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ORIGINAL ARTICLE

Editorial

The MMJ-MMSG: a call to referees and authors

Simon Attard Montalto

The Malta Medical Journals, now comprising the Malta Medical Journal (MMJ) and the Malta Medical School Gazette (MMSG), remain the only strictly peer-reviewed journals that focus on medicine and medical issues in Malta. They offer local clinicians and colleagues the option to publish their research with reasonable odds in favour of acceptance, when compared with large international journals where the number of submitted manuscripts and refusal to publish are considerably greater. Admittedly, a publication in the MMJ-MMSG will reach a much smaller audience since, despite all the commendable efforts of the outgoing editor, Prof Victor Grech, the MMJ remains outside of PubMed and PubMed Central. Essentially, a substantial captive local population and, more importantly, a steady influx of high quality publications is a pre-requisite for acceptance onto PubMed and PubMed Central.[1] Little can be done about the former and, although the MMJ-MMSG do receive and publish quality work, this could be improved.

There is little doubt that significantly more quality publications are 'out there' – one only has to review the quality and wide-ranging research that is presented by disparate departments and several authors in fora such as the Malta Medical School Conferences (MMSC). Unfortunately, many local researchers appear to be satisfied with their work achieving the level of an oral or poster publication at conference, and do not follow this up with a formal, academically 'superior' publication.

Cover Picture:

'Vegetable Open Market'

Watercolours

By Lina Janulova

Dr Lina Janulova qualified as a medical doctor from the Malta Medical School in 1985 and obtained a Masters in Public Health in 1997.

Position: Consultant in Public Health & the Medical Administrator, Mater Dei Hospital (>than 10 years).

I had the opportunity to pursue my passion for painting 4 years ago where I attend art classes with Mr George Farrugia in Qormi on a weekly basis.

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By rights, during the subsequent six months following a MMSC, one would expect the editorial board of the MMJ-MMSG to be inundated with submissions, yet this simply does not happen. This is a shame as, ultimately, prestige and longevity in one's research is garnered through a publication and not via a one-off presentation.

It is now pretty routine during many medical job interviews, to award credit for publications and, along the same lines, attainment of additional postgraduate degrees. These, by definition, involve some form of research and should, by default, generate material that is 'publishable'. Admittedly, the 'cream' is preferably sent to highly-cited journals, especially in the first instance. But surely (and we have all been there), this work is not always (usually doesn't!) accepted by the *Lancet, NJEM* or *Nature Genetics*, etc., and there is always valid data and results, sometimes 'spin-offs' from the core research, that would be eminently acceptable to the MMJ-MMSG. A gentle *caveat* in this regard: research and publications are important and do procure 'brownie points' at interview, but this should not be seen as a means to an end, and research should always be conducted properly, organised along accepted standards and contribute to knowledge. 'Research' simply with the aim of generating a publication, regardless of quality, is unacceptable, and will not skirt any hurdle supported by a peer-review process, including that of the MMJ-MMSG.

In case you are still in doubt, the MMJ-MMSG continues to welcome submissions of good quality research and papers. All those involved, in some form or another, in work relating to publications will know that this is a laborious and time-consuming exercise. This is not helped when manuscripts are submitted in sub-optimal or an incomplete state, or not in accordance with 'Instructions to Authors' and, as a minimum, will result in delays in publication if not an outright rejection of the article. ALL submitting authors MUST read and ADHERE to ALL the Instructions to Authors. Although it would seem 'obvious' that articles should be formatted as instructed, and the text, grammer, figures, tables, data, etc., are all double-checked, non-compliance in this regard remains a common problem. Indeed, the lead/senior author should ensure that all of the above has been completed before submission, particularly when manuscripts have been written by more junior and less experienced colleagues.

All submitted articles undergo editorial review and all, apart from guest editorials, are sent to expert referees for further review. The role of the referees cannot be understated: the entire peer-review process is propped up by these individuals who are generally busy people who undertake this lengthy process (a good review will take time, almost always no less than 30 minutes and, on occasion, several hours), for

no remuneration (although every three reviews will entitle referees employed by the Division of Health, Malta, to claim a merit award). Article reviews should, ideally, be returned within a period of six weeks, preferably using the Journal on-line portal. On the other hand, significant delays will hold up the manuscript and, if multiplied by several delayed articles, will delay the publication of the entire issue. Hence, as with other journals, referees are asked to declare whether they can complete in time and the editorial board would prefer a clear 'no' from the outset so that the manuscript in question can be passed on to a second referee. Problems trawling and maintaining quality refereeing is not unique to the MMJ-MMSG,[2] but is essential in ensuring 'a standard' as well as timely publication. On an international basis, this aspect of academic publication is reliant on collegiate support, no reward and little, if any, guidance, although some larger institutions do provide training.[3,4] Malta is no different and the MMJ-MMSG remains hugely dependant on good will of colleagues who offer their time and expertise 'gratis'.

The MMJ has come a long way from its origins as the St Luke's hospital based gazette in the 1980s. It is probably the oldest peer-reviewed journal in Malta that has been published, initially in paper format till 2014 and, like many other journals,[5] on-line since. It remains one of the key pillars that defines the Malta Medical School. The list of individuals who, in one way or another, have supported the MMJ/MMJ-MMSG is extensive, and I will not attempt to list these, given the inevitable risk of omission(s). The ultimate quality in the published product is the result of a multi-facetted effort, and is dependent on quality submissions, timely and in-depth manuscript review, and a dedicated and efficient production team. The latter incorporates a MMSJ-MMSG Board, editorial and secretarial team with most of the work being carried out at secretarial level. The Journals enjoy the continuing support from the Medical School: we expect Lecturers and members of the Faculty Board to contribute, particularly with accepting to referee submitted articles (greater support is required in this regard), and we continue to welcome quality submissions, both locally and from overseas.

Sub-note: *Given the relevance to both, this editorial has been published in both the MMJ and MMSG.*

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ORIGINAL ARTICLE

Evaluation of the levels of physical activity amongst Primary school children in Malta

Amanda Fenech, Nachiappan Chockalingam, Cynthia Formosa, Alfred Gatt

BACKGROUND

Malta is currently facing a childhood obesity epidemic. Almost 40% of primary and 42% of secondary school children are overweight or obese secondary to energy imbalances and increase in sedentary behaviour. Physical inactivity is another risk factor for childhood obesity and hence adult obesity, leading to various physical, psychological, social and economic implications. The aim of the study was to assess general levels of physical activity in Maltese primary school children.

METHOD

One hundred and twenty 9-year-old children from three state primary schools completed the Physical Activity Questionnaire for Older Children (PAQ-C). The PAQ-C measures the general levels of physical activity in children in terms of frequency and duration. It consists of ten items, covering different time-of-day segments for physical activity and scored using a five-point scale.

RESULTS

On average, children underwent physical activity twice in their spare time during week days. Children were mostly active during Physical Education lessons and school breaks rather than in their spare time. During the weekends, children were involved in active games an average of 2-3 times. In general, children described themselves as partaking in physical activity, 3-4 times during the whole week, which is less than once daily. Physical activity frequency is low in Maltese children potentially because of the extreme academic pressure as well as preferential involvement in sedentary activities.

CONCLUSION

School-based physical activity interventions should be implemented during physical education lessons and school breaks to maximize physical activity levels achieved by children as a public health strategy against childhood obesity.

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INTRODUCTION

Childhood obesity is a multi-factorial condition and is increasing worldwide, causing public health crises in several countries. Malta is no exception with 39.7% of primary school children and 42.6% of secondary school children being overweight or obese.[1] This is reflected in the latest Health Behaviour in School-aged Children (HBSC) study carried out in 2013/2014, in which Malta achieved the highest proportion of 11, 13 and 15-year-old children who were overweight or obese.[2]

As the risk of diseases related to sedentary behaviour in adulthood rises over time, it is highly important to prevent obesity during childhood. Lack of physical activity is a major factor in childhood obesity and obese children typically grow into obese adults.[3] Increased physical activity has been reported to lead to higher academic achievement,[4-5] in addition to known health benefits. However, the Maltese population's culture is deeply set in academia and does not recognise physical activity as important in its' own merit. This is highlighted in the HBSC study, in which Malta scored the highest proportion of 11, 13 and 15-year-old children pressured by schoolwork and who spend more hours on studying.[2] The study also showed that few Maltese children achieve the recommended 60 minutes of Moderate and Vigorous-intensity Physical Activity (MVPA) a day, with girls being less active than boys and MVPA decreasing with increasing age.[2] MVPA is the intensity level required for physical activity to have health benefits.

Physical activity (PA) is defined as bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level, and can involve anything from daily household chores to structured exercise and sport. PA can be categorized in various ways, including type, intensity, and purpose.[6] WHO recommends that children aged between five and seventeen years should accumulate at least 60 minutes of age-appropriate MVPA daily.[7]

Multiple studies emphasise the importance of PA patterns initiated during childhood as this lays the foundation for activity habits in adulthood.[8–10] Indeed, physical inactivity is identified by WHO as the fourth risk factor of global mortality, causing 6% of cases of cardiovascular disease, 7% of diabetes type 2, 10% of breast cancer, 10% of colon cancer, and hence causing an estimated 3.2 million deaths worldwide.[11]

On recognising Malta's obesity crisis, objective data on frequency of PA levels carried out by children were required. Numerous measurement techniques have been devised to specifically evaluate the levels of PA in children, each having their advantages and limitations.[12–14] Unfortunately, a reasonable 'gold-standard' measurement tool does not exist, and consequently, criterion validity cannot be assessed. The aim of this study was to assess general levels of PA and data was collected by means of a questionnaire. This study seeks to propose a strategy that maximises PA and elevates its' intensity in order to be beneficial for health

MATERIALS AND METHODS

One hundred and fifty 9-year old students in their fifth year of Primary school were invited to participate in this study. Three state schools within St Benedict's College in Malta were randomly chosen. St Benedict's College was chosen for this study as the

schools are provided with two regular Physical Education (PE) lessons taught by PE teachers, whereas in other schools, one is taught by the PE teacher and the other is to be carried out by the class teacher. In total, 120 students in eight classes accepted to participate.

Ethical approval for this study was sought and granted by the University Research Ethics Committee. Informed consent from the parents and an assent from the students were obtained, together with required permissions from the respective schools and the Education Department.

On the day of data collection, the researcher measured the participants' height, weight and waist circumference according to WHO guidelines[14-15] and provided a brief general presentation on PA to each class of students. Then the Physical Activity Questionnaire for older Children (PAQ-C) was distributed in Maltese[17] or English[18] according to the students' preferences. The PAQ-C was developed and validated for use in large-scale research with children.[18-19] It is a self-administered, 7-day recall questionnaire designed to measure general PA levels among children aged 8 to 14 years during the scholastic year. Test-retest (1-week) reliability for PAQ-C is 0.75 for males and 0.82 for females. It was previously validated against a seven-day activity recall questionnaire (r=0.46), Leisure Time Exercise Questionnaire (r=0.41) and Caltrac accelerometer (r=0.39).

PAQ-C consists of ten items, covering different time-of-day segments for PA and scored using a five-point scale.[21] The first question is a checklist of 22 common sports and leisure activities, plus room for additional activities. The aim of this question is to serve as a memory cue. The next three questions assess activity during school hours; mainly during PE lessons and both breaks. Three further questions evaluate children's activity right after school, later in the evening and during the weekend. In the eighth item the child is asked to choose the best statement to describe the amount of activity during the last seven days. The last activity question asks how often the child carried out PA for each day of the previous week. The tenth question assesses whether an illness prevented the child from doing his/her usual activity during the previous 7 days.[19] If illness was present, the child was excluded from activity assessment. It is not the purpose of the PAQ-C to evaluate caloric expenditure. Some advantages of the questionnaire include good compliance as it is filled with the researcher in class, takes less than 20 minutes to complete and uses memory cues to aid recall. Disadvantages comprise difficulty to completely capture short-burst nature of children's activity and recall bias. Permission for use of the questionnaire in this study was sought and granted from the authors. They were also asked for permission to replace the snow sports activities "ice skating", "ice hockey" and "cross-country skiing" with alternative locally common sports such as "gymnastics", "tennis" and "martial arts". The questions were read by the principal researcher, using an overhead projector, allowing enough time for students to fill in their answer, as well as providing support if difficulties were encountered regarding the questions. This modus operandi has been shown to enhance the quality of answers provided.[22] It was ensured that all students filled each question before proceeding to the next, so that questions did not remain unanswered.

Questionnaire data were inserted in Microsoft Excel 2016 software and subsequently analysed. Scoring the PAQ-C five-item Likert-scale responses was guided by the manual.[23]

The participants' body mass was measured using a portable GIMA PEGASO 27288 digital scale/stadiometer to the nearest 0.1kg. Standing height was measured to the nearest 0.5cm with the same stadiometer. Measurements were taken in thin socks, with feet together and knees and back straight according to WHO standardized techniques.[16]

In view of the limitations of BMI (Body Mass Index) as an indicator of excess fat mass and cardiometabolic risk especially in children,[24] waist circumference (WC) was also used in this study to improve the sensitivity of the findings. WC has been used as a proxy measure of central body fat which is better than overall body fat to predict adverse cardiovascular risk factors in both adults and children. [25] It is also known that children with a WC over the 90th percentile were more likely to suffer from cardiovascular risks than children with a WC lower than 90th percentile.[26] All anthropometric measurements were taken with the subjects standing behind a screen for privacy.

The height, weight and WC data were also inputted in Microsoft Excel® and AnthroPlus software developed by World Health Organization,[27] was used to convert height and weight measurements into BMI z-scores according to the 2007 WHO growth reference charts.[28] A BMI z-score of -1 and under implies underweight status, between -1 and 1 represents normal weight status, between 1 and 2, overweight status and above 2, obese status.

RESULTS

Subject demographics – including number of participants, gender, mean age (SD), mean BMI (SD), percentages of obese, overweight, normal weight, underweight students in the cohort are portrayed in Table 1 and Figure 1.

Of note, is the high proportion (54.6%) of the study population which is either overweight or obese.

Spare time PA took place on average, twice a week. The most common activities performed outside of school during the children's spare time were catch/tag (7.96%), jogging/running (7.68%) and football (6.23%). The least common activities were rowing (2.75%), badminton (3.03%) and triathlon (3.27%) (Figure 2).

One-way ANOVA verified there was a statistical significance of $p<0.01$ in physical activity levels between the days of the week, with Saturdays (15.68%) and Wednesdays (15.88%) being the most active days (Figure 3).

Table 2 and Figure 4 display the different time segments children undergo PA. Maltese children are most active during PE lessons and during school breaks (PAQ-C score is above 4). Whereas they are least active (PAQ-C score below 2) during their free time outside of school.

Figure 5 below illustrates the lack of correlation between BMI z-score and total PAQ-C score ($p=0.651$).

A strong positive and expected correlation can be observed between BMI z-score and waist circumference (Figure 6). However, there also was no significant correlation between WC and total PAQ-C score ($p=0.668$) (Figure 7).

Table 1 Descriptive statistics of the study cohort; *N*=120

	Mean	SD
Gender	-	-
Males	68	-
Females	52	-
Age (years)	9.389	0.268
Males	9.410	0.276
Females	9.363	0.263
Body height (cm)	133.579	5.924
Males	133.564	5.340
Females	133.794	5.611
Body mass (kg)	33.753	8.570
Males	34.165	8.337
Females	33.353	8.840
BMI z-score	0.844	1.371
Males	1.007	1.441
Females	0.655	1.275
Waist circumference (cm)	65.245	9.752
Males	66.529	10.026
Females	64.808	9.533

Figure 1 Weight status of the questionnaire cohort

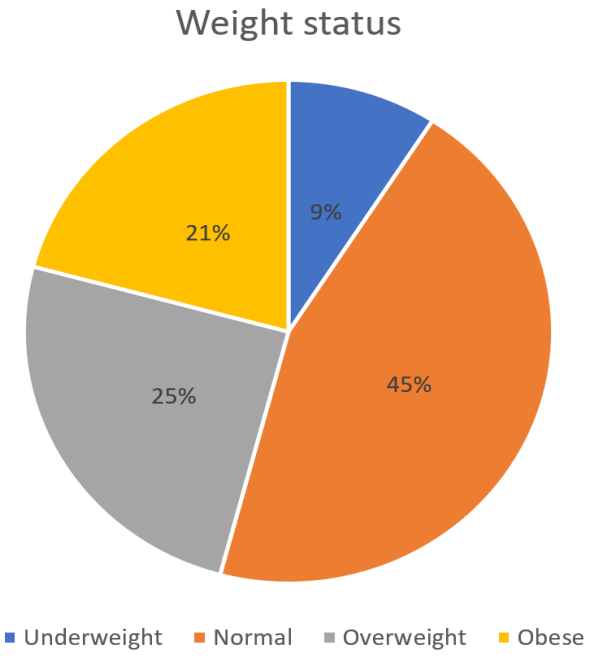

Figure 2 Physical activity performed during the Maltese children's spare time

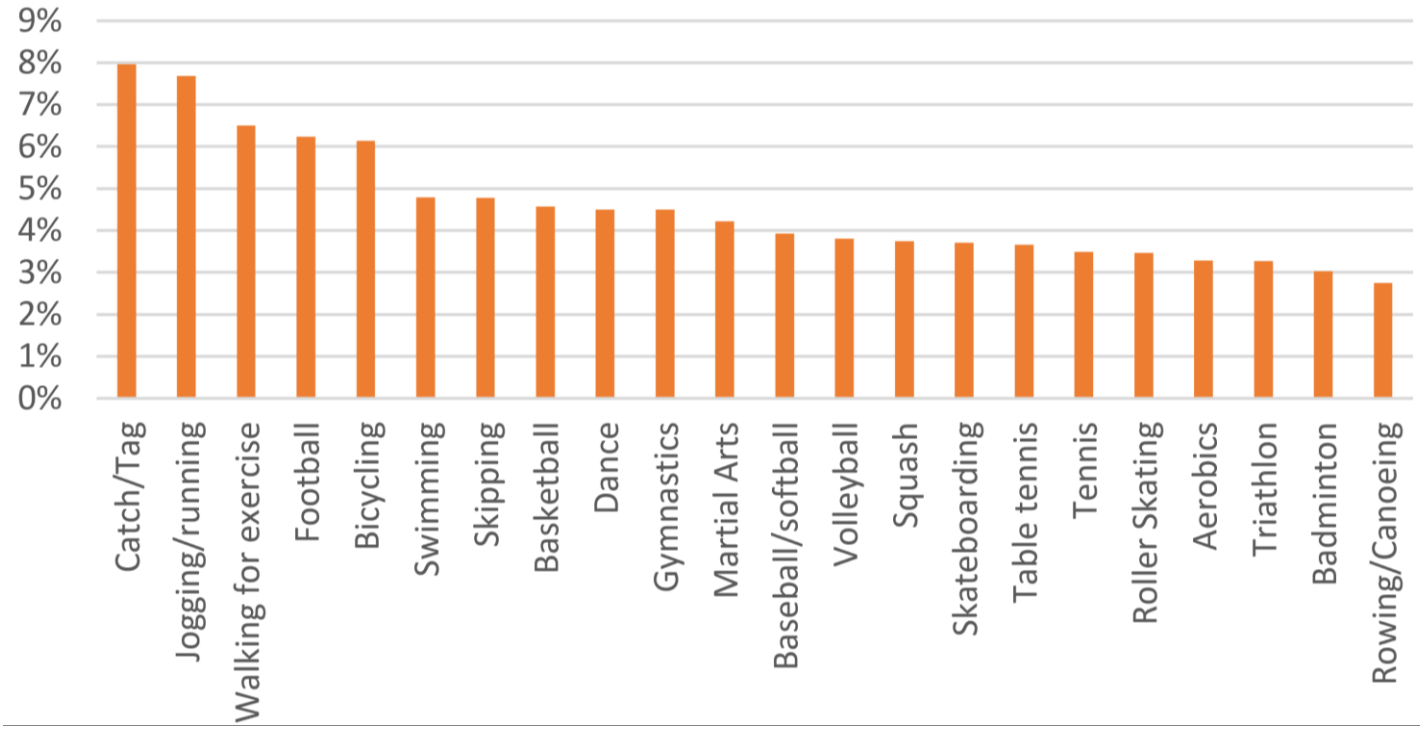

Figure 3 Weekly physical activity (PAQ-C score of 1=no PA, 2=rarely, 3=occasionally, 4 = often, 5 = very often).

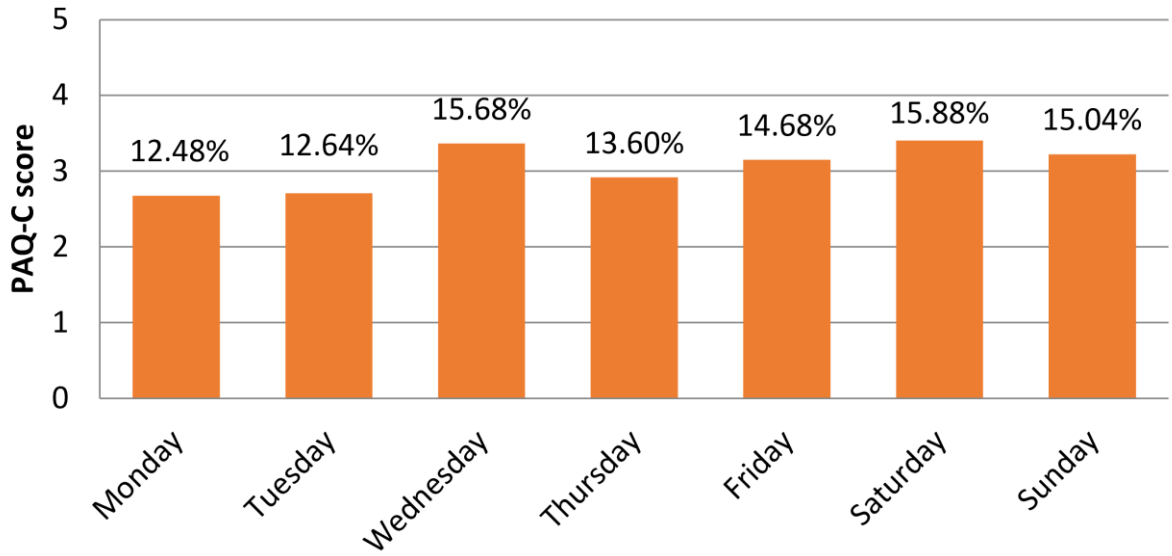

Table 2 Total PAQ-C scores and individual question scores (SD = standard deviation)

	Mean	SD
PAQ-C summary	**3.324**	**0.689**
Leisure and sport Q1	1.897	0.583
PE Q2	4.256	0.988
First break (morning) activity Q3	4.124	1.092
Second break (lunch) activity Q4	4.207	1.147
Afternoon activity Q5	2.975	1.332
Evening activity Q6	3.091	1.400
Weekend activity Q7	3.174	1.237
Free-time weekly activity Q8	3.132	1.533
Overall weekly activity Q9	3.064	0.986

Figure 4 Physical activity distribution within different time segments of the week (PAQ-C score of 1: no PA; 2: 1-2 times; 3: 3-4 times; 4: 5-6 times; 5: 7 or more times). Blue: PA in school; Orange: PA outside of school; Yellow: average and total scores.

