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"One thorn of experience is worth a whole wilderness of warning."

James Russell Lowell (1819 – 91)
American poet

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Editorial

Rehabilitation Medicine – The Final Frontier

Yee Sien Ng, [1]*MBBS, FRCP (Edin), FAMS*

Three stages of epidemiologic transitions have come and passed.[1] The first age of pestilence and famine was characterised by high birth rates and mortality. The advent of antibiotics heralded the second age of pandemic recession with subsequent exponential population growth. The third age of chronic, degenerative and man-made diseases was marked by the development of modern medicine, low birth rates and mortality. We now arrive at this final age. Advances in modern medicine and increasing longevity result in disability, diminished quality of life and a tremendous societal burden. The World Health Organization (WHO) reports that more than a billion people in the world face disability every day.[2] This number is more than any single disease. A fresh strategic paradigm is needed to face the enemy onslaught of disability.

Rehabilitation is the core weaponry in disability management. It enables the improvement, optimisation and maintenance of practical function across a wide range of diseases.[3] Rehabilitation medicine is the medical specialty that prescribes rehabilitation as its integral therapeutic modality.[3,4]

Overall operational plans have gradually emerged.[5] The recently developed WHO-International Classification of Functioning, Disability and Health (WHO-ICF) model provides the guiding map in the battle quagmire (Fig. 1).[2,5] It categorises the impact of disease into impairments of body structure and function, activity limitation and participation restrictions, and recognises the critical influence of environmental and personal contextual factors including self-efficacy and motivation.[2,5] The WHO-ICF also emphasises health and not merely the absence of disease or disability. It further emphasises the importance of community participation including mobility, work, leisure and interpersonal relationships to optimise function and quality of life.

Clinicians, researchers and administrators can now objectively assess outcomes and provide interventions in these domains while maintaining a clear focus of the overall rehabilitation thrust.[4] Indeed, shifts in healthcare funding from pure diagnostic-related group (DRG) casemixes to incorporate functional-related group (FRG)-based subventions recognise the additional impact and costs of disability.[6]

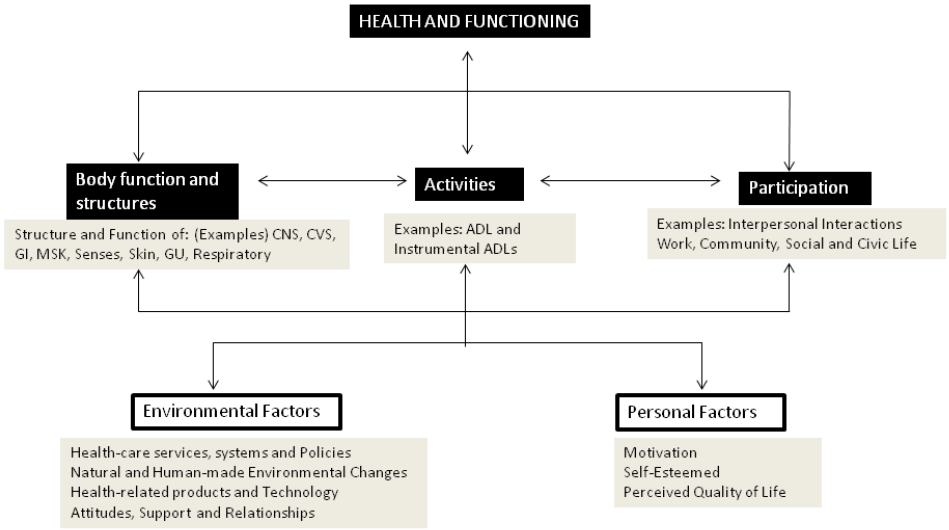

Fig. 1. The WHO-International Classification of Functioning, Disability and Health. The emphasis is on health and functioning in society, rather than impairments and disability. ADL: Activities of Daily Living; CNS: Central nervous system; CVS: Cardiovascular system; GI: Gastrointestinal; GU: Genitourinary; MSK: Musculoskeletal;

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Hippocrates' precept on medical practice to "cure sometimes, relieve often and comfort always" further translates to another important rehabilitation principle of restoration and compensation.[7] For each rehabilitation goal in the WHO-ICF domains, we aim to restitute where possible or apply compensatory strategies and provide environmental modifications when we cannot. For example, in a hemiparetic stroke, reaching tasks are achievable by strengthening the weak arm, compensating with the non-affected arm or modifying the environment by placing objects closer to the patient. The recent deployment of rehabilitation technology further illustrates this. There are training robots that aim to restore strength or walking, assistive technology (AT) such as wheelchairs and prosthetic limbs that substitute or compensate for motor impairments and public buses with automated wheelchair platforms that provide environmental modifications for community access.[3,7]

There is rapid progress in the development of rehabilitation sciences with significant increases in both the absolute volume and quality of research publications in diverse rehabilitation fields.[8] In the rehabilitation of neurological conditions, facilitating neuroplasticity through neuromodulation and sensorimotor learning has transformed contemporary practice.[9] Developments in the use of modulatory medications, constraint-induced therapy, brain-computer interfaces, non-invasive brain stimulation, virtual reality and rehabilitation robotics improve a wide variety of outcomes.[3] Musculoskeletal rehabilitation is characterised by the increasing use of objective imaging and advanced assessment tools such as ultrasound and biomechanics laboratories for rapid diagnosis and focused rehabilitation. Early comprehensive rehabilitation programmes after a major acute event have proven safe and effective in intensive care, cardiac and pulmonary rehabilitation with encouraging reductions in lengths of stay, readmissions and morbidity.[4,10] Cancer rehabilitation is a fast growing field of rehabilitation as survival rates increase, demanding specific approaches to specific impairments such as weakness, fatigue and cancer-related pain.[11] Paediatric rehabilitation is a significant need and practitioners require a broad knowledge of genetic, congenital and childhood diseases and disability, and interventions accounting for ongoing physiological and social development.[12] Geriatric rehabilitation has assumed national importance in developed countries with ageing populations and demonstrates yet another paradigm shift in rehabilitation. It emphasises community screening for the frail elderly and delivering pre-habilitation through a core exercise programme in otherwise healthy elders prior to the onset of disability.[13]

Systems of rehabilitation care have also concurrently developed.[3,4] These include the initiation of national rehabilitation databases to optimise limited resources and integrated pathways incorporating rehabilitation in common diseases. The early delivery of rehabilitation in intensive care units, early supported discharge programmes, regional health systems integrating acute and rehabilitation (community) hospitals, streamlining of outpatient rehabilitation and rehabilitation in nursing homes address increasing demands and raise rehabilitation standards.[3,10,14] Community rehabilitation including return to work, psychosocial support programmes and innovations such as remote telerehabilitation are important and continue to be developed.[11,15] An unfilled gap is the need for adolescent rehabilitation to manage yawning chasms in the transitions from childhood to young adulthood for congenital, developmental and acquired chronic disabilities. These need to be seamlessly and actively managed in order to allow the fulfillment of maximal functional and societal potentials where possible, and reduction of parental and sibling burdens.[12]

The battle requires not individuals, but a cohesive fighting force. There is an urgent need to train not just more rehabilitation clinicians to meet increasing demand for rehabilitation services but also to teach principles of rehabilitation to all healthcare clinicians. Competent functional assessments should be in the armamentarium of all physicians and transdisciplinary care models the norm in integrated rehabilitation.[4,5] High quality research is needed to identify promising interventions and to improve rehabilitation services delivery. Further, the army needs champions and rehabilitation medicine leaders are well poised to advocate for the frail and disabled in our society by prescribing rehabilitation to improve function, quality of life and health.

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Original Article

Transarterial Infusion Chemotherapy With and Without Embolisation in Hepatocellular Carcinoma Patients: A Systematic Review and Meta-Analysis

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Abstract

Introduction: The purpose of this meta-analysis was to compare the efficacy of transarterial chemoembolisation (TACE) and iodised oil infusion chemotherapy without embolisation (TAI) in patients with hepatocellular carcinoma. Materials and Methods: We searched for randomised controlled trials, retrospective cohort studies, and two-arm prospective studies that compared the clinical outcomes in patients who received TACE and TAI treatment. Database search was performed through 14 December 2016. Rates of survival and therapy response were compared using odds ratios (OR) with 95% confidence intervals (CI). Results: Survival rates and therapy response rates were similar between patients who received TACE and TAI treatments (pooled OR: 1.278; 95% CI , 0.783 to 2.086, *P* = 0.327; and pooled OR: 1.502; 95% CI, 0.930 to 2.426, *P* = 0.096, respectively). Conclusion: Our results suggest that treatment intensification by adding embolisation did not increase overall survival and therapy response over TAI in patients with hepatocellular carcinoma.

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Key words: Liver cancer, Liver disease, Transarterial chemoembolisation

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of malignant disease worldwide, with an increasing prevalence in industrialised countries.[1] Overall, the prognosis is very poor, and HCC is the second most common cause of death from cancer, with mortality closely matching incidence.[2] Curative therapies, such as liver resection, liver transplantation and percutaneous ablation (percutaneous ethanol injection and radio frequency ablation) are effective and lead to 50% 5-year survival rate.[3] However, these treatments are applicable only to patients with early-stage tumours, who make up only 30% to 40% of patients with HCC,[4] so most HCC patients are suitable for palliative care only. HCC is highly angiogenic and usually uses hepatic artery for blood supply, while the rest of the liver is predominantly supplied by the portal vein.[5] Therefore, arterial obstruction is a valid therapeutic option that can induce ischaemic tumour necrosis. Doyon et al was the first to describe the transarterial embolisation (TAE) in 1974.[6]

The process of TAE hepatic artery embolisation may be preceded by lipiodol administration, but no chemotherapeutic drugs are used. Transarterial chemoembolisation (TACE) procedure is a modification of TAE and includes injection of chemotherapeutic agents mixed with lipiodol into the hepatic artery prior to embolisation. Today, these 2 procedures are widely used to treat unresectable HCC.[3,7,8] TACE is also used for patients awaiting liver transplantation and can slow down tumour progression.[9] Despite the wide use of embolisation therapy for HCC treatment, embolisation is contraindicated in patients with severe liver dysfunction, portal vein thrombosis, and those with cancer in the very advanced stage, because of the high risk of hepatic failure and death.[10] Additionally, embolisation of the tumour-

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feeding artery may create a hypoxic and ischaemic tumour microenvironment. Ischaemia and hypoxia, in turn, may stimulate the expression of vascular endothelial growth factor, leading to neovascularisation, tumour regrowth, and progression.[11] This limitation may minimise the potential survival benefit.[12] An alternative approach designed to achieve higher therapeutic efficacy for patients in poor condition without embolisation is the hepatic arterial infusion therapy (TAI), in which an emulsion of iodised oil and anticancer agents are infused into the hepatic artery without any embolic substances.[13] Several studies comparing the rate of survival associated with TAI and TACE produced conflicting data. Maeda S et al[14] and Ikeda M et al[15] reported that the 2 therapies are comparable. Lu CD et al[16] showed that TAI was associated with improved survival compared to TACE in a subgroup of patients at high risk, while Hatanaka Y et al[17] and Takayasu et al[18] showed the opposite.

Given the unclear benefits of TACE over TAI, we performed the present meta-analysis study. The trials included in our study were randomised controlled trials (RCTs), retrospective cohort studies, and two-arm prospective studies published up until 14 December 2016, that assessed the efficacy of transarterial infusion chemotherapy with and without embolisation for patients with HCC.

Materials and Methods

Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance for systematic reviews of observational and diagnostic studies.[19] We searched the published literature using Medline, Cochrane, and Google Scholar databases with the following keywords combinations: transarterial chemoembolisation or TACE; transarterial infusion chemotherapy or TAI; and hepatocellular carcinoma or HCC. Additionally, we hand-searched references in relevant primary publications to identify other eligible trials. The described searches included original literature published up to 14 December 2016. For this meta-analysis, we included papers that assessed the effectiveness of TACE versus TAI in patients with primary HCC in RCTs, retrospective cohort studies, and two-arm prospective studies. We excluded Reviews, Letters, Comments, Editorials, Case reports, Proceeding, Personal communication, Expert opinions, and studies that did not report a quantitative outcome. Additionally, we excluded studies that analysed patients with extrahepatic metastases, portal vein thrombosis or portal vein obstruction.

Data Extraction

Data was extracted independently by 2 reviewers (YSF and CF). A third reviewer (RL) was consulted in case of disagreements. We extracted data on study population (number, age, and gender of subjects in each group), study design (including treatment protocols, interventions, and tumour characteristics), and the major outcomes.

Quality Assessment

We assessed the study quality using the Cochrane Risk of Bias Tool.[20] For non-randomised studies, we also assessed the quality by using Newcastle-Ottawa quality assessment scale. The quality assessment was performed by 2 independent reviewers (YSF and CF), and a third reviewer (RL) arbitrated on disagreements.

Statistical Analysis

A total of 11 studies were selected for analyses. Primary outcome measures were overall survival rates; disease-free or progression-free survival rates; and survival rates at certain follow-up time (e.g.1-year, 3-year, 5-year survival rates). Secondary outcome measure was the rate of complete or partial response to therapy. Odds ratio (OR) was used as the indicator of effect size; an OR >1 indicates higher survival rate or better response to therapy in patients treated with chemotherapy combined with embolisation compared to those without embolisation. Heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistic. The Q statistic was defined as the weighted sum of the squared deviations of the estimates of all studies; $P < 0.10$ was considered statistically significant for heterogeneity. For the I^2 statistic which indicated the percentage of the observed between-study variability due to heterogeneity, the suggested ranges were as follows: no heterogeneity ($I^2 = 0\%$-25%), moderate heterogeneity ($I^2 = 25\%$-50%), large heterogeneity ($I^2 = 50\%$-75%), and extreme heterogeneity ($I^2 = 75\%$-100%). The random-effect model (DerSimonian-Laird method) was used to generate pooled estimates across studies for each outcome. A two-sided P value <0.05 was considered statistically significant.

Subgroup analysis was performed according to types of study design (i.e., randomised trial, prospective and retrospective studies). Sensitivity analysis was carried out using a leave-one-out approach. To determine whether the method of pooling the data and the choice of anticancer drug influenced the results of our study, we performed additional sensitivity analyses. First, we analysed the data from individual studies using fixed-effect model. Second, we calculated pooled OR using random-effect model and excluded studies that did not use cisplatin in the treatment regimen. Next, we excluded studies that used a combination

of cisplatin and other drugs. We conducted a leave-one-out analysis to assess if any of the studies that used only cisplatin unduly influenced the results. All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Basic Characteristics of Included Studies

Study selection process is summarised in Figure 1. Our search yielded 219 clinical studies relevant to the topic of the present study. After reviewing the abstracts of the articles and applying exclusion/inclusion criteria, 180 of the 219 studies were excluded, and 39 were left for full-text reviewing. After full-text reviewing, 28 studies were excluded. The major reasons for study exclusion were: 1) study design did not fit our inclusion criteria (n = 23); and 2) study did not report the outcome of interest (n = 5). Figure 1 summarises the reasons for exclusion of the studies from the present analysis. Therefore, after considering inclusion and exclusion criteria, 11 articles were eligible for this review.[14-16,18,21-27]

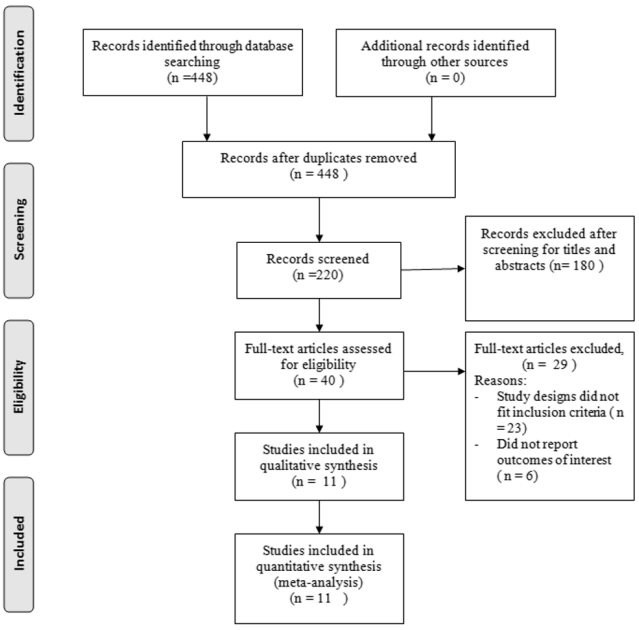

Fig. 1. Flowchart showing the selection of included studies.

Demographic and Clinical Characteristics of Included Studies

A total of 11 studies were included in the systematic review and meta-analysis. Three of the studies recruited participants from RCTs. A number of recruited participants ranged from 37 to 365, except for one prospective observational study that included 11,030 patients. In 4 studies, cisplatin was used as a single chemotherapy drug. The mean and median patients' age ranged from 41 to 74 years and the proportion of male patients ranged from 64.8% to 96.4%. Other clinical characteristics, including Child-Pugh Class, the presence of multiple tumours, type or stage of HCC, and hepatitis markers are summarised in Table 1.

The overall survival rates varied across studies, ranging from 15% to 68.1%. Nine studies reported complete or partial response to therapy that ranged from 18.9% to 80% (Table 2). Outcomes from included studies are summarised in Table 2.

