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EDITORIAL

What can be learnt from the 1980s Australian and New Zealand work-related musculoskeletal pain epidemics?

Many Australians and New Zealanders were involved in an epidemic of work-related musculoskeletal pain that lasted for about a decade; the Australian epidemic peaked about 30 years ago and was out of phase with that in New Zealand.\(^1,2\) That is, as the Australian epidemic was waning, the New Zealand epidemic was reaching its peak. In both countries, the incidence and prevalence of work-related musculoskeletal pain have now returned to usual endemic levels.

Although it was both convenient and plausible to attribute the epidemics to automation of the workplace, the introduction of keyboards and call centres, and consequently to mechanical factors, and to respond accordingly, the way in which affected people were managed, showed that little or nothing had been learnt from an almost 300-year history of recurrent and recorded epidemics of work-related musculoskeletal pain. It is also clear to the author, given recent discussions at occupational medicine conferences, that when the next epidemic does occur, that what might have been learnt from the most recent epidemics has already been forgotten.

Consequently, it is my opinion that unless the experiences of the last epidemic are clearly identified, the ‘inadequate’ response to the last epidemic will be repeated.

There is no excuse for naiveté in this context. The physician widely regarded as the ‘father’ of occupational medicine, Bernardino Ramazzini, described an epidemic of work-related musculoskeletal pain in Padua almost 300 years ago in 20 different occupational groups that were as diverse as musicians and clerical workers.\(^3\) It is noteworthy that his descriptions did not show any clear dose–response relationship in terms of mechanical workload and severity of the work-related musculoskeletal pain, but did emphasise the importance of the ‘work environment’. The latter includes the level of motivation of the worker, the degree of autonomy and so on. It is clear that epidemics have been occurring ever since, although during the 19th century, there was a fixation on describing a series of focal work-related musculoskeletal conditions, such as carpal tunnel syndrome and de Quervain’s tenosynovitis.\(^4,5,6\)

As cited above, the most recent epidemics occurred in the context of computerisation and workplace automation, and the advent of new workplaces such as call centres. It also coincided with an increased understanding of the biology of pain. For example, the clinical expression of some forms of pain disorder is now thought to have a high degree of heritability.\(^7\) It is also clear that the collective terms for the epidemic masked an extraordinary heterogeneity of pain disorder. These varied from very localised tendon injuries and inflammation, to widespread and diffuse pain in association with extrapyramidal motor disorders, disturbances of spinal cord dorsal column function and sympathetic nervous system dysfunction.

Health providers in Australia and New Zealand did not respond to the epidemic either uniformly or consistently. Although it is simplistic, the health provider community can be described as having disaggregated into three ‘ideological’ camps.

The first grouping regarded the conditions as essentially compensation-orientated and argued that there was a high degree of factitious disorders and malingering.\(^8\) The second grouping attempted to describe the epidemic in essentially biomechanical terms. This was inherent in some of the aetiological-diagnostic terminology applied to patients, such as occupational overuse syndrome, repetitive strain injury and work-related cumulative trauma disorders. Unfortunately, and as was clear from the reports of Ramazzini sometime beforehand,\(^3\) the absence of a dose–response relationship made any simple biomechanical explanation implausible.\(^2\) It is also noteworthy, as sufferers become increasingly pejoratively viewed, that the terminology changed as extant descriptors also assumed negative and critical connotations. Some sufferers were lampooned, such as the term ‘kangaroo paw’ in Australia.\(^9\)

The biomechanical grouping had significant support from workers’ advocacy groups and unions, at least in part because such an explanation enabled easier access for sufferers to workers’ compensation in Australia and to Accident Compensation and Rehabilitation Corporation (ACC) entitlement in New Zealand. Unfortunately, the same aetiological hypothesis led to both catastrophic views of the likely crippling nature of the condition,\(^2\) and to cycles of physiotherapy and orthopaedic surgery, which seldom served to reduce the overall level of pain experience. An unpublished review of a group of women
who worked at a call centre and were experiencing chronic musculoskeletal pain showed that although only a few of them had a history even suggestive of some musculoskeletal injury, each woman had received on average more than 100 physiotherapy treatments and four orthopaedic procedures. In addition, companies made considerable investments in ergonomic furniture and apparatus. Although this was presumably associated with an increase in comfort and hopefully productivity, major ergonomic reforms did not result in a significant change in the number of affected and or to the severity of the work-related pain experience for most people.

The final grouping of the health provider community adopted a biopsychosocial approach to the epidemic. Although such an approach was comprehensive and certainly to be recommended from a medical viewpoint, it was not necessarily well received, was somewhat in ‘conflict’ with workers’ compensation schema and the ACC regulations in New Zealand, did not always identify a treatment and management response beyond remaining active and staying at work, and was confused by many people who had work-related musculoskeletal pain as essentially implying that sufferers were ‘making it up’ or that it was ‘in their head’. Although a significant degree of many pain experiences is undoubtedly some form of somatoform expression, this was and remains poorly understood by the general community – and by members of the judiciary and many health providers as well. This confusion is sufficient to have warranted major changes to the diagnostic criteria and even to the nomenclature – to somatic symptom disorder – in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, Fifth edition.8

The controversy was exaggerated by a series of medical sociological reports of the time, and since, that claimed a significant negative effect on someone’s health of unemployment,10 a similarly significant negative effect on health and recovery if some form of compensation is awarded for the health problem or injury in question,11 health and recovery if some form of compensation is awarded for the health problem or injury in question,11 sickness absence rates and staff turnover.

A good diagnosis is essential. Whereas rest is an appropriate response to many specific musculoskeletal injuries, for people with more widespread pain disorders this is contrary to their best interests. Indeed, some form of activity, and preferably at work, is associated with significantly better outcomes. Most people with work-related pain, providing they do not have a simple and discrete musculoskeletal injury, require holistic and coordinated management that should include maintenance of activity and preferably at work, attention to aerobic fitness, pain-orientated cognitive behaviour therapy, and access to medication that is directed at chronic pain management.11 Physicians need to provide specific advice in this regard and often will have to engage in education processes, not only for the affected person, but also family, employers, unions and other advocacy groups.

From an employer perspective, first it is preferable not to make any distinction between work-related and coincident injuries and illnesses in regard to the support and systems available to injured and/or unwell workers. Compensation systems can assist by not linking company premiums to claims records as this will usually lead to some sort of gaming. Premiums based on the quality of systems that are in place are preferable.

Second, when the incidence or prevalence of work-related pain first increases in any workplace, the managerial response should include a review of the workplace processes involved, the work environment and other markers of workplace distress, such as absenteeism rates, sickness absence rates and staff turnover.

Some important lessons can be learnt from this experience, which are worthy of consideration in future epidemics.

Physicians need to ‘stick to their knitting’. Regardless of whatever controversy exists around particular diagnoses, it is important that physicians offer medical opinions, and not engage in legal and insurance entitlement debates, which are not usual areas of physician expertise.

Good history taking is the basis of any diagnosis. In the context of an occupationally related injury or illnesses, this history must include a good exposure history. A workplace visit is often required, both to identify obvious ergonomic issues that may be contributory to specific musculoskeletal injuries, and also to identify those workplaces, where a culture or management practices create an environment in which worker dissatisfaction, and hence illness, is likely.
Last, it is important that unions and other worker advocacy groups focus on the prevention of workplace injuries and illnesses, the best possible health outcomes for people who are injured or ill at work, and the maintenance of employment for their members, as compared with access to workers’ compensation schemes per se.

It is a matter of when and not if the next work-related musculoskeletal pain epidemic occurs. It would be unacceptable if that next epidemic were to be encountered with the same naiveté as the last.

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References

3 Ramazzini B. *De Morbis Artificum Diatriba (Diseases of Workers)*. From the Latin text of 1713, revised, with translation and notes by Wilmer Cave Wright. (Chicago: University of Chicago Press; 1940) *Am J Public Health* 2001; 91: 1380–2.
Polycystic ovary syndrome: a common hormonal condition with major metabolic sequelae that physicians should know about

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Key words polycystic ovary syndrome, insulin resistance, metabolic syndrome, hyperandrogenaemia, subfertility, obesity.

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Abstract
Polycystic ovary syndrome (PCOS) is a prevalent, chronic and heterogeneous endocrine condition, with reproductive, metabolic and psychological features. Insulin resistance and hyperandrogenaemia are the key pathophysiological hormonal abnormalities. Insulin resistance is a significant contributor to the reproductive and metabolic complications of PCOS, both independently and in the setting of excess bodyweight. While the diagnostic criteria are now internationally uniformly accepted, individual components of the criteria are ill-defined, making diagnosis challenging. This, along with low awareness of PCOS, has resulted in a significant proportion of women remaining undiagnosed. While reproductive features are best recognised in PCOS and form the basis of the diagnostic criteria, awareness of psychological and metabolic features, recommended screening protocols, and management strategies to prevent metabolic complications are important. In this review, we focus on diagnostic criteria, and reproductive, metabolic and psychological features of PCOS, as well as recommended screening and management strategies suggested by national and international evidence-based guidelines.

Introduction
Polycystic ovary syndrome (PCOS) is a common complex endocrine condition. It is present in 12–21% of women of reproductive age. PCOS causes a significant health burden, is distressing for women and accounts for significant national healthcare cost, which based on US-converted costs for the Australian health system and on PCOS prevalence is estimated in excess of $800 million per year. Until recently, evidence-based guidelines on PCOS were not available. Australia led this area internationally, and formed a PCOS Alliance with consumers including a leading non-government organisation (Jean Hailes), multidisciplinary health professionals and academics. Guidelines preparation, dissemination and translation were prioritised, government funding was obtained, and a comprehensive process including scope 28 separate systematic reviews, multidisciplinary interpretation and writing of the guidelines were completed. This was followed by consultation, National Health and Medical Research Council approval and a national dissemination and education programme. The PCOS evidence-based guideline processes have been commended by the US National Institute for Health and recognised by the World Health Organization, with a contract to expand this work internationally. Here, we present a summary of the guideline focused on PCOS management in Australia for the practising physician.

Women with PCOS are at a higher risk of developing pre-diabetes, gestational (GDM) and type 2 diabetes (T2DM), and have higher cardiovascular risk factors. Hence, it is increasingly recognised that PCOS is not only a reproductive issue, but a metabolic disease that carries important health risks from a young age.

Women are at risk if they have a family history of PCOS or T2DM. Obesity further increases both the prevalence and severity of PCOS. Some ethnic groups, including Australian Indigenous women, are at higher risks of developing this condition, exacerbated by higher levels of insulin resistance and higher rates of obesity. In a study of diabetes in urban indigenous women in Darwin (Northern Territory) of whom 15% had PCOS by the original National Institutes of Health (NIH) criteria, none was previously diagnosed with PCOS.

Aetiology, diagnostic criteria and clinical features
Insulin resistance is present in 85% of those with PCOS, including 65% of lean and 95% of obese affected
women, and hyperandrogenaemia is detected in 60–80% of affected women.\textsuperscript{5,10–13} These are the key hormonal disturbances underpinning PCOS and are exacerbated by weight gain (Fig. 1).\textsuperscript{10} Women with PCOS may present with a range of features, including reproductive (hyperandrogenism, hirsutism, anovulation, infertility), metabolic (insulin resistance, impaired glucose tolerance (IGT), GDM, T2DM, dyslipidaemia, obstructive sleep apnoea) and psychological features (increased anxiety, depression and worsened quality of life (QoL)).\textsuperscript{13–17} Presenting symptoms can vary with age. In younger women, reproductive and psychological symptoms predominate. The prevalence of metabolic features increases with age, but can also occur in younger women especially if they are overweight.\textsuperscript{5,7}

Historical controversies over the diagnostic criteria and a diverse range of symptoms have made the path to diagnosis difficult for many women, and up to 70% of women with PCOS in Australia remain undiagnosed.\textsuperscript{1} Rotterdam diagnostic criteria (Table 1) are the most widely accepted diagnostic criteria across Europe, Asia, United States and Australia.\textsuperscript{5,6,18,19}

Recommended diagnostic investigations include measurement of testosterone, calculated free testosterone or free androgen index, and sex hormone binding globulin, with additional androgens not recommended for routine diagnosis.\textsuperscript{5} A pelvic ultrasound can be performed to determine ovarian morphology if required for diagnosis and should be in the follicular phase of the menstrual cycle where possible.\textsuperscript{3} The presence of at least 25 small antral follicles (2–10 mm) in either ovary or both is indicative of polycystic ovaries;\textsuperscript{20} however, the presence of polycystic ovaries on ultrasound is ubiquitous and non-specific, especially in young women.\textsuperscript{3} Pelvic ultrasound is, therefore, not recommended in the diagnosis of adolescents (as 70–80% have polycystic ovaries) and vaginal ultrasound may be inappropriate; hence, only ovulatory disturbances and features of hyperandrogenism should be used for diagnosis in adolescence.\textsuperscript{3}

PCOS is a diagnosis of exclusion, and other endocrine conditions, including thyroid dysfunction and hyperprolactinaemia, should be excluded biochemically.\textsuperscript{5}
rare causes, including Cushing syndrome and non-classical congenital adrenal hyperplasia (CAH) if suspected clinically, are best referred to an endocrinologist for work-up.

Due to inaccuracies of current clinically available assays, measurement of insulin levels is not recommended. The presence of metabolic syndrome, increased waist circumference, high body mass index (BMI), low levels of sex hormone binding globulin and abnormal glucose metabolism best reflect metabolically relevant insulin resistance in this population.

Reproductive health consequences of PCOS

Reproductive and hormonal features are often the best-recognised features in PCOS as they form the basis of the PCOS diagnostic criteria. Reproductive health issues mainly include hyperandrogenism, and oligo/anovulation resulting in infertility. PCOS is the most common cause of anovulatory infertility. Fertility declines further with a BMI greater than 30–32 kg/m² and age more than 35 years. However, fertility is not necessarily impaired in all PCOS cases, and some women conceive without medical intervention, depending on the severity of the condition; hence, contraception is still relevant. An association between PCOS and endometrial cancer has also been described. Women with PCOS share many of the risk factors associated with the development of endometrial cancer, including obesity, hyperinsulinaemia, T2DM and anovulation with unopposed uterine estrogen exposure. While awareness of this association is recommended, routine ultrasound screening for endometrial thickness is not recommended in women with PCOS, unless risk factors or symptoms are present.

Metabolic consequences of PCOS

Screening, prevention and management of metabolic complications are vital in women with PCOS. The national PCOS guideline highlights the key role of insulin resistance in lean women with PCOS, with exacerbation by obesity. PCOS is associated with pre-diabetes, GDM (with around two- to threefold risk, independent of obesity) and T2DM (four- to sixfold risk, independent of obesity), and these occur at a younger age. PCOS is recognised by the International Diabetes Federation as a risk factor for T2DM. They also have an adverse cardiovascular risk profile, with dyslipidaemia, may be hypertensive and have obstructive sleep apnoea. Dyslipidaemia is common in women with PCOS compared with weight-matched controls, occurs independent of BMI, and leads to higher triglycerides and lower high-density lipoprotein cholesterol levels. The association of PCOS with non-alcoholic fatty liver disease has also been reported, but the available literature, especially in reference to the risk of non-alcoholic steatohepatitis (NASH), is incomplete.

These metabolic consequences of PCOS are associated with increased risk of cardiovascular disease. However, no well-designed large longitudinal studies have adequately addressed the risk of cardiovascular disease in PCOS, and this remains controversial.

Psychological consequences of PCOS

Women with PCOS are more likely to suffer from depression, anxiety, poor self-esteem, disordered eating and psychosexual dysfunction. This is relevant to clinical care as mood disturbance, in turn, impairs QoL and adversely affects lifestyle management. Challenges to feminine identity and body image due to obesity, acne, excess hair and infertility adversely affect mood and psychological well-being, and there is also evidence suggesting that the increased prevalence of depression and depressive symptoms in these women is independent of obesity and reproductive hormone status.

Obesity prevention, management and metabolic risk screening

Obesity appears to have a bidirectional relationship with PCOS, as women with PCOS are more prone to weight gain, and excess weight gain increases PCOS prevalence. Considering the implications of excess weight on reproductive, metabolic and mental health, lifestyle modification remains the first-line treatment for PCOS, focused both on prevention of weight gain and treatment of excess weight. This is also relevant in pregnancy where risk of GDM is significantly increased.

In terms of screening, an oral glucose tolerance test (OGTT) and lipid levels should be monitored regularly, generally two yearly – although recommendations on
frequency of testing vary internationally.\textsuperscript{5,19} Currently, fasting glucose levels have been shown to be inaccurate in PCOS, with an OGTT recommended.\textsuperscript{5} Fasting glucose may have a role in a two-step process to exclude some from progression to OGTT; however, more research is needed.\textsuperscript{27,28} Screening is particularly important in women on the combined oral contraceptive pill (COCP) or in those with other risk factors (Table 3). Early detection and diagnosis of pre-diabetes and cardiovascular risk factors are strongly recommended to enable intensified lifestyle, and where needed pharmacological intervention.\textsuperscript{5,19}

A lifestyle programme that addresses a healthy diet with caloric restriction and exercise is the best first-line

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**Table 2** Targeted treatment options for polycystic ovary syndrome. Adapted and reproduced with permission from Teede et al.\textsuperscript{14} COCP, combined oral contraceptive pill

<table>
<thead>
<tr>
<th>Oligomenorrhoea/amenorrhoea</th>
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<tr>
<td>• Lifestyle change (5–10% weight loss + structured exercise)</td>
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<tr>
<td>• Combined oral contraceptive pill (low oestrogen doses, eg. 20 μg may have less impact on insulin resistance)</td>
</tr>
<tr>
<td>• Cyclic progestins (eg. 10 mg medroxyprogesterone acetate 10–14 days every 2–3 months)</td>
</tr>
<tr>
<td>• Metformin (improves ovulation and menstrual cyclicity)</td>
</tr>
</tbody>
</table>

**Hirsutism**

• Self-administered and professional cosmetic therapy is first line (laser is recommended)

**Pharmacological therapy**

• Consider if there is patient concern or if cosmetic treatment is ineffective/inaccessible/unaffordable
• Should be trialled for at least 6 months before making changes in dose or medication
• Primary therapy is the COCP (monitor glucose tolerance in those at risk of diabetes)
• Anti-androgen monotherapy (eg. Spironolactone) should not be used without adequate contraception
• Combination therapy – if 3–6 months of COCP is ineffective, add anti-androgen to COCP (daily spironolactone, and if >50 mg twice daily)

**Infertility**

• Advise smoking cessation, optimal weight, exercise and folate supplementation
• Advise regarding the age-related decline in fertility to allow optimal timing of family planning
• Infertility therapies may include clomiphene, metformin, gonadotropins, aromatase inhibitors, surgery and in vitro fertilisation

**Cardiometabolic risk**

• Lifestyle change with a >5% weight loss in those who are overweight reduces diabetes risk by >50–60% in high risk groups
• Metformin* reduces the risk of diabetes by >50% in adherent high risk groups

*Metformin and the COCP are not currently approved for use to manage PCOS by many regulatory bodies. The COCP is indicated for contraception and metformin is indicated for diabetes. However, their use is supported by evidence and is recommended by international and national specialist societies.

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**Table 3** Recommendations for metabolic risk management in polycystic ovary syndrome (PCOS). BMI, body mass index.

**Recommendation for metabolic risk management in PCOS:**

• Encourage smoking cessation
• Monitor anthropometric factors including weight, BMI and waist circumference at most visits
• Measure fasting lipid profile every 2 years if normal and every year if abnormal and/or overweight or obese. The most common abnormalities are low high-density lipoprotein cholesterol (HDL-C) and high triglycerides
• Measure BP annually if BMI less than 25 kg/m\(^2\) or at every visit if BMI is more than 25 kg/m\(^2\)
• Screen for pre-diabetes (impaired fasting glucose and impaired glucose tolerance) and diabetes – start screening from a young age, especially preconception and early in pregnancy

The national guideline recommends an oral glucose tolerance (OGTT) test every 2 years in all women and every year in those with additional risks for diabetes (age, ethnicity, parental history of diabetes, history of high glucose levels, smoking and use of oral contraceptive pill or anti-hypertensive medications, physical inactivity and waist circumference more than 80 cm).

These recommendations remain controversial in terms of frequency of testing, but most organisations agree that an OGTT is needed as fasting glucose is insensitive in this population.\textsuperscript{5,19}
treatment to prevent weight gain and achieve weight loss. General recommendations include 150 min of exercise weekly, with 90 min of this exercise being aerobic activity at moderate to high intensity aiming to achieve modest goals (5% weight loss). Lifestyle with diet and exercise should always be a core part of management.

Weight loss also appears to offer considerable benefits to most women with PCOS who are already overweight. There is a large number of small trials demonstrating that weight loss achieved through lifestyle management decreases abdominal fat, hyperandrogenism and insulin resistance, and improves lipid profiles, ovulation, menstrual cyclicity, fertility, risk factors for T2DM, cardiovascular disease and psychological health, in women with PCOS who are overweight, although there are inadequate data on the effects on live birth rates as yet. Importantly, among women with PCOS and excess weight, a reduction of as little as 5% of total bodyweight has been shown to improve outcomes, and realistic goals of prevention of weight gain or small degrees of weight loss are important to increase engagement.

Reproductive health

Initial steps in fertility management include planning for early family initiation where possible, prevention of weight gain, and intensive lifestyle programmes with caloric restriction and regular exercise aiming for a BMI of less than 30 kg/m². Pharmacological options include ovulation induction with clomiphene citrate, metformin and gonadotropins, with additional options including surgery (laparoscopic ovarian drilling), and if ovulation induction is unsuccessful or there are other infertility factors, in vitro fertilisation (IVF). In women with oligo/amenorrhoea, intermittent progestin every 3 months may be used to induce a withdrawal bleed and protect the endometrium from hyperplasia. The COCP is effective in achieving menstrual cycle regularity; however, providing contraception and controlling hirsutism may be a negative influence on insulin resistance, and a low-dose COCP may be preferred. There is little therapeutic advantage in using the later generation progestins in hyperandrogenism, and given recently reported thromboembolic side-effects, low-dose COCP with levonorgestrel would appear a clinically reasonable choice. Smoking history, age, weight, metabolic and thromboembolism risks need to be taken into consideration when prescribing COCP.

Hirsutism is a consequence of excess androgens. The choice of therapeutic options depends on patient preference, impact on well-being, access and affordability, and includes first-line cosmetic therapy (laser and electrolysis) and a combination of medical (COCP) with potential addition of an anti-androgen in generalised hirsutism if required. Anti-androgens should be administered with contraception because of anti-androgenic effects in pregnancy.

Psychological health

The national guideline recommends emotional health screening, especially for depression and anxiety, and provides a simple evidence-based simple screening tool to facilitate this in women with PCOS. While management of psychological conditions is vital to enable lifestyle changes, lifestyle management improves QoL and depression in women with PCOS.

Therapeutic benefits of metformin in PCOS

While metformin is not first-line treatment in PCOS, it is of specific interest to physicians, and its role in PCOS remains controversial, hence it is discussed here. A systematic review and meta-analysis demonstrated that there was significant weight loss in trials using metformin compared with placebo in women with PCOS; however, metformin did not further reduce weight in patients using diet and exercise programmes. Hence, metformin may remain a treatment consideration for prevention of weight gain, management of obesity and prevention of diabetes in women with PCOS and IGT, if the patient fails with diet and exercise.

A recent meta-analysis of insulin sensitisers for the treatment of infertility in PCOS concluded that the use of metformin for improving live births in PCOS appears to be limited. Nevertheless, metformin has been shown to improve menstrual cyclicity and ovulation rate, and is readily available and is low-cost. Metformin, therefore, has a role in the regulation of menses and ovulation, especially where contraception is not desired. In infertility, a systematic review of metformin noted that in clomiphene-resistant women, metformin plus clomiphene led to higher live birth rates than clomiphene alone; metformin also led to higher live birth rates than laparoscopic ovarian drilling, and literature suggests that metformin may be more effective at a BMI <30 kg/m². In addition, metformin may prevent the development of ovarian hyperstimulation syndrome in women with PCOS receiving gonadotropin therapy for IVF.

Metformin is not currently approved for use in PCOS by Therapeutic Goods Administration as no application has been made by the pharmaceutical industry. However, its use is supported by evidence and is recommended by international and national specialist societies and is evidence based.

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Metformin studies have not been sufficiently powered to study its effect on acne and hirsutism, yet some studies show benefit, but it is likely to be less effective than the COCP. 29

**Conclusion**

PCOS is a common, lifelong condition that appears to be increasing in prevalence with increasing obesity, yet remains largely undiagnosed, limiting opportunities for prevention and management. Physicians should be aware of PCOS and seek to increase early diagnosis, as well as be aware of the significant metabolic features of this condition, both independent of and exacerbated by obesity. Comprehensive assessment is important, and management should focus on support, education and addressing psychological factors. Screening and prevention of psychological and metabolic features are recommended, along with a focus on prevention of weight gain, weight monitoring and treatment of obesity, starting with modest goals (5% weight loss). Cosmetic therapy is useful in hirsutism, and medical therapy includes the COCP and anti-androgens. Metformin has a role in inducing ovulation, managing weight where lifestyle has failed and potentially in infertility management. Clomiphene citrate and other agents are mainly recommended for infertility. The national PCOS guideline emphasises that an interdisciplinary team approach is often required for chronic care of reproductive, metabolic and psychological symptoms. Although further research is needed, new comprehensive evidence-based guidelines, with associated, freely available translation resources, now aid consumers and clinicians in the optimal assessment and management of women with PCOS.


**References**


12 Meyer C, McGrath BP, Teede HJ. Overweight women with polycystic ovary syndrome have evidence of subclinical cardiovascular disease.


18 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks.
33 Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulinsensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiroinositol) for women with polycystic ovary syndrome, oligoamenorrhea and subfertility. Cochrane Database Syst Rev 2010; CD003053.
36 Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Freitas V. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2009; CD006105.
Mutation profile of differentiated thyroid tumours in an Australian urban population

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Key words
thyroid cancer, mutation, BRAF, RAS.

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Abstract
Background: The majority of differentiated thyroid cancers are characterised by one of several point mutations or gene rearrangements. Limited data are available on the prevalence and clinical correlations of these mutations in the Australian population.

Aims: The aim of the present study was to characterise the mutation profile of differentiated thyroid tumours in the local population.

Methods: The study involved 148 patients with differentiated thyroid cancer. The following tumours were examined: 109 papillary carcinomas (PTC), 27 follicular carcinomas (FC) and 12 Hurthle cell carcinomas (HCC). Polymerase chain reaction (PCR) was performed for BRAF and RAS mutations (RNA and DNA) as well as for RET/PTC rearrangements and PAX8-PPARγ translocations (RNA). Clinicopathological parameters and outcome data were analysed according to BRAFV600E status in PTC and RAS mutation status in FC.

Results: BRAFV600E was identified in 74/109 (68%) PTC. BRAFV600E was not significantly correlated with clinicopathological features of aggressive disease. At a median follow up of 48 months, there was no significant difference between BRAFV600E and wild-type BRAF PTC with respect to the rates of nodal recurrence, distant metastases or disease-specific death. In FC, RAS mutations (five NRAS and three HRAS) were present in 8/27 (30%) tumours. RAS mutation was significantly associated with widely invasive histology (P = 0.01) and distant metastases (P = 0.01) on follow up.

Conclusion: In the present study, BRAF mutation was not associated with negative prognostic indicators or adverse outcomes in PTC. RAS mutation was positively correlated with aggressive features in FC suggesting potential prognostic utility, although confirmation is required from larger studies.

Introduction

Thyroid cancer is the most common endocrine malignancy. The worldwide incidence of thyroid cancer has increased significantly in recent years1 and Australian statistics confirm a similar trend in the local population.2

Differentiated thyroid cancer includes papillary carcinoma (PTC), follicular carcinoma (FC) and Hurthle cell carcinoma (HCC). Mutations in members of the mitogen-activated protein kinase (MAPK) signalling pathway are common in differentiated thyroid cancer, being present in up to 75% of tumours. Among thyroid cancers, mutations in the proto-oncogene B-Raf, primarily involving an amino acid substitution from valine to glutamate at codon 600 (BRAFV600E), are found exclusively in PTC. Rat sarcoma gene (RAS) mutations and translocations involving the RET proto-oncogene and genes constitutively expressed in thyroid follicular cells (RET/PTC) are found less commonly in PTC. In FC, RAS mutations and translocations involving the paired box 8 gene and peroxisome proliferator receptor gamma (PAX8-PPARγ) predominate.

Recently, there has been considerable interest in these mutations with respect to their potential impact on diagnosis, prognosis and therapy in thyroid cancer. Several
studies3–5 have demonstrated that detection of the aforementioned mutations in FNA specimens improves diagnostic accuracy over traditional cytology alone. The prognostic utility of BRAF mutation in PTC has been the subject of multiple investigations. Several large studies6–9 have reported an association of BRAF mutation with negative prognostic features; however, other studies10–12 have found no such association and the utility of the mutation over traditional histological features in PTC continues to be debated. RAS mutations have been less extensively studied, although an association with negative prognostic indicators has been suggested in several studies.13–15

A limited number of Australian studies has reported on the prevalence of mutations in thyroid tumours and these have primarily focused on either BRAF mutation16,17 or RET/PTC translocations18–20 in PTC. The aim of our study was to examine the mutation profile of differentiated thyroid tumours (including papillary, follicular and Hurthle cell subtypes) in the Victorian urban population. We further sought to correlate the presence of BRAF and RAS mutations with clinical and pathological features in PTC and FC respectively, as well as the impact on nodal recurrence, distant metastases and disease-related death.

Methods

Patients

The study involved 148 patients with differentiated thyroid cancer who underwent surgery between 2002 and 2013. Frozen and formalin-fixed paraffin-embedded (FFPE) tissue from a range of Victorian hospitals was accessed through the Victorian Cancer Biobank. The majority of patients included in the study were recruited on the basis of available tissue collected by the Biobank, while a minority were recruited in a sequential fashion on routine outpatient follow up with subsequent retrieval of archival tumour tissue. All patients gave written informed consent for the collection of tissue and gathering of clinical data. The following tumours were examined: 109 PTC (51 frozen and 58 FFPE), 27 FC (nine frozen and 18 FFPE) and 12 HCC (8 frozen and 4 FFPE). Tumours ranged in size from 7 mm to 100 mm.

For PTC, central lymph node dissection was not performed routinely but was rather at the discretion of the individual surgeon. The presence of lymph node metastases was determined on the basis of the histopathology report. Clinical follow up was sought for all patients with PTC and FC, and included data on recurrence, distant metastases and disease-specific death. For PTC, nodal recurrence was defined as the reappearance of malignancy in the neck after completion of initial treatment with thyroidectomy and radioactive iodine. Nodal recurrence was confirmed by ultrasound and fine-needle aspiration cytology.

RNA isolation

RNA was isolated from frozen tissue using the RNeasy Mini Kit (Qiagen, Hilden, Germany). RNA integrity was assessed by evaluation of the A260/A280 ratio and by determining the RNA integrity number (RIN) using the Agilent Bioanalyzer (Agilent Technologies, CA, USA).

Paraffin-embedded tissue, DNA isolation

Genomic DNA was extracted from paraffin sections with the QIAamp DNA FFPE Tissue Kit (Qiagen). DNA quality was assessed by evaluation of the A260/A280 ratio (Nanodrop spectrophotometer; Thermoscientific, Waltham, MA, USA).

For all tissues, a representative block was reviewed by a pathologist to ensure consistency with the histopathological diagnosis. The representative section was also scored for the percentage of tissue components such as stroma, inflammatory infiltrate and tumour. Only those tissues with at least 50% tumour component were included in the study.

RT-PCR

Total RNA (1 μg) was reverse-transcribed for 60 min at 50°C in a total volume of 20 μL using SuperScript III reverse transcriptase (Invitrogen, San Diego, CA, USA). First-strand synthesis was performed using 250 ng random hexamers.

RNA samples were used to test for BRAF and RAS (N-, H- and K-RAS) hotspot mutations as well as for RET-PTC1 and RET/PTC3 rearrangements and PAX8-PPARγ translocations. DNA samples were tested for BRAF and RAS mutations. PCR was performed on a Veriti 96-well Thermal Cycler (Applied Biosystems, Foster, CA, USA). The primers and PCR conditions for the reactions can be found in the Appendix. The PCR products were purified using a QIAquick Gel Extraction Kit (Qiagen). For each sample, forward and reverse sequences were determined using the PCR primers as sequencing primers and a BigDye Terminator Cycle Sequencing Ready Reaction Kit, v3.1 (Applied Biosystems), according to the manufacturer’s protocol. The analysis was carried out using ABI 3130xl Genetic Analyzer (Applied Biosystems) and assembled using Sequencher 3.1.1 software. Sequencing was performed by the Gandel Charitable Trust Sequencing Centre at the Monash Health Translation Precinct, Clayton, Melbourne Australia.
Statistical analysis was performed using Fisher’s exact test for categorical variables. Graphpad Prism software Version 6.0c was used for the analyses.

Results

Overall, the BRAF mutation at codon 600 (BRAFV600E) was detected in 74 out of 109 PTC (68%). One homozygous mutant was identified in a multifocal PTC lacking other aggressive features.

The relationship between BRAF mutation and several demographic and pathological features were examined. Analyses were undertaken for age, gender, tumour size, tumour subtype, lymph node metastases, extrathyroidal extension and multifocality (Table 1). The prevalence of BRAFV600E was significantly higher in classical PTC as compared with follicular variant PTC (74% vs 29%; \( P = 0.002 \)). The BRAF mutation was not significantly associated with other baseline clinical or pathological parameters.

RAS mutations or RET/PTC translocations were present in a minority of PTC that were negative for BRAF mutation. Two RAS mutations, both involving amino acid substitutions from glutamine to arginine at codon 61 in NRAS (Q61R), were detected and where RNA was available for analysis (\( n = 51 \)), two RET/PTC1 and no RET/PTC3 rearrangements were found.

Of the 109 patients with PTC included in the study, follow-up data were available for 97 (89%); clinical outcomes are shown in Table 2. At a median follow up of 48 months (range 6–146), the rate of nodal recurrence requiring reoperative surgery did not differ significantly between patients with BRAFV600E tumours and those with wild-type BRAF tumours (12% vs 10%; \( P = 1.00 \)). Similarly, the rate of distant metastases did not differ significantly by BRAF status and one death due to PTC occurred in each group.

In FC, RAS mutations were present in eight (five NRAS and three HRAS) out of 27 tumours (30%). Additionally, one PAX8-PPAR\( \gamma \) translocation was detected in the RNA group (\( n = 9 \)). Of note, no point mutations or translocations were found in the 12 HCC.

Discussion

In the present study, we examined the mutation profile of differentiated thyroid tumours in the Victorian population. In contrast to previous Australian studies that have focused on individual mutations in papillary tumours,\(^{16–20}\) we screened for a range of recognised mutations in PTC, FC and HCC. All tissues underwent pathological review in order to ensure majority tumour component and mutation analysis was by direct sequencing.

Overall, the BRAFV600E mutation was present in 68% of PTC. Consistent with other studies, BRAFV600E was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Relationship between BRAF mutation status and clinicopathological parameters in papillary carcinoma</th>
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<tbody>
<tr>
<td></td>
<td>BRAFV600E</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>&lt;45</td>
<td>30</td>
</tr>
<tr>
<td>&gt;45</td>
<td>44</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>22</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
</tr>
<tr>
<td>CPTC</td>
<td>70</td>
</tr>
<tr>
<td>FVPTC</td>
<td>4</td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>&lt;4 cm</td>
<td>59</td>
</tr>
<tr>
<td>( \geq 4 ) cm</td>
<td>15</td>
</tr>
<tr>
<td>LN mets</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>34</td>
</tr>
<tr>
<td>N</td>
<td>40</td>
</tr>
<tr>
<td>ETE</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>21</td>
</tr>
<tr>
<td>N</td>
<td>53</td>
</tr>
<tr>
<td>Multifocal</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>37</td>
</tr>
<tr>
<td>N</td>
<td>37</td>
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</tbody>
</table>

CPTC, classical papillary carcinoma; ETE, extrathyroidal extension; FVPTC, follicular variant papillary carcinoma; LN mets, lymph node metastases.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>BRAF mutation status and papillary carcinoma (PTC) outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRAFV600E</td>
</tr>
<tr>
<td>Follow up, median (range) (months)</td>
<td>47 (14–146)</td>
</tr>
<tr>
<td>Recurrence requiring reoperative surgery, ( n ) (%)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Distant metastases, ( n ) (%)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Death due to PTC, ( n ) (%)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

†Assessed using Mann–Whitney U-test. ‡Assessed using Fisher exact test.
significantly more common in classical PTC than in follicular variant PTC. However, there was no association between BRAF mutation and baseline histopathological features of aggressive disease in our cohort. In addition, clinical outcomes did not differ between BRAFV600E and wild-type BRAF PTC with respect to the rates of nodal recurrence requiring reoperative surgery, distant metastases or disease-specific death. We specifically examined the rate of clinically apparent, histologically confirmed nodal recurrence as ultrasound frequently detects subtle changes in lymph node architecture of uncertain significance and also because small-volume lymph node metastases often follow a benign course in PTC.21

Several (largely retrospective) studies including several meta-analyses have reported an association between BRAFV600E and aggressive clinicopathological features6–9,22 while others have found no such association.10–12,23 With respect to the specific question of whether BRAF status influences the rate of nodal recurrence, reports are similarly conflicting.11,17,23–29

Our study has several potential limitations. Patients were selected largely on the basis of available tissue stored in a Biobank; this may have influenced the demographic make-up of the cohort in that certain patients might be more likely than others to donate tissue. Being a retrospective, multicentre study, the approach to surgery and subsequent patient follow up (including radioactive iodine administration) was not uniform, although two-thirds of patients included in the study were enrolled from two centres with a consistent approach to the management of thyroid cancer. Central lymph node dissection was not performed routinely; this is in keeping with the current American Thyroid Association guidelines, which recommend prophylactic central lymph node dissection only for larger tumours and higher-risk cases. It is possible that variations in surgical practice influenced the rates of nodal recurrence, although BRAF mutation status was not known preoperatively and did not influence the extent of surgery. The median duration of follow up did not differ by BRAF status but was relatively short in the context of PTC where late recurrence is known to occur. However, a recent Australian study with longer follow up found a similar rate of nodal recurrence in BRAFV600E PTC, although the recurrence rate in PTC without BRAF mutation was lower in that study.17 In our cohort, disease-specific mortality was low in both groups, but given the prolonged survival of most patients with PTC, differences might only emerge on longer follow up.