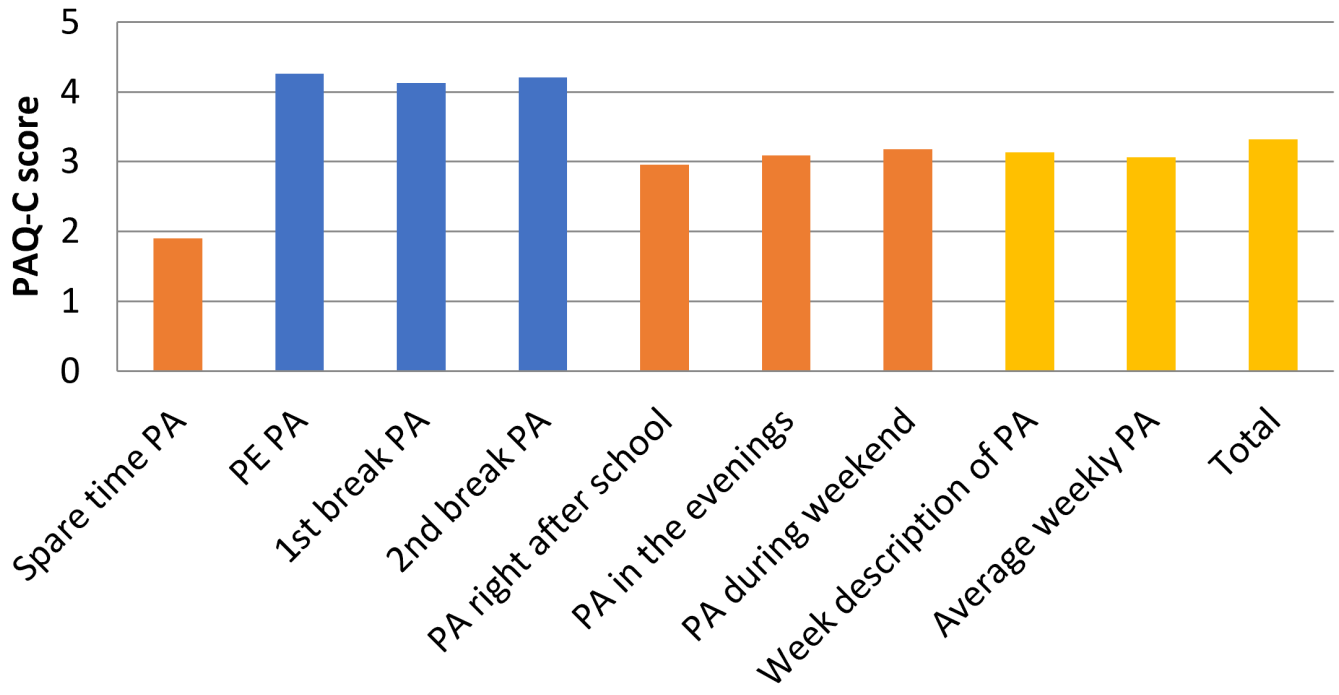

Figure 5 Absent correlation between BMI z-score and PAQ-C score

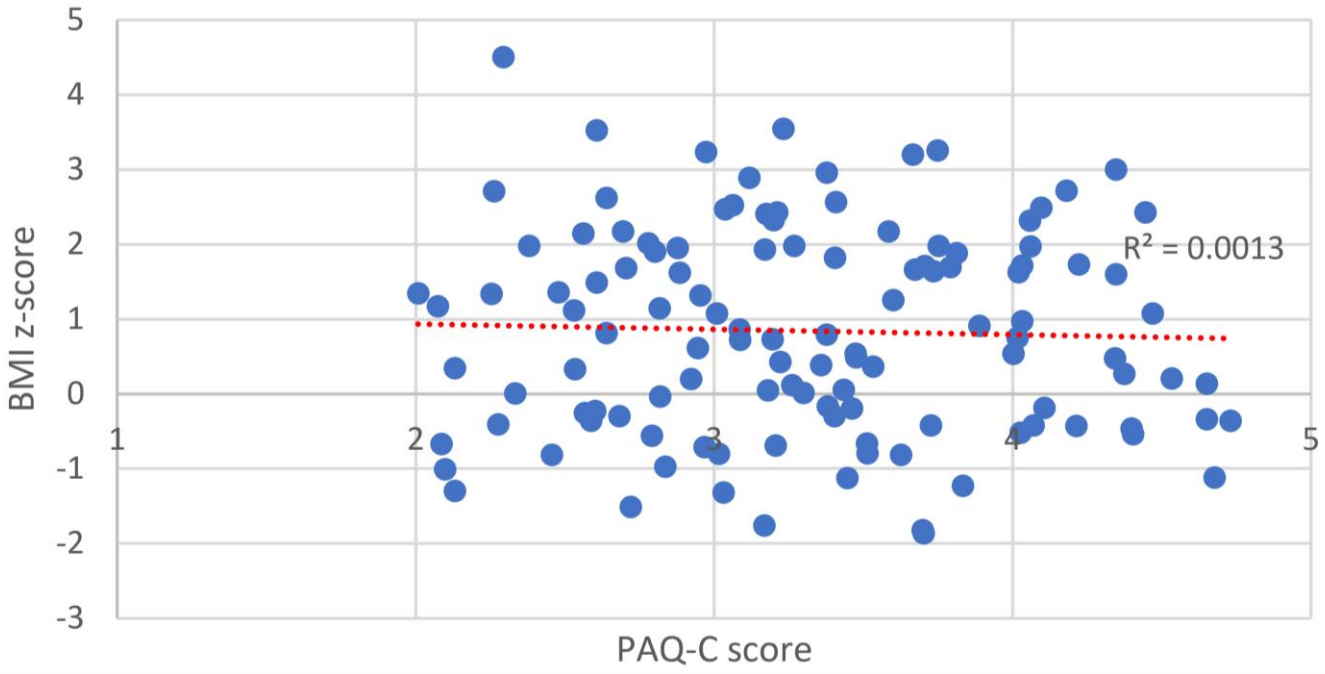

Figure 6 Positive correlation between waist circumference and BMI z-score

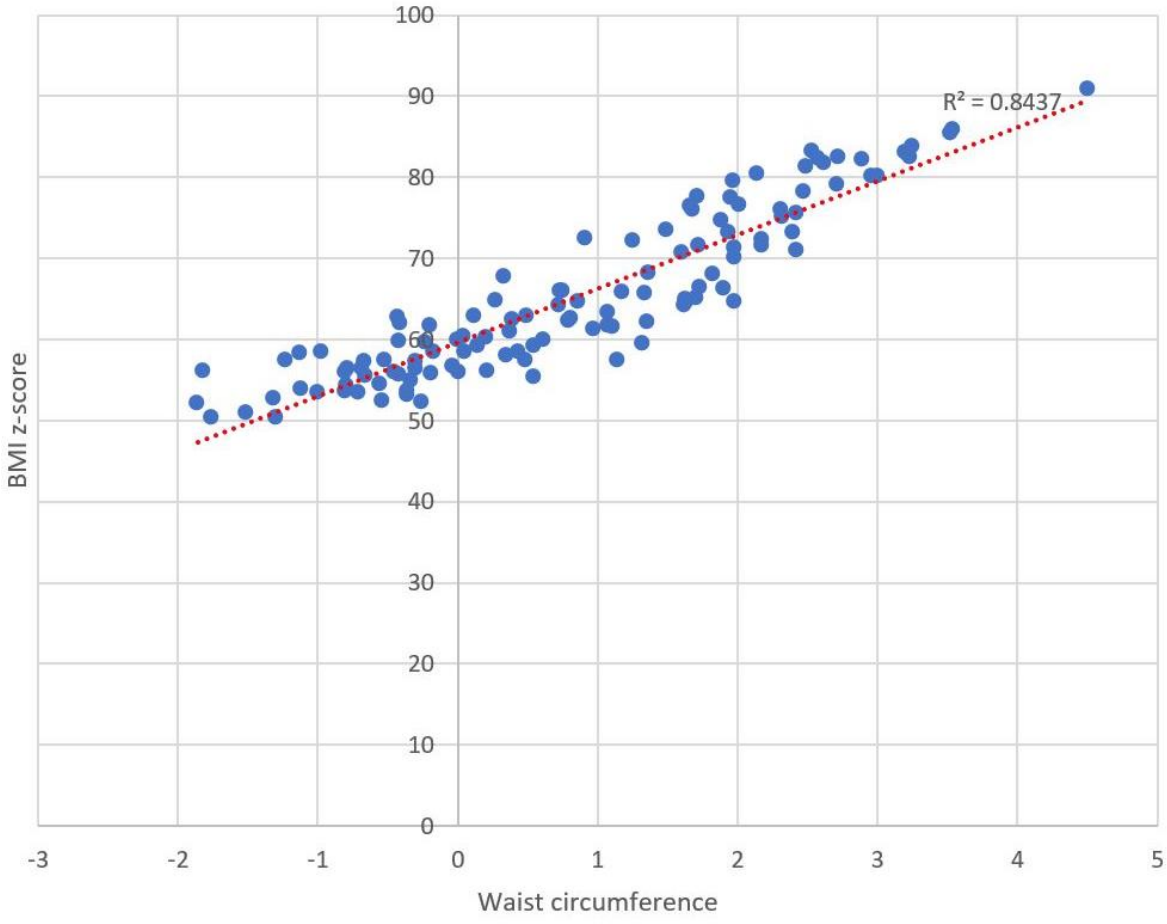

Figure 7 Correlation between Waist Circumference and PAQ-C score

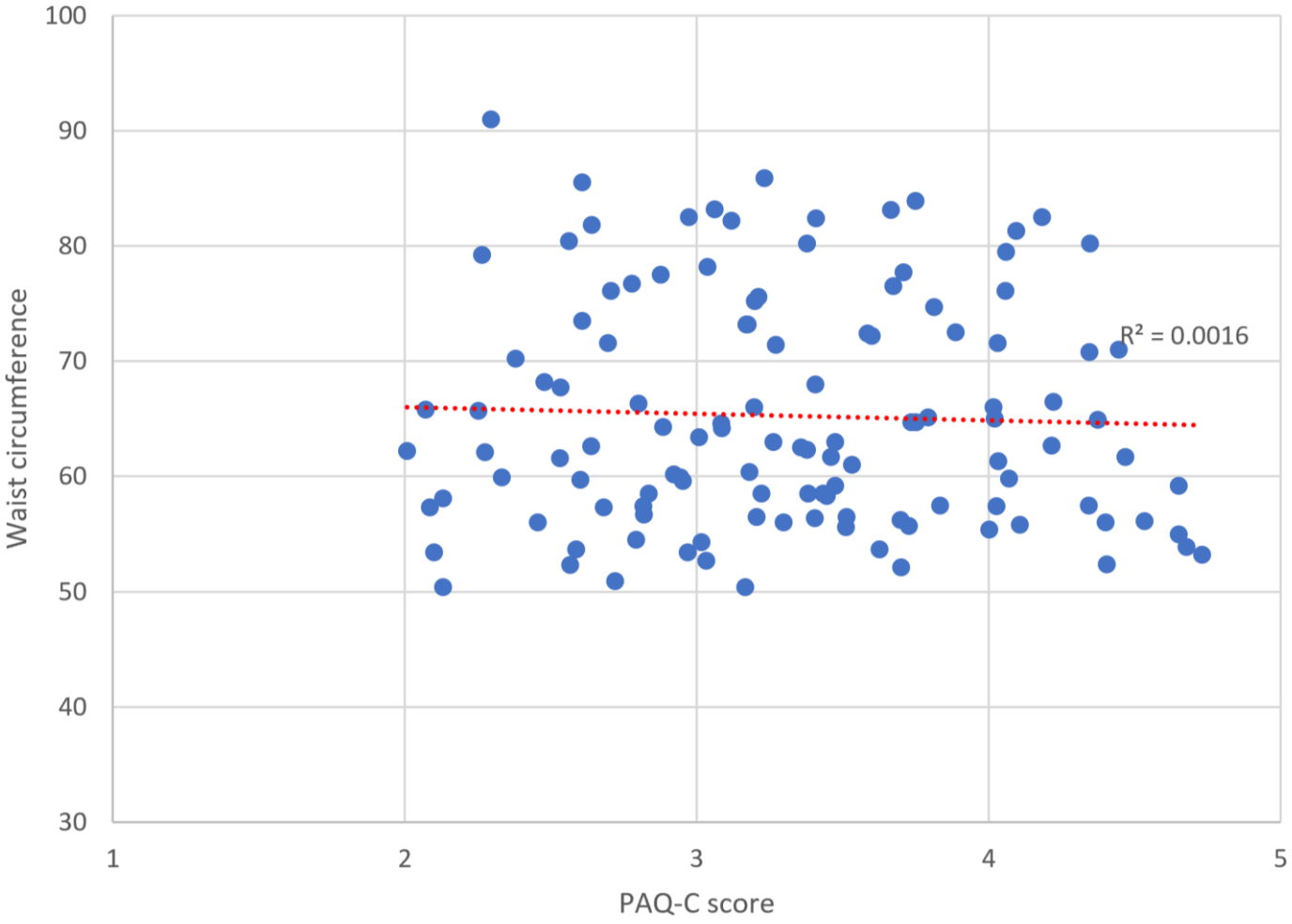

Table 3 PAQ-C scores according to weight status. SD = standard deviation; *n*=number of children

	Mean PAQ-C score	SD	*n*
Underweight	3.213	0.767	11
Normal weight	3.400	0.700	54
Over weight	3.248	0.705	30
Obese	3.270	0.622	25

On assessing PAQ-C scores according to weight status, the mean PAQ-C score and standard deviation were calculated for each weight category (Table 3).

Although children with normal weight have achieved the highest mean PAQ-C score, one-way ANOVA test determined that there were no significant differences of general PA between individuals of different weight status (p=0.564).

These results show that:

- Children perform minimal PA during their spare time. This is consistent with the latest HBSC study[2] which reported alarmingly high figures of daily television-watching of two hours or more during weekdays (sedentary behaviour) amongst Maltese children;
- Children perform more PA on Wednesdays and the weekend;

Higher quantities of general levels of PA were obtained during PE lessons and during school breaks when students are provided with scheduled time to divulge in physical activities.

Discussion

This study investigated the PA and fitness levels in Maltese children at the Primary school level. Our results clearly highlight low levels of PA. Whilst the reasons for these low levels have to be explored in detail, pressure for academic achievements is a strong causative factor. In addition, socio-cultural issues and sedentary entertainment are some of the contributing factors.[29]

Currently, children only undergo physical activity once a week or less. This probably reflects the fast pace within the modern family, in which both mother and father work and thus less time is available for children to partake in physical activities.

There is no significant correlation between the BMI z-score of the participants and the general levels of PA performed. However, it is important to note that PAQ-C questionnaire does not reflect the intensity of PA done so there is no distinction whether PA is done in MVPA which is beneficial for health or with less intensity. Additional tools such as activity monitors or systemic observation such as System of Observing Fitness Instruction Time (SOFIT), should be used both during PE lessons as well as during breaks, in which children are involved in free play, in order to determine the MVPA intensities during such time-segments.

Another issue is that the time segments in which the children are most active, namely in PE lessons and school breaks, are very limited quantitatively when compared to time segments outside school. PE lessons are usually carried out twice a week, each lesson lasting around 40 minutes. Moreover, children have two breaks each day, having a combined duration of 20 minutes of time allowed for free play in the school grounds. In total, this adds up to 180 minutes in a week as opposed to 4,080 minutes of spare time available in one-week (14 waking hours x 7 days) minus (6 hours of school x 5 days) times 60 minutes). Furthermore, if we deduct one hour a day for homework/studying/reading, the amount of free time available for PA is 3,660 minutes. Therefore, although time is still available for children to undergo plenty of physical activity, children still choose, or have no choice, to entertain themselves with sedentary activities rather than undergo in PA during this time.

Participants were recruited from one region in Malta. This poses a limitation to both internal and external validity, as the sample was non-random and not completely representative of the target population. Ideally, private and church schools were also included and random

sampling taken across Malta and Gozo in order to be able to better generalize result findings. Nevertheless, randomization was applied for the selection of schools that were recruited in the study from within the college. The national prevalence of overweight and obese children in all Year 5 students attending state, independent and church schools from the population study carried out in 2016 was 45.4%, [1] whereas the prevalence of overweight and obesity in this study is 54.6%. This highlights the higher BMIs affecting children in southern towns. Furthermore, the PAQ-C questionnaire required to be slightly modified in view of the different cultural contexts. New validity and reliability reports with the modifications were ideally conducted before the questionnaire's implementation.

These findings, along with the contemporary crisis of childhood obesity in Malta, strongly urge the need for action. Suggestions from these findings are in line with the recommendations brought forward by The National Policy for Sports in Malta and Gozo:[30]

- PE lesson curriculum should be research-based so that children spend > 50% of lesson time in health-enhancing MVPA intensity;
- Minimum number of hours of participation in PE (5% of total lessons) should be enforced and additional opportunities should be given;
- Schools should offer PA opportunities and sport clubs during breaks;
- Schools should consider offering after school PA opportunities;
- School playgrounds should be well equipped and with playground markings so as to provide multiple opportunities for children to employ in PA;
- Active school transport should be urged and promoted as it provides abundant opportunities for increased overall daily PA in children.
- Improve image of sports in Maltese mentality as one aiding academic achievement rather than detrimental.

In conclusion, this study plainly shows the limited amount of PA undertaken by children in Malta. In their spare time, children prefer to take up activities that do not involve exercise. Sedentary behaviour further exacerbated by the urbanisation of Maltese villages with ever-decreasing safe areas for children to play in. Parks and play areas should be actively created in each village and they should be repeatedly tended and updated, in order to attract families and promote physical exercise during play.[30]

It is also important to note the high quantities of PA obtained during PE lessons and school breaks. These particular time periods should be used to their best potential. Malta should make use of schools by implementing school-based interventions as a public health strategy to increase national quantities of physical activity levels and combat childhood obesity.

Summary Box

- Malta is currently faced with epidemic rates of childhood obesity
- Increased prevalence of sedentary behaviour in Maltese children from previous years
- High academic pressure is directed towards Maltese school children
- Maltese children participate in physical activity only 3-4 times in a week – less than once daily
- During their week, children undergo physical activity mostly during school breaks and Physical Education lessons
- These two time-segments should be used to their full potential; researched school-based physical activity interventions should be implemented in Maltese schools as part of a public health strategy against childhood obesity

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ORIGINAL ARTICLE

Outcome comparison between ileal conduit and orthotopic neobladder:

An extended literature review

Christine Mizzi

Introduction

Bladder cancer is the 10th most common malignancy worldwide and represents a burden on both patients and healthcare providers. The management strategy for muscle-invasive bladder cancer is radical cystectomy with urinary diversion. Ileal conduit has been regarded as the main method of urinary diversion for several years. Orthotopic neobladder has been its main competitor since the development of newer techniques.

Aim

The aim of this extended literature review to evaluate the evidence and outline arguments in favour or against ileal conduit and orthotopic neobladder with a special focus on morbidity, mortality, sexual dysfunction, tumour recurrence, renal function and quality of life.

Methodology

A total of 17 relevant studies were identified – 15 cohort studies and 2 systematic reviews. These were appraised to establish rigour, reliability and validity.

Results

Evidence from contemporary literature demonstrates that ileal conduit and orthotopic neobladder offer comparable outcomes when it comes to morbidity, mortality, relapse rates and acute or chronic kidney disease. However, neobladder could be the better option in consideration for the patient's sexual function and quality of life.

Conclusions

These findings were used to develop graded recommendations which could be applied to local clinical practice.

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Bladder cancer is the 10th most common malignancy worldwide.[1] Radical cystectomy is the recommended elective treatment for muscle-invasive bladder cancer. In males, radical cystectomy involves removal of the bladder, prostate, and seminal vesicles; in females, the bladder, ovaries, uterus, cervix and anterior vagina are resected.[2] Radical cystectomy then requires reconstruction of the lower urinary tract through urinary diversion.[3]

Oncological, physiological, social and technical issues, along with patient preference are factors that need to be taken into consideration when decided on the type of urinary diversion. For more than 30 years, the ileal conduit has been considered the gold standard urinary diversion method. However, since 1980, a number of orthotopic neobladders have been developed and improved. The most popular neobladder described is the Studer's method.[4]

In 2015, according to the British Association of Urological Surgeons (BAUS) Section of Oncology's radical cystectomy dataset, 80.6% of patients received an ileal conduit and only 6.9% had a neobladder.[5] Current practice relies heavily on the urologist's judgment in determining what type of urinary diversion is opted for. Controversies over this choice are partly due to the lack of effective ways of outcome assessment and unawareness of disease-specific problems related to ileal conduit and orthotopic neobladder.

An extended literature review to examine the evidence surrounding this topic was therefore performed to determine which method of urinary diversion offers the most favourable outcomes.

Aim

The aim of this literature review is to critically appraise the evidence for and against ileal conduit and orthotopic neobladder, taking into account patient health-related quality of life, symptoms, complication rates, mortality and long-term oncological outcomes. The findings of the literature review were used in the development of graded recommendations for clinical practice as the intended end-product.

Methodology

The PICO method (Table 1) was used to formulate the clinical question, which in turn assisted the development of a search strategy. The clinical question developed is: *In patients who undergo radical cystectomy for bladder cancer, how do ileal conduit and orthotopic neobladder as methods of urinary diversion compare in terms of postoperative outcomes?*

A systematic literature search was conducted using Ovid via Embase, Medline and Joanna Briggs Institute EBP Database. The keywords used were 'bladder cancer' AND 'radical cystectomy' AND 'urinary diversion' AND 'neobladder' AND 'ileal conduit' AND 'outcomes'. Another search using Pubmed was done using a combination of free text words and Medical Subject Heading (MeSH) terms to increase the sensitivity of the search. The database was searched using the following keywords: 'radical cystectomy' AND 'urinary diversion' AND 'neobladder' AND 'ileal conduit' AND 'outcomes'. The Cochrane Library database was also searched using the keywords 'radical cystectomy' AND 'ileal conduit' AND 'neobladder'.

Table 1 Acronym PICO to formulate a clinical question

PICO model for clinical questions	
Patient/Problem	Radical cystectomy for bladder cancer
Intervention	Ileal conduit as a method of urinary diversion following cystectomy
Comparison	Orthotopic neobladder as a method of urinary diversion following cystectomy
Outcomes	Morbidity and mortality Sexual dysfunction Tumour recurrence Renal function and metabolic abnormalities Quality of life

Inclusion criteria were articles on human subjects, both males and females, over 18 years of age, published between 2007 and 2017, that provided a direct comparison between ileal conduit and orthotopic neobladder and reported on at least one outcome measured after radical cystectomy. No restriction was made on origin of study. The search was limited to publications in the English language.

The search using Ovid via Embase, Medline and Joanna Briggs Institute EBP Database yielded 83 articles, of which 11 were relevant to the topic after screening abstracts and titles (**Table 2).** Reference listing was done with backward chaining employed to retrieve pertinent publications. Three further relevant articles were found.

The Pubmed database search yielded 127 articles, of which 10 were deemed to be relevant. Seven of these had already been identified in the previous search and were eliminated. No further relevant studies were identified from the Cochrane Library database search.

A total of 15 cohort studies and 2 systematic reviews were critically appraised using the

Table 2 Search results using Ovid via Embase, Medline and Joanna Briggs Institute EBP Database

	Keyword	Number of articles
1	bladder cancer	70976
2	radical cystectomy	13032
3	urinary diversion	16328
4	Ileal conduit	4295
5	neobladder	3520
6	outcomes	1489108
7	1 and 3 and 3 and 4 and 5 and 6	108
8	limit 7 to English language	100
9	limit 8 to human	89
10	limit 9 to year 2007-2017	83

Critical Appraisal Skills Programme (CASP) appraisal tool. The evidence grading tool applied for all studies is the Scottish Intercollegiate Guidelines Network (SIGN) grading system as described by Harbour & Miller (2001).[6] Grading of Recommendations was also done according to system by Harbour and Miller (2001).[6]

Results

Morbidity and mortality

Radical cystectomy with any type of urinary diversion is a complication-prone surgery, with the risk of developing a complication ranging from 16-66%.[7-8] A wide range of complications are quoted in different studies which can be attributed to the use of different reporting systems. The main finding in the study by Erber et al. (2012)[9] was the significantly higher incidence of ileus in patients undergoing ileal conduit. The authors also report better survival outcomes with orthotopic neobladder. In comparing the type, incidence and severity of 90-day morbidity, Abe et al. (2014)[10] revealed that overall complication rate did not vary between ileal conduit and orthotopic neobladder. More importantly, the type of urinary diversion was an independent risk factor for overall complications. Along with the study by Kim et al. (2014),[11] there was no significant difference in 90-day mortality. Aboumarzouk et al. (2014)[12] found no significant difference in comparison of individual and grouped complications, a finding reproduced in the study by Kim et al. (2014)[11] and Antonelli et al. (2015).[13]

Observations relating to morbidity must be interpreted with caution due to the confounding effect of heterogeneity in age, comorbidities and distribution of prognostic parameters between groups. The results are confounded by the propensity for surgeons to recommend neobladder to young healthy individuals. None of the studies identified any statistically significant difference in overall complications rate. The misconception that neobladder, being a more technically challenging type of surgery, is automatically associated with more complications is therefore unfounded.

1. Sexual dysfunction

Sexual dysfunction is one of the complications which is often overlooked, in the process of prioritising other outcomes such as cure with minimal risk of recurrence. The reported rate of sexual dysfunction after radical cystectomy is between 14%-80%.[14] The only study which directly addressed this issue was by Asgari et al. (2013)[15] which concluded that following an initial drop in erectile function, orthotopic neobladder patients demonstrated a significant improvement in sexual desire compared to their ileal conduit counterparts. In this study, no attempt at nerve-sparing was undertaken. The improved sexual desire in the neobladder group can be attributed to a less drastically altered body image.

The studies by Goldberg et al. (2016)[16] and Cerruto et al. (2016),[17] although not focused on sexual function as the primary outcome, also pointed out more favourable results in erectile function with orthotopic neobladder.

2. Tumour recurrence

Local recurrence of bladder cancer after radical cystectomy is often a result of surgical failure. Ileal conduit was favoured for a long time since it was thought to provide better cancer clearance than neobladder. However, the study by Pejcic et

al. (2007)[18] demonstrated no significant difference in recurrence rates between the two. The construction of a neobladder is therefore supported whenever there is the absence of tumour at the bladder neck or at the intramural or juxtavesical ureteral segment at cystectomy. With an improved understanding of pathology behind invasive bladder cancer, the majority of patients without prostatic or bladder neck involvement can now be offered neobladder without compromising cancer control.[19]

3. Renal function and metabolic abnormalities

Urinary diversion is associated with hyperchloremic metabolic acidosis and electrolyte metabolism abnormalities owing to absorption of ammonium through the intestinal mucosa. It is often believed that the metabolic challenge posed by ileal conduit is less than that of orthotopic neobladder due to a shorter bowel segment used and the absence of a reservoir.[20] However, Cho et al. (2017)[21] showed no significant differences in biochemical profiles between ileal conduit and neobladder. The authors also outlined a relationship between decreased renal function and acid-base status.

The incidence of acute kidney injury after radical cystectomy is 31-38% and is associated with higher incidence of chronic kidney disease and mortality.[22] According to Joung et al. (2016),[23] the incidence of acute kidney injury, its associated intensive care admission rate and length of hospital stay did not differ significantly between the two groups.

Jin et al. (2011)[24] showed that irrespective of the type of urinary diversion, a substantial proportion of radical cystectomy patients experience deterioration in renal function. However, the authors report better long term renal function with neobladder as compared to ileal conduit when patients were exposed to diabetes and hypertension.

Nishikawa et al. (2014)[25] observed renal deterioration in 46.2% of the study population after radical cystectomy, with hypertension and pyelonephritis being independent predictive risk factors. Yet, no significant differences were found between ileal conduit and neobladder.

4. Quality of life

Health-related quality of life, being a multifaceted and subjective concept, was the most challenging outcome to quantify in this literature review. Various questionnaires were encountered in the assessment of quality of life, thus it is difficult to achieve comparability of results. Not all questionnaires used in the appraised papers have been validated and they are very heterogenous in the assessed domains.

The urological community remains unconvinced regarding the quality of life benefits of neobladder over ileal conduit. However, most of the papers argue in favour of orthotopic neobladder, relying on perceived functional benefits and preservation of body image.[19-26] This, however, could be a reflection of selection bias since younger healthier patients with more favourable tumours are usually encouraged to receive a neobladder.

On the other hand, complications related to neobladder management are also highlighted, such as incontinence and reduced bladder control and sensation.[17] Counter arguments for ileal conduit can be put forward, especially since significantly higher urinary function scores were achieved

in comparison to neobladder, as shown in the papers by Huang et al. (2015),[27] Goldberg et al. (2016)[16] and Cerruto et al. (2016).[17]

Conclusion

After analysis of some conflicting evidence, the key results do not demonstrate any benefits of orthotopic neobladder over ileal conduit in terms of morbidity, mortality, renal function and recurrence, indicating that they are equally safe procedures. However, significant benefits can be appreciated with neobladder with regards to sexual function and quality of life, giving it a more appealing role particularly in younger patients. The recommendations shown in **Table 3** were developed as the end product of the critical appraisal of papers included in this literature review. They can provide a basis for future developments in such a dynamic and constantly evolving specialty as urological oncology. However, preceding the introduction of formal guidelines, more high level evidence derived from well-designed randomised controlled trials is required.

Table 3 Recommendations for practice

Recommendation 1 – Grade C
Based on current evidence, the choice of either ileal conduit or orthotopic neobladder as the method of urinary diversion following radical cystectomy does not significantly impact relapse rates for bladder malignancy, but ileal conduit is associated with lower survival rates. Erber et al. (2012) – Level 2+ Goldberg et al. (2016) – Level 2+ Kim et al. (2014) – Level 2++ Pejcic et al. (2007) – Level 2-.
Recommendation 2 – Grade C
Current best evidence suggests that the choice of urinary diversion after radical cystectomy translates into no significant difference in mortality rates between ileal conduit and orthotopic neobladder. Abe et al. (2014) – Level 2+ Aboumarzouk et al. (2014) – Level 2- Kim et al. (2014) – Level 2++ Jin et al. (2011) – Level 2+
Recommendation 3 – Grade C

It is suggested that ilela conduit and orthotopic neobladder following radical cystectomy may be associated with different rates of individual postoperative complications, but the overall complication rate is not significantly different.

Abe et al. (2014) – Level 2+

Crozier et al. (2016) – Level 2-

Aboumarzouk et al. (2014) – Level 2-

Kim et al. (2014) – Level 2++

Antonelli et al. (2015) – Level 2++

Recommendation 4 – Grade D

Current best evidence suggests that opting for orthotopic neobladder as the method of urinary diversion following radical cystectomy translates into longer operating time.

Abe et al. (2014) – Level 2+

Aboumarzouk et al. (2014) – Level 2-

Crozier et al. (2016) – Level 2-

Recommendation 5 – Grade C

Based on current evidence, orthtotopic neobladder offers the most benefits in sexual function outcomes and is the recommended option of urinary diversion after radical cystectomy whenever feasible, especially in younger men.

Asgari et al. (2013) – Level 2+

Goldberg et al. (2016) – Level 2+

Cerruto et al. (2016) – Level 2+

Recommendation 6 – Grade C

Current best evidence recommends the early identification and intervention for risk factors associated with renal impairment in attempt to minimize the decline in postoperative renal function in both ileal conduit and orthotopic neobladder patients. However, the proportion of patients developing chronic renal dysfunction does not significantly differ amongst the two methods of urinary diversion.

Nishikawa et al. (2014) – Level 2+

Jin et al. (2011) – Level 2+

Recommendation 7 – Grade C

According to current evidence, the formation of orthotopic neobladder after radical cystectomy leads to more favourable health-related quality of life outcomes in several domains in comparison to ileal conduit.

Philip et al. (2009) – Level 2-

Huang et al. (2015) – Level 2+ Singh et al. (2014) - Level 2+ Crozier et al. (2016)- Level 2- Cerruto et al. (2016) – Level 2+
Recommendation 8 – Grade C
It is suggested that ileal conduit after radical cystectomy offers more benefit in term of urinary function when compared to the orthotopic neobladder alternative. Huang et al. (2015) – Level 2+ Goldberg et al. (2016) – Level 2+ Cerruto et al. (2016) – Level 2+

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ORIGINAL ARTICLE

An audit of the management of Chronic Obstructive Pulmonary Disease (COPD) patients in an outpatient setting: looking beyond the respiratory illness

Malcolm Mintoff, Brendan Caruana Montaldo, Joelle Azzopardi

BACKGROUND

COPD is a major public health concern due to its associated morbidity and mortality, most of which is respiratory-related. However, a number of associated conditions exist, which independently contribute to morbidity and mortality, and therefore must be recognised and treated. The aim was to study the quality of management of outpatients with COPD, analyse whether associated comorbidities were being identified and treated, and if not, establish more effective ways of recognising missed opportunities.

