagnosis

EBUS: endobronchial ultrasound; ICU: intensive care unit; EBUS-TBNA: EBUS-transbronchial needle aspiration

and fungal investigations. However, all the results were negative. Patient was extubated the next day and she received palliative radiotherapy for suspected carcinoma but passed away 3 weeks later without histological confirmation of cancer.

Outcomes

The mean duration of EBUS in the ICU was 52 min (range, 20 to 110 min). Mean number of passes was 4 (range, 2 to 7). No major complications were encountered. No increase in ventilator or sedation requirements was observed after the procedures. None of the patients developed pneumothorax. Patient 1 had bleeding after EBUS-transbronchial lung biopsy but it stopped after local instillation of ice cold saline. Diagnostic yield was 87% and a specific histological diagnosis was made in 5 cases leading to definitive treatment management decisions (Table 1).

Discussion

EBUS appears to be safe and useful in mechanically ventilated patients in the ICU. EBUS appears to add

minimally to standard bronchoscopic complications like hypoxia, bronchospasm and pneumothorax even if the patients are on positive pressure mechanical ventilation.² The advantages of EBUS are that it is a portable bedside procedure and does not involve ionising radiation. Alternatives like surgical biopsy and mediastinoscopy have risks of general anaesthesia in patients who are often physiologically compromised, especially in the ICU.³ CT-guided biopsy has a high risk of pneumothorax even in non-intubated patients, which can be catastrophic on positive pressure mechanical ventilation.⁴ Transesophageal endoscopic ultrasound (EUS)—fine needle aspiration is an alternative for patients with subcarinal lymph node involvement such as Patients 1, 5 and 6. Unfortunately, EUS cannot replace the role of EBUS if the lymph node involvements are hilar, mediastinally to the right or the tumour mass abuts the trachea anteriorly or towards the right, such as Patients 2, 3 and 4.

Some technical issues to be aware of when performing EBUS in the ICU include: (i) ensuring endotracheal tube is at least 7.5 mm, but preferably 8 to 8.5 mm for ease of introducing the linear EBUS scope (outer diameter of 6.9

mm), (ii) lowering the PEEP during the transbronchial lung biopsy to reduce risk of causing pneumothorax, and (iii) ensuring adequate oxygenation throughout the procedure. It is of great importance to also ensure that the procedure is done within the shortest time possible as these patients have marginal physiological reserves. Therefore, this requires preparation (with respect to equipments, accessories, resuscitation trolley) in advance and coordination amongst bronchoscopists, intensivists, respiratory therapists and nurses throughout the procedure. Also, the bronchoscopist needs to be experienced in performing EBUS in an elective setting before doing one on an ICU patient who is mechanically ventilated.

Conclusion

In conclusion, EBUS can play an important diagnostic role in mechanically ventilated patients in the presence of lymphadenopathy or tumour adjacent to the airway, and when standard investigations or treatment are unyielding. Although the numbers are small with inherent “selection bias”, it appears to have reasonable yield and its risks are not higher than usual bronchoscopic procedures performed in the ICU. We recommend that intensivists and pulmonologists to consider EBUS in the armamentarium of diagnostic procedures in the ICU.

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REFERENCES

1. Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. *Eur Respir J* 2009;33:1156-64.
2. Phua GC, Wahidi MM. ICU procedures of the critically ill. *Respirol* 2009;14:1092-7.
3. Annema JT, van Meerbeeck JP, Rintoul RC, Doores C, Deschepper E, Dekkers OM, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010;304:2245-52.
4. Choi JW, Park CM, Goo JM, Park YK, Sung W, Lee HJ, et al. C-arm cone-beam CT-guided percutaneous transthoracic needle biopsy of small (≤ 20 mm) lung nodules: diagnostic accuracy and complications in 161 patients. *Am J Roentgenol* 2012;199:W322-30.