Outcome Measures

We analysed 2 RCTs, 3 prospective and 4 retrospective studies to assess the effect of TACE and TAI treatments on the overall survival rate. There was no significant heterogeneity among the studies (Q = 0.2, P = 0.654, I^2 = 0% for RCTs; Q = 2.5, P = 0.288, I^2 = 19.7% for prospective studies; Q = 2.7, P = 0.433, I^2 = 0% for retrospective studies). The pooled OR was 0.884 (95% CI, 0.513 to 1.522, P = 0.859) for RCT, 1.864 (95% CI, 1.656 to 2.097, P <0.001) for prospective studies and 1.108 (95% CI, 0.802 to 1.530, P = 0.535) for retrospective studies. The overall analyses revealed that there was no significant difference in the survival rate in patients who underwent TACE or TAI treatments (pooled OR: 1.278; 95% CI, 0.783 to 2.086, P = 0.327) (Fig. 2A).

There was moderate to extreme heterogeneity among the studies in the response to treatment outcome (Q = 5.1, P = 0.077, I^2 = 61.1% for RCTs; Q = 9.0, P = 0.003, I^2 = 88.8% for prospective studies; Q = 3.3, P = 0.188, I^2 = 40.1% for retrospective studies). The overall analyses revealed that there was no significant improvement in the rate of treatment response in patients who underwent TACE versus TAI therapy regardless of the study design (pooled OR: 1.369; 95% CI, 0.627 to 2.989, P = 0.431 for RCTs; pooled OR: 1.154; 95% CI, 0.403 to 3.309, P = 0.789 for prospective studies; pooled OR: 1.864; 95% CI, 0.886 to 3.919, P = 0.101 for retrospective studies). The pooled results showed similar estimates as those stratified by study design (pooled OR: 1.502; 95% CI, 0.930 to 2.426, P = 0.096) (Fig. 2B).

Quality Assessment

The quality assessment of the studies included for this meta-analysis was performed using the Cochrane Risk of Bias Tool (Fig. 3). The majority of the included studies had performance and detection bias. In addition, selection bias was present in all the studies except the Shi et al,[27] Okusaka et al[24] and Lu et al[16] trials. For non-randomised studies, we also assessed the quality by using the Newcastle-Ottawa quality assessment scale (Table 3). All studies had low risk in the

Table 1. Summary of Basic Characteristics of Studies Selected for Meta-Analysis

Study Name	Study Design	Groups	Iodised Oil Used	Embolising Agent	Number of Patients	Anticancer Agents	Mean Age (Years)	Male (%)	Child-Pugh Class	Multiple Tumours (%)	Type/Stage of HCC	Mean Follow-up Time
Shi (2016)	Retrospective	TACE	Yes	Yes	95	Epirubicin, mitomycin	Median: 56.7	87%	A: 96% B: 4%		Within the Milan criteria	44.2 months
		TAI	Yes	No	95		Median: 56.6	87%	A: 108 (86%) B: 17 (14%)			40.7 months
Nishikawa (2014)	Retrospective	TACE	Yes	Gelatin sponge	145	Epirubicin, mitomycin	72.5	64.8%	A: 69% B: 31%	≤5 tumours: 78.6%	BCLC stage B	1.8 years*
		TAI	Yes	None	81	Epirubicin, mitomycin	70.3	70.4%	A: 56.8% B: 43.2%	≤5 tumours: 71.6%		2 years*
Shi (2012)	Single-blind RCT	3-drug TACE	Yes	Gelatin sponge	122	Lobaplatin, epirubicin, and mitomycin C	≤50 y: 63.1% >50 y: 36.9%	94.3%	A: 57.4%	60%	BCLC stage B: 67.2% BCLC stage C: 32.8%	12 months
		3-drug TAI	Yes	None	121	Lobaplatin, epirubicin, and mitomycin C	≤50 y: 56.2% >50 y: 43.8%	93.4%	A: 52%	58%	BCLC stage B: 66.1% BCLC stage C: 33.9%	
		Single-drug TACE	Yes	Gelatin sponge	122	Epirubicin	≤50 y: 59% >50 y: 41%	89.3%	A: 56.6%	57%	BCLC stage B: 63.1% BCLC stage C: 36.9%	
Imai (2012)	Retrospective	TACE	Yes	Gelatin sponge	122	Miriplatin	Median: 72	65%		83.3%	Stage I: 9.3% Stage II: 46.3% Stage III: 39.5% Stage IVA: 4.9%	2.2 months*
		TAI	Yes	None	40	Miriplatin	Median: 74	75%				2.1 months*
Takayasu (2010)	Prospective	TACE	Yes	Gelatin sponge	8507	Doxorubicin, epirubicin, analog of doxorubicin, mitomycin C, cisplatin, or zinostatin stimalamer	<60 y: 22% ≥60 y: 78%	72%		57%	TNM stage I: 12% TNM stage II: 39% TNM stage III: 40% TNM stage IV: 9%	1.39 years*
		TAI	Yes	None	2523		<60 y: 24% ≥60 : 76%	73%		57%	TNM stage I: 13% TNM stage II: 34% TNM stage III: 37% TNM stage IV: 15%	0.95 years*

BCLC: Barcelona Clinic Liver Cancer; LPS: Lipiodol Cisplatin suspension; RCT: Randomised controlled trials; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolisation; TAE: Transarterial embolisation; TAI: Transarterial infusion; TNM: Classifications of Malignant Tumours; NA: Not available

*Data presented as median.

Table 1. Summary of Basic Characteristics of Studies Selected for Meta-Analysis (Cont'd)

Study Name	Study Design	Groups	Iodised Oil Used	Embolising Agent	Number of Patients	Anticancer Agents	Mean Age (Years)	Male (%)	Child-Pugh Class	Multiple Tumours (%)	Type/Stage of HCC	Mean Follow-up Time
Kawaoka (2009)	Retrospective	TACE	Yes	Gelatin sponge	62	Cisplatin	Median: 73	70%	A: 72.1% B: 27.9% C: 27.9%	59.8%	TNM stage I: 8.4% TNM stage II: 38.3% TNM stage III: 49.5% TNM stage IV: 3.7%	13 months
		TAI	Yes	None	45							
Okusaka (2009)	Open-label RCT	TACE	Yes	Gelatin sponge	79	Zinostatin stimalamer (SMANCS)	Median: 65	77.2%		83.5%	Stage I: 2.5% Stage II: 22.8% Stage III: 35.4% Stage IVA: 39.2%	2 years
		TAI	Yes	None	82		Median: 67	85.4%		86.6%	Stage I: 4.9% Stage II: 20.7% Stage III: 30.5% Stage IVA:43.9%	
Ikeda (2004)	Prospective	TACE	Yes	Gelatin sponge	74	Cisplatin	Median: 63	81%	A: 55% B & C: 45%	65%	Okuda stage I: 70% Okuda stage II: 30%	2.8 years*
		TAI	Yes	None	94		Median: 64	66%	A: 48% B & C: 52%	56%	Okuda stage I: 60% Okuda stage II: 40%	2.5 years*
Maeda (2003)	Retrospective	LPS group	Yes	Gelatin sponge	143	Cisplatin	63.8	66.4%	A: 33.6% B: 35% C: 31.5%		TNM stage I: 12.6% TNM stage II: 31.5% TNM stage III: 27.3% TNM stage IV: 28.7%	
		LPS/TAE group	yes	None	96		62.4	78.1%	A: 49% B: 29.2% C: 21.9%		TNM stage I: 5.2% TNM stage II: 22.9% TNM stage III: 38.5% TNM stage IV: 33.3%	

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Table 1. Summary of Basic Characteristics of Studies Selected for Meta-Analysis (Cont'd)

Study Name	Study Design	Groups	Iodised Oil Used	Embolising Agent	Number of Patients	Anticancer Agents	Mean Age (Years)	Male (%)	Child-Pugh Class	Multiple Tumours (%)	Type/Stage of HCC	Mean Follow-up Time
Sumie (2003)	Prospective	TACE	Yes	Only lipiodol	21	Epirubicin	Median: 67	76%	A: 61.9% B: 38.1% C: 0%		TNM stage II – III: 42.9% TNM stage IV: 57.1%	
		TAI	No	None	16	Cisplatin	Median: 66.5	75%	A: 43.8% B: 56.3% C: 0%		TNM stage II – III: 37.5% TNM stage IV: 62.5%	
Lu (1994)	RCT	TACE	Yes	Gelatin sponge	24	Cisplatin, adriamycin, mitomycin	41.4	95.8%	A: 16.7% B: 54.2% C: 29.2%			
		TAI	Yes	None	28		46.3	96.4%	A: 10.7% B: 64.3% C: 25%			

BCLC: Barcelona Clinic Liver Cancer; LPS: Lipiodol Cisplatin suspension; RCT: Randomised controlled trials; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolisation; TAE: Transarterial embolisation; TAI: Transarterial infusion; TNM: Classifications of Malignant Tumours; NA: Not available

*Data presented as median.

Table 2. Summary of Outcomes for Each Individual Study

Study Name	Groups	No. of Patients	Overall Survival	Complete or Partial Response to Therapy
Shi (2016)	TACE	95	62%	NA
	TAI	95	59%	NA
Nishikawa (2014)	TACE	145	32.7%	80%
	TAI	81	26%	66.7%
Shi (2012)	3-drug TACE	122	NA	45.9%
	3-drug TAI	121	NA	29.7%
	Single-drug TACE	122	NA	18.9%
Imai (2012)	TACE	122	NA	58%
	TAI	40	NA	33%
Takayasu (2010)	TACE	8507	25%	NA
	TAI	2523	15%	NA
Kawaoka (2009)	TACE	62	24%	NA
	TAI	45	16%	NA
Okusaka (2009)	TACE	79	48.2%	46.8%
	TAI	82	49.6%	32.9%
Ikeda (2004)	TACE	74	25%	73%
	TAI	94	18.3%	51%
Maeda (2003)	TACE	143	29.6%	57.4%
	TAI	96	24.2%	62.5%
Sumie (2003)	TACE	21	28.6%	23.8%
	TAI	16	37.4%	56.3%
Lu (1994)	TACE	24	60%	54.2%
	TAI	28	68.1%	71.4%

NA: Not available; TACE: Transarterial chemoembolisation; TAI: Transarterial infusion

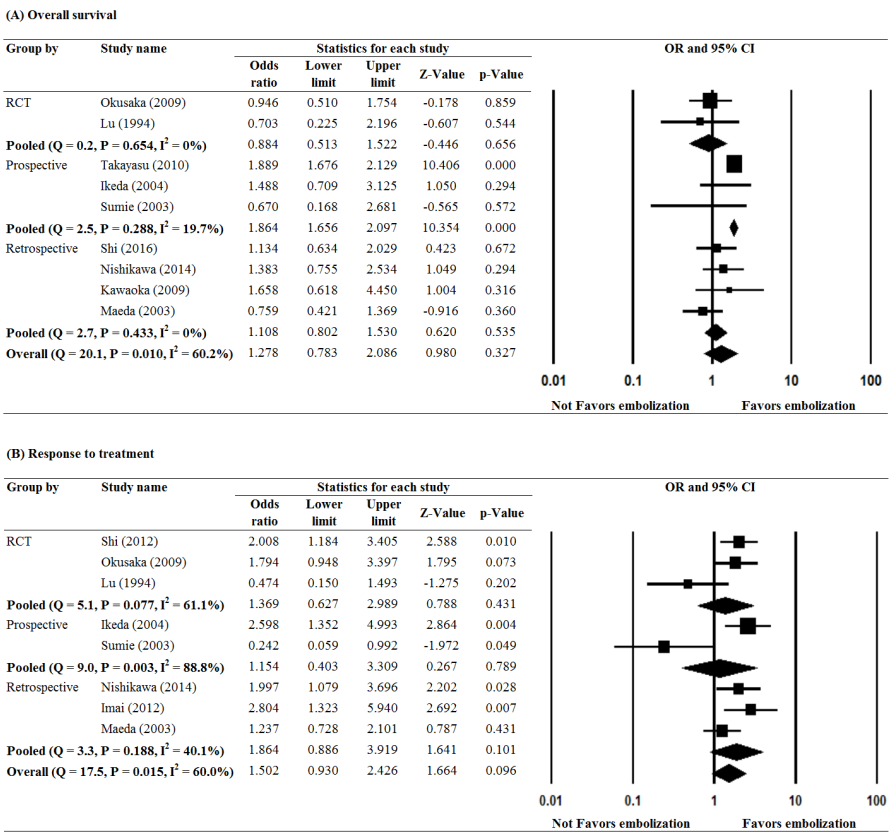

Fig. 2. Forest plot comparing treatment effect of transarterial lipiodol infusion chemotherapy with embolisation on (A) overall survival and (B) response to treatment.

Table 3. Quality Ratings for Included Non-Randomised Studies on the Basis of Newcastle-Ottawa Quality Assessment Scale

	Selection				Comparability	Outcome			
	Representative of Exposed Cohort	Selections of Non-Exposed Cohort	Assessment of Exposure	Absence of Outcome at Start of Study	Control for Age/Gender or Clinical Characteristics	Assessment of Outcome	Follow-up Period >1 Year	Adequacy of Follow-up	Total Score
Shi (2016)	1	1	1	1	2	1	1	1	9
Nishikawa (2014)	1	1	1	1	2	1	1	1	9
Imai (2012)	1	1	1	1	1	1	1	1	8
Takayasu (2010)	1	1	1	1	2	1	1	1	9
Kawaoka (2009)	1	1	1	1	2	1	1	1	9
Ikeda (2004)	1	1	1	1	2	1	1	1	9
Maeda (2003)	1	1	1	1	0	1	1	1	7
Sumie (2003)	1	1	1	1	0	1	1	1	7

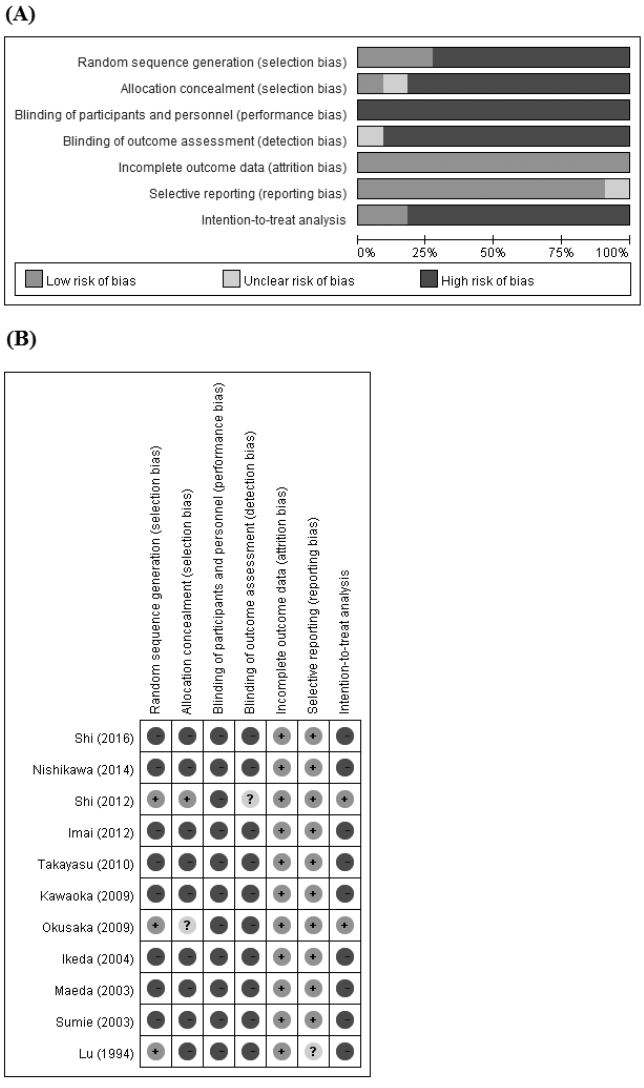

Fig. 3. Quality assessments results.

selection of study population, exposure ascertainment, and outcome measurement and follow-ups. Only 2 studies[14,22] did not perform statistical analyses taking into account demographic or clinical characteristics.

Sensitivity Analyses

Sensitivity analyses were performed using the leave-one-out approach. The sensitivity analysis was not performed for the overall survival outcome since only 2 studies were analysed. The Lu et al[16] trial had a significant impact on the response to treatment outcome. The removal of this study from the analyses led to a significant increase in the OR level (pooled OR: 1.918; 95% CI, 1.277 to 2.882, $P = 0.002$) (Fig. 4).

We analysed if the choice of anticancer drugs used for the treatment had any impact on the pooled results. Exclusion of studies using non-cisplatin chemotherapeutic agents did not have a significant treatment effect on the overall survival rate for patients treated with the combination treatment regimen (pooled OR: 0.995; 95% CI, 0.682 to 1.452, $P = 0.981$). Similar results were obtained when we excluded studies using either non-cisplatin agents or cisplatin combined with other drugs (pooled OR: 1.125; 95% CI = 0.675 to 1.875, $P = 0.651$). Leave-one-out sensitivity analyses were also performed for studies that used cisplatin as a single therapeutic agent. Sensitivity analyses results are summarised in Table 4.