METHODS

This retrospective study examined 37 out-patients with COPD seen by one respiratory firm in a Maltese tertiary centre. Out-patients were randomly selected between 2013 and 2015. The inclusion criterion was a post-bronchodilator FEV1/FVC ratio of <0.7 measured during their most recent spirometry. Outcome measures included an accurate diagnosis of COPD; documentation of smoking history and smoking cessation; appropriate COPD treatment including inhaler technique and assessment of non-adherence; appropriate prescription and usage of oxygen; referral to pulmonary rehabilitation; vaccination status; and consideration of comorbidities.

RESULTS

90% were male, mean age 68.5 years, and had all been correctly diagnosed with COPD, while 22% had a related comorbidity. The majority (81%) were ex-smokers. Virtually all were on inhaled bronchodilators, with 60% also on an inhaled corticosteroid. The uptake of Influenza and Pneumococcal vaccination was at 62% and 54% respectively. Only 24% of patients were given physical activity advice or referral to a pulmonary rehabilitation programme.

CONCLUSION

The investigators analysed whether practices from one firm are in-keeping with the recommended international guidelines. A number of practices were adequate, while others needed improvement. In order to narrow this discrepancy, the investigators suggest creating a template for COPD patients to be used at future visits which includes the factors investigated.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major worldwide public health concern due to its associated morbidity and mortality. In 2002, COPD was the 5th leading cause of death worldwide, and this is said to rise to the 3rd leading cause of death by 2030 according to estimates by the World Health Organisation.[1]

Although respiratory illness is the leading cause of morbidity and mortality in COPD[2], there are a number of associated conditions which independently contribute to morbidity and mortality. Thus, these factors ought to be sought and recognised if they are to be treated, and hence have a favourable effect on decreasing morbidity and mortality in this group of patients.

Despite the several treatments available to improve quality of life, decrease symptoms and reduce hospitalisation in COPD treatments, the only three modalities proven to decrease mortality are smoking-cessation programmes for patients with early disease, home oxygen treatment for persistent hypoxaemia, and lung volume reduction surgery (LVRS) for selected emphysema patients.

The aim of this audit was to study the quality of management of outpatients with COPD; analyse whether the associated comorbidities were being identified and treated; ensure that suitable candidates for mortality-modifying treatments were being prescribed them; and if not, establish more effective ways of recognising missed opportunities.

Materials and Methods

Participants and procedures

This retrospective study examined thirty-seven out-patients with COPD seen by one of four respiratory firms in a Maltese tertiary centre. Patients were randomly selected among those who visited the outpatient department over a 2-year period from September 2013 to September 2015. The inclusion criterion was a post-bronchodilator FEV1/FVC ratio of <0.7 measured during their most recent spirometry, as per diagnosis of COPD.[3]

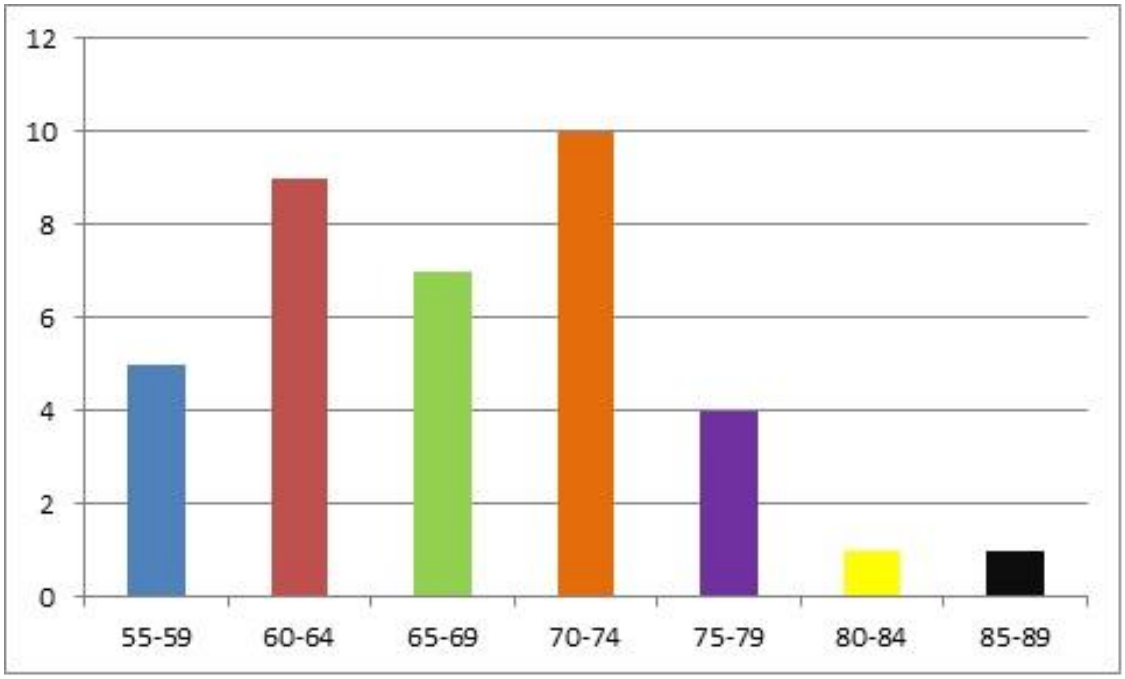
Outcome measures

Various outcomes were considered, namely whether the diagnosis of COPD had been accurately made; whether a smoking history had been documented and thus smoking cessation implemented; whether treatment and inhaler technique were appropriate; and whether non-adherence was an issue.

The study also analysed whether hypoxia was being checked for, and if so, whether supplemental oxygen had been prescribed and was being used appropriately. Where indicated, referral to Pulmonary Rehabilitation was audited.

The investigators were also interested in whether comorbidities had been considered, namely Heart Failure, Polycythaemia and Sleep Disordered Breathing. Since influenza and pneumococcal vaccination are pivotal in COPD care, the audit considered vaccination data on the subjects. Lastly, records of participants were analysed for End of life care documentation.

Figure 1 Distribution of patients according to age groups



Demographics and medical data

Data was retrieved manually from individual patients' clinical notes and electronically from iSOFT Clinical Manager (ICM). Spirometry testing was carried out by qualified spirometry nurses. Data was collected by two doctors not directly involved in the patients' care.

The data collected pertained to patient demographics, individual patient factors (e.g. weight, height, blood pressure (BP), respiratory symptoms, smoking status, and body mass index (BMI)), duration of care, spirometry results, smoking status, functional status, factors limiting self-care, treatment of COPD (e.g. medical treatment, treatment for smoking cessation and oxygen prescription), and influenza and pneumococcal vaccination status.

RESULTS

Demographics

The large majority (90%) of patients studied were male, with ages ranging from 56-88 years, and a mean age of 68.5. The elderly (patients over 65 years of age) made up almost two-thirds (64%) of the total patient population (**Figure 1**)

Spirometry severity grade

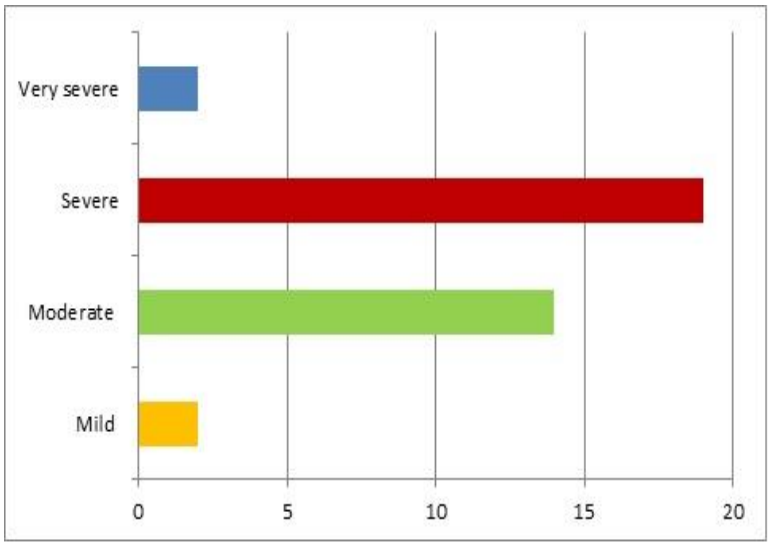
All patients included in the study had been correctly diagnosed as COPD, with a post-bronchodilator FEV1/FVC ratio of <0.7 as per diagnostic criterion for COPD.[3] Most patients were in the moderate (FEV1 50-79%) or severe (FEV1 30-49% predicted) group, with a minority in the mild (FEV1 ≥80%) and very severe groups (FEV1 <30%)[3] (**Figure 2**).

Smoking status

Although all patients were questioned about their smoking status at some point during their duration of care, documentation of smoking status within the previous 12 months was present in 79% of cases.

The majority of the population (81%) were ex-smokers, of which more than three quarters (76%) were former smokers and 5% recent

Figure 2 Distribution of patients according to severity of COPD based on FEV1 GOLD criteria



quitters (quit less than 6 months previously). 19% of patients were still smoking at the time of review (**Figure 3**). Of these (*n*=7), smoking cessation information was given to all patients at their most recent visit and during at least 1 other outpatient appointment during the prior 12 months, such that 86% received brief advice, 57% were referred to a smoking cessation programme, and 29% were prescribed pharmacotherapy (nicotine replacement or Varenicline). Data on 1 patient was not available.

Similar advice was also given to recent quitters in order to assist in preventing relapse.

COPD treatment

Virtually all study subjects were on inhaled short (SABA or SAMA) and long-acting bronchodilator (LABA or LAMA), with 60% also on an inhaled corticosteroid (ICS). A small proportion were on oral Theophylline, while none were on Leukotriene Receptor Antagonists, oral steroids (OCS) or LABA/ICS combinations (**Figure 4**). Inhaler technique was

Figure 3 Distribution of patients according to smoking status

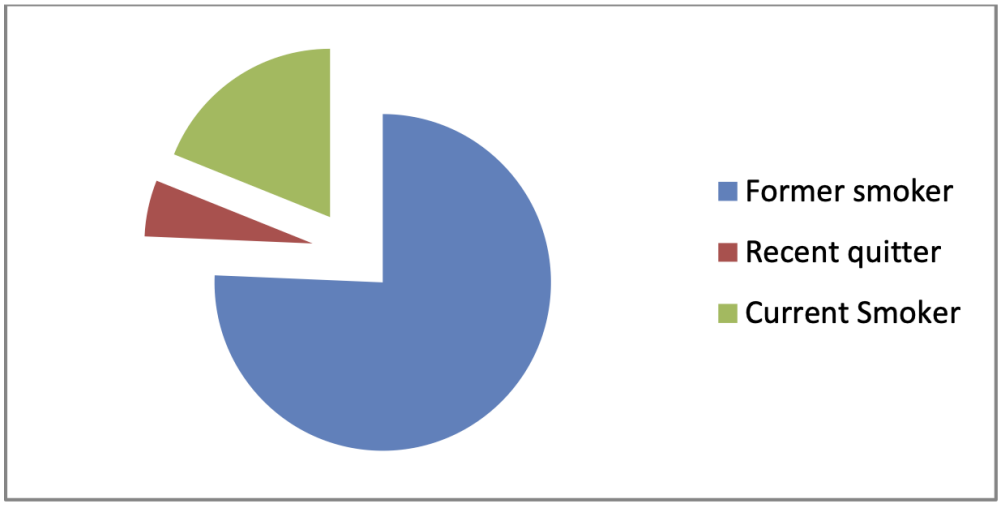
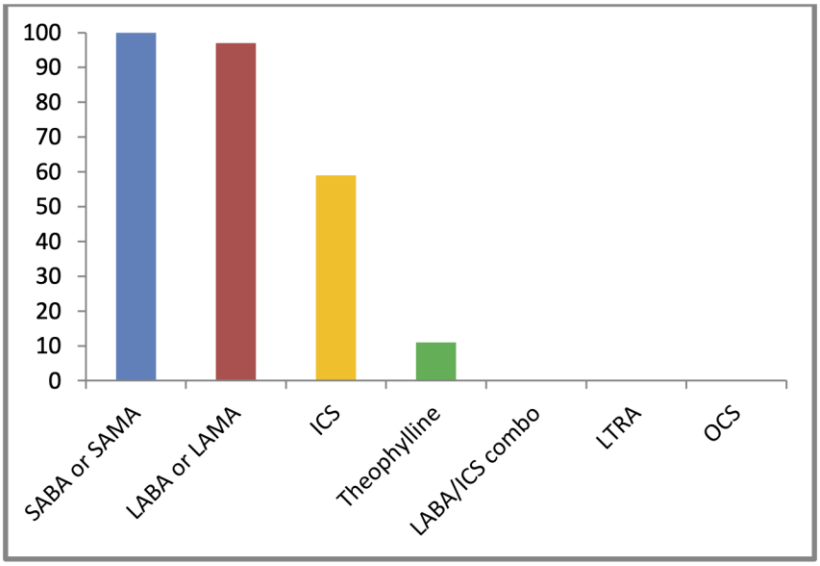


Figure 4 Percentage of patients on various COPD treatments

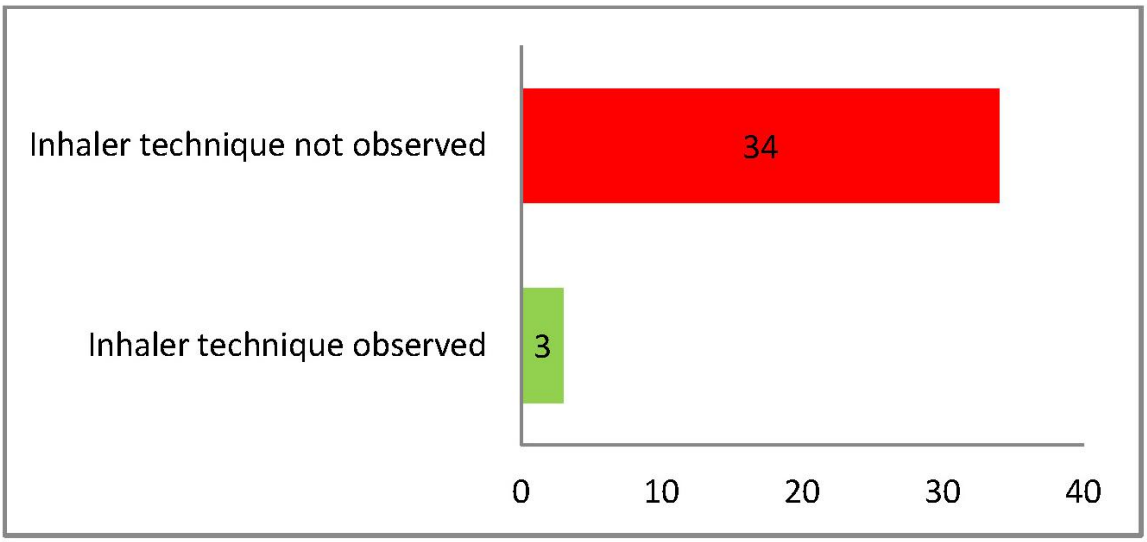


documented to have been assessed in the previous 12 months in only 8% of the study population (**Figure 5**).

Oxygen prescription

Practically all patients (97%) had pulse oximetry documented at an out-patient visit within the previous 12 months. 5 patients (13.5%) had a saturation of 90% or less, and these were already on long-term (LTOT) or short burst oxygen therapy (SBOT). Arterial blood gases were not available for any of the patients within the last 12 months. Only in 1 patient was LTOT being used unnecessarily, as the resting saturation on room air was documented at 96%. On review of all patients' haemoglobin, none were noted to be polycythaemic (haematocrit >55%). There was no mention in the notes of *cor pulmonale* as an indication for LTOT.

Figure 5 Assessment of inhaler technique in previous 12months



Vaccinations

The uptake of Influenza and Pneumococcal vaccination was relatively good, at 62% and 54% respectively (**Figure 6**). Of those that were not vaccinated, the influenza and pneumococcal vaccines appear not to have been offered by the physician in 27% and 38% of patients respectively. The remainder refused it or had a medical reason for not receiving it, whilst in 5% of cases respectively, the information was not available.

Physical activity advice/pulmonary rehabilitation

Only 24% of patients were given advice regarding starting, increasing, or maintaining physical activity. This included brief advice or referral to a physical rehabilitation (PR) programme. The investigators did not make a distinction between physical activity advice and actual referral for PR.

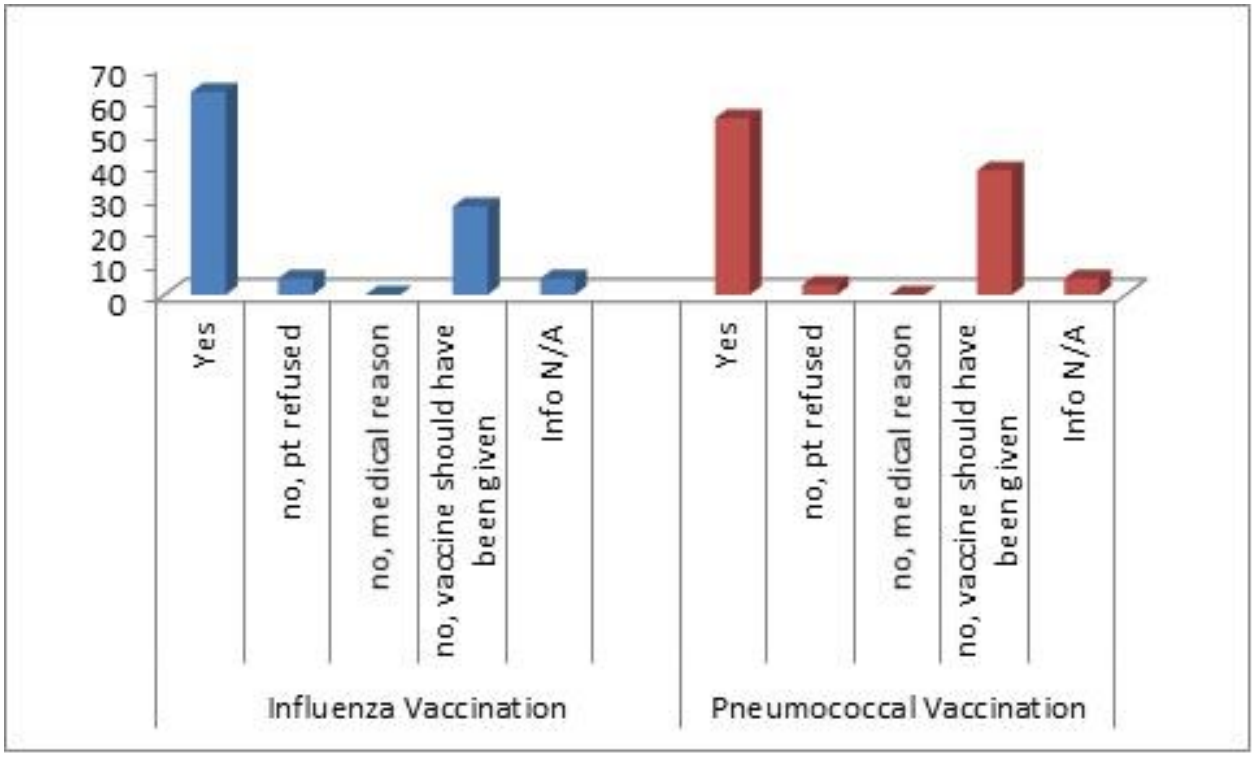
Comorbidities

BP was documented on all patients within the previous 12 months, and was shown to be well controlled, with a mean of 129/73. Of the population studied, three COPD-related comorbidities were actively looked for: cor pulmonale, a raised haematocrit and sleep disordered breathing (SDB). 22% had some form of SDB, with none having cor pulmonale or a raised haematocrit.

Functional status

Patients' functional status was categorised according to the Eastern Cooperative Oncology Group (ECOG) performance status[4]. Almost half (47%) were able to carry out physical work of a light intensity (ECOG 1), while just under a third (30%) were fully active (ECOG 0). A small proportion (8%) were "ambulatory and capable of all self-care but unable to carry out any work activities; up and

Figure 6 Percentage of study patients receiving Influenza and Pneumococcal vaccines respectively



about more than 50% of waking hours'' (ECOG 2) while 14% were ''capable of only limited self-care; confined to bed or chair more than 50% of waking hours'' (ECOG 3). None of the study patients were completely disabled (ECOG 4) (**Figure 7**).

BMI

All patients had a documented BMI from their spirometry records. Almost half of patients (43%) were noted to be overweight with a BMI of 25-29.9kg/m^2. There were equal numbers of patients in the normal BMI range (18.5-24.9kg/m^2) and the obese range (30-39.9kg/m^2) (27% respectively). One patient was grossly underweight with a BMI of 13.3kg/m^2.

Duration of care

Three quarters of the patients (74%) had been followed up for more than twelve months prior to auditing.

Factors limiting self-care

Some factors which were considered to potentially hinder patient self-care were recorded, notably psychiatric illness or cognitive impairment (8%), non-adherence to smoking cessation or to COPD-related treatment (47%) and other medical conditions (8%). Financial factors were not readily available in this group of patients.

Discussion and Limitations

The number of participants in this study was small, and the view point was only that of one out of four firms. However, the aim was to analyse a cohort of COPD patients for what may be being missed in their follow-up, so as to create a proforma to be used on all future COPD patients, which may then be disseminated amongst all four respiratory firms. Data can subsequently be collected from all four firms so as to audit adherence with guidelines.

All patients audited had been correctly diagnosed as having COPD, with an FEV1/FVC ratio on spirometry of <0.7. Investigators did not delve into the merits of whether patients were on the correct treatment depending on COPD Class according to COPD GOLD Guidelines 2014 (which have since been updated), as the CAT score was not recorded in the audit. However, results show that all patients were correctly on a short or long acting bronchodilator, and none were on

Figure 7 Functional status of patients classified according to ECOG

inhaled corticosteroids alone. It was disappointing to note that in only 8% of cases was inhaler technique documented to have been checked in the previous year.

Results show that in 21% of cases, a smoking history was not documented in the last 12 months. However, the investigators did not go into the merits of whether this group of patients were smokers or ex-smokers. A postulation is that the physician may have flipped through the case notes and noted that the patient had quit smoking, and therefore not questioned the patient. However, this is a misgiving, as nicotine addiction can notoriously cause relapse in a former quitter. Another explanation may be of not documenting what is asked.

One fifth of the study population was still smoking. Almost all received brief advice on quitting, just over half were referred to a smoking cessation programme, but less than one third were prescribed pharmacotherapy. These results are rather disappointing, as the evidence clearly shows that interventions that combine pharmacotherapy and behavioural support increase smoking cessation success compared to brief advice on quitting.[5]

Hypoxia was actively searched for by pulse oximetry. The audit design did not consider ABGs, and therefore hypoxia was defined as a resting oximetry saturation of <88%. Furthermore, review of oxygen prescription was not considered, whereas the guidelines indicate that oxygen prescription should be reviewed at 60-90 days to assess continued indication and effectiveness.[6]

Both influenza and pneumococcal vaccination uptake was relatively good in the population audited, in line with recommendations from the GOLD guidelines[3]. The GOLD guidelines distinguish between the 23-valent polysaccharide (PPSV23) and the 13-valent conjugate (PCV13) pneumococcal vaccines, stating that both PCV13 and PPSV23 should be given to all patients over the age of 65 years, whereas PPSV23 is also recommended for younger COPD patients with significant comorbid conditions including chronic heart or lung disease. The investigators in this audit did not differentiate between the 23-valent polysaccharide (PPSV23) and the 13-valent conjugate pneumococcal vaccination (PCV13). In the light of these guidelines, it is disappointing that vaccination was not offered to the study patients in a quarter to a third of cases.

Pulmonary rehabilitation has been shown to be the most effective therapeutic strategy to improve shortness of breath, health status and exercise tolerance.[7]

However, education about the benefits of exercise has not been shown to be effective, with an evidence Class C.[8] Thus, grouping 'advice on exercise' and 'referral to pulmonary rehab' in the same category was somewhat inaccurate in this audit. Even so, the uptake was poor, occurring in only a quarter of patients.

The study population was not shown to be hypertensive. However, COPD patients are known to have associated comorbidities. Of the population studied, three COPD-related comorbidities were actively looked for: *cor pulmonale*, a raised haematocrit and sleep disordered breathing (SDB). Other comorbidities known to affect COPD patients (depression, osteoporosis, IHD) were not investigated.

Despite COPD being known to be associated with mortality, whether independently or

through comorbidities, end of life discussion was not documented in the notes of any study subject within the last 12 months.

Conclusion

The audit attempted to investigate whether practices of one firm in a respiratory department of a tertiary hospital are in-keeping with what is recommended by international guidelines, namely GOLD (Global Initiative for Chronic Obstructive Lung Disease). Whereas a number of practices were up to scratch, a number of others needed refining. In order to narrow this discrepancy, the investigators suggest creating a template for COPD patients to include all the factors that were investigated in the audit, so as to make it easier for the physician to ensure all aspects have been addressed during the encounter, and in as efficient a time as possible. Thus, this audit served as a pilot study to create a template for a much larger study that will serve to analyse whether guidelines are being adhered to, and will be disseminated within the whole respiratory department.

Acknowledgements

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ORIGINAL ARTICLE

Psychotropic treatment in patients undergoing gynaecological procedures

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Background

Around 27% of the adult population in Europe has at some point suffered from a mental disorder in the past year. Patients with psychiatric illness have different needs and require specific medication review prior to surgery in view of the risks from anesthesia, the direct and indirect effects of psychotropics, risk of withdrawal symptoms, and risk of psychiatric recurrence or relapse. Gynaecological patients, particularly those going through the menopausal transition phase have an associated risk of psychiatric conditions especially mood disorders.

This audit is set to determine the link between psychotropic drug use in patients seen at gynaecological pre-operative assessment clinic (POAC), the most encountered diagnosis, how this relates to age together with analysis of most common drugs used to treat these patients.

Methods

Data about 123 patients from 24 weekly POAC was collected. The number of patients listed in each clinic was documented together with the patient's age. Patients on psychotropic medication were analysed to note diagnoses of each case and treatment used.

Results

21.1% of patients suffered from a mental health illness requiring psychotropic medication. Their average age was that of 51 years. The most common diagnosis was depression, summing up to 9.8% of all patients, followed by anxiety at 6.5%.

Conclusion

Depression and anxiety are leading mental health illnesses both in this cohort and the general population. Such patients have lower pain threshold which affects their recovery. Some psychotropics have severe interactions with anaesthetic thus need to be stopped prior to surgery after evaluation of risks such as drug withdrawal and deterioration in mental health.

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Introduction

Around 27% of the adult population in Europe has at some point suffered from a mental disorder in the past year. Such psychiatric conditions include psychotic disorders, anxiety, depression, substance abuse and eating disorders.[1]

Neuropsychiatric disorders in Europe accumulate to 15.2% of disability-adjusted life years (DALYs), thus being the 3rd most common cause, followed by cardiovascular diseases accounting for 26.6% and malignant neoplasms accounting for 15.4%.[2]

Overall females have significantly higher rates of mental health disorders when compared to males (except for substance use and psychotic illness). The female gender is a significant predictor of the need for prescription of mood altering psychotropic drugs. In the older population depression, organic brain syndromes and dementias are the leading mental health problems, with higher prevalence in females.[2]

Gynaecological patients, particularly those going through the menopausal transition phase have an associated risk of psychiatric conditions especially mood disorders. Several longitudinal studies revealed that females in the menopause transition are up to twice as likely to experience a depressive disorder, compared to the premenopausal period, independent of a history of depression.[3]

This audit is set to determine the link between psychotropic drug use and patients seen at gynaecological pre-operative assessment clinic (POAC), the most encountered diagnosis, how this relates to age together with analysis of most common drugs used to treat these patients.

Materials and Methods

The study was conducted at Mater Dei Hospital, Malta and approved by both the local audit committee and by the data protection management. Data from 24 weekly POAC of a gynaecological firm was collected. This accumulated to 6 months of POAC held, from September 2018 till February 2019. The total number of patients listed in each clinic was documented together with the patient's age. Patients who were on psychotropic medication were analysed further to note diagnoses of each case and what type of treatment was being given.

Results

Out of a total of 123 patients who attended one of the 24 POACs analysed for this study, 26 were suffering from at least one psychiatric condition requiring use of psychotropic medication, representing a total of 21.1% of the patients seen.