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Thyroid Hormone Resistance Due to a Novel THRβ Mutation

Dear Editor,

Resistance to thyroid hormone (RTH) is a syndrome of reduced responsiveness of target tissues to thyroid hormone. Patients with thyroid hormone resistance have elevated free triiodothyronine (fT3) and/or free thyroxine (fT4) with inappropriately normal or elevated thyroid stimulating hormone (TSH). It is a diagnosis to consider in newborns presenting with abnormal thyroid function. We report a case of a 1 year 8 months old boy with RTH who had a novel mutation of the THRβ gene. This mutation is, to the best of our knowledge, the first such mutation reported in Singapore.

Case Description

Our patient is a Chinese boy who first presented with persistently elevated free T4 and TSH levels since birth. He was born at term with birth weight of 2.82 kg. There was no family history of thyroid disorders. He had persistently elevated free T4 and TSH levels since birth (Table 1). Serial dilution of the TSH in our service lab showed a linear trend, and thus it is unlikely that there are heterophile antibodies which interfered with the TSH assays. His parents' thyroid function tests were normal.

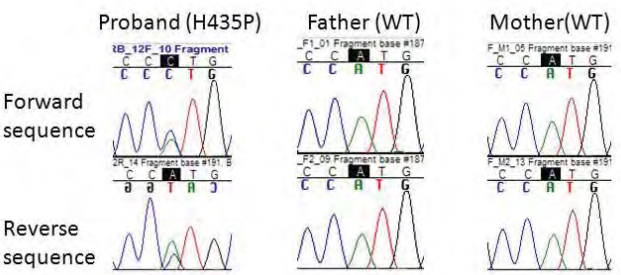


Fig. 1. Mutation analysis by direct sequencing of DNA from blood leucocytes.

The high fT4, fT3, inappropriately normal or elevated TSH, and high thyroglobulin are consistent with the diagnosis of thyroid hormone resistance. Clinically there were no overt symptoms of thyroid disorder or thyrotoxicosis. There was no goitre and pulse rate was 150 to 160/min. X-ray of the knees at 6 weeks of life showed the presence of distal femoral epiphysis which is expected to be present at birth. The proximal tibial epiphysis is also present, which normally appears at 1 to 3 months of age. Thus it is unlikely the baby has suffered significant delay in skeletal maturation in-utero due to this thyroid hormone (TH) resistance state.

Table 1. Serial Thyroid Function Related Tests at Various Time Points

Age	Birth (cord)	Day 4	Day 21	5 weeks	7 weeks	5 months
FreeT4 (pmol/L)	32.47 (12 – 22)	46.98 (19.35 – 33.41)	46.13 (19.35 – 33.41)	45.14 (14.45 – 23.99)	42.8 (10 – 23)	38.6 (10 – 23)
TSH (mIU/L)	10.04 (2 – 25)	20.598 (0.5 – 10)	10.294 (0.5 – 10)	6.561 (0.4 – 7)	5.75 (0.5 – 4)	4.1 (0.5 – 4)
T3 (nmol/L)				5.39 (1.23 – 3.48)		
FreeT3 (pmol/L)					13 (4.3 – 8.3)	
TSH Receptor Ab (IU/L)				<1 (<1.8)	1.1 (<1.8)	
Anti-TPO					<10 (0 – 50)	
Anti-TG					<20 (0 – 40)	
Thyroglobulin (g/L)					128 (0 – 110)	

The normal ranges are provided in brackets.

Direct sequencing of the thyroid hormone receptor beta gene (THR β) was performed for the proband and his parents (details available on request) using peripheral blood samples. The proband was heterozygous for a novel mutation His435Pro due to a single nucleotide substitution A>C at nucleotide 1304 which resulted in a change of histidine to proline at residue 435 (Fig. 1). The mutation likely represents a de novo mutation as it was not found in his parents, and was also not found in 50 Chinese controls.

PolyPhen-2 (polymorphism phenotyping) web service (available at <http://genetics.bwh.harvard.edu/pph2/index.shtml>) was used to predict the effect of amino acid substitution on the structure and function of THR β .¹ PolyPhen-2 predicted that the H435P mutation is probably damaging with a score of 1.000 (sensitivity 0.00, specificity 1.00).