The conflicting results in relation to BRAF mutation and its association with clinical features in PTC suggests that its usefulness and application in clinical practice remain uncertain. Given the generally favourable outcome of PTC, BRAFV600E may have limited prognostic utility, particularly in areas where the prevalence of the mutation is high, although conversely, the diagnostic potential of the mutation in these areas may be greater.

| Table 3 Clinical information for RAS mutation-positive follicular carcinoma |
|---|---|---|---|
| Age (years) | Gender | Mutation | Histopathology |
| FC1 76 | F | NRAS Q61K† | 60 mm widely invasive tumour with extensive vascular invasion; tumour extending to resection margin |
| FC2 63 | M | NRAS Q61R‡ | 100 mm tumour with poorly differentiated areas; vascular invasion and multiple lymph node metastases with extranodal spread |
| FC3 56 | F | NRAS Q61K | 70 mm widely invasive tumour with poorly differentiated areas; extensive capsular and vascular invasion, multifocal extrathyroidal extension and involvement of resection margins |
| FC4 79 | F | NRAS Q61R | 60 mm tumour with focal capsular and multifocal vascular invasion; intravascular tumour extending to margin, no extrathyroidal extension |
| FC5 66 | M | NRAS Q61R | 85 mm widely invasive tumour with vascular and lymphatic invasion, extending close to resection margin |
| FC6 58 | F | HRAS Q61R | 55 mm minimally invasive tumour with limited vascular involvement |
| FC7 80 | M | HRAS Q61R | 55 mm widely invasive tumour involving isthmus and right lobe; known vertebral metastasis |
| FC8 77 | F | HRAS Q61R | 8 mm minimally invasive tumour with limited vascular invasion |

†Q61K, amino acid substitution from glutamine to lysine at codon 61.
‡Q61R, amino acid substitution from glutamine to arginine at codon 61.

| Table 4 Correlation between RAS mutation status and clinicopathological parameters in follicular carcinoma |
|---|---|---|---|
| Mutant RAS | Wild-type RAS | P-value |
| Gender | Male | 3 | 10 | 0.68 |
| Female | 5 | 9 | |
| Age (years) | <45 | 0 | 2 | 1.00 |
| ≥45 | 8 | 17 | |
| Size | <4 cm | 1 | 7 | 0.36 |
| ≥4 cm | 7 | 12 | |
| Minimally invasive | 3 | 17 | 0.01 |
| Widely invasive | 5 | 2 | |
| Distant mets | Y | 5 | 3 | 0.01 |
| N | 2 | 16 | |

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Along with a high rate of BRAF mutation in PTC, we found a low rate of RAS mutations and RET/PTC rearrangements. These mutations were mutually exclusive with BRAF mutation, in keeping with the majority of previous studies. To maximise the detection rate of RET/PTC rearrangements, we restricted our analysis to RNA extracted from fresh tissue. RET/PTC translocations were present in only 4% of tumours in our series. A previous Australian study reported a similar low rate of RET/PTC rearrangements (8%) with RET/PTC1 the exclusive rearrangement detected. In contrast, two other Australian studies found much higher rates of RET/PTC rearrangements in PTC. The reason for this discrepancy is not clear, although the majority of tissues examined in the latter two studies were archival samples. Investigators from several Western countries have suggested that the mutation profile of PTC has changed over time with increasing rates of BRAF mutation and lower rates of RET/PTC rearrangements. Increasing iodine intake and/or exposure to other environmental pollutants along with reduced exposure to ionising radiation have been proposed to underlie these changes, but these hypotheses remain unproven.

RAS mutations were detected in 30% of (non-oncocytic) FC and NRAS codon 61 mutations were the most common. These results are in accordance with previously published studies. A PAX8-PPARγ translocation was found in only one FC; however, the number of RNA specimens was limited, precluding an accurate estimate of the population prevalence. In contrast to FC, no RAS mutations or PAX8-PPARγ translocations were detected in the HCC group. A low rate of RAS mutation and absence of PAX8-PPARγ translocations was reported in a recent genomic study of 27 Hurthle cell tumours. The basis of their mutation profile, as well as data on global copy number changes and gene expression, the authors suggest that HCC may be a unique type of thyroid cancer distinct from follicular and papillary carcinoma. Work in our laboratory examining the nuclear receptor expression profile of differentiated thyroid tumours has demonstrated downregulation of a wide range of nuclear receptors specifically in HCC further highlighting the uniqueness of this tumour subtype.

RAS mutations are found in a wide spectrum of thyroid lesions from benign adenomas to undifferentiated carcinomas and the prognostic significance of a RAS mutation is less well studied than BRAF. Several studies have suggested that at least in a subset of patients with differentiated thyroid cancer, the presence of a RAS mutation (particularly NRAS) is associated with adverse prognostic outcomes such as distant metastases and increased mortality. However, three of these studies included either PTC or a heterogeneous mixture of thyroid tumour subtypes, while only one study specifically examined the clinical correlates of RAS mutation in FC.

RAS mutations have also been found in a significant proportion of poorly differentiated carcinomas and a correlation with negative prognostic indicators in these tumours has been reported. These and other data support the notion that RAS mutation is an early event that may predispose well-differentiated tumours to subsequent de-differentiation with the acquisition of additional mutations. The mechanisms for this are not fully elucidated, although one study has suggested that oncogenic RAS promotes chromosomal instability by interfering with critical cell cycle check points through both MAPK-dependent and independent pathways.

Although the number of FC in the present study was relatively limited, we found significant associations between RAS mutation positivity and the degree of tumour invasion at the time of surgery as well as the development of distant metastases on subsequent follow up. NRAS mutant tumours, in particular, showed aggressive features. Four out of five NRAS mutant tumours were widely invasive on histopathology and the remaining tumour demonstrated multifocal vascular invasion. Two of these tumours contained poorly differentiated areas and on follow up all four of the patients with NRAS mutant tumours for whom data were available developed distant metastases. Given the relatively long survival of patients with differentiated thyroid cancer, even when distant metastases are present, an association between RAS mutation and mortality could not be assessed in the context of the limited follow-up period.

Conclusion
The present study of thyroid tumours in the Victorian population has demonstrated a high prevalence of BRAF mutation in PTC along with a low prevalence of RET/PTC translocations and RAS mutations. BRAFV600E was not associated with aggressive clinicopathological features at presentation nor with adverse outcomes on subsequent follow up. In the context of conflicting results in the literature, recommending more aggressive therapy on the basis of BRAF mutation would seem premature. Further large studies with long-term outcome data are required to determine how best to apply BRAFV600E in clinical practice.

RAS mutations were found in a significant minority of FC and our data suggest an association (particularly of NRAS) with more aggressive pathological and clinical features. This association is consistent with several other studies. Given the relatively small numbers of patients enrolled in these studies, confirmation of the results is required from larger series with longer follow up. If the
results are corroborated, RAS mutation testing may provide useful prognostic information as well as potentially having implications for therapy.

Acknowledgements

The authors acknowledge Dr Patrick Hosking (Department of Anatomical Pathology, Eastern Health), as well as the Victorian Cancer Biobank for assistance with tissue collection and in particular the support of Zdenka Prodanovic, Susan Hume, Yao Han, Daniela Surace and Paul Pinto Correia (Victorian Cancer Biobank). We also acknowledge Dr Jennifer Wong (Monash Health) with whom we engaged in helpful discussions.

References


Appendix I

PCR primer pairs and conditions
The PCR primer pairs used for cDNA (reverse transcribed from tumour RNA) and for tumour-derived DNA are listed below.

RNA primers
BRAF sense: GAGGGCTCCAGCTTGATCACC
BRAF antisense: CAATCCCAAATGCATATACATCT
N-ras sense: CCCGGTCTGTGGTCCTAAATC
N-ras antisense: CGCTGTCCCTCATGATTGCTCT
H-ras sense: CCCTGAGGAGCGATGAGGAA
H-ras antisense: TCCGAGTCTTTACGGTTTGTGAT
K-ras sense: CGCCATTTTACCTGGAGCCAG
K-ras antisense: GCCCTCCCCAGTCTGATATT
RET/PTC1 sense: GGAGACCAATTTTCAAGTCAAG
RET/PTC1 antisense: CCCTTCCCTAGAGTTTTTCAAAGA
RET/PTC3 sense: CCAGTGGTATCAAGCTTCTACA
RET/PTC3 antisense: GGGAATCCCATTGGATTCTC
PAX8-PPARγ exon 7 sense: AACCTCTGACTCCAGACCT
PAX8-PPARγ exon 9 sense: CGGACAGGCCAGCTATGC
PAX8-PPARγ antisense: GTTGTTGGCCAGAAATG

DNA primers
BRAF sense: TTACCTAAACTCTTCAATG
BRAF antisense: TCAATGACTTTCTAGAATCT
N-ras sense: CCTCCCTGCCCCCTACCTC
N-ras antisense: GAACACAAAGATCATCTTTC
H-ras sense: CCGTGGAGCGTGAGCCAGTG
H-ras antisense: TCCGAGTCTTACCGGTTTGAT
K-ras sense: ATATAGTCATCTACCTTT
K-ras antisense: TTATCTGATACTACCTAC

For all PCR reactions, the following conditions were used: denaturing at 95°C for 5 min and subsequently for 30 s, annealing for 30 s (at temperatures specific to each pair of primers; see below), and extension at 72°C for 40 s, with a final incubation for 5 min.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Annealing temperature for RNA primers (°C)</th>
<th>Annealing temperature for DNA primers (°C)</th>
</tr>
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<tbody>
<tr>
<td>BRAF</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>NRAS</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td>HRAS</td>
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<td>60</td>
</tr>
<tr>
<td>KRAS</td>
<td>60</td>
<td>50</td>
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<tr>
<td>RET/PTC1 and RET/PTC3</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>PAX8-PPARγ</td>
<td>62</td>
<td>62</td>
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Incidence of upper gastrointestinal haemorrhage in Maori and New Zealand European ethnic groups, 2001–2010

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Key words
upper gastrointestinal bleeding, peptic ulcer disease, epidemiology, upper gastrointestinal endoscopy.

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Abstract

Background: To date no incidence figures for upper gastrointestinal haemorrhage (UGIH) in New Zealand have been published.
Aims: To determine the incidence of UGIH in a demographically defined population, and to assess variation in incidence associated with demographic parameters.
Methods: Between 17 March 2001 and 12 October 2010, all patients presenting to Waikato Hospital with UGIH were prospectively ascertained, and clinical, epidemiological and laboratory data were collected. Incidence rates were calculated, and were age adjusted to the World Health Organization world standard population. Parameters associated with trends in incidence were examined.

Results: There were 1360 UGIH events, yielding a crude incidence of 59.2 per 100 000 adults (age ≥ 15 years) per year (all quoted incidence figures per 100 000 adults per year), and an age-adjusted incidence (AAI) of 46.4. AAI was higher for Maori compared with New Zealand Europeans (91.3 vs 37.0, rate ratio (RR) = 2.47, P < 0.001). Maori were more likely to have a gastric ulcer at endoscopy (odds ratio (OR) = 2.21, P < 0.001). For those tested for Helicobacter pylori (n = 702), Maori were more likely to be infected (OR = 2.12, P < 0.001). AAI was higher for males (61.1 vs 33.6, RR = 1.82, P < 0.001). Males were more likely to have a duodenal ulcer at endoscopy (OR = 1.79, P < 0.001). AAI incidence decreased from the first to the second half of the study period (53.6 vs 45.8, RR = 1.17, P < 0.001).

Conclusion: AAI of UGIH in the Waikato region was 46.4. This was significantly higher in Maori and in males, and decreased over the study period. These data will provide a comparison for future assessment of trends in UGIH.

Introduction

Upper gastrointestinal haemorrhage (UGIH) is defined as bleeding into the gastrointestinal tract, distal to the upper oesophageal sphincter and proximal to the ligament of Treitz. Patients with UGIH present with one or a combination of haematemesis, melaena, hypotension and collapse. Mortality in published series lies between 7% and 14%.1–4

Over the past 20 years, gastroscopy has become routine in the assessment of UGIH. This has led to the more accurate description of underlying pathologies causing UGIH.1–4 However, given that a significant proportion of UGIH cases have no cause identified at endoscopy, estimation of incidence remains reliant on clinical parameters.1 Published estimates vary significantly, between 48 and 172 per 100 000 adults per year (all incidence figures quoted per 100 000 adults per year).1–8 To our knowledge, no description of incidence of UGIH in Maori has been published.

This study reports the incidence of UGIH over a 10-year period in a demographically defined population in the Waikato region of New Zealand (NZ). The influence of ethnicity, sex and time period on incidence is examined. The association between incidence, clinical parameters and demographic parameters is analysed, illuminating factors influencing differences in incidence between demographic groups.

Methods

Patient identification

A prospective database, dedicated to recording gastrointestinal haemorrhage, captured all patients undergoing endoscopy with haematemesis or melaena as the indication from March 2001 to October 2010, in a single
tertiary referral hospital (Waikato Hospital, Hamilton, NZ). This is the only hospital in the region performing endoscopy for acute gastrointestinal bleeding.

Presenting symptoms were retrospectively confirmed and those without evidence of haematemesis or melaena were excluded. Bleeding events which occurred within 30 days of a sentinel bleeding event were classified as rebleeding events and were excluded. Patients who underwent more than one endoscopy for UGIH during the study period had their first event only included.

The study region was defined as the seven core districts of the Waikato region as geographically described by Statistics New Zealand: Hamilton City, Hamilton district, Waipa, South Waikato, Matamata-Piako, Otorohanga and Waitomo. Patients whose recorded domicile was not in the study area were excluded.

Data collection

Patient demographics, presenting symptoms and findings at endoscopy were prospectively recorded on the gastrointestinal haemorrhage database. Medication history was collected retrospectively from the paper clinical record and included use on admission of a proton pump inhibitor or anticoagulant (warfarin, aspirin, clopidogrel or dipyridamole), and non-steroidal anti-inflammatory drug (NSAID) use within 30 days of admission. Helicobacter pylori status was also assessed retrospectively, and was interpreted as positive or negative if performed within 30 days of the bleeding event. Testing was performed with serology (Genesis Diagnostics Hp-G ELISA Screen, Product code GD01, Genesis Diagnostics Ltd, Cambridgeshire, United Kingdom), histological examination of biopsy material using a Warthin–Starry stain, a urease test of stomach biopsy tissue using standardised urea broth (Fort Richard Laboratories Ltd, Auckland, NZ) or H. pylori faecal antigen testing (Hp StAR amplified IDEIA, Code: K663011, Oxoid Limited, Hampshire, United Kingdom).

Age, sex and ethnicity data for each patient were obtained from the hospital’s electronic patient information system, and matched to our cohort by National Hospital Index number, date of birth and surname.

Baseline demographic data for the study region were obtained from the statistics NZ website. Data taken from the 2006 census were used as the denominator to assess the influence of sex and ethnicity on incidence, and data from the 2001 and 2006 censuses were used to assess temporal trends in incidence. Demographic data were stratified by sex, ethnicity and age.

Statistics

Statistical analysis was performed using the R statistical computing environment. Crude incidence was calculated per 100 000 adults aged 15 and over. For assessment of temporal trends, the first half of the study period (17 March 2001–29 December 2005 using 2001 census data to define the at risk population) was compared with the second half of the study period (29 December 2005–12 October 2010 using 2006 census data to define the at risk population). To allow comparison between demographic groups with different age structures, incidence was adjusted to the World Health Organization (WHO) world standard population. Comparison of crude and age-adjusted incidence (AAI) rates between different demographic groups was made using Rate.Ratio test in R. Proportions of patients with risk factors for UGIH were compared between demographic groups using Prop.test in R, as were proportions of patients with each endoscopic diagnosis. This allowed association analysis between demographic parameters and risk factors for UGIH.

Results

Two thousand and eighty-nine bleeding events were recorded in the gastrointestinal haemorrhage database. Seven hundred and twenty-nine were excluded, and 1360 included in the final dataset (Fig. 1). Nine hundred and ninety nine patients (73%) identified as NZ
European, 268 (20%) Maori and 93 (7%) as other ethnicity. Eight hundred and four (59%) were male.

The adult population (those aged 15 or older) of the study region in 2006 was 239,690. Crude incidence over the 10-year study period was 59.2 per 100,000 adults per year. Incidence adjusted to the WHO standard population was 46.4. Incidence increased markedly with increasing age (Fig. 2).

Crude incidence stratified by ethnicity was not significantly different, while AAI was 2.5 times higher in Maori (Table 1, Fig. 2). Crude and AAI was 1.5 and 1.7 times higher respectively in males compared with females.

Figure 2. Incidence of upper gastrointestinal haemorrhage (UGIH) stratified by (a) age, (b) by age and ethnicity (Maori (n = 268), NZ European (n = 999)), (c) by age and sex (male (n = 804), female (n = 556)), and (d) by age and study period (2001–2005 (n = 694); 2006–2010 (n = 666)) (Error bars show 95% confidence interval).
Crude incidence was lower in the second half of the study period, and AAI significantly so (Table 1). This difference was most apparent in patients 60 years or older (Fig. 2).

The proportion of patients receiving each diagnosis, comparing Maori to NZ European, male to female, and the first and second part of the study period, is shown in Table 2. Of note, the proportion of Maori with gastric ulceration was significantly higher compared with NZ Europeans, and the proportion of males with duodenal ulceration was significantly higher compared with females. There was an increase in diagnosis of oesophageal or gastric varices over the study period.

One hundred and forty-five out of 268 (54%) of Maori and 500/999 (50%) of NZ Europeans were tested for *H. pylori* infection. For those tested, Maori had higher rates of *H. pylori* infection in comparison to NZ Europeans (59/145, 40.7% vs 122/500, 24.4%, *P* < 0.001). Maori had lower rates of aspirin use (93/268, 34.7% vs 488/999, 48.8%, *P* < 0.001). Males had lower rates of proton pump inhibitor (PPI) use (174/804, 22% vs 163/556, 29%, *P* = 0.014). The proportion of patients taking warfarin (81/694, 12% vs 120/666, 18%, *P* = 0.001) and clopidogrel (4/694, 0.6% vs 19/666, 2.8%, *P* = 0.011) increased significantly over the course of the study period, while there was a trend towards increased aspirin use (297/694, 43% vs 318/666, 48%, *P* = 0.07).

**Discussion**

**Incidence**

The incidence of UGIH in the population observed in this study is at the lower end of the spectrum of published figures. The wide range of published incidence figures for UGIH is due in part to differing study methodology. Our methodology, relying on identification of bleeding events through referral for endoscopy, may have led to an underestimation of true incidence. This method of patient selection will not record episodes of UGIH occurring in patients who do not present to hospital or in patients who present to hospital but are not referred for endoscopy. However, this method of case ascertainment has advantages over collection of UGIH events through discharge coding. Patients with a dubious UGIH event (e.g. suspected haematemesis with coffee ground vomitus, or positive faecal occult blood testing) may be recorded as having had UGIH on discharge coding. This is especially true in institutions where there is financial or other incentive to code multiple diagnoses for each admitted patient.

We performed an analysis of recorded UGIH by discharge coding in our hospital over the same time period as our study. This recorded a crude incidence of UGIH of 89.4, 50% higher than that recorded in our study. We believe that the difference between the two figures is likely to be the result of two factors: the presence of patients with UGIH who were not referred for endoscopy,
and the presence of patients without clear evidence of clinically significant UGIH who received this discharge code.

Patients who suffered UGIH and attended a distant hospital because they were away from home will not have been recorded in our study, and will have contributed to an underestimation of true population incidence. Eleven per cent (166 of 1526) of UGIH events in our dataset were in patients who lived outside our hospital’s catchment area, giving an approximate estimate of this error.

Reported incidence figures vary depending on the definition of the population at risk. Studies using the entire population tend to report lower incidence figures, while those using an ‘adult’ population over a cut-off age of between 15 and 20 tended to report higher incidence figures. Incidence of UGIH in children is significantly lower than in adults, and children make up a significant proportion of the population. In our study region in 2006, 24.7% of the population was less than 15 years of age, and inclusion of children in the at-risk population would have reduced estimation of incidence by approximately 25%. Despite the exclusion of children, the incidence we have observed is still at the lower end of the published range.

**Incidence in Maori**

AAI of UGIH was significantly higher in Maori, and increased rates of *H. pylori* infection and gastric ulceration were associated with this difference. *H. pylori* testing was compromised in our study – only 50% of patients had testing performed, and four different methods of testing were used. Additionally, urease tests taken during episodes of UGIH have previously been described as having a reduced sensitivity to *H. Pylori* infection. The incidence of *H. pylori* in Maori is lower than published rates in NZ ethnic groups of 35.8% (NZ European adults) and 57.4% (Maori adults). Despite these limitations, we feel the *H. pylori* results give useful insight into the aetiology of UGIH in Maori.

The difference in incidence could be attributed to genetic or environmental factors. Maori undergo poor in measures of education, income and life expectancy in comparison to the NZ European population. The higher rate of *H. pylori* infection in Maori is consistent with higher observed rates in other indigenous populations. *H. pylori* infection has previously been negatively correlated with socio-economic status, an association that may be due in part to higher *H. pylori* infection rates in deprived populations.

There was no difference in NSAID medication use between Maori and NZ Europeans, and Maori had a lower rate of aspirin use. Maori had a higher incidence of warfarin use that could plausibly be considered to be causally associated with an increased incidence of UGIH, but not with gastric ulceration.

The genotype of *H. pylori* prevalent in Maori (hpMaori) differs from that in Europe (hpEurope). Previous efforts to identify differing prevalence of virulence factors in *H. pylori* isolated from NZ Europeans and Polynesians (including Maori) demonstrated similar CagA levels by immunoblot, and higher cytotoxic VacA levels in *H. pylori* strains isolated from Polynesians. VacA-producing strains of *H. pylori* are associated with duodenal ulceration, and a higher prevalence of VacA-producing *H. pylori* strains among Maori is unlikely to explain the observed increased rate of gastric ulceration.

*H. pylori* infection has been more strongly associated with duodenal ulceration than with gastric ulceration. Our Maori cohort had an increased incidence of gastric and not duodenal ulceration, despite a higher proportion of *H. pylori* infection. The typical distribution of *H. pylori* infection associated with duodenal and gastric ulceration differs. Duodenal ulceration is associated with predominantly gastric antral infection and consequent hypersecretion of acid from the gastric body. Gastric ulceration is associated with infection of the entire body of the stomach, and low or normal acid secretion. Genetic or environmental factors may predispose to differing patterns of infection in Maori, and may explain the unusual predominance of gastric ulceration despite high *H. pylori* infection rates. Further research in this area may identify unrecognised contributors to the pathogenesis of gastric ulceration.

Maori have been shown to have high rates of intestinal metaplasia and gastric cancer, both associated with *H. pylori* infection. A significant proportion of gastric cancer in Maori is histologically diffuse. This study shows that in addition to increased rates of gastric cancer, there is an increased rate of gastric ulceration in Maori. Although unlikely to be part of the sequence of diffuse gastric cancer development, a higher rate of gastric ulceration in Maori is likely to be a related phenomenon, similarly consequent to chronic inflammation of the gastric mucosa.

**Incidence in males**

UGIH incidence was higher in males, as observed in previous studies. Male UGIH was associated with a significantly higher rate of duodenal ulceration, and a lower rate of PPI use.

The most likely explanation for a difference in UGIH and duodenal ulcer incidence between sexes is the modifying effect of sex hormones on ulcer formation and healing.
In animal studies, exogenous administration of oestrogen and progestogen has been shown to protect against ulcer formation, while testosterone administration aggravates it.25,26

Temporal trends in incidence

The incidence of UGIH has decreased over the past 20 years.3,12 Accepted risk factors include aspirin use, clopidogrel use, NSAID use,27 anticoagulation with warfarin28 and *H. pylori* infection,29 while PPI use is protective.25 Temporal alteration in prevalence of these factors may have contributed to the observed decrease. PPI use has increased over this time period30; however, aspirin use30 and warfarin use31 have also increased. Additionally, the incidence of UGIH is known to increase sharply with age, and our ageing population should contribute to an increasing crude (but not age adjusted) rate.

In our study, despite ageing of our population, crude incidence of UGIH reduced over the study period by 11%. This reduction was associated with an increase in warfarin and clopidogrel use, and a trend towards increasing aspirin use. There was no significant change in *H. pylori* infection rate, NSAID use or PPI use. It is likely that as the population ages further, there will be further increases in antiplatelet and anticoagulant use. The interplay of these factors is complex and it is not immediately evident whether incidence rates are likely to continue to decrease, or to increase with time.

Study limitations

This study has several limitations. First, incidence in our study may have been underestimated due to case ascertainment bias, and non-capture of bleeding events that occurred in our population while outside of our hospital’s catchment area. Second, endoscopic diagnosis was a subjective interpretation made by the 20 individual endoscopists performing endoscopy over the 10 years of the study. Last, retrospective collection of medication history from the clinical record is known to be inaccurate, particularly regarding NSAID use.

Conclusion

AAI of UGIH in the Waikato region was 46.4. This was significantly higher in Maori, in males, and decreased over the study period. Maori were noted to have higher rates of *H. pylori* infection and gastric ulceration. These data will provide a comparison for future assessment of trends in UGIH.

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References


Baseline characteristics and management of patients with atrial fibrillation/flutter in the emergency department: results of a prospective, multicentre registry in China

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Key words atrial fibrillation, risk factor, CHADS2 score, anticoagulation, anti-arrhythmic agent.

Abstract

Background/Aim: There have been several studies of atrial fibrillation (AF) over the past decades; however, data from Chinese patients are scarce. The aim of the study was therefore to describe the patient characteristics, risk profile and management strategies for Chinese AF patients presenting to emergency department (ED).

Methods: We conducted a prospective, multicentre registry of patients with AF or atrial flutter (AFL) in China. Participants were enrolled at 20 EDs, then data regarding baseline characteristics and treatment in EDs were collected.

Results: Of the 2016 Chinese patients, 1104 (54.8%) were female. Six hundred eighteen (30.7%) had paroxysmal AF, 452 (22.4%) had persistent AF and 945 (46.9%) had permanent AF. The most common comorbidity was hypertension (55.5%), followed by coronary artery disease (41.8%) and heart failure (HF, 37.4%). The prevalence of concomitant cardiovascular risk factors, such as HF and valvular heart disease, increased as AF progressed. Among the patients with non-valvular AF, 110 (12.7%) of those with CHADS2 (congestive HF, hypertension, age of 75 years and greater, diabetes mellitus and history of stroke) ≥ 2 were prescribed oral anticoagulants (OAC), while 119 (15.6%) of those with CHADS2 < 2 received such agents. Among the 324 patients with valvular AF, 134 (41.4%) actually were treated with OAC. The international normalised ratio value was within the target range (2.0–3.0) in 96 patients only (26.4%). Moreover, a total of 16.2% of the patients received ≥ 1 anti-arrhythmic agents, whereas rate control agents were used more frequently (68.4%).

Conclusions: According to the present study, the risk profile and management of Chinese patients with AF/AFL differed from that observed in previous studies. The use of OAC inadequately deviate from current guidelines.

Introduction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia and carries an increased risk of stroke, hospitalisation and mortality.1 In China, approximately 0.61% of the population suffered from AF, with an absolute number of cases of approximately 8 million.2 With ageing of the population, the prevalence of AF will rise by at least 2.5-fold by the year 2050.3,4 Accordingly, emergency department (ED) visits for AF is on the rise and can be expected to increase further.4

Over the past decades, many studies about AF have been conducted in Europe and North America,5 while there are few studies regarding the prevalence, risk profiles and treatment of AF in China.6,7 Furthermore, the management of AF in the ‘real world’ often lags behind evidence-based guidelines8 and differs greatly from the highly specific clinical trials.9,10 This study is the first observational, prospective study to describe the baseline characteristics, risk profiles and management of Chinese AF patients presenting to the ED.
Methods

This study was an observational, prospective, ED-based registry conducted in China. Consecutively, patients were enrolled when presenting to an ED with AF or atrial flutter (AF/AFL) as the primary or secondary diagnosis. AF/AFL was documented at enrolment using electrocardiogram, Holter monitoring, rhythm strips or pacemaker electrograms. Patients already participating in this registry or other studies were excluded.

A total of 20 investigator sites in China participated in this registry (See Appendix I). Registry sites included all the 13 centres participating in the Randomized Evaluation of Long-term anticoagulant therapY (RE-LY) study and seven other hospitals in China. The investigators were trained with regard to patient screening, enrolment and follow up. The central administrative office of the study was located at Fuwai Hospital, Beijing.

Independent ethics committee and hospital-based institutional review board approvals were obtained. The registry was conducted in accordance with the Declaration of Helsinki and local regulatory requirements. All patients provided their written informed consent for study participation, which was obtained in person by study personnel. No specific treatments, tests or procedures were mandated or withheld, and all patients were free to withdraw from the registry at any time.

Data collection

The clinical data were collected from a review of the patients’ ED charts and electronic medical records, as well as contact with patients and their treating physicians, including patient demographics, concomitant cardiovascular risk factors, management strategy in the ED and prior procedures and/or devices. The CHADS2 (congestive heart failure (HF), hypertension, age of 75 years and greater, diabetes mellitus (DM) and history of stroke) score was calculated to estimate risk of stroke in patients with non-valvular AF (NVAF). For patients on oral anticoagulants (OAC), the three most recent international normalised ratio (INR) values prior to the ED visit were collected and presented as the proportion of results between 2.0 and 3.0. All data were entered on specially designed case report forms (CRF) and faxed to Fuwai Hospital. On-site data quality control was performed by study monitors by reviewing 15% of the completed CRF against patient source documents. In addition, data entry quality control was performed by a supervisor through reviewing the electronic data of 5% random sample of patients against the paper CRF.

The results of the registry were reported in accordance with the STrengthening the Reporting of Observational studies in Epidemiology statement (www.strobe-statement.org).

Statistical analysis

The data were presented as absolute numbers and percentages for qualitative variables. Unless otherwise stated, population characteristics were summarised as the mean and standard deviation for continuous variables. Continuous variables were compared using an independent \( t \)-test, while dichotomous variables were compared using the Chi-squared test. A two-sided level of 0.05 was considered to be statistically significant. The statistical analyses were performed using the SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics on admission

Between November 2008 and October 2011, a total of 2016 patients was enrolled at 20 sites. AF was the presenting arrhythmia in 1961 (97.2%) patients, with AFL observed in 54 (2.7%) patients. At enrolment, the AF/AFL was paroxysmal in 618 patients (30.7%) and persistent in 452 patients (22.4%), while permanent in 945 patients (46.9%) were diagnosed with permanent AF and the type of AF/AFL was not available in one patient.

The characteristics of the 2015 patients included in the registry are shown in Table 1 according to the AF/AFL type. The mean age of the population was 68.5 years, and 1104 (54.8%) were female. The mean age and systolic blood pressure were highest among the permanent AF/AFL patients (\( P = 0.003 \)), while the body mass index was highest among those with paroxysmal AF/AFL (\( P < 0.001 \)).

Comorbidities and risk factors

Concomitant comorbidities and risk factors were shown in Table 1 according to types of AF/AFL. Hypertension was the most prevalent comorbidity, with a prevalence of 55.5%, followed by coronary artery disease (CAD, 41.8%) and HF (37.4%). The prevalence of hypertension and DM was similar among the groups, whereas patients with permanent AF/AFL had more comorbidities. The prevalence of CAD, HF, valvular heart disease (VHD) and stroke or transient ischaemic attack all increased in a stepwise fashion from paroxysmal to persistent to permanent AF/AFL.

Stroke risk and antithrombotic treatment

The distribution of the CHADS2 scores for the NVAF patients is shown in Table 2 according to the types of
AF/AFL. Overall, the average CHADS2 score was 1.9 ± 1.4 for the NVAF patients and increased as the severity of AF/AFL progressed from paroxysmal to permanent (P < 0.001). In addition, the proportion of patients with a CHADS2 score of ≥2 raised increased from 42.9% to 47.8% to 66.0% respectively (P < 0.001).

Stroke prevention remains one of the primary treatment goals in patients with AF/AFL. In this registry, 60 patients with documented contraindications (prior major bleeding events or haemorrhagic stroke) were excluded from the analysis of antithrombotic therapy. A total of 324 (16.6%) of the remaining 1956 patients had valvular AF (VAF) and required anticoagulation; however, only 134 (41.4%) received OAC, and no differences were observed in the antithrombotic treatment across the type of AF/AFL (Table 3).

**Table 1** Baseline characteristics and risk factors of patients according to types of AF (%)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Paroxysmal</th>
<th>Persistent</th>
<th>Permanent</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>2016 (100)</td>
<td>618 (30.7)</td>
<td>452 (22.4)</td>
<td>945 (46.9)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD) (years)</td>
<td>68.5 (13.3)</td>
<td>67.0 (13.6)</td>
<td>67.4 (13.8)</td>
<td>69.9 (12.7)</td>
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<td>Female (%)</td>
<td>54.8</td>
<td>53.6</td>
<td>54.4</td>
<td>55.8</td>
<td>0.682</td>
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<tr>
<td>SBP, mean (SD) (mmHg)</td>
<td>131.8 (23.5)</td>
<td>129.8 (22.9)</td>
<td>130.8 (22.0)</td>
<td>133.7 (24.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>DBP, mean (SD) (mmHg)</td>
<td>79.9 (14.9)</td>
<td>78.9 (13.8)</td>
<td>80.2 (14.2)</td>
<td>80.4 (15.8)</td>
<td>0.147</td>
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<tr>
<td>HR, mean (SD) (b.p.m.)</td>
<td>101.7 (29.4)</td>
<td>105.8 (30.3)</td>
<td>109.8 (30.9)</td>
<td>95.2 (26.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI, mean (SD) (kg/m²)</td>
<td>23.5 (3.6)</td>
<td>24.0 (3.4)</td>
<td>23.5 (3.6)</td>
<td>23.2 (3.7)</td>
<td>&lt;0.001</td>
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</table>

**Comorbidities and risk factors**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Paroxysmal</th>
<th>Persistent</th>
<th>Permanent</th>
<th>P-value</th>
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</thead>
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<tr>
<td>Hypertension</td>
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<td>57.6</td>
<td>51.5</td>
<td>56.0</td>
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<td>Myocardial infarction</td>
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<td>7.1</td>
<td>5.3</td>
<td>8.5</td>
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<td>Coronary artery disease</td>
<td>41.8</td>
<td>37.7</td>
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<td>46.9</td>
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<td>Heart failure</td>
<td>37.4</td>
<td>18.4</td>
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<td>&lt;0.001</td>
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<td>Valvular heart disease</td>
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<td>&lt;0.001</td>
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<td>1.8</td>
<td>2.6</td>
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<td>0.8</td>
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<td>0.4</td>
<td>0.4</td>
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<td>2.2</td>
<td>4.2</td>
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<td>3.8</td>
<td>3.2</td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15.5</td>
<td>14.7</td>
<td>14.6</td>
<td>16.4</td>
<td>0.563</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td>5.2</td>
<td>6.6</td>
<td>5.2</td>
<td>4.4</td>
<td>0.021</td>
</tr>
<tr>
<td>Current smoking</td>
<td>21.5</td>
<td>20.7</td>
<td>24.3</td>
<td>20.6</td>
<td>0.246</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; b.p.m, beats per minute; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack.

AF/AFL. Overall, the average CHADS2 score was 1.9 ± 1.4 for the NVAF patients and increased as the severity of AF/AFL progressed from paroxysmal to permanent (P < 0.001). In addition, the proportion of patients with a CHADS2 score of ≥2 raised increased from 42.9% to 47.8% to 66.0% respectively (P < 0.001).

Stroke prevention remains one of the primary treatment goals in patients with AF/AFL. In this registry, 60 patients with documented contraindications (prior major bleeding events or haemorrhagic stroke) were excluded from the analysis of antithrombotic therapy. A total of 324 (16.6%) of the remaining 1956 patients had valvular AF (VAF) and required anticoagulation; however, only 134 (41.4%) received OAC, and no differences were observed in the antithrombotic treatment across the type of AF/AFL (Table 3).