Discussion

TACE is an established treatment modality that was shown to improve survival in HCC patients in 2 RCTs[28, 29] and 3 meta-analyses of randomised trials.[4,30,31] TACE, however, is not recommended for patients with poor liver function and advanced stage of cancer. To prevent post-therapeutic

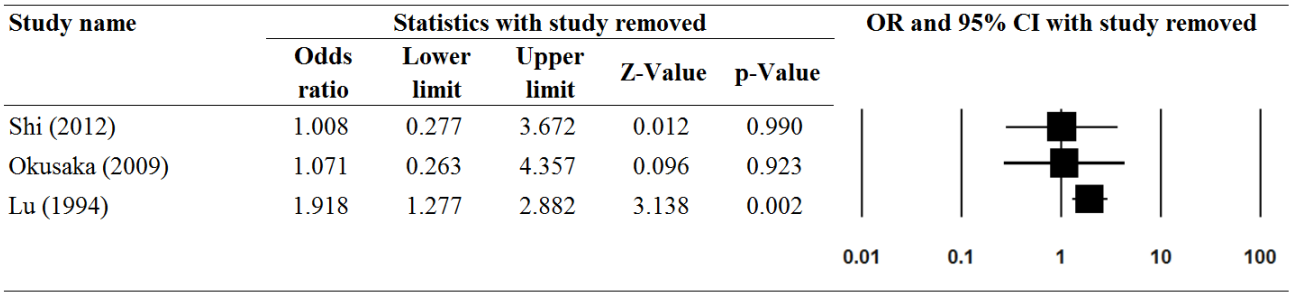

Fig. 4. Sensitivity analysis using leave-one-out approach on the treatment effect of transarterial lipiodol infusion chemotherapy with embolisation on response to treatment in RCTs.

Table 4. Sensitivity Analysis for Treatment Effect of Transarterial Lipiodol Infusion Chemotherapy with Embolisation on Overall Survival

	No. of Studies	Statistics with Studies Removed		
		OR	(5% CI)	*P* Value
Fixed-effect model	9	1.706	(1.531, 1.901)	<0.001
Excluding studies with drugs without cisplatin*	5	0.995	(0.682, 1.452)	0.981
Excluding studies with cisplatin combined with other drugs*	3	1.125	(0.675, 1.875)	0.651
Studies with chemotherapy with cisplatin only*†				
Excluding Kawaoka (2009)	2	1.022	(0.531, 1.967)	0.948
Excluding Ikeda (2004)	2	1.011	(0.483, 2.112)	0.978
Excluding Maeda (2003)	2	1.547	(0.855, 2.800)	0.149

*Random-effect model was performed.
†Sensitivity analysis using leave-one-out approach was performed.

hepatic failure and prolong survival in these patients, infusion therapy of an emulsion of iodised oil and an anticancer agent without gelatin sponge particles was developed. A number of studies were conducted in order to compare the clinical outcomes between TACE and TAI in HCC patients. Specifically, Okusaka et al[24] compared the clinical outcomes for HCC patients treated with TACE using zinostatin stimalamer and those treated with TAI using zinostatin stimalamer in RCT. This study reported that embolisation did not improve survival over TAI with zinostatin stimalamer. Another study reported that TACE using cisplatin suspended in lipiodol had a higher treatment efficacy than TAI using cisplatin suspended in lipiodol.[15] However, TACE did not significantly improve the survival of patients with HCC in the retrospective comparative analysis.[15] Therefore, these comparative studies produced inconsistent data regarding the superiority of either TAI or TACE in the treatment of HCC.

In this systematic review, we evaluated all published RCTs, retrospective cohort studies, and two-arm prospective studies that compared the clinical outcomes in patients who received TAI and TACE treatments in order to provide a more comprehensive understanding of the available data. Our analyses showed no significant difference in the overall survival and treatment response between patients who received TACE or TAI therapy. To further determine if any of the therapies would lead to a better outcome, subgroup analyses of treatment response outcome were performed and results were similar to those from pooled analysis. We did observe that TACE treatment was associated with significant improvement of survival in prospective cohort studies, but not in RCT or retrospective cohort studies. The most common side effects included fever and anaemia. Other uncommon side effects were renal failure,[27] hepatic failure,[16,21] upper gastrointestinal bleeding [16,21,23] and liver abscess.[21,22] Overall, the analysed studies did not report severe adverse events associated with the interventions, except for 3 cases of treatment-related mortality reported in the embolisation group.[15,27]

Numerous anticancer agents have been used to treat HCC, including epirubicin hydrochloride, mitomycin C, doxorubicin hydrochloride (ADM), cisplatin and zinostatin stimalamer. In our study, the sensitivity analyses showed that different choices of chemotherapy agents or their combinations did not affect the overall findings. With our growing understanding of the underlying molecular mechanism of HCC initiation and progression and the emergence of targeted therapeutics, treatments for advanced liver cancer will almost certainly be evolving in the coming years.

The results of this meta-analysis are subject to several limitations. First, differences in the baseline severity of illness in the population may lead to treatment group

assignment bias. Furthermore, selection criteria used to identify the candidates for TACE and TAI procedures vary dramatically between clinical centres. Second, variations in the chemoembolisation procedures (gelatin sponge size, for example) and their duration are also likely to influence the outcomes. In the study by Sumie et al,[23] gelatin sponge was not used for embolisation, and the only occlusive agent used in the TACE group was Lipiodol. The study by Mabed et al[32] used intravenous doxorubicin and did not use Lipiodol, and therefore was excluded from our analysis. Our study did not address several confounding factors, such as severity of the underlying liver disease, and number and size of the tumour lesions, which could also affect the accuracy of the results. We did, however, exclude patients with portal vein metastasis and/or thrombosis from our analysis (subgroup type-2 in Lu CD et al[16] study). Due to the nature of the disease and treatment, the included studies could not be performed blinded; therefore, the results may be skewed by detection and performance bias as well. Additionally, sample sizes of individual studies differed significantly. In the Takayasu et al study,[18] the sample size was much larger compared to other studies analysed. This difference in the sample size can significantly distort our analysis and lead to high risk of bias, especially in prospective cohort subgroup. To overcome the described limitations, future prospective studies with well balanced patients' groups are warranted.

Our meta-analysis demonstrated that HCC patients in the TAI and TACE groups had a similar prognosis, with neither treatment being favoured with a statistically significant increase in treatment response or overall survival over the other. Further studies with better controlled trials and well balanced patient groups are warranted. However, per our current results, both TACE and TAI can be equally valid therapeutic options for treating HCC.

Acknowledgements

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Original Article

Road Crashes in Older Persons and the Use of Comorbidity Polypharmacy Score in an Asian Population

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Abstract

Introduction: Age-related physiological changes predispose older road users to higher mortality from traffic crashes. We aimed to describe the injury epidemiology of these patients, and explore the association between the comorbidity polypharmacy score (CPS) and outcomes. Materials and Methods: This retrospective study utilised data from the Trauma Registry in the National University Hospital, Singapore, between January 2011 and December 2014. Patients involved in traffic crashes aged 45 years and above with injury severity scores (ISS) of 9 and higher were included. Results: There were 432 patients; median age was 58 (interquartile range, 51 to 65.5) years with predominance of male patients (82.2%) and Chinese ethnicity (66%). Overall mortality was 9.95%, with lower odds associated with higher Glasgow Coma Scale (odds ratio [OR] 0.73; 95% confidence interval [CI], 0.65 to 0.81, *P* <0.001), higher diastolic blood pressure (OR 0.98; 95% CI, 0.97 to 1.00, *P* = 0.031), and lower ISS of 9 to 15 (OR 0.10; 95% CI, 0.02 to 0.43, *P* = 0.002). The need for blood products was associated with higher mortality (OR 7.62; 95% CI, 2.67 to 21.7, *P* <0.001). CPS did not predict mortality. Independent predictors of discharge venue included length of stay, tier of injury and CPS group. Moderate CPS was statistically significant for nursing home placement (OR 10.7; 95% CI, 2.33 to 49.6, *P* = 0.002) but not for rehabilitation facility. Conclusion: CPS score is useful in predicting discharge to a nursing home facility for older patients with traffic crashes. Further larger studies involving other trauma types in the Asian population are needed to evaluate its utility.

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Key words: Elderly, Motor vehicle crashes, Trauma severity indices

Introduction

In 2014, 11.2% of Singapore residents were aged 65 years and older.[1] This proportion is projected to increase to 18.7% by 2030.[2] The ageing population will herald a larger number of older road users, especially as improved healthcare renders them community-ambulant. Physiological changes and underlying comorbidities may predispose them to traffic crashes and poorer outcomes despite a lower injury severity. In Singapore, road crashes were only second to falls as the most common mechanism of injury in the adult trauma population.[3]

Age-related physiological changes such as cognitive impairment reduces ability to process information; diminution in vision and hearing delays recognition of road hazards; and reduced flexibility can affect older drivers' response to traffic conditions.[4,5] Older drivers are also more likely to have medical illness as a causative factor for traffic crashes.[6-8] Additionally, older crash victims have higher admission and fatality rates compared with the younger age groups.[4,9-11]

Traditional trauma scoring systems such as the Injury Severity Score (ISS) and Revised Trauma Score (RTS) have been shown to be variable in predicting mortality in the older population.[12,13] To better predict outcomes in older trauma patients, the Comorbidity Polypharmacy Score (CPS) was developed by a group of physicians in

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the Ohio State University Wexner Medical Center and was first described in 2013.[14] CPS has been validated to predict mortality and likelihood of older trauma survivors being discharged home.[15-17] It has also been proposed to be a better measure of physiological age and frailty.[17,18] To the best of our knowledge, this novel scoring system has not been widely used or studied in the Asian trauma population.

The objectives of this study are: 1) To describe the injury epidemiological characteristics of older patients (aged 45 years and above) involved in motor vehicle crashes with an ISS of 9 and above; and 2) To explore the association between existing comorbidities and polypharmacy with outcomes using the CPS.

Materials and Methods

This retrospective study was carried out using data collected by the Trauma Registry in the National University Hospital, Singapore. Data was gathered from patients aged 45 years and above with T1 (ISS score ≥16) and T2 (ISS scores 9 to 15)[19] injuries, who were seen in the emergency department (ED) from January 2011 to December 2014. The local ethics committee approved waiver of informed consent. This age group was selected as they commonly have chronic medical conditions requiring long-term pharmacotherapy and polypharmacy[15,20] and the shift in the median age of the local population to 45 years by 2025 makes this an important watershed group to study.[21]

Detailed review of electronic medical records that included inpatient notes, ED charts and past medical history was performed by 2 independent data abstractors. Variables collected include the injury epidemiology, injury severity, outcome measures (mortality, ED disposition and discharge venues), and types of comorbidities and medications used. Any discrepancies were discussed and a third member of the study team was consulted to achieve a final consensus. CPS were calculated by adding pre-injury comorbidities (both past and current) and number of medications,[15-17] including over-the-counter medications or supplements for each patient. The CPS severities were then subdivided into minor (CPS of 0 to 7), moderate (8 to 14), severe (15 to 21) and morbid (≥22).[15]

Statistical Analysis

Results were analysed using Stata 14 (StataCorp LP, College Station, TX). Categorical data were analysed using chi-squared test or Fisher's exact test. Kruskal-Wallis and Mann-Whitney U tests were used for non-parametric variables; analysis of variance and Student's t test for parametric variables. Medians were reported with interquartile ranges (IQR) and means with standard deviations (SD). The outcomes of mortality, ED disposition and hospital discharge venue were examined. Variables with a P value of <0.10 were included for multivariate analysis. For the binary outcomes of mortality, logistic regression was used to obtain the odds ratio (OR) with its corresponding 95% confidence interval (CI).

For the analysis of discharge venue from the hospital for survivors, patients who were transferred to private or overseas hospitals were excluded because the study team could not obtain information on whether they required any step-down facility upon discharge. After the exclusion, univariate analyses were repeated for all the variables. Multinomial logistic regression was used to calculate ORs and 95% CIs for the likelihood of being discharged to a rehabilitation facility or nursing home compared to being discharged home. A P value of <0.05 was set for statistical significance after multivariate analysis.

Results

A total of 432 patients with T1 and T2 injuries from traffic crashes attended the ED between January 2011 and December 2014. The median age was 58 (IQR 51 to 65.5) years, with Chinese (n = 285, 66%) and male predominance (n = 355, 82.2%). Motorcycle riders constituted 45.6% (197/432) of the patients, 21.1% (91/432) were pedestrians and 12.5% (54/432) were cyclists. There were higher proportions of motorcycle riders in the younger groups, whereas pedestrians made up the majority in those 75 years and older (Table 1).

With regard to the severity of injuries, the majority (71.8%, 28/39) of the oldest group had an ISS of 16 and above, and advanced age was associated with a higher median length of stay (LOS) (Table 1). Patients aged 60 years and above were also more likely to require blood product transfusion, and have head and neck injuries compared to patients aged 45 to 59 years (Table 1).

The overall mortality was 9.95% (43/432), with higher proportion of deaths in the older groups (Table 2). After multiple logistic regression, higher Glasgow Coma Scale (GCS) scores (OR 0.73; 95% CI, 0.65 to 0.81, P <0.001), higher diastolic blood pressure values (OR 0.98; 95% CI, 0.97 to 1.00, P = 0.031) and lower ISS of 9 to 15 (OR 0.10; 95% CI, 0.02 to 0.43, P = 0.002) resulted in lower odds of mortality. The need for blood products transfusion in ED was associated with higher mortality (OR 7.62; 95% CI, 2.67 to 21.7, P <0.001).

The median CPS was 2 (IQR 0 to 6); 79.6% (344/432) had a CPS indicating minor severity, 18.3% (79/432) with moderate severity and 2.1% (9/432) in the severe group (Table 3). No patient had a morbid CPS score. Although higher CPS scores were not significantly associated with mortality, higher proportions of deaths were observed

Table 1. Injury Epidemiology, Severity and Mortality by Age Group

	45 to 59 Years n = 245 (%)	60 to 74 Years n = 148 (%)	≥75 Years n = 39 (%)	*P* Value
Resident status				<0.001
Citizen	165 (67.4)	130 (87.8)	38 (97.4)	
Permanent resident	22 (8.98)	5 (3.38)	0 (0.0)	
Foreign worker	56 (22.9)	9 (6.1)	0 (0.0)	
Tourist/foreigner	2 (0.8)	4 (2.7)	1 (2.6)	
Gender				0.003
Male	214 (87.4)	114 (77.0)	27 (69.2)	
Female	31 (12.7)	34 (23.0)	12 (30.8)	
Ethnic group				0.037
Chinese	146 (59.6)	108 (73.0)	31 (79.5)	
Malay	51 (20.8)	25 (16.9)	6 (15.38)	
Indian	31 (12.7)	11 (7.4)	1 (2.6)	
Others	17 (6.9)	4 (2.7)	1 (2.6)	
Injured person type				<0.001
Motorbike rider	132 (53.9)	58 (39.2)	7 (18.0)	
Pillion	9 (3.7)	2 (1.4)	0 (0.0)	
Pedestrian	30 (12.2)	38 (25.7)	23 (59.0)	
Cyclist	24 (9.8)	27 (18.2)	3 (7.7)	
Vehicle driver	32 (13.1)	15 (10.1)	3 (7.7)	
Back passenger	15 (6.1)	6 (4.1)	1 (5.1)	
Front passenger	3 (1.2)	1 (0.7)	1 (2.6)	
Unknown	0 (0.0)	1 (0.7)	0 (0.0)	
Vehicle type				<0.001
Not applicable (pedestrian)	30 (12.2)	38 (25.7)	23 (59.0)	
Motorcycle	140 (57.1)	61 (41.2)	8 (17.9)	
Pedal cycle	24 (9.8)	27 (18.2)	2 (7.7)	
Taxi	6 (2.4)	5 (3.4)	1 (2.6)	
Private car	16 (6.5)	5 (3.4)	4 (12.8)	
Van/pickup truck	11 (4.5)	5 (3.4)	0 (0.0)	
Heavy transport vehicle	15 (6.1)	5 (3.4)	0 (0.0)	
Bus	3 (1.2)	0 (0.0)	0 (0.0)	
Others	0 (0.0)	2 (1.4)	0 (0.0)	
Type of object collided with				0.001
None	50 (20.4)	11 (7.4)	1 (2.6)	
Car, pickup truck or van	87 (35.5)	70 (47.3)	20 (51.3)	
2- or 3-wheel motor vehicle	10 (4.1)	11 (7.4)	5 (15.4)	
Heavy transport vehicle	60 (24.5)	28 (18.9)	6 (15.4)	
Fixed or stationary object	28 (11.4)	24 (16.2)	4 (12.8)	
Pedal cycle	2 (0.8)	2 (1.4)	1(2.6)	
Unknown	8 (3.3)	2 (1.4)	0 (0.0)	

DBP: Diastolic blood pressure; GCS: Glasgow Coma Scale; HR: Heart rate; IQR: Interquartile range; ISS: Injury Severity Score; LOS: Length of stay; SBP: Systolic blood pressure; SD: Standard deviation; T1: Tier 1; T2: Tier 2

Table 1. Injury Epidemiology, Severity and Mortality by Age Group (Cont'd)

	45 to 59 Years n = 245 (%)	60 to 74 Years n = 148 (%)	≥75 Years n = 39 (%)	*P* Value
Median GCS (IQR)	15 (15 to 15)	15 (15 to 15)	15 (10 to 15)	0.004
Mean SBP/DBP (SD)	132 (33)/76 (20)	138 (36)/78 (21)	128 (50)/67 (26)	0.306/0.021
Mean HR (SD)	83 (21)	80 (23)	78 (28)	0.360
Trauma team activated	92 (37.6)	45 (30.4)	15 (38.5)	0.322
Blood products given in ED	23 (9.4)	27 (18.2)	9 (23.1)	0.009
Median LOS (in days)	5.8 (2.5 to 12.6)	6.8 (3.0 to 16.9)	11.6 (4.0 to 30.5)	0.037
Tier of injury				<0.001
T1 (ISS ≥16)	90 (36.7)	58 (39.2)	28 (71.8)	
T2 (ISS 9 to 15)	155 (63.3)	90 (60.8)	11 (28.2)	
Injury type				
Head	93 (38.0)	70 (47.3)	28 (71.8)	<0.001
Face	53 (21.6)	44 (29.7)	14 (35.9)	0.064
Neck	3 (1.22)	21 (14.2)	6 (15.4)	<0.001
Chest	121 (49.4)	75 (50.7)	20 (51.3)	0.956
Abdomen	31 (12.7)	17 (11.5)	7 (18.0)	0.559
Pelvis	34 (13.9)	23 (15.5)	7 (18.0)	0.765
Upper limb	56 (22.9)	48 (32.4)	15 (38.5)	0.033
Lower limb	82 (33.5)	70 (47.3)	15 (38.5)	0.024
Spine	69 (28.2)	31 (21.0)	12 (30.8)	0.220
Overall mortality	18 (7.3)	17 (11.5)	8 (20.5)	0.029

DBP: Diastolic blood pressure; GCS: Glasgow Coma Scale; HR: Heart rate; IQR: Interquartile range; ISS: Injury Severity Score; LOS: Length of stay; SBP: Systolic blood pressure; SD: Standard deviation; T1: Tier 1; T2: Tier 2

(*P* = 0.133) by chi-squared test for trend (Table 3). Of those who survived to admission (n = 415), 51.6% (214/415) were admitted to the general ward and 47.5% (197/415) required admission to the intensive care unit/high dependency (ICU/HD); this was not affected by age or CPS.