The patient remained clinically asymptomatic despite the TH excess and did not require any treatment. At 1 year 8 months, his development and growth has been appropriate, with weight on the 25th percentile and height 50th percentile (local chart).

Discussion

RTH is a rare cause of abnormal thyroid function test. It is a syndrome of reduced responsiveness of target tissues to TH.^{2,3} It is characterised by inappropriately normal or slightly elevated serum TSH in the presence of elevated serum fT4 and fT3 levels which are present in our patient.

The precise incidence is unknown. A limited neonatal survey by measuring blood T4 concentration, suggested the occurrence of one case per 40,000 live births.^{4,5} RTH has been found with equal frequency in both genders and prevalence vary among different ethnic groups. Familiar occurrence of RTH has been documented in approximately 75% of cases, and about 20% are de novo cases.²

Humans have 2 subtypes or isoforms of thyroid receptors (TR), namely TR α and TR β .² The expression and distribution of the 2 TR subtypes vary among tissues and during different stages of development. TR α and TR β are interchangeable, but the compensation in the absence of one isoform is incomplete. Differences in the degree of hormonal resistance in different tissues are due to the relative TR β and TR α expression. Compensation for hyposensitivity to thyroid hormones varies between individuals, and also between tissues, where features of TH excess and deficiency can co-exist in the same patient. A patient can have tachycardia and hyperactivity (thyrotoxicosis), but also delayed growth, bone maturation, and learning disability (hypothyroidism). The difference in degree of TH resistance in different tissues is due to relative levels of TR α and TR β expression. The hypothalamus and pituitary gland usually express more

of and therefore are dependent on TR β , thus exhibiting features of TH deficiency when there is TR β defect. The heart is more dependent on TR α , and thus will manifest features of TH excess in the presence of high circulating TH in patients with TR β defect.

RTH can be classified into generalised, pituitary and peripheral resistance on the basis of tissue resistance. In generalised TH resistance, patients are usually clinically euthyroid with normal stature, though some may have low IQ. The euthyroid state is due to sufficient compensatory rise in TH concentration. In pituitary TH resistance, patients have features of thyrotoxicosis due to lesser TH responsiveness at the pituitary gland compared to peripheral tissues, and thus there is inappropriately high pituitary TSH secretion which results in overproduction of T4 and T3. In peripheral TH resistance, patients have features of hypothyroidism, as peripheral tissues are less sensitive to TH than the pituitary, and thus TSH is usually in the normal range.²

About 90% of RTH patients carry mutations in their TR β gene and more than 100 mutations have been reported.^{2,3} RTH is not simply the consequence of a reduced amount of functional TR but is usually caused by the interference of the mutant TR with the function of the wild type TF (dominant negative effect).⁶ The mutation we found was a new mutation which has not been described in literature in a Singaporean.

Mutations in the same codon 435 was previously reported in 2 unrelated Japanese patients with RTH.⁷ One patient with generalised TH resistance had histidine to leucine substitution (CAT→CTT) while the other patient with pituitary selective TH resistance had histidine to glutamine (CAT→CAA) substitution. Although the mutations were at the same codon, the patients had different clinical phenotype, with the first patient having generalised resistance while the second patient having pituitary-selective resistance.⁷ It is increasingly clear nowadays that the spectrum of presentation may be a continuum, and the distinction is less clear as a variable degree of resistance can be found in pituitary and peripheral tissues of the same individual.²

Characteristics of the RTH syndrome is the paucity of specific clinical manifestations.² When present, they varied from one patient to another. Presenting symptoms and signs are goitre, hyperactive behaviour, learning disabilities, developmental delay and sinus tachycardia. The majority of subjects maintain a normal metabolic state at the expense of high TH levels. As discussed earlier, this compensation for the hyposensitivity to TH is variable not only among individuals but also in different tissues.² As a consequence, evidence of TH deficiency and excess often coexist.