**Table 2** Distribution of CHADS2 score in NVAF patients across different types of AF

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Overall</th>
<th>Paroxysmal</th>
<th>Persistent</th>
<th>Permanent</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 ≥2 (%)</td>
<td>53.8</td>
<td>42.9</td>
<td>47.8</td>
<td>66.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distribution (%)</td>
<td>0</td>
<td>16.5</td>
<td>23.4</td>
<td>20.9</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>29.7</td>
<td>33.7</td>
<td>31.3</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24.3</td>
<td>21.5</td>
<td>25.7</td>
<td>25.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>15.3</td>
<td>12.1</td>
<td>11.2</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>9.0</td>
<td>7.1</td>
<td>6.9</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4.3</td>
<td>2.1</td>
<td>3.8</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.8</td>
<td>0.3</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

CHADS2 score indicates a risk score for stroke, including congestive heart failure, hypertension, an age of >75 years, diabetes mellitus (1 point), and previous stroke or transient ischaemic attack (2 points). AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation; SD, standard deviation.
Based on current guidelines, NVAF patients with a CHADS₂ score of ≥2 are candidates for anticoagulation. In this registry, however, the proportion of such patients was only 12.7%, which was lower than that of patients with a CHADS₂ score <2 (15.6%). Furthermore, there were no relationships between oral anticoagulation treatment and the subset of AF among the NVAF patients with a CHADS₂ score ≥2 (P = 0.857), and, conversely, among the NVAF patients with a CHADS₂ score <2 (P = 0.031) (Table 4).

Of the 363 patients treated with OAC, INR measurements were obtained in 254 patients (70.0%). The INR values ranged from 0.9 to 5.4, with an average value of 1.9 ± 0.6. Although the INR value was within the therapeutic range (2.0–3.0) only in 96 patients (26.4%), the proportion of patients with an INR of <2.0 was as high as 40.5%.

**Rhythm control and rate control**

Only six patients (0.3%) underwent electrical cardioversion in the ED. In addition, 357 (17.7%) of the patients used anti-arrhythmic drugs (AAD) (propafenone, 4.2%; amiodarone, 12.5%), whereas rate control agents were more frequently prescribed to 1378 (68.4%) patients.

The distribution of AAD and rate control agents according to the type of AF/AFL is shown in Figure 1. Approximately one sixth (16.2%) of the patients received at least one AAD. Amiodarone and propafenone were both more frequently used in patients with paroxysmal AF/AFL than in those with persistent or permanent AF/AFL (P < 0.001).

Approximately one half of the patients received heart rate-lowering beta-blockers, while verapamil or diltiazem, and digitalis were used in 6.6% and 35.7% of the patients respectively. Beta-blockers and digitalis were more commonly prescribed for patients with permanent AF, while verapamil or diltiazem was used regardless of the type of AF (P = 0.614).

**Discussion**

This ED-based registry provides a unique snapshot of the characteristics, risk profile and initial management of different types of AF in daily practice in China. The main findings can be summarised as follows: (i) Chinese patients with AF/AFL seem to have multiple comorbidities, including hypertension, CAD and HF, with an increase in the prevalence of comorbidities as the severity of AF progressed from the paroxysmal to the persistent and permanent forms. (ii) A total of 41.4% of the VAF patients received OAC. Among the NVAF patients with CHADS₂ ≥2, this rate was as low as 12.5%, whereas 15.9% of the NVAF patients with CHADS₂ <2 used OAC. In addition, the INR value reached the therapeutic range (2.0–3.0) merely in only 26.4% of the patients who treated with OAC. (iii) Rate control agents were prescribed more frequently than AAD, especially in those with

<table>
<thead>
<tr>
<th>Table 3 Antithrombotic treatment in VAF patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Patients with VAF (n = 324)</td>
</tr>
<tr>
<td>OAC</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

OAC, oral anticoagulants; VAF, valvular atrial fibrillation.

<table>
<thead>
<tr>
<th>Table 4 Antithrombotic treatment in patients with NVAF and different CHADS₂ score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>NVAF patients with CHADS₂ score ≥2 (n = 869)</td>
</tr>
<tr>
<td>OAC</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>NVAF patients with CHADS₂ score &lt;2 (n = 763)</td>
</tr>
<tr>
<td>OAC</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

CHADS₂, congestive heart failure, hypertension, age of 75 years and greater, diabetes mellitus and history of stroke; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulants.
permanent AF/AFL, while the latter agents were chosen more frequently to convert paroxysmal AF/AFL.

**Patients characteristics, risk factors and comorbidities**

Several studies of AF have been published over the past decades; however, the participants in these trials included highly selected inpatient or office-based populations, especially in Europe and North America. This registry is the first prospective, multicentre, observational study conducted in China.

According to our results, Chinese AF patients were more likely to have multiple comorbidities, including hypertension, CAD, HF and so on. However, the prevalence of hypertension was lower than that in the Real-life global survey evaluating patients with AF trial (72.2%)\(^{11,12}\) and in the Central Registry of the German Competence NETwork on Atrial Fibrillation study,\(^5\) but higher than that in Chinese AF patients between 1999 and 2001 (40.3%). As we know, VHD is an important underlying cause of AF/AFL. Interestingly, VHD was present in 15.8% of the patients in this registry, which was substantially greater than that observed in other studies. However, the proportion is less than that in a previous study in China, which might reflect the lower socioeconomic status of the Chinese population.\(^{13}\) Similar to the finding of previous studies, the prevalence of risk factors and comorbidities increased as the severity of AF/AFL progressed from the paroxysmal to the persistent and permanent forms.\(^{11}\)

In summary, our findings confirm a unique risk pattern of Chinese AF/AFL patients, which is, to some extent, different from that noted in European and American patients, as well as in Chinese patients 10 years ago.

**Stroke risk and antithrombotic treatment**

The risk of stroke is often assessed based on the CHADS\(_2\) score in patients with NVAF. In this study, the CHADS\(_2\) scores of the Chinese patients (1.9 ± 1.4) were similar to those observed in previous real-world practice.\(^{5,11}\) In the
present study, OAC were used in 12.7% of the NVAF patients with a CHADS2 score of ≥2, who were eligible for oral anticoagulation therapy. These rates are much lower than those reported from the US,14 Canadian15 and European16 studies, and similar to those found in previous studies conducted in mainland China and Taiwan.17,18 The low rate of OAC usage in China might be due to concerns regarding excess bleeding related to the narrow safety window and the need for frequent dose adjustment to maintain optimal INR. In contrast, OAC were given to 15.6% of the NVAF patients with a CHADS2 score of <2. However, a large proportion of these patients were also likely eligible to receive OAC when applying the novel CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled)-vascular disease, age 65–74 and sex category(female)) score,1 an issue that should be further assessed in a future study.

In addition, a total of 324 VAF patients was considered to be at high risk for stroke and was mandated to receive anticoagulation therapy. However, only 41.4% of VAF patients were actually treated with such agents, while 57.1% of these patients received antiplatelet drugs, despite that these medications are substantially less effective than OAC.19 These medications were also inappropriately underutilised and their prescription deviated from guidelines, which may have resulted in suboptimal stroke prevention.

It has been reported that only an appropriate target INR range (2.0–3.0) provides a net clinical benefit for stroke prevention in patients with AF.20 However, in the present study, only 96 of 363 patients who received OAC exhibited an INR value within the therapeutic range, which was speculated to be associated with thromboembolic complications.

Thus, all the data above underscore a huge gap between clinical practice and guideline recommendations regarding the prevention of stroke due to AF. Immediate steps are necessary to promote the prophylaxis of thromboembolism in China.

Use of AAD and rate control agents

A rhythm control strategy has not been reported to result in greater survival benefits than a rate control strategy in patients with AF,21 and current guidelines recommend that clinicians choose the proper treatment based on the patient’s symptomatic status. Generally, rhythm control strategy was recommended to be used in symptomatic patients with AF.8 However, in daily practice, factors other than symptoms often influence the choice of treatment.11,22 In this registry, rate control agents were used more than AAD in Chinese AF/AFL patients. Potential explanation for this variability includes different populations and settings, the type of AF/AFL and understanding of the guidelines.3 In addition, in this registry, rhythm control strategy was more likely to be used in patients with paroxysmal AF, and rate control agents were prescribed to lower heart rate in patients with permanent AF.11

Limitations

Patients were enrolled in different centres with various levels of medical care in the registry to avoid bias; however, most of these patients were recruited from large academic hospitals. In addition, the CHA2DS2-VASc score is a novel risk score for identifying low-risk subjects and has a better predictive value for stroke; however, we did not collect data regarding the history of peripheral vascular disease or calculate the CHA2DS2-VASc score in this survey.

Conclusions

According to this prospective observational registry, Chinese patients with AF/AFL were found to be likely to have multiple comorbidities, such as hypertension, CAD and HF, especially in patients with permanent AF/AFL. Nevertheless, the risk profile observed in this study is not similar to that noted in clinical trials and registry studies performed in other countries. OAC were inadequately used for stroke prevention, and rhythm control or rate control strategy was not strictly chosen based on current guidelines.

Acknowledgement

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References


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Appendix I

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Lean mass modulates glomerular filtration rate in males of normal and extreme body composition

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Key words
glomerular filtration rate, lean mass, chronic kidney disease.

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Abstract

Background: Understanding determinants of glomerular filtration rate (GFR) is important in aiding prediction and interpretation of kidney function. Body composition is known to affect GFR but is not included in current screening of kidney disease. We investigated the association between GFR and body composition in healthy young men with differing body mass but without known diabetes or kidney injury.

Methods: Three groups were recruited: normal BMI (n = 22) with a body mass index (BMI) < 25 kg/m², muscular (n = 23) with BMI ≥ 30 kg/m² and bioelectrical impedance body fat ≤ 20% and obese (n = 22) with BMI ≥ 30 kg/m² and bioelectrical impedance body fat ≥ 30%. Dietary analyses, GFR clearance by 99m Tc-DTPA, urine protein and body composition by dual-energy X-ray absorptiometry were measured in all participants. Linear and nonlinear associations of constituents of body composition with GFR were assessed.

Results: Muscular men had a higher GFR (mean 186.4 mL/min; 95% CI 171.7–201.1) than normal BMI and obese groups (P = 0.0007). Urine protein and albumin excretion were not elevated in any participants. On multiple regression analysis (r² = 0.60), the variables with strong associations with GFR were age (P = 0.0009) and lean mass (P = 0.0001). Fat mass, protein intake and smoking status were not associated. Skeletal muscle mass correlated significantly with GFR in all subgroups.

Conclusion: Age and lean mass were strong determinants of GFR. Estimates of GFR should therefore be indexed to an estimate of lean mass.

Introduction

Insight into the factors affecting glomerular filtration rate (GFR) in subjects without kidney disease may assist with separating normal from abnormal kidney function and this may help provide strategies for prevention.

Although not entirely understood, in subjects with obesity, renal structure and function have been shown to be progressively altered. Several studies showed an association between obesity and glomerular hyperfiltration,1 chronic kidney disease (CKD)2 and end-stage renal failure.3 Glomerular hyperfiltration, signified by increases in GFR, often predicts development of nephropathy in patients with type 1 diabetes.4 Different mechanisms of hyperfiltration are postulated.5–7 In diabetes, the chain of events includes incremented glomerular intracapillary pressure and glomerulosclerosis with subsequent loss of GFR.

Hyperfiltration in obese individuals diminishes after a reduction in bodyweight,8,9 suggesting body composition may be involved in the regulation of GFR. However, it is not certain whether a reduction in lean or fat mass reduces hyperfiltration to normal levels. Current guidelines do not address how hyperfiltration should be incorporated into CKD screening.

Two important concepts regarding the effect of body composition on kidney function warrant investigations. First, although not widely documented, several studies have shown that lean mass is correlated with GFR.10–13 Second, there is growing evidence that normalising GFR to body surface area (BSA) may not be entirely appropriate as humans have a fixed number of nephrons that must increase filtration in order to meet the demands of body size.7 Therefore accuracy of prediction equations in estimating GFR is questionable especially for those with...
extremes of body size. This is crucial in clinical practice for purposes such as drug dosing, which is often guided by an estimate of GFR.

We therefore aimed to investigate the differences in GFR in subjects with different body compositions and to evaluate independent variables associated with GFR measured by 99m Technetium-diethylene triaminepentaacetic acid (DTPA). As the relative effects of fat versus lean mass on GFR are unknown, we also examined the hypothesis that body composition modulates GFR in healthy people.

Methods

Subjects

The study was given ethical approval by the Upper South B Ethics Committee (reference number: URB/09/051). We recruited age-matched males with ‘normal body composition’, and males with extremes of body composition, particularly those with an increased muscle mass, and those with a high body fat.

Participants were screened for body mass index (BMI) and body fat percentages by bioelectrical impedance (BIA) using a TANITA fat analyser scale. BMI was calculated using the formula, weight divided by height squared (kg/m²), and characterised using the World Health Organization’s definition of BMI reference range as: ‘normal’ BMI (BMI = 18.5–25 kg/m²) (n = 22); ‘muscular’ (BMI ≥ 30 kg/m², with a BIA body fat of <20 %) (n = 23); and ‘obese’ groups (BMI ≥30 kg/m², with a BIA body fat of >30%) (n = 22). Participants with known diabetes or thyroid dysfunction or unsuitable BMI or body fat percentages were excluded.

Tc-DTPA GFR, a 4-hour urine collection, dietary intake and body composition by dual-energy X-ray absorptiometry (DEXA) analysis were subsequently undertaken for all eligible participants. Values of GFR were reported as raw measured values (mL/min) and adjusted for body surface area (BSA) (mL/min/1.73 m²) by the Du Bois–Du Bois method.14 Samples were analysed for plasma and urine creatinine, cystatin C, high-sensitivity C-reactive protein, urine protein and urine albumin, and the results for the plasma samples were described elsewhere.15

Urine measurements

Urine protein and albumin concentrations were measured by immunoturbidimetric assays (Roche Diagnostics, Indianapolis, IN, USA). These were undertaken to confirm that participants were free from kidney dysfunction according to current guidelines.16

Dietary analysis

All eligible participants were asked to complete a 4-day diet record prior to the second study visit. Participants were asked not to change their habitual diet consumption, to estimate the quantities eaten using a combination of photographs and household measures,17 and to supply information on the intake of dietary supplements. Nutrient analyses for each participant were undertaken using Foodworks Professional 2009, Version 6.0.2562 (Xyris Software Ltd, Brisbane, Qld, Australia) to access New Zealand FOODfiles 2004 (Crop and Food and Research, Palmerston North, and Ministry of Health, Wellington, New Zealand).

Measurement of lean mass and estimation of skeletal muscle mass

Body composition was determined by DEXA in participants using a GE Lunar Prodigy Scanner (GE Medical Systems, Madison, WI, USA). DEXA determines mass and composition by using dual-energy X-rays and photoelectric absorption, and therefore differentiates between lean mass, fat mass, bone mineral content and regional distribution. Although BIA was used initially to screen participants, DEXA was used for end-point body composition analyses. Regional distributions are shown in Appendix I. The android region was defined as the region around the mid-section of the body, gynoid as the region around the hips and thighs, and appendicular as the combination of arms and legs. Skeletal muscle mass was calculated using the equation of Kim et al., based on appendicular lean tissue mass free of intermuscular fat.18

Statistical analysis

Statistical analyses were undertaken with MedCalc® Version 11.2.1.0 (Mariakerke, Belgium), SPSS (IBM SPSS Statistics for Windows, Version 20.0.0.2, Chicago, IL, USA) and NCSS statistical software (version 07.01.04). GFR distributions were normal using the Kolmogorov–Smirnov test (P = 0.50) and therefore logarithmic data transformation was not done. Multivariate analysis and Bonferroni adjustment for post hoc analysis were performed to determine the significance of differences between variables of interest within the three groups of participants. Linear and nonlinear regressions were determined for each variable plotted against raw GFR. To assess for nonlinearity, scatter diagrams between individual variables of interest versus GFR on the horizontal axis were viewed individually to determine whether a
nonlinear relationship with GFR existed. The SPSS curve fitting menu allowed quick evaluations of linear, quadratic, cubic, inverse, logarithmic and power functions. We assessed $r^2$ values and significance of curve based on the F test, $P$-values and whether the 95% confidence intervals (CI) for the parameter estimates included zero. For variables with a significant $P$-value, and assessed together with estimates differing from zero, we further explored inverse, quadratic and cubic functions.

The association of body composition with GFR was examined using raw GFR results which were uncorrected for BSA. Using the ‘all possible regression’ selection in NCSS, multiple regression analyses were performed to determine variables which had the most significant associations with GFR. This allowed assessment of models which were similar to those performed using forward stepwise regression. After the selection of ‘best fit’ variables, the variables were explored in the model using multiple linear regression analysis. $P$-values < 0.05 were deemed as statistically significant.

**Results**

**Participant characteristics**

The study group consisted of 67 males between 18 and 52 years. The normal BMI group included moderately, often physically active (≤ 3 h of exercise per week) subjects. The muscular group were physically active (at least 4 h of cardiovascular exercise per week), and comprised mainly of bodybuilders, rugby players and other sportsmen. Subjects in the obese group were not actively participating in physical exercise (< 3 h/week). In the whole group, only seven participants were current smokers, with only four smoking more than five cigarettes a day. Thirteen subjects reported the use of medication (no antihypertensive drugs). Table 1 summarises characteristics of the three groups.

Table 1 shows the differences in body composition for the three groups of participants. The muscular group had higher total lean mass: 75.5 kg (95% CI, 72.3–78.6) than the normal BMI: 58.7 kg (95% CI, 55.5–61.9); however, these were not different from those of the obese group: 64.1 kg (95% CI, 60.9–67.3). The obese group had the most body fat: 37.8 kg (95% CI, 35.2–40.3) ($P < 0.0001$). Appendix I further shows the distribution of lean and fat mass for the three groups of participants, and their correlations with GFR. There was no significant association between total lean mass and total fat mass ($r = 0.074$, $P = 0.55$) for the 67 subjects as a whole. Skeletal muscle mass was significantly associated with GFR in all subgroups ($P < 0.05$).

**Body composition results**

Table 1 shows the differences in body composition for the three groups of participants. The muscular group had higher total lean mass: 75.5 kg (95% CI, 72.3–78.6) than the normal BMI: 58.7 kg (95% CI, 55.5–61.9); however, these were not different from those of the obese group: 64.1 kg (95% CI, 60.9–67.3). The obese group had the most body fat: 37.8 kg (95% CI, 35.2–40.3) ($P < 0.0001$). Appendix I further shows the distribution of lean and fat mass for the three groups of participants, and their correlations with GFR. There was no significant association between total lean mass and total fat mass ($r = 0.074$, $P = 0.55$) for the 67 subjects as a whole. Skeletal muscle mass was significantly associated with GFR in all subgroups ($P < 0.05$).
**GFR results**

Interpretation of GFR is based on CKD staging by the National Kidney Foundation (NKF). A GFR > 90 mL/min was considered normal. When GFR was adjusted for BSA (GFR/BSA), the obese and normal BMI groups had similar GFR/BSA results ($P = 0.91$), which were within the expected range (Table 1). The muscular group had a significantly higher GFR/BSA values ($P = 0.0007$) than the other two groups (Table 1). Without adjusting for BSA, the muscular group had the highest GFR, followed by the obese and normal BMI groups ($P < 0.0001$) (Table 1, Fig. 1).

**Urine protein and microalbumin results**

None of the participants had overt proteinuria (urine protein/creatinine ratio > 22.9 g/mol), high urine albumin or impaired kidney function (GFR < 60 mL/min/1.73 m$^2$) by current criteria.16

**Nutrient analyses**

Fifteen subjects reported taking protein supplements (normal BMI – 4, muscular – 10, and obese – 1). For the three groups of participants, percentage energy from protein differed only between the muscular and obese groups ($P = 0.0072$, Table 1). Total fat intake, sodium consumption and water intake were not different amongst the groups (Table 1).

**Determinants of GFR**

GFR correlated with age ($r = -0.33$, $P = 0.005$), weight ($r = 0.57$, $P < 0.0001$), BMI $(0.49$, $P < 0.0001$), skeletal muscle mass ($r = 0.69$, $P < 0.0001$), lean mass ($r = 0.72$, $P < 0.0001$), urine creatinine excretion ($r = 0.32$, $P = 0.009$) and total protein intake ($r = 0.29$, $P = 0.02$) on univariate analyses of the whole cohort (Figs 1,2). Neither total fat nor percentage fat was associated with GFR in the whole cohort or in subgroup analyses (Fig. 3, Appendix I). There...
was no evidence of nonlinearity between variables of interest and GFR in this study cohort, therefore all subsequent multiple regression analyses utilised linear regressions.

Several models were further compared using multiple regression analysis to determine co-variables related to GFR (Table 2). Using the ‘all possible regression’ selection function identified age, total lean mass, truncal fat and gynoid lean mass as the four-variable model with the highest $r^2$ with a value of 0.64 with GFR. Forcing these same variables into a multiple linear regression model with GFR demonstrated that truncal fat ($P = 0.09$) was non-significant. Subsequent remodelling with the remaining three variables, that is, age ($P = 0.003$), lean mass ($P < 0.0001$) and gynoid lean ($P = 0.03$), were well correlated, $r^2 = 0.62$. As gynoid lean and total lean mass are not independent, we excluded gynoid lean as the less significant variable. Subsequent regression analysis yielded a good correlation ($r^2$ of 0.60) between GFR and the model which only included age and lean mass. The final derived multiple regression equation (Eqn 1) was:

$$\text{GFR} = 38.3 - 0.997 \times \text{(Age)} + 2.34 \times \text{(Total Lean Mass)}$$ (1)

We then evaluated the effect of bone mineral content as the ‘other’ body constituent in the above model, together with smoking and taking dietary supplements as categorical variables to predict GFR. Individually and in combination, the observed correlations did not provide a significant enhancement in $r^2$ values. Similarly, neither protein, water nor salt intake added significance to the age and lean mass model.

**Discussion**

The purpose of this study was to investigate whether body constituents and, secondarily, the effect of protein intake, could affect GFR in a population with varying body composition. We purposely chose subjects with normal body composition, together with subjects with extreme muscularity and extreme body fat, to determine the relative effects of lean versus fat mass on GFR. The unique inclusion of controls, muscular and obese subjects in similar proportions demonstrated little overall correlation between lean mass and fat mass ($r = 0.074$). Crucially this allowed clear discrimination between the effects of each ‘independent’ variable in the regression analyses in the whole cohort.

The study revealed that lean mass and age were the most important determinants of raw measured GFR and that this GFR was independent of protein intake and smoking status in a group of healthy young men. The increased measured Tc-DTPA GFR was observed in all study groups, and particularly the increased GFR levels in the obese group decreased to normal levels after normalisation to BSA (Table 1). This observation is clinically important and suggests that the historical practice of indexation of GFR to a BSA of 1.73 m$^2$ is inappropriate in those with extremes of body composition.

A model of age and lean mass only explained for 60% of GFR variance, suggesting other unaccounted-for factors. These may include blood pressure, which may account for the association of increased GFR levels in obese and muscular participants. However, the association of GFR with lean mass in the normal BMI group (Appendix I), considered to be healthy controls and theoretically likely to have normal blood pressure, suggests that lean mass may modulate GFR independently of blood pressure, and the presence of diabetes. The absence of proteinuria or microalbuminuria in the cohort suggests
that the association of lean mass with GFR was also independent of kidney injury.

Although our subjects presented with increased GFR levels which might be considered high, the study was not designed to investigate mechanisms of hyperfiltration. Documented mechanisms of hyperfiltration in other studies include: acute protein intake,\(^{19}\) chronic excessive habitual protein intake\(^{20}\) and androgen usage.\(^{21,22}\) Brenner and colleagues proposed that maladaptive glomerular haemodynamic changes occur in hyperfiltrating subjects in response to a reduction in functional nephron number.\(^{23}\) In most cases, renal structural abnormality is often present,\(^{5,21,22,24-28}\) which may perpetuate disease progression towards kidney dysfunction.

The effect of body composition on renal function has not been extensively investigated. Most studies of obesity have reported crude BMIs, but this parameter does not adequately differentiate body composition. One Japanese study, which included lean thigh volume measured using CT, suggested that lean rather than fat body mass could explain the association between BMI and increased creatinine clearance.\(^{11}\) Urine creatinine excretion declined with Cr-EDTA GFR in obese hyperfiltrating subjects after intestinal bypass surgery for weight loss in the study of Brochner-Mortensen et al.,\(^{8}\) suggesting improvement in GFR was a function of loss of muscle mass. Janmahasatian et al. reported that ‘over’-compensation of GFR (to a lower GFR) was evident in obese individuals after GFR normalised for bodyweight.\(^{29}\) After normalising GFR data against lean mass, no apparent difference in GFR between obese and control individuals was present, leading the authors to conclude that renal function is more closely related to lean body mass than fat mass.\(^{29}\) Similarly, correcting GFR to BSA in our obese participants inherently under-estimated high levels of measured GFR to normal levels. Delanaye et al. have criticised the practice of indexing GFR to BSA,\(^{30}\) and explained that ‘the higher the weight, the higher the BSA and the indexed GFR will decrease’. This calls for other types of correction to GFR, particularly an index that could consider the kidney’s role in regulating body fluid.

A recent report suggests that GFR is related to body fat distribution, and that central adiposity is associated with lower GFR.\(^{31}\) However, that study used waist-to-hip measurements as surrogates of central adiposity rather than direct measurements. Our study does not support the suggestion that central adiposity, defined by android and gynoid fat mass, is associated with GFR, nor did the ratio of android to gynoid fat mass (results not shown). Our data suggest that lean mass exerted a greater influence on GFR than any other variable as shown in the multiple regression analyses. We hypothesise that there is an important link between lean mass and GFR. First, a relationship between skeletal muscle mass and GFR in normal healthy people may exist through fluid balance. In compartmental models of body composition analysis, fat free mass compartments are divided into three basic physiological compartments: body cell mass, extracellular volume and extracellular solids.\(^{12}\) The association between skeletal muscle mass and extracellular volume in our study participants was \(r^2 = 0.47\) (\(P < 0.001\)). This association supports the idea that lean mass, which includes skeletal muscle together with the contained significant blood volume, can modulate GFR through renal fluid regulation. Teleologically, this could be explained by the need to excrete a toxic waste, creatinine, the major by-product of skeletal muscle mass and hence the need to regulate excretion through renal clearance.\(^{33}\)

Strengths of this study include the use of a gold standard GFR measurement and having three clearly defined and distinct groups separated by body composition. Assessment of dietary intake also allowed analysis of the effects of protein, salt (sodium), water intake and other micronutrients on renal function. Limitations of the study include the absence of blood pressure recordings and the applicability of results to only males and to subjects with normal to high GFR. Results from another study showed lean mass to be associated with creatinine clearance in subjects without hypertension, suggesting the association we observed here is independent of blood pressure.\(^{11}\) Finally, individuals with higher GFR levels in our study may be in a ‘pre-pathological’ state which should ideally be identified by screening and longitudinal follow-up.

Conclusion

Our study results suggest age and lean mass to be strong determinants of GFR. Based on our multiple regression modelling, we estimate that GFR decreases by 1 mL/min/year of age together with an increase of 2.3 mL/min/kg of lean mass in healthy men. This too warrants further investigation. The strong association of GFR with lean mass in our data supports the case for indexation of GFR to lean body mass. Renal impairment may then be assessed against a better estimate of expected physiological function.

Acknowledgements

We are also grateful to Dr John Pearson (University of Otago) for advice on statistical analysis, Madeleine Price (Canterbury District Health Board) and Hilary...
Dumbleton (Canterbury District Health Board) for assistance with the dietary data collection. The staff of Primorus Clinical Trials, including Dr Alison Luckey and Jo Kepple, are also acknowledged for providing support and clinical infrastructure.

References


29 Janmahasatan S, Duffull SB, Chagnac A, Kirkpatrick CM, Green B. Lean body


### Appendix I

Correlation of uncorrected glomerular filtration rate with regional lean and fat mass for subgroups.

<table>
<thead>
<tr>
<th>Body composition parameter</th>
<th>Mean results for regional body composition (kg) (95% CI)</th>
<th>[Correlation of individual variables (r) with GFR (mL/min) (P-values)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal BMI</td>
<td>Muscular</td>
</tr>
<tr>
<td><strong>Lean mass (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lean mass</td>
<td>58.7 (55.5–61.9) [0.49 (0.02)]*</td>
<td>75.5 (72.3–78.6) [0.76 (&lt;0.0001)]**</td>
</tr>
<tr>
<td>Total truncal lean</td>
<td>27.6 (25.9–29.2) [0.47 (0.03)]*</td>
<td>35.4 (33.7–37.0) [0.58 (0.003)]***</td>
</tr>
<tr>
<td>Total android lean</td>
<td>3.7 (3.5–4.0) [0.37 (0.09)]**</td>
<td>4.9 (4.6–5.1) [0.70 (0.002)]*</td>
</tr>
<tr>
<td>Total gynoid lean</td>
<td>8.7 (6.1–9.3) [0.40 (0.06)]**</td>
<td>11.1 (10.5–11.7) [0.60 (0.003)]***</td>
</tr>
<tr>
<td>Total appendicular lean</td>
<td>27.1 (25.4–28.8) [0.48 (0.02)]*</td>
<td>4.9 (4.6–5.1) [0.62 (0.002)]***</td>
</tr>
<tr>
<td>Total arm lean</td>
<td>7.6 (6.9–8.2) [0.48 (0.02)]*</td>
<td>11.0 (10.4–11.7) [0.23 (0.28)]*</td>
</tr>
<tr>
<td>Total leg lean</td>
<td>19.5 (18.3–20.7) [0.44 (0.04)]***</td>
<td>24.5 (23.3–25.7) [0.66 (0.0006)]***</td>
</tr>
<tr>
<td>Total skeletal muscle mass</td>
<td>32.2 (30.3–34.2) [0.49 (0.02)]*</td>
<td>42.3 (40.3–44.3) [0.62 (0.002)]***</td>
</tr>
<tr>
<td><strong>Fat mass (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fat mass</td>
<td>12.0 (9.4–14.5) [−0.03 (0.89)]**</td>
<td>21.6 (19.1–24.1) [0.24 (0.27)]**</td>
</tr>
<tr>
<td>Total truncal fat</td>
<td>6.9 (5.3–8.5) [−0.12 (0.60)]**</td>
<td>13.0 (11.4–14.6) [0.22 (0.32)]**</td>
</tr>
<tr>
<td>Total android fat</td>
<td>1.2 (0.86–1.5) [−0.37 (0.08)]**</td>
<td>2.2 (1.8–2.5) [0.20 (0.35)]**</td>
</tr>
<tr>
<td>Total gynoid fat</td>
<td>2.3 (1.9–2.8) [−0.32 (0.14)]**</td>
<td>3.9 (3.5–4.3) [0.12 (0.59)]**</td>
</tr>
<tr>
<td>Total appendicular fat</td>
<td>4.6 (3.3–5.9) [−0.25 (0.25)]*</td>
<td>7.9 (6.6–9.2) [0.22 (0.30)]**</td>
</tr>
<tr>
<td>Total arm fat</td>
<td>1.0 (0.6–1.4) [−0.21 (0.34)]**</td>
<td>1.9 (1.6–2.3) [0.08 (0.73)]**</td>
</tr>
<tr>
<td>Total leg fat</td>
<td>3.6 (2.6–4.6) [−0.26 (0.25)]**</td>
<td>6.1 (5.0–7.1) [0.25 (0.26)]**</td>
</tr>
</tbody>
</table>

Significant results are highlighted in bold. *Differences between normal BMI group and muscular group significantly different (P < 0.05). **Differences between normal BMI group and obese group significantly different (P < 0.05). ***Differences between the muscular group and obese group significantly different (P < 0.05). BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate.
Health economic impact of high-dose versus standard-dose cytarabine induction chemotherapy for acute myeloid leukaemia

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Key words
acute myeloid leukaemia, HiDAC, cytarabine, cost effectiveness.

Abstract

Background: Induction chemotherapy for acute myeloid leukaemia (AML) is one of the most resource-intensive cancer therapies delivered in hospitals.

Aims: To assess the health resource impact of different chemotherapy approaches for AML commonly used in Australia.

Methods: A retrospective analysis was undertaken in 63 patients aged 18–55 years with AML given induction with either 7 + 3 (cytarabine 100 mg/m² days 1–7 and idarubicin 12 mg/m² days 1–3) or HiDAC-3 (high-dose cytarabine 3 g/m² twice daily days 1, 3, 5 and 7 and idarubicin 12 mg/m² days 1–3) chemotherapy. Average costs of hospitalisation, pathology, radiology, chemotherapy and ancillary drugs were calculated and compared with current Victorian casemix funding. Two consolidation approaches, HiDAC (cytarabine 3 g/m² twice daily days 1, 3, 5 and 7) × either three or four cycles (following 7 + 3) and IcE (idarubicin 12 mg/m² days 1–2, cytarabine 100 mg/m² × 5 days and etoposide 75 mg/m² × 5 days) × 2 cycles (following HiDAC-3) were modelled, using a policy of discharge following completion of chemotherapy with outpatient monitoring.

Results: The cost (in AUD) of induction was similar between 7 + 3 ($58 037) and HiDAC-3 ($56 902), with bed day costs accounting for 61–62% of the total expense. Blood bank costs ranked second, accounting for 15%. Accumulated costs for HiDAC consolidation were $44 289 for a three-cycle protocol and $59 052 for four cycles ($14 763 per cycle) versus $31 456 for two cycles of IcE consolidation ($15 728 per cycle). Overall, the classical 7 + 3 → HiDAC approach ($102 326/$117 089 for three or four consolidation cycles) incurs a greater cost than a HiDAC-3 → IcE × 2 approach ($88 358). For patients requiring complete hospitalisation until neutrophil recovery, the estimated costs of treatment will be even higher, ranging between $122 282 for HiDAC-3 → IcE × 2, $153 212 for 7 + 3 → HiDAC × 3 and $184 937 for 7 + 3 → HiDAC × 4. State-based casemix funding for non-complicated AML therapy is currently $74 013 for 7 + 3 → HiDAC × 4, $64 177 for 7 + 3 → HiDAC × 3 and $54 340 for HiDAC-3 → IcE × 2 based on outpatient recovery after consolidation chemotherapy. These calculations do not take into account additional resource implications associated with complications of consolidation chemotherapy or reinduction for treatment failure.

Conclusion: Regimens minimising the total number of chemotherapy cycles may represent the most efficient use of limited health resources for the treatment of AML.

Introduction

Induction chemotherapy for acute myeloid leukaemia (AML) classically involves one cycle of standard-dose cytarabine (SDAC) for 7 days in combination with an anthracycline for 3 days, otherwise called ‘7 + 3’, followed by three or four cycles of high-dose cytarabine (HiDAC) in the post-remission or consolidation phase.1,2

Funding: None.
Conflict of interest: None.

This four or five-cycle approach results in an overall complete remission (CR) rate of 56–71%, with 15% of patients requiring reinduction for resistant AML, and a 3-year overall survival of 38%.2,3

The Australasian Leukaemia and Lymphoma Group (ALLG) has recently introduced a three-cycle approach using HiDAC induction in combination with idarubicin for 3 days (HiDAC-3), followed by two cycles of IcE consolidation, based on the consolidation approach used in the ALLG AML M7 study.4,5 Improved supportive care techniques have allowed HiDAC-based induction
(HiDAC-3) to be delivered safely to patients between 18 and 55 years with low treatment-related mortality (TRM), while maintaining the high first cycle CR rate associated with this approach.³

In the absence of data demonstrating the superiority of either a SDAC or HiDAC induction approach, we wish to model the potential health economic implications of these competing approaches in Australian practice. In 2009, The Alfred Hospital Haematology Unit underwent a change in policy from all patients receiving 7 + 3 upfront, to patients 55 years or younger receiving HiDAC-3 (unless found to have a core binding factor mutation in which case 7 + 3 was still given). To limit the confounding effect of changes in supportive care over time, data collection was limited to 2004 onwards.

**Methods**

A retrospective analysis of all patients aged 18–55 years treated at The AlfredHospital between 2004 and 2012 with 7 + 3 (cytarabine 100 mg/m² × 7 days and idarubicin 12 mg/m² × 3 days) or HiDAC-3 (3 g/m² twice daily days 1, 3, 5 and 7 and idarubicin 12 mg/m² × 3 days) was conducted. During the data collection period, 14 patients were enrolled in the ALLG M12 trial with IcE induction (cytarabine 3 g/m² twice daily days 1, 3, 5, 7; idarubicin 9 mg/m² days 1–3 and etoposide 75 mg/m² days 1–7), and an additional 22 patients were treated with IcE induction off study. As this investigation was focused on HiDAC-3 and 7 + 3 induction, these patients were not included. Consolidation options included ‘HiDAC’ (3000 mg/m² twice daily days 1, 3 and 5 for either three or four cycles) or ‘IcE’ (idarubicin 12 mg/m² days 1–2, cytarabine 100 mg/m² × 5 days and etoposide 75 mg/m² × 5 days for two cycles). CR was defined as <5% blasts in a normocellular bone marrow, with peripheral blood neutrophils >1.0 × 10⁹/L and platelets >100 × 10⁹/L.⁶

In Victoria, hospital casemix funding of AML is based on a parameter called the Weighted Inlier Equivalent Separation (WIES), a unit price based on a patient episode that is cost weighted according to the Australian Refined Diagnosis Related Groups patient classification (AR-DRG version 6.0 round 14)⁷ and adjusted for length of stay (LOS). The current WIES unit price is $4164.00 (AUD), and ‘Acute leukaemia’ is coded AR-DRG-R60A, with a WIES of 8.0256 units for a LOS of 13–29 days. Further LOS attracts a WIES of 0.2999 units/day. The actual cost of delivering AML induction was determined using AR-DRG/WIES to derive an inpatient admission ‘hotel’ cost only (excluding all other costs) and calculating all other costs independently, a method used recently by Heng et al.³ Costs associated with chemotherapy, supportive care medications, pathology and radiological investigations/procedures, blood transfusions and intensive care unit bed days were calculated manually (detailed in Supporting Information Table S1). For the consolidation phase of treatment, hospital funding was based on the AR-DRG-60B classifier, which attracts a WIES of 1.8837 for a LOS 1 to 17 days. Outpatient same day admissions attract a WIES of 0.2393 per day.