The age range of patient attending this clinic was between 19 to 83 years of age. The average age of the patients was 48 years, whilst the average age of the patients on psychotropic treatment was that of 51years. The most common diagnosis in this cohort of patients was mood disorder, specifically, depressive disorder of varied severity. In total 12 patients were at some point diagnosed with depression, that is 9.8% of all patients seen in clinic during the 6 months being analysed. Depression was the diagnoses in 46.2% of the patients having a form of psychiatric disorder. The second most common diagnosis was anxiety disorder, a total of 8 patients (6.5% of all patient seen and 31.9% of patients with a psychiatric diagnosis). Other diagnoses encountered during the analysis include; sleep disorders, developmental disorders (particularly attention deficit and hyperactivity

disorder, seen predominantly in the younger patients), psychosis and schizophrenia. The number of each case and their equivalent percentage of the total can be noted in the table below (table 1). Three of the patients seen, 11.5% (of psychiatric patient), reported more than one psychiatric condition.

The age groups of patients with mental health illness revealed that the majority of patients were post menopausal, the most common age group being that between 61 and 80 years of age. The second most common subgroup was females between the ages of 21 and 40 years. Other age groups and the percentage of patients in each can be noted in the table below (table 2).

Treatment analysis revealed that half of the psychiatric patients were prescribed monotherapy whilst the other half was making use of more than one psychotropic drug. The most common drug class prescribed was an antidepressant, 19 patients meaning 73.1% of psychiatric patients were on antidepressants, particularly selective serotonin reuptake inhibitor (SSRI) followed by serotonin–norepinephrine reuptake inhibitor (SNRI) and tricyclic antidepressant (TCA) (table 3). Antipsychotics were the second most common prescribed drug of choice in this cohort, atypical being more common than typical antipsychotics (8 versus 5 patients of the total) followed by benzodiazepines, antihistamines and mood stabilizers (table 4).

Table 1 Numbers of patient with different psychiatric diagnosis

Diagnoses	Number of patients (from a total of 123)	Percentage from total psychiatric cases	Percentage from total of patients seen
Mood disorders	12	46.2%	9.8%
Anxiety disorder	8	31.9%	6.5%
Psychosis/ Schizophrenia	4	15.4%	3.25%
Sleep disorder	3	11.5%	2.45%
Developmental disorder	2	7.7%	1.63%

Table 2 Ages of patients with psychiatric condition

Age group	Number of patients (from a total of 123)	Percentage from total psychiatric patients
<20	2	7.7%
21-40	6	23.1%
41-60	5	19.3%
61-80	12	46.2%
>81	1	3.8%

Table 3 Number of patients on different classes of antidepressants

Class of antidepressant	Number of patients (from a total of 123)	Percentage from total patient on psychotropic treatment
SSRI	16	61.5%
SNRI	2	7.7%
TCA	1	3.8%

Table 4 Number of patient on other psychotropic drugs

Drug class	Number of patients (from a total of 123)	Percentage from total patient on psychotropic treatment
Antipsychotics	13	50%
Benzodiazepines	6	23.1%
Antihistamines	6	23.1%
Mood stabilizers	3	11.5%

Discussion

Out of a total of 123 patients, 26 patients were suffering from at least one psychiatric condition requiring use of psychotropic medication, representing a total of 21.1% of the patients seen.

Depression is the most common mental health disorder encountered in this particular cohort of patients representing a total of 9.8% of 123 patients seen over 6 months. Mood disorder is followed by anxiety disorder at a rate of 6.5%. These numbers reflect general prevalence rates where 7.8% of the population is known to suffer from anxiety and depression, these being the most common mental health illness.[4]

Symptoms of anxiety include feeling worried, fearful, irritability, breathlessness, hyperventilation, palpitations, gastrointestinal disturbances, trembling and palpitations.

Symptoms of depression on the other hand include low mood, anhedonia, anergia, feeling of hopelessness, guilt, low self worth, inability to maintain concentration, changes in appetite and sleeping difficulties.

Certain links have been made between hormonal fluctuations and an increase in prevalence of depression in women particularly during the phases of puberty, prior to menstruation, during the postnatal period and in perimenopause, suggesting that hormone changes might be triggers for depressive symptoms.[5] Further studies however have found no well based correlation between hormonal changes, mainly the falling and fluctuating levels of estradiol and corresponding increases in levels of follicle-stimulating hormone (FSH) and luteinizing hormone. Thus, at present, the literature indicates no consistent relationship between circulating estradiol/FSH levels and depression.[6]

As previously noted, females in the menopause transition are up to twice as likely to experience a depressive disorder, compared to the premenopausal period, independent of a history of depression.[3] Low mood, sleep disturbance and low libido, are possible symptoms of depression but also happen to be common experiences of menopause independent of mood disturbance. Such a phenomenon is clinically significant for both management decisions and monitoring of response to treatment. Furthermore, this highlights the broad nature of menopausal symptoms and the potential clinical value in creating menopause-specific tools for mental health.

With regards to treatment, SSRIs were found to be the most commonly prescribed drugs amongst patients on regular psychotropic medication. SSRIs are in fact the first line treatment option when it comes to medication use in cases of depression and anxiety. TCAs are less used and one should keep in mind that this class of drugs carries a higher chance of overdose which could be dangerous in patient with risk of suicide. Some side effects of these SSRIs worth mentioning are headache, dry mouth, dizziness, insomnia, sexual dysfunction, nausea and weight changes. Metabolically, SSRIs do not tend to dysregulate glycaemic control as opposed to TCAs which have been found to cause deterioration in the metabolic situation of the patient.[7]

These patients being seen at preoperative clinic in preparation for surgery under general anaesthesia would need medication review. Some psychotropic drugs such as lithium, monoamine oxidase inhibitors, TCAs, and clozapine interact with certain types of

anesthesia; thus it is important to highlight their use to an anesthetist. These psychotropic drugs present with increased physical risks, including withdrawal symptoms, thus qualifying for American Society of Anesthesiologists Classification 3. On the basis of physical risks, they would require discontinuation however from the perspective of the risk of withdrawal together with psychiatric relapse and recurrence, these individuals deserve integrated management from both anaesthetist and psychiatrist. Some interactions of note include, TCAs causing an increased response to anticholinergics such as atropine which may lead to postoperative confusion. Serious side-effect have been reported in 21% of patients receiving antipsychotic treatment, these include extra-pyramidal symptoms such as sedation or hypotension.[8]

Mood stabilisers such as lithium, used in bipolar disorder, may cause hazardous risks in surgery. This is mostly seen when haemodynamic instability occurs and renal excretion becomes impeded. Therefore, lithium discontinuation is recommended before surgery. Lithium can be stopped at once because no withdrawal symptoms occur and thus should be discontinued 72 h before surgery since it has a half-life of 24–36 hours. Sodium depletion decreases renal excretion of lithium and can lead to lithium toxicity. Prevention of excess absorption of lithium can be prevented pre-emptively via the administration of sodium-containing IV fluids during the peri-operative period. ECG monitoring should be done to monitor various cardiac abnormalities due to lithium. In the post-operative period, once normal ranges of potassium, sodium and creatinine are obtained, and the patient is considered haemodynamically stable, she should be able and allowed to drink, and lithium should be restarted. This is most important because the psychiatric risk of recurrence or relapse is hazardous. The only reason not to stop lithium is minor surgery with local anaesthesia.[8]

The implications of outcome of psychiatric versus non psychiatric patients, mainly patients suffering from depression include; lower pain threshold, higher pain sensitivity and increased self reported pain intensity.[9] Furthermore, patients with depressive disorder were found to have associated pain and self reported anxiety symptoms. This can affect the postoperative state of the patient possibly resulting in the need for additional analgesia and prolonged hospital stay which can in itself place the patient at increased risk of hospital acquired infections, decline in independence with self care and risks from immobility as deep vein thrombosis and pressure sores. In cases of patient suffering from anxiety one might note an increase in patients' need for information about the procedure and to a certain extent demands of reassurance. In such instances the person obtaining consent for the surgery should be familiar with the procedure, risks and complications rates to give the patient clear details and offer reassurance when possible.

The limitations of this audit include the fact that the sample included only the patients seen over six months and that the cohort was limited to those seen by one specific consultant. One can also mention that some patients might have been in disease remission and not on active treatment when seen at POAC and thus not included in the number of patient suffering from mental health illnesses.

Conclusion

Out of a total of 123 patients who attend one of the 24 pre-operative assessment clinics

analysed for this study, 26 were suffering from at least one psychiatric condition requiring use of psychotropic medication, representing a total of 21.1% patients. Depression is the most common mental health disorder encountered in this particular cohort of patients representing a total of 9.8% of 123 patients and 46.2% of the mental health diagnoses seen in this particular clinic. The second most common reported diagnosis was anxiety disorder, representing 6.5% of all patients seen and 31.9% of the patients with a psychiatric diagnosis. The most common drug class prescribed was an antidepressant, 19 patients, meaning 73.1% of psychiatric patients were on antidepressants, most commonly an SSRI.

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ORIGINAL ARTICLE

Charting the Endometrial Cancer Care Pathway

A Baseline Audit

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Introduction

Longer waiting times from diagnosis to surgical resection have been found to negatively impact the overall survival and quality of life of women with endometrial cancer. The Cancer Care Pathway Directorate adopted the UK National Waiting Times Monitoring Dataset Guidance, to improve the timeliness of services along the cancer care pathway. From this, three key targets were identified: 1) Maximum 14-day wait from urgent GP referral for suspected cancer to first outpatient attendance (operational standard of 93%), 2) Maximum 31-day wait from decision to treat to first definitive treatment (operational standard of 96%), and 3) Maximum 62-day wait from urgent GP referral for suspected cancer to first treatment (operational standard of 85%). The aim of this baseline audit was to chart the time-frames of the various stages in the endometrial cancer pathway of patients diagnosed with this disease between 2015 and 2016 to assess for and identify delays in referral, investigation and care.

Methods

A tool was developed following consultation with key stakeholders. Data protection clearance was obtained. Patient medical and oncology files, hospital databases, and MDT documentation for confirmed endometrial cancer cases were reviewed between September 2017 – March 2018.

Results

A total of 101 endometrial cancer cases were included in the audit. The proportion of cases which met the 14-day, 31-day and 62-day wait KPIs operational standards were 39.1%, 81.2% and 17.2% respectively.

Conclusion

The endometrial cancer care pathway timeframes did not meet the KPIs operational standards. Fast-track coordinators and nurse navigators could improve continuity and coordination of patient care.

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Introduction

Endometrial cancers constitute 7.3% of cancer cases in women in Malta with a five-year average of 72 new cases per year between 2011 and 2015. Uterine cancer is the main cause for 4.3% of cancer death in Maltese women with a five-year average of 17 deaths annually between 2011 and 2015.[1] The 1-year and 5-year survival for uterine cancers diagnosed in 2000–2007 in Malta were 90.4% [95% confidence interval (CI) 86.9 – 94.1%] and 80.2% (95% CI 73.9 – 86.9%) respectively.[2] In a recent, population-based study, longer waiting times from diagnosis to surgical resection have been found to negatively impact the overall survival of women with endometrial cancer.[3] Furthermore, longer waiting times have been found to have a nocebo effect,[4] and poorer quality of life and patient satisfaction.[5]

The Cancer Care Pathway Directorate, which was established in 2014, adopted the UK National Waiting Times Monitoring Dataset Guidance, to improve the timeliness of services along the cancer care pathway.[6] From this, three key targets were identified:

- Maximum two weeks from urgent GP referral for suspected cancer to first outpatient attendance [Operational Standard of 93%].
- Maximum one month (31 days) from decision to treat to first definitive treatment [Operational Standard of 96%].
- Maximum two months (62 days) from urgent GP referral for suspected cancer to first treatment [Operational Standard of 85%].

The New Zealand Cancer Plan: Better, Faster Cancer Care 2015-2018 and the Australian Hospital Performance: Cancer surgery waiting times in public hospitals in 2012-13 have identical key targets.[7-8]

Timeliness in histopathology reporting ensures an appropriate level of patient care. The Royal College of Pathologists have produced a set of KPIs, two of which are related to histopathology reporting timeframes.[9]

1. Histopathology diagnostic biopsy turnaround times: Percentage of diagnostic biopsies reported, confirmed and authorised within 7 days of biopsy (RCPath Challenge: 80% by April 2012 increased to 90% by April 2014).
2. Overall Histopathology reporting turnaround times: Percentage of all histopathology and diagnostic cytology final reports available within 10 calendar days of procedure (RCPath Challenge: 80% by April 2012 increased to 90% by April 2014).

According to the UK National Waiting Times Monitoring Dataset Guidance, all subsequent treatments for primary and recurrent cancer need to have a 31-day period recorded.[6] The operational standards for subsequent surgery, drug treatment, and radiotherapy are 94%, 98% and 94%, respectively.

The aim of this baseline audit was to chart the time-frames of the various stages in the endometrial cancer pathway of patients diagnosed with this disease between 2015 and 2016 to assess for and identify delays in referral, investigation and care.

Methodology

A retrospective audit was conducted to chart the endometrial cancer pathway. The study sample was obtained from the histopathology

department information officer using the Laboratory Information System (LIS) of Mater Dei Hospital (MDH) and comprised patients who were diagnosed with cancer in 2015 and 2016.

The data collection tool was developed following consultation with key stakeholders in the field including consultant gynaecologists, as well as doctors and the Cancer Care Pathways Directorate.

Data protection clearance was obtained prior to the start of data collection which took place between September 2017 and February 2018. Data was retrieved from patients' personal medical and oncology files at MDH and Sir Anthony Mamo Oncology Centre, iSoft Clinical Manager, chemotherapy and radiotherapy databases, and email records for multidisciplinary team (MDT) meeting.

Descriptive and inferential analyses were performed through a combination of Microsoft Office Professional Plus 2010 Excel, and IBM SPSS Statistics version 22. In view of the heavy right skewed distributions for the various timeframes, medians and quartiles were preferentially used for the descriptive statistics. Tests performed were Fisher's Exact test and binary logistic regression.

RESULTS

Sample overview

The original dataset provided by the histopathology department information officer consisted of a total of 491 patients. 285 duplicate entries were removed. A total of 101 patient medical records were available and included in the final analysis presented in the report. The mean age at diagnosis of this group of patients was 61 years (standard deviation = 8.8 years, median = 60 years, range = 42-86 years). Diagnostic methods and cancer characteristics are summarised in Table 1.

The initial point of contact with the health care system including the date was identified in 94 out of 101 cases (93.1%) of endometrial cancer and are summarised in Table 2.

Table 1 Diagnostic methods and cancer characteristics

Variables	*n*	%
Biopsy method		
Intrauterine endometrial sampler	19	18.8%
D&C	76	75.2%
Unknown	6	5.9%
Preoperative imaging		
CT	54	53.5%
MRI	2	2.0%
Both	1	1.0%
None	44	43.6%
Histological diagnosis		
Endometrioid	92	91.1%
Other	9	8.9%
FIGO grading		
G1	66	65.3%
G2	19	18.8%
G3	16	15.8%
FIGO staging		
FIGO IA	67	66.4%
FIGO IB	18	17.8%
FIGO II	8	7.9%
FIGO IIIA	1	1.0%
FIGO IIIB	4	4.0%
FIGO IIIC1	1	1.0%
Unknown	2	2.0%

Table 2 Initial point of contact with the health care system

Initial Contact with the Health System (Day Zero)	*n*	%
GP referral to GOP	41	40.6%
GP referral to private gynaecologist	1	1.0%
GP referral to A&E	6	5.9%
Self-referral to A&E	9	8.9%
Private gynaecologist referral to GOP	37	36.6%
Unknown	7	6.9%

Key Performance Indicators (KPI)

The distribution of the number of days waiting for the KPI timeframes and the GOP new case appointment to post-biopsy GOP follow up (decision to treat) appointment timeframe were summarised in Table 3.

'14-day wait' from referral to specialist review at outpatients: 34 out of 87 patients with endometrial cancer (39.1%) were seen by a specialist at GOP within two weeks of referral. 52 out of 87 patients with endometrial cancer (59.8%) were seen by a specialist either at GOP or in the initial contact in private practice within two weeks.

'31-day wait' from decision to treat to receipt of first treatment: 69 out of 85 patients (81.2%) with endometrial cancer received first treatment following decision to treat within a 31-day timeframe.

'62-day wait' from referral to receipt of first treatment: Only 16 out of 93 patients (17.2%) with endometrial cancer received first treatment following referral within 62 days. 45 out of 93 patients with endometrial cancer (48.4%) received first treatment after being seen by a specialist either at GOP or in the initial contact in private practice within 62 days.

The '14-day wait' and '62-day wait' key performance indicator for the endometrial cancer care pathway could be analysed in those cases where date "day zero" and the date of the GOP new case appointment or first treatment were both known.

Intradepartmental Timeframes

The distribution of the number of days from procedure to histology report were summarised in Table 4.

Histopathology diagnostic biopsy turnaround times: 50 out of 94 histopathology reports (53.2%) were available within 7 calendar days of the diagnostic biopsy.

Histopathology surgical resection reporting turnaround times: 58 out of 99 histopathology reports (58.6%) were available within 10 calendar days of surgical resection.

The distribution of the number of days from the first oncology review to oncology treatment were summarised in Table 5. 9 out of 27 cases (33.3%) and 9 out of 10 cases (90%) received radiotherapy and chemotherapy respectively within 31 days from the first oncological review. Cases requiring radiotherapy had longer waits for treatment when compared to cases requiring chemotherapy from oncological review. However, 9 cases requiring radiotherapy received treatment after chemotherapy. After excluding these cases, 8 out of 18 cases (44.4%) received radiotherapy within 31 days from the first oncological review.

Table 3 Distribution of the number of days waiting for the three KPIs and GOP new case appointment to decision to treat timeframe

Number of Days from:	*n*	Mean	SD	Median	1st Quartile	3rd Quartile
Day Zero to GOP new case	87	32.5	27.5	25.0	9.0	54.0
Decision to treat to first treatment	85	23.2	25.5	15.0	10.0	27.5
Day Zero to first treatment	93	122.7	95.2	110.0	66.5	146.0
GOP new case to decision to treat	80	74.4	93.3	49.0	35.0	71.8

Table 4 Distribution of the number of days from procedure to histology report

Number of Days from:	*n*	Mean	SD	Median	1st Quartile	3rd Quartile
Diagnostic biopsy to histology report	94	9.4	6.1	7.0	6.0	11.3
Surgical resection to histology report	99	12.0	6.8	10.0	7.0	15.0

Table 5 Distribution of the number of days from first oncology review to oncology treatment

Number of Days from:	*n*	Mean	SD	Median	1st Quartile	3rd Quartile
First oncology review to radiotherapy	27	75.6	70.0	41.0	28.0	114.5
First oncology review to chemotherapy	10	24.6	19.1	25.0	10.0	31.0

Table 6 Distribution of the number of days of interdepartmental transitioning

GOP Appointment to Procedure Timeframes						
Number of Days from:	***n***	**Mean**	**SD**	**Median**	**1st Quartile**	**3rd Quartile**
GOP new case to diagnostic biopsy	75	56.1	92.1	26.0	17.0	48.0
Post-biopsy GOP follow up (decision to treat) to surgical resection	85	23.2	25.5	15.0	10.0	27.5
Histology Report to GOP Appointment Timeframes						
Number of Days from:	***n***	**Mean**	**SD**	**Median**	**1st Quartile**	**3rd Quartile**
Biopsy result to GOP follow-up	86	16.4	12.0	14.0	8.8	20.3
Surgical resection histology report to GOP follow-up	94	21.5	14.4	18.0	12.0	25.5
Preoperative Imaging						
Number of Days from:	**n**	**Mean**	**SD**	**Median**	**1st Quartile**	**3rd Quartile**
Post-biopsy GOP follow up (decision to treat) to imaging	46	8.5	15.3	4.0	0.0	9.8
Imaging to surgical resection	52	7.4	6.1	6.0	3.0	11.0
Multidisciplinary Team Meetings						
Number of Days from:	***n***	**Mean**	**SD**	**Median**	**1st Quartile**	**3rd Quartile**
Biopsy result to MDT meeting	20	31.9	26.3	24.0	12.0	42.0
Surgical resection histopathology report to MDT meeting	35	20.3	14.6	16.0	8.0	36.0
Oncology referral						
Number of Days from:	***n***	**Mean**	**SD**	**Median**	**1st Quartile**	**3rd Quartile**
Oncology referral to first oncology review	53	11.2	7.4	10.0	6.5	14.0

Interdepartmental Timeframes

The distribution of the number of days of interdepartmental transitioning were summarised in Table 6.

A Fisher's Exact test showed that the initial contact with the health system was associated with statistically significant differences with the 14-day wait KPI (p=0.005). Binary logistic regression showed that when compared to private gynaecologist referral, cases which were referred to GOP by GP referral were statistically significantly more likely to breach the 14-day wait KPI (see Table 7). When compared to GP referral, cases which were referred to A&E, went directly to A&E or were referred to GOP by a private gynaecologist were statistically significantly less likely to breach the 14-day wait KPI (p<0.05) (see Table 8).

A Fisher's Exact test showed that the initial contact with the health system was associated with statistically significant differences with the 62-day wait KPI (p=0.026). Binary logistic regression showed that when compared to private gynaecologist referral to GOP, cases which went to directly to A&E were statistically significantly less likely to breach the 62-day wait KPI (see Table 9). The single case referred by GP to a private gynaecologist was excluded from the analysis. When compared to GP referral to GOP, both GP referral to A&E and self-referral to A&E were less likely to breach the 62-day wait KPI (p<0.05) (see Table 10).

A Fisher's Exact test showed that there were no statistically significant differences between initial contact with the health system and the 31-day wait KPI (p=0.668). The single case referred by GP to a private gynaecologist was excluded from the analysis.

Table 7 Binary logistic regression between initial contact with the health system and 14-day wait KPI with private gynaecologist referral to GOP as the reference category

Initial Contact with the Health System	*n*	Odds Ratio	95% CI		*p* value
			Lower	Upper	
GP Referral to GOP	41	3.358	1.244	9.065	0.017
GP Referral to A&E	5	0.236	0.024	2.330	0.217
Self-Referral to A&E	6	0.472	0.076	2.921	0.420
Private gynaecologist referral to GOP*	35	-	-	-	0.015

*Reference category

Table 8 Binary logistic regression between initial contact with the health system and 14-day wait KPI with GP referral to GOP as the reference category

Initial Contact with the Health System	*n*	Odds Ratio	95% CI		*p* value
			Lower	Upper	
GP Referral to GOP*	41	-	-	-	0.015
GP Referral to A&E	5	0.070	0.007	0.710	0.024
Self-Referral to A&E	6	0.141	0.022	0.896	0.038
Private gynaecologist referral to GOP	35	0.298	0.110	0.804	0.017

*Reference category

Table 9 Binary logistic regression between initial contact with the health system and 62-day wait KPI with private gynaecologist referral to GOP as the reference category

Initial Contact with the Health System	*n*	Odds Ratio	95% CI		*p* value
			Lower	Upper	
GP Referral to GOP	41	4.707	0.91	24.345	0.065
GP Referral to A&E	6	0.483	0.073	3.187	0.450
Self-Referral to A&E	9	0.193	0.041	0.912	0.038
Private gynaecologist referral to GOP*	36	-	-	-	0.001

*Reference category

Table 10 Binary logistic regression between initial contact with the health system and 62-day wait KPI with private gynaecologist referral to GOP as the reference category

Initial Contact with the Health System	*n*	Odds Ratio	95% CI		*p* value
			Lower	Upper	
GP Referral to GOP*	41	-	-	-	0.026
GP Referral to A&E	6	0.103	0.011	0.988	0.044
Self-Referral to A&E	9	0.041	0.006	0.284	0.001
Private gynaecologist referral to GOP	36	0.212	0.041	1.099	0.065

*Reference category

Discussion

The results of this audit need to be considered in the light of several limitations. The convenience sampling and number of cases included may affect the generalisability of this audit. We estimate 72 new cases of endometrial cancer per year; the sample size analysed is 101 cases over the two-year period. The medical files of patients diagnosed with endometrial cancer in 2015 and 2016 who had died before the data collection phase of the audit could not be analysed. As this audit was retrospective, it was prone to missing data such as delay to treatment due to medical reasons. Additionally, it is unknown whether patients had their appointments rescheduled following non-attendance. Moreover, it was difficult to link the oncology consultation which lead to the first oncological treatment. Therefore, the first oncological new case appointment was used. This may have overestimated the oncology review to oncology treatment timeframes. Finally, the quality of the information provided in the ticket of referral written by a GP was not assessed in the current audit, and it should be acknowledged that this information may influence the urgency with which a case is reviewed at GOP.

The 14-day wait KPI, allowing a maximum two weeks from referral for suspected cancer to first outpatient attendance, was well below the accepted operational standard of 93% as described in the UK National Waiting Times Monitoring Dataset Guidance. When compared with GP referral to GOP, GP referral to A&E, self-referral to A&E, and private gynaecologist referral to GOP are less likely to exceed the 14-day wait KPI. Measures that could decrease the number of days from time of referral to GOP new case appointment include further education for primary care doctors and immediate vetting of referral letters.[10]

The 31-day wait KPI, allowing a maximum one month from decision to treat to first definitive treatment, was below the accepted operational standard of 96%. Preoperative imaging and post-biopsy MDT meetings were not found to delay definitive surgical treatment. Medical problems and other conditions which pose a problem for anaesthesia are possible causes for exceeding the 31-day wait KPI. Interdepartmental fast-track channels between gynaecology, anaesthesia and medical specialities would help improve this KPI.

The 62-day wait KPI, allowing a maximum two months from referral for suspected cancer to first treatment, was well below the accepted operational standard of 85%. When compared with GP referral to GOP, self-referral to A&E and GP referral to A&E are less likely to exceed the 62-day wait KPI. Private gynaecologist referral to GOP appeared less likely to breach the 62-day wait, however it did not reach statistical significance. Of note, the 62-day wait KPI was markedly worse when compared with the 14-day wait KPI with a difference of 21.9%. This finding prompted an analysis of the overall and interim inter- and intra-departmental timeframes between the GOP new case appointment and post-biopsy GOP follow up (decision to treat) appointment. Based on the three KPIs, the overall GOP new case to decision to treat timeframe should be 17 calendar days, assuming a maximum of 14 days from referral to GOP. However, based on the medians described in the results, there are potential delays in having a diagnostic biopsy, histology reporting and having a follow up appointment at GOP. Measures to decrease the time to diagnostic biopsy include training GPs to do intrauterine endometrial sampler

biopsies and setting up a one-stop shop for women referred with post-menopausal bleeding for hysteroscopy and curettage [11]. The post-menopausal bleeding (PMB) clinic at Mater Dei Hospital started in 2018. GP referral to the PMB clinic will most likely improve both 14-day and 62-day wait KPIs. The histopathology department can flag biopsies which are suspicious for cancer to be able to prioritise accordingly. Furthermore, once the histology report is ready, a follow up GOP appointment should be scheduled for the next outpatient session.

Up to three-fourths of cases referred to oncology had an oncological review within two weeks. Waiting times for radiotherapy treatment following oncological review were below the operational standard. Waiting times for chemotherapy treatment following oncology review were just below the operational standard. Measures to improve the waiting times for radiotherapy treatment, through restructuring of the radiotherapy department have been implemented in the interim between the audit years 2015 and 2016 and April 2018.

More research needs to be done to address the important limitations previously described. These include prospective and qualitative studies. Furthermore, there is a dire need for a robust business process across and within primary and secondary healthcare supported by an information technology infrastructure to readily track patients as they navigate the health care system. Such processes and infrastructure would make it easier to retrieve data to re-audit and close the audit cycle.

A fast-track coordinator and a nurse navigator would further ensure better continuity and coordination of patient care by tracking the patient from referral to diagnosis and from diagnosis onward respectively.

Conclusion

The endometrial cancer care pathway timeframes did not meet the 14-day, 31-day and 62-day wait KPIs operational standards. Seeking a private gynaecological consultation or referral to the emergency department have been shown to be the most efficient pathways for patients to get timely investigation and treatment when compared with GP referral to gynaecological outpatients. The introduction of the post-menopausal bleeding clinic is a step in the right direction to improve on these outcomes and decrease the load from emergency services.