Fortunately, in most subjects with RTH, the partial tissue resistance to TH is adequately compensated for by an

increase in the endogenous supply of TH and thus, treatment is not required. It is important not to intervene with the sole purpose of normalising TH levels. Sinus tachycardia can be controlled with the β -adrenergic blocking agent such as atenolol. Rarely, the compensation is incomplete and requires the judicious administration of supraphysiologic doses of the hormone. Since the dose varies greatly among cases, it should be individually determined by assessing tissue responses. In children, particular attention must be paid to growth, bone maturation and mental development.^{2,3} Also, prenatal diagnosis and counselling are particularly important in families whose affected members show evidence of growth or mental retardation.

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REFERENCES

1. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. *Nat Methods* 2010;7:248-9.
2. Dumitrescu AM and Refetoff S: Reduced sensitivity to Thyroid Hormone: Defects of Transport, Metabolism and Action (Chapter 58). In Werner & Ingbar's *The Thyroid: A Fundamental and Clinical Text*. Braverman, L.E., and Cooper D.S. (eds.), Wolters Kluwer / Lippincott, Williams & Wilkins Publications, Philadelphia, PA.
3. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. *Endocr Rev* 1993;1:348-99.
4. LaFranchi SH, Snyder DB, Sesser DE, Skeels MR, Singh N, Brent GA, et al. Follow-up of newborns with elevated screening T4 concentrations. *J Pediatr* 2003;143:296-301.
5. Tajima T, Jo W, Fujikura K, Fukushi M, Fujieda K. Elevated free thyroxine levels detected by a neonatal screening system. *Pediatr Res* 2009;66:312-6.
6. Yen PM, Chin WW. Molecular mechanism of dominant negative activity by nuclear hormone receptors. *Mol Endocrinol* 1994;8:1450-4.
7. Tsukaguchi H, Yoshimasa Y, Fujimoto K, Ishii H, Yamamoto T, Yoshimasa T, et al. Three novel mutations of thyroid hormone receptor beta gene in unrelated patients with resistance to thyroid hormone: two mutations of the same codon (H435L and H435Q) produce separate subtypes of resistance. *J Clin Endocrinol Metab* 1995;80:3613-6.

Boutonniere Deformity in a Young Male

A 27-year-old Malay male sought treatment for progressive pain and deformity at the proximal interphalangeal joint of the left middle finger and a painful mass like swelling along the ventral aspect of the wrist. He was known to have episodes of joint pain in the past. On examination, there was a flexion deformity at the proximal interphalangeal joint with extension of the distal interphalangeal joint noted at the third digit of the left hand. A tender swelling was also noted along the palmar side of the wrist and midhand. Radiograph of the left hand and post contrast magnetic resonance imaging (MRI) of the left wrist have been provided. The radiograph shows the presence of Boutonniere deformity (Fig. 1.). The MRI shows the presence of enhancing mass in the carpal tunnel (Fig. 2.).



Fig. 1. Radiograph of the hand shows Boutonniere deformity at the third finger. Also, note the lack of erosions.

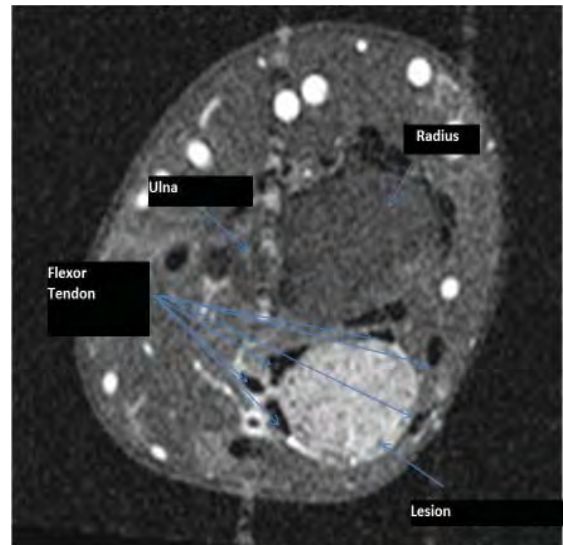


Fig. 2. Post contrast fat saturated T1 images shows heterogeneously enhancing lesion along the flexor tendons of the wrist. The median nerve cannot be seen separately from the lesion on this image.