The minimum costs of AML consolidation were modelled on a patient electively discharged after chemotherapy (day 6) without requirement for readmission to manage complications. Costs of supportive care, including antifungal prophylaxis (posaconazole), a single dose of pegylated granulocyte colony stimulating factor (G-CSF), inpatient and outpatient routine pathology costs, and outpatient follow up were estimated based on institution specific practices. Transfusion requirements were based on an average of three units of red cells and one pool of platelets per consolidation cycle, as determined at our institution. Costs of transfused units are detailed in Supporting Information Table S1. Outpatient follow up after discharge until peripheral blood count recovery was managed by the haematology unit. Additional costs incurred by visits to the local doctor and external scripts were minimal and therefore not included. The minimum cost of inpatient consolidation for a patient hospitalised without complications for an average of 21 days until neutrophil recovery was also determined.³⁰

**Statistical analysis**

Comparison of groups and calculation of P-values for continuous data was performed using an unpaired two-tailed t-test for mean values, with the exception of LOS and days to neutrophil recovery >0.5 × 10⁹/L, for which the median values were compared using the Mann–Whitney test (two-tailed, unpaired and non-parametric) to reduce the impact of outliers. Categorical data were analysed using a chi-squared test.

**Results**

**Patients and clinical outcomes after induction chemotherapy**

A total of 63 patients aged 18–55 years treated for a new diagnosis of AML at The Alfred Hospital between 2004 and 2012 was included. Of these, 27 received 7 + 3, and 36 received HiDAC-3 (Table 1). Patients receiving 7 + 3 (45.9 years) were slightly older than the cohort receiving HiDAC-3 (40.6 years; P = 0.02). There was a non-statistically significant higher first cycle CR rate with HiDAC-3 than 7 + 3 induction (83% vs 67%; P = 0.12). TRM was 7% with 7 + 3 compared with no deaths in
those receiving HiDAC-3. The median length of inpatient stay was 30 days for each group. Time to neutrophil recovery was 30 days for 7 + 3 and 28 days for HiDAC-3 (not significantly different). Transfusion requirements were also similar between the two groups (Table 1). Delivery of at least one cycle of consolidation was 77% after 7 + 3 and 90% after HiDAC-3.

**Analysis of costs (in AUD) associated with induction and consolidation chemotherapy**

The main cost associated with induction chemotherapy was the inpatient bed day cost, which is an amalgamation of the costs associated with hospital staff, equipment and consumables. The standard cost for a haematology ward bed was $1177 per day. The median duration of hospitalisation for a patient undergoing induction chemotherapy for AML was 30 days, which amounts to a total cost of $35 310. This accounts for 61–62% of the total cost of induction therapy. The National Blood Authority calculates a ‘cost’ of individual blood products. This is an estimate of the cost required to collect, prepare and dispense products, and is thought to represent only a fraction of the true cost of transfusion to the health system. Blood transfusion components made up the second largest cost ($8805–8846), accounting for 15.2–15.5% of the overall cost of induction. This is based on a median of 15.2 versus 15.9 units of red cells and 11.0 versus 11.3 platelet pools administered to each patient in our study for 7 + 3 and HiDAC-3 respectively. In Victoria, hospitals are not charged for blood products provided by the Australian Red Cross Blood Service. The averaged costs per patient associated with pathology testing ($2537 with HiDAC-3 vs $2587 for 7 + 3), radiology ($1883 vs $1748), chemotherapy ($1860 vs $2447) and ancillary medications ($4201 vs $2925) including G-CSF ($326 vs $488) and antifungal prophylaxis ($2309 vs $2601) were also determined (Table 2). The component elements and costs used to calculate these figures are detailed in Supporting Information Table S1. Summing these health resource provisions, the average overall cost of induction chemotherapy was surprisingly similar between patients receiving either HiDAC-3 ($56 902) or 7 + 3 ($58 037).

A simplified model for calculating the minimum cost of consolidation chemotherapy on the basis of a patient being discharged after completion of chemotherapy (6 days) is shown in Table 2. The cost of HiDAC consolidation was determined to be $14 763 per cycle, totalling $44 289 for a three-cycle protocol and $59 052 for a four-cycle protocol. The cost of IcE consolidation, while slightly more expensive per cycle, was overall considerably cheaper because of fewer number of consolidation cycles required ($15 728 per cycle, or $31 456 for two cycles). Based on these evaluations, the total minimum cost associated with HiDAC-3 → IcE × 2 is estimated to be $88 358 compared with $102 326 for 7 + 3 followed by three cycles of HiDAC consolidation and $117 089 for four cycles. In Victoria, hospitals are not currently charged for blood products. This is not the case in all states and territories. Excluding the cost of blood products, the total cost of treatment to the hospital will be $78 046 for HiDAC-3 → IcE × 2, $91 993 for 7 + 3 → HiDAC × 3 and $106 756 for 7 + 3 → HiDAC × 4.

**Analysis of casemix funding linked to intensive chemotherapy for AML**

Using the WIES/AR-DRG model (Table 3), the hospital funding for induction chemotherapy was the same for both 7 + 3 and HiDAC-3 chemotherapy, amounting to
The funding for each consolidation cycle was $9,837 (2.3623 WIES). The overall number of inpatient bed days required to treat a patient with 7+3 induction followed by three or four cycles of HiDAC consolidation chemotherapy and outpatient recovery was 48 and 54 days compared with 42 days for HiDAC-3 followed by two cycles of IcE consolidation.

$34,667 (8.3255 WIES). The funding for each consolidation cycle was $9,837 (2.3623 WIES). The overall number of inpatient bed days required to treat a patient with 7+3 induction followed by three or four cycles of HiDAC consolidation chemotherapy and outpatient recovery was 48 and 54 days compared with 42 days for HiDAC-3 followed by two cycles of IcE consolidation.

As inpatient bed costs account for most of the cost of treatment, a five-cycle chemotherapy regimen (17.7747 WIES or $74,013) has a greater health economic cost.

### Table 2

**Summary of costs incurred during induction and consolidation chemotherapy for AML**

<table>
<thead>
<tr>
<th>Induction</th>
<th>7+3 (n = 27) ($)</th>
<th>HIDAC-3 (n = 36) ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient bed costs (for 30 days)</td>
<td>35,310</td>
<td>35,310</td>
</tr>
<tr>
<td>Total pathology (including)</td>
<td>13,994</td>
<td>12,847</td>
</tr>
<tr>
<td>Routine blood tests</td>
<td>1,640</td>
<td>1,667</td>
</tr>
<tr>
<td>Transfusion (for 15.2 vs 15.9 RBC and 11.0 vs 11.3 platelet pools)</td>
<td>8,846</td>
<td>8,805</td>
</tr>
<tr>
<td>Microbiology</td>
<td>947</td>
<td>870</td>
</tr>
<tr>
<td>Radiology costs</td>
<td>1,748</td>
<td>1,883</td>
</tr>
<tr>
<td>Medications (including)</td>
<td>4,021</td>
<td>2,929</td>
</tr>
<tr>
<td>G-CSF</td>
<td>488</td>
<td>326</td>
</tr>
<tr>
<td>Antifungals</td>
<td>2,610</td>
<td>2,309</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1,860</td>
<td>2,447</td>
</tr>
<tr>
<td>Total induction cost</td>
<td>58,037</td>
<td>56,902</td>
</tr>
</tbody>
</table>

### Table 3

**Analysis of casemix funding for a patient undergoing intensive induction and consolidation chemotherapy without complications**

<table>
<thead>
<tr>
<th>Induction</th>
<th>7+3 (n = 27)</th>
<th>7+3 (n = 27)</th>
<th>HIDAC-3 (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median LOS in days/DRG60A WIES</td>
<td>30/8.3255</td>
<td>30/8.3255</td>
<td>30/8.3255</td>
</tr>
<tr>
<td>Median WIES funding</td>
<td>$34,667</td>
<td>$34,667</td>
<td>$34,667</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consolidation (number cycles)</th>
<th>HIDAC (3)</th>
<th>HIDAC (4)</th>
<th>IcE (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient length of stay/cycle (total)</td>
<td>6 days (18)</td>
<td>6 days (24)</td>
<td>6 days (12)</td>
</tr>
<tr>
<td>Outpatient same day admissions</td>
<td>2 (6)</td>
<td>2 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Median DRG60B WIES/cycle (total)</td>
<td>2,362.3 (7,086)</td>
<td>2,362.3 (9,442)</td>
<td>2,362.3 (4,724)</td>
</tr>
<tr>
<td>Median WIES funding/cycle (total)</td>
<td>$9,837 ($39,510)</td>
<td>$9,837 ($39,546)</td>
<td>$9,837 ($19,673)</td>
</tr>
<tr>
<td>Total treatment WIES/inpatient LOS</td>
<td>15,412/448 days</td>
<td>17,774/54 days</td>
<td>13,050/41 days</td>
</tr>
<tr>
<td>Total cost (without reinduction)</td>
<td>$64,177</td>
<td>$74,013</td>
<td>$54,340</td>
</tr>
</tbody>
</table>

HiDAC, consolidation protocol: cytarabine 3 g/m² twice daily days 1, 3, 5 and 7; HIDAC-3, induction protocol: cytarabine 3 g/m² twice daily days 1, 3, 5 and 7 and idarubicin 12 mg/m² days 1–3; IcE, consolidation protocol: idarubicin 12 mg/m² days 1–2, cytarabine 100 mg/m² × 5 days and etoposide 75 mg/m² × 5 days; RBC, red blood cells.
than either a four-cycle (15.4124 WIES or $64 177) or a three-cycle regimen (13.0501 WIES or $54 340).

**Discussion**

The best outcomes for patients with AML are observed in younger adults receiving intensive chemotherapy. In adults up to the age of 55, which comprises approximately one third of all patients with AML receiving induction chemotherapy, the expected 5-year survival is at least 50%, with early death rates <10%.11 Early studies investigating HiDAC-based induction chemotherapy showed that improved disease-free survival was offset by increased treatment related morbidity and early mortality.12,13 With improved modern supportive care techniques, the toxicity related to HiDAC-based induction has been substantially reduced, with early mortality rates now comparable with 7 + 3 chemotherapy.14,15 Another advantage is the potentially higher first cycle CR rate observed with HiDAC compared with SDAC, or 7 + 3 induction, thereby reducing the requirement for salvage chemotherapy.2,3 Although a small sample cohort, our retrospective comparison of HiDAC-3 versus 7 + 3 supports the safety (0 vs 7% early death) and first cycle remission efficacy (83% vs 67%) of HiDAC-3 compared with 7 + 3 in adults aged 18–55. The median duration of hospitalisation in our study was the same for both 7 + 3 and HiDAC-3 (30 days). This was comparable with a large randomised study, which also found the median duration of hospitalisation to be the same for both standard and HiDAC induction (29 days).13 The calculated cost of induction was very similar for both 7 + 3 and HiDAC-3 ($56 902–58 037) and also similar to induction chemotherapy costs for AML reported in other recent studies (Table 4). The costs attributed to inpatient care, pathology/radiology, drugs and chemotherapy were also remarkably consistent between these studies and the present study (Table 4).

The main differences in terms of resource use and therefore costs between HiDAC-3 and 7 + 3 were related to the number of consolidation cycles required as part of the overall therapy. Our analysis suggests that a HiDAC-3 approach may consume fewer health resources than 7 + 3, largely because HiDAC-3 is followed by 2, rather than three or four cycles of consolidation. This results in fewer overall days in hospital (42 vs 48/54 days) to deliver therapy based on a unit policy to manage suitable patients as an outpatient during the post-consolidation chemotherapy phase. This resulted in a lower total cost for HiDAC-3 → lEl × 2 compared with 7 + 3 → HiDAC × 3 or 7 + 3 → HiDAC × 4 (Table 2). Medical, psychosocial and geographical factors are important in determining whether an outpatient or inpatient consolidation approach is appropriate for a particular
patient. Consistent with published studies, unit practice was to consider early discharge and outpatient monitoring if the patient resided within 1 h of the hospital and had adequate social supports, transportation and was deemed fit medically and psychologically. In general, this is feasible in approximately 90%\(^{25,26}\) of cases, but will vary according to the catchment area serviced. Despite this, approximately 36–41% of patients treated with an outpatient consolidation protocol will require readmission for complications (predominantly febrile neutropenia).\(^{15,25}\) This study evaluated the minimum costs associated with consolidation assuming early discharge and no requirement for readmission. Not unexpectedly, costs associated with delivering consolidation and retaining patients in hospital until count recovery will be substantially higher. The estimated total cost for hospitalising a patient until neutrophil recovery for the entire AML treatment will be $122 282 for a three-cycle HiDAC-3 treatment approach, and either $153 212 or $184 937 for a four- or five-cycle 7 + 3 treatment approach, respectively (Table 2). Another factor in determining health resource cost is the likely higher number of reinduction cycles required after 7 + 3 to achieve first CR versus HiDAC-3. A recent pilot study examined the feasibility of early discharge during the neutropenic phase of 7 + 3 induction.\(^{27}\) Of 39 patients enrolled in this study, only 15 (38%) receiving induction were considered suitable for early discharge. Of the 15 patients discharged early, 13 required rehospitalisation over the ensuing few weeks for complications. Although preliminary, it appears unlikely that an aggressive discharge approach following 7 + 3 induction will lead to a superior health economic ‘balance-sheet’ compared with a HiDAC-3 approach, even in the short-term.

Induction chemotherapy for AML is one of the most resource-intensive cancer therapies delivered in hospitals. The long period of hospitalisation and complex supportive care requirements associated with AML induction makes this process an important one in terms of health resource considerations. This study is the first to compare the health economic impact of standard versus high-dose induction approaches for AML. It provides a contemporary assessment of the component costs of induction chemotherapy for AML and highlights the potential efficiencies associated with fewer consolidation cycles after HiDAC-3 compared with 7 + 3 therapy. We therefore conclude that HiDAC-3 induction appears safe and likely to be cost-effective compared with 7 + 3 induction for adults with AML between the ages of 18 and 55. The feasibility and ongoing safety of HiDAC-3 is currently being evaluated in the context of a nationwide multicentre Australian AML Registry, conducted by the ALLG. Furthermore, for patients older than 55, the ALLG is also examining the feasibility of 7 + 3 followed by two cycles of intermediate-dose cytarabine in combination with 2 days of idarubicin. This approach may broaden the health economic benefits of fewer cycles of consolidation applied to a larger cross-section of the AML population. The Australian Institute of Health and Welfare estimates that 865 patients with AML are diagnosed in Australia each year.\(^{28}\) If 66% receive intensive chemotherapy, as indicated by population-based registry studies,\(^{18}\) the national cost of delivering a 7 + 3 → HiDAC × 4 approach exceeds $66 million per annum. A switch to a three-cycle treatment approach for patients with AML younger than 56 years (representing ~50% of patients fit for intensive chemotherapy) could represent conservative cost savings of over $8 million per annum. Emerging randomised studies supporting HiDAC-based induction chemotherapy in younger adults and the requirement for fewer cycles of consolidation therapy to achieve satisfactory outcomes in AML support the broad-based adoption in practice of the most cost-effective treatment strategies to maximise efficient use of fiscally constrained public healthcare resources.\(^{29}\)

**Conclusion**

Clinical equipoise in outcomes relating to various AML regimens supports the adoption of treatment strategies utilising the fewest number of induction and consolidation cycles to maximise the health economic efficiency of delivered therapy.

**References**


5 Low M, Lee D, Couttsouvelis J, Patil S, Opate S, Walker P et al. High-dose cytarabine (24 g/m\(^2\)) in combination with idarubicin (HiDAC-3) results in high first-cycle response with limited gastrointestinal toxicity in adult acute

**Supporting information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1.** Component analysis of healthcare costs associated with AML therapy.
Metastatic breast cancer in young women: a population-based cohort study to describe risk and prognosis

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Key words
breast neoplasms, neoplasm metastasis, epidemiologic research design, prognosis, population characteristics.

Abstract

Background: There is limited information on the risk of metastatic breast cancer (MBC) to inform younger women, particularly those under 40 years.

Aims: We conducted a retrospective analysis of a population-based cohort study to describe the risk, site and prognosis of MBC in young women under 40 years with an initial diagnosis of non-metastatic breast cancer and compared with older women.

Methods: Data were extracted from the New South Wales Central Cancer Registry and the Admitted Patient Data Collection database between 2001–2007. Main outcome measures were 5-year cumulative incidence of MBC, prognostic factors for MBC and overall survival (OS) from the date of MBC diagnosis.

Results: Three hundred and ninety-five (6%) of 6640 women with non-metastatic BC were <40 years. The 5-year cumulative incidence of MBC was 24% (95% CI 20–29%) for women <40 years with non-metastatic BC, compared with 9% (95% CI 9–10%) for women ≥40 years. Significant independent risk factors for MBC ≤5 years were age <40, regional disease at diagnosis, low socioeconomic status and the presence of other non-breast primary. At first record of MBC, visceral sites were more common for women <40 years than ≥40 (54% vs 43%; P = 0.03). Median survival for women with MBC within 5 years was not significantly different between young and older women (<40 years 18 months vs ≥40 years 14 months; log–rank P = 0.21).

Conclusions: Women with non-metastatic BC before age 40 have a higher 5-year risk of developing MBC than older women. There were no significant differences in median survival following MBC between young and older women.

Introduction

More than 700 Australian women aged less than 40 years are diagnosed with breast cancer (BC) each year.1 These young women have unique psychosocial needs, with a BC diagnosis presenting a serious disruption to caregivers for young families and career-building plans. Information about prognosis is important to enable these women to make decisions regarding treatment options, survivorship plans and other lifestyle preferences.2 However, BC for women aged less than 40 years is rarely studied, and the lack of information about the incidence, prognosis and impact of this disease at relapse represents an important unmet need.3

Studies have reported on the 5-year risk of distant relapse for premenopausal women with early BC as 6–12%.4,5 However, these studies were based on highly select patient populations from clinical trials, with no separate data reported for women aged less than 40 years. Thus, this information is of limited applicability to the general population of young Australian women with a new BC.

In our recent Australian population-based cohort of patients diagnosed with non-metastatic-stage BC in the years of 2001 and 2002, we estimated a 5-year risk of subsequent distant relapse of 5% in women with initial node-negative cancer.4 The 5-year risk of distant relapse increased to 18% in women with nodal regional disease. Age at initial diagnosis was also independently associated with risk of distant relapse, with younger women at a greater risk as compared with older women.

Aims

In this paper, we extend our previous research to examine clinical outcomes in young Australian women aged less than 40 years diagnosed initially with non-metastatic BC.
Our goal is to provide young women and healthcare providers with better estimates of risk and impact of distant recurrence of BC in this vulnerable group of patient population.

Methods

Study population
As described in our previous paper, the study population included women over the age of 18 with a primary diagnosis of localised (node-negative disease confined to breast tissue) or regional (spread to regional lymph nodes or adjacent tissues, includes locally advanced disease) registered on the population-based New South Wales Central Cancer Registry (NSW CCR) between 1 January 2001 and 31 December 2002, who received care in an NSW hospital.6 Women were excluded if the extent of disease spread at BC diagnosis was recorded as distant (spread beyond the breast, adjacent tissues and regional lymph nodes) or unknown. The CCR classification of distant disease at diagnosis spread includes women with MBC recorded within 120 days of the date of their initial BC diagnosis.

Data sources
The CCR receives notification of all new cancer cases diagnosed in NSW residents from public and private hospitals, radiation oncology departments, nursing homes, pathology laboratories, outpatient departments and day-procedure centres as a statutory requirement.7 Dates (month, year) of birth, BC diagnosis and MBC diagnosis for each patient were extracted from the CCR up to 31 December 2007, together with information on the degree of spread at diagnosis, tumour type (International Classification of Diseases for Oncology, 3rd edition morphology codes), other primary neoplasms, country of birth and local government area of residence at BC diagnosis. We used local government area to classify area of residence as major cities or regional/remote using the Accessibility/Remoteness Index of Australia classification (ARIA)8 and socioeconomic status using the Socioeconomic Indexes for Areas classification.9

Health record linkage was undertaken by the Centre for Health Record Linkage (CHeRel) to obtain information about all hospital episodes of care recorded on the NSW Admitted Patient Data Collection (APDC) for the study population between 1 January 2001 and 31 December 2007. CHeRel constructs a master linkage key to link health records from different databases using probabilistic record linkage software with quality assurance procedures designed to achieve fewer than 0.5% false-positive matches and fewer than 0.5% false-negative matches where full identifiers are available.10

The APDC codes the principal diagnosis, additional diagnoses and procedures for all episodes of care, including day-only admissions, from NSW hospitals, private day-procedure centres and public nursing homes, using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) coding system. The date of the first ‘index’ hospital episode of care with an ICD-10-AM diagnosis code for secondary malignant neoplasms after an initial BC diagnosis, and the site(s) of secondary malignant neoplasms were extracted from the APDC. For patients having a second non-breast primary cancer, we only extracted this information if a matching CCR record was available to verify MBC status for that episode of care.

Ethics was approved by the NSW Population and Health Services Research Ethics Committee.

Outcomes
The primary outcome was the 5-year cumulative incidence of distant recurrence in women aged less than 40 years with an initial diagnosis of non-metastatic BC. We also reported median overall survival (OS) for young women with metastatic breast cancer (MBC) following an initial diagnosis of non-metastatic BC, and compared the OS difference with the older women. Risk factors for distant relapse were identified, and comparisons between the organ sites of distant disease between young and older women were also made.

Statistical analyses
Patients were classified as having MBC if they had a CCR record of MBC within 5 years of their initial diagnosis of BC. Women with no death or distant relapse event recorded were censored at 1 January 2008.

For our analysis of outcomes by age group, we selected an age cut-off of <40 years to classify young women, consistent with international consensus that defines adolescents and young adult as those aged between 15 and 39 years.11

Kaplan–Meier analysis was used to report time to MBC, and the 5-year cumulative incidence of MBC was calculated as the proportion of women diagnosed as not having MBC who had MBC recorded within 5 years. Time to MBC was defined as the time from the diagnosis of non-metastatic BC to the date of the first record of MBC on the CCR or the APDC, whichever occurred earliest. For patients who also had a second non-breast primary cancer, we used only the date of the first CCR record of MBC.
because MBC status could not be determined from an APDC diagnosis of secondary cancer. The log–rank test was used to test for differences in time to MBC by age group (<40 years, ≥40 years). The annual MBC hazard rate according to age group was also calculated.

Univariate using logistic regression analyses was used to identify factors associated with distant relapse-free survival. A multivariable logistic regression model was developed using backwards elimination, starting with all covariates and removing the least significant variable until only significant variables were retained.

We conducted a descriptive analysis of the site of distant disease for young women with MBC. We used Fisher’s exact test to analyse differences in sites of MBC. All analyses were two-sided, and \( P < 0.05 \) was considered significant. SAS, version 9.2 (SAS Institute, Cary, NC, USA) was used to perform all analyses.

**Results**

The study cohort comprised of 6640 women with non-metastatic BC. Of these women, 395 (6%) were aged less than 40 years, 1249 (19%) were aged 40–49 years, 1771 (27%) were aged 50–59 years, 1492 (22%) were aged 60–69 years and 1733 (26%) aged over 70.

In women aged less than 40 years, 200 (51%) had localised disease at diagnosis and 195 (49%) had regional disease. Ductal histology was recorded in 341 patients (86%), lobular or mixed ductal and lobular histology in 20 patients (5%), and other histological subtypes in the remaining 34 (9%) patients (Table 1).

When comparing young women aged less than 40 years versus women aged 40 years and older at initial non-metastatic BC diagnosis, a greater proportion of young women had regional disease (49% vs 37%; \( P < 0.0001 \)), had tumours of ductal histology (86% vs 75%; \( P < 0.0001 \)), and lived in a major city (81% vs 73%; \( P = 0.0019 \)), but fewer had other non-breast primary cancers (2% vs 5%; \( P = 0.0096 \)).

**Five-year cumulative incidence of metastatic breast cancer**

Following initial non-metastatic BC diagnosis, the 5-year risk of MBC was 24% (95% CI 20–29%) for women aged less than 40 years, compared with 11% (95% CI 9–13%) for women 40–49 years, 10% (95% CI 9–11%) for women 50–59 years, 8% (95% CI 7–9%) for women 60–69 years and 9% (95% CI 8–10%) for women 70 or over (log–rank \( P < 0.0001 \)). Among young women with an initial diagnosis of localised BC, the 5-year risk of MBC was 12% compared with 37% for young women with an initial diagnosis of regional disease. A similar difference in 5-year MBC risk for localised versus regional BC subgroups was also observed in older-age groups (Table 2).

The annual hazard rate for MBC was highest within the first 3 years following the initial diagnosis across all age groups. For women aged less than 40 years, the annual hazard rate for MBC was highest at 24–35 months (8.6%) and dropped to 4.0% at 48–60 months. In comparison, for women aged 40 and above, the annual

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**Table 1** Baseline characteristics by age group, non-metastatic breast cancer cohort, New South Wales Central Cancer Registry 2001–2002

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (%)</th>
<th>&lt;40 (%)</th>
<th>40–49 (%)</th>
<th>50–59 (%)</th>
<th>60–69 (%)</th>
<th>≥70 (%)</th>
<th>( P )-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of disease at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localised</td>
<td>4135 (62)</td>
<td>200 (51)</td>
<td>655 (52)</td>
<td>1081 (61)</td>
<td>1000 (67)</td>
<td>1199 (69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regional</td>
<td>2505 (38)</td>
<td>195 (49)</td>
<td>594 (48)</td>
<td>690 (39)</td>
<td>492 (33)</td>
<td>534 (31)</td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>5054 (76)</td>
<td>341 (86)</td>
<td>1014 (81)</td>
<td>1345 (76)</td>
<td>1115 (75)</td>
<td>1239 (71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lobular, mixed ductal/lobular</td>
<td>840 (13)</td>
<td>20 (5)</td>
<td>126 (10)</td>
<td>230 (13)</td>
<td>219 (15)</td>
<td>245 (14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>746 (11)</td>
<td>34 (9)</td>
<td>109 (8)</td>
<td>196 (11)</td>
<td>158 (11)</td>
<td>249 (14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major city</td>
<td>4873 (73)</td>
<td>319 (81)</td>
<td>978 (78)</td>
<td>1291 (73)</td>
<td>1058 (71)</td>
<td>1227 (71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regional area</td>
<td>1742 (26)</td>
<td>76 (19)</td>
<td>267 (21)</td>
<td>470 (27)</td>
<td>427 (29)</td>
<td>502 (29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other first primary</td>
<td>312 (5)</td>
<td>8 (2)</td>
<td>18 (1)</td>
<td>58 (3)</td>
<td>78 (5)</td>
<td>150 (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Socioeconomic status (quintiles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1276 (19)</td>
<td>65 (16)</td>
<td>217 (17)</td>
<td>337 (19)</td>
<td>307 (21)</td>
<td>350 (20)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1174 (18)</td>
<td>71 (18)</td>
<td>227 (18)</td>
<td>322 (18)</td>
<td>262 (18)</td>
<td>292 (17)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1333 (20)</td>
<td>75 (19)</td>
<td>242 (19)</td>
<td>339 (19)</td>
<td>296 (20)</td>
<td>381 (22)</td>
<td>0.19</td>
</tr>
<tr>
<td>4</td>
<td>1244 (19)</td>
<td>88 (22)</td>
<td>256 (21)</td>
<td>323 (18)</td>
<td>279 (19)</td>
<td>298 (17)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1612 (24)</td>
<td>96 (24)</td>
<td>306 (25)</td>
<td>450 (25)</td>
<td>348 (23)</td>
<td>412 (24)</td>
<td></td>
</tr>
<tr>
<td>Born in Australia or New Zealand</td>
<td>4531 (68)</td>
<td>257 (65)</td>
<td>825 (66)</td>
<td>1174 (66)</td>
<td>1011 (68)</td>
<td>1264 (73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

†Chi-squared test for comparison of distribution of characteristic by age at diagnosis. ARIA, Accessibility/Remoteness Index of Australia.
hazard rate for MBC was highest at 12–23 months with a rate ranging from 2.4% to 3.3%, before dropping to 1.0% to 1.8% by 48–60 months (Fig. 1, Table 3).

Median OS for women with MBC was not significantly different between those aged less than 40 years and the older women (18 months vs 14 months respectively; log-rank \( P = 0.21 \)) (Fig. 2).

**Table 2** Five-year metastatic breast cancer risk following an initial diagnosis of non-metastatic breast cancer by age group

<table>
<thead>
<tr>
<th>Developed distant disease during follow-up</th>
<th>All</th>
<th>&lt;40 (10)</th>
<th>40–49 (11)</th>
<th>50–59 (10)</th>
<th>60–69 (10)</th>
<th>≥70 (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (localised/regional)</td>
<td>673</td>
<td>96 (24)</td>
<td>142 (11)</td>
<td>169 (10)</td>
<td>116 (8)</td>
<td>150 (9)</td>
</tr>
<tr>
<td>Localised</td>
<td>218</td>
<td>23 (12)</td>
<td>41 (6)</td>
<td>53 (5)</td>
<td>45 (5)</td>
<td>56 (5)</td>
</tr>
<tr>
<td>Regional</td>
<td>455</td>
<td>73 (37)</td>
<td>101 (17)</td>
<td>116 (17)</td>
<td>71 (14)</td>
<td>94 (18)</td>
</tr>
</tbody>
</table>

**Figure 1** Annual hazard for metastatic breast cancer (MBC) diagnosis following an initial diagnosis of localised or regional disease, by age at initial breast cancer diagnosis. (1) Under 40; (2) 40–49; (3) 50–59; (4) 60–69; (5) 70+.

**Table 3** Annual metastatic breast cancer hazard rate

<table>
<thead>
<tr>
<th></th>
<th>&lt;12 months</th>
<th>12–23 months</th>
<th>24–35 months</th>
<th>36–47 months</th>
<th>48–60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>3.0</td>
<td>6.7</td>
<td>8.6</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>40–49 years</td>
<td>0.8</td>
<td>3.3</td>
<td>3.2</td>
<td>3.1</td>
<td>1.6</td>
</tr>
<tr>
<td>50–59 years</td>
<td>1.0</td>
<td>3.0</td>
<td>2.6</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>60–69 years</td>
<td>0.9</td>
<td>2.4</td>
<td>1.8</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>70+ years</td>
<td>1.5</td>
<td>2.7</td>
<td>2.4</td>
<td>2.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Regional versus localised disease at diagnosis (OR 3.93, 95% CI 3.31–4.66; \(P < 0.0001\)), living in an area of low versus high socioeconomic disadvantage (OR 1.46, 95% CI 1.23–1.74; \(P < 0.001\)) and the presence of other non-breast primary (OR 1.61, 95% CI 1.13–2.29; \(P = 0.008\)).

**Organ sites of metastatic breast cancer**

At first record of MBC, spread to visceral sites was more common for women aged less than 40 years than older women (54% vs 43%; \(P = 0.03\), Table 4). A significantly greater proportion of young women had brain metastases recorded than older women (15% vs 8%; \(P = 0.02\)). There was also a trend for more bone (42% vs 33%; \(P = 0.05\)) and liver (28% vs 20%; \(P = 0.05\)) metastases in younger women versus older women.

**Discussion**

In this study, we provide the first Australian population-based data on the risk of development of MBC in women aged less than 40 years at initial diagnosis of non-metastatic BC. We found that nearly 1 in 4 young women developed MBC within 5 years, compared with 1 in 11 for women 40 years and older, representing an approximately threefold-greater 5-year risk of MBC for younger women versus older women. More than half of these young women had visceral metastases as first organ sites.

<table>
<thead>
<tr>
<th>Site of MBC</th>
<th>All ages</th>
<th>95% CI</th>
<th>&lt;40 years (%)</th>
<th>95% CI</th>
<th>(\geq40) years (%)</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1166)</td>
<td></td>
<td></td>
<td>(n = 123)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any viscera</td>
<td>518 (44)</td>
<td>42–47</td>
<td>66 (54)</td>
<td>44–62</td>
<td>452 (43)</td>
<td>40–46</td>
<td>0.03</td>
</tr>
<tr>
<td>Bone</td>
<td>399 (34)</td>
<td>32–37</td>
<td>52 (42)</td>
<td>34–52</td>
<td>347 (33)</td>
<td>30–36</td>
<td>0.05</td>
</tr>
<tr>
<td>Brain</td>
<td>104 (9)</td>
<td>7–11</td>
<td>18 (15)</td>
<td>9–22</td>
<td>86 (8)</td>
<td>7–10</td>
<td>0.02</td>
</tr>
<tr>
<td>Liver</td>
<td>243 (21)</td>
<td>19–23</td>
<td>34 (28)</td>
<td>20–37</td>
<td>209 (20)</td>
<td>18–23</td>
<td>0.05</td>
</tr>
<tr>
<td>Lung and pleura</td>
<td>296 (25)</td>
<td>23–28</td>
<td>33 (27)</td>
<td>19–36</td>
<td>263 (25)</td>
<td>23–28</td>
<td>0.38</td>
</tr>
</tbody>
</table>
of disease, compared with approximately 2 in 5 for older women. However, we found no significant difference in median OS for women with MBC between young versus older women (18 vs 14 months respectively; P = 0.21).

Our findings are consistent with results from international studies that have reported age is an important risk factor for developing MBC. One of the largest of these studies, De Bock and colleagues found age under 40 years was associated with a relative risk increase of 79% for metastases in a pooled analysis of 3600 women enrolled in European Organisation for Research and Treatment of Cancer trials where 406 patients (11%) were under the age 40.\(^{12}\)

Our study provides clinically relevant contemporary information for the general population of young women with BC to complement data available from clinical trials. Our finding of a 5-year MBC risk for young women of 24% is higher than estimates available from clinical trial data. Randomised trials of adjuvant chemotherapy or chemoendocrine therapy in premenopausal women from the 1990s have reported 5-year MBC risk estimates from 6% to 12%,\(^{4,5}\) with the latter estimate reported from a population where approximately 50% of women had node-positive disease,\(^{3}\) similar to the present study population (49% node-positive). Of note, these trial estimates are based on premenopausal populations and are therefore likely to overestimate the risk for the subgroup of premenopausal women under 40 years. Trials also apply selection criteria for patient enrolment, such that trial populations represent a selected patient population with outcomes that may not be representative of the broader BC population.

Study estimates available from non-trial populations are more consistent with our findings for Australian women. A large retrospective United States study of 652 women aged less than 35 years at BC diagnosis, among whom 67% were node-positive, treated at the MD Anderson Cancer Centre from 1973 to 2006 reported the proportion of women who developed distant recurrence within 10 years was 40%.\(^{13}\) It will be valuable to determine the 10-year cumulative incidence of MBC in our population once more updated data have been extracted to compare with these results.

Population-based cohort studies have shown conflicting results for survival differences between young and older women with BC. Several of these studies\(^{14-16}\) have reported significantly inferior survival in young women after adjusting for prognostic variables. This finding might be reflective of the higher stage and grade of tumours as well as different biological phenotypes of BC in these women.\(^{17}\) However, other studies using cancer registry\(^{18,19}\) and hospital database\(^{20}\) data have not demonstrated a significant difference in OS between young and older women with breast cancer despite similar analyses adjusting for prognostic factors, including stage. Similarly, our study also did not reveal significant difference in OS in young and older women with MBC. Differences in the rate of chemotherapy and other systemic treatment utilisation, and study population characteristics could potentially explain the discrepant findings in these population studies.

We observed a significantly higher proportion of young women with visceral disease as first sites of metastases than older women. This observation could be explained by biological differences in tumours originating in young versus older women. Data from a gene expression study of early BC identified unique oncogenic signalling pathways in young women that are characterised by reduced hormone sensitivity and higher HER-2 and EGFR expression, with a subsequent analysis demonstrating these age-specific biological differences can be largely explained by age-specific differences in tumour grade and subtype, with young age associated with more aggressive subtypes.\(^{17,21}\) These tumour characteristics can be expected to influence the different patterns of distant spread as compared with older women. In addition to the poorer prognosis associated with more aggressive subtypes, the differences in MBC risk observed between young versus older women could also reflect poorer treatment outcomes for this subgroup. Recent survival gains from advances and increased use of adjuvant systemic treatment that delay recurrence or even cure certain subtypes of breast cancer may be less effective in the more aggressive subtypes that tend to recur with early visceral spread.

The major strength of our study is that we have used population cancer registry data so our results can be interpreted as representative of the general Australian population of women with BC. Furthermore, with a large cohort of more than 6000 women, it provides us with a substantial power to examine the impact of age difference on survival following an MBC diagnosis.

There are several limitations to our study. First, our estimates of MBC may be subject to notification bias because progression to MBC will only be notified to the CCR if a woman has a hospital inpatient or day-procedure admission, or a biopsy analysed in a pathology laboratory that triggers a notification. For a woman with a clinical diagnosis of MBC made in an outpatient setting without a biopsy, CCR will not be notified until this woman requires hospitalisation for investigation or treatment. Notification bias may result in underestimation of the reported 5-year MBC incidence in our study. Second, the CCR does not routinely collect information on hormone receptor and HER2 status or types of treatment received for analyses of the impact of these factors on survival in young women.
Results from this study could provide valuable and contemporaneous population-based information for oncologists to counsel young women with BC and formulate survivorship plans.

Acknowledgements

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References

High-dose chemotherapy with autologous stem cell transplantation in relapsed or refractory germ cell tumours: outcomes and prognostic variables in a case series of 17 patients

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Abstract

Background: Optimal therapy for men relapsing after initial chemotherapy for germ cell tumours (GCT) is poorly defined. Both conventional dose salvage regimens and high-dose chemotherapy with autologous stem cell transplantation (HDCT-ASCT) have been utilised.

Aims: To examine patients who received HDCT-ASCT for relapsed GCT within a single Australian centre.