Further recommendations include:

- Fast-track referral by GPs to secondary health care services for women with symptoms suspicious for endometrial cancer.
- Setting evidence-based targets and timelines which best suit our health care system.
- Communicate these targets and timelines to key stakeholders (namely primary health care and the departments of obstetrics and gynaecology, histopathology, radiology, outpatients and oncology).
- Engaging key workers to track patients along the care pathway.
- Re-audit following changes in the health service.

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ORIGINAL ARTICLE

Ulcerated lesions as a risk factor for Henoch-Schonlein purpura nephritis

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Objective

To determine the correlation between the severity of Henoch-Schonlein purpura skin manifestations and development of nephritis and to characterise the disease within the Maltese paediatric population.

Design

A retrospective analysis of the 96 cases diagnosed with Henoch-Schonlein purpura at Mater Dei Hospital between January 2008 and January 2016. Clinical notes were reviewed and anonymised data regarding the presentation, progression and follow-up of these cases was entered into a database.

Results

96 cases met the inclusion criteria with a male to female ratio of 1.35:1 and with a mean age at presentation of 6.4 years (interquartile range 3.5 years). 99% had the typical rash at presentation with 75% having other associated clinical findings. Renal involvement was found in 36.5%: isolated proteinuria in 19.8%, isolated haematuria in 13.5%, haematuria, proteinuria and hypertension in 3.1% and nephrotic range proteinuria in 2% of cases. A severe rash at presentation was shown to be a prognostic indicator for renal involvement.

Conclusion

Henoch-Schonlein purpura in the Maltese paediatric population is similar in incidence to that quoted in the literature. The majority of cases are uncomplicated and the outcome is frequently favourable. The presence of a severe rash at presentation significantly increases the risk of renal involvement and long term complications.

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INTRODUCTION

Henoch-Schonlein Purpura (HSP) is the commonest vasculitis in childhood with an incidence between 3-27 per 100,000 child population, with an increased prevalence in males.[1-2] It commonly presents between four and six years of age and is usually a self-limiting disease with rapid resolution of extra-renal symptoms. The long term prognosis correlates with renal involvement which involves about a third of cases. Chronic renal disease is estimated to occur in 1.8% of children and 10.4% of adults.[4] Reports have shown a difference in presentation between childhood-onset and adolescent-onset HSP, with the latter having increased incidence of musculoskeletal symptoms and a marginally increased risk of progression to end-stage kidney disease.[3] Korean and Japanese individuals also seem to have a higher prevalence of HSP as compared to other races.[4] There are a number of rare complications that can be associated with HSP including orchitis, cerebral and cerebellar haemorrhage and pulmonary haemorrhage.

Microscopically, the condition is characterised by the deposition of IgA immune complexes in the organ vasculature, hence its new nomenclature in the Chapel Hill classification, IgA vasculitis.[4,5,6] Common viral infections often precede the condition as demonstrated by a higher incidence in the winter months. Predisposed individuals have abnormal glycosylation sites on IgA1 antibodies. Viral upper respiratory tract infections and gastrointestinal infections lead to increased production of these abnormal IgA1 antibodies and these are recognised by circulating anti-glycan antibodies, leading to the formation of the circulating immune complexes with deposition in the organ vasculature.[7]

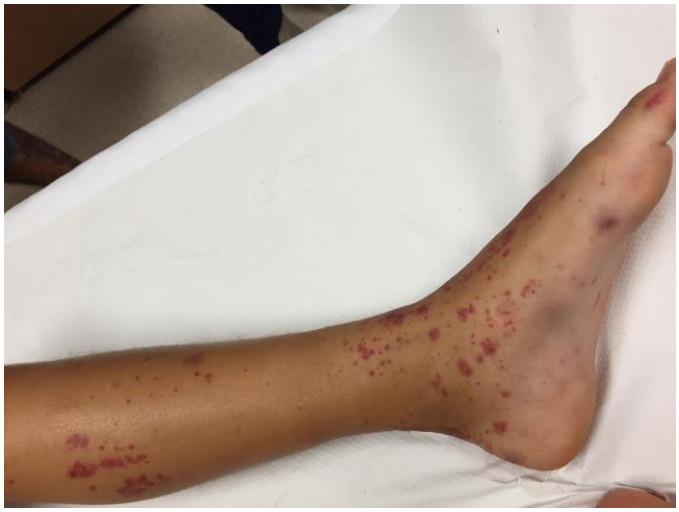
Laboratory tests at presentation commonly show raised inflammatory markers and IgA levels and a variable degree of haematuria and/or proteinuria.[8]

PATIENTS AND METHOD

The clinical notes of all patients aged less than 16 years (otherwise passed to adults) admitted with HSP to Mater Dei Hospital between January 2008 and January 2016 were reviewed. Data included demographics, clinical findings at presentation, laboratory test results and out-patient follow-up findings. All data was anonymised in a database.

We graded the severity of the rash as either mild, that is, a fine purpuric rash (figure 1), or severe, that is, palpable purpura with or without ulcerated lesions (figures 2 and 3).

Figure 1 Showing mild purpura



Blood tests were interpreted according to normal ranges for the patient's age and sex. HSP nephritis was monitored using urine dipstick and formal urinalysis and microscopy. Haematuria was defined as 1+ to 3+ on dipstick whilst proteinuria was defined as 1+ to 3+ or greater than 150mg/L on dipstick on three consecutive days. Proteinuria was quantified using the urine albumin: urine creatinine ratio. Nephrotic range proteinuria was defined as a

24hr urine protein of more than 40mg/m^2/hr whilst nephritic-nephrotic syndrome was defined as more than 200 red blood cells on urine analysis and 24hr urine protein of more than 40mg/m^2/hr and the presence of hypertension and/or biochemical findings of renal dysfunction. Blood pressure values were compared to age, sex and height-matched percentile values and hypertension was considered if the measured systolic and diastolic values exceeded the 95th percentile according to the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.[15]Recurrence of HSP was considered if a patient who was symptom-free for at least a month presented with fresh signs and/or symptoms related to HSP.

Figure 2 Showing more severe palpable purpura

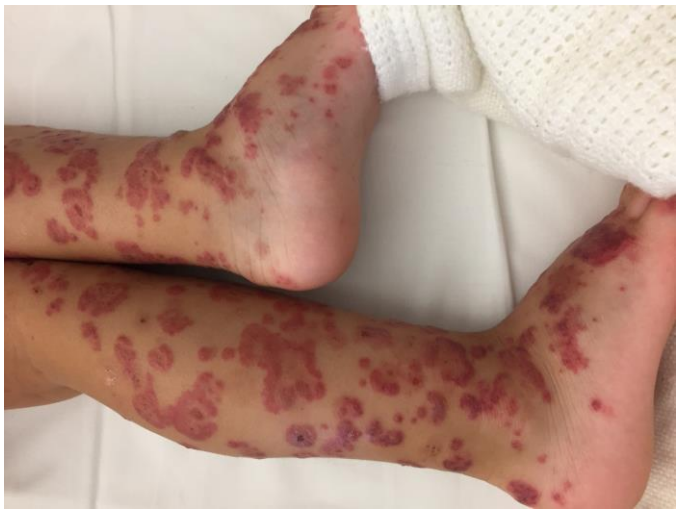
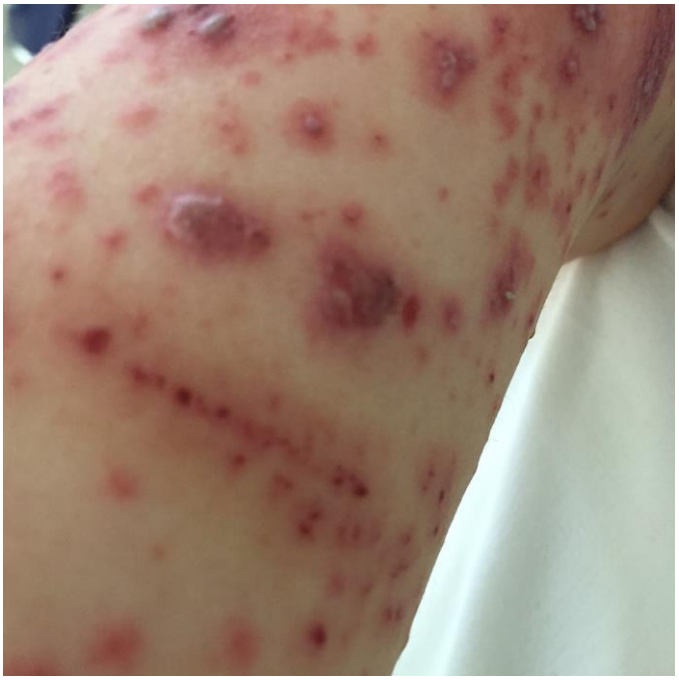


Figure 3 showing severe purpura with blistering and ulcerated lesions



Statistical analyses were performed using Microsoft Excel® 2010. Fisher Exact test was used to study the relationship between the severity of the skin rash and the presence of HSP nephritis.

RESULTS

Findings at presentation

96 children met the inclusion criteria. The male to female ratio was 1.35:1 with a mean age of 6.4 years (interquartile range 3.5 years). 65 cases (67.7%) presented in the months between September and March. A preceding infection, a mean of 2.8 weeks previously, was noted in 85 cases (88.5%), the majority being upper respiratory tract infections (82%).*Table 1 summarises the clinical findings at first presentation.*

95 children (99%) presented with the typical purpuric rash; one child presented with abdominal pain first, with the rash appearing within 3 days. Most children had a fine purpuric rash involving the lower limbs. 7 children

(7.3%) presented with palpable purpura whilst another 7 children (7.3%) had ulcerated lesions. The mean age of children presenting with mild purpura was 6.9 ± 2.3 years whilst the mean age of children presenting with severe purpura was 5.4 ±1.38 years p=0.0202 (CI 0.2392 - 2.76).

35 children (36.5%) had evidence of renal involvement within the first week of presentation: 19 (19.8%) had proteinuria and 13 (13.5%) had haematuria. Three children (3.1%) had a combination of haematuria ± proteinuria and hypertension at presentation. The clinical findings of the latter are shown in table 2.

Table 1 Summary of the signs and symptoms noted at first presentation

Clinical Signs And Symptoms At First Presentation		No. Of Cases	Percentage of Total (%)
Abdominal Pain		1	1
Typical Purpuric Rash		95	99
Type of Rash:	Fine purpuric Rash	82	85.4
	Palpable Purpura	7	7.3
	Ulcerated Purpuric Lesions	7	7.3
Rash distribution:	Mainly Involving Lower Limbs	75	79
	Mainly Involving Upper and Lower Limbs	13	13.6
	Rash Generally Distributed	7	7.4
Associated Clinical Findings		72	75
	Joint Pains and Swelling	54	56.3
	Gastro-intestinal Symptoms	47	48.9
	Abdominal Pain	39	40.6
	Nausea and/or vomiting	4	4.2
	Colitis and Intussusception	1	1
	Evidence of Renal Involvement	35	36.5
	Proteinuria only	19	19.8
	Haematuria only	13	13.5
	Proteinuria, Haematuria and Hypertension	3	3.1

Table 2 Summary of the signs and symptoms noted at first presentation

	Findings at presentation	BP (P95 systolic and diastolic value)	24hr Urine Protein g/day	UAUC mg/g	Serum albumin g/L	eGFR mL/min/ 1.72m^2
Case 1 Male 5yr old	• Palpable purpura over lower limbs and abdomen • Ankle swelling and pain. • No fluid overload	107/85mmHg (BP 108/68)	0.638	6690	24	118
Case 2 Male 10yr old	• Rash involving lower limbs and buttocks • No abdominal pain • No fluid overload	112/72mmHg (BP 115/75)	0.426mg	775	38	158
Case 3 Female 5yr old	• Difficulty walking • Abdominal pain, vomiting • Rash both lower and upper limbs on day 3 • Rash blistered and ulcerated by day 6. • Small amount of free fluid in RIF on ultrasound	128/82mmHg (BP 106/68)	not measured	2.5	44.7	106

One child with nephritic-nephrotic presentation underwent a renal biopsy. The histological findings were consistent with IgA nephropathy.

Two patients experienced serious medical complications. One child developed nephrotic syndrome with heavy proteinuria and hypoalbuminaemia resulting in significant fluid overload with pulmonary oedema. Another patient developed severe abdominal pain and was found to have intussusception, requiring air reduction. Other rare complications such as orchitis, cerebral and cerebellar haemorrhage and pulmonary haemorrhage were not encountered in our study.

Findings on follow-up

93 children (96.9%) were followed-up in clinic at least once; the rest were lost to follow-up. 84 cases (87.5%) showed complete resolution of signs and symptoms within 2 months from presentation and were subsequently discharged by 6 months from the first presentation. Rash recurrence occurred in 12 cases (12.5%), with the majority (75%) of these recurrences occurring within 2 months from the initial presentation with no easily recognisable trigger.

Interestingly, two of the three patients presenting with nephritis and hypertension (Table 2) had a recurrence of HSP and this was

associated with worsening of the kidney disease, as demonstrated in Table 3.

Table 4 and Table 5 represent a summary of the clinical findings that were observed in this study with Table 5 comparing the severity of the rash compared to the renal and extra-renal involvement.

Fisher Exact Test was used to correlate the severity of the rash with the incidence of renal involvement and this revealed a statistically significant association between the two; p=0.008, odds ratio is 0.21 (0.06-0.72) and a relative risk of 0.48 (0.39-0.59) with a severe, ulcerating rash more likely to be associated with nephritis. (Table 5)

Table 3 Clinico-pathological findings during the recurrent episodes of HSP

	Findings during first recurrence	Findings during subsequent recurrences	Kidney biopsy
Case 1 Male 5yr old 2 recurrences	• 5 months from first presentation • Palpable purpura over limbs and trunk, abdominal pain, scrotal swelling • BP 115/70 • Prednisolone 4mg/kg daily for 4 weeks	• 6 m from first presentation • Developed generalised oedema with pulmonary oedema and weight gain of 5.3 Kg • Serum albumin 16.8g/L • UAUC increased to 6690mg/g • Introduced mycophenolate mofetil to high dose oral steroids	IgA nephropathy
Case 2 Male 10yr old 1 recurrence	• 2 months from first presentation • Urine dipstick 4+ protein and 4+ blood • 24 hr urine protein 1.632g/d • BP 110/80mmHg • Started on angiotensin converting enzyme inhibitor (ACEi)	• No further recurrences • Persistent proteinuria. No haematuria • 24hr urine protein 0.6 – 0.7g/d • Receiving ACEi	Not performed
Case 3 Female 5yr old 3 recurrences	• 1 month from first presentation • Serum albumin 35g/L • UAUC 1480-1650mg/g • Hypertensive on ACEi • Introduced furosemide	• Second recurrence 7 months from first presentation, possibly precipitated by a viral URTI • Persistent haematuria 2+ and proteinuria 3+ • UAUC 280-300mg/g • Introduced ACEi • 3rd recurrence 5.5yrs from first presentation • Presented with abdominal pain and purpuric rash involving lower limbs • 24hr urine protein 0.3g/d • BP 120/80mmHg (P90 115/74)	Not performed

Table 4 Summary of clinical manifestations of HSP

HSP rash with involvement of:	number of cases	Fine non-palpable purpura	Palpable Purpura	Ulcerated/ blistering purpuric lesions
No other system	24	23	1	0
Renal system only	4	2	2	0
Renal and musculoskeletal only	16	12	1	3
Renal and gastrointestinal system only	12	11	0	1
Renal, musculoskeletal and gastro-intestinal system	6	3	1	2
Gastro-intestinal involvement only	2	0	1	1
Gastro-intestinal and musculoskeletal system only	27	26	1	0
Musculoskeletal/joints only	5	5	0	0

Table 5 Comparison of the renal and non-renal manifestations against the severity of the purpuric rash.

	Non-renal involvement	Renal involvement
Mild purpura	54	28
Severe Purpura	4	10

In children presenting with proteinuria and/or haematuria there was complete resolution in 47% of cases by 1 year and in 80% of cases by three years. Two cases developed proteinuria during follow-up rather than during the initial presentation with HSP. These occurred within the first four months from presentation and both required a follow-up of over one year for the proteinuria to disappear.

DISCUSSION

This is the first study that characterises the course of HSP in the Maltese paediatric population. The prevalence of HSP is higher in males with a male to female ratio of 1.35:1 which is slightly less than that of 1.8:1 quoted in the literature.[9] The mean age at presentation is similar to that quoted in the literature. The presenting feature of the disease is the ubiquitous rash with a variable

distribution and severity. The majority of the cases (79%) had the typical HSP rash presenting in the lower limbs with only a minority having the upper limbs also affected, or having a generalised rash. Childhood HSP does tend to affect the lower limbs whilst adolescent or adult onset HSP tends to affect mainly the upper extremities more commonly for reasons unknown.[3]

Gastrointestinal involvement, joint involvement and age over 8 years have been shown to be independent risk factors for developing nephritis, increasing the risk 2-3 fold.[3,16] From our study, it is apparent that the severity of the skin rash is significantly associated with the development of nephritis (p=0.008). We also noted that younger children developed a more severe rash than their older counterparts (p=0.02).

HSP associated nephritis (HSN) occurs in about a third of cases and determines the long-term prognosis. At presentation, 36% of cases in our study showed a degree of proteinuria and/or haematuria to suggest HSN and this persisted for at least 1 year of follow-up in half of the cases. A minority (3.1%) had proteinuria, haematuria and hypertension and two cases required immunosuppressive medication and ACE inhibition. The importance of monitoring the urine for proteinuria/haematuria and the blood pressure cannot be overemphasised and recommendations for long-term follow-up have been put forward. HSN tends to develop within the first 4 weeks after the onset of HSP and at most, within the first 3 months.[16]The presence of nephritis at presentation increases the likelihood of developing chronic renal disease.[16] A kidney biopsy may be warranted in selected cases together with consideration of immune suppressive therapy.[11] The use of ACE inhibitors and control of hypertension has been shown to be renoprotective.[12-13] The use of corticosteroids and immunosuppressive therapy is mainly limited to cases with severe nephritis and should be considered after kidney biopsy and consideration of the updated Oxford classification score which is useful in predicting long-term outcomes of HSP nephritis.[13-14]

HSP followed a mild course in the majority of the cases with complete recovery on follow-up. Most of these recoveries occurred in the first 3 months with the rash typically fading within the first 50 days. The recurrence rate was 12.5% and occurred within the first 2 months from the initial presentation but could take up to 5 months. No obvious trigger was identifiable for the recurrence in the majority of cases.

CONCLUSIONS

This study demonstrated that HSP in the Maltese paediatric population has similar presenting and long term clinical characteristics to that of other European populations.[9,10] A limitation of the study was that some mild cases of HSP presentations or relapses may have been treated in the community and would not have been included. Risk factors for developing nephritis are described as an older age at presentation (greater than 8 years), the presence of abdominal pain and recurrence of HSP. We have shown that increasing severity of the purpuric rash at presentation can also increase the likelihood of developing nephritis.

In most cases of HSP, the prognosis for complete remission is good and only a minority develop persistent renal disease requiring specialist management.

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ORIGINAL ARTICLE

Beyond the stigma of methadone maintenance treatment:

Neurocognitive recovery in individuals with opiate use disorders

Kristian Sant, Aloisia Camilleri, Anthony Dimech

Background

Studies of cognitive functioning in drug addiction have shown consistent impairments among substance dependent populations. Several attempts to highlight the neurocognitive recovery of former opioid dependent individuals who are stabilised on methadone, have resulted in contradictory conclusions. The aim of this study is to compare the cognitive function of recovering opioid dependent individuals on methadone maintenance treatment to those who are not on methadone treatment, relative to healthy controls.

Methods

The Montreal Cognitive Assessment Tool was administered to three groups of participants: 22 former opioid dependents receiving methadone maintenance treatment, 21 former opioid dependents withdrawn from all opiates and 22 healthy controls without a history of illicit substance dependence. The specific cognitive domains tested include executive function, visuospatial skills, naming, attention, language, abstraction, delayed recall and orientation.

Results

Visuospatial skills and executive function were significantly improved with methadone. The language domain appears to be significantly impaired in both opioid dependent groups with a strong negative correlation to the duration of dependency. Participants who had stopped methadone were significantly impaired in all other aspects of cognition tested apart from naming and orientation when compared to healthy controls. Participants on methadone did not significantly differ in the other areas of cognition when compared to controls.

Conclusions

Methadone treatment appears to be associated with an improvement in cognitive function in opioid dependent individuals. Thus, methadone may facilitate public health by ensuring compliance of opioid dependent individuals to their treatment plan with fewer relapse rates and mitigation of risky behaviours.

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Introduction

The pivotal notions conveyed by prominent medical definitions of substance addiction primarily include the persistent engagement in drug-related behaviours mirroring impaired control in the face of devastating repercussions.[1-2] Underlying pathological brain changes, which are put forth as induced by the repeated exposure to psychoactive substances, are manifested most noticeably through tolerance to drug effects and withdrawal symptoms on abrupt cessation. Most importantly, altered intellectual function, disrupting reward processing and executive tasks is driven primarily by the neurotoxic drug effects.[3]

The reported prevalence of cognitive impairment in substance use disorder (SUD) varies widely between 30-80%.[4-7] The overall impact of various drugs on cognition also varies, but research indicates that individuals with SUD have alterations in brain structures including the striatum, prefrontal cortex, amygdala, and hippocampus.[8-10] Exposure to substances including heroin which dates back to the neuro-maturation stages of adolescence is particularly worrisome in this regard.[11]

The brain regions and neural processes that underlie addiction overlap extensively with those that support cognitive functions; including executive functioning, learning, memory, attention, reasoning, decision-making and impulse control.[12] Cognitive shifts that drive continued drug use through maladaptive learning hinder the adoption of alternative behaviours that promote abstinence. This leads to poorer treatment outcomes through decreased treatment adherence, engagement and readiness to change.[13-14]

The evidence surrounding the extent of neurocognitive recovery with methadone maintenance treatment (MMT) for opioid disorders (OD) is often contradictory. Some have reported persistent impairments, while others have described comparable cognitive performance to that of healthy controls (HC) who have never abused any type of illicit substance.[15-16] Others found no significant deterioration in the cognitive performance of patients on long-term and relatively high dose MMT.[17] Nonetheless, MMT is associated with amelioration in specific cognitive domains amongst patients with OD, especially executive function and visuo-construction.[18] After two months of MMT, improvements in verbal learning and memory, visuospatial memory, and psychomotor speed, were recorded in a sample of persons with OD.[19]

When OD individuals engage with MMT, treatment retention is high and a significant proportion manage to reduce or stop opioid use.[20] It has been shown that MMT is many times more cost-effective than no treatment and the extent to which these improved outcomes are underpinned by a mechanism of cognitive enhancement is debatable.[21] MMT was associated with intact cognitive control in OD individuals, mitigation of risky behaviours and enhanced behavioural learning.[22] On the other hand, OD individuals are at an increased risk of relapse of illicit opioid use after methadone detoxification.[23]

A Cochrane review uncovered the superiority of MMT over non-opioid interventions, questioning the one-size-fits-all philosophy of traditional psychosocial interventions to OD.[24] The insistence on methadone cessation is not without risks and can precipitate adverse effects including elevated relapse and death rates.[25-27]

Unfortunately the integration of MMT in therapeutic communities is not mainstream, despite reported effectiveness.[28] The impact of an intervention with documented harm reduction benefits such as MMT on cognitive function is paramount, especially when one takes an overall view of the process of recovery which warrants the mobilisation of cognitive skills to confront the various individual challenges to reestablish a meaningful existence.

Methodological differences and various study limitations such as a small sample size and a vast array of confounding factors (polysubstance abuse, severity and duration of OD, attained educational level, duration of stability on methadone and abstinence from illicit drugs, methadone dose and the presence of neuropsychiatric conditions) make it difficult to conclusively determine whether methadone offers cognitive stability.[29]

The goal of the current study is to investigate the cognitive performance of individuals who have gained stability on MMT and attained abstinence in comparison to those who were previously on the same treatment, underwent detoxification and are currently abstinent for at least 1 month. A third matched group with no SUD history is included. To our knowledge previous comparisons of cognitive function were not carried out specifically on these groups with the aim of deciphering whether it is methadone detoxification or maintenance that impacts best on cognitive performance, in a way that fosters the ability to cope with further rehabilitation and the challenges of life in general.

The Montreal Cognitive Assessment Tool (MoCA) is a 10-minute 30-point test with known sensitivity to mild cognitive impairment and which has effectively detected cognitive deficits in SUD patients.[17] It is quick, easy to administer and also sheds light on the specific neural circuitry underlying habitual behaviour in addiction. In accordance with previous literature reports, we hypothesised that both groups of former opiate users would perform worse than the control group. We additionally hypothesised that MMT stabilises neurocognitive function in those individuals who abstain from the illicit drugs. OD individuals who stabilise on methadone are expected to have a better neurocognitive function than those who come off methadone to access traditional rehabilitation programmes.

Materials and Methods

Healthy male and female subjects, 18-50 years of age, were selected for inclusion in one of three groups based on their opioid use history: (1) Individuals having a history of OD who are stable on MMT; (2) Individuals having a history of OD who were on methadone but have undergone methadone detoxification (NOMT); and (3) HC individuals without a history of opioid or other illicit substance dependence, matched for gender, district and educational level. For inclusion in the MMT and NOMT groups, participants were required to fulfil a former DSM-5 diagnosis of OD and to have been free of any illicit drug for at least one month, confirmed through negative urine toxicology screening tests (excluding methadone in the MMT group).

The MMT participants were recruited either from (i) Mount Carmel Psychiatric Hospital, whereby, patients had been admitted and stabilised on methadone for at least one month, (ii) Substance Misuse Outpatients

Clinic, whereby patients were on a stable methadone dose or (iii) Substance Misuse Outpatients Clinic, whereby patients had been granted the Take Home Methadone Policy.

The NOMT participants were recruited from a residential drug rehabilitation program (Caritas or Sedqa). The inclusion criteria for this group consisted of prior MMT, followed by gradual methadone detoxification to complete abstinence. All NOMT participants required to be methadone-free for a minimum of one month.

The HC population participants were recruited from Bormla public health centre general practitioner's clinic attendees. A southern harbour health centre was chosen whilst attempting to select a healthy sample resembling the OD sample as much as possible, in accordance with the National Audit Office Report (2012) which stated that the district that registers the highest proportion of individuals with SUD is the southern harbour region.[30] Patients or their relatives who presented with a minor health complaint which was not psychiatric in origin and who had never used any type of illicit substance, underwent cognitive testing.

Exclusionary criteria for all participants were any current Axis I diagnosis (other than OD for the MMT and NOMT groups, and nicotine dependence for all groups), history of head trauma, brain injury, neurological disease, substance-induced psychoses, epileptic seizures, human immunodeficiency virus infection, pregnancy, or any other medical condition which might affect the individual's cognitive function. Individuals who were administered any opioid replacement strategy e.g. Buprenorphine / DHC / Tramadol / Codeine were excluded from this study. Those who refused to give urines were automatically excluded from this study. Routine screening tested the detection of amphetamines, cocaine, cannabinoids, methadone and opiates. Exclusion criteria for control subjects included current or past history of any illicit substance.

Initial screening for the MMT group was done through the Substance Misuse unit database, whereby eligible patients were contacted and informed about this current study. Similarly, potential NOMT participants who were enrolled in Caritas and Sedqa residential drug rehabilitation programs and expressed interest in participating were invited for a face-to-face interview, consisting of the Beck's Depression and Anxiety Inventories. Only those participants who did not suffer from any psychiatric condition which might impair cognitive function were selected and assessed with the MoCA. All interviews were conducted by the same clinician to eliminate any observer or systematic bias. No sampling method was used to recruit participants as all available patients who were benefiting from these addiction services throughout April-September 2017 and who met inclusion and exclusion criteria were recruited. In all, 22 participants satisfied the criteria for inclusion in the MMT group, 21 participants were included in the NOMT group and 22 HC participants were enrolled out of their own free will. This study was reviewed and approved by the Malta Health Ethics Committee Board and the Foundation for Social Welfare Services Ethics Committee.

A naturalistic cross-sectional comparative design was employed for this study. Randomization of the participants was not possible as the overall management of the participants depended on their own personal choice as to whether to engage in

MMT or enrol in a rehabilitation programme and stay NOMT. The dependent variable was overall cognitive functioning which was assessed at one specific time point through administration of the MoCA cognitive tool. The independent variable was treatment with methadone or not, as an opioid replacement. The duration of dependence/abstinence/enrolment in programme, comorbid dependencies, psychiatric treatment, dosage of methadone and the duration of methadone administration were also variables of particular interest.

