

A Decade of Progress in the Understanding, Prevention and Treatment of Age-related Macular Degeneration in Singapore

Ajeet M Wagle,^{1,2,3} MBBS, FRCS (Edin), FAMS (Ophth), Kah-Guan Au Eong,^{1,2,3} M Med (Ophth), FRCS (Edin & Glasg), FAMS (Ophth)

The year 2014 had marked the 10th anniversary of the nationwide Age-related Macular Degeneration (AMD) Awareness Week in Singapore.¹ This public health campaign, organised annually since 2005, aims to generate awareness and understanding of AMD by promoting the importance of education, early detection, and knowledge of treatment and rehabilitation options for the disease. Besides increasing the number of people aged 50 years and older who receive regular eye examinations, the campaign aims to preserve vision and improve the quality of life of individuals affected by AMD and increase the proportion of people with AMD who receive treatment and rehabilitation. At this significant public health milestone, it is timely to review the remarkable decade of progress that has been made in the understanding, prevention and treatment of AMD in Singapore.

AMD is the most important cause of irreversible vision loss among people aged 60 years or older in developed countries and accounts for 8.7% of all causes of blindness worldwide.² It is estimated that by 2020, about 196 million individuals could suffer from AMD globally and this number is likely to rise further to 288 million by 2040.²

The burden of AMD is enormous. Progressive deterioration of central vision from AMD has devastating implications especially when the disease involves both eyes. AMD adversely affects the quality of life with its impact on common vision-related tasks essential for daily living such as reading, recognising faces and driving. Visual loss in the elderly increases the risk of falls, hip fractures and the need for nursing care. It also has negative psychological implications such as depression associated with the visual limitations. The direct costs of managing AMD such as frequent consultations, investigations, repeated treatments and visual rehabilitation is substantial. The indirect costs to society in the form of loss of productivity, unemployment and caregiver expenses make the financial burden of AMD even higher.

The first area of major advances in Singapore in the last decade is the considerable improvement in our understanding

of the epidemiology of AMD and its impact on those suffering from the disease. AMD may be divided into early and late AMD. Based on the Wisconsin age-related maculopathy grading system, early AMD has either soft indistinct or reticular drusen, or both soft, distinct drusen plus retinal pigment epithelial abnormalities while late AMD has either neovascular features or geographic atrophy.³

Several key population-based studies published over the past 10 years have shown that AMD, once considered a disease that affects mainly Caucasians, is not rare in Singapore. The age-standardised prevalence of early and late AMD in Singapore is 5.1% and 0.5%, respectively.³ Interestingly, there is no major racial predilection for AMD in Singapore.³ Although early AMD is more common in Chinese and Indians compared to Malays, the prevalence of late AMD is similar among the 3 major races in Singapore.³ It is now known that the prevalence of bilateral AMD is comparable between Singapore Malays and Caucasians.³

AMD has several non-modifiable risk factors such as age, female gender and genetic predispositions. Among the known modifiable risk factors for AMD, cigarette smoking is the strongest. Local data have shown that current smokers have a significantly higher risk of developing late AMD (odds ratio (OR) 3.79) compared to non-smokers, especially if they smoke more than 5 packs per day.⁴ Another potentially modifiable risk factor, the lack of antioxidant micronutrients in the diet, has been associated with low levels of protective macular pigment (MP) in the eye. Atypical MP profiles have been reported among Singapore Chinese and this may be associated with an increased risk of AMD.⁵

We now better understand the adverse effects of AMD on the quality of life of Singapore patients. Singapore AMD patients are willing to trade off 1.9 years for every 10 years of their remaining life for a hypothetical treatment to restore vision.⁶ Also, they are willing to take a 14% risk of death and 10% risk of blindness in both eyes for a hypothetical treatment that can confer perfect vision.⁶

¹Singapore International Eye Cataract Retina Centre, Mount Elizabeth Medical Centre, Singapore

²International Eye Cataract Retina Centre, Farrer Park Medical Centre, Singapore

³Department of Ophthalmology and Visual Sciences, Khoo Teck Puat Hospital, Singapore

Address for Correspondence: Dr Kah-Guan Au Eong, International Eye Cataract Retina Centre, 1 Farrer Park Station Road #14-07/08, Farrer Park Medical Centre, Connexion, Singapore 217562.

Email: aekg@eyecataractretina.com

The second area of advances is the concrete actions taken for primary and secondary prevention of AMD in Singapore. Primary prevention aims at protecting healthy people from developing AMD while secondary prevention refers to preventing the progression of AMD after it has been diagnosed. Although AMD may not be totally preventable, primary prevention by tackling its modifiable risk factors and secondary prevention by encouraging early detection of the disease is vital to reducing its impact. Increasing the awareness of AMD and encouraging certain lifestyle changes such as abstaining from smoking, taking a diet rich in green leafy vegetables and fruits, controlling blood pressure and exercising regularly can potentially help to reduce the prevalence of AMD, especially if begun at an early age. In addition, screening of asymptomatic individuals allows early diagnosis, timely intervention and better outcomes.

The rapidly ageing population and increased longevity in Singapore is likely to result in a gradual rise in the prevalence of AMD.^{7,8} However, the awareness of AMD among the community is generally low.

A 2006 telephone survey of 520 Singapore residents, done a year after the first AMD Awareness Week was conducted, showed that only 7.3% respondents were aware of AMD.⁹ This puts Singapore among countries with a low awareness of AMD as seen in a global survey which showed AMD awareness levels ranging from 4% to 30%.¹⁰

The low awareness is part of the reason that prompted Singapore eye care professionals, led initially by the Department of Ophthalmology and Visual Sciences at Alexandra Hospital (and later at Khoo Teck Puat Hospital when the department relocated to its new location) to take concrete actions to tackle the looming public health crisis that the rapidly ageing population in Singapore is likely to face. The annual AMD Awareness Week was thus initiated in collaboration with the AMD Alliance International, a non-profit global alliance of organisations working to raise the awareness of AMD, and the now-defunct Singapore Action Group of Elders (SAGE). The campaign gradually expanded in size and scale over the next 10 years and now involves more than 30 participating organisations including the Health Promotion Board (HPB), patient support groups, educational institutions, hospitals, voluntary organisations, public libraries, community centres, nursing homes, senior citizen homes and religious places of worship.¹ The campaign actively engages ophthalmologists, optometrists and opticians from both the public and private sectors to increase its reach to the community.¹ Activities such as educational health talks on AMD, eye screenings for age-related eye diseases, patient support group meetings, smoking cessation campaigns, educational and art exhibitions on AMD have been organised to raise the awareness of AMD and its modifiable risk factors. Campaign messages have also been

broadcasted widely in the media including major newspapers, magazines, radio, television, public transport services (Mass Rapid Transit trains and buses) and the Internet.

It is gratifying to note that a 2011 follow-up telephone survey of 559 Singapore residents, 5 years after the initial survey in 2006, showed that the awareness of AMD had increased 4-fold from 7.3% to 28.1%.¹¹

Early detection of AMD can be effectively achieved through eye screenings for the elderly. In fact, the Scientific Advisory Board of AMD Alliance International recommends that individuals 55 years or older should have their eyes screened by an eye care professional at least once every 2 years if they have no symptoms.⁶ Patients with symptoms of blurring of vision or distorted central vision are recommended to see an eye care professional immediately.⁶

Not surprisingly, the awareness of smoking as a risk factor for AMD was also initially low in Singapore. In the 2006 survey, only 36.7% respondents considered smoking to be a risk factor for AMD.¹⁰ Another local study found that the awareness of the risk of blindness associated with smoking was far lower than that for other more commonly known smoking-related diseases such as lung cancer and heart disease.¹² In fact, only 42.5% of current smokers in the study were aware of the risk of blindness from smoking.¹² To meet this challenge, an anti-smoking campaign has been a major element of the AMD Awareness Week. Eye care professionals warned about the harmful effects of smoking on vision health in the media and scientific publications.¹³⁻¹⁵ They also lobbied and worked with the HPB to put a “Smoking causes blindness” graphic health warning on cigarette packs in Singapore to discourage the habit.¹⁶ The results of these efforts was reflected in the fact that a larger proportion of respondents who were familiar with AMD now knew that smoking is a risk factor for AMD (84.1% in 2011 vs 45.9% in 2006).¹¹

The AMD Awareness Week also highlights the use of nutritional supplementation to reduce the risk of progression of AMD as a form of secondary prevention.¹⁷ In individuals at high risk of developing advanced AMD, the Age-related Eye Disease Study (AREDS) showed that using high doses of antioxidants (vitamin C 500 mg; vitamin E 400 IU; β -carotene 15 mg) and zinc 80 mg significantly reduced the risk of developing advanced AMD by 25% over 5 years.¹⁸ However, as β -carotene intake was linked to an increased risk of lung cancer in smokers, a subsequent study, the AREDS2, recommended that β -carotene be replaced by lutein and zeaxanthin in the formulation.¹⁸

The last area of advancement is the huge improvement in treatment outcomes with newer treatment modalities. Slightly more than a decade ago, a diagnosis of AMD meant very few treatment options with little hope for saving sight. Fortunately, there have been great strides made in the

management of AMD in the recent 10 years, with hopes of restoring vision in some patients while stabilising vision in the majority.

Management options for neovascular AMD, which accounts for about 10% of all AMD cases but is responsible for most of the severe vision loss associated with the disease, have rapidly expanded from the dawn of the 21st century.¹⁹ Prior to 2005, only laser photocoagulation and photodynamic therapy (PDT) have been proven modestly beneficial in randomised control trials for treating neovascular AMD.²⁰ PDT, which uses a special laser wavelength to activate a photosensitive drug verteporfin (Visudyne®, Novartis AG, Basel, Switzerland) in the eye, is better than traditional thermal laser photocoagulation as it achieves ablation of the neovascular tissue in the eye while significantly limiting collateral retinal damage associated with thermal laser treatments.²⁰ PDT was approved for use by US Food and Drug Administration (FDA) in 2000 and by the Health Sciences Authority (HSA) in Singapore in 2001. PDT was found to be effective especially for a subtype of AMD called predominantly classic subfoveal choroidal neovascularisation (CNV).²⁰ However, PDT at best stabilises existing vision and is not associated with an improvement in visual acuity.

Recently, agents that effectively block the action of various growth factors such as the vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) responsible for neovascularisation have truly revolutionised the management of neovascular AMD. In the last 10 years, the HSA approved 3 anti-VEGF agents for treating neovascular AMD: pegaptanib sodium (Macugen®, Pfizer, New York, USA) (FDA approval 2004, HSA approval 2006), ranibizumab (Lucentis®, Novartis AG, Basel, Switzerland) (FDA approval 2006, HSA approval 2008), and aflibercept (Eylea®, Bayer HealthCare, Berlin, Germany) (FDA approval 2011, HSA approval 2013).²⁰ Besides these, another anti-VEGF agent called bevacizumab (Avastin®, Roche, Basel, Switzerland) which is approved for metastatic colorectal cancer, is widely used “off-label” for treating neovascular AMD. Together, these anti-VEGF agents provide, for the first time, a chance of improving vision with up to 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters visual acuity gain in at least one-third of the treated patients while effectively stabilising vision in the remaining majority.²⁰

In summary, while Singapore has seen major advances in the understanding, prevention and treatment of AMD over the last decade, there is no room for complacency. AMD remains an emerging public health challenge with Singapore’s rapidly ageing population and efforts must be kept up or even stepped up to reduce, if not eradicate, the burden of this sight-threatening condition.

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Anti-BP180 NC16A IgG Titres as an Indicator of Disease Activity and Outcome in Asian Patients with Bullous Pemphigoid

Sophie CS Cai, ^{1*}MD, Yen Loo Lim, ^{2*}MBBS (S'pore), FRCP (Edin), FAMS, Wenyun Li, ¹PhD, John Carson Allen, ¹PhD, Sze Hon Chua, ²MBBS (S'pore), FRCP (Edin), FAMS, Suat Hoon Tan, ²M Med (Int Med), Dip RC Path (DMT), FAMS, Mark BY Tang, ²M Med (Int Med), FRCP (Edin), FAMS

Abstract

Introduction: Anti-BP180 IgG titres were observed to parallel disease activity in case series of bullous pemphigoid (BP). This study aimed to examine whether anti-BP180 titres are an indicator of disease severity, clinical course and outcome in Asian patients with BP. **Materials and Methods:** This was a prospective observational study conducted between March 2005 and March 2008 in the Immunodermatology Clinic at the National Skin Centre, Singapore. Disease activity and anti-BP180 IgG titres were measured 4-weekly for 12 weeks and during disease flares and clinical remission. Associations between anti-BP180 titres and disease activity, disease flare, clinical remission and cumulative prednisolone dose were examined. **Results:** Thirty-four patients with newly diagnosed BP were recruited. Median follow-up duration was 3 years. Notable correlations between disease activity and anti-BP180 titres were at baseline ($r = 0.51$, $P = 0.002$), and disease flare ($r = 0.85$, $P < 0.001$). Lower titres at Week 12 were associated with greater likelihood of clinical remission ($P = 0.036$). Post hoc, patients with anti-BP180 titres above 87.5 U/mL at time of diagnosis who reached remission within 2 years of diagnosis received significantly higher cumulative doses (mg/kg) of prednisolone (median, 72.8; range, 56.5 to 127.1) than those with titres < 87.5 U/mL (median, 44.6; range, 32.5 to 80.8); $P = 0.025$). **Conclusion:** Anti-BP180 titres may be a useful indicator of disease activity at time of diagnosis and at disease flare. Lower titres at Week 12 may predict greater likelihood of clinical remission. Titres above 87.5 U/mL at time of diagnosis may suggest the need for higher cumulative doses of prednisolone to achieve remission within 2 years.

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Key words: Immunobullous disease, Subepidermal skin blistering, Tense skin blisters

¹Centre for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore

²Immunodermatology Clinic, National Skin Centre, Singapore

Address for Correspondence: Dr Mark Tang, National Skin Centre, 1 Mandalay Road, Singapore 308205.

Email: marktang@nsc.gov.sg

*Both SCS Cai and YL Lim are co-first authors of the study.

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Introduction

Bullous pemphigoid (BP) is a subepidermal blistering dermatosis characterised by circulating autoantibodies targeting BP180 and BP230 hemidesmosomal proteins. Anti-BP180 NC16A IgG antibodies have been demonstrated to be directly pathogenic in blister formation.^{1,2} Anti-BP180 IgG titres were noted to parallel disease activity in several case series,³⁻¹⁰ as well as reflect disease control and disease activity in larger studies.^{11,12} However, there are limited data regarding how anti-BP180 IgG titres vary over time with treatment, and whether antibody titres can be used to predict disease flares, remission, and cumulative prednisolone dose received by BP patients.

The aims of this prospective study were to determine

the temporal relationship between anti-BP180 IgG titres and disease activity, and whether antibody titres at specific follow-up time points were predictive of subsequent disease flare or remission. In addition, we investigated the association of anti-BP180 IgG titres with cumulative prednisolone dose received at remission.

Materials and Methods

Forty patients with newly diagnosed BP were recruited from the Immunodermatology Clinic at the National Skin Centre, Singapore between March 2005 and March 2008. BP was diagnosed based on clinical findings consistent with BP (tense bullae, urticarial plaques or erosions on the body, with or without oral mucosal involvement and

¹Centre for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore

²Immunodermatology Clinic, National Skin Centre, Singapore

Address for Correspondence: Dr Mark Tang, National Skin Centre, 1 Mandalay Road, Singapore 308205.

Email: marktang@nsc.gov.sg

*Both SCS Cai and YL Lim are co-first authors of the study.

without evidence of scarring) and at least 2 out of 3 of the following: subepidermal blister on histology, linear deposition of C3 and/or IgG along the basement membrane by direct immunofluorescence (DIF), and epidermal or epidermal and dermal binding of immunoglobulins on salt-split skin by indirect immunofluorescence (IIF). Exclusion criteria were treatment with systemic corticosteroids or immunosuppressants during the preceding 1 year, concurrent immune-related and neoplastic diseases, and negative anti-BP180 IgG titre (<9 U/mL) throughout the first 12 weeks of follow-up, pregnancy and lactation. Five patients were excluded due to persistently negative anti-BP180 IgG titres throughout the follow-up, and 1 patient was excluded due to underlying cancer. Thirty-four patients were included in the analysis. Informed consent was obtained from all study subjects and the study was approved by the National Healthcare Group Domain-Specific Review Board.

Disease activity of BP was evaluated using a standardised scoring method based on body surface area (BSA) involvement and number of non-epithelised erosions, blisters and urticarial plaques (Table 1). Serum anti-BP180 antibodies were measured by commercial enzyme-linked immunosorbent assay (ELISA) kits detecting IgG antibodies against the NC16A domain of BP180 (MBL Co., Ltd, Japan). IgG antibodies ≥ 9 U/mL was interpreted as a positive ELISA result and <9 U/mL as a negative result. Disease activity scoring and blood sampling were performed at diagnosis, at monthly intervals during the first 3 months, at first disease flare after Week 12, and at clinical remission.

Patients were treated based on standardised institutional guidelines and managed by a dedicated team of doctors in the Immunodermatology Clinic. Patients were started on oral prednisolone 0.3 to 0.8 mg/kg/day at diagnosis which was tapered gradually every 4 to 8 weeks depending on clinical

severity. Clinical remission was defined as a disease activity score of zero with a prednisolone dose of ≤ 3 mg/day for at least 1 month, after Week 12. Disease flare after Week 12 was defined as worsening of the prevailing disease activity requiring an escalation of treatment. Clinical remission and disease flare data were obtained from patient records from time of diagnosis until 31 November 2012.