Methods: Records between 2000 and 2012 were analysed for baseline characteristics, treatment-related toxicity and survival. Prognosis at the time of HDCT-ASCT was classified according to the International Prognostic Factors Study Group (IPFSG).

Results: Seventeen patients received HDCT-ASCT, median age 34 (21–46), with 41% having primary refractory disease and 53% with high/very high risk disease by IPFSG. The most common regimen utilised was paclitaxel/ifosfamide followed by high-dose carboplatin/etoposide (TI-CE; n = 12). The median duration of grade 4 (G4) neutropenia was 11 days (range 9–17) with febrile neutropenia in 90% resulting in four intensive care unit admissions (8%). Median duration of G4 thrombocytopenia was 10 days (range 8–19) requiring a median of two pooled platelets bags (range 0–33) per episode. Transplant-related mortality occurred in one patient (veno-occlusive disease). Twenty-seven per cent of HDCT-ASCT cycles were associated with grade 3 mucositis (median total parenteral nutrition days = 5 (0–23)). Two-year progression-free survival (PFS) and overall survival (OS) rates were 59% and 71%. Patients who received HDCT-ASCT as second or subsequent relapse fared worse than those treated with HDCT-ASCT at first relapse (hazard ratio 0.23 (95% confidence interval: 0.04, 1.37; P-value 0.09). Three-year OS for those who received TI-CE at first relapse was 90%.

Conclusions: HDCT-ASCT for relapsed GCT is effective with acceptable toxicity. There was encouraging PFS/OS, particularly in a poor-prognosis cohort.

Introduction

Germ cell tumours (GCT) are one of the most curable solid neoplasms with chemotherapy. There is robust evidence supporting cisplatin-based first-line therapy for those with metastatic disease.1 Unfortunately, depending on pre-treatment clinical features, a significant proportion will relapse2–4 and require salvage treatment. Systemic treatment choices at relapse include conventional dose chemotherapy (CDC) or high-dose chemotherapy with autologous stem cell transplantation (HDCT-ASCT), with genuine uncertainty as to which is

Key words
stem cell transplantation, testicular neoplasm, germ cell tumour, salvage therapy, autologous transplantation.

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Abbreviations: CDC, conventional dose chemotherapy; FN, febrile neutropenia; G4, grade 4; GCT, germ cell tumours; HDCT-ASCT, high-dose chemotherapy with autologous stem cell transplantation; IPFSG, International Prognostic Factors Study Group; OS, overall survival; PFS, progression-free survival; TI-CE, paclitaxel/ifosfamide followed by high-dose carboplatin/etoposide; TIP, paclitaxel, ifosfamide and cisplatin; TPN, total parenteral nutrition; TRM, transplant-related mortality; VOD, veno-occlusive disease.

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better. Impressive results have been reported with either approach, but patient selection factors make comparison of reported outcomes difficult. Most of the data regarding HDCT-ASCT are retrospective and indicate significant morbidity and treatment-related mortality between 3% and 21%.9

Given the uncertainty regarding the best choice for first-line line salvage, CDC versus HDCT-ASCT is being investigated in a prospective, randomised, international clinical trial.6 When not participating in a clinical trial, clinicians usually base their decision on their own interpretation of published non-randomised data, the availability of HDCT and an assessment of prognosis, with HDCT-ASCT often favoured for those cases with a worse prognosis.

Several series have reported a variety of prognostic variables for patients undergoing HDCT-ASCT, but none with strong predictive value.7–9 An international collaboration of 1984 unselected patients at first relapse (International Prognostic Factors Study Group (IPFSG)) used multivariate analysis to identify non-seminomatous histology, primary mediastinal site, primary refractory disease, high pre-salvage tumour marker levels and the sites of metastases at relapse as prognostic.7 These factors were used to classify cases into five prognostic groups. The 3-year overall survival (OS) ranged from 77% in the very low-risk group to 6% in the very high-risk group.

We report here our institution’s experience of HDCT-ASCT for relapsed or refractory GCT. The pre-defined primary aim was to describe patient characteristics and assess morbidity and mortality of those who underwent HDCT-ASCT. The secondary aims included assessing prognostic variables associated with improved outcomes according to the previously published prognostic criteria.9

Methods

This retrospective case series reviewed patients with GCT who received HDCT-ASCT between 2000 and 2012 at Peter MacCallum Cancer Centre, Melbourne, Australia. Patients were identified from institutional databases and were included if they had histologically or tumour marker proven relapsed GCT treated with HDCT-ASCT with a minimum follow up of 30 days. Clinical and laboratory data were retrieved from a ‘transplant’ database, medical records and pathology databases. Patient characteristics, time to relapse, salvage chemotherapy details, detail of transplant-conditioning regimens, treatment-related morbidity and mortality, progression-free survival (PFS) and OS data were collected prospectively. Grade 4 (G4) neutropenia, thrombocytopenia and nephrotoxicity were defined by CTCAE v4.0 (NCI, DHS, USA).10 Haematological nadir counts were collected prospectively into the ‘transplant’ database and were cross-checked with retrospective review. Grade 3 (G3) mucositis was defined by total parenteral nutrition (TPN) requirement, given the inadequacy of retrospective documentation of enteral feeding. Patients received HDCT-ASCT under the discretion of the treating haematologist and medical oncologist. The paclitaxel/ifosfamide followed by high-dose carboplatin/etoposide (TI-CE) regimen was most commonly used which consisted of two cycles of paclitaxel (200 mg/m2, d1) and ifosfamide (2 g/m2/day, d2–4) for stem cell mobilisation given 14 days apart followed by three cycles of high-dose carboplatin (dosed to Area-Under-Curve divided over 3 days) and etoposide (400 mg/m2/day d1-3), each with autologous stem cell support planned to be given at 21-day intervals.11 The study design, data retrieval and analyses were conducted after institutional ethics committee approval.

Statistical analysis

Data were collected for patients who received at least one stem reinfusion. Morbidity data for continuous variables were reported as median and range and as percentages for qualitative variables. PFS was measured from the first day of stem cell reinfusion to disease progression or death from any cause. OS was measured from stem cell reinfusion to death from any cause. PFS and OS were estimated using the Kaplan–Meier product limit method. OS comparisons between those who received CDC at first relapse with subsequent HDCT at further progression versus upfront HDCT at first relapse were measured from the commencement of first-line salvage chemotherapy. Univariate associations with PFS and OS were investigated using the log-rank test and Cox proportional hazards regression for the following variables: first salvage chemotherapy regimen, initial remission duration, pre-transplant tumour marker levels, IPFSG prognostic category and histology. A P-value of <0.05 was considered statistically significant. Statistical analysis was performed using Excel (Microsoft, Redmond, WA, USA), GraphPad Prism 6 (Graphpad Software, La Jolla, CA, USA) and R version 2.15.2 software (R Development Core Team 2009, Vienna, Austria).

Results

Baseline characteristics of the 17 patients who received HDCT-ASCT are shown in Table 1. The median age was 34 (range 21–46). Thirteen out of 17 (77%) had non-seminoma histology and 7/17 (41%) of patients had primary refractory disease (defined as <90 days remission duration post-primary therapy). Demographics prior to transplant are shown in Table 2. A total of 49 cycles of
HDCT-ASCT was given (2 patients received 2 cycles, 15 received 3 cycles). The most common regimen was TI-CE in 12/17 (71%) patients. The average amount of CD34 cells delivered per patient was $4.69 \times 10^6$/kg (range 2.01–15.25 $\times 10^6$/kg).

The median duration of Grade 4 neutropenia was 11 days (range 9–17), which was associated with febrile neutropenia (FN) in 16/17 (94%) of patients (Table 3). Four patients were admitted to ICU with FN, and recovered. The median duration of Grade 4 thrombocytopenia was 10 days (range 8–19) with a median of two pooled bags of platelets transfused per patient (range 0–33). Eight out of 17 (47%) patients had Grade 3 mucositis documented by median duration of TPN use of 5 days (range 0–23). Five out of 17 (29%) patients had documented Grade 3 nephrotoxicity (of which 3/5 patients returned to within 10% of baseline), and 1/17 (6%) had documented Grade 3 ototoxicity.

The median follow up for survivors was 3.9 years (1.9–12.8). There was one death attributed to HDCT-ASCT in our cohort related to veno-occlusive disease (VOD). No risk factors for VOD were identified but VOD developed after receiving a third cycle of HDCT with carboplatin and etoposide as part of therapy for second relapse.

The PFS and OS at 2 years for the whole group were 59% (95% confidence interval (CI): 33–78%) and 71% (95% CI: 43–87%) respectively (Figs 1,2). Relapse after HDCT-ASCT occurred in four of five cases who received HDCT as second or later salvage, compared with two of 12 patients who received HDCT as first salvage (hazard ratio 0.23 (95% CI: 0.04, 1.37). The 2-year OS in each group was 60% and 83% respectively ($P$-value 0.09) (Fig. 3) when measured from the date of first salvage therapy, recognising that this is likely to underestimate the potential advantage of HDCT-ASCT as some patients receiving conventional dose chemotherapy for first relapse underwent salvage HDCT-ASCT at the time of second relapse.

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics prior to transplant</th>
<th>n = 17</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) (years)</td>
<td>34 (21–46)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-seminoma</td>
<td>13</td>
<td>77</td>
</tr>
<tr>
<td>Seminoma</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>IGCCG at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Poor</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Progression-free interval from initial chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>0–90 days</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>90–365 days</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Organ metastasis prior to salvage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Node</td>
<td>15</td>
<td>88</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>No. salvage regimens prior to high-dose chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 regimen</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>1 regimen (2 patients with TIP, I, E)</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>2 regimen (1 patient who received VeIE and cisplatin/etoposide)</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2 Characteristics prior to transplant

<table>
<thead>
<tr>
<th>Characteristics of HDCT-ASCT</th>
<th>n</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TICE</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>Conditioning with VIP prior to 3 cycles of CE as ASCT</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Conditioning with VIP prior to 2 cycles of CE as ASCT</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Conditioning with TC prior to 2 cycles of CE as ASCT</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Conditioning with TIP then received single sequential cycles of ASCT with CE, cyclophosphamide/carboplatin/mitoxantrone and doxorubicin/etoposide</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Consolidation after HDCT-ASCT

| No further treatment | 5 | 30 |
| Surgery             | 8 | 47 |
| Radiotherapy        | 2 | 12 |
| Missing             | 2 | 12 |

C, carboplatin; E, etoposide; HDCT-ASCT, high-dose chemotherapy with autologous stem cell transplantation; I, ifosfamide; P, cisplatin; T, paclitaxel; V, vinblastine.

### Table 3 Toxicity associated with HDCT-ASCT

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>16/17 (94%)</th>
<th>11 (9–17)</th>
<th>4/17 (24%)</th>
<th>10 (8–19)</th>
<th>2.3 pooled bags (0–33)</th>
<th>8/17 (47%)</th>
<th>5 (0–23)</th>
<th>1/17 (5.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median grade 4 neutropenia (range) (days)</td>
<td>16/17 (94%)</td>
<td>11 (9–17)</td>
<td>4/17 (24%)</td>
<td>10 (8–19)</td>
<td>2.3 pooled bags (0–33)</td>
<td>8/17 (47%)</td>
<td>5 (0–23)</td>
<td>1/17 (5.5%)</td>
</tr>
<tr>
<td>ICU admissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median grade 4 thrombocytopenia (range) (days)</td>
<td>16/17 (94%)</td>
<td>11 (9–17)</td>
<td>4/17 (24%)</td>
<td>10 (8–19)</td>
<td>2.3 pooled bags (0–33)</td>
<td>8/17 (47%)</td>
<td>5 (0–23)</td>
<td>1/17 (5.5%)</td>
</tr>
<tr>
<td>Median no. platelet transfusions (range)</td>
<td>16/17 (94%)</td>
<td>11 (9–17)</td>
<td>4/17 (24%)</td>
<td>10 (8–19)</td>
<td>2.3 pooled bags (0–33)</td>
<td>8/17 (47%)</td>
<td>5 (0–23)</td>
<td>1/17 (5.5%)</td>
</tr>
<tr>
<td>Grade 3/4 mucositis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HDCT-ASCT, high-dose chemotherapy with autologous stem cell transplantation; ICU, intensive care unit; TPN, total parenteral nutrition.</td>
<td></td>
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</tr>
</tbody>
</table>
salvage may have progressed and died without receiving HDCT-ASCT. For the patients who received HDCT as second or later salvage (n = 5), four received it as second salvage and one received it as third-line salvage. Patients who received TI-CE at first relapse (n = 10) had a 3-year OS of 90% compared with 50% for those who did not receive TI-CE (n = 2).

There was no statistical difference seen on univariate analyses with regards to remission duration from primary therapy, tumour markers prior to salvage, organ metastases prior to salvage or histology (Table 4). Of the eight patients with IPFSG very-low, low and intermediate prognostic category, three subsequently relapsed, compared with four of nine patients with IPFSG high/very...
high prognostic category (hazard ratio 2.39 (95% CI: 0.43, 13.2). The 3-year OS in each group was 75% and 56% respectively (P-value 0.30) (Fig. 4).

Discussion

This is the first Australian report of HDCT with ASCT for relapsed GCT, showing that it is deliverable, with promising results and an OS of 71% at 2 years. The OS data are better than other comparable published reviews5,11–15 and may reflect that most patients received three sequential transplants using a modern regimen emphasising rapid cycling of effective cytotoxics (TI-CE). Indeed, 3-year OS for those who received TI-CE at first relapse was impressive at 90% (9 of 10). An alternative explanation is that these better than expected results are due to chance.

Table 4 Factors predicting OS in univariate analyses

<table>
<thead>
<tr>
<th>Factor</th>
<th>n</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
<th>2-year OS with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial remission duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90 days</td>
<td>8</td>
<td>2.00</td>
<td>(0.37, 11.0)</td>
<td>0.41</td>
<td>75% (32%–93%)</td>
</tr>
<tr>
<td>≥90 days</td>
<td>9</td>
<td>0.37</td>
<td>(0.04, 3.93)</td>
<td>0.21</td>
<td>67% (28%–88%)</td>
</tr>
<tr>
<td>HCG prior to salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 IU/L</td>
<td>6</td>
<td>1.03</td>
<td>(0.19, 5.64)</td>
<td>0.98</td>
<td>67% (20%–90%)</td>
</tr>
<tr>
<td>≥12 IU/L</td>
<td>10</td>
<td>2.00</td>
<td>(0.37, 11.0)</td>
<td>0.41</td>
<td>70% (33%–89%)</td>
</tr>
<tr>
<td>AFP prior to salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 ug/L</td>
<td>8</td>
<td>4.09</td>
<td>(0.42, 39.5)</td>
<td>0.19</td>
<td>88% (39%–98%)</td>
</tr>
<tr>
<td>≥10 ug/L</td>
<td>7</td>
<td>1.77</td>
<td>(0.18, 17.0)</td>
<td>0.62</td>
<td>57% (17%–84%)</td>
</tr>
<tr>
<td>LDH prior to salvage</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;400 U/L</td>
<td>5</td>
<td>0.82</td>
<td>(0.016, 4.08)</td>
<td>0.81</td>
<td>80% (20%–97%)</td>
</tr>
<tr>
<td>≥400 U/L</td>
<td>8</td>
<td>1.77</td>
<td>(0.18, 17.0)</td>
<td>0.62</td>
<td>63% (23%–86%)</td>
</tr>
<tr>
<td>Organ metastases prior to salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not node only</td>
<td>8</td>
<td>1.77</td>
<td>(0.18, 17.0)</td>
<td>0.62</td>
<td>63% (23%–86%)</td>
</tr>
<tr>
<td>Node only</td>
<td>9</td>
<td>0.82</td>
<td>(0.016, 4.08)</td>
<td>0.81</td>
<td>78% (37%–94%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td>62% (31%–82%)</td>
</tr>
<tr>
<td>Non-seminoma</td>
<td>4</td>
<td>1.02</td>
<td>(0.016, 4.08)</td>
<td>0.81</td>
<td>100% (undefined)</td>
</tr>
</tbody>
</table>

AFP, alpha-fetoprotein; CI, confidence interval; HCG, beta human chorionic gonadotropin; LDH, lactate dehydrogenase; OS, overall survival.
given the small sample size and relatively short follow up. Transplant-related mortality (TRM) occurred in one case (5.5%). This is an improvement from early studies of HDCT-ASCT with TRM reported between 2% and 21% but similar to more recent data with ASCT.2,5,12–16

Given the limited sample size, we were unable to demonstrate statistical differences of validated prognostic variables.9 In terms of survival comparisons, in our cohort, very low to intermediate risk IPFSG category (n=8) was associated with 3-year survival of 75% compared with the published survival outcome of 53–77% in the original IPFSG report. When looking at high- and very high-risk IPFSG category (n=9), we had an excellent OS rate of 56% compared with 6–27% in the published report. Interestingly, even those with primary refractory GCT achieved remarkable outcomes with 75% disease free at 3 years (six of eight), showing the therapeutic utility of HDCT-ASCT for what is considered to be a poor prognostic group. A multivariate analysis to assess other factors associated with improved outcome was not appropriate due to the small sample size.

There is a strong rationale to use high-dose chemotherapy for GCT, particularly given the chemosensitivity of this malignancy, established high response rate, the relatively young age of those affected and infrequency of bone marrow involvement.17 The largest retrospective review of 184 patients who received high-dose chemotherapy followed by a single infusion of peripheral blood stem cells showed an encouraging PFS of 90% at 2 years with TRM at 3%.1 In that study, using HDCT at first salvage was associated with improved outcomes compared with using it for subsequent salvage with a hazard ratio of 2.2 (95% CI: 1.4–3.6). This result is similar to our cohort, with four out of five who had at least two lines of prior therapy relapsing after HDCT-ASCT. Hence the recommended options and regimens for high-dose salvage are less well defined in second relapse and therapy should be customised according to prior therapy and clinical characteristics.

More recent data have shown activity with the addition of paclitaxel to salvage therapy. Investigators at Memorial Sloan-Kettering Cancer Centre reported encouraging results with CDC utilising paclitaxel, ifosfamide and cisplatin (TIP) in men with relapse and a favourable prognosis18 and the TI-CE regimen19 in those with an unfavourable prognosis. In the phase II study using TI-CE, the 5-year OS was 52%.12 TI-CE was the most common HDCT used in our cohort and our data are encouraging with a 3-year OS of 90%, although a direct comparison is not appropriate given variations in patient selection and our limited follow up.

What is currently unknown is which patients to select for HDCT or CDC at first relapse in GCT. Beyer et al. analysed 55 matched pairs of patients receiving HDCT or CDC with hazard ratios for OS favouring HDCT between 0.77 and 0.83.20 Additionally, in the retrospective analysis from the IPFSG, improvement in PFS and OS was seen in each prognostic group (apart from low risk) for upfront HDCT over CDC.21

Figure 4 Overall survival according to the International Prognostic Factors Study Group (IPFSG) prognostic groups. IPFSG very low, low and intermediate groups were associated with improved outcomes compared to IPFSG high and very high group (hazard ratio (HR) 2.39, 95% confidence interval (CI): 0.43–13.2; 3-year overall survival (OS) 75% vs 56%; P-value 0.30). (—), Very low–intermediate; (——), high–very high.
Only one randomised prospective trial has aimed to address this question. In that study, only a single cycle of HDCT was used and the primary end-point showing superiority of HDCT was not met. Criticisms of this trial include that only a single cycle of HDCT was used, not all patients randomised on the HDCT arm went on to treatment and the higher than expected mortality rate that was seen in the HDCT arm. Using more than a single cycle of HDCT is supported by another trial showing that three cycles of high-dose carboplatin and etoposide is safer than one cycle of higher dose carboplatin, etoposide and cyclophosphamide.

Despite improving toxicity profiles of HDCT-ASCT and better prognostication of patients in the relapse setting, optimal treatment remains unclear. This question remains one of the most pressing in GCT and the conflict between retrospective and prospective data leads to a variation of approaches being used. In the IPFSG data set, 52% of patients were treated with CDC compared with 48% with HDCT. At Peter MacCallum Cancer Centre, only 30% of first relapse GCT between 2000 and 2012 were treated with CDC, although this likely reflects selection bias of a tertiary referral centre.

In this study, we have shown that TI-CE for first relapse is feasible and has provided promising outcomes, especially apparent in those with poor prognostic features at relapse. The TIGER study, a randomised prospective comparison between TIP and TI-CE in relapsed GCT, should be a high priority study internationally and supported in the Australian environment. The TIGER study will not answer all of the outstanding questions, such as the optimal number of cycles of HDCT-ASCT and whether subgroups of patients can be identified that should be managed differently (e.g. primary mediastinal GCT). Efforts are underway to develop international collaboration and clinical registries to try to answer such questions.

Our current approach, until the TIGER clinical trial becomes available, is to use TI-CE for the majority of men at first relapse with the possible exception of those with a very good prognosis or those not suitable for HDCT-ASCT (e.g. haemorrhagic cerebral metastases). Treatment at second relapse needs to be customised according to the patient’s characteristics and prior therapy. Post-chemotherapy surgical resection of residual masses is a key component of successful therapy. There is strong evidence that patients with a poor-prognosis undergoing first-line therapy have a better outcome when treated at a high volume centre and it is very likely that the same is true for men who relapse. We strongly recommend that patients with relapsed GCT be managed in a centre with specialised expertise, access to expert surgeons and appropriate experience with HDCT-ASCT.

**Conclusion**

This retrospective audit demonstrates that HDCT with ASCT for relapsed GCT is feasible, with a toxicity profile consistent with other published series. Additionally, we have shown promising outcomes with HDCT, especially using the TICE regimen and in those with poor prognostic features. Multimodality management at a centre of expertise is strongly recommended.

### References

Venous thromboembolism and underutilisation of anticoagulant thromboprophylaxis in hospitalised patients with inflammatory bowel disease

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Key words
Crohn disease, inflammatory bowel disease, ulcerative colitis, venous thromboembolism, anticoagulant.

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Abstract
Background: Venous thromboembolism (VTE) is a well-recognised extra-intestinal manifestation of inflammatory bowel disease (IBD). Despite the widespread support for anticoagulant prophylaxis in hospitalised IBD patients, the utilisation and efficacy in clinical practice are unknown.

Aims: The aim of this study was to assess the prevalence and clinical features of VTE among hospitalised IBD patients and ascertain whether appropriate thromboprophylaxis had been administered.

Methods: All patients with a discharge diagnosis of Crohn disease or ulcerative colitis and VTE were retrospectively identified using International Classification of Diseases, tenth revision codes from medical records at our institution from July 1998 to December 2009. Medical records were then reviewed for clinical history and utilisation of thromboprophylaxis. Statistical analysis was performed by Mann–Whitney test and either χ² tests or Fisher’s exact tests.

Results: Twenty-nine of 3758 (0.8%) IBD admissions suffered VTE, 13 preadmission and 16 during admission. Of these 29 admissions (in 25 patients), 24% required intensive care unit and 10% died. Of the 16 venous thrombotic events that occurred during an admission, eight (50%) did not receive anticoagulant thromboprophylaxis and eight (50%) occurred despite thromboprophylaxis. Most thromboembolism despite prophylaxis occurred post-intestinal resection (n = 5, 63%).

Conclusion: Thromboprophylaxis is underutilised in half of IBD patients suffering VTE. Prescription of thromboprophylaxis for all hospitalised IBD patients, including dual pharmacological and mechanical prophylaxis in postoperative patients, may lead to a reduction in this preventable complication of IBD.

Introduction
Venous thromboembolism (VTE) is a well-recognised extra-intestinal manifestation of inflammatory bowel disease (IBD) and hospitalised patients are at increased risk.1 The rate of VTE in IBD in clinical studies ranges between 1% and 8%3,4 and up to 39% in post-mortem studies.4 In population-based studies, IBD patients are twofold to threefold more likely to develop deep vein thrombosis (DVT) or pulmonary embolism (PE) compared with age- and sex-matched controls3,6 and eight-fold more likely during a disease flare.7 Furthermore, VTE may also occur in atypical sites including cerebral venous sinus,8 portal vein,9 hepatic vein,10 mesenteric vein11 and retinal vein.12 The risk of mortality of these IBD-related thromboses is high, rising to 22% to 25% in some series.2,11

The pathophysiology of VTE in IBD is multifactorial and may include increased thrombin generation during active disease,14 platelet activation and aggregation15 and impaired fibrinolysis.16 Furthermore, during hospitalisation-acquired risk factors including active inflammation, immobilisation and surgery17 may further increase the risk of VTE. Moreover, VTE is increasingly prevalent among hospitalised IBD patients and is
associated with a greater mortality and higher in-hospital costs compared with non-IBD patients.1 Anticoagulant prophylaxis has been shown to reduce the risk of symptomatic VTE in at-risk hospitalised medical patients by over half.18 Several practice guidelines including the European Crohn and Colitis Organisation (ECCO) consensus statements for the management of ulcerative colitis (UC) and Crohn disease (CD) advocate the use of thromboprophylaxis in all hospitalised IBD patients.19,20 Despite the widespread support for anticoagulant prophylaxis for preventing VTE in hospitalised IBD patients, the utilisation and efficacy in clinical practice is largely unknown. The aim of this study was to assess the rate and clinical features of VTE among hospitalised IBD patients and ascertain whether appropriate anticoagulant thromboprophylaxis had been administered in this high-risk population.

Methods

Data source and identification of cases

All patients with diagnostic and procedural codes for IBD and thromboembolism according to the International Classification of Diseases, tenth revision (ICD-10)21 were identified in the Southern Health Network database (Victoria, Australia) from July 1998 to December 2009. Cases included patients of all ages with a discharge diagnosis for CD, UC or indeterminate colitis and VTE (see Supplementary Table S1 for ICD-10 codes). All cases of VTE in IBD patients were confirmed by review of hospital records and imaging procedures. When PE and DVT were concurrent, the diagnosis of PE was only used in analysis. In VTE cases, IBD location, behaviour and severity were assessed according to the Montreal classification.22 Patient demographics, VTE risk factor assessment and medications were obtained from medical record review. We reported VTE prophylaxis as any hospitalised patient who had received subcutaneous low molecular weight heparin (enoxaparin 40 mg daily or 20 mg daily if glomerular filtration rate < 30 mL/min), subcutaneous unfractionated heparin (5000 units 8- or 12-hourly) or warfarin prior to a venous thromboembolic event. The use of mechanical methods of thromboprophylaxis such as graduated compression stockings and intermittent pneumatic compression (IPC) devices was not assessed in this study. The study was conducted with the approval of local ethics committees.

Statistical analysis

Data are presented as mean and standard error of the mean (SEM) or proportions. We calculated data in IBD patients as a whole and in CD and UC patients separately. Differences between CD and UC were analysed using Mann–Whitney test for continuous variables and either χ² tests or Fisher’s exact tests for proportions or categorical variables. Two-tailed P-values of < 0.05 were considered significant.

Results

There were 3758 admissions with a diagnosis of IBD during the study period, of which 25 patients had 29 (0.8%) venous thromboembolic events. This included 12 (48%) patients with CD and 13 (52%) patients with UC. Mean length of hospital stay for patients with VTE was 27 ± 5 days. There were three (10%) deaths during an admission with VTE and seven (24%) cases required admission to the intensive care unit (ICU).

Type of VTE and clinical features of hospitalised IBD patients with VTE

Table 1 shows the location of VTE suffered by IBD patients. Most IBD patients with VTE suffered DVT (n = 8, 28%) or PE (n = 18, 62%). Four patients had concurrent DVT and PE. One patient with UC had transverse and sigmoid cerebral venous sinus thrombosis resulting in left occipital and temporal lobe infarcts. The clinical profile of patients with IBD and VTE is shown in Table 2. Mean age of patients with VTE was 54 years. Disease distribution in CD patients with VTE was predominantly colonic or ileocolonic whereas in UC a significant proportion of patients had pancolitis. The majority of patients with UC and VTE had at least moderate disease severity according to Montreal classification.22 Over half of patients were receiving corticosteroids at time of VTE. In comparison, few patients were receiving immunomodulator (azathioprine, 6-mercaptopurine or methotrexate) or anti-tumour necrosis factor-alpha therapy at time of VTE. When serum markers were available, the majority of IBD patients had raised C-reactive protein (CRP) (CRP >
Table 3 VTE risk factors in hospitalised IBD patients with VTE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CD (n = 15)</th>
<th>UC (n = 14)</th>
<th>Total (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of VTE (%)</td>
<td>5 (33)</td>
<td>1 (7)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Postoperative (%)</td>
<td>4 (27)</td>
<td>4 (29)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Advanced age (&gt;65 years) (%)</td>
<td>7 (47)</td>
<td>3 (21)</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>0 (0)</td>
<td>1 (7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Central venous catheter (%)</td>
<td>5 (33)</td>
<td>1 (7)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Trauma/immobility (%)</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30) (%)</td>
<td>2 (13)</td>
<td>2 (14)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>OCP/HRT (%)</td>
<td>0 (0)</td>
<td>1 (7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Thrombophilia (%)</td>
<td>0 (0)</td>
<td>1 (7)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Data are number (%) for all comparisons between CD and UC. P = not significant except for *P < 0.01 for x² comparison. Utilisation of anticoagulant thromboprophylaxis

Of the 29 venous thromboembolic events, 13 (45%) occurred as the admitting diagnosis and prior to the utilisation of thromboprophylaxis and 16 (55%) occurred during the hospital admission. Of the VTE during admission, eight (50%) did not receive thromboprophylaxis. Of the eight patients with VTE despite thromboprophylaxis, five (63%) were post-intestinal resection and a further two patients (25%) had prior VTE. In these patients with VTE despite anticoagulant prophylaxis, three (19%) patients received prophylactic dose low molecular weight heparin, four (25%) patients received prophylactic dose unfractionated heparin and one (6%) patient was taking warfarin prior to VTE with therapeutic international normalised ratio level.

When VTE events were analysed according to admission date (prior to or since 1 May 2004), the percentage of inpatient VTE events in patients not receiving thromboprophylaxis decreased from 62% to 40% (P < 0.05) in the more recent cohort. A subsequent 6-month audit of thromboprophylaxis rates for all hospitalised IBD patients from July 2010 to January 2011 following reinforcement of pre-existing hospital thromboprophylaxis protocols (Fig. 1) through email and direct verbal education to treating gastroenterology registrars revealed that 69 of 91 (76%) IBD patients received appropriate thromboprophylaxis.

Discussion

To our knowledge, this is the first study to document the utilisation of anticoagulant thromboprophylaxis in patients with IBD. We found half of hospitalised IBD patients suffering VTE were not receiving thromboprophylaxis despite being recommended in IBD practice guidelines. The rate of VTE in hospitalised patients with IBD in this study was 0.8%. One of the earliest epidemiology studies of VTE in hospitalised IBD patients reported a 0.9% rate of VTE over an 11-year period at the Mayo clinic. Although VTE is relatively infrequent in IBD, the morbidity and mortality of these patients are high. We found an in-hospital mortality rate of 10% and a mean duration of hospital stay of 27 days including a significant proportion of patients requiring admission to an ICU. Therefore, this represents a potentially preventable area of morbidity and mortality in IBD patients.
Despite efficacy of thromboprophylaxis regimens in hospitalised medical patients, previous studies have also reported the underutilisation of VTE prophylaxis in acutely ill medical patients. Possible reasons for low use of anticoagulant thromboprophylaxis in IBD patients may relate to active gastrointestinal haemorrhage, coexistent anaemia, renal impairment or recent surgery. However, early clinical trials using heparin as treatment for severe steroid-refractory UC suggested anticoagulants are safe with respect to complications of bleeding. Furthermore, catheter-directed thrombolysis has been used for IBD-associated thromboembolism and appears to be well tolerated in terms of haemorrhagic complications. Current ECCO practice guidelines for the management of IBD advocate the use of antithrombotic prophylaxis in all hospitalised UC and CD patients. However, adherence to practice guidelines in IBD has been noted to be suboptimal in previous studies. Our results also suggest that despite registrar education regarding thromboprophylaxis protocols in IBD at our institution, utilisation of anticoagulant prophylaxis remains inadequate. Therefore, increased awareness of VTE in IBD as well as improved implementation of current clinical guidelines is necessary.

Another novel finding of this study is that of patients who developed VTE after admission for IBD, half of patients were receiving standard thromboprophylaxis at the time. Whether these were new VTE events or pre-existing subclinical thromboses that became clinically apparent after admission to hospital is unclear. Additional studies are needed to determine the prevalence of asymptomatic VTE in IBD patients and whether screening tests such as D-dimer or lower limb ultrasounds would be cost-effective in this population. However, it raises the possibility that a subset of IBD patients may actually require higher dose or extended duration anticoagulant prophylaxis. We found that the vast majority of these patients had significant prothrombotic risk either being post-intestinal resection or with previous VTE. Recommendations for patients at high risk for VTE following abdominal-pelvic surgery who are not at high risk for major bleeding complications suggest adding mechanical thromboprophylaxis. There is little evidence to support the efficacy of mechanical prophylaxis although one randomised trial showed a reduction in asymptomatic DVT using IPC in patients with intracranial haemorrhage. Nevertheless, dual pharmacological and mechanical thromboprophylaxis...
may be advisable in IBD patients undergoing intestinal resection. We also found that over 20% of IBD patients with VTE had prior venous thromboembolic events. Patients with IBD are at increased risk of recurrent VTE compared with controls and consideration should be given to long-term anticoagulant therapy for IBD patients with a second episode of unprovoked VTE given the risk of recurrence.

It is likely that we identified more VTE in the cohort due to the presence of active disease as indicated by raised CRP, anaemia and corticosteroid use. Grainge et al. also found a higher rate of VTE at time of IBD flare as defined by a period 120 days after new corticosteroid prescription. Active IBD may promote VTE due to reduced mobility, specific immune factors and the possible effects of systemic medications such as corticosteroids. However, despite significant disease activity, relatively few patients in our cohort were receiving immunomodulator or biologic therapies. This may represent an underprescription given that disease remission may reduce thromboembolic risk in IBD. Alternatively, this may reflect a cohort effect as biologic therapy was not widely available during the early study period. Nevertheless, not all thromboembolic events occur during disease flare which gives rise to the question of whether IBD itself is prothrombotic or is associated with inherited thrombophilic disorders. We found that despite over one fifth of thromboembolic events occurred in patients with a history of VTE, only one patient had a documented history of a thrombophilic disorder. Although testing for inherited thrombophilia was beyond the scope of this present study, previous data have shown a lower rate of inherited risk factors in IBD patients.

Limitations to this present study include possible diagnostic coding errors, which are inherent in any observational case series using administrative databases. However, to minimise this error, all cases of IBD and VTE were confirmed with medical chart review. Moreover, results from case series may be confounded by selection bias such as hospitalised patients drawn from single healthcare network. Whether our results reflect the non-hospitalised IBD population is unknown. We were also unable to compare VTE and thromboprophylaxis rates with non-IBD medical patients. However, previous studies have also documented suboptimal anticoagulant thromboprophylaxis rates among at-risk medical patients of 40–60%.

Conclusion

In summary, VTE in IBD patients are associated with significant morbidity and mortality and anticoagulant thromboprophylaxis is underutilised in hospitalised patients. Major efforts to reduce VTE in IBD patients should focus on correction of acquired risk factors including early patient mobilisation and the use of anticoagulant prophylaxis in the absence of life threatening haemorrhage. Furthermore, dual pharmacological and mechanical prophylaxis in IBD patients undergoing intestinal resection may reduce VTE postoperatively. Improved adherence with IBD practice guidelines including thromboprophylaxis for all hospitalised IBD patients may lead to a reduction in this preventable extra-intestinal manifestation of IBD.

References

Table S1  ICD-10 codes for IBD and VTE as per the International Classification of Diseases, 10th revision.21

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:
Medical service redesign shares the load saving 6000 bed days and improving morale

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Key words
continuous quality improvement, duty hour/work hour, healthcare quality improvement, hospital medicine, lean management.

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Abstract

Background and Aims: In 2010, demand on the Auckland City Hospital general medical service exceeded capacity. A review by the Royal Australasian College of Physicians was critical of training offered to registered medical officers, and low morale was a problem across the service. Management offered support for an improved model that would solve these problems.

Methods: A project to redesign the general medical service was undertaken. Baseline analysis found uneven workload and insufficient capacity at peak times for patient presentations. Workshops involving the entire service led to a new model that splits workload and teams into patients likely to have a short stay from those requiring longer, ward-based care. Admissions are now distributed over 12 teams on weekdays and 4 on the weekends. There was an increase of approximately 2.5 in consultant full time equivalents but no change in registrar or house officer staffing.

Results: Since the introduction of the new model, the average length of stay has fallen from 3.7 to 3.2 days (14%) and the median length of stay by 28%, resulting in a saving of 6000 bed days per year. Readmission, inpatient and 30-day mortality rates are unchanged. These results have been sustained over 18 months with signs of continuing improvement.

Conclusion: This project owes its success to the following factors – management support; iterative engagement of a range of staff; provision of timely data analysis; increases in senior medical officer staffing and reorganisation leading to more predictable and fair work practices. One challenge is discontinuity, whether between doctors and patients or within the medical team.

Introduction

Auckland City Hospital has 1200 beds and serves a local catchment of 500 000 as well as providing regional and national services. The general internal medical (GIM) service admits an average 42 patients a day. There are 12 medical teams, four medical inpatient wards, and a short-stay inpatient unit next to the emergency department (ED). The assessment of general practitioner-referred patients occurs in the admission and planning unit (APU) that doubles as the short-stay unit for both medicine and surgery.