Age was also not found to be a significant predictor of discharge venue (Table 4). Higher CPS, resident status, median GCS, injured person type, vehicle type, trauma team activation, median LOS and tier of injury were significantly associated with discharge venue (Table 4). After multinomial logistic regression, only LOS, tier of injury and CPS group remained statistically significant (Table 5). An increase in each day of stay in hospital was associated with higher odds of placement in a nursing home (OR 1.04; 95% CI, 1.02 to 1.05) or a rehabilitation facility (OR 1.02; 95% CI, 1.01 to 1.04). A lower ISS of 9 to 15 has lower likelihood for transfer to a rehabilitation facility (OR 0.41; 95% CI, 0.21 to 0.82); lower ISS also showed a trend towards a lower likelihood for nursing home placement albeit not statistically significant (OR 0.31; 95% CI, 0.07 to 1.49). Moderate CPS score, however, was only statistically significant for nursing home placement but not for placement into a rehabilitation facility (Table 5). When we examined the raw CPS scores, every 1-point increase in CPS increased the odds of nursing home placement compared to being discharged home by 18% (OR 1.18; 95% CI, 1.03 to 1.34, *P* = 0.017).

Discussion

Motor vehicle crashes are of global health concern. In the World Health Organization's (WHO) 'Global Status Report on Road Safety: Time for Action', it was reported that 50 million road users are injured globally per year due to traffic crashes, with more than 1.2 million deaths.[22] Pedestrians, cyclists and motorcyclists are collectively known as "vulnerable road users" as they constitute half of the road fatalities.[22] These casualties take a toll on a country's health resources and economy. Deaths from automobile crashes are postulated to increase from the 9th leading cause of deaths in 2004 to the 5th cause worldwide by 2030.[23] Yet, road traffic injuries and deaths are eminently preventable.

The top 3 groups of injured persons in our cohort, namely pedestrians, motorcyclists and cyclists, correspond to WHO's "vulnerable road users" who have higher risks of death.[24] This indeed warrants further action to ensure they are protected. The majority of patients (75 years

Table 2. Mortality At Discharge

	Survived, n = 389 (%)	Died, n = 43 (%)	*P* Value
Age (in years)			0.029
45 to 59	227 (58.4)	18 (41.9)	
60 to 74	131 (33.7)	17 (39.5)	
≥75	31 (7.97)	8 (18.6)	
Injured person type			0.522
Motorbike rider	181 (46.5)	16 (37.2)	
Pillion	11 (2.8)	0 (0.0)	
Pedestrian	77 (19.8)	14 (32.6)	
Cyclist	48 (12.3)	3 (14.0)	
Vehicle driver	46 (11.8)	0 (9.3)	
Back passenger	20 (5.1)	0 (7.0)	
Front passenger	5 (1.3)	0 (0.0)	
Unknown	1 (0.3)	0 (0.0)	
Vehicle type			0.101
Not applicable (pedestrian)	76 (19.5)	14 (32.6)	
Motorcycle	192 (49.4)	15 (37.2)	
Pedal cycle	48 (12.3)	4 (14.0)	
Taxi	11 (2.8)	1 (2.3)	
Private car	25 (6.4)	0 (2.3)	
Van/pickup truck	15 (3.9)	2 (2.3)	
Heavy transport vehicle	17 (4.4)	3 (7.0)	
Bus	3 (0.8)	0 (0.0)	
Others/unknown	2 (0.5)	1 (2.33)	
Type of object collided with			0.089
None	61 (15.7)	1 (2.3)	
Car, pickup truck or van	161 (41.4)	16 (37.2)	
2- or 3-wheel motor vehicle	25 (6.4)	2 (4.7)	
Heavy transport vehicle	79 (20.3)	15 (34.9)	
Fixed or stationary object	50 (12.9)	5 (16.3)	
Pedal cycle	5 (1.3)	0 (0.0)	
Unknown	8 (2.1)	2 (4.7)	
Trauma team activated	128 (32.9)	24 (55.8)	0.003
Blood products given in ED	42 (10.8)	17 (39.5)	<0.001
Tier of injury			<0.001
T1 (ISS ≥16)	135 (34.7)	41 (95.4)	
T2 (ISS 9 to 15)	254 (65.3)	2 (4.6)	
CPS group			0.133
Minor	313 (80.5)	31 (72.1)	
Moderate	69 (17.7)	10 (23.3)	
Severe	7 (1.8)	2 (4.7)	

CPS: Comorbidity Polypharmacy Score; ED: Emergency department; ISS: Injury Severity Score; T1: Tier 1; T2: Tier 2

and above) who were involved in traffic crashes were pedestrians (59%, n = 23). The age-related physiological changes, comorbidities and polypharmacy in these patients that prevented them from operating vehicles, continue to impair them even as pedestrians. Older pedestrians often require more time for crossing at traffic junctions,[25,26] hence modifications to pedestrian crossings should be considered. One example locally is the extension of crossing time for older pedestrians at selected traffic junctions using special concession cards.[27] Reducing speed limits at traffic junctions and establishing vehicle-free network of pedestrian routes may also protect these road users.[24]

In the age groups of 45 to 74 years, the greatest proportion of injured person type was the motorcyclists. Older riders are at higher risk for severe injuries and hospitalisation compared to younger ones.[28] Regular health checks, licensing and regulations, and encouraging the use of safer alternative transport are important in reducing traffic crashes in this group of road users.[24] Cyclists were the third largest group to be involved in road accidents (12.5%, n = 54) in our cohort. In order to minimise their risk of crashes and mortality from head injuries, dedicated cycling paths and mandatory helmet use should be established.[24,29]

Of note, the proportion of head and neck injuries was significantly higher in the older patients. This could possibly translate to more catastrophic injuries such as intracranial haemorrhages and cervical spine injuries, leading to drastic functional decline. Furthermore, close to half (47.5%) of the study cohort required ICU/HD admission, indicating a need for higher intensity monitoring and management. The older patients also tended to have longer hospital stay leading to higher consumption of healthcare resources. Mortality rates also increased as the age increases, in congruence with previous studies.[4,9-11,30]

As the ageing population grows with increasing incidence of chronic diseases, there will be a greater proportion of ambulant elderly road users on chronic medications. Apart from the injuries, the underlying comorbidities and interaction of polypharmacy may add to their frailty and compound their injury severity. Therefore, a better prognosticating tool for these patients is needed. The CPS was developed with such an intention to better quantify their true frailty, rather than rely on their "chronological age".[15,17,31]

Part of our results differs from previous studies, which had demonstrated that CPS is an independent predictor of mortality[15,16,32] and discharge to a facility.[18,31] Our results did not show a significant association between CPS and mortality. This could be due to the low mortality (n = 43, 9.95%) in our cohort and the lack of power due to small numbers. The need for blood products in the ED as a predictor for mortality was also plausibly due to survival

Table 3. Demographics, Severity and Mortality by CPS Group

	CPS Minor (0 to 7) n = 344	CPS Moderate (8 to 14) n = 79	CPS Severe (15 to 21) n = 9	*P* Value
Age (in years)				<0.001
45 to 59	218 (63.4)	26 (32.9)	0 (11.1)	
60 to 74	99 (28.8)	42 (53.2)	7 (77.8)	
≥75	27 (7.9)	11 (13.9)	1 (11.1)	
Gender				0.037
Male	289 (84.0)	60 (76.0)	3 (66.7)	
Female	55 (16.0)	19 (24.0)	3 (33.3)	
Ethnic group				0.269
Chinese	225 (65.4)	52 (65.8)	4 (88.9)	
Malay	64 (18.6)	17 (21.5)	1 (11.1)	
Indian	35 (10.2)	8 (10.1)	0 (0.0)	
Others	20 (5.8)	2 (2.5)	0 (0.0)	
Resident status				<0.001
Citizen	245 (71.2)	79 (100.0)	5 (100.0)	
Permanent resident	27 (7.9)	0 (0.0)	0 (0.0)	
Foreign worker	65 (18.9)	0 (0.0)	0 (0.0)	
Tourist	7 (2.0)	0 (0.0)	0 (0.0)	
Trauma team activated	118 (34.3)	30 (38.0)	4 (44.4)	0.402
Blood products given in ED	36 (10.5)	21 (26.6)	2 (22.2)	<0.001
Median LOS (in days)	6.3 (2.8 to 13.8)	6.8 (2.5 to 24.0)	8.0 (1.7 to 30.0)	0.708
Tier of injury				0.919
T1 (ISS ≥16)	138 (40.1)	36 (45.6)	1 (22.2)	
T2 (ISS 9 to 15)	206 (59.9)	43 (54.4)	7 (77.8)	
Disposition from ED				0.538
General ward	173 (50.3)	35 (44.3)	6 (66.7)	
HD/ICU	157 (45.6)	37 (46.8)	2 (33.3)	
OT	3 (0.9)	1 (1.3)	0 (0.0)	
Died in ED	11 (3.2)	6 (7.6)	0 (0.0)	
Overall mortality	31 (9.0)	10 (12.7)	2 (22.2)	0.133
Discharge venue for survivors (n = 389)				0.006
Home	267 (85.3)	51 (73.9)	6 (85.7)	
Rehab facility	34 (10.9)	10 (14.5)	1 (14.3)	
Nursing home	4 (1.3)	7 (10.1)	0 (0.0)	
Other hospitals	8 (2.6)	1 (1.4)	0 (0.0)	

CPS: Comorbidity Polypharmacy Score; ED: Emergency department; HD: High dependency; ICU: Intensive care unit; ISS: Injury Severity Score; LOS: Length of Stay; OT: Operating theatre; T1: Tier 1; T2: Tier 2

bias, since patients who were more severely injured were more likely to require transfusion and thus have higher mortality. Nevertheless, our study showed that patients with moderate CPS have higher risk of being admitted to a nursing home compared to patients with minor CPS. Unfortunately, we did not have any patients in the severe CPS group who were admitted to the nursing home for analysis.

The lack of significant association between CPS and discharge to a rehabilitation unit could be due to their admission criteria. Generally, only patients who are able to participate in rehabilitation would be accepted and patients with higher CPS may be too incapacitated for any rehabilitation. We postulated this as a proportion of patients who were discharged home had moderate (15.7%) or severe (1.9%) CPS. Notwithstanding, knowledge that patients with more comorbidities and medications have higher

Table 4. Discharge Venues for Survivors

	Home n = 324 (%)	Rehab Facility n = 45 (%)	Nursing Home n = 11 (%)	Other Hospitals n = 9 (%)	*P* Value
Age (in years)					0.188
45 to 59	192 (59.3)	23 (51.1)	4 (36.4)	6 (88.9)	
60 to 74	109 (33.6)	16 (35.6)	5 (45.5)	0 (11.1)	
≥75	23 (7.1)	6 (13.3)	2 (18.2)	0 (0.0)	
Resident status					0.006
Citizen	250 (77.2)	40 (88.9)	9 (81.8)	1 (33.3)	
Permanent resident	22 (6.8)	2 (4.4)	0 (0.0)	0 (0.0)	
Foreign worker	47 (14.5)	3 (6.7)	2 (18.2)	2 (55.6)	
Tourist	5 (1.5)	0 (0.0)	0 (0.0)	1 (11.1)	
Median GCS (IQR)	15 (15 to 15)	15 (14 to 15)	15 (9 to 15)	15 (10 to 15)	<0.001
Injured person type					<0.001
Motorbike rider	158 (48.8)	15 (33.3)	1 (9.1)	7 (77.8)	
Pillion	9 (2.8)	2 (4.4)	0 (0.0)	0 (0.0)	
Pedestrian	59 (18.2)	10 (22.2)	6 (54.5)	1 (22.2)	
Cyclist	39 (12.0)	8 (17.8)	1 (9.1)	0 (0.0)	
Vehicle driver	38 (11.7)	6 (13.3)	2 (18.2)	0 (0.0)	
Back passenger	17 (5.2)	3 (6.7)	0 (0.0)	0 (0.0)	
Front passenger	4 (1.2)	1 (2.2)	0 (0.0)	0 (0.0)	
Unknown	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	
Vehicle type					<0.001
Not applicable (pedestrian)	58 (17.9)	10 (22.2)	6 (54.5)	1 (22.2)	
Motorcycle	167 (51.5)	17 (37.8)	1 (9.1)	6 (77.8)	
Pedal cycle	39 (12.0)	8 (17.8)	1 (9.1)	0 (0.0)	
Taxi	9 (2.8)	0 (0.0)	2 (18.2)	0 (0.0)	
Private car	23 (7.1)	2 (4.4)	0 (0.0)	0 (0.0)	
Van/pickup truck	11 (3.4)	4 (8.9)	0 (0.0)	0 (0.0)	
Heavy transport vehicle	15 (4.6)	2 (4.4)	0 (0.0)	0 (0.0)	
Bus	1 (0.3)	2 (4.4)	0 (0.0)	0 (0.0)	
Others/unknown	1 (0.3)	0 (0.0)	1 (9.1)	0 (0.0)	
Type of object collided with					0.092
None	58 (17.9)	2 (4.4)	1 (9.1)	0 (0.0)	
Car, pickup truck or van	131 (40.4)	19 (42.2)	5 (45.5)	3 (55.6)	
2- or 3-wheel motor vehicle	20 (6.2)	3 (6.7)	1 (9.1)	1 (11.1)	
Heavy transport vehicle	65 (20.1)	11 (24.4)	1 (9.1)	2 (22.2)	
Fixed or stationary object	43 (13.7)	5 (11.1)	1 (9.1)	1 (11.1)	
Pedal cycle	3 (0.9)	1 (2.2)	1 (9.1)	0 (0.0)	
Unknown	3 (0.9)	4 (8.9)	1 (9.1)	0 (0.0)	
Trauma team activated	98 (30.3)	22 (48.9)	6 (54.6)	2 (22.2)	0.029
Median LOS (in days)	5.9 (3.0 to 12.5)	19 (13.0 to 31.3)	62.8 (43.0 to 99.2)	5.5 (2.0 to 25.3)	0.001

CPS: Comorbidity Polypharmacy Score; GCS: Glasgow Coma Scale; IQR: Interquartile range; ISS: Injury Severity Score; LOS: Length of stay; SBP: Systolic blood pressure; SD: Standard deviation; T1: Tier 1; T2: Tier 2

Table 4. Discharge Venues for Survivors (Cont'd)

	Home n = 324 (%)	Rehab Facility n = 45 (%)	Nursing Home n = 11 (%)	Other Hospitals n = 9 (%)	*P* Value
Tier of injury					<0.001
T1 (ISS ≥16)	97 (29.9)	26 (57.8)	8 (72.7)	3 (44.4)	
T2 (ISS 9 to 15)	227 (70.1)	19 (42.2)	3 (27.3)	5 (55.6)	
CPS group					0.006
Minor	267 (82.4)	34 (75.6)	4 (36.4)	7 (88.9)	
Moderate	51 (15.7)	10 (22.2)	7 (63.6)	1 (11.1)	
Severe	6 (1.9)	1 (2.2)	0 (0.0)	0 (0.0)	

CPS: Comorbidity Polypharmacy Score; GCS: Glasgow Coma Scale; IQR: Interquartile range; ISS: Injury Severity Score; LOS: Length of stay; SBP: Systolic blood pressure; SD: Standard deviation; T1: Tier 1; T2: Tier 2

Table 5. Results from Multinomial Logistic Regression on Discharge Venue

	Rehab vs Home		NH vs Home	
	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
LOS (days)	1.02 (1.01 to 1.04)	0.001	1.04 (1.02 to 1.05)	<0.001
Tier of injury				
ISS (≥16)	1.00		1.00	
ISS (9 to 15)	0.41 (0.21 to 0.82)	0.011	0.31 (0.07 to 1.49)	0.145
CPS group				
Minor	1.00		1.00	
Moderate	1.33 (0.60 to 2.99)	0.484	10.7 (2.33 to 49.6)	0.002
Severe	1.59 (0.17 to 14.8)	0.683	No patients	

CPS: Comorbidity Polypharmacy Score; ISS: Injury Severity Score; LOS: Length of stay; NH: Nursing home; OR: Odds ratio

risk of nursing home placement may prompt clinicians to undertake early discharge care planning to prevent prolonged hospital stay.