The MoCA was administered manually using paper and pencil testing. Two versions were available, depending on the participant's preference of daily spoken language; an English and Maltese version (the latter had been already translated and validated in another study).[31] A score of 26 or more is considered normal. The specific cognitive domains tested include executive function, visuospatial skills, naming, attention, language, abstraction, delayed recall and orientation.

Statistical Analysis

SPSS software was used for statistical analysis. Initial analyses compared groups on demographics with analysis of variance (ANOVA) for continuous variables and Chi-square analyses for categorical variables. Any demographic variable that significantly varied across groups, was entered into later analyses as a covariate. The individual cognitive domains tested were compared across groups by conducting a one-way analysis of variance to examine group (MMT, NOMT and HC) effect, followed by post-hoc testing with Bonferroni multiple comparison analysis. Backward stepwise multivariate linear regression was carried out to examine the effects of comorbid cocaine dependence and different classes of psychiatric treatment on cognitive performance and thus, determine the presence and account for any confounders. The effects of duration of dependency/abstinence/methadone administration/enrolment in program and methadone dosage were examined by conducting a correlation analysis.

In reporting the results, a *P* value of 0.05 was considered as showing statistical significance.

Results

Participant Demographics

MMT, NOMT and HC groups did not significantly differ with respect to gender *(x^2 =2.167, P=0.338)* and district locality *(x^2 =7.197, P=0.707)* by Pearson Chi-Square analysis. Neither did the three participant groups differ with regards to years of education *(F=1.284, P=0.284)* by ANOVA. However, they demonstrated significant difference with respect to age *(F=4.059, P=0.022)*. HC participants were the youngest with a mean age of *31.64* ±*8.244*, followed by NOMT participants with a mean age of *34.90* ±6.340 and finally MMT participants being the eldest with a mean age of *37.59* ±*6.005* (Table 1).

Cognitive Domain Performance

One-way ANOVA was applied to test for any significant difference among the participant groups (MMT, NOMT and HC) for each cognitive domain tested. A significant difference was present for visuospatial skills and executive function *(F=13.621, P= 0.000)*, attention *(F=4.777, P=0.012)*, language *(F=9.760, P=0.000)*, abstraction *(F=4.813,*

P=0.011) and delayed recall *(F=5.573, P=0.006)*. No significant difference was noted among the groups for naming *(F=1.049, P=0.356)* and orientation *(F=1.012, P=0.369)*. A highly significant difference was observed among the three groups for the overall total cognitive score *(F=15.782, P=0.000)*. The total cognitive score was previously obtained by adding the score of each individual cognitive domain for each participant in their respective groups. In every cognitive domain tested, the NOMT group obtained the lowest mean score, followed by the MMT group and finally the HC with the highest score (Figure 1).

Post-hoc Bonferroni analysis of multiple comparisons (Table 2) was carried out for each cognitive domain. The NOMT group scored significantly lower than the HC *(P=0.000)* and MMT *(P=0.010)* group for visuospatial / executive function. The difference between MMT and HC was not significant *(P=0.105)*.

There was a significant difference between the NOMT and HC for attention *(P=0.010)*, delayed recall *(P=0.006)*, and abstraction *(P=0.013)* with the NOMT group obtaining the least mean score out of all groups. No difference was observed between the MMT group and HC for attention *(P=0.213)*, delayed recall *(P=0.077)* and abstraction *(P=1.000)* or between MMT and NOMT for attention *(P=0.644)*, delayed recall *(P=0.987)* and abstraction *(P=0.069)*.

HC scored significantly higher than MMT *(P=0.014)* and NOMT group *(P=0.000)* for language. There was no significant difference between the MMT and NOMT group *(P=0.479)*.

The HC overall total score was significantly higher than both MMT *(P=0.007)* and NOMT group *(P=0.000)*. No statistically significant difference existed between MMT and NOMT groups *(P=0.052)*.

Multiple Linear Regression Analysis and Backward Stepwise Multivariate Linear Regression Modelling

The participants' age was entered as a covariate in a secondary analysis comparing each neurocognitive domain performance across groups. Multiple linear regression analysis was carried out to adjust for age since the latter was statistically significantly different among the three groups. Nonetheless, age was not significant in any of the models for each different cognitive domain score.

Backward stepwise multivariate linear regression modelling was used to examine and account for any possible confounders to the MoCA score among the participant groups. Comorbid cocaine dependence and different classes of psychiatric treatment were studied for any effect on cognitive performance. No confounder was found to be statistically different for the neurocognitive score across the three groups.

Correlation Analysis

The relationships between the individual cognitive domain score and duration of dependency/abstinence from heroin were examined by conducting a correlation analysis specific to the MMT and NOMT group participants only. The dose and duration of methadone administration were also correlated exclusively to the MMT group, while the duration of enrolment in the drug rehab program was correlated with each cognitive domain score exclusively to the NOMT group.

Table 1 Demographic data of Methadone Maintenance Treatment, Not on Methadone Treatment and Healthy Control Groups

Group	Control HC (*n*=22)	Opioid Dependent MMT (*n*=22)	Opioid Dependent NOMT (*n*=21)	Statistic	Significance *P*
Gender					
Male	15(68.2%)	18 (18.8%)	13(61.9%)		
Female	7 (31.8%)	4 (18.2%)	8 (38.1%)	x^2 2.167, df=2	0.338
District					
Southern Harbour District	14(63.6%)	10 (45.5%)	10(47.6%)		
Northern Harbour District	4 (18.2%)	6 (27.3%)	4 (0.19%)		
South Eastern District	0 (0.0%)	2 (9.1%)	3 (14.3%)		
Western District	2 (9.1%)	2 (9.1%)	1 (4.8%)		
Northern District	2 (9.1%)	1 (4.5%)	1 (4.8%)	$x^2$7.197,df=10	0.707
N/A (Outside Malta)	0 (0.0%)	1 (4.5%)	2 (9.5%)		
Education (years: mean ± S.D.)	11.23 ± 2.202	11.91 ± 1.925	10.81 ± 2.657	F=1.284	0.284
Age (years: mean ± S.D.)	31.64 ± 8.244	37.59 ± 6.005	34.90 ± 6.340	F=4.059	0.022

S.D.Standard Deviation, df Degrees of freedom, x^2 Chi-Square,F-statistic

Figure 1 A comparison of the percentage mean score for each cognitive domain across the groups

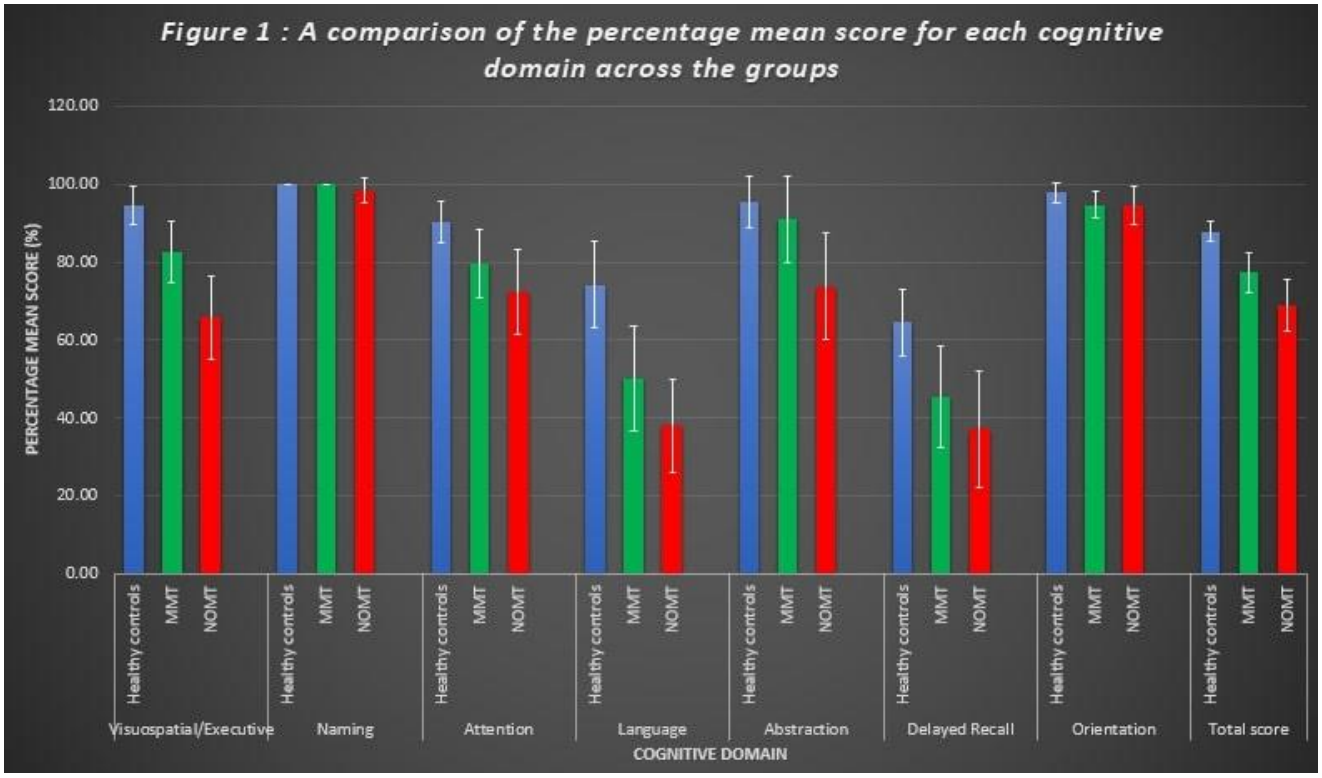


Table 2 Neurocognitive domain performance of MMT, NOMT and HC participant groups

Group	Control	Opioid Dependent		Statistic	Significance *P*	Paired Comparison
	HC	MMT	NOMT			
		Mean ± S.D.				
ANOVA						
Visuospatial/Executive	4.73 ± 0.550	4.14 ± 0.889	3.29 ± 1.189	F=13,621	0.000	B,C
Naming	3.00 ± 0.000	3.00 ± 0.000	2.95 ± 0.218	F=1.049	0.356	_
Attention	5.41 ± 0.734	4.77 ± 1.193	4.33 ± 1.426	F=4.777	0.012	B
Language	2.23 ± 0.752	1.50 ± 0.913	1.14 ± 0.793	F=9.760	0.000	A,B
Abstraction	1.91 ± 0.294	1.82 ± 0.501	1.48 ± 0.602	F=4.813	0.011	B
Delayed Recall	3.23 ± 0.973	2.27 ± 1.486	1.86 ± 1.6221	F=5.573	0.006	B
Orientation	5.86 ± 0.351	5.68 ± 0.477	5.67 ± 0.658	F=1.012	0.369	_
Total Score	26.36 ± 1.677	23.18 ± 3.375	20.71 ± 4.361	F=15.782	0.000	A,B

Figure 2 Scatterplot showing the variability of Language score with Duration of Dependency

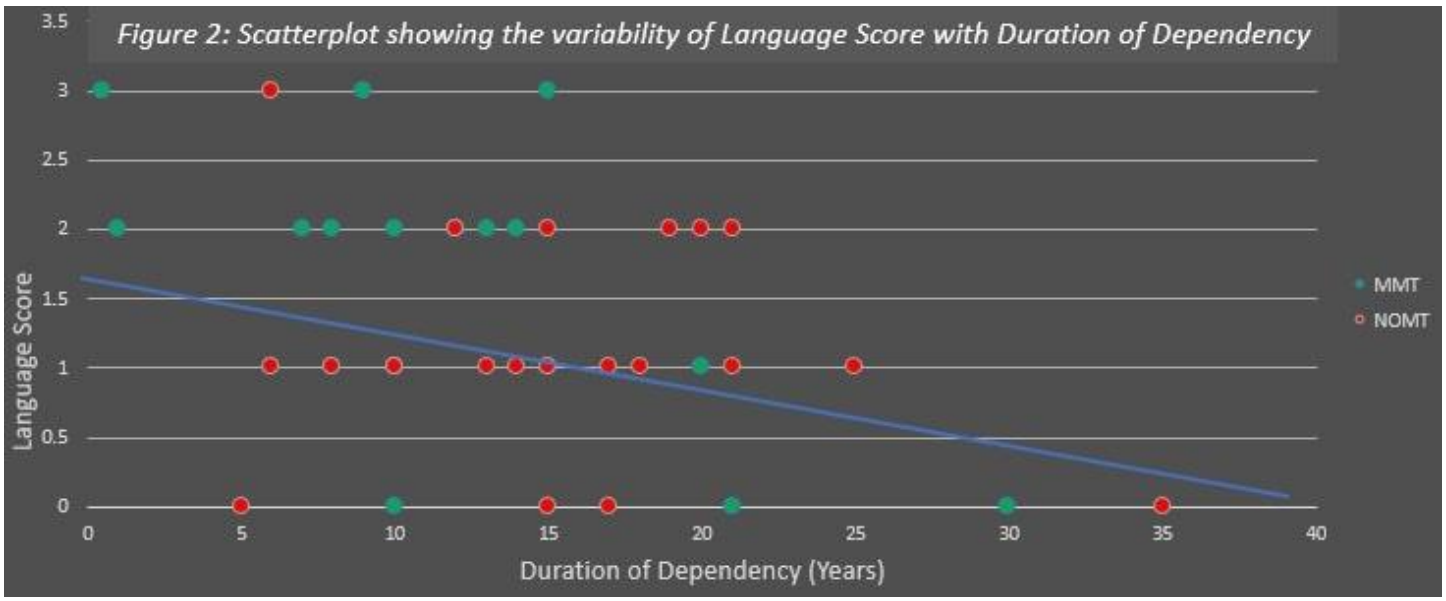
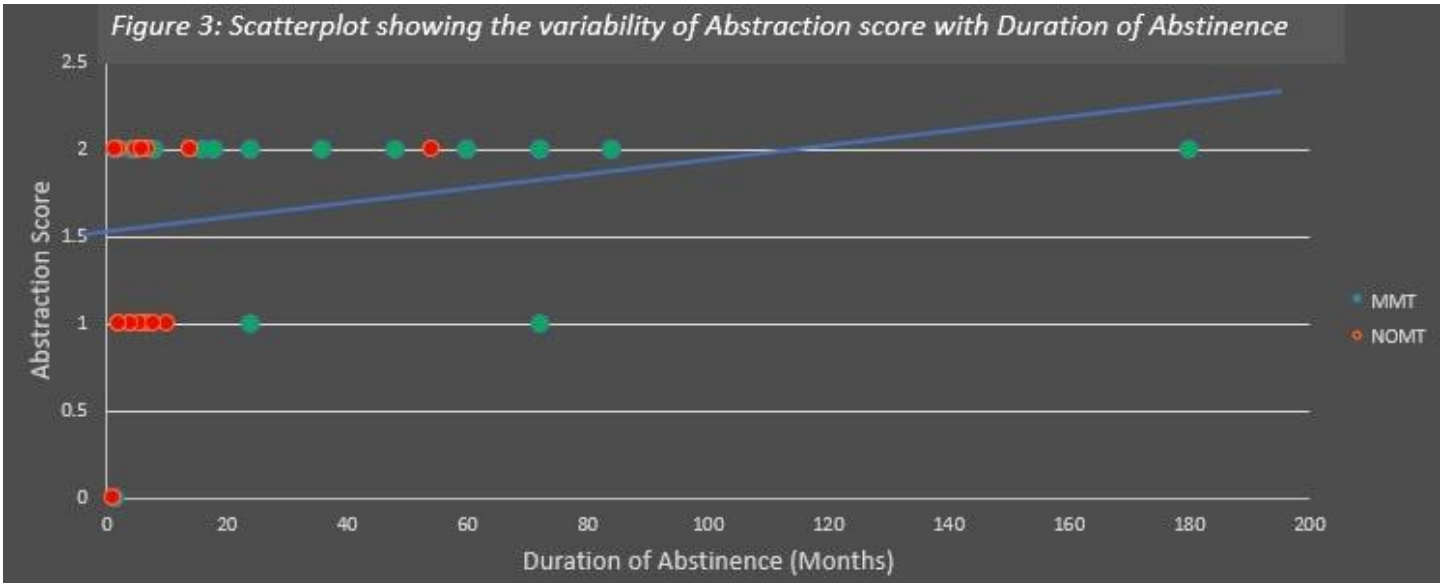


Figure 3 Scatterplot showing the variability of Abstraction score with Duration of Abstinence



The duration of dependency was noted to be negatively correlated with the language domain for both MMT and NOMT groups *(P=0.012)* (Figure 2). An analysis of the language domain as the dependent variable with group, as the between-subject factor (MMT and NOMT) and duration of dependency as covariate, did not reveal a statistically significant effect of group *(P=0.437)*. The covariate of duration of dependency remained

statistically significant *(P=0.017)*. Thus, the difference in language between MMT and NOMT groups is not significant in the presence of the duration of dependency. The duration of dependency was not significantly correlated to any other cognitive domain, nor was it correlated to the overall total score *(P=0.140)*.

The duration of abstinence was noted to be positively correlated with the abstraction domain for both MMT and NOMT groups *(P=0.50)* (Figure 3). An analysis of the abstraction domain as the dependent variable with group, as the between-subject factor (MMT and NOMT) and duration of abstinence as covariate, did not reveal a statistically significant effect of group *(P=0.251)*. The covariate of duration of abstinence from heroin did not remain statistically significant *(P=0.258)*. The duration of abstinence was not significantly correlated to any other cognitive domain, nor was it correlated to the overall total score *(P=0.082)*.

No significant correlation was observed for dose and duration of methadone administration with each cognitive domain tested and with the overall total score for the MMT group *(P=0.585* and *P=0.897* respectively). Similarly, no significant correlation was noted for the duration of enrolment in the drug rehab program with each cognitive domain tested and with the overall total score for the NOMT group *(P=0.529)*.

Discussion

Individuals with no history of SUD tend to exhibit superior cognitive functioning compared to those who abuse opioids and other psychoactive substances, as highlighted in this study and elsewhere. The present research sheds further light on factors that can affect cognitive function in an already impaired group.

Individuals who are stable on methadone appear to have significant problems primarily in the language domain compared to controls whilst those who are weaned off methadone exhibit impairments in multiple cognitive domains, in particular visuospatial and executive function, attention, language, abstraction and delayed recall. Visuospatial impairment was previously reported in an NOMT group in a similar comparison.[16] Another study highlighted enhanced attention in the MMT group, consistent with this study.[18] Executive functions such as impulse control, verbal learning and memory, visuospatial memory, and psychomotor speed, were also previously shown to be superior in the MMT group.[19]

Though the significant language domain impairment of the MMT group in this study influenced the total MoCA score leading to a minimal overall difference compared to the NOMT group, methadone stabilisation appears to offer some sort of stabilisation, if not recovery, especially with regards to visuospatial abilities and executive function. Our findings did not show significant differences between the majority of the cognitive domains tested in the MMT and the HC groups. This was not the case when the HC and NOMT groups were compared, with contrasting levels of cognitive function in multiple domains.

Figure 1 clearly illustrates a typical crescendo pattern, with the mean score for each cognitive domain of the NOMT group being the lowest, reflecting poorest cognitive function, while the HC scoring the highest. The MMT group mean scores appear to lie in between the other two groups, highlighting

the fact that methadone may promote neurocognitive recovery in individuals who had previously been dependent on heroin. This contrasts markedly with the findings of a study where the abstinent group reportedly had an overall better cognitive performance than the MMT group.[15] However, the researchers admittedly included subjects with current illicit drug use and performed retrospective comparisons, increasing the effect of confounders.

The present study and others have sustained the view that individuals with OD who are retained on MMT seem to exhibit better cognitive function compared to those who underwent detoxification, at least partially explaining the superiority of MMT over interventions with a drug-free ideology. The enhanced cognitive stability offered by MMT can come in handy when such patients are subjected to the challenges of psychosocial interventions such as cognitive behavioural therapy. Individuals with OD have an increased risk of emotional dysregulation primarily as a result of impaired cognitive reappraisal.[13-14] In a study comparing the effects of MMT and CBT on cognitive emotional regulation, both were shown to be significantly effective and the authors suspect this may be one of the underlying mechanisms of MMT which instigates improved cognitive function.[32]

This study also revealed a strong correlation between the duration of the OD career with the degree of impairment in the language domain; methadone did not seem to stabilise cognition in subjects who accumulated more brain changes over a longer exposure to opioids. This justifies the Bonferroni analysis for the language domain where both MMT and NOMT groups scored significantly lower than the HC. One possible interpretation of this finding is that a ceiling effect exists in our drug-using participants due to the severity of OD that may have masked any differential effect of chronic opiate use on cognitive function.

The results of this study have important implications in management. Individuals who are on methadone are frequently stigmatised and encouraged to come off methadone at a stage when risk of relapse is still significant. In particular, there is a blanket approach to those planning to join a residential drug rehabilitation programme. For some, methadone detoxification prior to rehab not only lowers their ability to cope with the challenges of the programme due to a possible deterioration in executive function, but exposes them to associated risks. Cognitive function plays a key role in treatment efficacy. Prohibiting proven medical treatments at all costs in rehab programmes may be limiting the effectiveness of the same programmes apart from depriving individuals with complex needs from making progress through their full cognitive potential. In addition, specific interventions targeting neurocognitive dysfunction should become an essential component of all interventions in the addiction field.

Limitations of this current study include a small population size, a demographic difference of age among the group participants and illicit substance use history measures have been collected based on the participants' self-reports. Routine urine testing does not identify all abused illicit drugs, such as the widely consumed synthetic cannabis receptor agonists. A cross-sectional study was performed as opposed to a longitudinal design with MMT patients pre and post methadone detoxification. It is also fairly well recognised that opiate addicts have abused a variety of illicit substances which are

usually under-reported. It is therefore, possible that any type of illicit substance might lead to cognitive deficits due to a direct toxic insult to the brain. In addition, the unhealthy lifestyle associated with severe OD might include malnutrition, exposure to violence or infections which could indirectly contribute to a decreased cognitive performance. We have specifically asked all our participants recruited in this study for any history of head trauma or probed for medical conditions which could affect cognition.

This study is unique in rigorous exclusion of comorbid Axis I and Axis II disorders which could affect cognitive function. In addition, abstinence was ensured by repeated screening for any illicit substance and automatic exclusion of individuals who failed to submit a urine sample or who have abused any illicit substance in the last month. All interviews were conducted by the same clinician to minimise the chances of observer or systematic bias.

Conclusion

Despite its limitations, our study addresses the issue of cognitive impairment in rigorously screened abstinent heroin addicts. Our results indicate that methadone offers a better level of cognitive function compared to premature opioid substitute cessation. Given the extent of opioid addiction in the community, MMT provides public health benefits by augmenting cognitive performance and social function in former OD individuals. It can ensure compliance with treatment plans, reduce relapse rates and risky behaviours in heroin addicts, thus fostering productivity and resumption of important responsibilities. It highlights the importance of performing neuropsychological assessments as an aspect of patient evaluation in drug rehab programmes and other venues of care, thus, identifying and acknowledging significant cognitive impairment, and providing appropriate care packages.

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ORIGINAL ARTICLE

Surgical admissions to Intensive Therapy Unit at Mater Dei Hospital: a prospective 3 month study

Anthony Pio Dimech, Carmel Abela, Gordon Caruana Dingli

Introduction

Patient care in an acute hospital is divided into 4 levels, with level 0 being least demanding and level 3 comprising intensive care. A surgical high dependency unit (HDU) offers level 2 (intermediate) care and is indispensable when escalating or de-escalating from lower or higher levels of care respectively. Mater Dei Hospital lacks such a dedicated unit.

Methods

Data was prospectively collected over a 3-month period and included all surgical patients admitted to the intensive therapy unit (ITU), including subspecialties. The duration and reasons for admission to hospital and ITU were documented. Hospital admissions were either planned or emergency. Reasons for ITU admission were either planned or unplanned after elective surgery, following emergency surgery, directly from the Emergency Department or following clinical deterioration in a level 0 ward. Number of organs supported, any surgical interventions during admission and the final outcome were noted.

Results

There were 173 surgical patients admitted to ITU (116 males) with mean age 61.2 years. Most were post-surgery (71.7%, *n*=124) or after being stabilised at the Emergency Department (21.4%, *n*=37). Fewer required escalation from normal ward-based care (6.94%, *n*=12). Transfers from other hospitals occupied 3 ITU beds (1.73%). Mean ITU stay was 3.4 days per patient, with 6.5 beds being occupied by surgical cases on a daily basis. Forty-one percent of patients met the criteria for HDU.

Conclusion

With an ever growing population, there is a need to set up a local surgical HDU. This will help relieve the recurrent shortage of ITU beds without compromising the level of healthcare delivered.

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Introduction

In an acute general hospital catering for patients with varying complaints, the level of healthcare delivery is divided into four categories. Level 0 is the least demanding and includes normal ward-based care of otherwise stable, non-complex patients without the need of specially trained nursing staff. Level 1 care encompasses more demanding patients at risk of deterioration. This can be in the form of escalation from level 0, or de-escalation from a higher level of care. Although their needs can be met in a normal ward, additional critical care back-up is necessary. Level 2 is equivalent to a High Dependency Unit (HDU), with a nurse-to-patient ratio of 1:2. Patients falling in this category are those who have a single failing organ system, are admitted as a precautionary measure (such as post-major or complex surgery) or when de-escalating from higher levels of care. Level 3 is highly specialised care which is provided in an Intensive Therapy Unit (ITU). Patients often require advanced respiratory support (sedation and invasive ventilation) or less invasive airway support in the presence of at least two deteriorating organ systems. Any patient with multi-organ failure also falls in this category.[1-2]

Out of approximately 1000 beds in our main acute hospital, 20 are assigned to a combined HDU/ITU without a dedicated surgical HDU (table 1 below shows the basic setup for manning a HDU).[3] As bed space is a recurring issue, sometimes it becomes difficult to provide care in the most appropriate environment. Health care cost is also an important factor, with ITU beds being the most expensive to run. The objective of this audit was to define the load on our ITU from surgical admissions who could be cared for on a HDU. The main criteria assessed were mode of admission, number of organs requiring support, length of stay in ITU and in hospital, caring specialty and outcome after hospital stay.

Methods

Data protection approval from Mater Dei Hospital was obtained before commencing the anonymous prospective data collection from patient's notes and daily progress charts. The first author recorded information on paper which was later transferred to a dedicated spreadsheet created using Microsoft Excel 2007. This was kept in a password-protected database and updated regularly. Statistical analysis was carried out using the same software.

All surgical patients admitted to ITU between 1st February 2018 and 30th April 2018 (3 months) were included. Non-surgical patients including those falling under obstetrics and gynaecology were excluded. Demographic details such as age, gender, comorbidities and American Society of Anaesthesiologists (ASA) score were recorded. The duration and reasons for admission to hospital and ITU were documented. Mode of admission to hospital was classified into either emergency or elective. Reasons for ITU admission were categorised into: planned admission after elective surgery, unplanned admission after elective surgery, as an emergency directly from the Emergency Department, after emergency surgery or following deterioration in the ward. Proper justification for escalating to level 3 and the primary caring specialty were also documented. Patients were followed-up until the end of their stay in hospital and the final outcome was recorded. Particular attention was given to the number of organs supported, name of surgical procedures performed and any complications suffered.

Table 1 Basic HDU requirements. A HDU has to be geographically linked with the ITU and resources for resuscitation of the critically ill must be immediately available.[3]

Medical staff	A medical/surgical trainee with appropriate training and experience available 24-hours a day.
	An attending Intensive Care Specialist who is also responsible for admissions to the HDU.
	Designated Medical Director trained in Intensive Care medicine.
Nursing staff	Nurse-to-patient ratio of 1:2. The majority of senior nurses should be qualified in intensive care or high dependency care nursing. HDU Charge Nurse should have a degree in Intensive Care medicine.
Services	Seamless access to ITU, opecrating theatres, radiology, pharmacy and pathology laboratories.
	Regular input from physiotherapists and other health care professionals (including occupational therapy, dietician, tissue viability services, etc).
	Technical and clerical staff.
Operational	Guidelines on admission, management and discharge of patients.
	Formal auditing procedures and policies to implement changes.
	Infection control/isolation protocols (including designated cubicles).
	Access to facilities for continuous professional development.
	Formal introductory program for new recruits.