In 2010, the service was struggling for several reasons. These included uneven work distribution with some teams having more than 20 patients and others as few as 2 or 3. In the weekends, the two medical teams on call were unable to cope with large workload. Registrars and House Officers, collectively known as resident medical officers (RMO), felt they were treated as ‘cogs in a wheel’ with little attention to training. One consultant who had been a champion of general medicine died unexpectedly. Resistance of the staff to change had led to a long-term Clinical Director (DS) to resign from the post and another (AN) reluctantly agreed to take on an interim role. There were gaps in the RMO rosters that needed to be filled by the senior medical officers (SMO) and SMO shortages. The morale among all GIM staff was very low.

Methods

A project sponsored by a senior manager (BS) was led by the interim clinical director and the improvement project manager (TD) who has experience in Lean/Six Sigma. A series of workshops was held with physicians, nursing and allied health staff. A working group was formed of a small number of motivated physicians, the service...
manager (SM) and the chief medical resident (AJ). A baseline analysis measured patient flow, occupancy, waiting times, presentation volumes by time of day and workload per medical team.

Four key problems were identified:
1. Patients spread over whole hospital: Each medical team was responsible for patients on the four general medical wards and in APU and the ED. This led to long ‘safari’ ward rounds, poor communication with the separate multidisciplinary teams, delays in the admitting registrars getting down to start work in the APU/ED, and probably longer-than-necessary hospital admissions. The discharge plans were often not written until late in the day patients, so patients appropriate for discharge from APU ended up being admitted to the wards.
2. Uneven workload: While there were 12 medical teams, only four teams took new patients on a weekday and only two teams on the weekend. The medical roster was eccentric, leading to ‘boom and bust’ workloads. Occasionally, one team would have as many as 30 patients, while another had just a couple. For patients at the tail end of the very long ward, round decisions were made late and possibly poorly.
3. Insufficient supervision: The SMO in GIM were present in the mornings, but many had clinics in the afternoons. This left the on-call registrars unsupported in the later part of the day. There was an impression that patients who may have been discharged from hospital were kept in for an SMO review the next day. More worryingly, sick patients could wait for 24 h before consultant review.
4. Excessive weekend workload: Having only two teams rounding on the weekends meant that patients beyond an agreed cap of 30 new patients were referred to subspecialty services that were not always resourced to take care of these acute medical patients. Weekend rounds were long, and there was no opportunity to review patients who might be fit for discharge. Very few patients other than those seen on the post-acute ward were discharged on the weekend.

With the assistance of engineering science students, the project group designed a new model of care based on the following principles:
1. The workload would be balanced daily across the medical teams.
2. Teams would be strictly ward based (pure geographical care).
3. Teams should be restricted to either acute care or ward responsibilities at any one time (division of work based on stratification of patient complexity).
4. There would be increased SMO support for the RMO in the afternoon and evening.
5. An enhanced teaching programme for RMO would be developed.

Description of the new work model

In the new model, there is a total of 12 teams, two on each of the four medical wards and four based on accident and emergency department (AED)/APU. Each medical team spends 1 week based in APU/ED followed by 2 weeks on their inpatient ward. Longer rotations were considered, but other work commitments of many SMO led to this as the preferred option.

The new model requires 20 SMO to run the service (an increase from 16), five for each of the four ward-based teams. At any time, four SMO per ward-based team are on the schedule, three working clinically as described earlier, and the fourth on a rostered ‘week four’ off the wards for non-clinical work, teaching and assistance with covering sick leave or roster gaps. At the end of their non-clinical week, the four SMO (one from each team) are on call for the weekend, together with their team’s RMO working in APU/ED.

On every weekday, each patient admitted over the previous 24 h is assigned to one of the eight teams working on the four wards or to one of the four teams based on APU/ED. On the weekend, the patients are evenly distributed across the four teams rounding. Duty managers endeavour to admit patients to the home ward of the RMO who had admitted the patient, but if this is not possible and the patient goes to another medical ward, their care is transferred to the teams based on that ward. This means that there are no outliers other than those on non-medical wards.

The SMO trialled, then after some initial reluctance, agreed to incorporate into the new model a ‘4 pm to 8 pm’ shift when they are on call. This occurs one night in 20 across the year. During this period, the SMO carries the referral phone. This has the dual benefit of providing expert advice to general practitioners that may allow the patient to be managed as an outpatient, as well as freeing up the evening RMO to admit. Usually, the SMO will also review patients for possible discharge without an overnight stay and any who are unstable. They also supervise and teach medical students on the evening shift. This occurs every day including the weekends, in recognition of the need to provide consultant-led care 7 days a week.1,2

Several other changes were made to match better the workload with the patterns of referral. The number of admitting registrars from 4 pm to 10 pm increased from two to three over the winter months. In summer, this third registrar is on call-back. The overnight staffing was changed so that instead of a registrar dedicated to subspecialty work and a general medical registrar and house officer, there are now three registrars who divide up the work of the night shift evenly between them. The priority here was for patient safety because the workload meant...
there was little opportunity for the registrar to supervise the inexperienced house officer. Finally, the service committed to the employment of medical officers (MO) who are senior non-training doctors without specialist qualifications employed to work on the admitting floor both receiving referrals and admitting patients. They also oversee the RMO and distribute work to maintain flow. Recently, an additional MO has been employed with extension of their roster until 8 pm on weeknights and daily on the weekends, but this is not included in the analysis.

On the appointment of a clinical director with experience in leading service development and change (RT), the previous interim clinical director took over the redesign and supervision of an enhanced teaching programme for the RMO. Now, all RMO in the department are supervised by one of four dedicated educational supervisors. This person ensures that RMO have regular meetings with their clinical supervisor, participate in audits, case presentations and mini-clinical evaluation exercises. In addition, a new 8 am teaching programme occurs 3 days a week for those not required to attend handover. This includes a weekly case-based tutorial for registrars.

Outcomes

Records were obtained from the hospital’s electronic database. For the purposes of this analysis, data were collected for two time-periods, the pre-change period (November 2009 to November 2011) and the post-change period (December 2011 to December 2013). The new model was implemented in December 2011. Any seasonal variations in patient volumes and diagnoses would affect both groups equally.

Five main outcomes were studied. These include mean and median length of stay (LOS), readmission rates, proportion of patients discharged over the weekends and proportion of patients discharged from APU/ED. LOS was measured in days and calculated for each patient using admission and discharge times. Readmission rates were measured as the proportion of patients from each time period that were readmitted within 7 days of discharge. The weekend discharges were measured as the proportion of all discharges that occurred on Saturdays or Sundays. The APU/ED discharges were measured as the proportion of all general medicine discharges that occurred from APU/ED. Patient volumes were measured in each period to ensure any changes in the outcomes were not due to changing workload.

Statistical analysis

To determine whether there was a significant difference in median LOS, we used a Mood’s median test comparing the median LOS in the pre-change period to the median LOS in the post-change period. The median is a preferable test to detect a difference because it modulates the influence of outliers in the samples. The difference in mean LOS was assessed using a two-sample t-test. Run charts of both mean and median LOS were produced to visualise any trends or step changes. A significant difference in mean LOS allows for an estimate of cost-savings. The differences between the two time periods in discharges occurring from APU/ED, discharges occurring from the entire service during weekends, and per cent of patients readmitted within 7 days following their discharge, were all assessed using the difference in proportions test.

Results

During the two study periods, a total of 23,148 patients was discharged from general medicine in the pre-change period and 26,171 in the post-change period. Figure 1 shows the mean monthly LOS from 2007 to the end of the post-change study period. A step change is apparent immediately following implementation of the new model. The mean LOS in the post-change period was statistically significantly shorter than in the pre-change period (3.145 days vs 3.525 days, P < 0.001). This equates to approximately 6000 bed days per annum saved.

Figure 2 shows the median LOS during the same time period as earlier. The median LOS is significantly shorter in the post-change period (1.355 days vs 1.843 days, P < 0.001). To ensure that these statistically significant differences were not the result of a continuously down-trending LOS because of other factors in the hospital or service environment, we analysed each year independently with 95% confidence intervals. The yearly averages were fairly constant until the model change. This stability is also apparent on the run charts (Figs 1, 2).

Figure 3 shows weekly 7-day readmission rates. There is no difference between the two study periods. (7.3% pre-change vs 7.1% post-change). The total number of weekend discharges seems to be trending positively since 2010 when nurse facilitated discharges were introduced and is explained in part by increasing volumes. However, there was a clear improvement in the proportion of total discharges occurring on weekends after the model change (Fig. 4) (8.2% pre-change vs 11.0% post-change, P < 0.001). The proportion of patients who were discharged from APU and ED increased significantly in the post-change period (Fig. 5) (42.5% pre-change vs 46.3% post-change, P < 0.001).

There was no further decanting of patients to subspecialties with the new model. There were other positive effects of the change that are palpable throughout the service. A survey of staff 6 months after the
change showed that most were happy, and now, no SMO would prefer the old system. Anonymous feedback from RMO shows that they are very happy with the teaching programme, which continues to develop. Recruitment of SMO posts has improved with full staffing and a growing waiting list of job applicants.

**Discussion**

This paper documents the process and successful outcomes of a comprehensive service redesign. This was a radical departure from the traditional roster where all teams did the same type of work each week.
About half of the patients are discharged from AED/APU. To increase continuity of teams with patients, the bed managers make it a priority to admit patients to the home ward of the team. Initially, patients may be cared for by one of the other two teams on the home ward, but once the AED/APU doctors rotate upstairs, they may catch up with these patients. There are concerns that patients who might now see three or occasionally more consultants during their hospital stay would receive poorer care as a result. There is no evidence to suggest that this is the case and some indicators to the contrary. Each day, the level two patients are divided evenly between the four SMO, and on the inpatient wards, the new patients are divided between the two SMO so that each sees a small number of new patients. This allows time to review carefully the electronic clinical record and previous day’s results in a way that was not possible previously. The additional SMO reviews function as second and sometimes third opinions with potential improvements in diagnosis and care. In addition, there are no more safari ward rounds, with teams working nearly exclusively on one ward for the day. This fosters a closer relationship between the medical teams, and the nursing and allied health staff, and efficiency in areas of team communication and discharge planning.

A more problematic issue is maintaining continuity of supervision. In the new model, RMO rotate on a three-weekly basis between APU/ED and the wards. This is out of step with the SMO who are on a 4-week rotation and who occasionally come off the roster altogether for leave. Previously, a consultant physician could expect to work with the same registrar for at least 4 months. Now, they work with all four team registrars (and house officers) on a continually rotating basis. The notion of a ‘team’ has been adjusted. It consists of the six to eight SMO, four registrars, four house officers and final year students, all attached to one ward. Within this framework, RMO has the opportunity to work with consultants who have a

Figure 3 Proportion of patients discharged from the accident and emergency department and the admission and planning unit (Level 2). LCL, lower confidence limit; UCL, upper confidence limit.

Figure 4 General medicine weekend discharges from inpatient wards.
range of skills and styles during their 6-month attachment. There is one educational supervisor for each team tasked with oversight of training for all that team’s RMO while in general medicine. Evaluations are more balanced and fair because input regarding RMO performance is required from the wider SMO team. Recently, RMO expressed a desire to spend longer periods in one place. Currently, we are piloting a change in the roster that has the RMO spending 2 weeks in APU/ED and 4 weeks on the ward.

After 18 months, most SMO are comfortable with working alongside their RMO in the ED after-hours. While no-one enjoys holding the referral phone, the benefits of a closer working relationship with and support for the RMO on duty are obvious. In addition, the medical students get the opportunity to admit an acutely unwell patient with SMO supervision. While the 5% increase in the numbers of patients discharged from the short-stay areas is most likely the result of having dedicated medical teams based on the floor, the increased SMO presence with greater confidence to discharge safely a patient without an overnight stay will have helped. An alternative explanation is that the increase in presentations that we (and all other ED) are seeing is of people with minor conditions that would normally be dealt with in primary care. In fact, there has been a relative increase in the more serious triage categories attending the ED over this time. However, in 2013, the percentage of patients seen by ED and referred to specialty services, particularly to surgery, increased. This is presumably the effect of improved compliance with the 6-h rule. There is also a peak in July most years related to the high workload. Neither of these phenomena aligns with the clear increase in discharges that was seen as soon as the new model was introduced.

Conclusion

We have observed significant benefits as a result of this bundle of changes to our work model, the main components of which include spreading the workload over a wide range of teams (line averaging), stratifying short-versus long-staying patients to different teams, allocating patients and teams geographically, and increasing the SMO resource to the service, in particular their presence on the admitting floor after hours. There is no indication that the shorter LOS has been associated with poorer quality care, with the 7-day readmission rate staying at 7% and the 30-day mortality numbers, the lowest in a decade. Decreased mortality has been reported by others in association with decreased LOS. Staff satisfaction with the new model has not been formally evaluated after the initial survey at 6 months, but anecdotal comments are consistently positive in relation to the change despite the increased after-hours workload for SMO. There is competition for general medical registrar and house officer posts and a waiting list for SMO positions.

References

1 Academy of Medical Royal College. Seven day consultant present care: implementation considerations, 2013. [cited 2014 Jun 28]. Available from URL: http://www.aomrc.org.uk/doc_view/9728-seven-day-consultant-present-care-implementation-considerations

2 Knietowicz Z. More consultant ‘generalists’ are needed to deliver seven day hospital care, report says. BMJ 2013; 347: 60915.


Effect of endurance training on expiratory flow limitation and dynamic hyperinflation in patients with stable chronic obstructive pulmonary disease

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Key words
COPD, exercise training, expiratory flow limitation, dynamic hyperinflation, exercise endurance.

Abstract
Background: Expiratory flow limitation (EFL) is the primary pathophysiological hallmark of chronic obstructive pulmonary disease (COPD). However, the effect of lower-extremity endurance training alone on EFL in patients with COPD remains largely unknown.

Aim: This study aims to determine the effects of endurance training on EFL and dynamic hyperinflation in patients with stable COPD.

Methods: This was a prospective, single-blinded, non-randomised controlled 12-week study recruiting Chinese patients with stable COPD in an endurance training group (n = 15) or a control group (n = 13). Before and at the end of the study, we measured the EFL, pulmonary function, peak inspiratory flow (PIF) and maximum inspiratory pressure (MIP); moreover, the patients underwent a constant work rate exercise test in which Borg dyspnoea scale, tidal breathing flow volume curves and inspiratory capacity (IC) were determined every other minute.

Results: Exercise training significantly improved the exercise endurance time (7.00 ± 3.05 vs 18.13 ± 6.44 min, \( P < 0.001 \)), MIP (69.49 ± 16.03 vs 80.18 ± 15.97 cmH2O, \( P < 0.001 \)) and PIF (3.96 ± 1.01 vs 4.51 ± 1.13 L/s, \( P = 0.014 \)), but not EFL (3.33 ± 0.49 vs 3.40 ± 0.51, \( P = 0.334 \)). Subjects on training had decreased breathing frequency (26.26 ± 7.13 vs 23.15 ± 5.34 breaths/min, \( P = 0.002 \)), minute ventilation (30.28 ± 7.52 vs 26.85 ± 4.17 L, \( P = 0.013 \)), tidal peak expiratory flow (1.53 ± 0.22 vs 1.32 ± 0.20 L/s, \( P = 0.006 \)), mean expiratory flow (0.87 ± 0.19 vs 0.68 ± 0.15 L/s, \( P = 0.011 \)) and Borg dyspnoea score (7.20 ± 1.15 vs 3.93 ± 1.39, \( P < 0.001 \)), as well as increased IC (1.50 ± 0.34 vs 1.67 ± 0.45 L, \( P = 0.002 \)), expiratory time (1.47 ± 0.62 vs 1.72 ± 0.62 s, \( P = 0.004 \)) and inspiratory flow reserve (2.05 ± 1.10 vs 2.95 ± 1.19 L/s, \( P = 0.002 \)) at isotime. These changes were not observed in the control group.

Conclusion: Endurance training may benefit stable COPD patients in improving exercise endurance, inspiratory muscle strength, ventilatory requirements, exercise-induced hyperinflation and exertional dyspnoea.

Introduction
Chronic obstructive pulmonary disease (COPD) is predicted to be the third leading cause of mortality and the fifth leading cause of chronic disability in the world by 2020.1 Exercise intolerance is the major complaint of these patients, due to pulmonary conditions, peripheral skeletal muscle dysfunction,2 psychological factors and cardiovascular abnormalities.3 Expiratory flow limitation (EFL) is the primary pathophysiological hallmark of COPD.4 According to a recent hypothesis, EFL plays an important role in the transition from peripheral airway disease to overt COPD in smokers.5 The presence of EFL during tidal breathing promotes dynamic hyperinflation (DH) and intrinsic positive end-expiratory pressure (PEEPi), with concurrent dyspnoea and exercise limitation.6

Pulmonary rehabilitation (PR) is recognised as a standard, effective therapy in patients with stable COPD, resulting in improvements in symptoms, exercise tolerance and health-related quality of life7–9 and substantial savings in healthcare costs.9 Lower extremity endurance training is recommended by guidelines (Evidence A) as the cornerstone of successful PR.10,11 O’Donnell et al.
reported that DH was a major contributor to exercise limitation in COPD.\textsuperscript{12,13} Porszasz \textit{et al.} showed that lower extremity endurance training decreased ventilatory requirements and exercise-induced hyperinflation in high-intensity constant work rate exercise test in advanced COPD.\textsuperscript{14} However, the effect of lower extremity endurance training alone on EFL in patients with COPD remains largely unknown.

The aim of this study was to determine whether endurance training abolished EFL at rest and/or reduced DH and dyspnoea during exercise in advanced COPD.

\section*{Methods}

\subsection*{Study design}

This was a prospective, single-blinded, non-randomised controlled study (ChiCTR-TNRC-08003057). The study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China). All subjects gave written informed consent after a detailed description of the purpose. In addition, to be recruited for this study, the subjects also had to sign the ‘Participant Duties and Confidentiality Understandings’, by which they agreed and promised to abide by the following stipulations throughout the present study: (i) the participants were not allowed to be involved in any other clinical trials, (ii) they should report immediately to the investigators on any unscheduled hospital visits or any changes in medication from baseline, (iii) in any occasions, they should not reveal the group assignment to any of the others including the investigators.

An independent, well-trained physiotherapist was designated by the investigators to be responsible for the group assignment and supervised the subsequent 12-week endurance training by rigorously following the study protocol. After a face-to-face interview with the physiotherapist, the subjects were assigned to the training group or the control group, principally based on logistical reasons with regard to the patients’ regular availability for the twice-a-week training, the distance they usually had to cover to reach the hospital and the convenience in the traffic transportation for doing so.

The investigators examined all the subjects at the beginning (baseline) and the end of the 12-week study. All investigators were blinded to the group assignment until statistical analysis of the collected data.

The flowchart of this study is shown in Figure 1.

\subsection*{Study participants}

A total of 33 subjects was recruited between March 2006 and May 2007, from the outpatient clinic of the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China). All included subjects had been diagnosed with moderate to severe COPD prior to enrollment. The diagnosis of COPD was based on the clinical symptoms and signs, self-reported smoking history and the presence of flow limitation as reflected by post-bronchodilator forced expiratory volume in 1 s (FEV\textsubscript{1}) to forced vital capacity (FVC) ratio <70\% by spirometry. COPD severity was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.\textsuperscript{15}

Inclusion criteria were: (i) a post-bronchodilator FEV\textsubscript{1} 30–60\% of the predicted value, with an FEV\textsubscript{1}/FVC < 70\%; (ii) aged 55–75 years old; (iii) pulse oximetric saturation (SpO\textsubscript{2}) at rest >90\% under air breathing; and 4) no change in medication dosage, and no worsening of symptoms during the preceding 4 weeks.

Exclusion criteria were: (i) dyskinesia of the lower extremities, (ii) serious cardiovascular disease (unstable angina pectoris, uncontrolled congestive heart failure or recent myocardial infarction), (iii) uncontrolled hypertension (systolic pressure ≥160 mmHg and/or diastolic pressure ≥90 mmHg), (iv) frequent atrial or ventricular premature beats (>5 premature b.p.m.), (v) severe pulmonary hypertension (pulmonary artery pressure more than 45 mmHg by echocardiography), (vi) history of post-exercise syncope, (vii) previous pulmonary rehabilitation at any time, (viii) cardiac pacemaker, (ix) malignancy, severe renal dysfunction or hepatic diseases, (x) locomotive or neurological conditions, or disability impairing exercising and (xi) inability to comply with the training programme or to abide by the regulations as required in the ‘Participant Duties and Confidentiality Understandings’.

Subjects in the training group were scheduled to undergo cycle ergometer endurance training twice weekly for 12 weeks at the State Key Laboratory of Respiratory Disease (Guangzhou, China). Subjects in the control group received no exercise training and were allowed to keep their daily activities as usual. They visited the hospital only at the beginning and at the study end, to undergo the examinations. Medications of all the subjects were kept the same during the study period. Thirteen patients in the training group and 10 in the control group were prescribed inhaled fluticasone propionate/salmeterol (50/250), and all patients were receiving oral theophylline.

\section*{Measurements at baseline and at the end of study}

The investigators examined all the subjects prior to (baseline) and at the end of the 12-week study. Each session of the examination was performed in two visits, with the
first visit for pulmonary function test and incremental exercise test, and the second visit for measurement of maximal inspiratory pressure (MIP), expiratory flow limitation (EFL) and the constant work rate (CWR) test within 1 week from the first visit. Only subjects with a complete data set from two sessions of examination were included in the data analyses.

**Pulmonary function**

Standard forced expiratory spirometry, slow vital capacity, maximal voluntary ventilation, diffusion capacity for carbon monoxide and lung volumes were performed before and after training according to the American Thoracic Society guidelines (Cosmed, Albano Laziale, Rome, Italy). Normal predicted values were based on European Coal and Steel Community.

**Maximal inspiratory pressure**

MIP was measured at rest using a differential pressure transducer (P-300B; Jin Shan-jing Sensing Technology Corp., Peking, China), while the patient performed maximal inspiratory efforts, at or close to residual volume, sustained for at least 1 s against an occluded airway, using a flanged mouthpiece with a 1-mm leak to prevent glottis closure. Several measurements were made, and the highest pressures reached during three attempts that differed by less than 5% were averaged and recorded for analysis.

**Expiratory flow limitation**

EFL was assessed at rest with negative expiratory pressure (NEP) technique, as previously described. EFL was scored by an independent researcher who was experienced in the interpretation of NEP tests according to the 5-point score systems.

**Endurance training**

Peak exercise work rate was assessed before and after training using a standard 7 W/min incremental,
symptom-limited cycle ergometer test (Cosmed, Albano Laziale, Rome, Italy). A CWR test was conducted at the same work rate both before and after training. The intensity of CWR increased testing was set at 70% of the peak pretraining work rate. During CWR testing, subjects breathed room air through a mouthpiece attached to a pneumotachograph (MLT1000L, AD Instruments, Bella Vista, Australia), recorded with a PowerLab system supported by the Chart 5.0 software (AD Instruments, Sydney, NSW, Australia). Tidal breathing flow volume curves and inspiratory capacity (IC) were measured while sitting at rest and every other minute during the whole CWR testing. Assuming that total lung capacity while sitting at rest and every other minute during the CWR test was undertaken to ensure that a total of 24 sessions was completed. Withdrawal was considered if a patient failed to attend four successive training sessions.

Study outcomes
The primary outcomes were EFL at rest and IC both at rest and at isotime. Secondary outcomes were exercise capacity, pulmonary function, PIF, MIP and minute ventilation (V̇e), breathing frequency (f), tidal volume (V̇T), inspiratory flow, expiratory flow and visualised Borg dyspnoea scale at isotime.

Statistical analysis
Statistical analysis was performed using SPSS 10.0 (SPSS, Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation (SD). The Student’s paired t-test was used to compare data before and after training. An independent samples t-test was used for comparisons between the training and control groups. The chi-squared test was used for categorical variables. P-values < 0.05 were considered significant.

Results
Of the 33 subjects, 19 were assigned to receive endurance training, and the remaining 14 were allocated to the control group. During the 12-week study, four patients were withdrawn from the training group due to lung cancer (n = 1) or discontinuation of the training (n = 3); one patient was withdrawn from the control group due to missing assessment data at week 12. None of the subjects experienced an acute exacerbation during the study. All patients cooperated and complied well with the study protocol. There were no significant differences between two groups in any of the baseline characteristics (Table 1).

Changes in pulmonary function and MIP at rest
In the training group, endurance training increased MIP (from 69.49 ± 16.03 to 80.18 ± 15.97 cmH2O, P < 0.001) and PIF (from 3.96 ± 1.01 to 4.51 ± 1.13 L/s, P = 0.014), but without changes in IC or other variables of pulmonary function at rest (Fig. 2). No changes in pulmonary function at rest were observed in control group (Table 2).

5-point EFL score
After the training period, no significant alterations in 5-point EFL score were observed both in training group
**Table 1** Baseline demographic and pulmonary function data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Training group</th>
<th>Control group</th>
<th>T value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>66.00 ± 4.89</td>
<td>67.38 ± 5.99</td>
<td>-0.673</td>
<td>0.507</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1:4:1</td>
<td>13:0</td>
<td>0.899 [χ²]</td>
<td>0.343</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.07 ± 7.06</td>
<td>166.31 ± 5.69</td>
<td>-0.914</td>
<td>0.369</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.50 ± 8.14</td>
<td>62.08 ± 8.33</td>
<td>-0.185</td>
<td>0.855</td>
</tr>
<tr>
<td>Smoking index (pack-years)</td>
<td>45.87 ± 21.50</td>
<td>48.27 ± 25.34</td>
<td>-0.271</td>
<td>0.789</td>
</tr>
<tr>
<td>Smoking status (active:prior)</td>
<td>6:9</td>
<td>5:8</td>
<td>0.007 [χ²]</td>
<td>0.934</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.02 ± 0.23</td>
<td>1.06 ± 0.20</td>
<td>-0.496</td>
<td>0.624</td>
</tr>
<tr>
<td>FEV₁/pred (L)</td>
<td>41.31 ± 7.31</td>
<td>41.27 ± 7.95</td>
<td>0.015</td>
<td>0.988</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.71 ± 0.72</td>
<td>2.68 ± 0.40</td>
<td>0.150</td>
<td>0.882</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>38.63 ± 6.52</td>
<td>40.09 ± 7.05</td>
<td>-0.569</td>
<td>0.574</td>
</tr>
<tr>
<td>MVV (L)</td>
<td>46.43 ± 9.95</td>
<td>50.22 ± 11.38</td>
<td>-0.940</td>
<td>0.356</td>
</tr>
<tr>
<td>D(CO)/V₅, pred:% (%)</td>
<td>91.75 ± 19.47</td>
<td>92.84 ± 24.64</td>
<td>-0.131</td>
<td>0.879</td>
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<tr>
<td>RV/TLC (%)</td>
<td>53.29 ± 6.13</td>
<td>50.59 ± 6.95</td>
<td>1.092</td>
<td>0.185</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>4.58 ± 0.87</td>
<td>4.30 ± 0.65</td>
<td>0.990</td>
<td>0.331</td>
</tr>
<tr>
<td>IC (L)</td>
<td>2.15 ± 0.44</td>
<td>2.31 ± 0.32</td>
<td>-1.068</td>
<td>0.295</td>
</tr>
</tbody>
</table>

The chi-squared [χ²] test was used for statistical comparisons of categorical variables. DLCO, diffusion capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; MVV, maximum voluntary ventilation; RV, residual volume; TLC, total lung capacity; VA, alveolar gas volume.

**Figure 2** Effects of training on 5-point EFL score, MIP, PIF and IC at rest. EFL, expiratory flow limitation; IC, inspiratory capacity; MIP, maximal inspiratory pressure; PIF, peak inspiratory flow. ① Baseline; ② end of study.
IC (from 1.50 ± 0.013) and visualised Borg dyspnoea scale (7.20 ± 0.002) (Fig. 3) and increased maximal inspiratory flow reserve (from 3.46 ± 0.52 to 3.31 ± 0.63, P = 0.337) (Fig. 2).

Exercise endurance time

Endurance time of the CWR test increased from 7.00 ± 3.05 to 18.13 ± 6.44 min (P < 0.001) after training. Six patients went into a steady state. No significant change was observed in the control group (7.23 ± 3.11 to 7.38 ± 2.29 min, P = 0.849).

Changes in parameters measured at isotime during high-intensity CWR exercise test

In the training group, training decreased the respiratory rate (from 26.26 ± 7.13 to 23.15 ± 5.34 breaths/min, P = 0.002), V̇i (from 30.28 ± 7.52 to 26.85 ± 4.17 L, P = 0.013) and visualised Borg dyspnoea scale (7.20 ± 1.15 to 3.93 ± 1.39, P < 0.001) at isotime (Fig. 3), and increased IC (from 1.50 ± 0.34 to 1.67 ± 0.45 L, P = 0.002) (Fig. 3), inspiratory time (from 0.96 ± 0.28 to 1.07 ± 0.29 s, P = 0.002) and expiratory time (from 1.47 ± 0.62 to 1.72 ± 0.62 s, P = 0.004) at isotime. No significant changes were observed in other variables, as well as in controls (Table 3).

The training group also had decreased tidal peak inspiratory flow (from 2.01 ± 0.64 to 1.67 ± 0.35 L/s, P = 0.007), tidal peak expiratory flow (from 1.53 ± 0.22 to 1.32 ± 0.20 L/s, P = 0.006) (Fig. 3), and mean expiratory flow (from 0.87 ± 0.19 to 0.68 ± 0.15 L/s, P = 0.011) (Fig. 3) and increased maximal inspiratory flow reserve (from 2.05 ± 1.10 to 2.95 ± 1.19 L/s, P = 0.002) at isotime. No significant changes were observed in controls (Table 4).

Discussion

The lung emptying depends on expiratory flow and expiratory time. During exercises, ventilatory demand is abruptly increased, accompanied by greater tidal volume, faster respiratory rate and shorter expiratory time. EFL occurs when expiratory flow reaches a maximum during tidal breathing and cannot be further increased by increasing expiratory muscles effort unless the operating lung volumes move towards total lung capacity. The presence of EFL may induce DH that would result in exertional dyspnoea and exercise intolerance. Therefore, reducing EFL will have important benefits for COPD patients in improving dyspnoea and exercise limitation. Endurance training was not demonstrated to reduce EFL at rest in COPD in our study. In contrast, Yoshimi et al. showed that a multidisciplinary pulmonary rehabilitation programme improved EFL at rest.23 We speculated that the use of respiratory conditioning in Yoshimi’s research,23 but not in ours, may explain for this difference. It could be probable that breathing training appears more effective than endurance training in improving EFL at rest in COPD, although further studies are required for clarification. To our best knowledge, the present study represented the first attempt to evaluate the effects of endurance training alone on EFL in subjects with COPD. Regardless that NEP technique is currently recommended as a new GOLD standard to detect EFL, we did not use the NEP technique to detect...
the EFL in exercises, owing to patient discomfort and the difficulty to stay exercising with NEP in a status of rapid breathing. Tantucci proposed that EFL are more readily to develop during exercise by increasing mean tidal expiratory flow and reducing the expiratory flow reserve.4 In our study, the mean expiratory flow and tidal peak expiratory flow at isotime decreased significantly after training. There was also a trend towards an increase in maximal expiratory flow reserve during exercise. Hence, we conjectured that endurance training might reduce EFL during exercise in COPD.

DH was one of the main determinants of exercise performance in COPD.12,15 When increasing ventilatory demands are required during exercise, DH constrains the increases in tidal volume.26 The inability to expand tidal volume contributed to exercise intolerance in COPD. In the present study, there was a remarkable increase in endurance time in the CWR test after training, which was associated with reduced ventilation, DH and visualised Borg dyspnoea scale at isotime. The data supported the previous findings.14,19,20 DH can be reduced by either improving expiratory airflow27,28 or prolonging expiratory time. In the current study, we observed notable decreases in respiratory rate and expiratory flow, which suggests that the improvement in DH after endurance training was mainly due to prolonged expiratory time.

Figure 3  Training-induced physiological response at isotime. VE: minute ventilation; IC, inspiratory capacity. ■, Baseline; □, end of study.
Inspiratory flow reserve (L/s) 2.05

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Expiratory flow reserve (L/s) 1.55

Mean expiratory flow (L/s) 0.87

Tidal peak expiratory flow (L/s) 1.53

Tidal peak inspiratory flow (L/s) 1.28

Respiratory rate (breaths/min) 26.26 ± 7.13

VE (L) 30.28 ± 7.52

VT (L) 1.28 ± 1.10

IC; inspiratory capacity; Te; expiratory time; Ti; inspiratory time; Ttot; duration of one breath; VE; minute ventilation; VT; tidal volume.

rather than increasing expiratory flow. Some researchers suggested that decreased lactic acid levels and hypoxia after training might play important roles in the reduction of respiratory rate. Casaburi reported training induced a slower and deeper respiratory pattern during exercise. However, no changes in VT were observed in our study. The inconsistency might be underlain by the different training intensity between two studies. Our findings agreed with O’Donnell et al. who pointed out that no changes in VT are expectable because VT is relatively fixed after endurance training. Thus, we speculated that subjects with faster inspiratory flow after addition of IMT might have shorter inspiratory time during exercise, and have more time to expirate. It raised the possibility that increased exercise muscle function might be a contributor to the improvement in exercise endurance.

It has been generally accepted that PR by itself does not improve lung function. In accordance, there were no significant changes in FEV1, FVC, PEF and IC after endurance training in our study.

Several limitations in the present study should be acknowledged. First, this study was clinical trial in the real world. Although the demographic data and baseline characteristics were comparable between the training and control groups, selection bias may potentially be introduced in that some patients in the training group could be more interested in practising exercise, suggesting that the real-world outcomes of post-COPD pulmonary rehabilitation can be affected by several social and cultural factors rather than exercise training alone. Second, although significant improvements in exercise endurance were noted among patients after training, the sample size in this trial was relatively small with few females included. Third, the study population was limited.

Table 3 Effects of training on respiratory parameters at isotime during constant work rate test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Training group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-training</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>26.26 ± 7.13</td>
<td>23.15 ± 5.34</td>
</tr>
<tr>
<td>VT (L)</td>
<td>1.28 ± 0.39</td>
<td>1.22 ± 0.34</td>
</tr>
<tr>
<td>VC (L)</td>
<td>30.28 ± 7.52</td>
<td>26.85 ± 4.17</td>
</tr>
<tr>
<td>Ti (s)</td>
<td>0.96 ± 0.28</td>
<td>1.07 ± 0.29</td>
</tr>
<tr>
<td>Te (s)</td>
<td>1.47 ± 0.62</td>
<td>1.72 ± 0.62</td>
</tr>
<tr>
<td>Ti/Ttot</td>
<td>0.39 ± 0.05</td>
<td>0.39 ± 0.06</td>
</tr>
<tr>
<td>Ti/Te</td>
<td>0.65 ± 0.13</td>
<td>0.65 ± 0.15</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.50 ± 0.34</td>
<td>1.67 ± 0.45</td>
</tr>
<tr>
<td>Borg dyspnoea scale</td>
<td>7.20 ± 1.15</td>
<td>3.93 ± 1.39</td>
</tr>
</tbody>
</table>

Table 4 Effects of training on respiratory flow at isotime during constant work rate test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Training group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-training</td>
</tr>
<tr>
<td>Tidal peak inspiratory flow (L/s)</td>
<td>2.01 ± 0.64</td>
<td>1.67 ± 0.35</td>
</tr>
<tr>
<td>Tidal peak expiratory flow (L/s)</td>
<td>1.53 ± 0.22</td>
<td>1.32 ± 0.20</td>
</tr>
<tr>
<td>Mean expiratory flow (L/s)</td>
<td>0.87 ± 0.19</td>
<td>0.68 ± 0.15</td>
</tr>
<tr>
<td>Inspiratory flow reserve (L/s)</td>
<td>2.05 ± 1.10</td>
<td>2.95 ± 1.19</td>
</tr>
<tr>
<td>Expiratory flow reserve (L/s)</td>
<td>1.55 ± 0.47</td>
<td>1.71 ± 0.62</td>
</tr>
</tbody>
</table>
to patients with moderate to severe COPD. It is inappropriate to extrapolate the results of this study to all COPD patients. Last, other factors known to be associated with impaired exercise capacity in patients with COPD, such as anxiety, depression37 and skeletal muscle dysfunction,38 were not assessed. Future studies with multi-centre collaboration in a larger study population are needed to validate our findings.

Conclusion

This clinical study showed that endurance training may not reduce EFL at rest, but may lead to several benefits during exercise, including improved exercise capacity, increased inspiratory muscle force, reduced ventilatory demands and DH and alleviated dyspnoea. Moreover, training decreased mean expiratory flow and tidal peak expiratory flow at isotime after training.

Acknowledgements

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References

23 Martinez JA, Straccia L, Sobrani E, Silva GA, Vianna FO, Filho JT. Dyspnea scales...
Can frailty predict complicated care needs and length of stay?

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Key words
Frailty, discharge destination, mortality, length of hospital stay.

Abstract
The Reported Edmonton Frail Scale was used to describe the prevalence of frailty in an acute general medical unit. The relationship between frailty, discharge destination, mortality and length of hospital stay was explored. We found that age was associated with frailty, and frailty correlated to an increasing length of hospital stay. Significantly, frailty was associated with complexity in discharge, and this process created a longer length of hospital stay.


Frailty has recently been defined as ‘A medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death’.\(^1\) Significantly the concept of frailty directs a view of the elderly away from the static constraints of age and comorbid diagnosis, and considers a dynamic process with the potential for reversibility.\(^7\)

Measures of frailty have been derived from the examination of the physical performance, subjective opinion or indexes of clinical deficits.\(^3\) The Reported Edmonton Frail Scale (REFS)\(^4\) is a validated Australian scale developed for use in the acute hospital setting. It combines a report of physical performance before the current illness, with indexed assessment of multifunctional domains (general health, independence, social support, medication, nutrition, mood, continence) and screens cognition with a clock-drawing task.