The cohort studied here had a median CPS score of only 2, which could be real or artefactual. They may have been genuinely healthy or were simply non-compliant with medications or underdiagnosed due to a lack of health-seeking behaviour. In the National Health Survey 2010, younger residents were found to be less likely to undergo health screening compared to those aged 60 to 69 years.[33] Given the generally low CPS, we found it more meaningful to consider the raw CPS scores without categorising them. Each 1-point increase in CPS was associated with higher odds of need for nursing home placement.

Strengths of this study include the novel use of the CPS score in an Asian trauma population. As alluded to earlier, to the best of our knowledge, this scoring system has not been studied in the Asian context. The epidemiology of road traffic crashes in older persons is also not widely explored. Previous studies on automobile crashes done locally were mainly on fatalities and the general population.[34-38] This study provides an understanding of the injury epidemiology specifically in the older cohort who are more susceptible to severe injuries and death, thus providing insight to the healthcare resources utilised in the management and more importantly, prevention of injuries from traffic crashes for this population.

Limitations

There are some limitations to this study. First, its retrospective design harbours inherent weaknesses. Second, we were not able to contact the patients' primary physicians for added comprehensiveness in data collection of medications and comorbidities, as this information was not available electronically. Third, the numbers of patients discharged to rehabilitation facility and nursing home were relatively small, resulting in imprecise OR estimates. The raw CPS scores however, gave a more precise risk estimate for nursing home placement. We were also unable to examine the effect of severe CPS on nursing home admission. A type II error could not be excluded since the number of survivors admitted to a rehabilitation facility was relatively small

(11.6%, n = 45). However, these results can be used for hypothesis generation and more studies should be conducted to look at a larger cohort, including other trauma types in our local population.

Lastly, most previous studies on CPS were performed on trauma cohorts with various mechanisms of injuries, except for one conducted in burns patients.[18] Hence, its application on a cohort that comprises patients from road crashes may be an oversimplification. This raises the question of whether patients in traffic crashes behave differently from the rest of the trauma subgroups. One postulation is that these patients could be a self-selected group; they are likely to be less frail compared to patients of other trauma types on the basis that they are community-ambulant.

Conclusion

Older victims of road traffic crashes have higher morbidity and mortality compared to their younger peers. The CPS score could potentially be used as an adjunct to current trauma scoring tools to predict the need for discharge to a step-down facility; but larger studies need to be done for further evaluation of its usefulness in Asian populations.

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Original Article

Outcomes of Dose-Attenuated Docetaxel in Asian Patients with Castrate-Resistant Prostate Cancer

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Abstract

Introduction: High levels of toxicities have been observed when docetaxel is administered at the standard dose of 75 mg/m² every 3 weeks (Q3W) in the real-world treatment of Asian patients with metastatic castrate-resistant prostate cancer (CRPC). This study aimed to evaluate the efficacy and tolerability of 2 attenuated regimens more widely used in an Asian setting to minimise toxicity – 60 mg/m² Q3W and weekly docetaxel (20 mg/m² to 35 mg/m²). Materials and Methods: Medical records of 89 CRPC patients between December 2003 and April 2013 were reviewed. Pairwise statistical analysis was performed, comparing efficacy and safety outcomes of 75 mg/m² Q3W and weekly docetaxel with 60 mg/m² Q3W. Treatment endpoints used were prostate-specific antigen (PSA) response (decrease of ≥50% from baseline), pain improvement after cycle 2, overall survival, time to disease progression and radiological response. Results: Patients who received docetaxel at 75 mg/m² Q3W were younger than those who received 60 mg/m² Q3W (62 years and 66 years, respectively; *P* = 0.0489). Both groups had similar response rates. Compared with patients on 60 mg/m² Q3W, more patients on weekly regimens were symptomatic at baseline (63.2% and 87.5%, respectively; *P* = 0.0173). Longer overall survival was observed in the 60 mg/m² Q3W arm than the weekly docetaxel arm (16.9 months and 10.6 months, respectively; *P* = 0.0131), though other measures of response did not differ significantly. Conclusion: Our data supports the use of 60 mg/m² Q3W docetaxel which has similar efficacy and an acceptable toxicity profile compared to the standard 75 mg/m² Q3W regimen. Weekly docetaxel has significant palliative benefits among symptomatic patients despite lower overall survival.

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Key words: Chemotherapy, Genitourinary, Toxicity

Introduction

The incidence of prostate cancer is rising in Asia.[1] In Singapore, prostate cancer is the third most prevalent cancer among males, with an age-standardised rate of 28.0 per 100,000 a year from 2007 to 2011.[2] Castration resistance develops in a subset of prostate cancer patients, during which disease progression occurs despite castrate levels of androgens. Docetaxel chemotherapy is a standard treatment for castrate-resistant prostate cancer (CRPC) patients with metastatic disease, as it has been shown to improve survival rates and pain control at a dose of 75 mg/m² every 3 weeks (Q3W),[3] as well as at a dose of 60 mg/m² when combined with estramustine.[4] In May 2004, docetaxel was approved by the United States Food and Drug Administration (US FDA) for the treatment of metastatic CRPC with a dosing guideline of 75 mg/m² Q3W.

A lower dose of docetaxel (60 mg/m² Q3W) is widely administered in breast cancer, lung cancer and prostate cancer in Asian countries such as Japan and Singapore[5,6] due to observations of increased toxicity[7] with the higher dose (75 mg/m² Q3W). There have been no data regarding this attenuated regimen in terms of efficacy and safety in Asian prostate cancer patients. An alternative weekly chemotherapy regimen in prostate cancer is also commonly

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used to minimise toxicities experienced, especially for patients who are at a higher risk of developing serious myelosuppressive effects. While symptomatic benefits have been reported, there is less benefit to overall survival compared to 75 mg/m^2 Q3W docetaxel.[3,8,9] A recent study with a 2-weekly regimen was studied in a prospective randomised manner, showing that it was a better tolerated option compared to the Q3W regimen amongst CRPC patients.[10] However, this regimen has not been used locally at present.

In this study, we retrospectively evaluate efficacy and tolerability in a single large Asian cancer centre on the use of 60 mg/m^2 Q3W docetaxel in patients with CRPC, compared with patients receiving the recommended 75 mg/m^2 Q3W or weekly docetaxel (dosage: 20 mg/m^2 to 35 mg/m^2; day 1, 8 Q3W) in a real-world setting.

Materials and Methods

Study Population

All CRPC patients who were treated with docetaxel-based chemotherapy between December 2003 and April 2013 were reviewed. Institutional Review Board (IRB) approval was obtained prior to study commencement.

Data Collection

Medical records, blood tests and radiographic assessment results, inpatient discharge summaries as well as chemotherapy prescriptions and administration records were reviewed. Information about the patients' baseline characteristics, treatment details and outcomes were collected. Eastern Cooperative Oncology Group (ECOG) performance status scores were also obtained. The following treatment endpoints were used: a decrease in prostate-specific antigen (PSA) from baseline of more than 50%, symptomatic improvement of pain experienced after the end of the second cycle, radiological response based on the Response Evaluation Criteria in Solid Tumors (RECIST), overall survival and time to disease progression. For patients who terminated treatment due to disease progression or intolerable side effects, the date of disease progression was defined as the date of the last cycle of docetaxel chemotherapy received. For patients who ended treatment while still responding satisfactorily and experienced little to no side effects, the date of progression was defined to be the date during which a different line of treatment commenced.

Information was also collected for selected adverse events experienced during chemotherapy treatment (the period from the initiation of chemotherapy to 3 weeks after the last dose was administered). These included the number and cause of hospitalisations, febrile neutropaenia which resulted in hospitalisation and grade 3 or 4 neutropaenia defined by the Common Toxicity Criteria for Adverse Events (CTCAE) (version 4.0).

Statistical Analysis

Pairwise analysis was performed comparing the 75 mg/m^2 Q3W and weekly group (20 mg/m^2 to 35 mg/m^2) against the 60 mg/m^2 Q3W group. All statistical analysis was performed using R version 3.0.1. Pearson's chi-square test of independence and Fisher's exact test was used to compare categorical variables such as patients' race, number of prior hormonal manipulations, PSA response and reason for stopping chemotherapy treatment. Welch's t-test was used to compare the means of patient age and number of cycles of docetaxel received. Overall survival and time to disease progression data was analysed using the Cox proportional hazards model. A P value of ≤ 0.05 was deemed as statistically significant.

Results

Baseline Characteristics

The baseline data of the 89 patients reviewed is shown in Table 1. A total of 38 patients started their treatment with 60 mg/m^2 Q3W, 11 started with 75mg/m^2 Q3W and 40 started with a weekly regimen (doses range from 20 mg/m^2 to 35 mg/m^2).

The mean age of the 75 mg/m^2 group (62 years) was lower than that of the 60 mg/m^2 group (66 years) (P = 0.0489). The racial composition of the 75 mg/m^2 group was also significantly different, with a higher proportion of Malays (27.3% vs 10.5%), Indians (18.2% vs 5.3%) and Caucasian/Eurasians (18.2% vs 0.0%), and a lower proportion of Chinese (36.4% vs 84.2%) (P = 0.0047) than that of the 60 mg/m^2 group. There was a higher proportion of patients on the weekly regimen who were symptomatic before the start of treatment (87.5%) than those on the 60 mg/m^2 Q3W regimen (63.2%) (P = 0.0173).

Treatment Endpoint

The outcomes of the docetaxel treatment administered are summarised in Table 2. Kaplan-Meier curves for overall survival and treatment progression are shown in Figures 1 and 2, respectively, and waterfall plots of PSA change after the first and second cycle are shown in Figure 3. No significant difference between the groups was observed in the rate of PSA response (>50% decline in PSA from baseline), symptomatic response (reduction of pain after the second cycle) and radiological response. No difference was observed either in the time to disease progression

Table 1. Demographics/Baseline Information of Patients

	60 mg/m² Q3W n (%)	75 mg/m² Q3W n (%)	*P* Value*	Weekly n (%)	*P* Value†
No. of patients	38	11		40	
Age at first treatment, mean (range)	66 (50,83)	62 (52,68)	0.0489	68 (53,88)	0.240
Race, n (%)			0.0047		0.719
Chinese	32 (84.2)	4 (36.4)		34 (85.0)	
Malay	4 (10.5)	3 (27.3)		4 (10.0)	
Indian	2 (5.3)	2 (18.2)		1 (2.5)	
Caucasian/Eurasian	0 (0.0)	2 (18.2)		1 (2.5)	
Number of cycles, median (range)	5 (1,9)	7 (2,15)	0.0924	4 (1,8)	0.138
Symptomatic					
Symptomatic	24 (63.2)	9 (91.8)	0.300	35(87.5)	0.0173
Pain	20 (52.6)	6 (54.5)	1.00	24 (60.0)	0.648
Impending/current obstructive uropathy	4 (10.5)	2 (18.2)	0.605	12 (30.0)	0.0489
Gleason score			0.695		0.807
6 – 7	12 (31.6)	2 (18.2)		14 (35.0)	
8 – 10	23 (60.5)	7 (63.6)		22 (55.0)	
Not available	3 (7.9)	2 (18.2)		4 (10.0)	
Prior treatment					
Prostatectomy	4 (10.5)	2 (18.2)	0.605	6 (15.0)	0.738
Radical radiotherapy	11 (28.9)	2 (18.2)	0.703	11 (27.5)	1.00
Palliative radiotherapy	13 (34.2)	3 (27.3)	1.00	22 (55.0)	0.0736
Hormonal manipulations			0.327		0.102
≤2	6 (15.8)	0 (0.0)		15 (37.5)	
3 – 4	23 (60.5)	9 (81.8)		21 (52.5)	
≥5	7 (18.4)	2 (18.2)		4 (10.0)	
ECOG performance score			1.00		1.00
≤2	27 (71.1)	9 (81.8)		27 (67.5)	
3 – 4	2 (5.3)	0 (0.0)		3 (7.5)	
Not evaluated	9 (23.7)	2 (18.2)		10(25.0)	
Extent of disease					
Bone metastasis	33 (86.8)	10 (90.9)	1.00	36 (90.0)	0.734
Visceral metastasis	10 (26.3)	3 (27.3)	1.00	13 (32.5)	0.624
Lymph nodes involvement	22 (57.9)	6 (54.5)	1.00	27 (67.5)	0.483

ECOG: Eastern Cooperative Oncology Group; Q3W: Every 3 weeks

*Statistical analysis performed comparing the 75 mg/m² Q3W group and the 60 mg/m² Q3W group.

†Statistical analysis performed comparing the weekly docetaxel group and the 60 mg/m² Q3W group.

between patients in the 75 mg/m² and 60 mg/m² groups as well as the weekly and 60 mg/m² group. The median overall survival of the 60 mg/m² Q3W chemotherapy arm (median: 16.9 months) was higher than that of the weekly docetaxel arm (median: 10.6 months) (hazard ratio [HR]: 1.91; $P = 0.01$), but did not differ significantly from the overall survival of the 75 mg/m² Q3W group (median: 18.0 months) (HR: 1.34, $P = 0.5$).

Adverse Events

Table 3 outlines the adverse events experienced during chemotherapy treatment. There was no significant difference in the frequency or cause of hospitalisation between the groups. The incidence of febrile neutropaenia and of treatment termination due to toxicity-related reasons between the groups also did not differ significantly. Of the 89 patients reviewed, 4 (4.5%) died within 4 weeks of last

Table 2. Docetaxel Chemotherapy Outcome

	60 mg/m² Q3W n (%)	75 mg/m² Q3W n (%)	*P* Value†	Weekly n (%)	*P* Value†
>50% fall in PSA from baseline			0.300		1.00
No. evaluated	36	11		39	
Response	18 (50.0)	8 (72.7)		18 (46.2)	
Reduction of pain at the end of second cycle			0.430		0.178
No. evaluated	19	6		19	
Response	18 (94.7)	5 (83.3)		14 (73.7)	
Time to treatment progression			0.72		0.191
No. evaluated	38	11		40	
Median (range), months	3.6 (0, 50.8)	7.9 (0.7, 14.6)		3.0 (0, 22.1)	
Hazard ratio		0.883		1.35	
Overall survival			0.453		0.0131
No. evaluated	38	11		40	
Median (range), months	16.9 (1.9, >58.2)	18.0 (7.4, 31.2)		10.6 (1.4, 59.4)	
Hazard ratio		1.34		1.91	
Radiological response			0.226		0.606
No. evaluated	8	6		16	
Partial response	3 (37.5)	3 (50.0)		8 (50.0)	
Stable disease	2 (25.0)	3 (50.0)		5 (31.3)	
Progressive disease	3 (37.5)	0		3 (18.8)	
Reason for stopping treatment			0.913		0.705
No. evaluated	38	11		40	
Progressive disease	9 (23.7)	2 (18.2)		14 (35.0)	
Toxicity	14 (36.8)	6 (54.5)		11 (27.5)	
PD + toxicity	5 (13.2)	1 (9.1)		3 (7.5)	
Completed treatment	6 (15.8)	2 (18.2)		5 (12.5)	
Patient preference	1 (2.6)	0 (0.0)		1 (2.5)	
Oncologist's preference	1 (2.6)	0 (0.0)		4 (10.0)	
Death	2 (5.3)	0 (0.0)		2 (5.0)	

PD: Progressive disease; Q3W: Every 3 weeks

*Statistical analysis performed comparing the 75 mg/m² Q3W group and the 60 mg/m² Q3W group.

†Statistical analysis performed comparing the weekly docetaxel group and the 60 mg/m² Q3W group.

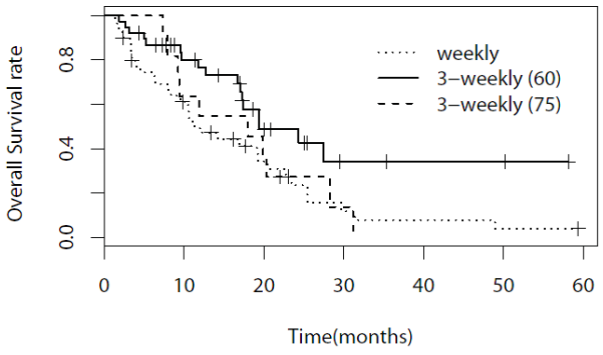

Fig. 1. Kaplan-Meier estimates for the probability of overall survival.