Statistical Analysis

Spearman correlations were computed to assess the degree of association between disease activity, cumulative prednisolone dose, and anti-BP180 IgG titres. Wilcoxon signed-rank tests were performed to compare within-patient changes in anti-BP180 IgG titres and cumulative prednisolone dose at baseline, Week 4, 8 and 12. Wilcoxon rank-sum tests were used to compare anti-BP180 IgG titre levels and cumulative prednisolone doses between patient groups with and without disease flare, patients achieving and failing to achieve clinical remission, and patients receiving adjuvant therapy versus those receiving prednisolone alone. Cox regression was used to assess the influence of change (rise) in anti-BP180 IgG titres on time to clinical remission beyond the 12-week follow-up period. Linear regression was conducted to evaluate whether adjuvant therapy was a confounding factor in the relationship between cumulative prednisolone dose and anti-BP180 IgG titres. Simple linear regression was used to characterise the relationship of disease activity with anti-BP180 IgG titres at baseline, follow-up times, disease flare and remission.

Post hoc subgroup analysis was performed on patients achieving clinical remission within 2 years. The Wilcoxon rank-sum test was used to compare median anti-BP180 titres between patients who had disease flare after remission and those who did not, in the subgroup of patients with positive ELISA results (≥ 9 U/mL) at remission. Fisher's exact test was used to compare risk of disease flare after remission between patients with positive titres at clinical remission and those with negative titres. Statistical significance was set at $P < 0.05$ on a per test basis. P values are reported, thus leaving to reader prerogative any decision to adjust significance levels due to multiple tests and choice of adjustment method. All analyses were performed using SAS 9.2 (SAS® Carey, NC, USA).

Results

Demographics

Thirty-four patients were included in the analysis of which 21 were men and 13 were women (Table 2). Median age was 75 years (range, 27 to 96). The ethnic distribution of patients was 79.4% Chinese, 14.7% Indians and 5.9% Malays; 82.4% of patients had generalised BP, and median

Table 1. Components of the Disease Activity Score: Percentage Involvement of Body Surface Area (BSA), and Number of Non-Epithelised Erosions, Blisters or Urticarial Plaques

Disease Activity Score Component*		
Component Score	Percentage Involvement of Body Surface Area (% BSA)	Number of Non-Epithelised Erosions/Blisters/Urticarial Plaques
5	>30	>30
4	16 – 30	21 – 30
3	11 – 15	11 – 20
2	5 – 10	5 – 10
1	1 – 4	1 – 4
0	0	0

*For each patient, component scores are summed to obtain the disease activity score.

Table 2. Patient Characteristics at Baseline and Outcomes during Follow-up*

Variable	All Patients n = 34	Flare n = 27	No Flare n = 7	P Value	Remission n = 25	No Remission n = 9	P Value
Age	75 (27,96)	77 (27, 96)	68 (51, 81)	0.063	77 (27,96)	75 (59,85)	0.368
Gender							
Male	21 (61.8)	16 (59.3)	5 (71.4)	0.682	15 (60.0)	6 (66.7)	1.000
Female	13 (38.2)	11 (40.7)	2 (28.6)		10 (40.0)	3 (33.3)	
Ethnicity							
Chinese	27 (79.4)	21 (77.8)	6 (85.7)	0.260	20 (80.0)	7 (77.8)	0.788
Malay	2 (5.9)	1 (3.7)	1 (14.3)		1 (4.0)	1 (11.1)	
Indian	5 (14.7)	5 (18.5)	0 (0)		4 (16.0)	1 (11.1)	
Type of BP at diagnosis							
Localised	2 (5.9)	2 (7.4)	0 (0)	0.720	2 (8.0)	0 (0)	0.447
Generalised	28 (82.4)	21 (77.8)	7 (100)		19 (76.0)	9 (100)	
Acral	4 (11.8)	4 (14.8)	0 (0)		4 (16.0)	0 (0)	
Beyond 12 weeks of follow-up	32 (94.1)	27 (100)	5 (71.4)	0.037	25 (100)	7 (77.8)	0.064
Duration of follow-up (year)	3.0 (0.1, 7.3)	3.7 (0.4, 7.3)	0.5 (0.1, 1.8)	<0.001	3.7 (1.3, 7.3)	0.5 (0.1, 5.0)	0.001
Concomitant immunosuppressant	12 (35.3)	10 (37.0)	2 (28.6)	1.000	8 (32.0)	4 (44.4)	0.687
Azathioprine	2 (5.9)	2 (7.4)	0 (0)	1.000	2 (8.0)	0 (0.0)	1.000
Methotrexate	1 (2.9)	1 (3.7)	0 (0)	1.000	1 (4.0)	0 (0.0)	1.000
Dapsone	7 (20.6)	6 (2.2)	1 (14.3)	1.000	5 (20.0)	2 (22.2)	1.000
Nicotinamide/tetracycline	4 (11.8)	3 (11.1)	1 (14.3)	1.000	1 (4.0)	3 (33.3)	0.048

BP: Bullous pemphigoid

*Continuous variables are summarised using median (min, max); categorical variables using count (%). Wilcoxon rank-sum test used for continuous variables, Fisher's exact test for categorical variables.

disease activity score at diagnosis was 5 (range, 2 to 10). All patients received prednisolone as first-line therapy. Twelve (35.3%) patients received adjuvant therapies: dapsone (5), azathioprine (2), nicotinamide/tetracycline only (2); methotrexate only (1), with 2 patients receiving both dapsone and nicotinamide/tetracycline.

Duration of Follow-up and Time to Disease Flare or Remission

Median duration of follow-up was 3 years (range, 0.1 to 7.3) (Table 2). Thirty-two (94.1%) patients were followed up beyond Week 12, of which 25 (73.5%) achieved clinical remission. Twenty-seven (79.4%) patients experienced a flare after Week 12. Median elapsed time from diagnosis to first disease flare was 0.9 years (range, 0.3 to 6.6) and from diagnosis to first clinical remission was 1.2 years (range, 0.6 to 3.2).

Antibody Titres and Disease Activity during 12-week Follow-up

A total of 177 serum samples were analysed for an average of 5.2 samples per patient. Anti-BP180 IgG titres and disease activity decreased in unison over the first 12 weeks but increased during disease flare (Fig. 1). Within-patient reductions in anti-BP180 IgG titres and decline in disease activity scores from baseline to Week 4 ($P < 0.0001$), Week 4 to 8 ($P < 0.0001$), and Week 8 to 12 ($P < 0.0001$) were all statistically significant. Within-patient decline in disease activity scores from baseline to Week 4 ($P < 0.0001$), Week 4 to 8 ($P = 0.013$), and Week 8 to 12 ($P = 0.042$) were also statistically significant.

Correlations between anti-BP180 IgG titres and disease activity scores at study follow-up times were: baseline, $r = 0.51$ ($P = 0.002$); Week 4, $r = 0.36$ ($P = 0.053$); Week 8, $r = 0.40$ ($P = 0.024$); and Week 12, $r = 0.22$ ($P = 0.243$). Trend

lines showing relationships between disease activity and anti-BP180 IgG titres at study follow-up times are plotted in Figure 2. The falling lines and shrinking line lengths from baseline through remission reflect progressive reductions over time in both disease activity and anti-BP180 IgG titres. This is indicative of treatment efficacy with passing time. Trend line parallelism indicates that regardless of disease activity level, the expected change in disease activity as a function of change in BP180 IgG titre remains constant.

Disease Flare after 12-week Follow-up

A statistically significant correlation was observed between anti-BP180 IgG titres and disease activity score at disease flare ($r = 0.85$, $P < 0.001$). Anti-BP180 IgG titres within the 12-week follow-up period were not significantly different between patients with disease flare after Week 12 and those without (Table 3).

Only at the time of disease flare was a significant difference in anti-BP180 titres observed between patients who needed adjuvant therapy and those who did not ($P = 0.030$). Median (min, max) anti-BP180 titres at disease flare were 65.5 (10.8, 224.5) in patients who needed adjuvant therapy and 27.6 (7, 48.7) in those receiving prednisolone alone.

Clinical Remission after 12-week Follow-up

Patients who achieved clinical remission after 12 weeks had significantly lower antibody titres at Week 12 (median, 17.8; range, 3.9 to 88.7) compared to those who did not achieve remission (median, 62.3; range, 24.5 to 142.1) ($P = 0.036$) (Table 3). Furthermore, using the 4 to 12 week remission rate as reference, the post 12-week remission rate decreased on average 24% for every 1% weekly increase in anti-BP180 IgG titres (hazard ratio, 0.76; 95% CI, 0.58 to 0.93).

Cumulative Prednisolone Dose Received

A statistically significant positive correlation was observed between cumulative prednisolone dose received (mg/kg/patient) and anti-BP180 IgG titres at Week 4 ($r = 0.37$, $P = 0.048$); i.e. higher antibody titres at Week 4 were associated with higher cumulative doses of prednisolone. Correlations at other study time points were: Week 8, $r = 0.32$ ($P = 0.074$); Week 12, $r = 0.29$ ($P = 0.117$), disease flare, $r = 0.42$ ($P = 0.093$) and clinical remission, $r = 0.42$ ($P = 0.060$).

There were no significant differences in cumulative prednisolone dose received (mg/kg/patient) at any study time point between patients who experienced a flare and those who did not: Week 4 ($P = 0.766$), Week 8 ($P = 0.469$), and Week 12 ($P = 0.781$). Similarly, there were no significant differences in cumulative prednisolone dose received at

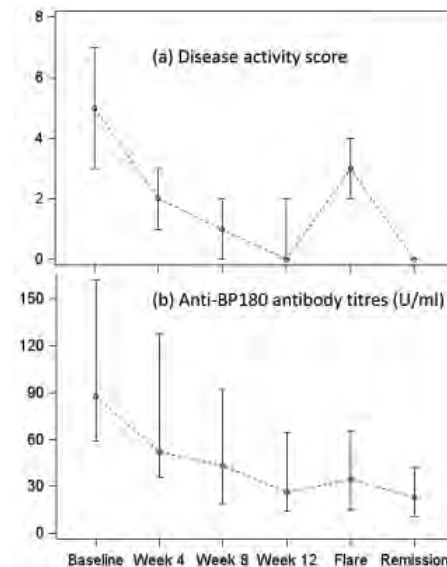


Fig 1. (a) Mean disease activity scores and (b) mean anti-BP180 antibody levels (95% CI) at follow-up times, disease flare and clinical remission.

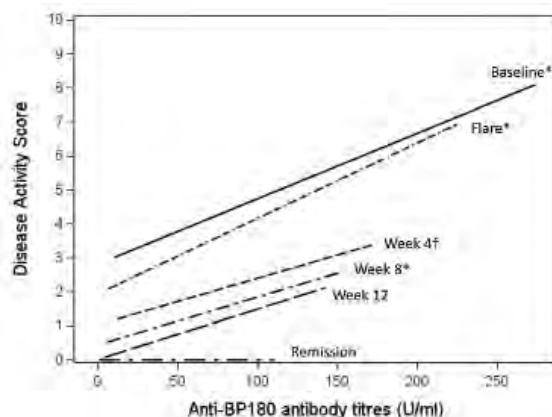


Fig 2. Trend lines showing relationships between disease activity and anti-BP180 IgG titres at baseline, 4-, 8- and 12-week follow-up times, and at remission and disease flare. Note: *Correlations between anti-BP180 titres and BP disease activity were statistically significant at baseline ($P = 0.002$), Week 8 ($P = 0.024$) and disease flare ($P < 0.001$); †nearly significant at Week 4 ($P = 0.053$); and at Week 12, $P = 0.243$. Falling trend lines and shrinking lengths over time is indicative of treatment efficacy. Parallelism indicates that regardless of disease activity, the expected change in disease per unit change in BP180 IgG titre remains constant.

any time between patients who achieved clinical remission and those who did not (Table 4).

We found no evidence that use of adjuvant therapy modified the relationship between anti-BP180 titres and cumulative prednisolone dose received. After adjusting for length of follow-up, there was no difference in cumulative

Table 3. Anti-BP180 Titres during the 12 Week Follow-up Period in Patients with and without Flare and in Patients with and without Remission*

Follow-up	Flare (n = 27)	No Flare (n = 7)	P Value	Remission (n = 25)	No Remission (n = 9)	P Value
Baseline	81.3 (9.9,273.5)	137.8 (59.1, 208.7)	0.125	81.3 (9.9, 273.5)	103.5 (50.1, 208.7)	0.640
Week 4	48.1 (12.5,171.2)	139.7 (50.2, 145.8)	0.075	48.1 (12.5, 171.2)	65.4 (45.6, 145.0)	0.303
Week 8	28.4 (5.4, 136.3)	63.6 (28.2, 152.7)	0.154	28.2 (5.4, 136.3)	72.2 (43.1, 152.7)	0.062
Week 12	22.4 (3.9, 88.7)	63.9 (16.2, 142.1)	0.095	17.8 (3.9, 88.7)	62.3 (24.5, 142.1)	0.036

*Results are reported in median (min, max); P values from Wilcoxon rank-sum test.

Table 4. Cumulative Prednisolone Dose Received (mg/kg/patient) over 12 Weeks Starting from Baseline*

Time Period	Entire Cohort (n = 34)	Flare (n = 27)	No Flare (n = 7)	P Value	Remission (n = 25)	No Remission (n = 9)	P Value
Till Week 4	13.6 (0, 34.4)	13.2 (0, 26.4)	14.0 (0, 34.4)	0.766	13.2 (0, 34.4)	14.0 (0, 21.1)	0.740
Till Week 8	23.6 (0, 50.9)	23.3 (0, 50.9)	28.7 (0, 48.1)	0.469	23.3 (0, 50.9)	24.7 (0, 39.6)	0.828
Till Week 12	31.2 (7.7, 64.6)	30.9 (7.7, 63.1)	34.3 (17.5, 64.6)	0.781	31.3 (7.7, 64.6)	31.1 (17.5, 54.8)	0.897

*Results are reported in median (min, max), P values from Wilcoxon rank-sum test.

prednisolone dose at any time point between those who received adjuvant therapy and those who did not.

Subgroup Analyses

The majority of patients (19/25, 76%) achieved clinical remission within 2 years. This provided a reasonable basis for a post hoc analysis exploring association between level of anti-BP180 IgG titres at the time of diagnosis and cumulative prednisolone dose at the time of clinical remission, within 2 years of diagnosis. The linear regression slope relating cumulative prednisolone dose at remission to anti-BP180 IgG titres at time of diagnosis was positive and statistically significant ($P = 0.0037$). Using the median value of anti-BP180 IgG titres at time of diagnosis (87.5 U/mL) as a cutoff value, it was noted that 9 patients with antibody titres above 87.5 U/mL at time of diagnosis, and in remission within 2 years of diagnosis, had received significantly higher cumulative doses of prednisolone at the time of clinical remission (median, 72.8; range, 56.5 to 127.1), compared to the 10 patients with titres below 87.5 U/mL (median, 44.6; range, 32.5 to 80.8; $P = 0.025$) (Fig. 3).

In a second subgroup analysis, 17 of 25 patients (68%)

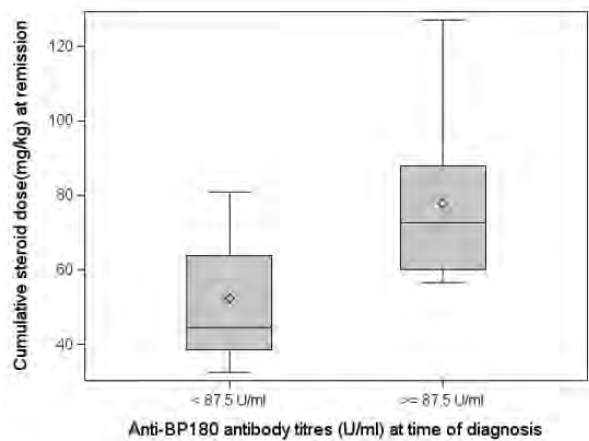


Fig 3. Cumulative prednisolone dose received (mg/kg/patient) at clinical remission within 2 years using an anti-BP180 antibody level cutoff of 87.5 U/mL at time of diagnosis. Note: The bottom and top edges of the box indicate the interquartile range (25th to 75th percentile). The line within the box and the diamond symbol represent the median and mean value, respectively. The whiskers extend from the box in both directions to represent the minimum and maximum observations.

were found to have positive anti-BP180 IgG titres despite achieving clinical remission. The median antibody titre in this subgroup was 33.9 (range, 9.2 to 109.9). Thirteen (76.5%, 95% CI, 50.1% to 93.2%) of the 17 patients with elevated titres at clinical remission had subsequent disease flare after remission. However, we did not find a significant difference in median antibody titres at clinical remission in patients who had subsequent disease flares, compared to those who did not. Among the 8 patients with negative titres at clinical remission (median 4.9, range, 0.6 to 8.2), 4 (50%, 95% CI, 15.7% to 84.3%) had disease flare after remission. However, comparing patients with positive titres at remission versus those with negative titres, we found no significant difference in the subsequent risk of flare ($P = 0.36$, Fisher's exact test).

Discussion

This study showed a statistically significant positive correlation between anti-BP180 IgG titres and BP disease activity at time of diagnosis (baseline) and at disease flare. Anti-BP180 IgG titres exhibited a “nearly” statistically significant correlation with disease activity at follow-up Week 4, a statistically significant correlation at Week 8 and a non-significant correlation at Week 12. The non-significant correlation at Weeks 4 and 12 are likely a consequence of the simultaneous reduction of both disease activity and anti-BP180 IgG titres. Correlation is a function of the range of data values, and the shrinking range in outcome values for both variables would have the effect of reducing statistical power for detecting correlation. The simultaneous diminution of antibody titres and disease activity scores with the passage of time is evidence of treatment efficacy.