Vulnerability in the elderly has often been recognised.\(^5\) Unfortunately, this state has largely resulted in inappropriate labelling of the frail elderly with maladaptive terminology (acopia,\(^3\) gomer,\(^6\) bed-blocker\(^7\)) that does not reflect function and misses substantial undiagnosed pathology.\(^7\) Early research\(^8\) indicated this group of patients was likely to have an unrecognised geriatric syndrome or malignancy. Frailty is now widely recognised as a predictor of poor outcomes in elderly hospitalised patients.\(^5\) Multiple studies suggest that frailty is an important marker for disability and mortality.\(^2,3,10,11\)

The prevalence of frailty is higher in older age groups, although advanced age alone does not predict frailty. In Australia, 14% of the population is aged over 65 years, and this is expected to double by 2050.\(^12\) An international review\(^13\) reported a large variance in the prevalence of frailty from about 5% in the community-dwelling population and up to 50% within residential aged care services. One Australian study in an acute general medical ward reported more than half of the patients were frail.\(^4\)

Frailty is an important marker for length of hospital stay (LOS).\(^4\) LOS has been considered a measure of discharge effectiveness and an economic performance indicator.\(^14\) However, LOS is not a quality indicator, as LOS cannot measure positive or clinically relevant outcomes.\(^15\) LOS will fall with a rise in mortality, or inappropriately accelerated discharge from hospital. There are concerns this may drive premature entry of patients into residential aged care (RAC).\(^16\) Decreasing LOS is only significant when patient outcomes are taken into account.

Detailed information regarding transitions between hospital and discharge destinations is limited. A national study\(^17\) found LOS varied considerably with post-hospital destination. Patients returning home were found to have shorter LOS. Although different hospital diagnoses were associated with different LOS, patients moving to permanent RAC were likely to have spent longer times in hospital. There were unexplained patterns of flow across the states and territories. Surprisingly, an earlier study\(^18\) found the proportion of hospital beds used by the elderly was not increasing. It was thought this trend may not continue in the future.\(^19\)

We describe the prevalence of frailty in an acute general medical unit and explore the associations between severity of frailty, discharge destination, mortality, and hospital LOS. It is anticipated this will help identify a population that would benefit from early implementation of prevention and treatment strategies and improve perceptions of discharge efficiency linked to the elderly.

We conducted a prospective cohort study of admissions to a private hospital in Melbourne between May 2012 and June 2012. Patients were assessed by the REFS within the first week of their admission. This consisted of a clinician administered interview with the patient or carer, and took on average 10 min to complete. Consecutive patients admitted to a general medical unit aged 70 years or older were eligible for inclusion. Of 162 eligible patients, 27 (16.7%) were excluded, because they refused to participate (\(n = 4\)), or were not able to complete the REFS, predominantly clock drawing (\(n = 23\)). One patient returned home after a period of residential care. This participant was considered atypical of the target patient groups and was excluded from the study. The medical records of the remaining 133 participants were reviewed to gather demographic data (age, sex), comorbidities (using the Charlson index)\(^20\) and outcome (LOS, discharge destination and death). t-Tests for independent samples were used to assess the difference between means for age, frailty and Charlson scores from different discharge destination groups. A \(P\)-value of <0.05 was considered statistically significant. LOS had a skewed distribution and median differences between discharge groups were assessed using Kruskal–Wallis tests. Linear regression analysis was used to explore associations between discharge destination and age, frailty and Charlson index. Multinomial logistic regression was used to assess associations between discharge destination and frailty and LOS. This study was approved by the Cabrini Human Research Ethics Committee. Informed consent was obtained for all participants. Carers gave consent when participants were unable.

Frailty was measured with the REFS (score range 0 to18) and grouped into five categories: non-frail (score...
Table 1 shows the characteristics of the study population, including the domains measured in the REFS. Cognitive impairment, as screened by clock drawing, was present in 91 (68%) of the study population. There were minor spacing errors in 27 (20%), and other errors recorded in 64 (48%) of participants. There was a greater proportion of women (n = 81, 60.9%) compared to men (n = 52; 30.1%). Median LOS was 8.5 days (range 1 to 52).

Linear regression analyses showed that frailty score was associated with age, increasing on average by 0.22 points for each year increase in age (P < 0.05). Similar analyses indicated that LOS was associated with higher frailty score, increasing on average by 0.49 days for each point increase in frailty score (P < 0.05).

We established five discharge destination groups (Table 2): patients returning home from home (n = 41), patients returning to the same level of residential care from residential care (n = 11), patients requiring some form of restorative care, (rehabilitation, geriatric evaluation and management (GEM) or transitional care) (n = 47), patients who changed their residence (n = 21) and patients who died or were transferred to a hospice for palliative care (n = 13).

Frailty differed between patients returning home and patients returning to residential care (P < 0.05). Charlson index was greater in those returning to residential care than those returning home (P < 0.05), although both groups had similar age and length of stay. We found the patients changing residence were older (P = 0.002), had higher frailty score (P < 0.005) and longer LOS (P < 0.005), compared to patients returning home, although their Charlson index was similar. The patients who died or required palliative care had an increased frailty (P < 0.005) and LOS (P = 0.01) when compared to the group returning home, although age and Charlson index were similar. Patients requiring restorative care, either by rehabilitation, GEM or transitional care had lower Charlson index (P = 0.04) and longer LOS (P < 0.005) compared to those returning home. A subgroup analysis indicated a greater LOS in patients attending GEM (P = 0.005) or transitional care (P = 0.004) compared to patients requiring rehabilitation, although numbers in both GEM and transitional care groups were small.

The proportion of discharge destinations related to frailty severity is shown (Fig. 1). In general, patients considered not frail either returned home or attended a restorative care programme. As frailty increased, there was a greater complexity to the discharge destination. Fewer patients returned home or attended restorative care programmes when frailty was greater.

Table 1 Characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>86.5 (6.1)</td>
</tr>
<tr>
<td>Sex (M : F)</td>
<td>52:81</td>
</tr>
<tr>
<td>Frailty, mean (SD)</td>
<td>7.8 (3.9)</td>
</tr>
<tr>
<td>Charlson index, mean (SD)</td>
<td>1.9 (1.8)</td>
</tr>
<tr>
<td>LOS, mean (SD)</td>
<td>8.5 (1.52)</td>
</tr>
<tr>
<td>REFS dimensions, n (%)</td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
</tr>
<tr>
<td>Clock drawing</td>
<td>No errors 42 (32)</td>
</tr>
<tr>
<td>Minor spacing errors</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Other errors</td>
<td>64 (48)</td>
</tr>
<tr>
<td>Health status</td>
<td></td>
</tr>
<tr>
<td>Admissions to hospital</td>
<td>No admissions 52 (39)</td>
</tr>
<tr>
<td>1–2 admissions</td>
<td>54 (40)</td>
</tr>
<tr>
<td>&gt;2 admissions</td>
<td>27 (21)</td>
</tr>
<tr>
<td>Description of health</td>
<td></td>
</tr>
<tr>
<td>Excellent/very good/good</td>
<td>51 (38)</td>
</tr>
<tr>
<td>Poor</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Functional independence</td>
<td></td>
</tr>
<tr>
<td>Activities requiring help†</td>
<td>0–1 activities 44 (33)</td>
</tr>
<tr>
<td>2–4 activities</td>
<td>34 (25)</td>
</tr>
<tr>
<td>5–8 activities</td>
<td>55 (42)</td>
</tr>
<tr>
<td>Support</td>
<td></td>
</tr>
<tr>
<td>Someone able to help</td>
<td>Always 108 (81)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Never</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Five or more medications</td>
<td>No 40 (30)</td>
</tr>
<tr>
<td>Yes</td>
<td>93 (70)</td>
</tr>
<tr>
<td>Forget to take medication</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>85 (64)</td>
</tr>
<tr>
<td>Yes</td>
<td>48 (36)</td>
</tr>
<tr>
<td>Nutrition</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>No 97 (73)</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (27)</td>
</tr>
<tr>
<td>Mood</td>
<td></td>
</tr>
<tr>
<td>Sadness or depression</td>
<td>No 109 (82)</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (18)</td>
</tr>
<tr>
<td>Contience</td>
<td></td>
</tr>
<tr>
<td>Loss of urinary control</td>
<td>No 98 (74)</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (26)</td>
</tr>
<tr>
<td>Self-reported performance</td>
<td></td>
</tr>
<tr>
<td>Heavy work without help‡</td>
<td>No 110 (83)</td>
</tr>
<tr>
<td>Yes</td>
<td>23 (17)</td>
</tr>
<tr>
<td>Stairs without help</td>
<td>No 95 (71)</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (29)</td>
</tr>
<tr>
<td>Walk 1 km without help</td>
<td>No 51 (38)</td>
</tr>
<tr>
<td>Yes</td>
<td>82 (62)</td>
</tr>
</tbody>
</table>

†Activities requiring help were meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications. ‡Heavy work was washing windows, walls, floors. LOS, length of stay; REFS, Reported Edmonton Frail Scale.
care. More patients changed residence, died or had palliative care needs. The proportion of patients returning to the same level of residential care increased at mild to moderate levels of frailty. This trend was not maintained at severe levels frailty, reflecting a possible change in care needs.

Linear regression showed a positive association between frailty and age. Multinomial logistic regression of frailty on discharge destination revealed an association between frailty score and destination. Including age in the model did not change this relationship significantly. Linear regression of LOS on discharge destination, age and frailty showed separate associations between destination and LOS, age and frailty. However, when all terms were included in the model, only discharge destination was associated with LOS. Compared with patients who returned home, those going to restorative care or changing residence had significantly longer LOS, and this was independent of either frailty or age.

There were some limitations to this study. Our sample size was powered to detect the presence of frailty, and this could have limited our subgroup analysis. The study population was from our medical unit (convenience sample) and may not be representative of all medical patients within our hospital. Also the patients were in a private hospital and may be perceived to have characteristics differing from those within the public setting. Patients were excluded if they could not undertake the

Table 2
Comparisons of age, frailty, Charlson index and LOS by discharge destination

<table>
<thead>
<tr>
<th>Destination</th>
<th>Sex (M : F)</th>
<th>Mean</th>
<th>SD</th>
<th>CI (95%)</th>
<th>Test (P-value)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Returning home (n = 41)</td>
<td>20:21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>84.9</td>
<td>5.9</td>
<td>[82.9–86.9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>6.0</td>
<td>3.6</td>
<td>[4.8–7.3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>2.0</td>
<td>1.9</td>
<td>[1.4–2.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS§</td>
<td>7</td>
<td></td>
<td>(2, 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Returning to residential care (n = 11)</td>
<td>3.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>87.9</td>
<td>4.5</td>
<td>[84.9–90.9]</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>11.9</td>
<td>1.7</td>
<td>[11.0–12.6]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>3.0</td>
<td>1.5</td>
<td>[2.2–3.8]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>LOS§</td>
<td>7</td>
<td></td>
<td>(2, 21)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Restorative care (n = 47)</td>
<td>13:34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>85.5</td>
<td>5.6</td>
<td>[83.9–87.0]</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>6.3</td>
<td>3.1</td>
<td>[5.4–7.2]</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.3</td>
<td>1.4</td>
<td>[0.9–1.7]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>LOS§</td>
<td>11</td>
<td></td>
<td>(4, 46)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation (n = 39)</td>
<td>9:30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>84.9</td>
<td>5.6</td>
<td>[83.1–86.7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>6.2</td>
<td>3.0</td>
<td>[5.2–7.1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.2</td>
<td>1.3</td>
<td>[0.8–1.7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS§</td>
<td>9</td>
<td></td>
<td>(11, 45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM and transitional care (n = 8)</td>
<td>4.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>88.1</td>
<td>3.2</td>
<td>[85.5–90.8]</td>
<td>0.12‡</td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>7.0</td>
<td>3.4</td>
<td>[4.2–9.8]</td>
<td>0.48‡</td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.6</td>
<td>1.7</td>
<td>[0.2–3.0]</td>
<td>0.47‡</td>
<td></td>
</tr>
<tr>
<td>LOS§</td>
<td>19</td>
<td></td>
<td>(15, 46)</td>
<td>&lt;0.05‡</td>
<td></td>
</tr>
<tr>
<td>Change of residence (n = 21)</td>
<td>7:14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>90.6</td>
<td>7.5</td>
<td>[87.2–94.0]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>11.2</td>
<td>3.0</td>
<td>[9.9–12.6]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.8</td>
<td>1.2</td>
<td>[1.3–2.3]</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>LOS§</td>
<td>15</td>
<td></td>
<td>(52)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Death and palliative care (n = 13)</td>
<td>9.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>87.8</td>
<td>5.5</td>
<td>[84.4–94.1]</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>10.5</td>
<td>3.0</td>
<td>[8.7–12.3]</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>3.0</td>
<td>2.5</td>
<td>[1.5–4.5]</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>LOS§</td>
<td>13</td>
<td></td>
<td>(1, 29)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

*P-values from regression analyses with comparison group returning home except where alternative comparison group indicated. ‡t-Test against rehabilitation. §Summary statistics for LOS are median and (range). CI, confidence interval; GEM, geriatric evaluation and management; LOS, length of stay; SD, standard deviation.
REFS, predominantly clock drawing. The main reason for this was delirium or under-recognised cognitive impairment, and this may have excluded the frailest patients from the study.

Nevertheless almost all of our patients were referred from our emergency department and have characteristics we regard comparable to patients found in medical units within the public system. We found that age was associated with frailty, and frailty could be correlated to an increasing LOS. Significantly, frailty was associated with complexity in discharge, and this process created a longer LOS. We observed patients who had an accessible discharge destination (patients returning home, or patients who could return to their level of residential care) had similar LOS. This may reflect factors influencing access to new discharge destination were independent of inpatient diagnoses or complications.

We consider frailty as a useful marker of vulnerability that is not captured by classical surgical or medical diagnosis related codes. The identification of frailty may help direct care and resources towards complex patient groups, whose needs may be distorted by employing descriptive measures, such as LOS. Care pathways may assist this group,15 and further studies to examine their role in complex care are warranted.

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**References**

1 Gordon AL, Masud T, Gladman JRF. Now that we have a definition for physical frailty, what shape should frailty medicine take? *Age Ageing* 2014; 43: 8–9.
3 Hubbard R, Ng K. Australian and New Zealand Society for Geriatric Medicine [homepage on the Internet]. Sydney: Australian and New Zealand Society for Geriatric Medicine [updated 6 Feb 2014]
The changing place of liver biopsy in clinical practice: an audit of an Australian tertiary hospital

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Key words
liver biopsy, viral hepatitis, indication.

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Abstract
Liver biopsy is an important tool in hepatology, with a role now generally limited to cases of diagnostic uncertainty. A retrospective audit performed at the Royal Melbourne Hospital aimed to identify the indications for liver biopsy and its impact on management. Ten per cent (20/195) of biopsies lacked a strong clinical indication, with hepatology involvement in only 8/20. We recommend prior hepatologist assessment to minimise unnecessary biopsies.
Liver biopsy has been a valuable tool for both diagnosis and staging of liver disease in cases where diagnostic uncertainty remains after biochemical, serological and radiological assessment.1 Although associated risks are less than previously reported, it remains an invasive procedure with recent data showing all cause mortality risk ranging from 0.2% to 1% per year.2–4 It is therefore vital that this procedure is performed only on patients where the outcome of the biopsy is expected to guide management, and should involve discussion between patient and clinician regarding risk versus benefit.

Large numbers of biopsies were undertaken in the past in the setting of chronic viral hepatitis (both hepatitis B and C), as this was required prior for reimbursement from the Pharmaceutical Benefits Scheme for antiviral therapies in Australia. Removal of this requirement in 2005 for hepatitis C, and 2011 for hepatitis B, has resulted in a significant decline in the number of biopsies performed.5,6 It is anticipated that the emergence and increasing use and accuracy of non-invasive imaging modalities for determining the severity of liver fibrosis may further reduce the number of biopsies.

In our institution, and in many other tertiary centres, liver biopsies are performed in the radiology department by radiologists. Policies for requesting liver biopsy are not always clearly established or enforced. Liver biopsies can be ordered by any medical officer through the radiology department without consultation with the hepatology service, which may allow biopsies that do not have a strong clinical indication to be performed.7

The aims of our study were to review the following:
1 The indications for non-targeted liver biopsies ordered in a tertiary centre
2 How the information from the liver biopsy altered patient management

3 Complication rates of biopsies performed by radiology using ultrasound marking

A retrospective audit of all non-targeted liver biopsies conducted at Royal Melbourne Hospital between January 2009 and December 2011 (36 months) was performed. This included a review of medical records of all patients who had a liver biopsy, noting the indication provided, complications, histology and any resultant change in management that occurred. All clinical information regarding the biopsies was then reviewed independently by two senior consultant hepatologists, with no knowledge of subsequent management, to assess the clinical need. The subsequent clinical management was then reviewed and the relationship to the biopsy findings assessed.

A total of 195 liver biopsies was undertaken over the 36 months. The male to female ratio was 5:3 with a median age of 44 years (range 16 to 78 years). The patient population included 70 patients with hepatitis B, 32 patients with hepatitis C, 3 with mixed viral hepatitis, 63 patients with abnormal liver function tests for evaluation, and the remaining patients with other indications for biopsy (as detailed in Table 1).

According to the consensus opinion of the two hepatologists, 20/195 (10%) of liver biopsies that were ordered did not have a strong clinical indication, as the results were felt unlikely to influence future management decisions. All of these 20 cases had biopsies for viral hepatitis. Sixty-four biopsies were ordered without review or discussion with a hepatologist, of which 18.8% (12/64) were considered avoidable. There were no deaths or major complications recorded in this cohort. Only one minor complication occurred in a patient, which was an unexplained mild febrile illness post-biopsy, resulting in a 24-h hospital stay for a short period of antibiotics (0.5%).

This study demonstrated that hepatology input helps to identify the patients in whom liver biopsies could be avoided.

<table>
<thead>
<tr>
<th>Indication for liver biopsy</th>
<th>Number of biopsies (n = 195)</th>
<th>Altered clinical management (yes)</th>
<th>Deaths/complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2009 (70)</td>
<td>2010 (70)</td>
<td>2011 (55)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>24</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>19</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Mixed viral hepatitis</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal LFT for investigation</td>
<td>16</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Presumed fatty liver disease</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>To assess fibrosis/cirrhosis</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Fibroscan result suggesting cirrhosis</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Mixed liver disease</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

†1 patient (only) lost to follow up in each group. LFT, liver function tests.
There is a changing indication for liver biopsy in Australia as a result of removal of this result to access government subsidised hepatitis B antiviral medications. It is anticipated that the number of biopsies will decrease further with increasing use of non-invasive technologies to assess fibrosis; however, we were surprised to see that the Fibroscan® result was the trigger for some biopsies. In retrospect, the elevated Fibroscan® results were due to the presence of steatosis and/or inflammation, both well recognised as a cause for false elevation in transient elastography, and in none of these cases was significant fibrosis found. It is appreciated that liver biopsy is the definitive way of staging disease, but other non-invasive technologies for estimating liver fibrosis may reduce the need for biopsy. However, these must be used in conjunction with clinical information to make an accurate assessment, as there is a moderate error rate, and failure rate that should be considered for each individual. The FIBROSTIC study group noted that the diagnostic accuracy of non-invasive tests was high for cirrhosis but poorer for significant fibrosis. Therefore, the superiority of liver biopsy over non-invasive testing for the staging of intermediate fibrosis still remains; however, this requires careful consideration of risks versus benefits, and necessitates an individualised approach with each patient.

Over the years, practice has changed from hepatologists or hepatologists-in-training performing liver biopsies due to established safety and efficacy of the ultrasound-guided approach. Although there is no longer opportunity to be directly involved in the process of liver biopsy, case-based hepatology involvement, whether as an inpatient or outpatient, might add value to the diagnostic process by supporting the need for liver biopsy or providing advice on newer alternatives.

Other non-invasive methods of assessing liver disease severity include: the serological tests: hepascore, fibrotest, fibrometer and aspartate aminotransferase (AST) to platelet ratio index; and other elastography: acoustic radiation frequency impulse imaging; shear wave elastography and magnetic resonance elastography.

Liver biopsy is an imperfect assessment tool, largely due to sampling error, as it has been used for many decades and its limitations are reasonably well understood by pathologists and hepatologists. Nudo et al. quote that although excellent when accurately done, sampling errors in liver biopsies can account for 1–67% of incorrect staging of fibrosis.

There were a few common patterns of non-targeted biopsies noted, as referred to in the results, which are demonstrated through the following cases.

**Case 1.** A 44-year-old woman with chronic hepatitis C virus presented for a routine review. Investigations revealed genotype 1a status with a viral load of 316,696 IU/mL. The AST : alanine aminotransferase (ALT) ratio was <0.8, and the platelet count was above 200. There were no clinical or biochemical features of cirrhosis; however, a liver biopsy was ordered to stage fibrosis. According to the Metavir score, she was classed as A2F2. The decision was made to commence treatment regardless of the results. At this point in time, the guidelines did not necessitate liver biopsy prior to commencement of therapy, and this patient would have been a suitable candidate for treatment with or without a biopsy.

**Case 2.** A 24-year-old patient in phase 1 (immune-tolerant) of chronic hepatitis B virus infection, eAg positive, high viral load and serially normal liver function tests was referred after an isolated instance of an elevated ALT level at 86. A biopsy was organised based on the elevated ALT. Liver biochemistry was normal on all other occasions, both prior to and following the liver biopsy. Liver histology showed no fibrosis and minimal necroinflammation (metavir A1F0). With no evidence for treatment pre- or post-biopsy, observation was continued. Pratt et al. showed that there is a poor correlation between the degree of liver damage and the level of the aminotransferases, and the yield of a liver biopsy is low, unless a sustained trend of transaminitis is seen. This case demonstrated the importance of the trend of transaminases and careful consideration of the timing and appropriateness of further testing.

Liver biopsy is an invaluable tool in the diagnosis of undifferentiated liver disease, but its role in staging a known liver disease is expected to decrease. The results of non-invasive tests, such as Fibroscan® must be interpreted with caution as there are many confounding variables.

**Acknowledgements**

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References

2. West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. *Gastroenterology* 2010; 139: 1230.
Pathogenic role of antibodies against monomeric C-reactive protein in tubulointerstitial nephritis and uveitis syndrome

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Key words
autoantibodies, monomeric CRP, tubulointerstitial nephritis, uveitis.

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Abstract
Antibodies against monomeric C-reactive protein, which is a target antigen expressed both in kidney tubules and uveal cells, have been recently detected in patients with active tubulointerstitial nephritis and uveitis syndrome. We report the case of an 65-year-old woman with acute renal failure caused by biopsy-proven tubulointerstitial nephritis and the onset of uveitis 21 months later. The expression of monomeric C-reactive protein in kidney oligobiopsy was confirmed by immunohistochemical staining using mouse monoclonal antibody against human monomeric C-reactive protein. The levels of antibodies against monomeric C-reactive protein were 117% of the reference during the flare and 22% during the remission of the disease. The difference in the levels of antibodies against monomeric C-reactive protein during flare and remission, and above all positive biopsy staining, supports their pathogenic role in this disease.

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease that was first described by Dobrin in 1975 in two patients with renal failure due to diffuse eosinophilic interstitial nephritis and bilateral anterior uveitis.1,2 The first component of the disease – acute interstitial nephritis – is a cause of 10–15% of acute kidney failures, and can be idiopathic, drug-induced or infection-related. Fever, fatigue, weakness, arthralgia and myalgia are the most common systemic symptoms, and oedema, abdominal or flank pain, haematuria, and pyuria are specific for kidney injury. Ocular symptoms, such as eye pain, redness, blurred vision and photophobia, are other features of TINU syndrome.3

The pathogenesis of TINU syndrome remains unknown, but the process is believed to be immune-mediated. Recently, the role of monomeric CRP (mCRP) as a target antigen, which is expressed both in kidney tubular and uveal cells, had been discussed.4 Compared with native pentameric CRP (pCRP), mCRP has distinct physicochemical properties, and the conversion from pCRP to mCRP takes place under specific conditions (like altered pH, high urea concentration or low calcium level).3 Antibodies, which are directed against mCRP (anti-mCRP Abs), have already been detected in patients with active TINU syndrome phase.4 Here, we present the case of TINU syndrome, in which the recurrence of acute kidney injury was associated clearly with increased anti-mCRP Abs titre.

We report the case of an 65-year-old woman with acute renal failure caused by biopsy-proven tubulointerstitial nephritis and the onset of uveitis with concomitant recurrence of increased creatinine level diagnosed 21 months later. One week before first hospitalisation in the nephrology department (in June 2009), the patient administered herself non-steroidal anti-inflammatory drugs (NSAID) because of acute respiratory tract infection with fever. Laboratory tests showed increased level of serum creatinine 539.2 μmol/L, C-reactive protein 26.5 mg/L, anaemia with haemoglobin level 80.7 g/L, hypoproteinaemia (61.0 g/L) with hypoalbuminaemia (30.0 g/L) and decreased complement haemolytic activity (69 units). Serological tests for anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies (anti-GBM) and anti-nuclear antibodies, (ANA) were negative.

Due to an acute renal failure, the patient required haemodialysis for 1 month. The kidney oligobiopsy performed at that time showed tubulointerstitial nephritis...
with infiltration by typical inflammatory cells (lymphocytes, macrophages and eosinophils) and oedema in the renal interstitium (Fig. 1A). The expression of mCRP in tubular epithelial cells was confirmed by immunohistochemical staining using monoclonal antibody against human mCRP (hematoxylin, ×400). (C) TINU: negative immunohistochemical reactivity of irrelevant antibody- anti-IgA (haematoxylin, ×400). (D) TINU: negative immunohistochemical reactivity of irrelevant antibody- anti-IgM (haematoxylin, ×400). (E) Control biopsy non-IgA mesangial proliferative GN: lack of tubular mCRP expression (haematoxylin, ×400). (F) Control biopsy lupus nephritis International Society of Nephrology/Renal Pathology Society class IV: mCRP expression (haematoxylin, ×400). mCRP, monomeric CRP; TINU, tubulointerstitial nephritis and uveitis.

To verify the specificity of anti-mCRP Abs, the immunohistochemical staining with irrelevant antibodies – anti-IgA (Fig. 1C) and anti-IgM (Fig. 1D) of the diseased biopsy – was performed. Negative immunohistochemical reactivity of irrelevant antibodies was revealed. To present a negative control, non-IgA mesangial proliferative glomerulonephritis (GN) biopsy was stained, and the lack of tubular mCRP expression was shown (Fig. 1E). The tubular and glomerular expression of mCRP in lupus nephritis (LN) International Society of Nephrology/Renal Pathology Society class IV biopsy is also a confirmation for anti-mCRP Abs specificity (Fig. 1F).

As a result of the steroid treatment (intravenously methylprednisolone pulses in the total dose of 3.0 g, with conversion to prednisolone 1 mg/kg of bodyweight per day in tapering doses), the patient recovered and the renal function stabilised at serum creatinine level 238.7–256.4 μmol/L. The patient was admitted to the nephrology department again (in March 2011) because of increased creatinine (319.1 μmol/L) and urea nitrogen level (41.4 mmol/L) with hyperuricaemia (529.4 μmol/L), slightly elevated C-reactive protein (6.4 mg/L), leucopenia (3.5 × 10^3 cells/μL), neutropenia (1.5 × 10^3 cells/μL) and anaemia (Hb 103.0 g/L). Urine tests showed erythrocyturia 7–11 hpf without proteinuria. The soreness and redness of the left eye, with massive inflammatory exudate in the vitreous of left eye and a smaller in the right eye, was diagnosed as uveitis.

The patient was given steroids intravenously (40 mg methylprednisolone per day for 7 days) and then orally in tapering doses again. Ocular symptoms disappeared and the stabilisation of serum creatinine level was observed. Laboratory tests were controlled every 2–3 months with stable creatinine levels (194.5–221.0 μmol/L), without erythrocyturia and proteinuria. During one
of the ambulatory visits in October 2012 (18 months after), the remission still persisted and the patient received 15 mg of prednisone every second day.

Serum samples were collected during the flare of TINU syndrome and during the remission with stable levels of creatinine (Fig. 2A), without oedema and ocular symptoms. Samples were drawn to clot and kept frozen at −70°C until analysis of anti-mCRP Abs levels. The presence of anti-mCRP Abs was tested with the use of in-house enzyme-linked immunosorbent assay, as described in the literature. Each sample was measured in quadruplicate; the specific absorbency value was normalised with 100% assigned to reference high anti-mCRP lupus erythematosus serum value, and the results were averaged. The cut-off value of the enzyme-linked immunosorbent assay was set as the mean ± 2 standard deviation of the 31 normal controls and was 7% of the reference.

The anti-mCRP Abs levels were 117% of the reference during TINU flare and 22% during the remission (Fig. 2B). In comparison, mean anti-mCRP Abs concentrations in the group of 48 patients with active LN were 24.2 ± 25.7% (median 13.6%) and in the group of 31 patients with non-active LN 21.6 ± 27.7% (median 11.0%). In the group of 31 patients with different GN types, anti-mCRP Abs levels were 5.5 ± 9.7% (median 2.7%), and in the group of 31 healthy volunteers 4.3 ± 4.8% (median 2.0%). Histopathological diagnosis of GN in tested patients were mesangial GN (nine patients), membranous GN (five patients), proliferative GN (five patients), focal segmental glomerulosclerosis (six patients), minimal change disease (four patients) and GN without biopsy-proven diagnosis (two patients).

Antibiotics and NSAID have been reported as a cause of TINU syndrome, and the administration of NSAID may have contributed to the development of the disease in the present case. There is no specific immunological biomarker for TINU syndrome; however, ANCA, anti-GBM and ANA antibodies may be positive. In the present case, except decreased complement haemolytic activity, all classical immunological tests were negative.

In one of the studies, the presence of autoantibodies, recognising a common antigen found both in kidney tubules and uveal cells, was demonstrated; however, the antigen was not identified. Recently, upregulated expression of mCRP in the cytoplasm of tubules and interstitia of renal biopsies from patients with TINU syndrome was described. Renal and uveal expression was also shown in kidney cortex obtained from patients with kidney tumours during nephrectomy, and iris and ciliary body obtained during trabeculectomy. Different from the Tan et al. report, in biopsy specimen taken from our patient, mCRP was present mainly in tubular epithelium; however, mCRP was shown also in glomeruli, of note without any injury in the glomerular structures.

Anti-mCRP Abs in serum had already been detected in patients with active TINU syndrome phase, and these antibodies were also present in high concentrations, especially during disease flare, in the present case. The anti-mCRP Abs might be important as a biomarker of active TINU syndrome. As these antibodies bind to mCRP overexpressed in renal and uveal cells, they could have pathogenic properties, similarly as in LN. However, further investigations are needed.
Autoantibodies against mCRP were also previously found in patients with autoimmune diseases (systemic lupus erythematosus, systemic sclerosis, autoimmune hepatitis, primary biliary cirrhosis and Sjögren syndrome). The occurrence of these autoantibodies was most common in patients with active LN. The levels of anti-mCRP Abs were associated with the score of interstitial lesions, which was possibly caused by the presence of mCRP in tubular cells and antigen–antibody complexes deposition in situ; however, in the present study, concentrations of these antibodies were the highest in the patient with TINU syndrome, even compared with patients with active LN (117% vs 24.2 ± 25.7%).

Autoantibodies against mCRP are a rare finding in patients with other non-autoimmune kidney diseases – drug-induced tubulointerstitial nephritis, IgA nephropathy, minimal change disease and amyloidosis. In our study, positive anti-mCRP Abs were found in low concentrations (5.5 ± 9.7%, median 2.7%) in 6 out of 31 patients with primary GN.

In conclusion, mCRP, which is present both in kidney tubules and uveal cells, might be a target, cross-reactive autoantigen in TINU syndrome. The difference in the levels of antibodies against mCRP during flare and remission, and above all positive biopsy staining, supports their pathogenic role in this disease.

References
Testosterone deficiency and quality of life in Australasian testicular cancer survivors: a prospective cohort study

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Key words
Testicular cancer, hypogonadism, quality of life.

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Abstract
This is the first prospective study in a contemporary Australian/New Zealand population to determine the prevalence of testosterone deficiency in testicular cancer survivors at 12 months from treatment, and any association with poorer quality of life. Hormone assays from 54 evaluable patients in a prospective cohort study revealed biochemical hypogonadism in 18 patients (33%) and low-normal testosterone in 13 patients (24%). We found no association between testosterone levels and quality of life (all $P > 0.05$). Hypogonadal patients should be considered for testosterone replacement to prevent long-term morbidity.

Testicular cancer has one of the highest 5-year relative survival for males (97%)1 and affects young men expected to live normal lifespans. Understanding physical and psychological morbidity of treatment is vital to survivorship care. Decreases in quality of life (QoL) have been attributed to the sequelae of hypogonadism, including fatigue, loss of libido, impaired fertility, weight gain, depression and osteoporosis.2–9 Testicular cancer survivors (TCS), at least those treated with chemotherapy and/or radiation therapy, also have a higher incidence of cardiovascular risk factors, including metabolic syndrome, and increased incidence of cardiovascular events. Hypogonadism may be a contributor to increased cardiovascular risk.6

TCS often demonstrate low-normal serum testosterone levels and elevated luteinising hormone (LH) levels, with rates of biochemical hypogonadism of 15–40% reported at a minimum follow-up of 5 years.1,10 Longitudinal data confirm peak rates of hypogonadism of 45% at 6–12 months following treatment, increasing with intensity of treatment, and gradual return of gonadal function in some patients with rates declining to 25% by 5 years.11,12

This study aimed to determine the prevalence of testosterone deficiency among a contemporary Australasian population of TCS at 12 months from treatment, and any association with QoL or psychological morbidity. We hypothesised that participants with biochemical hypogonadism would be more likely to report fatigue, depression and poor functional well-being.

The first 100 patients from an ongoing Australasian multicentre cohort study of the impact of chemotherapy on cognition (Australia and New Zealand Clinical Trial Registry 12609000545268) were chosen for analysis.13 Eligible patients from 16 participating centres included those with a diagnosis of testicular cancer of any stage, surgery planned or completed within the previous 2 months, and/or chemotherapy starting within the next month. They were required to be aged 18 years or older and to be fluent in English. Patients were excluded if they received prior chemotherapy or had evidence of cognitive impairment.

Participants were regularly tested for serum levels of the sex hormones testosterone, follicle stimulating hormone (FSH) and LH, and completed QoL and mood
questionnaires (Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and symptom-specific scales). For this substudy, we used assessments at 12 months after surgery or (where relevant) chemotherapy. Participants were evaluable if they had data for sex hormone levels, HADS and FACIT-F at 12 months postsurgery or chemotherapy. Eligible, consenting participants were classified in the following categories: (i) biochemical hypogonadism if testosterone concentration was lower than lower limit of normal (LLN) and/or LH was greater than upper limit of normal, (ii) low-normal testosterone if testosterone concentration was greater or equal to LLN but less than 12 nmol/L; and (iii) high-normal testosterone if testosterone concentration was greater or equal to 12 nmol/L. LLN was based on each study centre’s National Association of Testing Authority-accredited local laboratory assay normal reference range (LLN median 8 nmol/L, range 6–11 nmol/L) and not centrally reviewed. QoL scores at 12 months from treatment were compared among the three groups using general linear models (GLM), adjusting for age, chemotherapy and radiotherapy. Statistical tests were two-sided using a 5% level of significance and were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

The Human Research Ethics Committee at the University of Sydney and all participating centres approved the study. All participants provided written informed consent.

One hundred participants were enrolled from August 2007 to August 2010, and 54 had evaluable data. Participant characteristics are shown in Table 1. Evaluable and inevaluable patients did not differ significantly in age, tumour histology or treatment received. Thirty-nine participants (72%) had received chemotherapy, and 15 (18%) underwent orchidectomy alone. Two patients were receiving testosterone supplementation: both were treated with surgery and chemotherapy, one being classified as hypogonadal and the other in the low-normal testosterone group. At 12 months from treatment, 52 of 54 patients had no definite evidence of disease.

At 12 months after surgery or chemotherapy, the median testosterone level was 13 nmol/L, one third had biochemical hypogonadism and one quarter had low-normal testosterone (Table 1). There was a clinically meaningful but not statistically significant difference in biochemical hypogonadism between those who received chemotherapy compared with surgery alone (38% vs 20%, \( \chi^2 P = 0.20 \)).