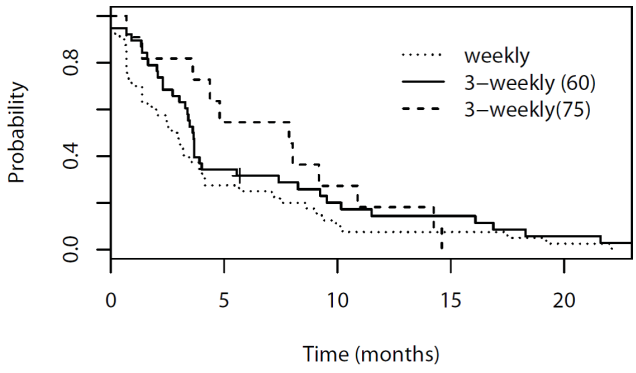

Fig. 2. Kaplan-Meier estimates for the probability of treatment progression.

Table 3. Toxicity Experienced

	60 mg/m² Q3W n (%)	75 mg/m² Q3W n (%)	*P* Value*	Weekly n (%)	*P* Value†
Hospitalisation					
Hospitalised	12 (29.7)	5 (45.5)	0.468	14 (36.6)	0.632
Toxicity‖	8 (18.9)	4 (36.4)		8 (22.0)	
PD‖	2 (5.4)	0 (0.0)	0.592	4 (9.8)	1.00
Others‖	2 (5.4)‡	1 (9.1)§		2 (4.9)‡	
Febrile neutropaenia	4 (10.8)	1 (9.1)	1.00	3 (7.3)	0.702
Stopping treatment due to toxicity					
Toxicity/PD + toxicity/ treatment-related death	21 (55.3)	7 (63.6)	0.737	16 (40.0)	0.257
Grade 3 or 4 neutropaenia					
Neutropaenia	7 (18.4)	4 (36.4)	0.237	3 (7.5)	0.187
Death during chemotherapy					
Death	2 (5.3)	0 (0.0)	1.00	2 (5.0)	1.00

PD: Progressive disease; Q3W: Every 3 weeks
*Statistical analysis performed comparing the 75 mg/m² Q3W group and the 60 mg/m² Q3W group.
†Statistical analysis performed comparing the weekly docetaxel group and the 60 mg/m² Q3W group.
‡Hospitalisation reason – administration of chemotherapy.
§Hospitalisation reason – bilateral percutaneous nephrostomy (PCN) change.
‖First hospitalisation cause.

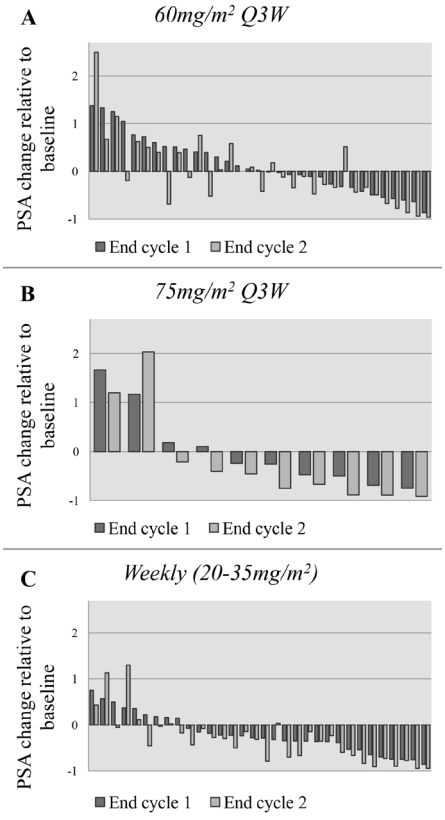

Fig. 3. Waterfall plot of PSA change at the end of cycles 1 and 2 relative to baseline for patients who received A) 60 mg/m² of docetaxel Q3W, B) 75 mg/m² of docetaxel Q3W, C) weekly docetaxel.

dose of chemotherapy. Causes of death were docetaxel-induced pneumonitis (60 mg/m² Q3W) (n = 1), ischaemic heart disease (weekly) (n = 1), progressive disease (weekly) (n = 1). Data was not available as to the cause of death for the last patient.

Regimen Change or Dose Reductions

Of the 38 patients who were treated with 60 mg/m² Q3W, 3 (7.9%) had their docetaxel dose increased to 75 mg/m² from cycle 2 (2 eventually had their doses decreased again) and 1 patient (2.6%) had his regimen changed to a weekly docetaxel regimen from cycle 4. Of the 11 who started out with 75 mg/m², 3 (27.3%) had their dose permanently decreased from cycle 2, and 1 patient (9.1%) switched to a weekly regimen from cycle 2. In addition, one of the 40 (2.5%) who started with a weekly regimen had his regimen changed to a Q3W (60 mg/m²) one from cycle 3.

Discussion

We have shown that docetaxel has significant palliative benefits in terms of symptomatic relief and PSA response regardless of regimen administered. Patients who received 60 mg/m² Q3W and patients who received 75 mg/m² Q3W had similar responses in terms of PSA decrease, pain relief, objective tumour response, time to progression and overall survival. The PSA response rates we observed (50.0% for

60 mg/m^2 and 72.7% for 75 mg/m^2) are comparable to those reported by Tannock et al (45%) and Petrylak et al (50%).[3,4] Median overall survival (16.8 months for 60 mg/m^2 and 18.0 months for 75 mg/m^2) were also similar to those observed in the above studies (18.9 months in Tannock et al and 17.5 months in Petrylak et al). Hence, it is likely that treatment efficacy had not been compromised with a lower dose of docetaxel Q3W. We would like to highlight that during the study period, newer agents like abiraterone acetate, enzalutamide and cabazitaxel were not available and hence, not used by patients on this study. Usage of these newer therapies could have confounded the findings but that was not the case here.

In terms of tolerability, although toxicities were not statistically different in patients receiving 60 mg/m^2 Q3W compared to those who received 75 mg/m^2 Q3W, both hospitalisations and incidences of grade 3 or 4 neutropaenia were proportionally higher in the 75 mg/m^2 arm. We also observed that 36.4% of patients who initially received 75 mg/m^2 had their regimen changed after the first cycle of treatment due to side effects experienced. Dose reductions were likely done in order to mitigate the side effect profile and as such, support the notion that the 75 mg/m^2 Q3W patients had higher toxicities. Among patients who received 60 mg/m^2 Q3W, chemotherapy treatment was relatively well tolerated. Toxicities in terms of the incidence of grade 3 or 4 neutropaenia was similar to the randomised trials by Tannock et al and Petrylak et al (32% and 16.1%, respectively).[3,4]

When compared to patients receiving 60 mg/m^2 Q3W, patients who received weekly chemotherapy had a significantly lower overall survival (median of 16.9 months and 10.6 months, respectively). However, we did not observe significant differences for other measures of response. The weekly regimen findings in our study was similar to the study by Berry et al – the median overall survival of 60 metastatic CRPC patients who received weekly docetaxel (36 mg/m^2 on days 1, 8, 15, 22, 29 and 36 every 8 weeks) was 9.4 months and the proportion of patients who had a PSA response, defined as ≥50% decrease of PSA with stabilisation or improvement in performance status lasting 2 months or longer, was 41%.[8] In a phase II trial by Beer et al, the median overall survival for a group of significantly symptomatic patients on weekly docetaxel (36 mg/m^2 administered weekly for 6 consecutive weeks followed by 2 weeks without treatment) with compromised performance status was 9.8 months and PSA response rate was 46%.[9] These trials also observed low rates of treatment-related toxicity.

At our institution, patients who had received weekly docetaxel at our centre were largely more symptomatic (87.5%) than those who received 60 mg/m^2 Q3W (63.2%). This was not surprising as the patients treated with a weekly regimen were likely to be less fit with higher disease burden accounting for the symptoms. Hence, a lower overall survival in the weekly group could be explained by both the lower total doses of treatment received by the group and the likelihood of higher diseases burden with shorter projected survival to start with.

There have been numerous studies comparing docetaxel pharmacokinetics (PK) in Asian countries compared to their Western counterparts. These studies seem to show that although interethnic differences were not seen in terms of docetaxel PK values, there seems to be higher toxicities seen in Asians compared to their Western counterparts.[11] These studies lend support to the use of the lower dose of docetaxel in our local population of advanced prostate cancer patients as well.

Limitations

This study was limited by the fact that it was a small non-randomised retrospective study of patients treated at a single institution. Treatment regimens were largely allocated by a number of different physicians. This resulted in slightly differing profiles of patients across the 3 groups. It is therefore possible that some of the comparisons here may be affected by such bias. However, since toxicities were apparently higher in the 75 mg/m^2 Q3W group, which would have otherwise been expected to be fitter than patients receiving 60 mg/m^2 Q3W, our results are likely to be representative. We are also aware that the weekly docetaxel group with a dose varying between 20 mg/m^2 to 35 mg/m^2 on day 1 and day 8 Q3W is not commonly used in many parts of the world and is peculiar to the Singapore setting and presents another limitation to the extrapolation of these results elsewhere. Another limitation was that data on other prognostic factors like haemoglobin, lactate dehydrogenase and alkaline phosphatase were not collected and hence, not controlled for in the analysis. This study also does not have data on the number of patients who needed granulocyte colony-stimulating factor (G-CSF) support as secondary prophylaxis for febrile neutropaenia. None of the physicians in this study had used G-CSF as primary prophylaxis even with the higher dose of docetaxel. This could account for the higher rates of grade 3/4 neutropaenia in this group.

Apart from the above limitations, this study reflects the treatment outcomes of a sample representative of the metastatic CRPC patients treated in Singapore in a real-world setting and provides support for the continued use of docetaxel 60 mg/m^2 Q3W in Asian patients with CRPC.

Conclusion

As far as we know, this is the first real-world treatment

data to show that docetaxel can be safely administered to metastatic CRPC Asian patients with a dosing guideline of 60 mg/m^2 Q3W instead of the standard 75 mg/m^2, with similar efficacy and an acceptable toxicity profile. A weekly docetaxel regimen at dosing guidelines of 20 mg/m^2 to 35 mg/m^2 has significant palliative benefits among symptomatic patients despite lower overall survival compared to the Q3W regimens.

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PAtient Safety in Surgical EDucation (PASSED): A Pilot Study Using iPad Game to Teach Patient Safety in Undergraduate Medical Curriculum

Dear Editor,

In 1991, after the Harvard Medical Practice Study reported on the adverse events and negligence in hospitalised patients, there was a major tsunami in the healthcare systems around the world to improve patient safety in the hospitals.[1] While healthcare outcomes have improved significantly over the past 3 decades, the complexity of medical technology and service demands has also escalated the risks in patient safety. Therefore, patient safety education is extremely crucial in cultivating the practice of safe medicine. Recognising that the newer generation medical students have very different learning habits as a result of rapid development of computers and easy access to the Internet, harnessing the unique features of mobile devices such as an iPAD can help to bridge the gap in the learning habits of these students. Serious games in healthcare is increasingly gaining popularity as it allows repeatable safe training before the learners move on to work as healthcare professionals in the real world.

Materials and Methods

The Undergraduate Education Team from the Department of Surgery, Yong Loo Lin School of Medicine at the National University of Singapore created an iPAD game called PASSED, which stood for "**PA**tient **S**afety in **S**urgical **Ed**ucation". It was a 10-scenario interactive game which was developed using cases from the archive of sentinel events and serious reportable events in the hospital. The scenarios explored the concepts of patient safety in 3 main areas (Table 1): Group A – Interpretation of critical investigation results; Group B – Identifying correct tools and equipment in administering critical medications; and Group C – Prioritisation of multiple tasks or communications with healthcare workers in critical situations.

We conducted the pilot study in June 2014 with a group of Phase III medical students (n = 53), who were doing surgery rotation. The session started with a presentation on the principles of patient safety using the World Health Organization (WHO) Patient Safety Curriculum Guide for Medical Schools.[2] The game started with a page showing brief instructions on how to play the game. The students played the role of a surgical resident and interacted with the nurses in the surgical ward during a night call. As the story progressed, there were intermittent interjections of critical lab results or calls from nurses to inform on ill patients (Fig. 1). The intention was to simulate busy night calls where prioritisation of critical tasks was required. We added interesting features such as extra bonus marks

Table 1. Grouping of Scenarios According to the Area of Interest

Group A		
Interpretation of critical x-ray/ laboratory results	Scenario 1	Pneumoperitoneum representing perforated viscus.
	Scenario 4	NG tube in right bronchus on x-ray.
	Scenario 6	ECG showing hyperkalaemic changes.
Group B		
Identifying correct tools/instruments and correct administration of medications	Scenario 2	NG tube testing with litmus paper vs CXR.
	Scenarios 5A and 5B	Hypotension needing fluid resuscitation – choosing correct drip, appropriate rate to run the fluid.
	Scenarios 9A to 9E	Correcting hyperkalaemia using correct vial of actrapid, correct insulin syringe, drawing correct volume, giving it according to correct method and lastly, on the correct site of the peripheral IV cannula.
Group C		
Learning prioritisation of tasks/appropriate communication methods in critical situations	Scenario 3	Patient with seizure vs reviewing at repeat CXR.
	Scenario 5C	Appropriate reaction to trigger call from nursing staff.
	Scenario 7	Prioritisation of 3 tasks at the same time.
	Scenario 8	Appropriate response to call centre informing critical laboratory results.
	Scenario 10	Appropriate response to critical radiological report trigger on workphone.

CXR: Chest x-ray; ECG: Electrocardiogram; IV: Intravenous; NG: Nasogastric

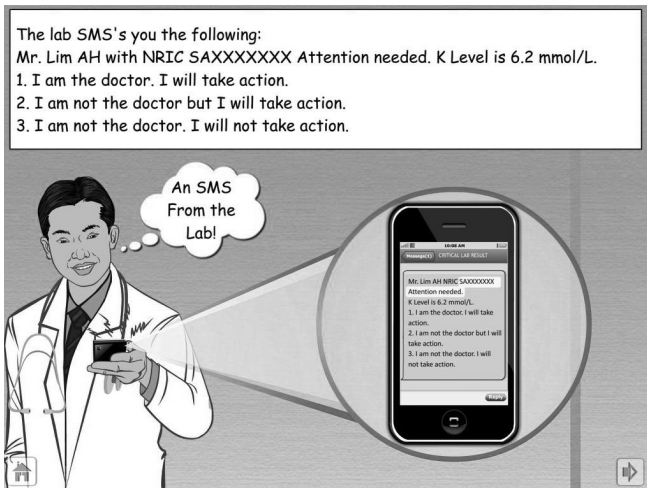

Fig. 1. One of the scenarios where students were required to prioritise the tasks that were linked to patient safety.

for correct answers given within 10 seconds. Each step allowed a maximum of 2 attempts. Each wrong attempt entailed demerit points. Each student could view their performance in each of the scenario in detail at the end of the game. Perception of students' patient safety awareness was conducted using the Attitude to Patient Safety Questionnaire-III (APSQ-III) before and after the game.[3]

Results

Table 2 shows the overall performance score of the students in this cohort.

Group A – Interpretation of Critical X-rays or Lab/ Investigation Results (Table 3)

In Scenario 1, more than half (41.5%) of the students missed the pneumoperitoneum (after 2 attempts). A Ryles tube was misplaced into the right bronchus as noted on the chest x-ray (CXR) in Scenario 4 and 81.1% of students spotted the problem and chose to pull the tube out entirely and reinsert. In Scenario 6, a similar proportion of students (84.9%) was able to identify the hyperkalaemic changes on electrocardiogram at the first instance.

Group B – Identifying the Correct Tools/Instruments and Correct Administration of Medication (Table 3)

In Scenario 2, students were asked about the most reliable method to check the position of the Ryles tube and 51.0% answered correctly. Majority of students answered correctly in Scenarios 5A (92.6%) and 5B (96.3%). In Scenario 9, where intravenous insulin was used to correct hyperkalaemia, 11.3% failed to choose the correct type insulin on their first attempt (9A), 37.8% chose the wrong

Table 2. Overall Performance Score of Students on PASSED iPAD Game in this Pilot Cohort

	Median	Range	Mean	SD
Overall posting 1 scores	27	9 to 41	27.11	7.28
Group A Score	5	-1 to 7	4.57	1.64
Scenario 1	1	0 to 3	0.89	0.95
Scenario 4	1	-3 to 2	1.55	1.03
Scenario 6	1	-1 to 7	1.83	0.43
Group B	16	3 to 29	15.26	6.63
Scenario 2	2	-1 to 3	1.68	1.45
Scenarios 5A and 5B	7	-4 to 9	5.92	3.03
Scenarios 9A to 9E	16	3 to 29	15.34	6.69
Group C	17	5 to 19	15.06	3.52
Scenario 3	3	-1 to 3	2.38	1.27
Scenario 5C	7	-4 to 9	5.92	3.03
Scenario 7	2	0 to 2	1.83	0.47
Scenario 8	2	0 to 2	1.92	0.39
Scenario 10	3	3 to 3	3.00	0.00

SD: Standard deviation

syringe to draw the Actrapid insulin (9B), 32.1% chose the wrong volume of Actrapid insulin on their first attempt (9C), 51.9% administered wrongly on their first attempt (9D) and 24.5% chose the arm with arteriovenous fistula in an end-stage renal failure patient to administer the medications (9E).