Notably, our study showed that lower anti-BP180 IgG titres at Week 12 were associated with a higher likelihood of achieving subsequent clinical remission. This is consistent with other studies which found that antibody titres significantly decreased after remission,^{5,8,12,13} or during treatment toward disease control.^{9–11} However, an interesting finding was that 68% of patients had persistent elevated antibody titres despite achieving clinical remission and that the antibody titres in these patients were not predictive of subsequent disease flare. A previous study also reported that there was no significant decrease in anti-BP180 titres in a group of BP patients whose lesions had been resolved by oral corticosteroid treatment.¹⁴ This seems to indicate that a clinical remission may not always accompany with serological remission.¹⁵ In our practice, the management of such patients needs to be individualised and the risks and benefits of long-term immunosuppression should be discussed with the patients and family. The decision to withdraw, taper or maintain long-term, low dose immunosuppressive agents depends on several factors such

as patient comorbidities, severity of initial disease, number of recent flares, duration and sustainability of remission, and the presence of any adverse effects of the medications used. In general, most patients can be continued on very low dose prednisolone if there are no contraindications. It also appears that a disease flare may not always be reflected in a rise in antibody titres. It has been reported that anti-BP180 titres could fail to show a rise during disease flare.⁷ Nonetheless, 2 previous studies found that a higher anti-BP180 titre at remission was a risk factor for relapse within the subsequent 3 months¹¹ or 1 year.¹² However, these 2 studies included patients with negative titres, in contrast to our analysis which included only patients who had positive titres (≥ 9 U/mL).

The limited usefulness of anti-BP180 IgG titres for predicting flares may be related to several factors. First, downstream factors such as complement activation, mast cell degranulation, macrophage activation and neutrophilic chemotaxis, which are not measured by antibody levels, play an important role in causing subepidermal splitting, after the initial binding of the antibodies to BP180 antigens.^{1,16,17} Second, specific IgG subclasses such as IgG1 and IgG4, as well as anti-BP180 IgE antibodies,^{18–20} have been shown to have differential disease-causing potential and may be differentially associated with disease activity and remission respectively, and these were not measured by the current ELISA assay.^{21–23} Third, epitope spreading over time may generate pathogenic antibodies against other epitopes of BP180 (including the non-NC16A domain) and BP230.^{24–28} Finally, long-lived memory plasma cells may produce non-pathogenic anti-BP antibodies that would not result in disease flare.^{29,30}

In this study, we also found a positive and statistically significant correlation between the cumulative prednisolone dose received and anti-BP180 titres at week 4 ($r = 0.37$, $P = 0.048$). This is consistent with a previous study which showed that the dose of prednisolone necessary to suppress new blister formation was significantly correlated with the antibody titre³ as well as another recent study which found that high anti-BP180 titres correlated with increased effective prednisolone dose ($r = 0.37$, $P < 0.05$).³¹ Of note, we recognise that the relationship between disease activity, antibody titres and cumulative prednisolone dose are not independent parameters. Hence, patients with higher antibody titres are more likely to have higher disease activity, and hence, receive greater cumulative doses of prednisolone over time.

While there was no difference in cumulative prednisolone dose between patients who received adjuvant therapy and those who did not, across all follow-up times, after controlling for cumulative prednisolone dose at disease flare, we noted that at disease flare patients with adjuvant

therapy had higher anti-BP180 titres compared to patients without adjuvant therapy. This may be explained by the fact that adjuvant therapy was added during flares or in cases with poor disease control, when the anti-BP180 titres were expectedly high.

We observed that patients who achieved clinical remission within 2 years and had antibody titres above a threshold of 87.5 U/mL at time of diagnosis, exhibited cumulative prednisolone doses at clinical remission that were significantly higher than in patients with titres below that threshold. Thus, antibody titres at time of diagnosis may be useful in prognosticating the cumulative prednisolone dose needed to achieve clinical remission and hence guide dosing in patients. Indeed, as antibody titres correlate with disease activity, early detection and therefore timely treatment are important in the management of BP. However, because this finding was based on post hoc analysis it must be viewed as hypothesis generating. Thus future studies would be essential to confirm this finding.

Strengths of our study include a relatively large cohort of patients compared to previous case series, the prospective tracking of antibody titres and disease activity over fixed time points, and a long follow-up duration (median 3 years, maximum 7.3 years) compared to previous studies where the follow-up ranged from several months to a year.³⁻¹² We were also able to assess the cumulative prednisolone dose received in relation to antibody titres and disease course. A limitation is that we used a simplified but standardised lesion scoring method, as no published validated scoring system was available at the time this study was initiated. Our scoring system is similar to the recently developed Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)³² and assesses BSA involvement and extent of active lesions but not the involvement of oral mucosa. However, we believe our scoring system was sufficiently comprehensive to adequately reflect disease burden, as most of our study patients did not have oral involvement and the gradation in the quantification of lesions was sensitive enough to reflect changes in disease activity. Our scoring system was similar to those used in previous published studies^{33,34} before the availability of the ABSIS scoring method. The other limitation was that it was not possible to standardise the duration of follow-up after the first 3 months, and there were differences noted in the follow-up duration for patients with and without disease flare, as well as those with and without remission. This may have affected antibody titres and total cumulative prednisolone doses received. Finally, high antibody titres with values above 150 U/mL, which only accounted for 8% of all results, will need to be interpreted with caution as the linearity of the ELISA assay cannot be ascertained beyond this level, since no further sera dilutions were performed. However, we have verified that our key results

and conclusions remained unchanged with no significant differences detected after repeat analysis, using 150 U/mL as the upper limit of detection (data not shown).

Conclusion

This is the first study to investigate correlations of anti-BP180 antibody titres with disease activity and cumulative prednisolone doses received at fixed time points of disease evolution in a collective cohort of patients. The study showed positive and statistically significant correlations of antibody titres with disease activity at baseline and at disease flare. Thus, anti-BP180 antibody titres may be a useful indicator of disease activity at the time of diagnosis and at disease flare. Importantly, we demonstrated that antibody titres at 12 weeks after diagnosis may be useful in predicting clinical remission. We also found a significant correlation between the cumulative prednisolone dose received and antibody titres at Week 4. Notably, titres above 87.5 U/mL at time of diagnosis may be an indicator that higher cumulative prednisolone doses are needed to reach clinical remission within 2 years.

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An External Independent Validation of APACHE IV in a Malaysian Intensive Care Unit

Rowena SY Wong, ¹*MSc*, Noor Azina Ismail, ¹*MSc, PhD*, Cheng Cheng Tan, ²*MBBS, MAnaes*

Abstract

Introduction: Intensive care unit (ICU) prognostic models are predominantly used in more developed nations such as the United States, Europe and Australia. These are not that popular in Southeast Asian countries due to costs and technology considerations. The purpose of this study is to evaluate the suitability of the acute physiology and chronic health evaluation (APACHE) IV model in a single centre Malaysian ICU. **Materials and Methods:** A prospective study was conducted at the single centre ICU in Hospital Sultanah Aminah (HSA) Malaysia. External validation of APACHE IV involved a cohort of 916 patients who were admitted in 2009. Model performance was assessed through its calibration and discrimination abilities. A first-level customisation using logistic regression approach was also applied to improve model calibration. **Results:** APACHE IV exhibited good discrimination, with an area under receiver operating characteristic (ROC) curve of 0.78. However, the model's overall fit was observed to be poor, as indicated by the Hosmer-Lemeshow goodness-of-fit test ($\hat{C} = 113$, $P < 0.001$). Predicted in-ICU mortality rate (28.1%) was significantly higher than the actual in-ICU mortality rate (18.8%). Model calibration was improved after applying first-level customisation ($\hat{C} = 6.39$, $P = 0.78$) although discrimination was not affected. **Conclusion:** APACHE IV is not suitable for application in HSA ICU, without further customisation. The model's lack of fit in the Malaysian study is attributed to differences in the baseline characteristics between HSA ICU and APACHE IV datasets. Other possible factors could be due to differences in clinical practice, quality and services of health care systems between Malaysia and the United States.

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Key words: Mortality, Prognostic models, Severity of illness

¹Department of Applied Statistics, Faculty of Economics and Administration, University of Malaya, Malaysia

²Department of Anaesthesia and Intensive Care, Hospital Sultanah Aminah Johor Bahru, Malaysia

Address for Correspondence: Dr Noor Azina Ismail, Department of Applied Statistics, Faculty of Economics and Administration, University of Malaya, 50603 Kuala Lumpur, Malaysia.

Email: nazina@um.edu.my

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Introduction

Over the past 30 years, different versions of severity of illness scoring systems and prognostic models have been developed for prediction of patient outcomes in critical care.¹ These physiological-based systems and models allow patients to be stratified according to their severity of illness and provide prediction of in-hospital mortality.² The concept of using intensive care unit (ICU) prognostic models is considered relatively new in Malaysia, despite these models being widely applied in most developed nations. At present, performance assessment of ICUs across the country is managed by the Malaysian Registry of Intensive Care (MRIC), through annual national audits. Assessment and rating of performance in ICUs is primarily

based on computation of the simplified acute physiology score (SAPS) II³ severity of illness scores.⁴ A limitation of this assessment is that it considers only the severity of illness scoring component alone, without fully utilising the prediction component. In our opinion, the current assessment approach can be further improved through implementation of a suitable prognostic model that not only provides a severity of illness stratification system, but is also capable of predicting objective mortality risk estimates.

One of the main considerations in this study is to choose a suitable benchmark model among the various available models. We have chosen the acute physiology and chronic health evaluation (APACHE) IV⁵ as the reference model in our study after much consideration. An advantage of

¹Department of Applied Statistics, Faculty of Economics and Administration, University of Malaya, Malaysia

²Department of Anaesthesia and Intensive Care, Hospital Sultanah Aminah Johor Bahru, Malaysia

Address for Correspondence: Dr Noor Azina Ismail, Department of Applied Statistics, Faculty of Economics and Administration, University of Malaya, 50603 Kuala Lumpur, Malaysia.

Email: nazina@um.edu.my

this model is that it is able to provide more information on the physiological conditions of ICU patients since it has the most number of physiological variables compared to its contemporaries, i.e. SAPS 3 admission score^{6,7} and the mortality probability model (MPM0-III) admission models.⁸ Bearing in mind that the APACHE IV predictive equation was developed using data from multiple institutions, we are aware of the possibility that it may not be applicable in a single centre setting. However, the decision to choose APACHE IV as our reference model is also motivated by the promising potential shown in several recent external validation studies,^{9,10} that suggested the possibility of APACHE IV being robust enough for application in other countries and in single centre settings.

Materials and Methods

Data

We conducted a prospective independent validation study at the single centre ICU in Hospital Sultanah Aminah (HSA). This hospital is considered one of the several larger government tertiary referral hospitals in Malaysia. The multidisciplinary ICU in HSA admits general medical, surgical and trauma patients. It is equipped with mechanical ventilation facility and has a current bed size of 16.

Data collection involved consecutive admissions to HSA ICU between 1 January 2009 and 31 December 2009. The study followed the eligibility criteria defined in APACHE IV. For this study, we excluded patients below 16 years old, with less than 4 hours stay in the ICU, transferred from another ICU, and with incomplete clinical information. We have also excluded burns, transplant and postcardiac surgical patients from the study since they are treated in separate units. As for readmission cases, we only considered data from the first admission for analysis.

All data from patients are analysed anonymously. We did not obtain informed consent from all participants since this requirement is waived by the Medical Research and Ethics Committee, Ministry of Health, Malaysia, which is also responsible for approving this study. Data collection was manually performed by HSA ICU nurses and transferred to an online web-based database by medical officers. Details of the data collected are shown in Table 1. The admission diagnoses for each patient are determined by the ICU specialist on duty and subsequently verified by the intensivist.

Statistical Analysis

We performed manual calculation of the acute physiology score (APS) for each patient using Microsoft® Excel 2007, by combining the points for the worst physiological variables over the first day of stay in the ICU. Patients with incomplete first day APS information were excluded from the analysis. Missing physiological values were assumed normal and assigned zero points.¹¹ We validated APACHE IV by fitting in data that were obtained from HSA ICU patients into the APACHE IV multiple logistic regression equation in order to generate individual mortality estimates.

Model accuracy was evaluated through 3 measures, i.e. the model's discrimination, calibration and standardised mortality ratio (SMR). The model's ability to discriminate between surviving and non-surviving patients was tested through area under a receiver operating characteristic (ROC) curve. Analysis of model discrimination was performed using MedCalc version 10.4, in which estimation of area under ROC was based on a non-parametric approach.¹² Calibration was used to measure the degree of correspondence between predicted and actual mortality risk. The model's overall calibration was assessed through a calibration curve and

Table 1. Types of Data Collected in HSA ICU

Type of Data	Details	Frequency of Collection
Demographic	age, gender, ethnic group	once (ICU admission)
ICU admission	date and time, source prior to admission, principal admission diagnosis, operative status, pre-ICU length of stay	once (ICU admission)
Chronic health	AIDS, hepatic failure, lymphoma, metastatic cancer, leukaemia/multiple myeloma, immunosuppression, cirrhosis, diabetes	once (ICU admission)
Physiological and laboratory variables	pulse, mean blood pressure, temperature, respiratory rate, ABGs (PaO ₂ , FiO ₂ , A-aDO ₂ , PaCO ₂), hematocrit, white blood cell count, creatinine, urine output, blood urea nitrogen, sodium, albumin, bilirubin, glucose, arterial pH, GCS score, mechanical ventilation status	physiological (hourly) laboratory (approximately twice per day) neurological (between 4 to 6 times/day)
ICU discharge	vital outcome status, discharge location	once (ICU discharge)

HSA: Hospital Sultanah Aminah; ICU: Intensive care unit; ABG: Arterial blood gas; GCS: Glasgow Coma Scale; AIDS: Acquired immunodeficiency syndrome

the Hosmer-Lemeshow goodness-of-fit test,¹³ where P value <0.05 was used to imply a model's overall lack of fit. The model's SMR was calculated by taking the ratio of the mean observed deaths over the mean predicted deaths for the duration of study.

We applied a first level customisation strategy¹⁴ to improve calibration of the APACHE IV model. The approach involves fitting a simple logistic regression model with the observed in-ICU mortality rate being the dependent variable, and the original logit term in the APACHE IV model being the independent variable. The new estimated probability of death for each patient is then calculated from the customised model and calibration is re-evaluated for the customised model. We performed all statistical analysis using SPSS 17.0 for Windows.

Results

Baseline Characteristics of Study Population

A total of 1084 patients were admitted to HSA ICU from 1 January 2009 to 31 December 2009. After applying APACHE IV exclusion criteria, 916 eligible admissions were considered for analysis. Postoperative coronary artery bypass graft (CABG) patients were treated in a separate unit and were excluded from the study. A comparison of the differences in demographic and clinical characteristics between HSA ICU and APACHE IV (developmental) datasets is shown in Table 2. Admissions to HSA ICU recorded a higher percentage of male patients (60.6%) compared to the APACHE IV developmental sample (54.2%). The ethnic composition between Malaysia and the United States is different, where ethnic groups in HSA ICU were divided into 4 categories (Malay, Chinese, Indian and Others).

Admissions to HSA ICU for the period of study were almost equally divided between non-operative and postoperative patients, whereas approximately 70% of admissions used in the development of APACHE IV were non-operative. Difference in types of admissions between HSA ICU and APACHE IV was also reflected through a higher percentage of emergency surgery patients in HSA ICU (36.6%), compared to APACHE IV (5.7%). The principal diagnostic categories according to major organ-related functions for both operative and non-operative admissions to HSA ICU for the period of study are shown in Figure 1. The majority of postoperative patients were admitted due to trauma, whereas most of the non-operative patients were those with cardiovascular-related diseases.

The mean age of patients in HSA ICU at 43.44 years was notably lower compared to the corresponding mean of 61.51 years in APACHE IV. Younger patients formed the majority of HSA ICU admissions, with nearly 30% below

Table 2. Demographic and Clinical Characteristics of Admissions to HSA ICU (January 2009 to December 2009) and APACHE IV

Characteristics	HSA ICU (n = 916)	APACHE IV (n = 66,270)
Gender (% male)	60.6	54.2
Ethnic group		
White	NA	69.3
Malay	56.4	NA
Chinese	24.1	NA
Indian	10.7	NA
Others	8.7	NA
Mean age (years)	43.44 $\pm$ 0.58	61.51 $\pm$ 0.07
Mean APS	69.59 $\pm$ 1.06	38.83 $\pm$ 0.10
Mean pre-ICU length of stay (square root days)	0.794 $\pm$ 0.023	0.786 $\pm$ 0.004
Died in ICU (%)	18.8	13.6
With comorbidities (%)	3.7	10.3
Emergency surgery (%)	36.6	5.7
Postoperative patient (%)	49.2	30.9
Ventilated on ICU Day 1 (%)	83.0	35.1
Unable to assess GCS (%)	23.1	8.0

HSA: Hospital Sultanah Aminah; APACHE: Acute physiology and chronic health evaluation; NA: Not applicable; APS: Acute physiology score; ICU: Intensive care unit; GCS: Glasgow Coma Scale

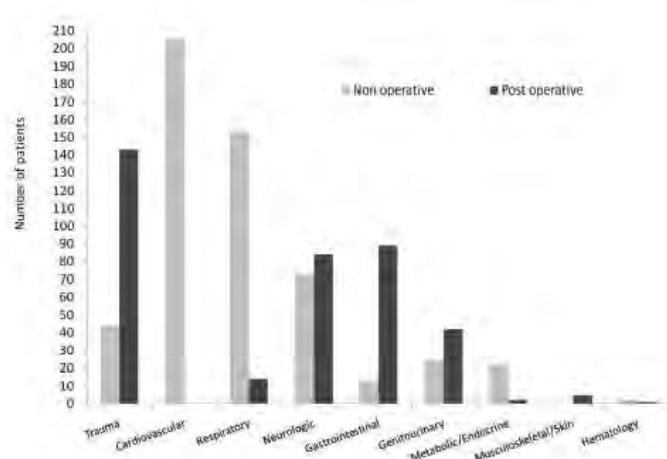


Fig. 1. Graph showing breakdown of principal diagnostic categories according to major organ functions for postoperative and non-operative HSA ICU admissions in year 2009.

the age of 30 years. These patients were mostly admitted to HSA ICU for trauma-related illnesses (Fig. 2). Patients in the middle age groups were mostly admitted due to cardiovascular and respiratory diseases, whereas those who

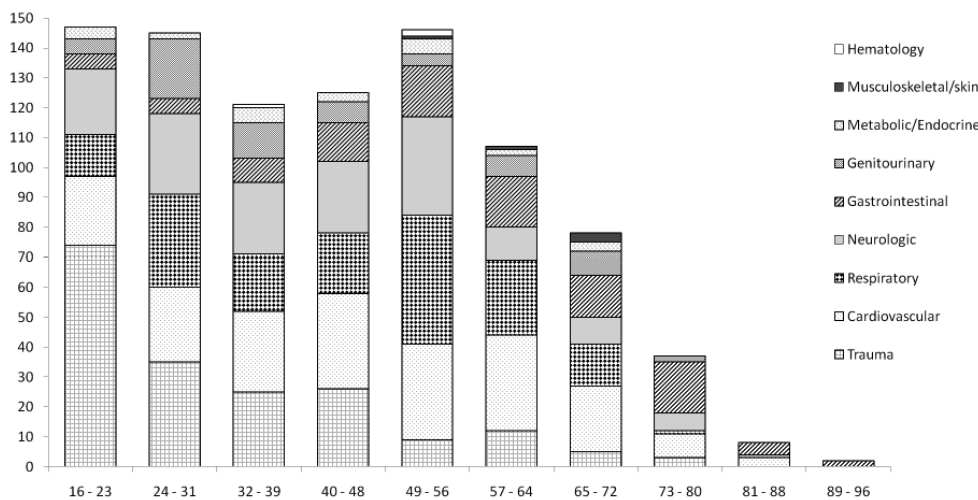


Fig. 2. Graph showing the detailed principal diagnostic categories according to age group for HSA ICU admissions in year 2009.

were older than 70 years old were mostly admitted due to gastrointestinal problems. A small percentage of HSA ICU patients (3.7%) disclosed that they have at least 1 of the 7 comorbidities defined in APACHE IV, with one-third having immunodeficiency disorders. It is possible that some of the patients who were admitted to HSA ICU could have been deliberately withholding important information about their underlying conditions, or could not provide accurate information due to lack of awareness of their previous medical condition.