According to the HADS, 13% reported mild symptoms on the anxiety subscale and 6% reported moderate symptoms. For the depression subscale, 6% reported mild symptoms. Median scores (interquartile range)

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>Total (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic and disease characteristics</strong></td>
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<tr>
<td>Age, median (range) (years)</td>
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<tr>
<td><strong>Histology, n (%)</strong></td>
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<tr>
<td>Pure seminoma</td>
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<tr>
<td>Non-seminoma/mixed</td>
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<td><strong>Treatment, n (%)</strong></td>
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<tr>
<td>Surgery</td>
<td>51 (94%)</td>
</tr>
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<td>Chemotherapy</td>
<td>39 (72%)</td>
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<td><strong>Testosterone (nmol/L)</strong></td>
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<td>Median (IQR)</td>
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<td>≤ ULN</td>
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<td>&gt; ULN</td>
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<tr>
<td>Orchidectomy alone</td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>15/39 (38%)</td>
</tr>
<tr>
<td><strong>Gonadal status</strong></td>
<td></td>
</tr>
<tr>
<td>Biochemical hypogonadism</td>
<td>18 (33%)</td>
</tr>
<tr>
<td>Low-normal testosterone</td>
<td>13 (24%)</td>
</tr>
<tr>
<td>High-normal testosterone</td>
<td>23 (43%)</td>
</tr>
<tr>
<td><strong>Quality of life at 12 months following treatment</strong></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td></td>
</tr>
<tr>
<td>Anxiety subscale</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>44 (81%)</td>
</tr>
<tr>
<td>Mild</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>Depression subscale</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>51 (94%)</td>
</tr>
<tr>
<td>Mild</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>FACIT-F†</td>
<td></td>
</tr>
<tr>
<td>Physical well-being subscale</td>
<td>27 (25–28)</td>
</tr>
<tr>
<td>Emotional well-being subscale</td>
<td>21 (19–24)</td>
</tr>
<tr>
<td>Functional well-being subscale</td>
<td>25 (22–28)</td>
</tr>
<tr>
<td>Social well-being subscale</td>
<td>26 (21–27)</td>
</tr>
<tr>
<td>Fatigue well-being subscale</td>
<td>47 (40–50)</td>
</tr>
</tbody>
</table>

†Ranges for FACIT-F (worst, best) are physical (0, 28), emotional (0, 24), functional (0, 28), social (0, 28) and fatigue (0, 52). FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FSH, follicle stimulating hormone; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; LH, luteinising hormone; LLN, lower limit of normal; ULN, upper limit of normal.
on all FACIT-F subscales were close to normal: physical well-being 27 (range 25–28), emotional well-being 21 (range 19–24), functional well-being 25 (range 22–28), social/family well-being 26 (range 21–27) and fatigue 47 (range 40–50). Examination of symptom-specific QoL questions directly addressing sexual function, as a clinical surrogate of hypogonadism, did not differ by treatment received.

When comparing the different QoL subscales across the three testosterone groups, there were no significant associations between testosterone levels and psychological variables (depression, anxiety and QoL including fatigue), as measured by HADS, or QoL and fatigue as assessed by the FACIT-F (GLM adjusted for age, chemotherapy and radiotherapy, all $P > 0.05$; Fig. 1). In particular, the mean adjusted FACIT-F total scores at 12 months from treatment were 140.3 (95% confidence interval 131.1–149.4) in the biochemical hypogonadism group, 136.9 (125.8–148.1) in the low-normal testosterone group and 143.3 (135.4–151.2) in the high-normal testosterone.
Discussion

This prospective cohort study of contemporary treatment of testicular cancer in an Australasian population found testosterone deficiency in a high proportion of participants at 12 months following primary treatment. One third of participants had biochemical hypogonadism, and a further quarter showed testosterone levels lower than expected for their age. Few patients reported QoL outside the normal range. Our study detected a clinically meaningful doubling in the rate of hypogonadism in participants receiving chemotherapy relative to those receiving surgery alone. This was not statistically significant, potentially because our cohort is underpowered. It did not detect poorer QoL in participants with biochemical hypogonadism.

Earlier studies of long-term survivors treated in the 1980s and 1990s have demonstrated an association between hypogonadism and poorer QoL. Huddart et al. found among 680 survivors that those with lower testosterone levels had poorer sexual, physical, social and role functioning.1 Wiechno et al. found among 326 survivors that those with lower testosterone levels had poorer physical well-being and higher depression ratings.9 Our study differs in demographic characteristics, follow-up, and QoL instruments from Huddart and Wiechno, who enrolled an older cohort (median 44 and 37 years, respectively), at a longer duration from primary treatment (median 10.2 and 4.9 years). Sex hormone levels are known to decline with age. Both studies also utilised QoL scales particularly weighted to sexual function, whereas our HADS and FACIT-F reflected QoL more broadly.

Testosterone is produced by the Leydig cells of the testis and is regulated by the hypothalamic–pituitary–testicular axis. Mechanisms of testosterone deficiency in survivors of testicular cancer are multifactorial, and include pre-existing testicular defects, replacement of Leydig cells by tumour or their loss by bilateral orchidectomy, effects of chemotherapy and radiotherapy, and age-related decline.3,16 Current theories of the aetiology of testicular cancer include potential damage to testicular development in utero, potentially affecting both testes. A proportion of patients have an abnormal remaining testis, on the basis of size and histology.

The risk of testosterone deficiency increases with escalating treatment intensity. Nord et al. found increased relative risk compared with age-matched controls at a median of 11 years after unilateral orchidectomy alone (relative risk (RR) 1.8), radiotherapy (RR 3.6), standard-dose chemotherapy (RR 4.4) and high-dose chemotherapy (RR 7.0). Huddart et al. found a significant proportion with testosterone deficiency at a median of 60 months after surgery alone (17%), chemotherapy (23%), radiotherapy (26%), and combination of chemotherapy and radiotherapy (56%).1,10 Testosterone deficiency immediately post-orchidectomy is a strong predictor of subsequent deficiency out to 36 months.11 Impaired QoL is a significant consequence of testicular cancer treatment. Hypogonadism has complex physiology. While it was not directly correlated with QoL in this study, it is an important and treatable syndrome. We recommend that physicians monitor hormone levels, consider testosterone deficiency as a potential causative factor in undifferentiated clinical presentations and consider TCS with biochemical hypogonadism for andrology assessment. Future research could assess the temporal profile of hypogonadism after treatment for testicular cancer and whether testosterone levels persistently at the lower end of the normal range are also at greater risk of these chronic diseases, and thus may also benefit from testosterone replacement.16,17

There is a lack of standardised evidence-based guidelines about the timing of screening for testosterone deficiency or replacement in this group.3 The UK Medical Research Council advocates testing testosterone and LH at 2, 5 and 10 years, along with blood pressure, glucose and fasting cholesterol. Princess Margaret Hospital recommends testing testosterone, FSH and LH annually for 9 years (B. Tran, pers. comm., 2013). The European Association of Urology guidelines recommend replacement in patients with hypogonadism associated with multiple signs and symptoms, sexual dysfunction, or low bone mass.18 There is a need for better evidence identifying and selecting appropriate patients for testosterone therapy and the potential role for hypogonadism in QoL and long-term morbidity.

Biochemical hypogonadism was found to be common in TCS, but was not correlated with QoL, as reflected in the indices measuring depression, fatigue and functional well-being in this study. Clinicians should be mindful of symptoms of hypogonadism, and consider screening and testosterone replacement to reduce long-term complications.

Acknowledgements

We thank patients for their commitment to the study the principal investigators, co-investigators and the study coordinators at the participating centres for their dedication and enthusiasm; and the staff at the National Health and Medical Research Council Clinical Trials Centre in Sydney, Australia, who were responsible for central coordination and data management of the trial.
References


LETTERS TO THE EDITOR

Clinical-scientific notes

Ertapenem-associated psychosis and encephalopathy

Ertapenem is a carbapenem antibiotic with a wide spectrum of antibacterial activity against Gram-positive and Gram-negative organisms due to its significant stability against hydrolysis by penicillinas, cephalosporinas and extended spectrum beta-lactamas. It is used in hospital settings to treat moderate to severe polymicrobial infections, including diabetic foot infections, complicated skin and skin structure infections, intra-abdominal and pelvic infections, as well as monomicrobial-resistant Gram-negative infections. Like other carbapenems, ertapenem can cause seizures but rarely causes other neurological side-effects.

We report two rare cases of ertapenem-associated psychosis and encephalopathy.

A 54-year-old man initially presented to the hospital with right great toe gangrene from diabetic foot infection. He had right great toe amputation followed by forefoot amputation. He had multiple mixed cultures including group B Streptococcus, methicillin-susceptible Staphylococcus aureus, Eikenella corrodens, Klebsiella pneumoniae, Escherichia coli, Morganella species and methicillin-resistant S. aureus. He was initially treated with ticarcillin-clavulanate and metronidazole, followed by ceftriaxone and vancomycin. Due to interstitial nephritis, the antibiotics were changed to oral linezolid 600 mg twice daily and intravenous ertapenem 1 g daily. Creatinine increased to 137 mcmol/L (estimated glomerular filtration rate (eGFR) 41 mL/min by Chronic Kidney Disease Epidemiology Collaboration formula) from baseline 65 mcmol/L (eGFR > 90 mL/min).
Letters to the Editor

The patient developed persecutory delusions, visual hallucinations and increasing confusion 5 days after changing the antibiotics, and was admitted to the hospital. There were no features of worsening infection clinically and biochemically (white cell count $10 \times 10^9/L$ and C reactive protein $11 \text{ mg/L}$). He was disoriented, and had nystagmus and myoclonus without other focal neurological signs.

Investigations (cerebrospinal fluid culture, blood culture, electrolytes, renal function (eGFR 46 mL/min), liver functions, computed tomography of the head and echocardiogram) did not reveal a cause for the neurological deterioration. Electroencephalogram revealed diffuse slow waves consistent with encephalopathy. The patient’s condition deteriorated to a semi-comatose state while investigations were done, and only at this point ertapenem was thought to be the cause of neurotoxicity.

Ertapenem was changed to linezolid and piperacillin-tazobactam. His mental state improved, and after 10 days of withdrawing ertapenem he was discharged from the hospital with normal mental state.

A 48-year-old man was admitted to the hospital with a comminuted left tibial plateau fracture. Additional salient history included stable depression on sertraline 50 mg daily. He developed a compartment syndrome and underwent immediate fasciotomy, followed by debridement and open reduction and internal fixation. He underwent two further debridements due to pus around the wound, knee joint and the metalwork. Enterobacter cloacae was isolated from multiple clinical specimens. Initially, he was treated with ticarcillin-clavulanate 3.1 g six hourly, and gentamicin and vancomycin being added subsequently.

As he developed worsening fevers and markers of sepsis, these antibiotics were ceased and ertapenem $1 \text{ g daily}$ was commenced. The fevers settled and the inflammatory markers improved.

In the subsequent 10 days, the patient developed confusion, disorientation, and visual and auditory hallucinations especially at night. The medications at that time were ertapenem, fentanyl, sertraline, oxycontin, paracetamol, ranitidine, and coloxyl and senna. The wound was healing clinically without signs of worsening infection. Fentanyl was ceased on the day of the development of confusion. Further investigations carried out to ascertain the cause of confusion were negative (blood cultures, urine cultures, CXR, full blood count, electrolytes, thyroid function test, syphilis serology and CT head). He remained afebrile and the inflammatory markers remained stable. Oxycontin and sertraline were ceased 6 days after the onset of confusion. Even after 4 days of cessation of oxycontin and sertraline, the confusion became worse and developed into severe hallucinations and agitations. At this stage, he was on ertapenem, ranitidine, and coloxyl and senna only. Ertapenem was ceased as this was thought to be a possible drug-related psychosis, and oral trimethoprim/sulphamethoxazole double-strength one tablet twice daily was commenced. His eGFR remained above 90 mL/min throughout this period.

The confusion slowly resolved and the patient’s mental state returned to normal 3 days after ceasing ertapenem. He continued on oral trimethoprim/sulphamethoxazole as metalwork remained in the knee. He was not re-challenged with ertapenem, but the confusion and hallucinations never returned on subsequent clinic reviews.

Ertapenem can cause neurological complications, such as seizures, mainly in moderate to severe renal impairment, due to accumulation of the compound in the central nervous system mediated by gamma-aminobutyric acid receptors. Other carbapenems, such as imipenem and meropenem, can cause altered mental status. However, confusion, visual or auditory hallucinations, and agitation due to ertapenem have rarely been reported.

Literature search from 2000 to 2012 in MEDLINE for ertapenem and neurotoxicity apart from seizures revealed two case reports only. Duquaine et al. reported two elderly men who developed delirium evident by nonsensical, tangential thoughts and visual hallucinations. Ertapenem withdrawal resulted in the improvement of the mental status. Another case report by Kong and Beckert was of a 58-year-old man who had visual hallucinations with ertapenem. The hallucinations resolved with discontinuation and returned on re-challenge. In both case reports, thorough investigations did not reveal any other cause for neurotoxicity.

In our case series, the patients developed visual and/or auditory hallucinations and confusion 5–10 days after initiating ertapenem. The temporal relationship of the development of confusion, hallucinations and agitation in our patients was a strong indicator of ertapenem-related neurotoxicity. The use of Naranjo probability scale indicated a probable relationship for the patients between the adverse events and the ertapenem use. Ertapenem was continued while investigations were done, and neurotoxic features became worse in these patients.

Ertapenem is highly protein bound in vivo (95% bound at an approximate plasma concentration of $<100 \mu g/mL$ to approximately 85% bound at an approximate plasma concentration of $300 \mu g/mL$). Low albumin concentration can cause higher levels of free ertapenem. Our patients, even though unwell, maintained near normal albumin levels which would not lead to higher free ertapenem levels to cause ertapenem toxicity.

Ertapenem is primarily eliminated by the kidneys. The area under the curve (AUC) changed with renal
impairment, that is AUC increased 1.5-fold with moderate renal impairment (eGFR 31–59 mL/min) and 2.6-fold in severe renal impairment (eGFR 5–30 mL/min). Although no dose adjustment was recommended, the increased AUC in moderate renal impairment could lead to increased availability of ertapenem causing psychosis and encephalopathy.

Although rarely encountered, ertapenem can cause altered mental status, such as visual hallucinations, confusion, agitation and delusions. Clinicians should be aware of this possible adverse effect of ertapenem. With growing resistance to carbapenems worldwide, judicious use of these antibiotics is essential, and withdrawing the medication on the onset of encephalopathy should be considered with pending investigations.

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References

Fever-induced recurrent rhabdomyolysis due to a novel mutation in the ryanodine receptor type 1 gene

A 43-year-old man was referred for two episodes of severe rhabdomyolysis preceded by viral infections. He had no relevant medical history, never had anaesthesia, and there was no family history of neuromuscular disease.

The first episode at the age of 36 had started with a febrile throat infection with nausea, vomiting and shivering. A few days later, he developed generalised muscle cramps and dark urine. Physical examination was normal, with temperature of 37.9°C. Laboratory investigations revealed creatine kinase (CK) levels of 521 500 IU/L, myoglobinuria and serum creatinine levels of 815 µmol/L, indicating renal failure. He was effectively treated with intravenous hyperhydration and received antibiotics. After 4 weeks, CK levels had decreased to 5700 IU/L. At the age of 43, he suffered from a similar rhabdomyolysis episode following a febrile throat infection (40°C).

He was subsequently referred to our neuromuscular centre, and on initial assessment reported mild exercise-induced myalgia without second wind phenomenon. Remarkably, religiously motivated prolonged fasting had never prompted rhabdomyolysis. Neurological examination was normal, as were electromyography and laboratory investigations, including investigations for carnitine deficiency and fatty acid oxidation defects. A muscle biopsy revealed mild myopathic changes and unevenness of oxidative enzyme staining (Fig. 1), subtle features that can be seen in skeletal muscle ryanodine receptor (RYRI) gene involvement as previously reported in patients with exertional rhabdomyolysis due to this genetic background.1 Respiratory chain enzyme analysis was normal.

Mutation analysis of LPIN1, CPT2 and ACADVL was normal. RYRI sequencing prompted by suggestive clinical and histopathological features revealed a novel heterozygous missense mutation, c.10219G>T; p.(Ala3407Ser), affecting a highly conserved amino acid.

Rhabdomyolysis is a potentially lethal condition that results from acute muscle fibre breakdown. Patients are
often referred to the general physician for investigation of the underlying cause. Non-traumatic rhabdomyolysis can usually be attributed to prescribed or illicit drugs, alcohol, or infection.\(^2\) When investigating the cause of recurrent fever-induced rhabdomyolysis, metabolic investigation for a fatty acid oxidation defect is usually the first step. Once this has been excluded, only a limited number of alternative explanations is left.\(^3\)

The type 1 ryanodine receptor serves as a sarcoplasmic reticulum calcium release channel with an important role in skeletal muscle contraction.\(^4\) Mutations in the \(\text{RYR1}\) gene are among the most common causes of inherited neuromuscular disease, associated with the malignant hyperthermia susceptibility (MHS) trait, and a variety of congenital myopathies.\(^3,4\) \(\text{RYR1}\) mutations have been recently identified in 14 families presenting with rhabdomyolysis episodes mainly triggered by exercise in the absence of anaesthetic triggers.\(^1\)

We postulate that the \(\text{RYR1}\) mutation in this patient caused an increased susceptibility to fever-induced rhabdomyolysis. To our knowledge, this has previously only been reported in two patients without personal or familial history of MHS.\(^3\) Furthermore, two other families with \(\text{RYR1}\)-related fever-induced rhabdomyolysis have been reported, but in these patients a genetic background was suspected because of familial occurrence of the same phenotype or of MHS.\(^1,6\) There has been one other patient described with an \(\text{RYR1}\) mutation and rhabdomyolysis during a febrile episode, but this may have been confounded by concomitant ondansetron treatment.\(^7\)

Our findings indicate that \(\text{RYR1}\) mutations have to be considered in patients presenting with fever-induced rhabdomyolysis, particularly if recurrent, even without a personal or familial history of MHS. In contrast to some metabolic myopathies associated with fever-induced rhabdomyolysis, fasting apparently does not trigger episodes. Accurate diagnosis is crucial because of the possible associated malignant hyperthermia risk in the patient and his/her relatives.

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References

1 Dlamini N, Voermans NC, Lillis S, Stewart K, Kamsteeg EJ, Drost G et al. Mutations in \(\text{RYR1}\) are a common cause of exertional myalgia and rhabdomyolysis. \(\text{Neuromuscul Disord}\) 2013; \(23\): 540-8.
3 Quinlivan R, Jungbluth H. Myopathic causes of exercise intolerance with rhabdomyolysis. \(\text{Dev Med Child Neurol}\) 2012; \(54\): 886-91.
4 Treves S, Jungbluth H, Muntoni F, Zorzato F. Congenital muscle disorders with cores: the ryanodine receptor calcium channel paradigm. \(\text{Curr Opin Pharmacol}\) 2008; \(8\): 319-26.
5 Groom L, Muldoon SM, Tang ZZ, Brandom BW, Bayarsaikhan M, Bina S et al. Identical de novo mutation in the \(\text{RYR1}\) gene associated with fatal, stress-induced malignant hyperthermia in two unrelated families. \(\text{Anesthesiology}\) 2011; \(115\): 938-45.
7 Gener B, Burns JM, Griffin S, Boyer EW. Administration of ondansetron is associated with lethal outcome. \(\text{Pediatrics}\) 2010; \(125\): 1514-17.
Epstein–Barr virus-associated post-transplant lymphoproliferative disorder of plasma cell type following allogeneic haemopoietic stem cell transplant treated with rituximab

An 18-year-old woman underwent myeloablative allogeneic haemopoietic stem cell transplant (HSCT) for T-lymphoblastic lymphoma. The donor was a single allele mismatched unrelated male. Conditioning included cyclophosphamide (60 mg/kg on day –6 and –5) and total body irradiation (2Gy twice daily on days –4 to –2), and immune suppression with anti-thymocyte globulin Fresenius (30 mg/kg on day –1), methotrexate (10 mg/m² IV on days 1, 3 and 6) and cyclosporine. Engraftment occurred on day 17. On day 65, she developed otalgia, hearing loss and sore throat. Computed tomography imaging showed extensive paranasal sinus opacification and a soft tissue mass in the nasopharynx. Naso-endoscopy showed an ulcerated mass extending from the nasopharynx to the upper oesophagus. Biopsy showed a monomorphic infiltrate of plasma cells with positive immunoperoxidase staining for CD79a, CD138, MUM1, CD25, CD99 and strong positivity for Epstein–Barr virus (EBV) and lambda light chains by in situ hybridisation (ISH). The cells were negative for CD2, CD3, CD4, CD8, CD1a, CD20 (scattered positive cells), TdT, CD10, CD30 and CD56. The Ki-67 was approximately 50%. Fluorescent ISH for X and Y chromosomes showed the plasma cells to be of male (donor) origin. Peripheral blood EBV DNA was quantified at 98 600 copies per millilitre of whole blood (Nanogen kit for EBNA1 gene). Protein electrophoresis demonstrated three IgG lambda paraproteins with a total of 15 g/L and three IgG kappa paraproteins with a total of 1 g/L. Serum kappa light chains were 11.3 mg/L and lambda light chains 80.5 mg/L (kappa to lambda ratio 0.14). Skeletal survey did not show any lytic lesions, and there was no increase in plasma cells on bone marrow assessment. Fluoro-deoxyglucose positron emission tomography scanning did not show any lesions beyond the nasopharyngeal mass, which was PET-avid. The diagnosis was localised EBV-positive, monomorphic post-transplant lymphoproliferative disorder of plasma cell type and of donor origin.

Immunosuppression was rapidly tapered over 3 weeks and rituximab was given weekly for 2 weeks (375 mg/m²). Four weeks later, the serum paraprotein had fallen to a total of 10 g/L and lambda light chains to 50 mg/L. Serum quantitative EBV DNA was undetectable. At 12 months following transplantation there has been no recurrence of the nasopharyngeal mass; however, she still has a low level of paraprotein.

There are no treatment guidelines for plasmacytoma post-transplant lymphoproliferative disorder (PTLD). Case reports suggest radiotherapy, surgical resection and standard systemic myeloma therapy.1 Rituximab is important in the treatment of PTLD, which are typically CD20-positive. As was the case here, plasma cells rarely express CD20.2 We hypothesised that purging B cells with rituximab would eliminate the EBV reservoir thought to be responsible for the plasmacytoma. This was corroborated by a rapid reduction in EBV titre, a slower reduction in paraprotein level and complete resolution of the pharyngeal mass on follow-up imaging.

Plasma cell PTLD is extremely rare in the setting of HSCT, with most cases occurring following solid organ transplants.3,4 This is the first reported case where a CD20-negative PTLD in the context of allogeneic HSCT has been effectively treated with rituximab alone.

References

2 Kapoor P, Greipp PT, Morice WG, Rajkumar SV, Witzig TE, Greipp PR.
General correspondence

Returning to medical practice following illness or injury

Returning to work after illness or injury may be difficult for people in all occupations. In its position statement titled *Health of Doctors* (May 2013), The Royal Australasian College of Physicians specifically addresses the issue of doctors returning to medical practice following illness or injury. Returning to practice may be challenging for numerous reasons, including long working hours, the inherently demanding nature of medical practice and the difficulties in arranging part-time work. The College’s statement highlights the importance of vocational rehabilitation in managing a doctor’s return to work. A vocational rehabilitation approach (or ‘return to work plan’) is supported by evidence for achieving optimal outcomes, and is best facilitated by an occupational and environmental medicine or rehabilitation physician. This approach will likely include gradually increasing workload and responsibilities, with regular reviews.

Having recently suffered a medical illness, I was thankfully able to participate in a ‘return to work plan’. This rehabilitative approach allowed me to continue practising and training without a major interruption, while facilitating my recovery and avoiding a ‘boom or bust’ situation. I hope that similar support for returning to medical practice is available across Australasia, in keeping with the College’s position statement. Medical practitioners should be encouraged to access vocational rehabilitation support if required, either for themselves or for their patients in other occupations.

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Reference


Stakes are high when caring for the dying

The research performed by Marck et al. looks at the care for dying cancer patients in emergency departments. This is a significant area where the quality of care has ramifications well beyond routine admissions due to the finality of the presentation and the highly vulnerable state of the patients, their families and friends. Further studies could focus on measuring the adequacy of symptom relief for terminal patients during their time in emergency departments and subsequent transfer to hospital wards. While it is important to consider the impact of advanced care plans and pathways, I suggest that ensuring optimal symptom control is the most fundamental issue. To illustrate this, I will briefly outline the circumstances of my 41-year-old brother’s death from melanoma in 2004.

Antony presented on a Friday to the emergency department of a large Melbourne hospital after being discharged the day before. Although stoic by nature, he was at the end of the line with unremitting nausea, vomiting and severe pain, from widespread metastases and malignant ascites. Forty-five hours later, he was dead. He spent approximately 16 h in the emergency department; approximately 30 min in an ambulance, being taken to another facility where a bed was not available and then brought back to the emergency department; approximately 12 h in a four-bedded bay in a thoracic ward and approximately 16 and a half hours in a single room in an oncology ward, where he died. In the early morning, 4 h before he died, I asked him if he was in pain and he nodded emphatically. A trainee physician at the time, I had to prompt staff periodically that he needed further analgesia. His partner, who sat with him throughout the admission, does not recall him looking settled until soon before his death.

I cannot recount the details and doses of medications, or wish to lay blame with particular individuals. Antony’s family and friends were aware he was dying. In retrospect, perhaps we should have vociferously complained
that he had ongoing discomfort, but it is surprisingly difficult to think when clouded by exhaustion and grief. The way my brother suffered during his final hours has had lasting effects. Months later when his partner told me that she was ‘not afraid of dying, just dying in pain like Antony did’, I was ashamed for the hospital system. She also recalled the loneliness of sitting by his side while staff performed their duties and then seemed to disappear. The consolation is to prevent this from happening to others in the future. If the answer to the simple question, ‘Are you in discomfort?’ is ‘Yes’, then this must be followed up by a management plan that is periodically reviewed. Charts that use existing pain scales and have time frames for the reassessment for symptoms could be implemented with minimal expense. These could be part of subsequent audits into the quality of care. When we inadequately treat the discomfort of our dying, it diminishes us all.

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References

7 + 3 idarubicin is still an effective induction therapy in acute myeloid leukaemia

We note the recent publication by Low et al,1 and subsequent correspondence from Jackson et al2 indicating the lack of benefit in adding etoposide to induction chemotherapy. We would add that the survival benefit of high-dose cytarabine in induction is uncertain.3–5 We have obtained similar results using an ‘old-fashioned’ induction of 3 days of anthracycline and 7-day infusion of cytarabine.

We have recently conducted an audit of outcomes in patients with newly diagnosed acute myeloid leukaemia (AML) aged less than 65, treated at St George Hospital between 1 January 2007 and 31 December 2011. Patients were identified from registry data from South Eastern Sydney Local Health District Clinical Cancer Registry. Ethics approval was obtained, and a retrospective review of medical records was undertaken to confirm diagnosis, obtain baseline prognostic data and determine outcomes.

We treated 31 patients with a median age of 51 years (range 25–63). Three patients received daunorubicin 50 mg/m² daily for 3 days and cytarabine 100 mg/m² daily as a continuous infusion for 7 days. Twenty-eight received idarubicin 12 mg/m² daily for 3 days and cytarabine 100 mg/m² daily as a continuous infusion for 7 days. Patients received consolidation with high-dose cytarabine. Karyotyping was successful in 29 patients. Stratification according to the updated Grimwade criteria6 characterised 13.7% as low risk, 58.6% as intermediate and 27.5% as high risk.

The complete remission (CR) rate after one cycle of induction chemotherapy was 71% (22/31). There was one induction death within 30 days of completion of induction chemotherapy in a patient who was not in remission. One patient had refractory disease and failed subsequent re-induction treatment. One patient proceeded to allogeneic transplant following induction with primary refractory disease. The six remaining patients achieved CR after a second induction with a different protocol. The CR rate after one or two induction cycles was 90%. Eleven patients were transplanted in first CR (35%), including the six patients requiring a second induction. At a median follow up of 43 months in survivors, 3-year relapse-free survival and overall survival were 42% and 55% respectively (Figs 1,2).

Our small series supports the use of ‘7 + 3 Idarubicin’ as an effective and well-tolerated induction regimen. Our CR rate after a single round of induction is similar to recent publications using high-dose daunorubicin in induction.7,8 The majority of patients not achieving CR can be salvaged with a second cycle of induction and safely delivered to allogeneic transplantation. The recent German AML Intergroup publication showed no difference between five treatment strategies compared against a common standard arm of ‘7 + 3’
followed by high-dose cytarabine consolidation. This supports previous studies that showed no survival benefit from high-dose cytarabine in induction.3,5 We would argue that high-dose cytarabine is an important component of therapy for AML; however, its use in first induction should be evaluated by randomised clinical trial.

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References


Author reply

Ramanathan et al.1 have responded to recent reports by Low et al.2 and Jackson et al.,3 which suggested that outcomes with high-dose cytarabine (HiDAC: 24 g/m² total)-based induction regimens in acute myeloid leukaemia (AML) were not compromised by the omission of etoposide. Ramanathan et al.1 report their single institution experience with 31 patients receiving 7 + 3 induction for AML and conclude that standard-dose cytarabine (SDAC)-based induction is still a useful approach in AML. Our report2 and that by Jackson et al. were not directed at whether SDAC was inferior to HiDAC for AML induction. Rather, both reports concluded that etoposide added toxicity without clear efficacy in combination with idarubicin and HiDAC-based induction approaches. The arguments regarding the merits of either SDAC or HiDAC for AML induction have been ongoing for more than two decades.

Randomised studies in the 1990s showed improved event-free survival with HiDAC induction (total 24 g/m²) that was offset by higher treatment-related mortality, thereby eliminating an overall survival (OS) benefit compared with SDAC.4 More recent studies by the Haematology Oncology Foundation for Adults in The Netherlands group using lower doses of HiDAC (total 10 g/m²) have also failed to show a survival benefit compared with SDAC in AML induction.5 A recent European Organisation for Research and Treatment of Cancer-Gruppo Italiano Malattie Ematologiche dell’ Adulto (EORTC-GIMEMA) study in 1942 newly diagnosed patients with AML showed that HiDAC induction (total 24 g/m²) significantly improved the complete remission (CR) rate, 6-year event-free survival and 6-year OS in comparison with SDAC induction in a subgroup analysis of patients aged between 15 and 45 years old.6 Additional multivariate analyses suggested HiDAC induction was beneficial in patients with secondary and FLT3 internal tandem duplication AML. Other studies performed by the Australasian Leukaemia and Lymphoma Group support the limitation of HiDAC induction to younger patients <50–55 years with AML to minimise the risk of treatment mortality observed in older populations.7 Decisions regarding optimal treatment approaches in AML should also consider the requirement for salvage chemotherapy in those failing to achieve remission as well as the total number of cycles required in consolidation and the collective impact this has on overall health resource utilisation. A prospective randomised study confirming the benefit of HiDAC over SDAC in younger adults with AML, as reported by the EORTC-GIMEMA study group, is unlikely to be conducted. Future goals in AML will be prioritised to focus on the role of novel agents added to induction or on strategies to reduce relapse risk in the post-remission period after CR has been attained. Continued use of either HiDAC or SDAC in induction is likely to be guided by institutional familiarity or linked to standard of care chemotherapy backbones contained within clinical AML study protocols.

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References

Familial haemophagocytic lymphohistiocytosis: Australian experience and perspectives

The recent article by Mayson et al. on the life-threatening immunoregulatory disorder familial haemophagocytic lymphohistiocytosis (FHL) warrants wider discussion in the Australian context, particularly given our laboratory’s preparedness to undertake post-natal genetic and immunological testing when this is requested by physicians who wish to exclude the diagnosis (see below).

Primary FHL is an autosomal recessive disorder first described clinically in the 1950s, but it took over 40 years to define its molecular basis. In the past 15 years, genetic linkage analyses revealed the association between FHL and inactivating (null) mutations in a potent pore-forming toxin perforin (PRF1) and three other proteins responsible for its secretion: MUNC13-4 (UNC13D), syntaxin 11 (STX11), and its binding partner MUNC18-2 (STXB2). Around half of all primary FHL is caused by defects in the perforin (PRF1) gene, and the remainder by failure to deliver perforin to the immune synapse through exocytosis.

Normally, perforin is secreted into an immune synapse formed between a cytotoxic T lymphocyte (or a natural killer cell), whose major function is to kill virus-infected or transformed target cell, and the target. There, it forms transmembrane pores in the target cell membrane to deliver granzyme proteases into the cell’s cytosol and induce rapid apoptosis. In FHL, this mechanism fails and the consequence is uncontrolled systemic inflammation. Infants most commonly present with a hyperinflammatory syndrome marked by unexplained intractable fever, pancytopenia and marked hepatosplenomegaly. The disorder is generally restricted to cytotoxic lymphocyte dysfunction, although some patients with STXB2 mutations may present with gastrointestinal abnormalities.

For decades, FHL was solely considered a paediatric disorder, with most cases presenting within 12 months of birth. However, there is growing clinical and experimental evidence that FHL actually represents a spectrum of immunoregulatory disorders that can manifest at a much older age (the oldest reported patient was 59 years old), often with atypical symptoms.

Several years ago, our laboratory explained the basis for these delayed/atypical presentations, based on the inheritance of hypomorphic PRF1 alleles, in other words those that confer some residual perforin activity. Under these circumstances, perforin dysfunction is related to misfolding of the protein that results from a point mutation encoding a single amino acid substitution. Remarkably, around half of these patients presented with a spectrum of haematological malignancies. The mechanism underlying malignancy is unclear, but most of the cases had no known viral basis. We suspect that these cases represent a breakdown of immune surveillance of cancer, given that >60% of Prf1-null mice spontaneously develop B-cell lymphoma. Of the non-cancer presentations, a few patients presented with protracted viral infections, particularly Epstein–Barr virus, while the remainder presented in childhood, adolescence or early adulthood with variable and partial manifestations of infantile FHL, often making the diagnosis difficult.

With increased awareness, the number of reported cases of atypical FHL associated with mutations in any of the four genes has increased worldwide. Thus, ‘acute’ FHL in infants only represents a subset of a broad spectrum of congenital immune dysregulation disorders associated with cytotoxic lymphocyte dysfunction. This leads us to suspect that the condition may be underdiagnosed in childhood and adolescence, especially if there is no obvious family history. Treatment with non-specific anti-inflammatory medications, such as corticosteroids, may further mask symptoms and delay the diagnosis. For example, clinical colleagues in Melbourne recently treated an 8-year-old patient for acute steroid-dependent interstitial pneumonitis for many months, without obvious symptoms of FHL. Our genetic analysis revealed bi-allelic PRF1 mutations, one of which caused complete loss of function, while the other, A91V, reduces function by around 70%.

Given our laboratory’s interest in the immunological aspects of this disease, we provide gene sequencing and appropriate immunological assays if requested by a physician. While the focus of our initial work was PRF1, we have now set up sequencing protocols for UNC13D, STX11 and STXB2. Over the past 7 years, we have received

### Table 1 Spectrum of suspected FHL patients tested in our laboratory

<table>
<thead>
<tr>
<th>Mutations in suspected FHL patients</th>
<th>Number assessed</th>
<th>Age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRF1, bi-allelic</td>
<td>4</td>
<td>1 month, 1 month, 6 years, 11 years</td>
</tr>
<tr>
<td>PRF1, mono-allelic†</td>
<td>6</td>
<td>3 months–33 years</td>
</tr>
<tr>
<td>UNC13D, bi-allelic†</td>
<td>28</td>
<td>6 months, 6 years</td>
</tr>
<tr>
<td>STX11, bi-allelic</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>STXB2, bi-allelic</td>
<td>18</td>
<td>5 months</td>
</tr>
</tbody>
</table>

†All 46 patients had PRF1 sequencing completed; some were tested for mutations in UNC13D, STX11 and STXB2 in the Bryceson Laboratory (Karolinska Institute, Stockholm), depending on clinical indications, results of immunological assays and knowledge of genetic bases of FHL at the time (STX11 mutations were discovered in 2005, but immunological assay was developed only in 2007). STXB2 mutations in FHL patients were discovered in 2009. PRF1 mutations, which result in a significant or complete loss of function, §detected in a research laboratory of Dr Y.T. Bryceson at Karolinska Institute (Stockholm), and subsequently confirmed by us. FHL, familial haemophagocytic lymphohistiocytosis.
samples from 46 unrelated patients with suspected FHL, from four mainland states, of whom 12 were under the age of 2 years, 13 between the ages of 2 and 13 years, and 21 older than 13 years. We identified FHL-causing mutations in 13 of the 46 patients (28%), mostly but not exclusively in PRF1 (Table 1). Although we operate a research lab, we are happy to assist with post-natal genetic diagnosis of this group of diseases if requested to by a clinician.

In conclusion, we suspect that atypical FHL is a far commoner disorder than previously thought, and it should be considered in the differential diagnosis of unexplained systemic inflammatory diseases, both in paediatric patients and young adults.

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References
**Book Review**

**BOOK REVIEW**

**Deadly medicines and organised crime: how big pharma has corrupted healthcare**


This provocative book explores the relationships between pharmaceutical companies and healthcare. This is the fifth such book by the author that challenges the standard dogma about how we manage patients. Peter Gøtzsche began life as a science graduate, then worked within the pharmaceutical industry for 8 years with clinical trials and regulatory affairs, before leaving to study medicine and post-graduate clinical pharmacology plus epidemiology. He has been involved with the Cochrane Collaboration since its inception in 1993. He has over 50 publications in the ‘Big 5’ journals (the *Annals of Internal Medicine*, the *British Medical Journal*, *The Lancet*, the *New England Journal of Medicine* and *JAMA*) and is currently a professor of clinical research design and analysis at the University of Copenhagen. This 310-page book with 21 chapters and over 1100 references takes a scathing look at how the pharmaceutical industry has influenced government pharmaceutical regulators, universities, journals, medical education, patient support groups and the prescribing doctors to the direct advantage of industry rather than patients. He quotes examples of ghost writing, plagiarism and disparity between recorded and published results. His examples cover drugs used in every field of medicine. He does provide constructive criticism upon how clinical research data should be collected and retained in independent accessible sites. He also recommends that scientific journals, instead of publishing the results of major clinical drug trials, write critical reviews and editorials on the studies. Many of his thoughts and views are supported by several high-profile former editors of *BMJ*, *NEJM* and *JAMA*, to name a few. These editors describe his style of writing to include ‘strong blunt language and colourful metaphors’, and I would agree 100%. This book is an easy read, and I suggest will strongly influence the way doctors think and practise medicine.

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