What is the diagnosis?

- A. Neurofibroma
- B. Rheumatoid arthritis
- C. Gout
- D. Sarcoidosis
- E. Ganglion Cyst

Discussion

Gout in the hand presents as arthritis, skin ulceration, sinus formation, infection and tenosynovitis. Flexor tenosynovitis is a rare manifestation of gout in the hand. The deposits of gout can occur in various structures including flexor tendons, tendon sheaths, carpal tunnel floor, and the transverse carpal ligament and also along the median nerve. The median nerve may be directly involved or compressed by the tophaceous deposits resulting in Boutonniere deformity and carpal tunnel syndrome.¹

Answer: C

Boutonniere deformity is characterised by flexion at the proximal interphalangeal joints and extension at the distal interphalangeal joints and is commonly seen in conditions like rheumatoid arthritis and trauma and is very rare in gout.

Most cases of carpal tunnel syndrome are idiopathic. Gout is a rare cause of carpal tunnel syndrome. The most common pathomechanics is increased volume in the carpal tunnel resulting from gouty tenosynovitis, nodular tophi and gouty deposits on the median nerve as well as direct infiltration of the intrinsic muscles. The carpal tunnel syndrome can also be caused by reduced volume resulting from infiltration of the transverse carpal ligament.² In our patient, there was a focal mass in the carpal tunnel, which involved the ring finger flexor digitorum superficialis and little finger flexor digitorum profundus muscle as confirmed on surgery. Histopathology of the excised mass revealed nodular tophaceous deposits of crystalline eosinophilic material surrounded by multinucleate giant cells histiocytes and inflammatory cells. Although polarised light microscopy was not done to show negatively birefringent urate crystals, the tophaceous material suggests gout was the cause of the finger deformity. Biochemical investigations revealed elevated serum uric acid levels. Radiographs in our patient did not show the characteristic tophaceous punched out lesions in the carpal bones. No joint effusion or synovial thickening was noted.

Tophaceous deposits can be identified on MRI. The lesions are isointense to muscle on T1 weighted images. They are heterogeneously hyperintense on T2 weighted images. They may have hypointense foci within them on the T2 weighted images. The hyperintense foci may be due to proteinaceous contents. The hypointense foci are due to calcification, fibrous tissue, crystals and hemosiderin deposition or proton immobility. Heterogeneous enhancement is generally observed on the post contrast images. The diagnosis of carpal tunnel syndrome was radiologically confirmed by the compression and flattening of the median nerve, edema within the nerve and outward bowing of the flexor retinaculum. The differential diagnosis based on clinical and radiological findings include neurofibroma, other arthropathies (such as rheumatoid arthritis, haemophilic arthropathy and dialysis related arthropathy), sarcoidosis and pigmented villonodular synovitis.³

REFERENCES

1. Moore JR, Weiland AJ. Gouty tenosynovitis of the hand. *J Hand Surg Am* 1985;10:291-5.
2. Janssen T, Rayan GM. Gouty tenosynovitis and compression neuropathy of the median nerve. *Clin Orthop Relat Res* 1987;216:203-6.
3. Chen CK, Chung CB, Yeh L, Pan HB, Yang CF, Lai PH, et al. Carpal tunnel syndrome caused by tophaceous gout: CT and MR imaging features in 20 patients. *AJR Am J Roentgenol* 2000;175:655-9.