The first day APS values for patients who were admitted to HSA ICU for the period of study varied between 11 and 171, with the majority having values between 41 and 50. There were also isolated cases of patients having APS values that were greater than 140. The mean APS value for ICU Day 1 admissions to HSA ICU (69.59) is significantly higher than the mean APS value for APACHE IV (38.83). This value implies that the severity of illness of patients who were admitted to HSA ICU was much greater compared to the APACHE IV cohort. The overall number of deaths in HSA ICU for the period of study was 172 (18.8%). Application of APACHE IV in HSA ICU produced a significantly higher overall predicted in-ICU mortality rate of 28.11% and an overall SMR value of 0.67.

Validation of APACHE IV Model

On the whole, APACHE IV appeared to exhibit good discrimination when applied to HSA ICU, with an area under ROC of 0.78 (Fig. 3). Despite having good discrimination, the model's calibration in HSA ICU was found to be poor, as reflected in the calibration curve (Fig. 4) and results obtained from the Hosmer-Lemeshow goodness-of-fit tests (Table 3). Model fit is considered to be perfect when the observed values lie exactly on the diagonal line of a calibration curve. From the calibration curve, model fit appeared to be quite acceptable for the first 3 risk deciles. However, predictions were inaccurate starting from the fourth decile onwards, where the observed outcomes were much lower than predicted outcomes. The majority of patients in HSA ICU were in the first 3 groups and were associated with lower mortality risk. A significant improvement was observed in calibration after applying first level customisation on the APACHE IV equation (Table 3). The overall fit for the customised model was found to be good although there was no improvement in discrimination.

Discussion

There has been considerable debate over the use of SMR as

Table 3. Performance Indicators of APACHE IV and the First-level Customised Model

	SMR	Area under ROC Curve	Hosmer-Lemeshow χ^2	$\hat{C}$ Statistic P Value
APACHE IV	0.67	0.78	113	< 0.0001
Customised model	1.00	0.78	6.39	0.78

SMR: Standardised mortality ratio; ROC: Receiver operating characteristic

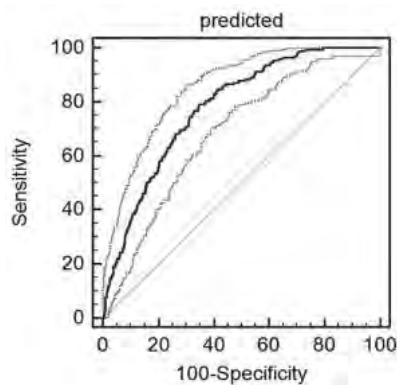


Fig. 3. Area under receiver operating characteristic curve for HSA ICU admissions in year 2009.

a valid indicator of quality of care that is being provided in an ICU.¹⁵⁻¹⁷ We acknowledge that SMR may not be a perfect indicator to evaluate model performance and interpretation of this index should be done with caution. However, SMR is still a universal standard approach for reporting of hospital mortality and has been applied to evaluate model performance in many well established hospital prognostic systems, including APACHE IV. In this study, external validation of APACHE IV in HSA ICU yielded a low SMR value of 0.67. There are 2 possible interpretations of a low SMR value, i.e. it could indicate that HSA ICU performed well with very ill patients, or it could suggest poor calibration of APACHE IV in the Malaysian ICU. We do not think that our ICU did an excellent job with very ill patients as Malaysia is still a developing country and the ICU was seriously short of trained staff at the time the study was conducted. We believe that significant differences in case mix (age distribution, types of admission, admission diagnoses) between HSA ICU and APACHE IV contributed towards the lower SMR.

APACHE IV exhibits good discrimination but tends to overestimate in-ICU mortality, especially for mid- to high-risk ranges in this study. Our study reveals that APACHE IV equation for prediction of in-ICU mortality risk does not fit well and is not suitable for application in HSA ICU. The model's lack of fit is likely due to differences in patient characteristics between APACHE IV and HSA ICU datasets, especially in terms of age, types of disease and admission types. While most of the patients involved in the development of APACHE IV were elderly, a significant number of HSA ICU patients were from the younger age groups with trauma-related illnesses. These patients were mostly victims of road accidents, who were transferred from the Accident & Emergency (A&E) unit.

Discrepancy in the mean APS between HSA ICU and

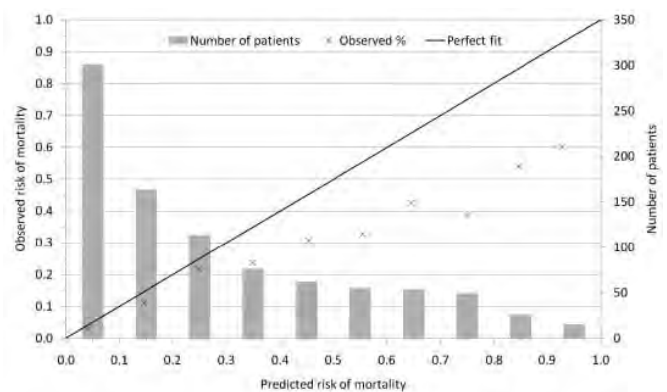


Fig. 4. Calibration curve to compare observed and predicted in-ICU mortality rates across 10% intervals of predicted risk.

APACHE IV is probably another influential factor that affected APACHE IV's prediction accuracy. The mean APS in HSA ICU is considerably higher compared to APACHE IV. Differences in quality and health care systems could probably account for the discrepancy in APS between HSA ICU and APACHE IV admissions. The physiological components of a patient are also affected by factors such as genetics, lifestyle and cultural habits. Moreover, the calculation approach in APACHE IV considers points that are assigned to the worst values of each physiological variable. The choice of worst values is highly dependent on data variation. It is highly possible that variability in data is greater for HSA ICU patients, resulting in extreme values being chosen as worst values and thus contributing to higher APS values. In our study, frequency of data collection followed the current practice in HSA ICU, where data collection intervals were not equal time-spaced for all physiological variables. Some variables were monitored on an hourly basis, whereas other variables were measured less frequently. Differences in the data collection intervals play an important role in influencing the choice of worst values for physiological variables. We believe that the choice of worst values for infrequently measured variables may be affected by detection bias¹⁸ where variables are only detected if they are measured and unmeasured variables are assumed normal.

The majority of patients who were admitted to HSA ICU reported that they do not have existing chronic health conditions. Although APACHE IV (non-CABG model) did not list diabetes as one of the chronic health conditions, this information was collected in our study. Interestingly, 184 patients (20.1%) revealed that they were diabetic patients. This figure is consistent with the findings in a recent study¹⁹ that reported the overall prevalence of diabetes in Malaysia (11.6%) to be higher than other regions in the world. In view

of the high percentage of diabetic patients in HSA ICU, there is a possibility that this variable may potentially be a significant predictor of in-ICU mortality risk in the context of our Malaysian study. In addition, although ethnicity was not included as one of the main predictors in APACHE IV, the importance of this variable merits further investigation. Further work is required to evaluate whether differences in cultural and dietary habits among various ethnicities in Malaysia play an important role in predicting in-ICU mortality outcomes in the local context.

There are several limitations to our study. First, due to the single centre nature of this study, findings that are obtained in HSA ICU may not be representative of other ICUs in Malaysia. Potential differences in case mix, clinical practice, discharge policies and quality of care between HSA ICU and other ICUs may limit the generalisation of our findings. Second, the sample size in our single centre study is considered relatively small and our case mix may not be sufficiently diverse compared to APACHE IV. The small sample size is a limiting factor in the analysis of uniformity of fit among different subgroups in our study. Although a multi centre study will probably mitigate issues regarding sample size and case mix, we were unfortunately not able to obtain cooperation from other ICUs in the country due to limited manpower and funding resources.

Conclusion

In this study, we have shown that APACHE IV has poor calibration and acceptable discriminatory power when applied to a Malaysian ICU cohort. There is great potential in using prognostic models to enhance the quality of critical care in Malaysia. A good prognostic model will definitely serve as a clinical decision support tool that is beneficial to medical practitioners in the long run. To the best of our knowledge, this is the first study on external validation of APACHE IV in Malaysia. This study is beneficial in the sense that it provides an insight on the characteristics of patients who were admitted to HSA ICU.

Acknowledgements

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Prevalence of Chronic Mental and Physical Disorders, Impact on Work Productivity and Correlates of Alcohol Use Disorders and Nicotine Dependence across Occupations

Janhavi Ajit Vaingankar, ¹*MSc*, Mythily Subramaniam, ^{1,2}*MHSM*, Siow Ann Chong, ¹*MMed*, Vincent YF He, ¹*BSc*, Edimansyah Abidin, ¹*PhD*, Louisa Picco, ¹*MPH*, Wei Yen Lim, ^{1,2}*PhD*, Sin Eng Chia, ²*MD*

Abstract

Introduction: This study assessed occupational differences in the prevalence of mental and physical disorders in an employed general population sample in Singapore and investigated the impact of these disorders on work productivity losses in terms of work-loss days and work-cutback days. The association of occupation with alcohol use disorders (AUD) and nicotine dependence (ND) was also investigated. **Materials and Methods:** Data from a population-based mental health survey of a representative sample of multi-ethnic residents aged 18 years and above were used. The World Health Organization's (WHO) Composite International Diagnostic Interview (CIDI) was administered to establish the lifetime diagnosis of key mental disorders. Self-report on sociodemographic characteristics, productivity loss, ND, and lifetime physical conditions were obtained. Nine occupational groups were included in this analysis. **Results:** The sample comprised 4361 participants with a mean (SD) age of 42.2 (11.9) years, ranging between 19 to 80 years. 'Associate professionals and technicians' (26.2%), 'Services and sales workers' (17.7%) and 'Professionals' (15.4%) were the 3 predominant occupational categories. Sociodemographic characteristics differed significantly across occupations ($P < 0.001$). The lifetime prevalences of having 'any mental disorder' and 'any physical disorder' were 13.0% and 37.9%, respectively; major depressive disorder was the most prevalent mental disorder (5.9%) and hypertension was the most common physical disorder (15.6%). There were no significant differences in work productivity loss across occupations. Sociodemographic and occupational correlates for AUD and ND were identified. **Conclusion:** Sociodemographic and health disparities exist in the major occupational categories in Singapore. The strength of the associations between occupation and AUD and ND are significant, indicating the need for preventative measures in select occupations.

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Key words: Major depressive disorder, Multi-ethnic, Population-based

¹Research Division, Institute of Mental Health, Singapore

²Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Address for Correspondence: Ms Janhavi Ajit Vaingankar, Research Division, Institute of Mental Health, 10 Buangkok View, Singapore 539747.

Email: janhavi_vaingankar@imh.com.sg

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Introduction

Singapore is an island city-state in Southeast Asia with a multi-ethnic population comprising 74.2% Chinese, 13.4% Malays, 9.2% Indians, and the rest belonging to 'Other' ethnic groups.¹ In 2011, 78% of the resident population aged 25 to 64 years was employed² and there were over 2 million residents in the workforce with 90% in full-time employment. Of these, 47.8% were in professional, managerial, executive and technical (PMET) occupations and 52.2% held non-PMET jobs. While working conditions and workplace health and safety are regularly monitored to achieve sustainable improvement in the health of workers in Singapore,³ limited information on the effect of occupation on mental and physical health of workers has been documented.

Studies conducted elsewhere have reported the impact of job characteristics, such as environmental and working conditions, and physical and psychological demands of the job on health outcomes.⁴⁻⁶ Sociodemographic determinants of health also vary in occupational groups as recruitment criteria differ across jobs, which are also mediated by education and, in turn, linked to illnesses. The nature of the job itself influences health, such as exposure to hazardous materials or psychologically stressful working conditions.⁷ Differences in the prevalence of major depression and anxiety,^{8,9} alcohol abuse,¹⁰ cigarette smoking and nicotine dependence (ND),¹¹ hypertension,¹² diabetes,¹³ cardiovascular diseases,¹⁴ and cancers¹⁵ have been established among employed populations by occupational

¹Research Division, Institute of Mental Health, Singapore

²Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Address for Correspondence: Ms Janhavi Ajit Vaingankar, Research Division, Institute of Mental Health, 10 Buangkok View, Singapore 539747.

Email: janhavi_vaingankar@imh.com.sg

levels. Studies have also documented the impact of mental and physical health on loss of work productivity^{6,16} with a higher risk of productivity loss being associated with physical health conditions in the presence of comorbid psychological distress and depression.¹⁷ Addictive behaviours such as excessive drinking and smoking with or without dependence, can lead to health and safety issues at workplaces,¹⁸ and are associated with work strain, dysfunctional occupational performance and productivity loss.¹⁹

The association of employment status with various physical and mental conditions is well documented in Singapore.²⁰⁻²⁴ The prevalence of mental illness alone and comorbid mental-physical disorders is 2.5% and 2.4% respectively, in Singapore's employed population, and there exists a nearly 3-fold higher risk of productivity loss in these groups as compared to the healthy population.²² However, to the best of our knowledge, a limited number of studies have reported prevalence disparities and determinants of illnesses across occupational levels using a standard occupational classification²⁵⁻²⁷ and there is a lack of generalisable knowledge on the prevalence and impact of chronic disorders among different occupations in Singapore.

The purpose of this study was to assess occupational differences in the prevalence of mental and physical disorders in a large representative sample of residents in Singapore. In addition, the impact of these disorders on work productivity losses in terms of work-loss days and work-cutback days was assessed. Given the link between addictions and health and safety risks in occupations,²⁸ the study also investigated the effect of occupation on alcohol use disorders (AUD) and ND after controlling for other sociodemographic characteristics.

Materials and Methods

Data collected during the Singapore Mental Health Study (SMHS) were used. The study design and procedures are described in detail elsewhere.²⁹ Briefly, the SMHS is a representative cross-sectional survey of the Singapore population aged 18 years and above. The survey was conducted between December 2009 to December 2010. Singapore residents (citizens and permanent residents) were randomly selected from a sampling frame of all residents using a national database. Residents aged 18 years and above, and those capable of providing informed consent and completing the interview in English, Mandarin or Malay languages were included in the study. Exclusion criteria were institutionalisation or residence outside Singapore during the survey period, non-resident status, being under 18 years of age, and the inability to complete the survey due to severe physical or mental conditions or language barriers. Disproportionate stratified sampling was used to oversample older residents aged 65 years and above and

residents of Malay and Indian ethnicity. The study was approved by the institutional ethics committee and written informed consent was obtained from all participants and parents/guardians of participants aged 18 to 20 years. A total of 6616 residents participated in the survey, giving a response rate of 75.9%. A total of 71% of the respondents were employed. Data from 4361 participants (constituting 65.9% of the total study sample and 94.9% of 4594 employed participants) could be categorised under the Singapore Standard Occupational Classification (SSOC).³⁰

Classification of Occupation

Participants reported their current employment status at the time of the survey to the interviewers as: employed (regardless of full-time or part-time employment), unemployed (those looking for work/unemployed, temporarily laid off, never worked, or disabled) or economically inactive (comprising homemakers, students, and retirees). In the pilot phase of the survey ($n = 174$), a list of occupational categories based on the 2003 Standard Occupational Classification (SOC) (USA) was presented to the employed participants. However, interviewers and participants required considerable time to verify against the standard definitions leading to administrative burden. Given the length of the survey (an average of 2 hours) and that occupational data were being collected as a secondary study objective, a decision to use an open-ended question on occupation was taken. Employed participants were then asked to describe the type of work they normally did and their job title using an open-ended question ("What is your job called?"). Interviewers were specifically trained to obtain adequate and correct information. In instances where participants held multiple jobs, information on the job where they spent the most time was recorded, and if they spent equal amounts of time, details of the job that required higher skill/educational requirement were collected. These data were first reviewed by two team members (JAV and VH) and then categorised under the guidance of another team member (SEC), who is an occupational physician with more than 20 years practice in occupational health, into 10 major occupational groups based on the SSOC:

- 1) Business owners: Business owners or partners, entrepreneurs and contractors who employed other professionals were categorised under this group.
- 2) Legislators, senior officials and managers: Participants who belonged to senior or top management such as chief executive officers, chairmen or directors, or managed, directed or supervised activities at various government or non-government organisations or businesses were grouped under this category.
- 3) Professionals: This group included professional roles that applied scientific, analytical, accounting, research or

artistic theories or provided consultation on these.