RESULTS

Out of a total of 173 patients admitted to ITU, 67.1% (*n*=116) were males and 32.9% (*n*=57) were females. Mean age was 61.2 (range 2-90) years. Elective hospital admissions that were later transferred to ITU amounted to 82 patients while 91 were emergency admissions. Most patients were taken to intensive care following surgery (71.7%, *n*=124) or after being stabilised at the Emergency Department (21.4%, *n*=37). Fewer required escalation from normal ward-based care (6.94%, *n*=12). Transfers from other hospitals occupied 3 ITU beds (1.73%).

Modes of admission to ITU

- **Transfers to ITU following elective hospital admission**

The majority of elective hospital admissions that later required ITU had a pre-booked level 3 bed and followed elective surgery (86.6%, *n*=71). Five patients (6%) had an unplanned ITU admission after elective surgery. One involved deviation from the original surgical approach (laparoscopy converted to open subtotal colectomy), 2 experienced intra-operative hypoxic events and 2 had cardiovascular instability (1 being hypotension secondary to haemorrhage). Two of these patients later passed away. Four patients (5%) underwent emergency surgery for complications acquired during elective procedures (such as bowel perforation at colonoscopy) or unrelated to previous surgery (laparotomy for faecal impaction and perforation). A minority (1.16%, *n*=2) suffered deterioration in the ward from other causes and required escalation of care.

- **Transfers to ITU following emergency hospital admission**

A significant number of emergency admissions were taken directly from the Emergency Department to intensive care (40.6%, *n*=37) or underwent emergency surgery prior to ITU transfer (39.6%, *n*=36). Four patients (4.4%) were taken to ITU after semi-elective interventions (2 vascular and 2 neurosurgical patients). Four others were unplanned admissions after encountering problems during femoral fracture fixation, semi-elective femoral hemiarthroplasty, laparoscopic cholecystectomy and one case of diverticulitis that became complicated by abscess formation and sepsis requiring Hartmann's procedure one month into the admission. A proportion of emergency hospital admissions that were initially cared for in a level 0 setting required escalation to level 3 at some point during their stay (5.78%, *n*=10). Figure 1 summarises the nature of emergency admissions to hospital requiring ITU.

Length of stay

The cumulative number of ITU days occupied by surgical patients was 589, or 6.5 beds per day with a mean ITU stay of 3.4 days (table 2 and figure 2).

Organ support

The organ systems requiring physiological support were divided into brain/central nervous system, renal, cardiovascular, respiratory, metabolic and immune system (figure 3). The number of organs supported per patient is displayed in figure 4. Of those with single organ support (*n*=75), the cardiovascular system was addressed in 42 patients, while 14 required neurological support namely neurocharting after neurosurgical intervention, intracranial pressure monitoring and monitoring after severe head injury. Fourteen patients received respiratory assistance. Renal function was supported in 5 other patients in the form of haemodialysis for metabolic derangement, support after renal transplant and management post-nephrectomy.

ASA scores are shown in table 3. There is a general trend towards more organs requiring assistance in subjects admitted as an emergency and in patients with a higher ASA score (figure 5).

Figure 1 Breakdown (patient numbers) of emergency admissions to hospital requiring immediate transfer to ITU. Mortality in this group was 46% (17 patients). They mainly suffered polytrauma (30%) after motor vehicle accidents or falls from height. There was one case of non-traumatic splenic rupture resulting from malignant infiltration.

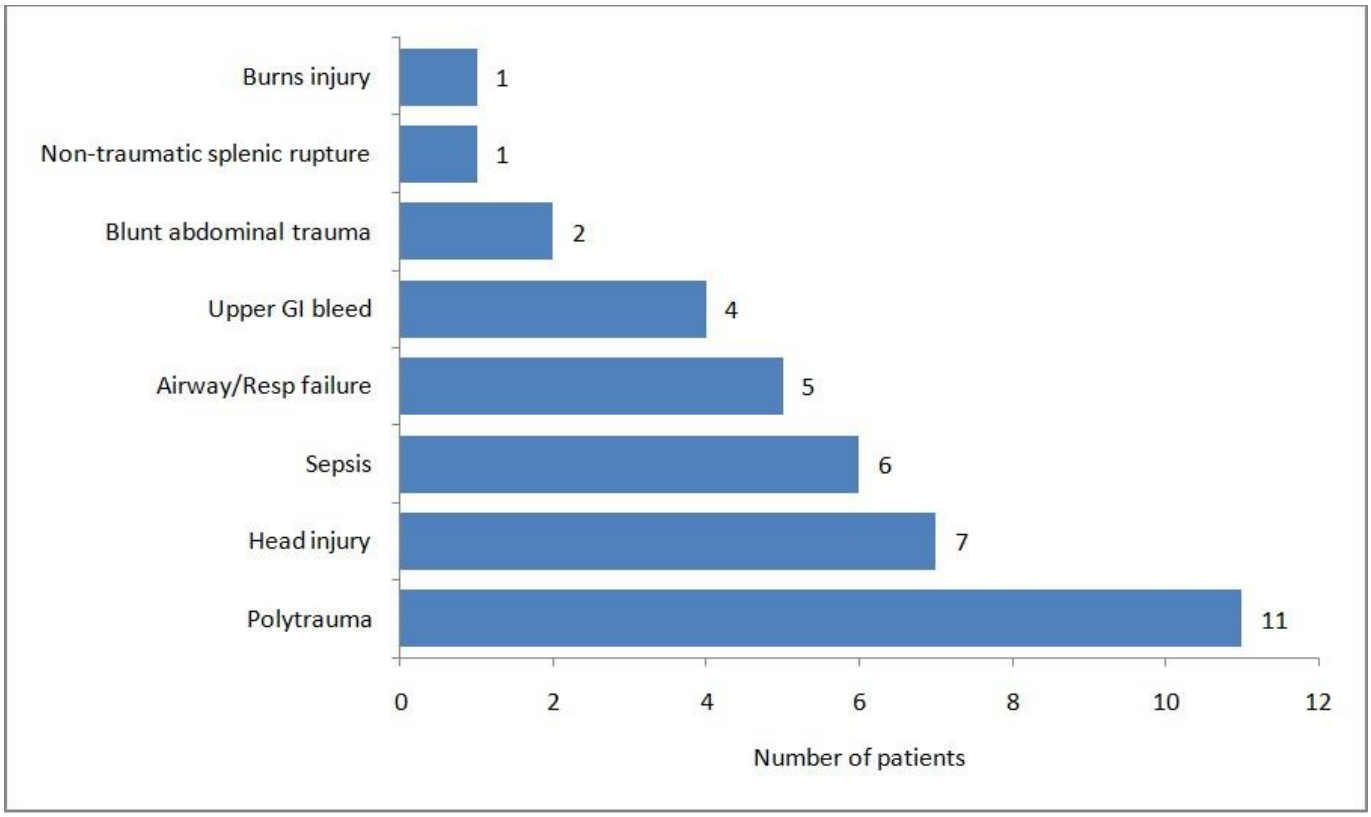


Table 2 Admission days by specialty.

	Cumulative days spent in ITU (range, mean)	Cumulative days spent in hospital (range, mean)	Number of patients (*n*)
General surgery	133 (1-9, 2.66)	877 (1-68, 17.5)	50
Vascular surgery	50 (0-11, 1.43)	560 (2-60, 16.0)	35
Neurosurgery	120 (1-16, 4.62)	558 (1-74, 21.5)	26
Orthopaedics and trauma	79 (0-24, 3.76)	444 (1-68, 21.1)	21
Upper gastrointestinal surgery	90 (1-62, 6.92)	245 (2-69, 18.8)	13
Urology	45 (0-26, 4.09)	195 (4-54, 17.7)	11
ENT	27 (1-8, 4.5)	275 (8-147, 45.8)	6
Transplant surgery	17 (2-5, 3.4)	174 (9-104, 34.8)	5
Endocrine surgery	8 (1-5, 2.67)	22 (5-10, 7.33)	3
Paediatric surgery	4 (2*)	40 (9-31, 20)	2
Plastic surgery	16	23	1
Total :	589	3434	173

Figure 2 Types of organs supported in the cohort of patients. Note that a particular patient may have more than one organ needing support.

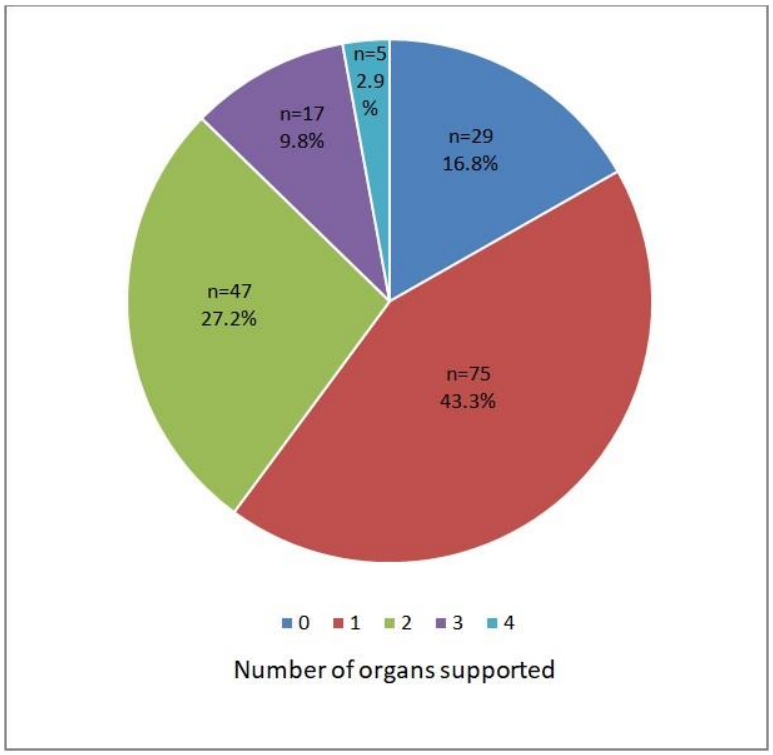


Figure 3 Number of organs supported per patient. Most required none or single organ support. No organ support often implied a short post-operative precautionary ITU stay as normal ward-based care was deemed unsafe in the immediate post-operative period should the patient deteriorate.

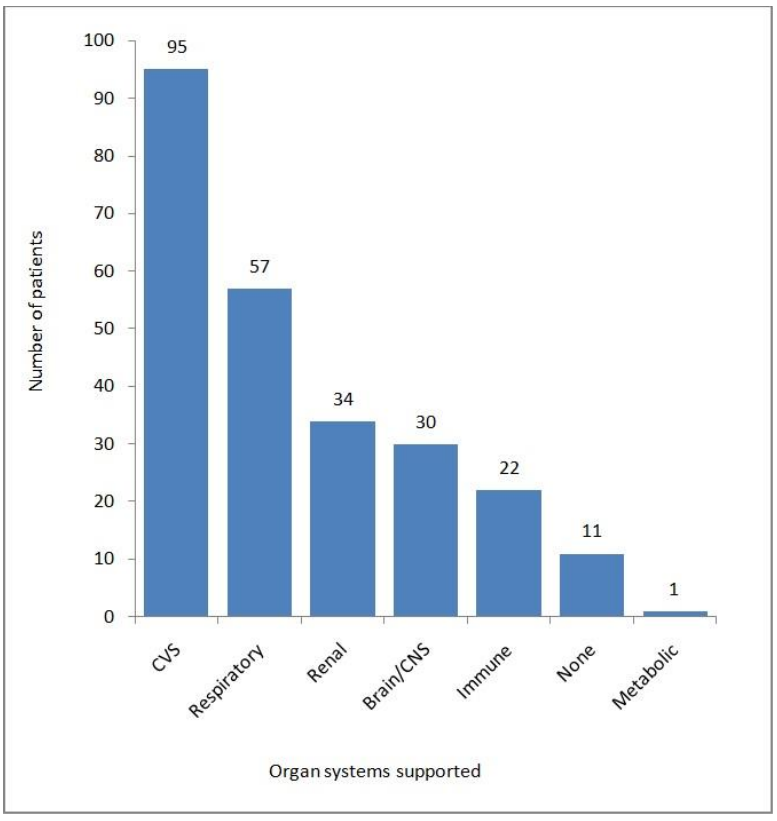


Figure 4 Mean number of organs supported in relation to ASA score. As a general rule, with worsening physiology, patients become increasingly demanding as more organs need attention.

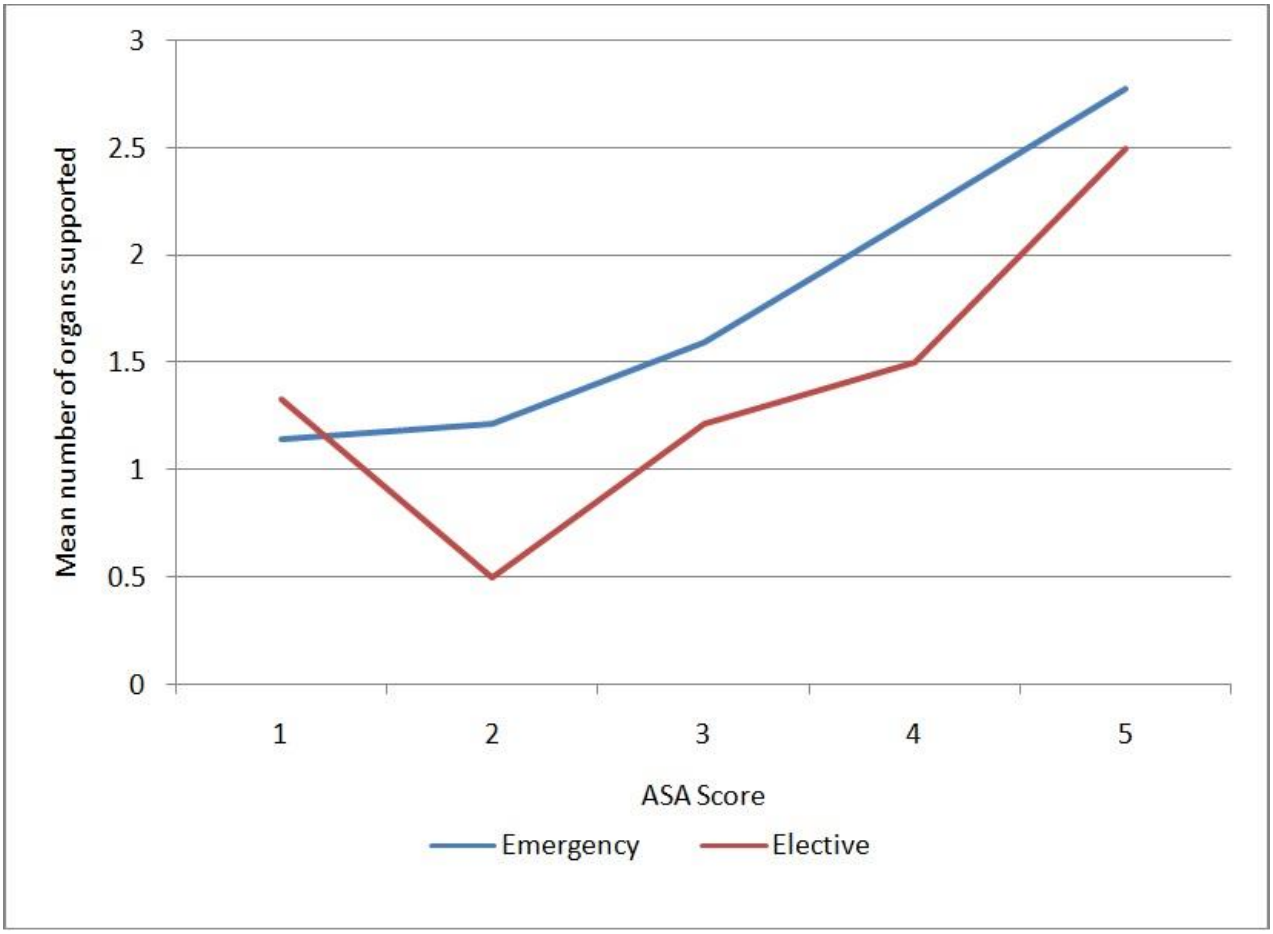
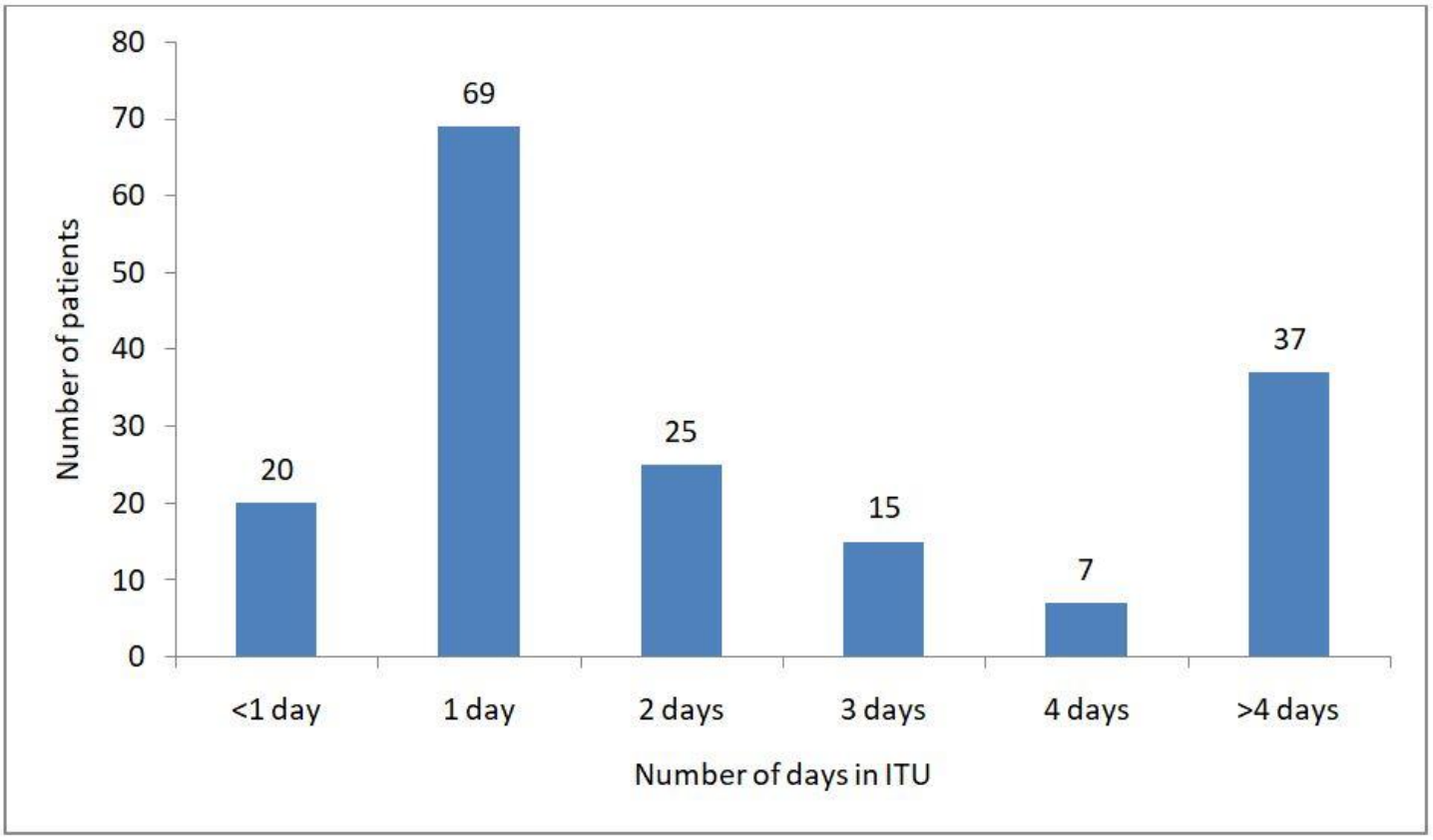


Table 3 ASA scores in relation to admission type. For the column displaying percentage patients, the total number of participants (*n*=173) was used as the denominator.

ASA Score	Mode of admission	Number of patients (*n*)	Percentage patients	Mean number of organs supported
1	Emergency	14	8.09%	1.14
	Elective	3	1.73%	1.33
2	Emergency	14	8.09%	1.21
	Elective	30	17.3%	0.50
3	Emergency	32	18.5%	1.59
	Elective	41	23.7%	1.22
4	Emergency	22	12.7%	2.18
	Elective	6	3.47%	1.50
5	Emergency	9	5.20%	2.78
	Elective	2	1.16	2.50

Figure 5 Distribution of patients according to days spent in ITU.



Patient outcomes

Mortality was recorded in 19.7% (*n*=34) of patients and this rose exponentially as the number of organ failures increased. Indeed, seven 7 had a single deteriorating organ function while 27 deceased patients had two or more organ failures. No deaths were reported in the cohort that required monitoring post-operatively without invasive organ support. A significant proportion were discharged home after completing their hospital stay (71.7%, *n*=124). Nine were transferred to a non-acute hospital and 6 flown to other centres overseas.

Discussion

The National Confidential Enquiry into Peri-Operative Deaths recommends that high-risk surgery should be avoided unless facilities for post-operative care are available and proposes a list of measures aimed at reducing post-operative mortality. This led to the concept of surgical HDUs in some institutions which offer intermediate care between ITU and the general wards.[4-5] Such unit was introduced by the Department of Anaesthesia and Intensive Care at St Luke's Hospital as an annex to the ITU. Upon migration to Mater Dei Hospital, this became a single ITU/HDU. Presently the Cardiac Intensive Care Unit also admits elective post-operative vascular surgical patients to offload the demand from the main ITU/HDU. Nevertheless, there is a need for a dedicated surgical HDU at Mater Dei Hospital as can be seen by this prospective study.

Our results showed that 71 (41%) ITU surgical patients received no organ support or cardiovascular support alone. These spent a combined total of 97 days in intensive care, making up 16.5% of total surgical ITU bed days

over the 3-month period of data collection. These numbers are significant, implying that a large proportion of patients admitted to a level 3 ward could have been safely managed in a level 2 environment. Literature also states that up to one-third (21-40%) of ITU beds may be occupied by high-dependency patients at any point. Conversely, a proportion of patients requiring HDU care may be inappropriately managed in a level 0 ward.[6]

Setting up a surgical HDU is not an easy feat. Apart from allocating physical space, it involves purchasing modern equipment, regular training of specialised staff, development of guidelines and protocols (including admission and discharge criteria based on risk assessment – table 3), and liaison between departments such as pharmacy, medical stores, sterile services and information technology among others. Healthcare professionals such as physiotherapists, dieticians and outreach teams must be accessible and there should be 24-hour surgical consultant availability. Since HDUs are typically manned by surgical teams (including on-call trainees outside regular hours) and not led by anaesthetists, proper backup plans must be in place in case of patient deterioration with the requirement of invasive respiratory support. Therefore, close proximity to the ITU is a plus.[5,7]

HDU care incorporates three basic principles: fluid and electrolyte balance, analgesia and proper oxygenation. It also offers the possibility of continuous cardiovascular monitoring and in some instances, inotropic cardiovascular support. Not every patient is a candidate for HDU, but those benefitting from it are often the ones at risk of renal and cardiac impairment, especially the elderly and emergency surgical cases (Table 4). Close attention to fluid balance with immediate correction reduces the incidence of these complications. In the study by Jones et al comparing post-operative outcomes of general surgical patients after HDU care vs no-HDU, the former resulted in significantly less hypotensive episodes, arrhythmias, wound and chest infections. Hospital stay was also less but did not reach statistical significance.[6] A study by Solberg et al from the Netherlands showed no difference in mortality rates with the introduction of HDU but there was better utilisation of intensive care facilities.[8]

Table 4 Example of criteria for selecting patients who might benefit from HDU care.[4]

Need of support for a single failing organ excluding requirement of advanced respiratory or renal support.
Patients undergoing major, complex surgery requiring close post-operative observation who would benefit from more detailed monitoring than can safely be provided on the ward, including patients requiring complicated fluid management and frequent drug intervention.
Patients who no longer need intensive care but are not fit enough for the general ward.
Post-operative patients who need close monitoring for more than a few hours expectedly or otherwise.

In a study evaluating satisfaction and quality of care, nurses felt that level 0 healthcare delivery improved after the opening of a HDU because the removal of more demanding patients enabled them to dedicate more time to their less acute cohort. On a similar note, nurses working in the HDU felt they could provide better holistic patient care which in

turn translated in a high job satisfaction. These findings also reflect patient satisfaction which is heavily dependent on carer availability, attitude and empathic approach rather than expertise alone. Furthermore, time to analgesic administration was superior in the HDU.[9]

One must also appreciate the educational potential of HDUs for surgical trainees, which parallels the teaching aims of our main acute general hospital. The Royal Surgical Colleges give particular importance to critical care and the subject regularly features in examinations and related courses. Apart from having formal rotations within the unit during surgical training, feedback from experienced surgical teams and nursing staff in such a demanding environment helps the trainee to build a comprehensive educational and practical portfolio. Exposure to several complex cases which are followed closely on a day-to-day basis allows the best possible continuity of care and therefore better understanding of the disease and recovery process. Communication with patients and relatives makes trainees better at breaking bad news and builds their confidence when discussing treatment plans with medical and non-medical individuals.[10]

Limitations of this study include its non-controlled nature. Missing data due to unobtainable records of deceased patients prevented the authors from compiling a full list of physiological scores and nursing time allocation as was originally planned. Re-admissions were considered as separate entries in the data collection. Seasonal variation might influence ITU admissions and no record was kept on those patients who were refused ITU admission or had their elective surgery postponed due to bed shortage. Furthermore, there was no record of vascular patients admitted to cardiac intensive care unit or patients requiring level 2 care but not referred to ITU.

Conclusion

This study confirms the general impression that many patients currently admitted in our ITU/HDU could be treated in a level 2 surgical facility (surgical HDU). Although one might argue that HDU is costly to set up, it then becomes more cost-effective over time. HDU can be a standalone unit or even an extension of an existing ward, but the latter is difficult to implement because staff needs to be highly trained and constantly updated with regards to modern techniques and equipment. Allocating personnel to man such ward-based HDUs also implies depriving the less dependent patients from nursing care, as staff will instinctively dedicate more of their time caring for the sicker cohort.[6] Therefore, the best way to treat those patients who are not fit for a normal ward but do not have the criteria for intensive care is to admit them to a separate surgical HDU. This will help relieve the shortage of ITU bed space without compromising the level of healthcare delivered and potentially eliminates problems such as premature discharge from intensive care or delaying elective major surgery.[4,5] Similarly, some of the elective post-operative patients in this study could have been admitted to a Post-Anaesthesia Care Unit (PACU).

Although a larger, prospective, hospital-wide study would be required to define the total population that could benefit from a surgical HDU, the authors believe that such a unit would improve patient safety and support the current overstretched level 2/3 facility. This offsets the additional running costs. From a surgical department point of view, this would require additional training in Intensive Care for surgical trainees and resident specialists

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REVIEW ARTICLE

Parkinson's Disease - Current Treatments and the Possible Use of Cannabis

Joseph Ignatius Azzopardi, Peter Ferry

Parkinson's disease is a progressive neurodegenerative movement disorder common in old age. The current prevalence of this condition in the western world is estimated to be 0.3% of the entire population, and this value is expected to increase due to the ageing world population.

Although there is no cure for Parkinson's disease, many therapies aimed to relieve patients from its motor and/or non-motor symptoms exist, both pharmacological and surgical such as levodopa and deep brain stimulation, respectively. However, these therapies have their own problems and disadvantages, for instance levodopa-induced dyskinesia.

As there is currently a movement bringing about the legalisation of cannabis use for medicinal purposes, many studies are being carried out to discover if cannabis or cannabinoids can be used as a treatment modality, hopefully with less side effects than current treatments, to alleviate patients suffering from Parkinson's disease from their symptoms.

In this paper we seek to review the current treatment options available to these patients and what the latest studies in cannabinoids have determined with regards to their use in Parkinson's disease.

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Parkinson's Disease ... What's in a Name?