Group C – Learning Prioritisation of Tasks/Appropriate Communication in Critical Situations (Table 3)

In Scenario 3, 88.7% of the students responded correctly to prioritise treating a patient who had suddenly developed seizures over reviewing a repeat CXR following Ryles tube insertion. In the rest of the scenarios, more than 90% of students responded correctly – Scenario 5C (98.1%), Scenario 7 (86.8%), Scenario 8 (96.2%) and Scenario 10 (100%).

The students felt that the various aspects of patient safety awareness according to the APSQ-III was significantly better after the game (Fig. 2).

Discussion

Using computer or video games for training in military, education, manufacturing, health and medicine is defined as serious games.[4] Considering the learning habits of the current generation of students, serious games can help to increase interest in training and education. In addition, evaluation of user performance can be easily conducted.[5,6] This PASSED game aims to impart knowledge and raise awareness for patient safety in medical students. Different

Table 3. Responses of Students on the Scenarios in the PASSED Game

Scenario	Results	%
Group A: Interpretation of critical x-rays or lab/investigation results)		
Scenario 1 – Pneumoperitoneum on CXR	Wrong after 2 attempts	41.5
	Correct at second attempt	37.7
	Correct at first attempt	11.3
	Bonus correct 10 seconds*	9.4
Scenario 4 – NG tube in right bronchus	Wrong after 2 attempts	1.9
	Correct at second attempt	17.0
	Correct at first attempt	81.1
Scenario 6 – ECG showing hyperkalaemic changes	Wrong after 2 attempts	3.8
	Correct at second attempt	5.7
	Correct at first attempt	90.6
Group B: Identifying correct tools/instruments and correct administration of medications		
Scenario 2 – NG tube placement (testing with litmus paper vs CXR)	Wrong after 2 attempts	15.1
	Correct at second attempt	33.9
	Correct at first attempt	3.8
	Bonus correct 10 seconds*	47.2
Scenario 4 – NG tube in right bronchus	Wrong after 2 attempts	1.9
	Correct at second attempt	17.0
	Correct at first attempt	81.1
Scenario 5A – Hypotension resuscitation (drip type)	Correct drip chosen at first attempt	39.6
	Correct drip chosen at second attempt	52.8
	Wrong drip after 2 attempts	7.6
Scenario 5B – Volume and rate of drip	Correct volume and rate at first attempt	90.6
	Correct volume and rate at second attempt	5.7
	Wrong volume and rate after 2 attempts	3.8
Scenario 9 – Correcting hyperkalaemia using insulin		
Scenario 9A – Choice of correct type of insulin	Chose correct insulin at first attempt	88.7
	Chose correct insulin at second attempt	3.8
	Wrong insulin chosen after 2 attempts	7.5
Scenario 9B – Choice of correct syringe	Chose correct insulin syringe at first attempt	62.3
	Chose correct insulin syringe at second attempt	34.0
	Wrong insulin syringe chosen after 2 attempts	3.8
Scenario 9C – Choice of correct insulin volume	Chose correct insulin volume at first attempt	67.9
	Chose correct insulin volume at second attempt	18.9
	Wrong insulin volume chosen after 2 attempts	13.2
Scenario 9D – Choice of correct method of administration	Correct method to administer IV insulin at first attempt	49.1
	Correct method to administer IV insulin at second attempt	47.2
	Wrong method after 2 attempts	3.8
Scenario 9E – Choice of correct site to administer	Correct arm to administer (non-AVF arm)	75.5
	Wrong arm to administer (arm with AVF)	24.5
Group C (Learning prioritisation of tests/appropriate communication methods in critical situations)		
Scenario 3 – Attending to seizure vs reviewing repeat CXR first	Chose to refer neuro first (10 seconds)	71.7
	Chose to refer neuro first	17.0
	Chose to look at CXR first (wrong)	11.3

AVF: Arteriovenous fistula; CXR: Chest x-ray; ECG: Electrocardiogram; IV: Intravenous; NG: Nasogastric; SMS: Short message service
*Students were awarded additional points if they answered correctly within the first 10 seconds of the scenario.

Table 3. Responses of Students on the Scenarios in the PASSED Game (Con't)

Scenario	Results	%
Group A (Interpretation of critical x-rays or lab/investigation results)		
Scenario 5C – Appropriate reaction to trigger call from nursing staff	Correct trigger response to nurse call (within 10 seconds)	73.6
	Correct trigger response at first attempt	22.6
	Correct trigger response after second attempt	1.9
	Wrong after 2 attempts	1.9
Scenario 7 – Prioritisation of 4 tasks at the same time	Correct rate at first attempt	86.8
	Correct rate at second attempt	9.4
	Wrong rate after 2 attempts	3.8
Scenario 8 – Appropriate response to call centre informing of critical lab results	Read back and thanked the operator (correct)	96.2
	Said yes but ignored the results (wrong)	3.8
	Unhappy at being called by the call centre (wrong)	0.0
Scenario 10 – Appropriate response to critical radiology report sent by SMS	Noted the report and went to review patient and case sheet	100.0
	Ignored the report	0.0

AVF: Arteriovenous fistula; CXR: Chest x-ray; ECG: Electrocardiogram; IV: Intravenous; NG: Nasogastric; SMS: Short message service

from the usual simulation training, where large simulation machines or mannequins connected to computer systems are required, PASSED game only requires the students to bring mobile devices such as an iPad, and the gaming session can be conducted anywhere as long as there is wireless Internet connection. The portability and convenience is certainly a great advantage as compared to conventional simulation that requires large space facilities to house the simulation systems and machines.

Many studies have clearly shown that adverse events occur not because of negligent healthcare professionals intentionally harming patients, but rather the system of healthcare is so complex that the successful treatment and outcome for each patient is not dependent on the competence of an individual healthcare provider alone.[2] Using this gaming system, students can learn about patient safety in a safe environment. Another added advantage of this system is the repeatability of the games. In Group A, students were assessed on their ability to detect critical abnormalities on radiographs and laboratory investigations that could lead to severe morbidity and mortality. Under the gaming setting, students were allowed to revisit this scenario to enhance their memory and experience. At the same time, the experience of the whole cohort was uniform. Indeed, we have shown that students who learnt the concepts of patient safety repeatedly under a safe environment had better awareness in this area.[7,8]

Human factor is a well recognised entity in patient safety studies. It studies the interrelationship between humans, the tools and equipment they use in the workplace, and the environment in which they work.[9] Majority of the

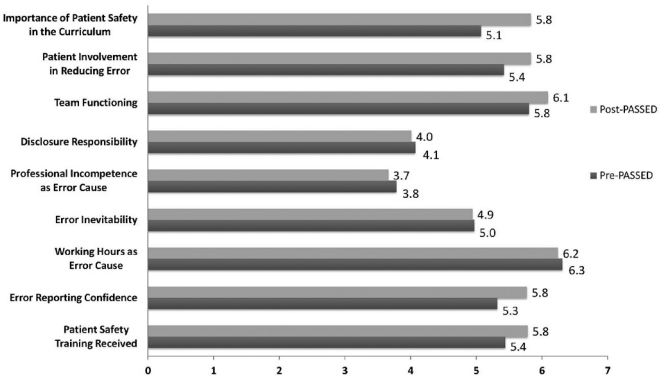

Fig. 2. Perception of patient safety before and after the PASSED test using APSQ-III questionnaire.

students did well in the interpersonal communication skills under critical situations. This reflected the earlier training that the students received in the preclinical years where the concept of "situation-background-assessment-recommendation" helped to enhance their understanding on the importance of effective communications between other healthcare workers. When a healthcare professional has to handle multiple tasks simultaneously, the distractibility of human beings comes into play. Our ability to be distracted predisposes us to commit error and this could be harmful to patient care.[10] Scenario 7 tested on this aspect and the students responded well. However, in real-life situations, the challenges could be more daunting. Therefore, in healthcare, human factors knowledge can help to design processes that make it easier for doctors and nurses to do their job

right. Currently, abnormal investigation results are sent as a trigger to the on-duty doctors in the form of short-text messages, similar to that in Scenarios 8 and 10. To enhance patient safety in the healthcare practice, a system must be built to endure that critical investigation results are sent to the doctors and nurses immediately with reminders that are automatically sent unless actions are taken to reduce the patient safety errors in hospitals.[10]

In this era, undergraduate medical curriculum must be focused, yet robust. While the core knowledge of medicine can be taught using conventional methods, certain areas such as patient safety concepts could be delivered in a more interesting way. We believe that using iPad gaming system to teach patient safety is effective as it provides additional avenue to allow uniform exposure outside of conventional textbook teaching.

Conclusion

By using PASSED to enhance patient safety teaching, we found that medical students were good at basic communications with other healthcare workers and prioritisation of multiple tasks. Likewise, they performed well in interpreting critical investigation results. However, students did not do well when specific practical knowledge on instruments and administration of medications were evaluated. This unique teaching pedagogy using interactive gaming system can help identify gaps in patient safety training and raise awareness amongst future doctors in order to improve the healthcare system. Future research ideas for patient safety education could include games that train students on surgical competencies, time-out concepts, hospital infection control and the use of 2 patient identifiers to avoid misidentification. More interactivity could be created in future games as well.

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This paper is a pilot study on the performance of the students with the game. The paper titled, "Innovative patient safety curriculum using iPAD game (PASSED) improved patient safety concepts in undergraduate medical students", published in World Journal of Surgery, Vol. 16, 2016, contained data only on the perception of the students on aspects of patient safety based on the APSQ-III.

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Letter to the Editor

A Single Centre Experience with Selective Termination of Anomalous Foetus in Multifoetal Pregnancies

Dear Editor,

The percentage of multiple births has increased over the past 3 decades, primarily as a result of advanced maternal age, the greater use and success of assisted reproductive technologies. The incidence of foetal malformations is higher in multifoetal pregnancies compared to singletons.[1] In dizygotic (DZ) twins, there is essentially more than twice the risk per pregnancy (independent probabilities per foetus); while in monozygotic (MZ) twins, there is an increased risk of structural malformations and the rates of Mendelian and chromosomal abnormalities are comparable to those of singletons. In both MZ and DZ twins, nearly 85% of cases have malformation that is confined to one foetus and the co-twin is normal.

After the diagnosis of foetal anomaly with an apparently normal co-twin, a couple would be faced with the dilemma of the following 3 options: expectant management, terminate the whole pregnancy or selective termination (ST) of the abnormal foetus. Aberg et al[2] reported the first successful selective birth from a twin pregnancy discordant for Hurler syndrome in 1978 following which Kerenyi and Chitkara[3] reported selective birth for twins discordant for Down syndrome in 1981. Throughout the 1980s, a number of small series of second trimester selective terminations appeared in the literature, showing high loss rates and morbidity.[4-6] The main variable in selecting the technique of ST is chorionicity. In dichorionic (DC) twins, intracardiac injection of potassium chloride (KCl) in the affected foetus is safe for the normal co-twin as vascular communications do not exist; while in monochorionic (MC) pregnancies, the risk of passage of KCl into the circulation of the normal co-twin through placental anastomosis precludes this technique.

Materials and Methods

All cases of DC twins and triplets discordant for congenital defect that underwent selective termination from August 2005 and December 2012 at the KK Women's & Children's Hospital were analysed retrospectively. Parents were informed about the technical aspects and the pros and cons including procedure-related foetal loss rate prior to the procedure. They were counselled by neonatologists and paediatric surgeons regarding perinatal management, postnatal course, surgery and prognosis of congenital defect. Hospital ethics committee approval was sought. ST was performed at the Antenatal Diagnostic Centre as an outpatient procedure by trans-abdominal percutaneous injection (by 20 G spinal needle) of intracardiac KCl in the anomalous foetus under ultrasonographic guidance. A concentration of 7.45% KCl was used and 3 mL to 10 mLwas enough to achieve foetal asystole.

Data were collected on indications for the procedure, the week the procedure was performed, which foetus was terminated (presenting vs non-presenting foetus), pregnancy losses, and gestational age at delivery, birth weight and neonatal outcome. Indications were divided into chromosomal aberrations and structural anomalies. Foetal loss was defined as unintended loss of the whole pregnancy before 24 weeks of gestation. Perinatal data were obtained by the clinical charts for neonates delivered in our centre.

Results

This series consists of 12 DC multifoetal pregnancies discordant for congenital defect in which ST was performed. Mean maternal age was 35 years (range, 30 to 40). Eleven out of 12 were in vitro fertilisation (IVF) pregnancies. Congenital defects of the anomalous foetus are shown in Table 1. Ten mothers (83.3%) had ST for foetuses with structural defects, 4 (40%) of which were abnormalities of the central nervous system. Two (16.7%) of the cases had ST for trisomy 18 foetuses with associated structural defects.

The mean gestational age (GA) at the time of the procedure was 18.3 weeks (range, 15 to 22; SD), and 7 (58.3%) were performed before 18 weeks. In 2 cases (16.7%), the lower or presenting foetus was terminated. In 8 pregnancies (66.7%), twins were reduced to singleton. Four (33.3%) were triplets, out of which 2 were trichorionic triamniotic and reduced to twins due to structural anomaly and 2 were DC triamniotic reduced to singleton. One of them being with MC pair with stage III b twin-to-twin transfusion syndrome (TTTS) and so reduced to singleton. The second patient had foetal reduction in her native country in the first trimester and later did ST due to omphalocele at our institution. ST was technically successful in 100% of the reported cases; there were no failed procedures.

Perinatal outcomes are shown in Table 2. One mother went back to her native country after ST and was lost to follow-

Table 1. Congenital Defect of the Anomalous Foetus

Indication (n = 12)	n (%)
Chromosomal defects	
Trisomy 18 (47XX + 18)	2 (16.7%)
Strawberry head, VSD, persistent Left SVC	
Cleft lip, absent right forearm, cerebellar gap	
Structural abnormality and normal chromosomes	10 (83.3%)
CNS	
Arnold-Chiari malformation, hydrocephaly, lumbar spina bifida, meningocele	
Caudal regression syndrome	
Spina bifida, lumbar spine kyphosis	
Spina bifida at L3 with neural tissue	
Non-CNS	
VSD, overriding aorta, cardiomegaly, poor contractility	
Hypoplastic left heart, single ventricle complex, pulmonary atresia, cystic hygroma	
Omphalocele	
Body stalk anomaly/severe oligohydramnios	
Body stalk anomaly/spine abnormality/heart outside body	
Stage IIIb TTTS*	

CNS: Central nervous system; SVC: Superior vena cava; TTTS: Twin-to-twin transfusion syndrome; VSD: Ventricular septal defect
*Triplets reduced to singleton terminating monochorionic pair.

Table 2. Overall Perinatal Outcomes

	n = 11†
Foetal loss <24 weeks	0
Other complications	
PPROM	2
Preterm delivery of the terminated twin	0
Healthy newborns	13*
GA at delivery (weeks)	35 weeks
<33 weeks	3
33 – 36 + 6 weeks	4
37 – 40 weeks	4
Birth weight (g)	2194.6 g
Hospital stay	
Admission (average stay)	
Peripheral ward	6 (2.6 days)
Special care nursery	3 (20.3 days)
Neonatal ICU	2 (80.5 days)

GA: Gestational age; ICU: Intensive care unit; PPROM: Preterm premature rupture of membranes; ST: Selective termination
*Includes 2 sets of twins.
†One went back after ST.

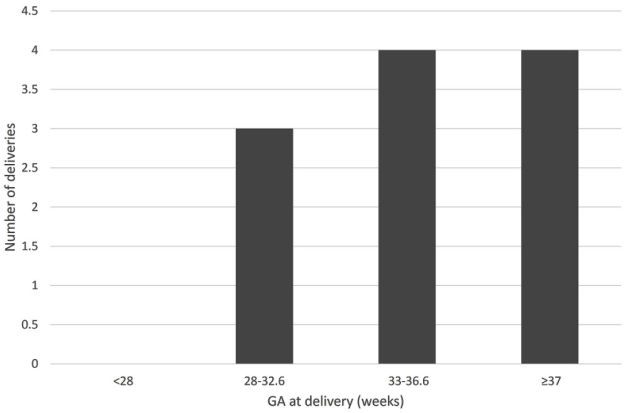

Fig. 1. Gestational age distribution at delivery.

up. ST was followed by the delivery of a healthy newborn in 100% (13/11 with 2 sets of twins) of the cases. There was no report of unintended loss of the whole pregnancy before 24 weeks. Two cases had perinatal complications. The first case was a ST at 16 weeks of a non-presenting foetus affected by caudal regression syndrome. At 25+1 weeks of gestation, the patient had preterm premature rupture of membranes (PPROM). She was managed expectantly and gestation ended at 32.1 weeks with a healthy newborn of 1548 g with Apgar of 6,7. The baby required neonatal ICU care and was discharged stable on 65th day of life. The second case was ST at 18 weeks of a non-presenting foetus with body stalk anomaly. The patient presented with PPROM at 19+1 weeks. Antibiotic therapy was given and later corticosteroids for foetal maturation were administered at 24+4 weeks. The patient delivered spontaneously at 28.4 weeks to a baby girl that weighed 1066 g with Apgar of 0,5. She required prolonged intensive care unit (ICU) stay with issues of hyaline membrane disease, persistent pulmonary hypertension, neonatal systemic hypertension. The baby was stable at discharge.