4) Associate professionals and technicians: Participants who provided subordinate or related tasks to the professional categories were grouped here.

5) Clerical support workers: This included administrative and clerical support staff responsible for recording, organising and carrying out other clerical duties affiliated with finances, operations, information and appointments.

6) Services and sales worker: Service provision in retail, wholesale, travel, housekeeping, catering, transport, personal care and hygiene, etc were classified in this group.

7) Agricultural and fishery workers: Participants were included under this category if they were responsible for growing and harvesting animals, plants or fishery to generate income for themselves or others.

8) Craftsmen and related trades workers: Participants with specific knowledge and skills in construction, maintenance, machinery, handicrafts, etc, were included in this group.

9) Plant and machine operators and assemblers: Participants classified in this group operated or assembled industrial or agricultural machinery or equipment.

10) Cleaners, labourers and related worker: This group included participants who performed simple routine tasks that required considerable manual work and physical effort.

Apart from these 10 occupational groups, the SSOC also lists an additional category 'X' which comprises all other professions which cannot be classified into the above and these include army, navy and civil defense personnel among others. The category 'Agricultural and fishery workers' ($n = 3$) and 'X' ($n = 218$) were not included in this analysis due to low sample size and high heterogeneity, respectively, and in order to avoid misinterpretation of the estimates.

Assessments

Mental disorders: The World Mental Health (WMH) Composite International Diagnostic Interview 3.0 (CIDI 3.0) was used to establish the lifetime diagnosis of mental disorders as per the Diagnostic and Statistical Manual, Fourth Edition, of the American Psychiatric Association (DSM-IV).³¹ Select modules of the CIDI 3.0 were administered by trained interviewers to the participants to establish diagnoses of mood disorders (major depressive disorder, dysthymia, bipolar disorder), anxiety disorders (generalised anxiety disorder, obsessive compulsive disorder) and AUD (alcohol abuse, alcohol dependence) using diagnostic rules of hierarchy.

ND: ND was established with the 6-item modified Fagerstrom Test for Nicotine Dependence (FTND) scale.³² It establishes point prevalence of nicotine dependence by determining difficulty in refraining from smoking where

it is forbidden, smoking more in the morning, inability to give up the first morning cigarette, smoking when bedridden because of illness, depth of inhalation and time after awakening before smoking the first cigarette. A total score of 5 and above denotes significant ND.³³ The internal consistency of the scale in the present study was high (Cronbach's alpha of 0.73).

Chronic physical conditions: Participants were presented with a list of 15 chronic physical conditions and asked to report if they were 'ever told by a doctor' that they had any of these. The disorders were then reclassified into 8 types of physical disorders: 1) respiratory disorders (asthma, chronic lung disease such as chronic bronchitis or emphysema), 2) diabetes, 3) hypertension and high blood pressure, 4) chronic pain (arthritis or rheumatism, back problems including disk or spine, migraine headaches), 5) cancer, 6) neurological disorders (epilepsy, convulsion, Parkinson's disease), 7) cardiovascular disorders (stroke or major paralysis, heart attack, coronary heart disease, angina, congestive heart failure or other heart disease), and 8) ulcer and chronic inflamed bowel (stomach ulcer, chronic inflamed bowel, enteritis, or colitis).

Work productivity: Select items from the 30-day functioning module of the CIDI 3.0 were used to assess the impact of mental and physical disorders on work productivity in terms of work-loss days (absenteeism) and work-cutback days (presenteeism). Participants were asked to report the number of days where they were totally unable to work or had to cut back on the type or quantity of work due to 'problems with their physical health, mental health, or use of alcohol or drugs' in the month prior to the survey.

Sociodemographic characteristics: In addition to the above, information on participants' age, gender, ethnicity, marital status, highest education level attained and all sources of personal income, (in Singapore dollars in the year prior to the interview) was collected during the survey.

Statistical Analysis

Sampling weights were derived for the data based on the Department of Statistics, Singapore's population estimates for the year 2007. Weighted analyses to adjust for the oversampling and post-stratification by age and ethnicity were carried out using the Statistical Analysis Software (SAS) System version 9.2 (SAS Institute, Cary, NC). Mean and standard deviations (SD)/standard errors (SE) were calculated for continuous variables. Frequencies and percentages were calculated for categorical variables. Bivariate associations between occupational groups and other categorical variables were investigated with chi-square (χ^2) tests, while analysis of variance (ANOVA) was carried out to establish mean differences in work productivity

by occupations. Determinants of AUD (participants having either alcohol abuse or dependence) and ND were investigated using multiple logistic regression model by evaluating multivariate significance using Wald (χ^2) tests based on design-corrected coefficient variance-covariance matrices. SE and significance tests were estimated using the Taylor series linearisation method to adjust for the weighting. Statistical significance was set at $P < 0.05$ using 2-sided tests.

Results

Occupation and Sociodemographic Characteristics

The study sample comprised 4361 participants with a mean (SD) age of 42.2 (11.9) years, ranging between 19 and 80 years. The distribution of occupation and sociodemographic characteristics within this study sample is presented in Table 1. Majority of the participants were aged 35 to 49 years (41%), followed by 18 to 34 years (31.3%), 50 to 64 years (23.7%) and 65 years and above (4%); secondary level education (27.8%) was the largest educational group in the sample. The top 3 occupational categories were ‘Associate professionals and technicians’ (which constituted 26.2% of the sample), ‘Services and sales worker’ (17.7%) and ‘Professionals’ (15.4%). Age, gender, ethnicity, marital status, education and income differed significantly ($P < 0.001$) across the 9 occupational categories (Table 2). The most common occupational group among participants who were single (32.3%) or married (24.3%) were ‘Associate professionals and technicians’, whereas ‘Services and sales’ was the most common occupation among those separated or divorced (26.2%), and ‘Cleaners, labourers and related workers’ (30.9%) was the most common group among participants who were widowed.

Prevalence of Mental and Physical Disorders by Occupation

Table 3 presents the prevalence of lifetime mental and physical disorders among participants in the various occupations. The lifetime prevalence of any mental disorder and any physical disorder was 13% and 37.9%, respectively. Major depressive disorder (MDD) (5.9%) was the most prevalent DSM-IV mental disorder. AUD which constituted participants with either alcohol abuse or dependence were the second highest (4.3%), followed by obsessive compulsive disorder (3.2%). A total of 5.3% of the participants had ND. The prevalence of AUD and ND was significantly different ($P < 0.001$) across the occupational groups (Table 3). The highest prevalence of AUD was among ‘Business owners’ (12%) while ND was highest among ‘Craftsmen and related trades workers’ (24.8%) (Table 3).

Hypertension was the most common physical disorder (15.6%), followed by chronic pain (14.1%) and respiratory

conditions (8.6%) (Table 2). Significant differences were observed at the bivariate level in the prevalence of diabetes ($P = 0.002$), hypertension ($P = 0.001$) and neurological conditions ($P = 0.003$) across occupations. ‘Craftsmen and related trades workers’ showed the highest prevalence of these 3 disorders—diabetes (14.8%), hypertension (26.5%) and neurological conditions (11.9%) (Table 3).

Comorbid mental and physical disorders were highest among the ‘Legislators, senior officials and managers’ (10%) and lowest among ‘Cleaners, labourers and related workers’ (2.3%). Detailed estimates are reported in Table 4.

Table 1. Sociodemographic Characteristics of the Sample (n = 4361)

	n	Adjusted % (SE)
Age (years)		
18 – 34	1465	31.3 (0.0)
35 – 49	1829	41.0 (0.0)
50 – 64	983	23.7 (0.0)
65 and above	84	4.0 (0.0)
Gender		
Men	1866	47.2 (1.1)
Women	2495	52.8 (1.1)
Ethnicity		
Chinese	1375	77.6 (0.0)
Malay	1498	11.6 (0.0)
Indian	1304	8.2 (0.0)
Others	184	2.6 (0.0)
Marital status		
Single	1122	27.9 (0.9)
Married	2987	65.9 (0.9)
Separated/divorced	191	4.7 (0.5)
Widowed	61	1.5 (0.3)
Education level		
Pre-primary	89	2.6 (0.4)
Primary	511	12.7 (0.7)
Secondary	1298	27.8 (0.9)
Pre-U/junior college/diploma	882	21.2 (0.9)
Vocational	531	8.8 (0.6)
University	1050	26.9 (0.9)
Income (SGD)*		
Below 20,000	1623	35.0 (1.0)
20,000 – 49,999	1787	41.9 (1.0)
50,000 and above	894	23.1 (0.9)

SE: Standard error

*Denotes personal income in Singapore dollars in 1 year prior to the interview.

Table 2. Occupation and Sociodemographic Distribution (in Percentage) of the Participants (n = 4361)

All Occupations	Business Owners†	Legislators, Senior Officials and Managers†	Associate Professionals and Technicians†	Clerical Support Workers†	Services and Sales Workers†	Craftsmen and Related Trades Workers†	Plant and Machine Operators and Assemblers†	Cleaners, Labourers and Related Workers†
Overall sample	3.2	12.3	15.4	26.2	17.7	2.9	6.6	7.0
Age (years)*								
18–34	1.4	9.2	2.6	35.0	19.3	1.4	2.6	1.5
35–49	3.8	15.4	16.9	25.4	14.3	2.9	6.5	5.8
50–64	4.9	11.3	6.5	18.0	22.0	4.4	11.5	12.8
65 and above	0.3	10.8	11.7	15.7	14.2	5.1	9.1	27.6
Gender*								
Men	4.6	15.3	16.6	24.7	14.4	4.0	11.6	5.7
Women	1.7	9.0	14.0	28.0	21.3	1.6	0.9	8.5
Ethnicity*								
Chinese	3.6	12.7	15.5	25.7	17.5	3.1	6.6	6.7
Malay	0.9	3.8	9.3	30.3	21.0	3.1	8.0	11.6
Indian	2.3	12.0	18.0	28.9	17.3	1.2	6.6	5.7
Others	2.6	39.5	30.9	15.0	9.8	0.3	-	-
Marital status*								
Single	1.7	9.6	2.1	32.3	16.4	2.8	3.6	4.5
Married	3.8	13.6	14.2	24.3	17.5	3.0	7.6	7.5
Separated/divorced	3.1	11.4	8.7	22.4	26.2	3.0	8.6	6.0
Widowed	4.1	7.3	0.9	9.4	22.4	0.3	11.5	30.9
Education level*								
Pre-primary	-	-	0.2	13.0	16.5	9.7	17.6	42.6
Primary	4.3	1.5	1.1	9.8	27.7	10.0	16.3	24.5
Secondary	3.8	8.2	3.5	22.8	27.8	2.8	9.0	7.8
Pre-U/junior college/diploma	3.8	12.9	16.3	39.9	13.6	0.6	1.5	1.2
Vocational	4.5	4.6	5.2	34.1	20.5	4.2	12.6	3.2
University	1.4	24.8	38.6	25.4	5.0	0.2	0.3	0.3
Income (SGD)*‡								
Below 20,000	2.1	1.4	6.4	18.7	28.3	4.6	10.6	18.2
20,000–49,999	4.1	8.2	15.5	33.8	16.3	2.6	6.8	1.3
50,000 and above	2.7	36.0	29.4	23.8	4.0	0.7	0.5	0.3

*Significant differences in proportions at $P < 0.001$ between occupational groups, chi-square test.

†Table presents weighted row percentages.

‡Denotes personal income in Singapore dollars in 1 year prior to the interview.

Table 3. Prevalence of Lifetime Mental and Physical Disorders across Occupational Categories (n = 4361)

Lifetime Conditions	All Occupations		Business Owners		Legislators, Senior Officials and Managers		Professionals		Associate Professionals and Technicians		Clerical Support Workers		Services and Sales Workers		Craftsmen and Related Trades Workers		Plant and Machine Operators and Assemblers		Cleaners, Labourers and Related Workers	
	%		%		%		%		%		%		%		%		%		%	
MDD	5.9		4.1		6.9		6.9		6.2		4.9		7.7		2.2		3.5		2.2	
Bipolar disorder	1.2		0.5		1.6		1.0		1.0		2.6		1.6		-		1.2		0.2	
GAD	0.8		0.5		1.2		1.0		0.7		2.1		0.6		-		0.2		0.1	
OCD	3.2		2.2		2.4		3.1		5.0		3.8		2.7		-		2.5		1.6	
Alcohol abuse†	3.8		11.1		6.6		2.5		3.9		1.1		1.8		7.3		6.6		1.8	
Alcohol dependence†	0.5		0.9		1.1		0.4		0.1		0.2		1.2		-		0.3		-	
Alcohol use disorder (Abuse/dependence)†	4.3		12.0		7.7		2.9		4.0		1.3		3.0		7.3		6.9		1.8	
Nicotine dependence†	5.3		4.6		5.5		1.9		4.7		2.6		5.2		24.8		9.3		6.2	
Diabetes*	6.2		1.7		6.5		2.4		6.0		5.9		5.7		14.8		11.0		10.9	
Hypertension*	15.6		16.0		12.7		11.3		14.4		16.4		14.5		26.5		25.7		21.7	
Respiratory conditions	8.6		2.3		9.0		9.3		10.5		9.1		9.0		3.8		6.1		4.2	
Chronic pain	14.1		14.1		13.5		15.1		15.3		12.4		14.9		16.3		11.0		10.1	
Cancer	0.4		-		1.2		0.1		0.5		0.1		0.4		-		0.1		0.1	
Neurological conditions*	3.0		1.8		0.8		4.3		2.7		2.4		3.9		11.9		1.2		2.7	
Cardiovascular conditions	1.8		4.1		2.0		1.8		1.2		0.1		1.8		4.2		4.4		1.7	
Ulcers	2.1		2.1		2.2		4.2		1.9		2.9		1.6		2.5		0.6		0.3	

GAD: Generalised anxiety disorder; MDD: Major depressive disorder; OCD: Obsessive compulsive disorder

*Significant differences at $P < 0.05$.†Significant differences at $P < 0.001$ between occupational groups, chi-square test.

Table 4. Prevalence of Lifetime Mental and Physical Disorders across Occupational Categories (n = 4361)

Lifetime Disorders	All Occupations			Business Owners			Legislators, Senior Officials and Managers			Professionals			Associate Professionals and Technicians		
	%	SE	95% CI	%	SE	95% CI	%	SE	95% CI	%	SE	95% CI	%	SE	95% CI
MDD	5.9	0.5	5.0–6.9	4.1	2.5	1.2–13.0	6.9	1.5	4.4–10.6	6.9	1.3	4.7–10.0	6.2	1.0	4.6–8.4
Dysthymia	0.3	0.1	0.2–0.6	-	-	-	0.5	0.5	0.1–3.0	0.7	0.5	0.2–2.6	0.2	0.1	0.1–0.4
Bipolar disorder	1.2	0.2	0.9–1.8	0.5	0.3	0.1–1.9	1.6	0.8	0.6–4.2	1.0	0.5	0.3–2.9	1.0	0.4	0.5–2.0
GAD	0.8	0.2	0.5–1.3	0.5	0.3	0.1–1.9	1.2	0.6	0.4–3.4	1.0	0.5	0.3–2.8	0.7	0.3	0.3–1.6
OCD	3.2	0.4	2.6–4.1	2.2	1.8	0.4–0.2	2.4	0.9	1.2–4.8	3.1	0.9	1.7–5.6	5.0	0.9	3.5–7.2
Alcohol abuse†	3.8	0.4	3.0–4.6	11.1	4.1	5.2–21.9	6.6	1.6	4.1–10.5	2.5	0.7	1.4–4.4	3.9	0.8	2.6–5.9
Alcohol dependenc†	0.5	0.1	0.3–0.8	0.9	0.7	0.2–3.7	1.1	0.5	0.4–2.9	0.4	0.2	0.1–1.1	0.1	0.1	0.0–0.3
Alcohol use disorder (abuse/dependence)†	4.3	0.4	3.5–5.2	12.0	4.1	5.9–22.7	7.7	1.7	5.0–11.7	2.9	0.8	1.7–4.8	4.0	0.8	2.7–6.0
Nicotine dependence*	5.3	0.5	4.4–6.2	4.6	2.6	1.5–13.2	5.5	1.5	3.2–9.2	1.9	0.8	0.8–4.4	4.7	0.8	3.4–6.5
Diabetes*	6.2	0.5	5.3–7.3	1.7	0.6	0.8–3.4	6.5	1.6	3.9–10.5	2.4	0.9	1.1–5.0	6.0	1.1	4.2–8.5
Hypertension*	15.6	0.8	14.1–17.2	16.0	4.7	8.9–27.3	12.7	2.1	9.1–17.4	11.3	1.8	8.2–15.3	14.4	1.6	11.6–17.7
Respiratory conditions	8.6	0.6	7.5–9.8	2.3	1.8	0.5–10.5	9.0	1.8	6.0–13.3	9.3	1.5	6.7–12.7	10.5	1.2	8.3–13.2
Chronic pain	14.1	0.7	12.7–15.6	14.1	4.5	7.4–25.4	13.5	2.0	9.9–18.0	15.1	2.0	11.5–19.5	15.3	1.5	12.6–18.5
Cancer	0.4	0.1	0.2–0.7	-	-	-	1.2	0.7	0.4–3.6	0.1	0.1	0.0–0.4	0.5	0.3	0.2–1.7
Neurological conditions*	3.0	0.4	2.3–3.9	1.8	1.8	0.2–11.5	0.8	0.5	0.2–2.8	4.3	1.1	2.5–7.2	2.7	0.7	1.6–4.5
Cardiovascular conditions	1.8	0.3	1.3–2.5	4.1	2.5	1.2–13.0	2.0	0.8	0.9–4.4	1.8	0.8	0.7–4.4	1.2	0.5	0.5–2.6
Ulcers	2.1	0.3	1.6–2.9	2.1	1.8	0.4–11.0	2.2	0.9	0.9–5.0	4.2	1.1	2.5–7.0	1.9	0.6	1.0–3.6
Any mental disorder	13.0	0.7	11.7–14.4	18.5	4.9	10.7–30.0	16.5	2.3	12.5–21.5	12.6	1.7	9.6–16.4	14.0	1.4	11.5–17.1
Any physical disorder	37.9	1.0	35.9–40.0	31.7	5.9	21.5–44.1	36.5	3.0	30.8–42.6	34.0	2.6	29.1–39.3	39.9	2.0	36.0–44.0
No mental or physical disorder	54.4	1.1	52.3–56.5	54.7	6.3	42.3–66.5	55.5	3.1	49.4–61.5	58.6	2.7	53.2–63.8	52.4	2.1	48.3–56.4
Only mental disorder	6.7	0.5	5.8–7.8	11.8	4.1	5.9–22.5	6.5	1.5	4.2–10.0	6.8	1.3	4.6–9.8	6.9	1.0	5.2–9.3
Only physical disorder	32.6	1.0	30.7–34.6	26.9	5.6	17.4–39.1	28.0	2.8	22.8–33.8	28.8	2.5	24.1–33.9	33.6	2.0	29.8–37.6
Mental and physical disorder	6.3	0.5	5.4–7.4	6.6	3.1	2.6–15.9	10.0	1.9	6.8–14.4	5.9	1.2	3.9–8.7	7.1	1.1	5.3–9.5

CI: Confidence interval; GAD: Generalised anxiety disorder; MDD: Major depressive disorder; OCD: Obsessive compulsive disorder; SE: Standard Error

*Significant differences at $P < 0.05$.