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Dr Tham Cheok Fai: “Father” of Neurosurgery (8 October 1925 – 4 December 2013)*

How His Legacy Began

Although not the first neurosurgeon in Singapore, Dr Tham is acknowledged as the “father” of Singapore neurosurgery. Dr Tham was already a Consultant Orthopaedic Surgeon at “C” Orthopaedic Unit, Singapore General Hospital (SGH), with a special interest in spinal surgery when Dr Tseng Yuen Lin, the first fully trained neurosurgeon in Singapore, passed away.

In 1962, he was sent by the Ministry of Health to train in neurosurgery under Dr Murray Falconer at Guy’s, Maudsley and King’s College Hospitals in London. He returned in 1965 to start a section in Neurosurgery at the Department of Surgery under Dr Choo Jim Eng at the Thomson Road Hospital, with only Tuesdays to do his operations.

I was posted to Thomson Road Hospital in 1972 as a houseman. Each month, one houseman would be posted to the Surgery Suite to assist consultants during operations. When my turn came on the first Tuesday, I asked Dr Tham whether I could assist him. He happily agreed.

Dr Tham was meticulous in his operations. In those days, neurosurgery was carried out on the same day following imaging with ventriculograms or cerebral angiogram. With the patient intubated under general anaesthesia, a burr-hole was made and about 20 ml of air was introduced into the lateral ventricle. We would then accompany the still-anaesthetised patient to the Radiology Suite. There, we had to lift and turn the unconscious patient over one full turn to make the air flow into the other ventricles before taking X-rays. Using the primitive equipment available then, routine operations sometimes lasted more than 12 hours. One needed patience and a strong mental and physical constitution to do neurosurgery.

In 1973, the Department of Neurosurgery and Neurology was set up at Tan Tock Seng Hospital (TTSH) as recommended by the Committee on Medical Specialisation. Dr Tham was to head the Department of Neurosurgery until his retirement. To train more neurosurgeons, he reached an agreement with Dr John Lekias and Dr Bryant Stokes of the Neurosurgery Services in Perth, Western Australia to

send trainees there to train under the Neurosurgery Training Programme of the Royal Australasian College of Surgeons.

The Patient Always Comes First

Dr Tham had a fearsome reputation as a strict disciplinarian. This was only because he cared so much for his patients. He insisted on “doing things right the first time, all the time”. He taught his doctors by example the basic requirements of surgery: Firstly, to have good clinician skills before becoming good surgeons; secondly to develop good surgical habits, and last but not least, to be humanistic and ethical. Many doctors, including myself, were inspired by him to train in neurosurgery.

Dr Tham was dedicated to his patients and would often spend more than an hour taking the history, examination and consent for operation, patiently explaining the procedure and answering all the patient’s questions. All these would be carefully documented in the case records with his beautiful cursive writing.

Valuable Foresight

At a time when Singapore doctors were looking toward Britain for their surgical training, Dr Tham was one of the first to realise the need to learn from North America. Between 1974 and 1976, he arranged with the Foundation for International Education in Neurosurgical Surgery for 12 neurosurgeons from the US and one from Canada to serve in Singapore on rotation, providing consultancy service and training young neurosurgeons. This was the start of our collaboration with North American neurosurgeons. With doctors training in both Australia and North America, the number of trained neurosurgeons in the department gradually increased.

The first dedicated Brain CT Scan in Singapore at TTSH in 1977 was also Dr Tham’s initiative. It was then the most expensive radiological equipment in Singapore, and indeed the only in the region! This was the start of the modern era of neuro-imaging in Singapore.

*This article first appeared at NeusLink (Issue 2, July-December 2013), National Neuroscience Institute.

For his excellent work, Dr Tham was awarded the Public Administration Medal (Gold). He was also honoured by the Australasian College of Surgeons and the American Association of Neurological Surgeons for his achievements.

Since those early days, the Department of Neurosurgery has grown in size and achievements, and is now acknowledged as one of the finest in the region. All these are due to him in no small measure. In the words of Isaac Newton: “If we have seen further it is by standing on the shoulders of giants.”

Dr Tham Cheok Fai has passed away and we all mourn his loss, but his legacy lives on in the department he has built up.

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