Spontaneous delivery between 28 to 33 weeks and 33 to 36+6 weeks of pregnancy occurred in 3 cases (27.3%) and 4 (36.4%), respectively. The remaining 4 (36.4%) mothers delivered at term (Fig.1). The mean birth weight was 2194 g (range, 1066 g to 3205 g).Seven mothers were delivered by caesarean section while the remaining 4 had vaginal delivery. Six (54.5%) newborns were admitted to peripheral ward with an average 2.6 days of stay, 3 (27.2%) went to special care nursery for an average duration of 20.3 days and 2 (18.1%) of them required ICU care with an average stay of 80.5 days. All surviving newborns were well at discharge except 3/13 (23%) who had postural talipes equinovarus.

There were no instances of clinically evident or laboratory-diagnosed coagulopathies in mothers. No ischaemic damage or coagulopathies were observed among the surviving neonates. No significant linear relationship between GA at-procedure and GA at-delivery was noted.

Discussion

ST was initially developed for severe anomalies with a risk of handicapped- or mentally-challenged infants. Nowadays, it is even contemplated in DZ twins discordant for lethal defects. The decrease in foetal loss rate associated with the procedure, compared with the risk of adverse perinatal outcome for the normal foetus in some lethal defects, such as polyhydramnios in anencephaly, and the psychological impact on the parents if the pregnancy reaches term, has led to ST becoming an option.[7-8]

The natural history and outcome of pregnancies complicated by a variety of discordant anomalies in twins have been addressed by a number of studies which suggested increased likelihood of premature delivery.[9-10] Lynch et al[11] studied 69 DC twin pregnancies that underwent ST for structural, chromosomal or Mendelian disorders at a mean GA of 19 weeks. There were only 2 women who miscarried and the remaining delivered at a mean GA of 36 weeks. Selectively terminated gestations had a lower rate of preterm delivery than control twin pregnancies. GA of 20 weeks or more and termination of the presenting twin increased the risk of preterm delivery and low birth weight. Yaron et al[12] reported a pregnancy loss rate of 9.7% after first trimester ST, compared to 7.8% for terminations done later in gestation. Another international collaborative study[13] involving 402 DZ pregnancies managed by ST reported foetal loss rate of 7.5%. Eddleman et al[14] reported overall foetal loss rate after ST of 4% (2.4% in twins and 12.5% in triplets). In 2012, Eugenia Antolı´n Alvarado et al[15] reported similar results.

Conclusion

In spite of the limitations of the present study (i.e. its small numbers and retrospective nature), the selective termination for a DZ abnormal twin appears to be safe and effective in experienced hands. The incidence of premature deliveries was relatively low and spontaneous loss rate was none. Perinatal outcomes are good and maternal morbidity is minimal. Hence, our series reported good outcomes although careful patient selection and comprehensive discussion with parents are essential. The benefits expected from selective termination should be weighed against the potential risk of the procedure concerning the unaffected twin.

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Letter to the Editor

Relation of Cardiac Arrhythmias to Hypoxic Time and Lowest Oxygen Saturation in Patients with Obstructive Sleep Apnoea in an Asian Context: A Singapore Sleep Centre Study

Dear Editor,

The association between cardiac arrhythmias and obstructive sleep apnoea (OSA) is well established.[1-5] Both conditions lead to significant morbidity and mortality if left untreated.[6]

Recurrent episodes of apnoea, hypoxaemia and hypercapnia in patients with OSA lead to chemoreceptor excitation, increased sympathetic drive and cardiac arrhythmias.[7-9] Given the crucial role of oxygen desaturation in arrhythmogenesis, evidence describing lowest oxygen saturation (LSAT), duration of LSAT (hypoxic time) and cardiac arrhythmias in OSA patients is lacking from existing studies. Moreover, accurately establishing predictors of cardiac arrhythmia is crucial in order to accurately identify high-risk OSA patients who require closer monitoring during overnight polysomnography, outpatient follow-up and more aggressive treatment. This is because the risk of sudden cardiac death during sleep is increased in OSA patients with cardiac arrhythmias. Cardiac deaths may be due to ventricular arrhythmias from left heart remodelling, overwork and ischaemia; sinus arrest or atrioventricular block while asleep from higher vagal tone.[10-13]

Therefore, this study was undertaken to evaluate the relationship between hypoxic time and cardiac arrhythmias, and identify the predictors of cardiac arrhythmias in a cohort of patients with OSA.

Materials and Methods

Of the 1457 patients diagnosed with OSA during overnight in-laboratory polysomnogram at a single tertiary institution from January 2011 to December 2012, retrospective chart reviews were performed on 117 patients with coexisting cardiac arrhythmia. Patients with cardiac arrhythmia not previously evaluated were referred to a cardiologist for further investigation.

Demographical data (including gender, age, ethnicity, neck circumference and body mass index [BMI]) were recorded. All patients underwent overnight in-laboratory polysomnography (diagnostic gold standard), which included continuous monitoring of electroencephalogram, submental and anterior tibial electromyogram, chest wall and abdominal excursions with plethysomography, oxygen saturation with finger oximeter, and cardiac monitoring with modified lead II electrocardiogram (ECG) tracing. Patients with cardiac arrhythmias (atrial, ventricular, conduction delay arrhythmias) detected during polysomnogram were included in the study. Hypopnoea was defined as incomplete cessation of breathing lasting longer than 10 seconds whereby there was decreased ventilation of ≥50% leading to reduction in oxygen saturation of ≥4%. Apnoea was defined as complete cessation of breathing lasting longer than 10 seconds. The apnoea-hypopnoea index (AHI) was the number of apnoeic or hypopnoeic events per hour based on the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2. OSA was defined as AHI of ≥5, and further stratified into mild (AHI 5-14), moderate (AHI 15-30) and severe (AHI >30). Hypoxic time was defined as the duration (min) when lowest oxygen saturations (LSAT) were <85% and <90%.

Predictors of cardiac arrhythmias in patients with OSA were identified using univariate analysis with chi-square test and Mann Whitney U test (R 3.0.2). *P* value <0.05 was considered statistically significant. Prediction performance of hypoxic time when LSAT were <85% and <90% were analysed using receiver operating characteristic (ROC) curve from a univariable logistic model. A cutoff point which achieved best sensitivity and specificity was obtained. Log transformation was used to reduce the skewness of hypoxic time.

Results

Of the 1457 patients diagnosed with OSA, 117 patients (8%) had cardiac arrhythmias. Out of the 117 patients with cardiac arrhythmias, 22 were pre-existing. Age (P <0.01), neck circumference (P = 0.036), BMI (P = 0.006), AHI (P = 0.004), LSAT (P = 0.006) and hypoxic time when LSAT <90% (P = 0.013) and <85% (P = 0.002) were significantly associated with incidence of cardiac arrhythmias. Table 1 shows the characteristics of the study population. Demographics of patients with cardiac arrhythmias were statistically similar to those without arrhythmias. Cardiac arrhythmias encountered in our study include atrial arrhythmias (n = 38, 32.5%), ventricular arrhythmias (n = 57, 48.7%), conduction delay arrhythmias (n = 8, 6.8%) and multiple arrhythmias (n = 14, 12.0%).

Table 1. Patient Demographics

	Arrhythmia (n = 117; 8%)	No Arrhythmia (n = 1340; 92%)	*P* Value
Gender n (%)			0.538
Female	31 (26.5)	315 (23.5)	
Male	86 (73.5)	1025 (76.5)	
Race n (%)			0.069
Chinese	85 (72.6)	1068 (79.7)	
Others	32 (27.4)	264 (19.7)	
Age (mean)	54.3	47.6	<0.01
Neck circumference (mean)	42.2	40.9	0.036
BMI (mean)	32.0	29.7	0.006
AHI (mean)	43.0	34.5	0.004
LSAT (mean)	73.7	77.3	0.006
Hypoxic time (SpO_2 <90%) (mean)	40.4	61.6	0.013
Hypoxic time (SpO_2 <85%) (mean)	36.1	22.2	0.002

AHI: Apnoea-hypopnoea index; BMI: Body mass index; LSAT: Lowest oxygen saturation

Table 2. OSA Severity among Patients with Cardiac Arrhythmias

Severity, AHI (Events/Hr)	No. of Patients (%)
Mild, 5 – 15	28 (23.9%)
Moderate, 15 – 30	25 (21.4%)
Severe, >30	64 (54.7%)

AHI: Apnoea-hypopnoea index; OSA: Obstructive sleep apnoea

OSA patients with cardiac arrhythmias were further stratified according to OSA severity (Table 2). The association between hypoxic time and cardiac arrhythmia was dependent on the severity of OSA ($P = 0.028$). Analysis with ROC curve showed that when LSAT <85%, hypoxic time cutoff of 4.2 min had 64% sensitivity and 50% specificity of predicting cardiac arrhythmia (area under ROC curve, AUC = 0.59). When LSAT <90%, hypoxic time cutoff of 13.2 min had 63% sensitivity and 53% specificity (AUC = 0.59). Therefore, the sole utilisation of hypoxic time as predictor of cardiac arrhythmia showed poor performance.

When age and BMI were included in a multivariable model: for LSAT <85%, adjusted odds ratio (aOR) was 1.22 (AUC = 0.7, $P = 0.11$); for LSAT <90%, aOR was 1.25 (AUC = 0.69, $P = 0.097$).

Analysing AHI as a continuous variable in a univariate model showed that when LSAT <85%, aOR was 1.38 ($P = 0.005$); LSAT <90%, aOR was 1.45 ($P = 0.002$). Results were not significant when age, BMI, AHI and LSAT were included in a multivariate model.

Discussion

Our study found that patients with older age, larger neck circumference, higher BMI, more severe OSA, lower LSAT and longer hypoxic time were more likely to have cardiac arrhythmias. This is similar to the predictors identified in several studies.[1-5,13-14]

However, the prevalence of cardiac arrhythmias in our study (8%) is lower compared to others. In a study conducted by Hoffstein et al,[2] 58% of OSA patients had cardiac arrhythmias. The higher prevalence in their study could be due to a greater proportion of patients with severe OSA (AHI >30)—74.4% vs 54.7% in our study. It is known that patients with more severe OSA have higher risk of cardiac arrhythmias. Guilleminault et al[1] analysed 400 OSA patients and found 48% had cardiac arrhythmias during overnight polysomnography. This could be attributed to lower LSAT range in their study population, given that mean age and OSA severity were similar in both studies.

Although hypoxic time when LSAT <85% and <90% were significantly associated with cardiac arrhythmia, using hypoxic time as sole predictor of arrhythmia produced poor results. However, the inclusion of age and BMI makes hypoxic time a better predictor of cardiac arrhythmia. Patients with older age and higher BMI were 1.22 times more likely to have cardiac arrhythmias when hypoxic time >4.2 min at LSAT <85% (AUC = 0.7) and 1.25 times when hypoxic time >13.2 min at LSAT <90% (AUC = 0.69). Therefore, these high-risk patients should be monitored more closely when hypoxic time of >13.2 min is detected with LSAT <90% as the risk of cardiac arrhythmias significantly increases. There is currently no other study demonstrating the association between specific hypoxic time cutoffs and the risk of cardiac arrhythmias for comparison. Our study is the only study that looked at this factor in arrhythmogenesis.

One of the limitations of our study was that comorbid diseases (hypertension, hyperlipidaemia, diabetes mellitus, cardiovascular disease and stroke) were not analysed as these parameters were not recorded at the time of polysomnography. Hence, the confounding effects of comorbid conditions on cardiac arrhythmias in OSA patients could not be analysed. In addition, only a single ECG lead (modified lead II) was available for analysis. Although this is unlikely to affect the detection of cardiac arrhythmias, the absence of a full 12-lead ECG meant that abnormal axis and ST-T wave abnormalities in other leads could possibly be undetected. Ambulatory 24-hour Holter

monitoring results were not available for all patients with cardiac arrhythmias. Hence, the association of cardiac arrhythmias between wakefulness and sleep were not established. Lastly, day-to-day variability in the frequency of cardiac arrhythmias could not be demonstrated as the cardiac arrhythmias were identified during a single overnight polysomnography session. This may not reflect the actual severity of arrhythmias in our study population.

Conclusion

Our study aims to evaluate the relation of cardiac arrhythmias to hypoxic time and LSAT in patients with OSA. Older age, larger neck circumference, higher BMI, more severe OSA, lower LSAT and longer hypoxic time significantly increases the risk of cardiac arrhythmias in OSA patients. Although hypoxic time when LSAT <85% and <90% were significantly associated with cardiac arrhythmia, using hypoxic time as sole predictor of arrhythmia produced poor results. However, when age and BMI were taken into consideration, hypoxic time is a good predictor of cardiac arrhythmia—relative risk of 1.22 (LSAT <85%) to 1.25 (LSAT <90%). This enables identification of high-risk patients for closer follow- up and more aggressive treatment of OSA and cardiac arrhythmias.

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Sudden Flagellate Rash after Barbecue

A 40-year-old Malay gentleman presented to the dermatology clinic after an abrupt onset of an itchy rash over his trunk 2 days after attending a barbecue session. The patient reported having eaten seafood and some lightly grilled shiitake mushrooms.

The patient was treated for dermographic urticaria by his primary care physician with antihistamines. He otherwise denied trauma, sea-bathing, prior consumption of other drugs, complementary medication or excessive sun exposure. He had no known food or drug allergies.

Physical examination revealed non-tender, whiplash-like erythematous streaks on the patient's trunk, arms and thighs (Fig. 1), sparing the mid-back. Mucosal abnormalities, fever and other systemic symptoms were absent.

Based on the patient's history and physical examination, which one of the following is the most likely diagnosis?

A. Bleomycin-induced erythema
B. Dermatomyositis-associated centripetal erythema
C. Shiitake dermatitis
D. Adult onset Still's disease
E. Contact dermatitis to plant or jellyfish

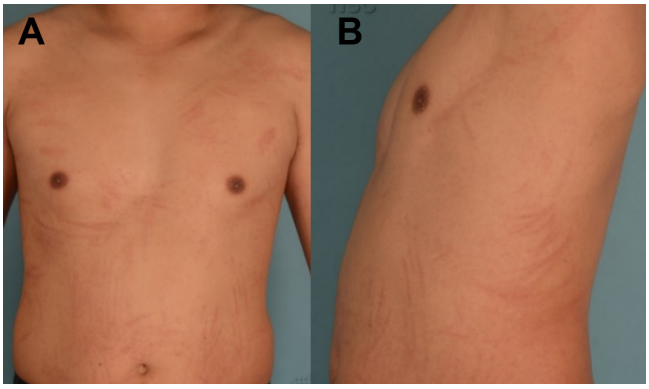

Fig. 1. Flagellate dermatitis on the trunk: A) Front view B) Side view.

Discussion

Based on the characteristic clinical findings and food exposure history, the diagnosis of shiitake flagellate dermatitis was made.

Shiitake dermatitis typically manifests, about 48 hours after consumption of poorly cooked shiitake mushrooms, as widespread linear erythematous papules and plaques.[1] Linear grouping of these papules is the result of scratching and Koebner phenomenon, paralleling the marks from the Middle Ages practice of self-flagellation. Marked pruritus is a common complaint as well. Hence, the distribution of the rash typically occurs at areas accessible to scratching. Spontaneous resolution of the skin symptoms usually occurs within a few days to several weeks.

In shiitake dermatitis, it is postulated that a toxic reaction, involving the thermolabile polysaccharide lentinan found in the mushroom is responsible.[2] Thus, the reaction can be avoided by ensuring that the mushrooms are well cooked. However, the precise pathogenesis of shiitake dermatitis is not yet fully understood.

Flagellate erythema can occur in other instances.[3] They can be differentiated based on clinical history and appearance: Bleomycin-induced flagellate erythema typically occurs 1 to 9 days after administration of bleomycin, appearing as hyperpigmented streaks. In contrast to shiitake dermatitis, post-inflammatory hyperpigmentation and involvement of the mucous membranes are common features, while itching is rare. History of recent use of this drug or its derivatives should raise suspicion of this aetiology.

Dermatomyositis-associated flagellate erythema occurs rarely in patients with dermatomyositis. It has a centripetal linear appearance, which correlates with the disease severity. Pruritus or pain is usually present without hyperpigmentation.

The salmon-coloured cutaneous eruption of adult onset Still's disease is part of the presenting triad of fever, arthralgia and a rash. It is typically non-pruritic and its appearance mirrors the fever spikes, occurring predominantly on the trunk and extremities.

Answer: C

Plant contact dermatitis can manifest as allergic, urticarial, irritant and a phytophotodermatitis. A linear but asymmetrical distribution of the rash is suggestive in the context of plant exposure or recent outdoor activity can be suggestive.

Jellyfish dermatitis usually presents as an immediate painful vesicopapular eruption along the distribution of the sting. Severe systemic symptoms such as loss of consciousness may ensue.

There are no specific laboratory or histopathological findings for this condition. The diagnosis is made through typical skin lesions and a characteristic history. Skin biopsy is not pathognomonic and shows a spongiotic dermatitis with lymphocytic infiltrates, eosinophils and dermal oedema.

Conclusion

Shiitake dermatitis is typically self-limiting; symptomatic treatment with topical steroids and antihistamines is the mainstay. In severe cases, oral steroids can be considered. Most importantly, patients have to be advised to ensure that the mushrooms they consume are adequately cooked to prevent future occurrence.

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