†Significant differences at $P < 0.001$ between occupational groups, chi-square test.

Table 4. Prevalence of Lifetime Mental and Physical Disorders across Occupational Categories (n = 4361) (Con't)

Lifetime Disorders	Clerical Support Workers			Services and Sales Workers			Craftsmen and Related Trades Workers			Plant and Machine operators and Assemblers			Cleaners, Labourers and Related Workers		
	%	SE	95% CI	%	SE	95% CI	%	SE	95% CI	%	SE	95% CI	%	SE	95% CI
MDD	4.9	1.3	2.9–8.2	7.7	1.4	5.5–10.9	2.2	1.8	0.4–0.4	3.5	1.5	1.5–8.0	2.2	0.9	1.0–4.9
Dysthymia	0.1	0.1	0.0–0.4	0.2	0.1	0.1–0.5	-	-	-	-	-	-	0.8	0.8	0.1–5.7
Bipolar disorder	2.6	1.2	1.1–6.1	1.6	0.6	0.8–3.2	-	-	-	1.2	0.8	0.3–4.4	0.2	0.1	0.0–0.8
GAD	2.1	1.1	0.7–5.8	0.6	0.3	0.2–1.8	-	-	-	0.2	0.1	0.1–0.8	0.1	0.1	0.0–0.8
OCD	3.8	1.4	1.8–7.8	2.7	0.7	1.6–4.4	-	-	-	2.5	1.3	1.0–6.6	1.6	0.9	0.5–4.6
Alcohol abuse†	1.1	0.6	0.4–3.3	1.8	0.5	1.0–3.3	7.3	3.4	2.8–17.5	6.6	2.2	3.4–12.3	1.8	0.8	0.8–4.3
Alcohol dependence†	0.2	0.1	0.0–0.6	1.2	0.5	0.5–2.8	-	-	-	0.3	0.2	0.1–1.0	-	-	-
Alcohol use disorder (abuse/dependence)†	1.3	0.6	0.5–3.3	3.0	0.7	1.8–4.9	7.3	3.4	2.8–17.5	6.9	2.2	3.7–12.5	1.8	0.8	0.8–4.3
Nicotine dependence*	2.6	1.1	1.1–5.7	5.2	1.0	3.5–7.0	24.8	5.8	15.2–37.7	9.3	2.5	5.4–15.6	6.2	1.8	3.5–11.0
Diabetes*	5.9	1.7	3.3–10.4	5.7	1.1	3.9–8.2	14.8	4.8	7.6–26.8	11.0	2.7	6.7–17.4	10.9	2.7	6.6–17.6
Hypertension*	16.4	2.7	11.7–22.6	14.5	1.9	11.3–18.6	26.5	5.8	16.8–39.2	25.7	3.8	18.9–33.9	21.7	3.7	15.3–29.9
Respiratory conditions	9.1	1.9	6.0–13.5	9.0	1.4	6.7–12.0	3.8	2.1	1.3–10.7	6.1	1.9	3.3–11.1	4.2	1.3	2.3–7.6
Chronic pain	12.4	2.3	8.6–17.6	14.9	1.8	11.7–18.9	16.3	4.8	8.8–28.0	11.0	2.6	6.9–17.2	10.1	2.5	6.1–16.2
Cancer	0.1	0.1	0.0–0.6	0.4	0.3	0.1–2.0	-	-	-	0.1	0.1	0.0–0.8	0.1	0.1	0.0–0.5
Neurological conditions*	2.4	1.1	0.9–6.0	3.9	1.1	2.2–6.9	11.9	5.0	5.1–25.4	1.2	0.9	0.3–4.9	2.7	1.4	1.0–7.2
Cardiovascular conditions	0.1	0.1	0.0–0.6	1.8	0.6	0.8–3.6	4.2	2.8	1.1–14.5	4.4	1.7	2.0–9.2	1.7	0.9	0.6–4.5
Ulcers	2.9	1.3	1.2–6.8	1.6	0.6	0.7–3.4	2.5	2.0	0.5–11.7	0.6	0.3	0.2–1.5	0.3	0.2	0.1–0.9
Any mental disorder	12.6	2.3	8.7–17.8	13.0	1.6	10.2–16.6	9.1	3.8	3.9–19.8	10.5	2.5	6.5–16.4	5.5	1.5	3.2–9.3
Any physical disorder	37.0	3.5	30.5–44.1	36.4	2.4	31.8–41.3	53.0	6.7	40.0–65.6	43.5	4.2	35.5–51.9	38.2	4.1	30.4–46.5
No mental or physical disorder	53.1	3.6	46.1–60.0	55.2	2.5	50.2–60.0	44.2	6.7	31.8–57.3	51.3	4.2	43.0–59.6	57.7	4.2	49.4–65.6
Only mental disorder	8.7	2.0	5.4–13.6	7.3	1.2	5.2–10.0	2.3	2.0	0.4–12.1	4.9	1.7	2.5–9.6	3.2	1.2	1.5–6.5
Only physical disorder	34.3	3.4	28.0–41.3	31.8	2.4	27.4–36.6	46.7	6.7	34.1–59.8	38.2	4.1	30.5–46.5	36.8	4.1	29.1–45.2
Mental and physical disorder	3.9	1.2	2.2–6.9	5.8	1.2	3.9–8.5	6.8	3.3	2.5–16.9	5.6	1.9	2.8–10.6	2.3	0.9	1.1–5.0

CI: Confidence interval; GAD: Generalised anxiety disorder; MDD: Major depressive disorder; OCD: Obsessive compulsive disorder; SE: Standard Error

*Significant differences at $P < 0.05$.†Significant differences at $P < 0.001$ between occupational groups, chi-square test.

Impact of Mental and Physical Disorders on Work Productivity

Mean work-loss days (absenteeism) and work-cutback days (presenteeism) due to mental and physical health problems in the month prior to the survey are shown in Table 5. Although differences by occupation in the work-loss days and work-cutback days did not reach statistical significance, wide variations were seen across the 9 groups. ‘Services and sales workers’ reported the highest work-loss (mean 0.74) and work-cutback (mean 0.83) days due to their health.

Correlates of AUD and ND

After adjusting for all sociodemographic variables and occupations in multivariate analyses, younger participants (those aged 18 to 34 years), men, those with secondary education (versus university education), having a physical condition, and ‘Business owners’ and ‘Legislators, senior officials and managers’ (versus ‘Associate professionals and technicians’) were more likely to have lifetime AUD (Table 4). ‘Business owners’ were 4 times more likely (OR 3.99, 95% CI, 1.46 to 10.88) to have AUD when compared to ‘Associate professionals and technicians’. Younger participants (those aged 18 to 34 years), men, Malays (versus Chinese), those with secondary education or below (versus university education) and ‘Craftsmen and related trades workers’ (versus ‘Associate professionals and technicians’) were more likely to have ND (Table 6).

Discussion

This is the first population-based study in Singapore that examined the associations between occupational groups, sociodemographic characteristics, and the prevalence of key chronic mental and physical disorders using a representative sample of the population. The large sample size allowed adequate investigation of all the subgroups and provided generalisable estimates. Differences in age, gender, ethnicity, education, marital status and personal income across occupational groups were observed. This is expected and consistent with reports from studies in other populations.^{34,35}

Among the employed, the overall prevalence of MDD was 5.9%, which is very close to the prevalence in Singapore’s general population (5.8%).³⁶ Contrary to the low prevalence of mental disorders among the skilled and unskilled manual jobs in our population, the highest prevalence of hypertension was found among ‘Craftsmen and related trades workers’ (26.5%), ‘Plant and machine operators and assemblers’ (25.7%) and ‘Cleaners, labourers and related workers’ (21.7%). Prevalence estimates across all occupations ranged between 11.3% (seen in ‘Professionals’)

Table 5. Work Days Lost and Cut Down across Occupations Due to Mental-physical Health Problems

Occupational Category	Work-loss Days (in 1 Month)		Work-cutback Days (in 1 Month)	
	Mean	SE	Mean	SE
Business owners	0.12	0.07	0.38	0.19
Legislators, senior officials and managers	0.19	0.05	0.38	0.15
Professionals	0.20	0.04	0.29	0.06
Associate professionals and technicians	0.54	0.13	0.51	0.08
Clerical support workers	0.36	0.14	0.52	0.21
Services and sales worker	0.74	0.33	0.83	0.33
Craftsmen and related trades workers	0.35	0.21	0.31	0.21
Plant and machine operators and assemblers	0.61	0.24	0.62	0.25
Cleaners, labourers and related workers	0.37	0.15	0.36	0.15

SE: Standard error

to 26.5% which is comparable to an American sample which ranged from 10.5% to 28%.³⁷

Various theories have tried to explain health disparities among different occupations. Based on Karasek and Theorell’s demand-control theory,³⁸ jobs with high strain, low decision latitude (one’s control over the work they do) and high physical and psychological demands are associated with negative health outcomes such as physical illnesses and depression. This has been replicated in studies that have shown high prevalence of depression in jobs with higher strain.^{39,40} Similarly, higher prevalence of cardiovascular diseases,⁴¹ diabetes⁴² and hypertension⁴³ were seen in strenuous occupations or job roles.

The highest effect of mental and physical health problems on work-loss days and work-cutback days was seen for ‘Services and sales workers’ and lowest among ‘Business owners’. It is possible that ‘Business owners’ had employed subordinates to perform their roles in their health-related absence or alternatively, it could be due to the lack of a formal reporting structure or regular work-hours, as for example, in office-bound jobs, there was an underestimation of the productivity-loss.

The strong independent relationship of occupational

Table 6. Correlates of Alcohol Use Disorders and Nicotine Dependence

Parameter	Alcohol Use Disorders (Abuse/Dependence)				Nicotine Dependence			
	OR	95% OR Confidence Limits		P Value	OR	95% OR Confidence Limits		P Value
Age (years)								
18 – 34	Ref.				Ref.			
35 – 49	0.4	0.22	0.72	0.0024	0.59	0.35	0.98	0.0433
50 – 64	0.17	0.07	0.41	<.0001	0.45	0.22	0.91	0.0251
65 and above	0.46	0.10	2.25	0.3395	0.54	0.15	2.03	0.365
Gender								
Men	Ref.				Ref.			
Women	0.30	0.18	0.52	<.0001	0.23	0.14	0.40	<.0001
Ethnicity								
Chinese	Ref.				Ref.			
Malay	0.69	0.44	1.08	0.1069	1.48	1.03	2.13	0.0336
Indian	1.19	0.79	1.79	0.4042	1.15	0.79	1.68	0.4711
Others	9.24	4.70	18.18	<.0001	1.99	0.91	4.38	0.0866
Marital Status								
Single	Ref.				Ref.			
Married	1.07	0.59	1.95	0.8275	0.94	0.56	1.56	0.8007
Separated/divorced	2.28	0.93	5.60	0.0714	1.30	0.54	3.13	0.5634
Widowed	-	-	-	-	3.99	0.90	17.78	0.0693
Education								
Pre-primary	2.20	0.32	15.27	0.4242	4.53	1.14	17.97	0.0316
Primary	2.65	0.79	8.95	0.1158	3.92	1.23	12.46	0.0208
Secondary	3.91	1.57	9.77	0.0035	3.09	1.26	7.60	0.0141
Pre-U/junior college/diploma	2.40	1.17	4.94	0.0175	1.06	0.48	2.35	0.8953
Vocational	3.30	1.27	8.59	0.0144	2.23	0.87	5.76	0.0964
University	Ref.				Ref.			
Occupation								
Business owner	3.99	1.46	10.88	0.0069	0.74	0.21	2.67	0.6451
Legislators, senior officials and managers	2.69	1.19	6.08	0.0179	1.65	0.77	3.54	0.197
Professionals	1.01	0.47	2.17	0.9868	0.55	0.20	1.52	0.247
Associate professionals and technicians	Ref.				Ref.			
Clerical support workers	0.46	0.15	1.41	0.1739	0.69	0.26	1.85	0.4556
Services and sales worker	0.75	0.36	1.54	0.4272	0.92	0.49	1.72	0.7831
Craftsmen and related trades workers	1.89	0.61	5.84	0.2682	4.09	1.89	8.87	0.0004
Plant and machine operators and assemblers	1.52	0.64	3.62	0.348	0.94	0.47	1.91	0.8693
Cleaners, labourers and related workers	0.73	0.25	2.12	0.5631	1.03	0.40	2.67	0.951
Income (SGD)*								
Below 20,000	Ref.				Ref.			
20,000 – 49,999	1.05	0.59	1.87	0.8824	1.47	0.90	2.40	0.1231
50,000 and above	0.71	0.27	1.85	0.4806	0.84	0.35	2.01	0.699
Any physical disorder								
No	Ref.				Ref.			
Yes	2.18	1.41	3.36	0.0004	0.89	0.58	1.36	0.5924

OR: Odds ratio

*Denotes personal income in Singapore dollars in 1 year prior to the interview.

level with AUD and ND after adjusting for the effect of confounders indicates that the findings are of clinical significance, especially in ‘Business owners’ and ‘Craftsmen and related trades workers’. Similar results were found in other studies that identified high alcohol abuse and/or dependence among business owners and increased risk of smoking and cancers among low-skilled occupations.^{44–47} The relationship of AUD and ND with occupation level—as with addictions and education level—is non-linear with higher prevalence observed towards the outward ends of the occupational spectrum.¹⁹ While affluence, nature of social networks and means to access are factors that drive alcohol use and smoking behaviours in the higher occupational categories, work-strain and stress have been linked to these among the low-skill manual occupations. In our sample, 3.2% of the participants were ‘Business owners’ with a mixed representation of all sociodemographic characteristics including education. The higher prevalence of ND among residents in ‘Craftsmen and related trades’ as compared to ‘Associate professionals’ is significant considering that these occupational groups are also more likely to be exposed to other hazardous substances through their work.

A key limitation of the study is the cross-sectional design which did not allow assessment of causality. Difference in the time periods for the assessment of mental and physical health conditions and their effect on work productivity is another limitation of the study. Lifetime prevalence of health conditions was used for the analysis, whereas work productivity was rated during the 30 days prior to assessment and occupation was assessed at study entry, which makes the interpretation of associations challenging. It is also proposed that effect of past and present occupations should be considered while investigating its role in health, with preference given to longitudinal study designs.⁴⁸ The inclusion of industrial classification in addition to occupation level could have further facilitated the specification of groups at risk; however, this information was not available. This limitation can be addressed by collecting additional data on the industry affiliation of the respondents in future studies. Inclusion of the income as a continuous variable can also aid in elucidating the effects of occupational and industrial categories more robustly. Another important limitation was the use of self-report to obtain information on chronic physical disorders. While such data are believed to have moderate to high reliability, some level of under-reporting is possible, and it may differ by occupational groups. Although there were no statistically significant differences among respondents and non-respondents (24%) in terms of age, gender and ethnicity, systematic differences in the proportion of employed residents could not be assessed due to inadequate data for attrition analyses.

Conclusion

This is the first comprehensive description of chronic mental and physical disorders (via self-report) in the multi-ethnic workforce in Singapore and highlights disparities in disease prevalence and risk factors across occupations. Occupational groups vary in their sociodemographic characteristics which in turn have been linked to several disabling mental and physical disorders in Singapore’s population.^{36,49–51} This significant difference in the distribution of sociodemographic characteristics and mental-physical disorders by occupational level underscores the importance of occupation-specific analyses. Given the impetus for sustaining employees in the workforce and the resulting changes in workforce demographics, there will likely be a differential pattern of mental and physical disorders among occupations based on their composition of risk factors, thereby affecting work productivity in these occupations. Therefore, it is important to tailor effective workplace health interventions based on risk profiles by occupational groups. In addition, business owners, craftsmen and related trades’ workers should be made aware of the increased risks associated with AUD and ND. Public health initiatives in these groups should focus on primary and secondary prevention in lifestyle and behaviours. Longitudinal studies would complement the present study to determine causality of the mental and physical disorders in the workforce.

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Dietary Protein Intake in a Multi-ethnic Asian Population of Healthy Participants and Chronic Kidney Disease Patients

Boon Wee Teo, ¹MB, BCh, FASN, Qi Chun Toh, ¹BSc, Hui Xu, ¹MD, PhD, Adonsia YT Yang, ¹BSc, Tingxuan Lin, ¹Dip (Biotech), Jialiang Li, ²PhD, Evan JC Lee, ¹MD

Abstract

Introduction: Clinical practice guidelines recommend different levels of dietary protein intake in predialysis chronic kidney disease (CKD) patients. It is unknown how effectively these recommendations perform in a multi-ethnic Asian population, with varied cultural beliefs and diets. We assess the profile of protein intake in a multi-ethnic Asian population, comparing healthy participants and CKD patients. **Materials and Methods:** We analysed the 24-hour urine collections of the Asian Kidney Disease Study (AKDS) and the Singapore Kidney Function Study (SKFS) to estimate total protein intake (TPI; g/day). We calculated ideal body weight (IDW; kg): $22.99 \times \text{height}^2$ (m). Standard statistical tests were applied where appropriate, and linear regression was used to assess associations of continuous variables with protein intake. **Results:** There were 232 CKD patients and 103 healthy participants with 35.5% diabetics. The mean TPI in healthy participants was 58.89 ± 18.42 and the mean TPI in CKD patients was 53.64 ± 19.39 . By US National Kidney Foundation (NKF) guidelines, 29/232 (12.5%) of CKD patients with measured glomerular filtration rate (GFR) <25 (in mL/min/1.73 m²) had a TPI-IDW of <0.6 g/kg/day. By Caring for Australasians with Renal Impairment (CARI) guidelines, 76.3% (177/232) of CKD patients had TPI-IDW >0.75 g/kg/day. By American Dietetic Association (ADA) guidelines, 34.7% (44/127) of CKD patients with GFR <50 had TPI-IDW between 0.6 to 0.8 g/kg/day. Only 1/6 non-diabetic CKD patients with GFR <20 had a protein intake of between 0.3 to 0.5 g/kg/day. A total of 21.9% (25/114) of diabetic CKD patients had protein intake between 0.8 to 0.9 g/kg/day. **Conclusion:** On average, the protein intake of most CKD patients exceeds the recommendations of guidelines. Diabetic CKD patients should aim to have higher protein intakes.

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Key words: Asian continental ancestry group, Diet, Kidney failure, Malnutrition

¹Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

²Department of Statistics and Applied Probability, Faculty of Science, National University of Singapore, Singapore

Address for Correspondence: A/Prof Boon Wee Teo, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, Level 10 NUHS Tower Block, Singapore 119074.

Email: mdctbw@nus.edu.sg

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Boon Wee Teo, ¹MB, BCh, FASN, Qi Chun Toh, ¹BSc, Hui Xu, ¹MD, PhD, Adonsia YT Yang, ¹BSc, Tingxuan Lin, ¹Dip (Biotech), Jialiang Li, ²PhD, Evan JC Lee, ¹MD

Abstract

Introduction: Clinical practice guidelines recommend different levels of dietary protein intake in predialysis chronic kidney disease (CKD) patients. It is unknown how effectively these recommendations perform in a multi-ethnic Asian population, with varied cultural beliefs and diets. We assess the profile of protein intake in a multi-ethnic Asian population, comparing healthy participants and CKD patients. **Materials and Methods:** We analysed the 24-hour urine collections of the Asian Kidney Disease Study (AKDS) and the Singapore Kidney Function Study (SKFS) to estimate total protein intake (TPI; g/day). We calculated ideal body weight (IDW; kg): $22.99 \times \text{height}^2$ (m). Standard statistical tests were applied where appropriate, and linear regression was used to assess associations of continuous variables with protein intake. **Results:** There were 232 CKD patients and 103 healthy participants with 35.5% diabetics. The mean TPI in healthy participants was 58.89 ± 18.42 and the mean TPI in CKD patients was 53.64 ± 19.39 . By US National Kidney Foundation (NKF) guidelines, 29/232 (12.5%) of CKD patients with measured glomerular filtration rate (GFR) <25 (in mL/min/1.73 m²) had a TPI-IDW of <0.6 g/kg/day. By Caring for Australasians with Renal Impairment (CARI) guidelines, 76.3% (177/232) of CKD patients had TPI-IDW >0.75 g/kg/day. By American Dietetic Association (ADA) guidelines, 34.7% (44/127) of CKD patients with GFR <50 had TPI-IDW between 0.6 to 0.8 g/kg/day. Only 1/6 non-diabetic CKD patients with GFR <20 had a protein intake of between 0.3 to 0.5 g/kg/day. A total of 21.9% (25/114) of diabetic CKD patients had protein intake between 0.8 to 0.9 g/kg/day. **Conclusion:** On average, the protein intake of most CKD patients exceeds the recommendations of guidelines. Diabetic CKD patients should aim to have higher protein intakes.

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Key words: Asian continental ancestry group, Diet, Kidney failure, Malnutrition

Introduction

Clinical practice guidelines recommend different amounts of dietary protein intake for chronic kidney disease (CKD) patients.¹⁻³ The recommended daily protein intake varies according to the level of kidney function (glomerular filtration rate (GFR) in mL/min per 1.73 m² body surface area). It is unknown how effectively these recommendations perform in a multi-ethnic Asian population, with its cultural beliefs and different diets.^{4,5} In this cross-sectional study, we compare dietary protein intake in a multi-ethnic Asian population of CKD patients versus a cohort of healthy participants.

Materials and Methods

This is a sub-study of data from the Singapore Kidney Function Study Phase 1 (SKFS1) and the Asian Kidney Disease Study (AKDS), approved by the institution review board.⁶

Participants

In SKFS1, we recruited 103 healthy volunteers presenting to the National University Hospital Singapore (NUHS). The inclusion criterion was non-pregnant adults (>21 years). Volunteers were excluded if they had any of the

¹Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

²Department of Statistics and Applied Probability, Faculty of Science, National University of Singapore, Singapore

Address for Correspondence: A/Prof Boon Wee Teo, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, Level 10 NUHS Tower Block, Singapore 119074.

Email: mdctbw@nus.edu.sg

following: inability to consent, physical conditions that render phlebotomy for blood samples difficult, inability to collect urine samples successfully, use of regular medications, hypertension, diabetes, possible kidney dysfunction (by urinalysis, or on renal imaging), and any condition that potentially interferes with the accuracy of the measurement of GFR. Volunteers were screened with urine dipsticks for haematuria, leukocyturia, proteinuria and microalbuminuria.

In AKDS, we recruited 232 patients with CKD presenting to the outpatient nephrology clinics in NUHS. The inclusion criteria were non-pregnant adult (>21 years), serum creatinine with an estimated or measured GFR (MDRD, Cockcroft-Gault⁷ or creatinine clearance) of 10 mL/min to 90 mL/min, “stable CKD” defined as 2 serum creatinines measured >60 days apart of less than 20% difference, and the definition of CKD that followed the clinical practice guidelines.⁸ Patients were excluded if they had any of the following: inability to consent, physical conditions that render phlebotomy for blood samples difficult, inability to collect urine samples successfully, acute kidney function deterioration, or any condition that potentially interferes with the accuracy of the measurement of GFR.

Laboratory Tests

All participants performed a 24-hour urine collection and presented the following day for GFR measurement, and provided blood and urine samples. GFR was determined by 3-sample plasma clearance of an intravenous bolus of 99mTc-DTPA.⁹ Body surface area is calculated using the du Bois equation.¹⁰ Urine urea nitrogen (g/day) was measured in the 24-hour urine collections to estimate dietary protein intake using the following formulae: total protein intake (g/day) = 6.25 × urine urea nitrogen + 30 × weight (kg).

Statistics

Ideal body weight (IDW) for Asians was calculated as: weight (kg) = 22.99 × height² (m).¹¹ We expressed total protein intake per actual body weight and per IDW for comparisons. Data is presented as mean ± 1 SD, or median and interquartile range depending on distribution. We used standard statistical tests including t-test, analysis of variance (ANOVA), chi-square test, and linear regression where appropriate. Significance was taken at the 5% level. Analyses were performed on JMP (Cary, NC, USA).

Results

There were 335 participants (Table 1). Using a body mass index (BMI) of 22.99 as the normal upper limit in Asians, normal participants were on average 5.0 ± 10.4 kg overweight, and CKD patients were 11.8 ± 13.6 kg

Table 1. Characteristics of Participants

	SKFS1 (n = 103)	AKDS (n = 232)	P Value
Age (years)	42.5 ± 14.3	58.4 ± 12.8	<0.001
Male (n, %)	51 (49.5)	120 (51.0)	0.72
Ethnicity (n, %)			<0.001
Chinese	35 (34.0)	94 (40.5)	
Malay	25 (24.3)	74 (31.9)	
Indian	23 (22.3)	56 (24.1)	
Others	20 (19.4)	8 (3.5)	
Smokers (n, %)	22 (21.4)	46 (20.0)	0.77
Diabetes (n, %)	0	119 (51.3)	<0.001
Hypertension (n, %)	0	192 (82.8)	<0.001
Height (m)	1.62 ± 0.10	1.59 ± 0.09	0.008
Weight (kg)	65.7 ± 12.8	70.3 ± 15.9	0.010
Body mass index (kg/m ²)	24.9 ± 4.03	27.6 ± 5.45	<0.001
Body surface area (m ²)	1.70 ± 0.20	1.73 ± 0.01	0.35
Ideal body weight (kg)	60.7 ± 7.2	58.5 ± 6.7	0.008
Measured glomerular filtration rate (mL/min/m ²)	101 ± 16	52 ± 27	<0.001
Serum creatinine (μmol/L)	70 ± 16	153 ± 92	<0.001
Serum carbon dioxide (mmol/L)	28.2 ± 2.7	25.8 ± 3.4	<0.001
Serum total protein (g/L)	72.7 ± 4.1	72.2 ± 5.7	0.36
Serum albumin (g/L)	43.5 ± 2.6	41.8 ± 3.2	<0.001
24-hr urine volume (L)	1.58 ± 0.70	1.76 ± 0.78	0.042
24-hr urine total protein (g)	0.07 (0 – 0.11)	0.6 (0.12 – 0.67)	<0.001
24-hr urine urea nitrogen (g/day)	7.45 ± 2.80	6.47 ± 2.92	0.004
Total protein intake (g/day)	58.9 ± 18.42	53.6 ± 19.39	0.021
Protein intake/actual body weight (g/kg/day)	0.91 ± 0.27	0.77 ± 0.26	<0.001
Protein intake/ideal body weight (g/kg/day)	0.97 ± 0.28	0.91 ± 0.30	0.102

AKDS: Asian Kidney Disease Study; SKFS1: Singapore Kidney Function Study Phase 1

overweight. The average serum total protein was similar between normal and CKD participants but serum albumin was lower in CKD patients (-1.76 g/L, 95% CI, -2.46 to -1.06).

Protein Intake and Metabolic Acidosis

Overall (n = 335), the total protein intake (TPI, g/day) is

lower in CKD patients ($P = 0.021$), women ($P < 0.001$), and diabetic patients ($P = 0.0038$) (Table 2). “Others” had the highest intake (65.9 ± 19.7 g/day), which is significantly more than in Malays (50.9 ± 17.7 g/day, $P < 0.001$), Indians (55.1 ± 18.9 g/day, $P = 0.00102$), and Chinese (56.3 ± 19.6 g/day, $P = 0.034$). TPI is positively correlated with height ($P < 0.001$), weight ($P < 0.001$), BMI ($P < 0.001$), serum albumin ($P = 0.0032$), and GFR ($45.965 + 0.139 \times \text{GFR}$, $P < 0.001$).

When normalised to IDW, protein intake (TPI-IDW, g/kg/day) is similar in both normal kidney function and CKD patients. Distribution of TPI-IDW is shown in Figures 1a to 1d. Overall TPI-IDW was lower in women ($P = 0.019$), Indians (vs “Others”, $P < 0.001$), and diabetics ($P = 0.015$). It is positively correlated with weight ($P < 0.001$), BMI ($P < 0.001$), serum albumin ($P = 0.0044$), and GFR ($0.809 + 0.00181 \times \text{GFR}$, $P < 0.001$).

TPI-IDW in healthy participants was highest in the “Others” group ($P = 0.0262$) but did not vary with age or gender. It increases with weight ($P = 0.024$) and BMI ($P = 0.0076$) only. In CKD patients however, it was lower in women ($P = 0.0110$) and decreased with age ($P = 0.041$), but increased with weight ($P < 0.001$), BMI ($P < 0.001$), serum albumin ($P = 0.014$), and GFR ($0.785 + 0.00248 \times \text{GFR}$, $P < 0.001$).

According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiatives (NKF KDOQI) guidelines, amongst CKD patients with GFR < 25 mL/min/1.73 m², only 2.2% (5/232) patients had a protein intake of about 0.6 g/kg/day (using the range of 0.55 to 0.65 for this analysis).¹ By the Caring for Australasians with Renal Impairment (CARI: <http://www.cari.org.au/guidelines.php>) guidelines, 76.3% (177/232) of CKD patients had protein intake > 0.75 g/kg/day.² Using American Dietetic Association guidelines (now renamed Academy of Nutrition and Dietetics: www.eatright.org), 34.7% (44/127) of CKD

patients with GFR < 50 mL/min/1.73 m² had protein intake between 0.6 to 0.8 g/kg/day.³ Only 1/6 non-diabetic CKD patients with GFR < 20 mL/min/1.73 m² had a protein intake between 0.3 to 0.5 g/kg/day. For diabetic CKD patients, 21.9% (25/114) had protein intake between 0.8 to 0.9 g/kg/day. The distribution of protein intake (TPI-IDW) is shown in Figures 1a to 1d, showing lower protein intake in diabetic CKD patients.

Serum carbon dioxide decreased with declining GFR ($\text{CO}_2 = 23.418 + 0.0467 \times \text{GFR}$, $P < 0.001$), and 16.4% (38/232) of CKD patients had levels < 22 mmol/L. These patients had lower dietary protein intake (0.79 ± 0.26 vs 0.94 ± 0.30 g/kg/day, $P = 0.0074$).

Discussion

Existing literature suggests that a planned very low protein diet with adequate caloric intake can retard the progression of CKD and delay the need for renal replacement therapy.^{1,12} But this has to be balanced against the risk of protein-energy malnutrition at the initiation of renal replacement therapy, which may be a risk for adverse outcomes.^{1,2} Therefore, most guidelines recommend protein restriction to about 15% to 20% of daily energy intake.^{1,2}

The NKF KDOQI guideline recommends protein restriction from 0.6 g/kg per day (preferred) to at least 0.75 g/kg per day in patients with GFR < 25 mL/min.¹ The CARI guidelines also support restriction of dietary protein in predialysis CKD patients, but recommend a minimum daily protein intake (DPI) of 0.75g per kg of IDW per day to avoid protein malnutrition and a negative nitrogen balance.² It is notable that protein intake of our CKD patients is well in excess of guidelines, and the majority of patients did not achieve target ranges. Protein intake is however lower in diabetic CKD patients and in Indians. Therefore, in future studies, we need to explore the impact of cultural differences in dietary practices in a multi-ethnic population.

Table 2. Distribution of Daily Total Protein Intake by Ethnicity

		Chinese	Malay	Indian	Others
Total protein intake* (g/day)	Normal	55.7 $\pm$ 15.0	55.8 $\pm$ 20.1	57.7 $\pm$ 17.1	69.7 $\pm$ 20.4
	CKD	56.6 $\pm$ 21.1	49.3 $\pm$ 16.6	54.1 $\pm$ 19.6	56.3 $\pm$ 15.1
Total protein intake per actual body weight† (g/kg/day)	Normal	0.90 $\pm$ 0.26	0.84 $\pm$ 0.27	0.89 $\pm$ 0.24	1.03 $\pm$ 0.28
	CKD	0.86 $\pm$ 0.29	0.66 $\pm$ 0.20	0.77 $\pm$ 0.24	0.83 $\pm$ 0.31
Protein intake per ideal body weight‡ (TPI-IDW, g/kg/day)	Normal	0.93 $\pm$ 0.24	0.92 $\pm$ 0.29	0.94 $\pm$ 0.24	1.14 $\pm$ 0.34
	CKD	0.95 $\pm$ 0.33	0.85 $\pm$ 0.26	0.92 $\pm$ 0.30	0.94 $\pm$ 0.25

CKD: Chronic kidney disease; TPI-IDW: Total protein intake-ideal body weight

*Normal participants: Others $>$ Chinese ($P = 0.0064$), Others $>$ Malay ($P = 0.011$), Others $>$ Indian ($P = 0.031$); CKD patients: Others $>$ Malay ($P = 0.16$).

†Normal participants: Others $>$ Malay ($P = 0.014$); CKD patients: Chinese $>$ Malay ($P < 0.001$), Chinese $>$ Indian ($P = 0.032$), Indian $>$ Malay ($P = 0.019$).

‡Normal participants: Others $>$ Chinese ($P = 0.0065$), Others $>$ Malay ($P = 0.0091$), Others $>$ Indian ($P = 0.19$); CKD patients: Chinese $>$ Malay ($P = 0.029$).

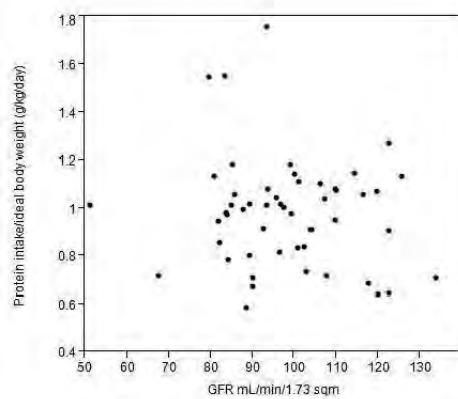


Fig. 1a. Protein intake per ideal body weight against measured GFR for healthy men.

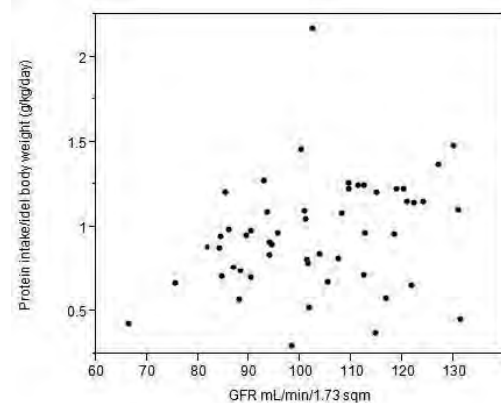


Fig. 1b. Protein intake per ideal body weight against measured GFR for healthy women.

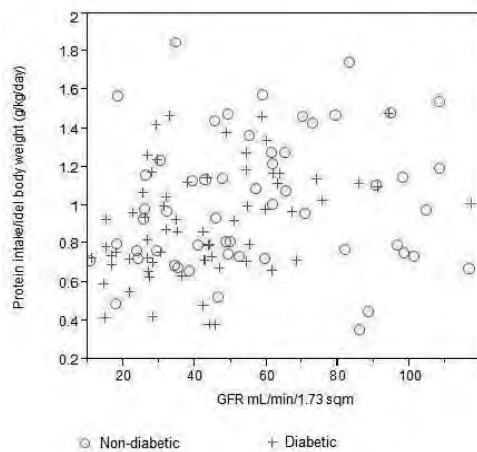


Fig. 1c. Protein intake per ideal body weight against measured GFR for men with chronic kidney disease.

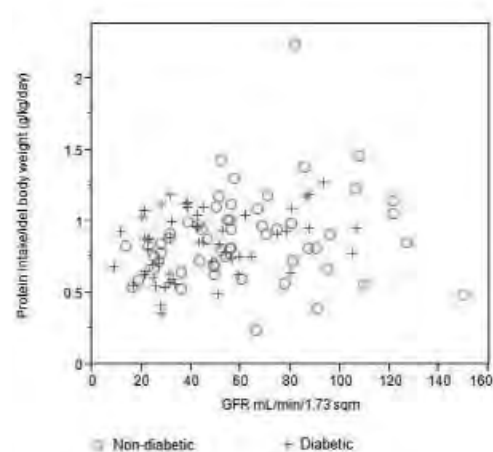


Fig. 1d. Protein intake per ideal body weight against measured GFR for women with chronic kidney disease.

One of the difficult and potentially contentious issues of protein assessment is the method of normalising (or standardising) intake values in predialysis Asian CKD patients. US NKF KDOQI guideline recommends referencing to standard body weight from second US Health and Nutrition Examination Survey (NHANES II) data.¹ The CARI guidelines recommend normalising to ideal body weight.² Therefore, what should be the “ideal” body weight for referencing Asians? Do separate standards apply for Chinese, Indian, and Malay ethnicities? The goal of adequate protein intake is to ensure protein balance and prevent skeletal muscle atrophy. In Asian CKD patients, the assessment may be confounded by 1) CKD-associated edema, and 2) higher body fat composition per body weight.¹³ Therefore, we believe that a better indicator is derived when protein intake is normalised to IDW obtained from healthy BMI for Asians.¹¹ Protein intake has to be at

least that needed to sustain lean body mass balance for an Asian at the upper limit of ideal BMI. Nonetheless, this attracts the problem of inadequate clinical outcomes data supporting such an evaluation method. There is currently no clear scientific base to support a consensus guideline on the most appropriate method of standardising protein intake in predialysis CKD patients.

Some of our CKD patients did not have adequate correction of metabolic acidosis, which may have a negative impact on protein intake and utilisation. The CARI guidelines recommend correction of metabolic acidosis in CKD patients, to avoid skeletal muscle breakdown and urinary nitrogen loss, before enforcing a protein-restricted diet.² Therefore, metabolic acidosis needs to be corrected before recommending increased protein intake, especially in CKD patients with diabetes.

Our normal participants appear to have slightly higher daily protein intake than the 10th percentile of the general population in the Report of the National Nutrition Survey 2010 published by the Health Promotion Board, Singapore.¹⁴ It should be noted that the survey estimated protein intake through the use of dietary practices and food frequency questionnaires. Our healthy subjects may have been healthier than the general population because we excluded participants with diabetes and hypertension. The CKD patients in our study however, have a daily protein intake that is slightly lower than the 10th percentile of the general population. It is unclear how much of this is due to the effect of dietary interventions, and a future study should quantify their effect size.

The strengths of our prospective study include the fairly large study size for patients with reference GFR measurements and systematic urine collections for objective urea nitrogen assay, which were consistently performed by the same research personnel. Recruitment was strategised to ensure a spread of healthy and CKD patients over the GFR range with adequate numbers of participants' representative of ethnicity and gender. We are limited by the lack of information on previous formal dietetic assessment and intervention by a dietitian, although most patients would have received dietary advice during follow-up.

Conclusion

Protein intake of most CKD patients exceeds recommendations of guidelines. Diabetic CKD patients should aim to have higher protein intakes.

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Pyoderma Gangrenosum Mimicking Early Acute Infection Following Total Knee Arthroplasty

Dear Editor,

Pyoderma gangrenosum (PG) is an ulcerative neutrophilic dermatosis of uncertain aetiology. Known associations include inflammatory bowel disease, myeloproliferative disease and various arthritides.¹ There have been 4 published cases of PG following total knee arthroplasty (TKA).³⁻⁶

Case Report

A 56-year-old male presented 6 days post-TKA with findings mimicking wound infection. He underwent wound debridement limited to the cutaneous and subcutaneous layers, followed by a Vacuum Assisted Closure® (VAC) dressing (KCI, Texas, USA), as there was no apparent involvement of the knee joint. He was started on intravenous amoxicillin and clavulanate once intraoperative cultures were taken.

Debridement was performed again 9 days post-TKA. Extensive subcutaneous necrosis and skin pustules were noted. Debridement, arthrotomy, exchange of the polyethylene insert and VAC dressing were done.

He underwent further debridements at 11 and 14 days post-TKA. There was never any pus or slough within the joint cavity and debridements were performed to healthy margins. All 8 tissue samples sent were negative for microbial growth. Histological studies revealed non-specific acute inflammatory and reactive changes. Notably, surgery seemed to aggravate the cutaneous and subcutaneous involvement. Figure 1A shows an intraoperative photo at the third round of debridement.

Fifteen days post-TKA, a dermatologist was consulted and a diagnosis of PG was made. Atypical features of this case include the lack of associated conditions, seronegativity for rheumatoid factor and an absence of satellite lesions. Oral prednisone (at 0.5 mg/kg) was started. Repeat debridement 2 days later showed improvement at the cutaneous and subcutaneous layers (Fig. 1B). C-reactive protein (CRP) and white blood cell (WBC) counts trended lower. The insert was changed, intra-articular washout performed and wound coverage achieved with a medial gastrocnemius flap and split skin grafting (Fig. 1C). Oral prednisone was tailed off over a period of 30 days. The flap and skin graft healed well, without any recurrence of PG.

Discussion

PG can mimic an acute infection after TKA, often resulting in debridement, arthrotomy and washout of the joint. This leads to a vicious cycle as surgery aggravates the condition via the pathergic response. It remains a clinical diagnosis without specific serological or histological markers. Treatment of PG usually requires systemic immunosuppressants. First-line therapy includes corticosteroids and cyclosporine.¹ Other options include anti-TNF α agents, colchicine, minocycline, and even topical treatments. Prolonged immunosuppression may be required. In a post-TKA setting, broad-spectrum prophylactic antibiotic coverage and meticulous wound care are vital to prevent secondary infection.



Fig. 1. Series of images showing intraoperative findings before prednisolone (Fig. 1A), after prednisolone (Fig. 1B), and after medial gastrocnemius flap with split skin grafting (Fig. 1C).

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Jing Hui Yik, ¹*MBBS, MRCS*, Paul Lorenz Bigliardi, ²*MBBS, MD*, Sandeep Jacob Sebastin, ³*MBBS, MMED (Surg), FAMS*, Nixon J Cabucana, ¹*MD, FPOA, FPCS*, Indumathi Venkatachalam,⁴*MBBS, FRACP*, Lingaraj Krishna, ¹*MBBS, FRCS (Orth)*

¹Department of Orthopaedic Surgery, National University Health System, Singapore

²Department of General Medicine (Dermatology), National University Health System, Singapore

³Department of Hand and Reconstructive Microsurgery, National University Health System, Singapore

⁴Department of Infectious Diseases, National University Health System, Singapore

Address for Correspondence: Dr Yik Jing Hui, Department of Orthopaedic Surgery, University Orthopaedic, Hand and Reconstructive Microsurgery Cluster, National University Health System, 5 Lower Kent Ridge Road, Singapore 119074.

Email: jing_hui_yik@nuhs.edu.sg

Diagnosing Bacteraemia Early in Older Adults

Dear Editor,

Sepsis is a prevalent and important cause of morbidity and mortality in the general population. Approximately 750,000 patients in the United States alone develop severe sepsis each year. Of this, more than 60% are patients older than 65 years.¹ Morbidity and mortality remain high in spite of advances in the management of patients with sepsis,² and are increased in older adult patients.³ However, early identification and institution of appropriate management in older adult patients with septic shock has been shown to improve outcome.⁴

Few studies have been done to analyse the difference in response to sepsis between older adults and younger patients. We performed a study comparing the clinical parameters and biochemical markers of patients with *Klebsiella Pneumoniae* bacteraemia, and assessed the differences between the older adults and younger population. We also hoped that the results would shed light on important factors that help identify sepsis in the elderly.

Materials and Methods

A total of 100 patients with *Klebsiella Pneumoniae* bacteraemia from September 2007 to December 2008 were retrospectively analysed in our study. Demographics, comorbidities, clinical parameters at the time of blood taking, biochemical markers, maximum body temperature and clinical outcomes were reviewed.

Results

Fifty patients were less than 65 years old and 50 were 65 and older. The mean age of patients was 62.7. There were 58 males and 42 females. Patients with known malignancy, end-stage renal failure, and those on immunosuppressant were excluded from the study.

Older adults patients had statistically significant higher incidences of diabetes mellitus ($P = 0.009$), hypertension ($P < 0.001$), hyperlipidaemia ($P = 0.002$), ischaemic heart disease ($P = 0.001$), cerebrovascular accidents ($P = 0.009$) and dementia ($P = 0.0032$) than younger patients. From reviewing the discharge summaries, 39 of the patients were diagnosed by the attending team to have a gastrointestinal source, 34 were genitourinary, 22 respiratory, and 5 from

other or unknown sources.

There were 24 mortalities; 16 of them were in the older adults age group and 8 were in the younger age group. Older adult patients with *Klebsiella Pneumoniae* bacteraemia were 2 times more likely to die than younger patients. All of the 8 younger patients were admitted to intensive care unit (ICU) versus 5 in the older group.

Of all the variables analysed (Table 1), the temperature when blood culture was taken, maximum temperatures during hospital stay, and serum urea levels showed significant association with age. The mean temperature during bacteraemia in older adult patients was 37.13°C (95% CI, 36.82 to 37.45), whereas mean temperature in younger patients was 38°C (95% CI, 37.61 to 38.39). The mean maximum temperature during hospital stay in older adult patients was 38.15°C (95% CI, 37.84 to 38.46) and that in younger patients was 38.91°C (95% CI, 38.64 to 39.18).

We further analysed our results based on temperatures $\geq 37^\circ\text{C}$, $\geq 37.2^\circ\text{C}$ and $\geq 37.5^\circ\text{C}$. Eighty percent of younger patients with bacteraemia had a temperature of $\geq 37^\circ\text{C}$ at blood culture taking whereas only 46% of older adults had temperatures $\geq 37^\circ\text{C}$. Only one-third of older adult patients had a “significant febrile response” if a higher temperature of 37.5°C was used.

Mean serum urea level in older adult patients during bacteraemia was 12.49 mmol/L (95% CI, 10.09 to 14.49) compared to 9.55 mmol/L (95% CI, 7.33 to 11.78) in younger patients. Older adult patients were 1.6 times more likely to have a raised urea defined as >7 mmol/L than younger patients.

There was no statistical significance of the heart rate, respiratory rate, alteration in mental status, total white cell count, platelet count, coagulation profile, lactate, albumin, glucose, creatinine, C-reactive protein or procalcitonin between older and younger patients.

Discussion

The mean temperature when blood cultures were taken in the elderly was 37.13°C, whereas mean temperature when blood cultures were taken in younger patients was 38°C. Eighty percent of younger patients with bacteraemia had a temperature of $\geq 37^\circ\text{C}$ within 24 hours of blood culture taking

Table 1. Comparison of Outcomes between Older Adults and Younger Patients

Variable	Age <65 (n = 50)	Age ≥65 (n = 50)	P Value
Outcome			
Death	8 (16%)	16 (32%)	0.061
Discharge to own home	38 (76%)	29 (58%)	0.056
Nursing home	0 (0%)	4 (8%)	0.041
Step-down care	3 (6%)	1 (2%)	0.307
Discharge against advice	1 (2%)	0 (0%)	0.315
ICU admission	15 (30%)	17 (34%)	0.668
No. of days in ICU	2.4	1.52	0.940
Duration of hospital stay (days)	14.94 ± 11.238	12.38 ± 9.678	0.252
Clinical markers			
Confused mental state	12 (24%)	16 (32%)	0.050
Sedation	5 (10%)	3 (6%)	0.050
Dementia	0 (0%)	3 (6%)	0.050
Functional decline	0 (0%)	4 (8%)	0.050
Mean (± 2 SD)			
Mean temperature at time of culture	38 ± 2.71	37.132 ± 2.20	<0.001
Mean of max. temperature during stay	38.908 ± 1.90	38.146 ± 2.19	<0.001
Heart rate	104.82 ± 50.21	96.4 ± 43.51	0.101
Respiratory rate	23.4 ± 11.10	21.94 ± 15.46	0.090
Total white blood cell count (×10 ⁶)	15.858 ± 16.00	14.1378 ± 15.34	0.188
Absolute neutrophil count	14.132 ± 14.99	14.098 ± 24.10	0.318
Platelet	220.92 ± 296.27	230.16 ± 244.38	0.450
Prothombin time	17.29 ± 8.91	17.052 ± 5.62	0.755
INR	10.833 ± 103.57	1.3407 ± 0.55	0.913
Partial thromboplastin time	40.967 ± 21.98	40.352 ± 17.79	0.867
Lactate	4.2 ± 7.14	2.895 ± 3.70	0.450
Albumin	31.21 ± 18.68	31.28 ± 14.67	0.750
Glucose	12.091 ± 15.42	12.598 ± 19.43	0.759
Urea	9.554 ± 15.31	12.494 ± 16.95	0.005
Creatinine	138.42 ± 227.02	138.74 ± 157.12	0.167
C-reactive protein	207.97 ± 212.74	168.07 ± 220.98	0.386
Procalcitonin	133.29 ± 333.33	56.7186 ± 112.06	0.813

ICU: Intensive care unit; INR: International normalised ratio

whereas only 46% of older adults had temperatures $\geq 37^{\circ}\text{C}$. Only one-third of older adult patients had a “significant febrile response” if a cut-off of 37.5°C was used. Also, the mean maximum temperature during hospital stay in older adult patients was 38.15°C , and that in younger patients was 38.91°C .

Currently, many hospitals and doctors use the cut-off of 38°C for taking blood cultures. We would like to use this study to stress how older people are unable to mount a similar response to sepsis. We also wish to recommend a review of the traditional cut-off to pick up bacteraemia.

Our study showed a higher mortality in the older group with bacteraemia, similar to other studies. Early recognition and treatment of sepsis could improve mortality and morbidity drastically.

Blood urea nitrogen appears to be a significant marker of bacteraemia in the older adults. This could be due to several factors. Older adults are known to have impaired thirst sensation, which could be aggravated in the setting of bacteraemia due to debilitation and altered mental status. Impaired renal function is more likely to occur in the older adults and could result in decreased clearance of

urea in the setting of an acute catabolic stress. The CURB-65 score and pneumonia severity index (PSI) incorporate raised blood urea nitrogen into their models of predicting mortality in the setting of infection. Studies done to validate the CURB-65 score found that age >65 years and blood urea nitrogen >7mmol/L were associated with significantly higher mortality regardless of the overall CURB-65 score.⁵ A raised urea could therefore lead the clinician to a higher index of suspicion of the presence of underlying bacteraemia in an older adult.

Conclusion

In summary, our results show that older adult patients respond differently to sepsis compared to younger patients. Clinicians need to have higher indexes of suspicion in older adults so as not to miss the underlying diagnosis. In particular, fever is a poor guide to bacteraemia in the older adults, and they warrant blood cultures at a lower threshold of temperature than younger patients. The role of urea as a marker of sepsis in the older adults has not been well studied. Its role as a prognostic factor and guide in the management of sepsis in the older adults should also be reviewed.

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Li Fang Tan, ¹MBBS, Kamun Tong, ²MBBS, MRCP, FAMS,
Joshua TM Hoe, ³MBBS, Shen Liang, ⁴PhD,
Reshma A Merchant, ⁵MBBS, MRCP, FRCP

¹Department of Medicine, National University Health System, Singapore

²Department of Medicine, St Luke's Hospital, Singapore

³Department of Medicine, Singapore General Hospital, Singapore

⁴Centre for Health Services Research, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁵Department of Geriatric Medicine, National University Health System, Singapore

Address for Correspondence: Dr Tong Kamun, 2 Bukit Batok Street 11, Singapore 659674.

Email: kamuntong1@gmail.com