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder – it is the commonest movement disorder and the second commonest neurodegenerative disorder following Alzheimer disease, occurring mostly in old age. The current prevalence of PD in the western world is estimated to be 0.3% of the entire population, rising to 1% in people aged over 60, with the prevalence expected to increase as the size of the geriatric population in many countries is on the rise.[1–4]

The disease was described for the first time in 1817 by Dr James Parkinson calling it a "shaking palsy".[5] While the disease is mostly characterised by its motor symptoms such as bradykinesia, gait disturbance, rigidity and a resting tremor; non-motor symptoms such as depression, apathy, anxiety, insomnia, orthostatic hypotension, erectile dysfunction, constipation and fatigue amongst others can also occur.[6]

Pathologically, PD is characterised by the loss of the dopaminergic neurons found in the substantia nigra pars compacta and the presence of Lewy bodies and Lewy neurites in the remaining neurons. Onset of symptoms occurs when approximately 80% of the dopaminergic neurons in the substantia nigra are lost.[7]

A Short History of Medical Cannabis

The medicinal use of cannabis (*Cannabis sativa*) spans thousands of years, with the earliest written evidence being found in the world's first pharmacopeia – *pen-ts'ao ching* – which was based on oral traditions passed from one generation to another since 2,7000 B.C.[8-9]

The introduction of cannabis as a form of medication in Western medicine was made possible by the work of Dr William Brooke O'Shaughnessy, an Irish physician. The use of cannabis for medical purposes then became widely disseminated by the 19th century.[9]

In the 1930's and 1940's however, the medical use of cannabis quickly fell out of use due to fears of the socially deviant behaviours which were attributed to the recreational use of this drug, leading to many countries banning the cannabis from its use in medicine. Things have recently started to change, with many countries, including Cyprus, Malta and the United Kingdom starting to overturn their ban on the use of cannabis in medicine.[9–12]

Despite the recent legalisation of marijuana, a recent survey has showed that many experts in the field of PD still have a lack of knowledge in how cannabis can be used in the treatment of PD, probably because of the lack of high-quality data and education about the effects of cannabis on this disorder.[13] The aim of this review is to bring the latest information about cannabis use in the treatment of Parkinson's disease in one document to facilitate the acquirement of knowledge about this subject.

Current Modalities of Treatment of PD and their Caveats

No cure for PD has yet been found, therefore all current treatments are strictly symptomatic; they can neither halt nor reverse the progressive nature of this disease. The current drugs marketed for the treatment of PD symptoms work either by increasing the dopamine levels in the brain or by mimicking the effects of dopamine.[7]

Levodopa

The gold-standard treatment for PD is levodopa, a dopamine precursor which it breaks down into dopamine once in the brain. To prevent its breakdown in the periphery, levodopa is co-administered with a DOPA-decarboxylase inhibitor such as carbidopa or benserazide. The use of levodopa is not without its problems; for instance, it is ineffective for the control of non-motor symptoms of PD. Furthermore, 'on-off' and 'end-of-dose' motor fluctuations frequently occur after several years of treatment with this drug.[7] Controversy on whether levodopa is actually toxic to dopaminergic neurons also exists.[14]

COMT Inhibitors

Catechol-O-methyl transferase (COMT) inhibitors such as entacapone are commonly used as adjuncts to co-beneldopa and co-careldopa such as in Stalevo to overcome motor fluctuations.[15]

Common side effects of entacapone include constipation, orthostatic hypotension (which could theoretically increase the risk of fractures from falling) and confusion. Caution must be taken when entacapone is prescribed to individuals with a history of ischaemic heart disease as this drug is known to increase its risk.[16-17]

Tolcapone, another COMT inhibitor effective in the control of motor fluctuations has been reported to have caused four cases of acute hepatotoxicity resulting in three fatalities. As a result, the use of this drug has been either completely withdrawn or severely restricted in many countries.[18–21]

Dopamine Receptor Agonists

Dopamine receptor agonists (DRAs) are another modality of treatment of PD, whereby they stimulate dopamine receptors by mimicking the dopamine molecule. DRAs can be used as adjuncts to levodopa in the advanced stages of PD or as monotherapy during the initial stages of PD to delay the need for levodopa.[7,22]

DRAs can be divided into two main classes; the ergot derivatives such as pergolide, and the non-ergot derivatives such as pramipexole and ropinirole. The latter are preferred over the former because of the risks of retroperitoneal fibrosis, pleuropulmonary fibrosis and fibrotic heart valvular disease associated with their use.[23-24]

The non-ergot derivates are not without their problems as they are associated with compulsive gambling and hypersexual behaviour.[25]

MAO-B Inhibitors

Monoamine oxidase B (MAO-B) inhibitors such as rasagiline inhibit the metabolism of dopamine such that they enhance the effect of levodopa if they are used in conjunction.[7]

Patients on MOA-B inhibitors must be advised to limit their intake of tyramine as a potentially lethal hypertensive crisis can result when large amounts of this amino acid are consumed.[26]

Amantadine

Amantadine, an aminoadamantane originally used as an antiviral agent, is a non-competitive NMDA receptor antagonist which is now being used to treat early PD symptoms, and increasingly more as a treatment for dyskinesias caused by levodopa in those with

advanced PD.[27–29] However, several clinical studies have shown that treating PD patients with amantadine prior to initiating levodopa treatment is ineffective in delaying or reducing the onset of levodopa-induced dyskinesias.[30,31]

Some clinical trials have also shown a relation between amantadine treatment and a reduction in the previously mentioned 'impulse control disorders' found in PD patients.[32,33] The author of one of these studies hypothesise that this reduction could be due to the anti-glutamatergic properties of amantadine.[33] While the results from these studies are encouraging, further clinical trials, which are larger in size, are needed to shed more light on the possible use of this drug as a treatment modality for impulse control disorders in PD patients.

Unfortunately, both the use and the withdrawal of amantadine are marred by a range of adverse effects, which might make the clinician cautious about using this drug as the risks might easily outweigh any benefit that treatment with this drug may convey.

Side effects of amantadine treatment on the vision and eyes have been reported widely, including oculogyric crises, visual loss, mydriasis, corneal oedema and hallucinations amongst others.[34–36]

Some papers also report some interesting cases where the use or withdrawal of amantadine in PD was associated with adverse effects not usually attributed to it, such as the development of patulous Eustachian tubes (PET),[37] dropped head syndrome,[38] severe psychosis,[39] right ventricular outflow tract tachycardia[40] and syndrome of inappropriate antidiuretic hormone secretion.[41]

Anticholinergics

Anticholinergic agents, in the form of alkaloids derived from the Solanaceae family,[42] are the oldest medication in use for the treatment of PD after their antiparkinsonian effects were first described by Leopold Ordenstein in 1868.[43] Since then, anticholinergic agents remained the only pharmacological treatment option for PD for almost a century until the introduction of levodopa and amantadine in the 1960's.[44]

Although the use of anticholinergics for the treatment of motor symptoms in PD has declined due to the increasing use of levodopa and other drugs,[45] they are still the first-line treatment for bladder dysfunction, the commonest autonomic disorder in PD which also tends to be non-responsive to levodopa.[46-47]

As anticholinergic drugs are often prescribed for the treatment of sialorrhea in patients with cerebral palsy, sublingual atropine has been investigated for potential use in treating sialorrhea in PD patients.[48,49] While sublingual atropine did result in an amelioration in sialorrhea, 3 out of the 7 study subjects experienced adverse effects, mainly of cognitive nature.[49] Due to such results, the use of atropine in the management of sialorrhea in PD patients is only recommended by the NICE guidelines if the "risk of cognitive adverse effects is thought to be minimal".[50-51]

In 2018, a case report was published where a 75-year-old gentleman with a known case of PD developed psychosis and delirium following the commencement of sublingual atropine.[50]

Indeed, although studies have shown anticholinergic agents to be more effective in treating motor symptoms in PD than placebo, their adverse effects, especially on cognitive function in PD patients - who due to the cholinergic dysfunction associated with their disease makes them more prone to anticholinergic effects – greatly limit their use.[17,52]

Deep Brain Stimulation

Deep brain stimulation of the subthalamic nucleus is the preferred surgical treatment for advanced PD, especially in those who respond to pharmacological treatment but have motor fluctuations. While in general, the quality of life of the patients undergoing this surgery increases as the symptoms are improved, side effects and complications do exist. Pneumonia (amongst other infections) and intracranial haemorrhage are the commonest complications associated with the surgical procedure itself, albeit the frequency of such complications is relatively low, occurring at a rate of 0.6% and 2.2%, respectively. Furthermore, the mortality rate and the rate of permanent surgical morbidity were found to be 0.4% and 1%, respectively.[53] Adverse effects to the stimulation are possible but are often reversible and can be alleviated by adjusting the kind of stimulation.[54] In most cases, the incidence of complications can be reduced or prevented by carefully selecting the patients for surgery which are the most likely to benefit from such a procedure while having a low risk profile vis-à-vis surgical complications.[55]

Cannabis ... The Future of PD Treatment?

A 2017 report on the health benefits of cannabis "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research" carried out by the "National Academies of Sciences, Engineering and Medicine" concluded that while there is conclusive or substantial evidence that cannabis/cannabinoids are effective for the treatment of chronic pain in adults and as antiemetics to name a few, there is insufficient evidence to prove or disclaim the effectiveness of cannabis or cannabinoids in the treatment of PD.[56] In this paper, we will be reviewing the current state of evidence that exists for and against the use of this drug for the treatment of PD and what led the "National Academies of Science, Engineering and Medicine" to come to this conclusion.

Cannabis contains over 100 different phytocannabinoids – compounds occuring in plants that interact the endocannabinoid system. The main phytocannabinoids responsible for the therapeutic effects of cannabis are Δ^9-tetrahydrocannabidiol (THC) which is the primary psychoactive component of cannabis and cannabidiol (CBD), a non-psychoactive compound that has been shown to possess anti-inflammatory, anti-psychotic, neuroprotective and analgesic properties.[57,58] These compounds interact with the endocannabinoid system – a system composed of the cannabinoid type 1 and 2 receptors (CB_1 and CB_2 respectively), the endogenous ligands that bind to these receptors, known as endocannabinoids, and the proteins that are responsible for the syntheses, reuptake and degradation of these ligands.[59]

While CB_1 receptors are expressed both in the central nervous system and the periphery, they are most abundant in the former, especially in

the structures that are related to movement i.e. basal ganglia, prefrontal cortex, hippocampus and cerebellum.[60] Indeed, CB1 receptors are the most widely distributed G-protein-coupled receptor in the CNS.[61]

Several studies have reported an upregulation of CB_1 receptors in the basal ganglia as a response to the depletion in dopamine typically seen in PD; highlighting the possibility of employing cannabinoids as therapeutic agents in the treatment of the motor symptoms associated with PD.[62]

Basal ganglia are the subcortical nuclei which, in connection with the brainstem, thalamus and motor cortex, they modulate voluntary motor movements through two pathways: (1) the direct pathway which is mediated by D1 receptors and promotes movement, and (2) the indirect pathway which is mediated by D2 receptors which inhibits movement.[63–65] Normally, these two pathways are in balance with each other; this balance is lost in PD as the depletion of dopamine in the striatum causes inhibition of the direct pathway and activation of the indirect pathway. This loss in balance results in an over-inhibition of the thalamus leading to an excessive inhibition of motor symptoms which in turn results in parkinsonian motor features.[63–66]

Via the CB_1 receptors located at the level of the presynaptic region of the glutamatergic terminal, cannabinoids can reduce the glutamatergic overactivity that results from the change in the balance between the direct and indirect pathways.[67]

CB2 receptors levels are usually very low in the healthy brain but increase in cases of injury or inflammation. They occur mostly in the periphery such as in the thymus and spleen.[67–69]

Pertwee argues that CBD antagonises the action of CB_1 and CB_2 receptor agonists, acting as an inverse agonist of these receptors [70]. Some of the latest studies have suggested that CBD acts as a non-competitive negative allosteric modulator of both CB_1 and CB_2 receptors.[71,72] Some of the effects of CBD seem to result from the increase in the anandamide levels induced by the aforementioned cannabinoid as it inhibits its enzymatic hydrolysis and uptake.[73]

Mitochondrial dysfunctions, such as those due to the alterations in mitochondrial DNA, bioenergetic defects, reactive oxygen species generation and dysfunctional calcium homeostasis have all been associated with the mechanisms underlying the neuronal death in PD.[74] Interestingly, studies have found that CBD acts on the mitochondria by increasing the activity of the mitochondrial complexes I, II, II-III and IV in rats. CBD has also been reported to reverse the epigenetic modifications of mitochondrial DNA induced by iron overload in rats. Iron overload induces pathological changes that resemble neurodegenerative disorders like PD.[75,76]

As already mentioned, levodopa, while effective in treating the motor symptoms of PD, it is ineffective in the treatment of non-motor symptoms, which can have as much of devastating effects on the patient as much as the motor symptoms. A 2009 study found that treating PD patients with CBD for 4 weeks resulted in a decrease in the psychotic symptoms without affecting the motor function or causing adverse effects.[77]

A randomised, double-blind placebo-controlled, crossover study involving five participants showed a significant reduction in levodopa-induced dyskinesia and in the symptoms associated with rapid eye movement sleep behaviour disorder in those

treated with nabilone (a synthetic cannabinoid similar to THC) when compared with those taking the placebo.[78]

Another 2014 study by Chagas *et al.* also that treating PD patients with CBD results in an improvement in their quality of life, even if their symptoms are not ameliorated. This finding has been suggested that it might be due to the anxiolytic, antipsychotic and antidepressant effects that they exert.[79] The same finding has been reported in another study in which participants treated with 75 mg or 300 mg daily doses of CBD failed to report any change in PD symptoms as assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) but they did report an improvement in the quality of life as assessed using the Parkinson's Disease Questionnaire (PDQ-39).[80]

In a 2015 study based on self-administered surveys found that more than 70% of PD patients that made use of cannabis that were surveyed reported improvement in mood and sleep.[81]

Although these studies herald an opportunity for the treatment of PD with levodopa in conjunction with CBD to control both the motor and non-motor symptoms, they were unfortunately underpowered and therefore the samples are not representative of the general PD population. Furthermore, the study carried out by Lotan *et al.* was open-label, increasing the risk of bias in the results obtained one must therefore be cautious when analysing such results.

Other studies have failed to show optimistic results regarding the use of cannabis in treating PD. For instance, in studies carried out by Carroll *et al.* and Mesnage *et al.* involving seventeen and eight participants respectively failed to show any significant improvement in motor or non-motor symptoms when treated with Cannador and Rimonabant, respectively.[82-83]

While back in 1999, the Institute of Medicine declared the short-term use of cannabinoids to be safe, little has been done to determine the safety of cannabinoids in the long-term use.[84] If the cannabinoids are administered by smoking the cannabis plant, certain side effects related to the act of smoking can be expected, such as chronic bronchitis or other respiratory diseases.[85]

While many studies have shown that CBD has an antipsychotic effect,[84] Udow *et al.* argue that since patients with PD have an inherent risk of psychosis, they are more likely of developing psychosis if they are subjected to cannabinoids. Udow *et al.* presented a case study where a 70-year old woman with a 12-year history of PD developed an exacerbation of psychosis following the ingestion of nabilone.[86]

This difference in the literature is due to the generalisation made by Udow *et al.* where they attribute the occurrence of psychosis with cannabinoids in general. In their same paper, they specify that the 70-year old lady had exacerbation following the ingestion of nabilone – a synthetic chemical that mimics THC, the psychoactive agent in cannabis which studies have found to cause psychotic symptoms. On the other hand, the antipsychotic effect has only been reported in CBD, a non-psychoactive agent. Hence, one must not make the mistake of generalising all the cannabinoids together, as there can be major differences pharmacological action between one cannabidiol and another.

Conclusion

In agreement with the 2017 report by the "National Academies of Science, Engineering and Medicine" the current evidence in favour of cannabinoids for the treatment of PD is of low quality and inconclusive. Further studies and clinical trials involving larger sample sizes and better methods are needed to reach a conclusion on whether cannabidiols are the future of PD treatment or not.

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CASE REPORT

Multifocal pyomyositis following normal vaginal delivery

A case based report

Charmaine Lia, Chris Cremona, Ryan Giordimaina, John Thake, Charles Malia Azzopardi

Here we present a rare case of a 38-year-old Caucasian primigravida with persistent pelvic pain postpartum after normal vaginal delivery. MR imaging was unremarkable and after being managed conservatively she was discharged on the fourth post-partum day. However, she represented two weeks later at the A&E department with features of sepsis, requiring an admission at the local intensive care unit.

Repeat MR imaging showed multifocal pyomyositis affecting the right lower psoas and ipsilateral iliacus muscle, right multifidus and erector spinae musculature, ipsilateral piriformis and the gluteus maximus muscle. This was associated with septic arthritis of the sacroiliac joints. The patient was stabilised and started on potent broad-spectrum antibiotics. An incision and drainage was performed with pus cultures being positive for *Escherichia coli* and *Streptococcus gallolyticus.* Despite treatment, patient was still febrile and subsequent MR imaging showed persistent abscess formation in the iliacus together with septic arthritis. A CT guided drain insertion to which she responded well. After this 16-day hospital stay the patient was discharged in a stable general condition, being able to maintain all her previous activities of daily living. She was followed up regularly at orthopedic outpatients.

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Introduction

Iliopsoas abscess formation is a rare phenomenon with an incidence of 0.4 in 100,000 per year in the UK (Shields et al, 2012) being three times commoner in males (Agrawal et al., 2002). Patients who are immunosuppressed, diabetic or suffer from renal failure are at increased risk. Psoas abscesses can be either primary through hematogenous spread or secondary through infection or inflammation in the surrounding areas.

Case Report

A 38-year-old previously healthy caucasian primagravida reported persistent pelvic pain postpartum after normal vaginal delivery. MR imaging of her pelvis was unremarkable. She was discharged home on NSAIDs and a pelvic support, however two weeks post discharge the patient was readmitted in view of a three-day history of deterioration in general condition – febrile with a fever of 39 degrees Celsius & exhibiting features of sespsis, requiring admission to intensive care. A full septic screen was performed together with a repeat MRI of the pelvis. The latter showed multifocal pyomyositis affecting the right lower psoas and ipsilateral iliacus muscle bellies, right multifidus and erector spinae musculature, ipsilateral piriformis and the gluteus maximus muscle bellies (Figures 1,2,3.).

Figure 1 Cross-sectional T1 weighted MR imaging of patient's pelvis with multifocal pyomyositis and noticeable involvement and oedeomatous changes at right sacro-iliac joint

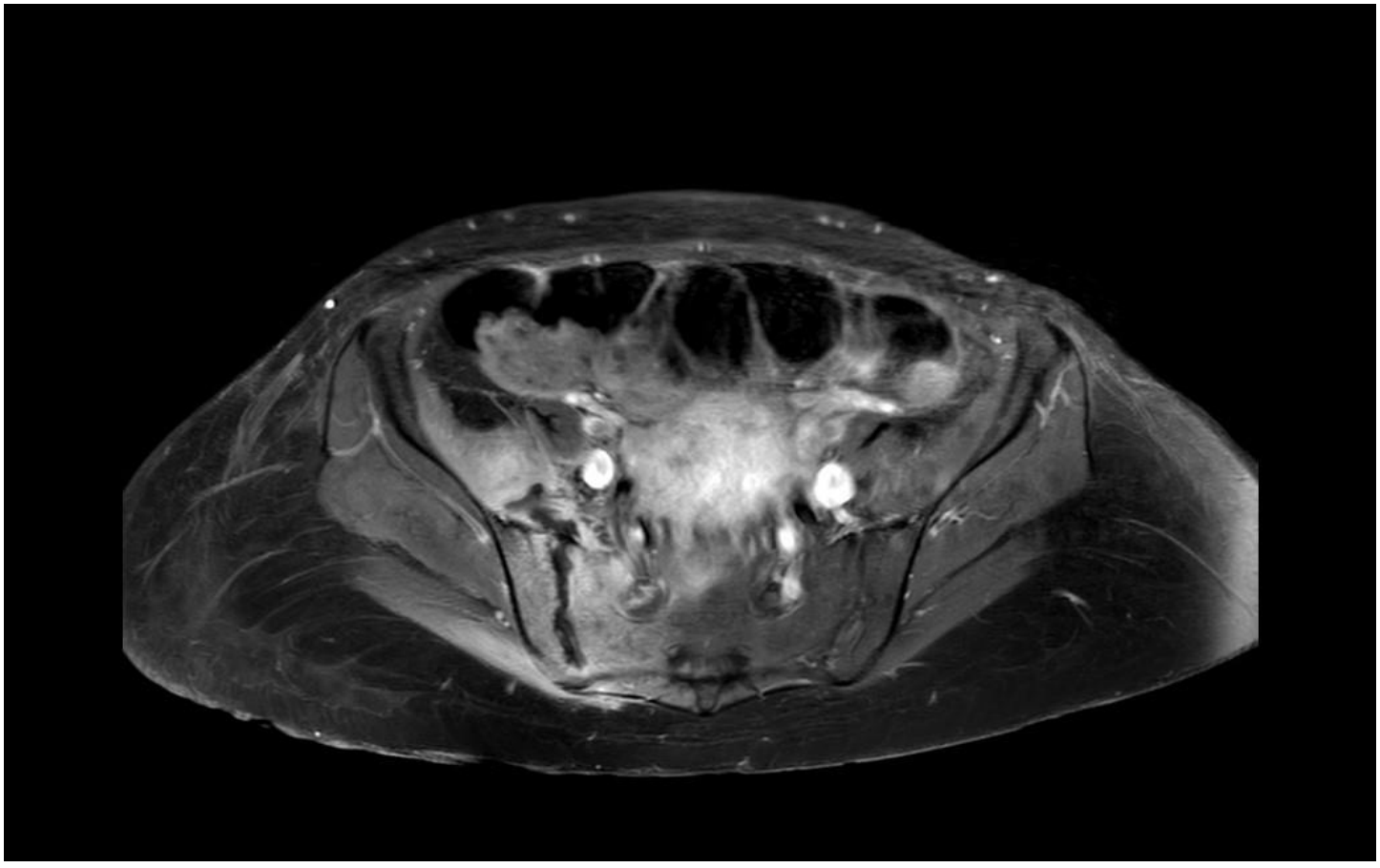


Figure 2 Cross-sectional T1 weighted MR imaging showing an abscess underneath the iliacus muscle in frontal to the SI joint

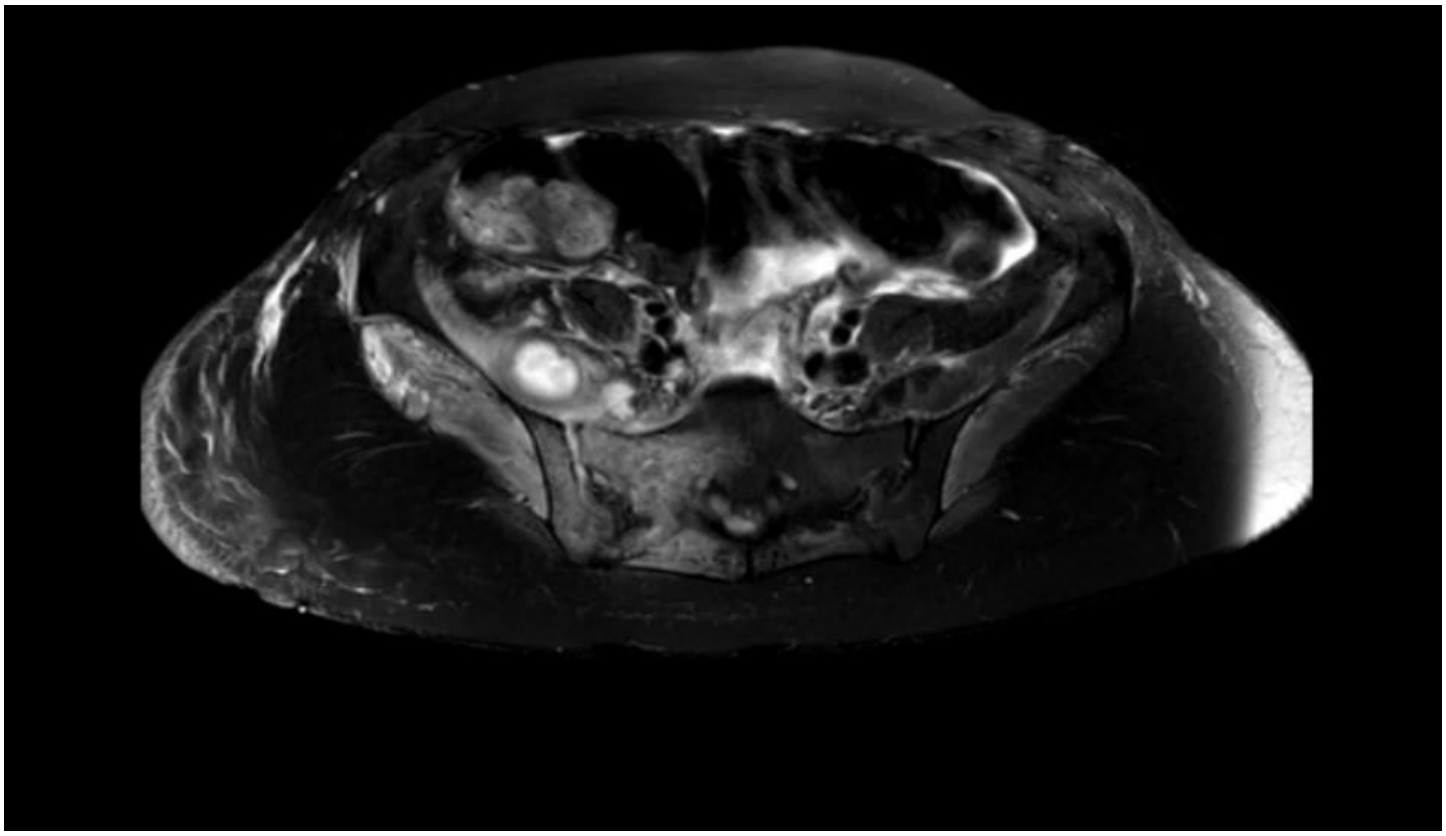


Figure 3 Cross-sectional T1 weighted MR imaging showing the abscess tracking over the sacroiliac joint to the muscles of the back

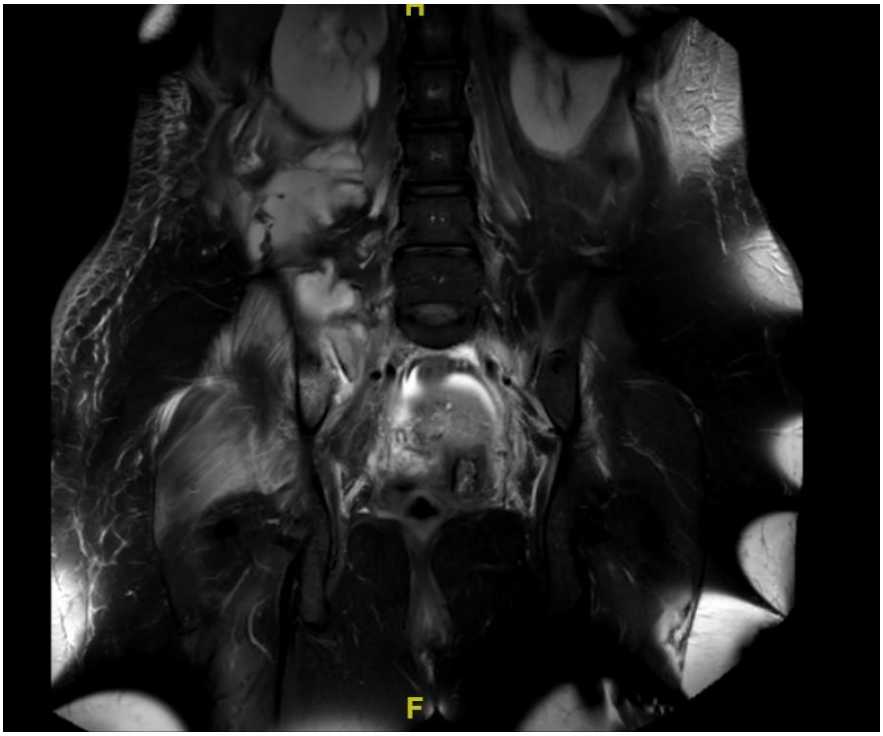
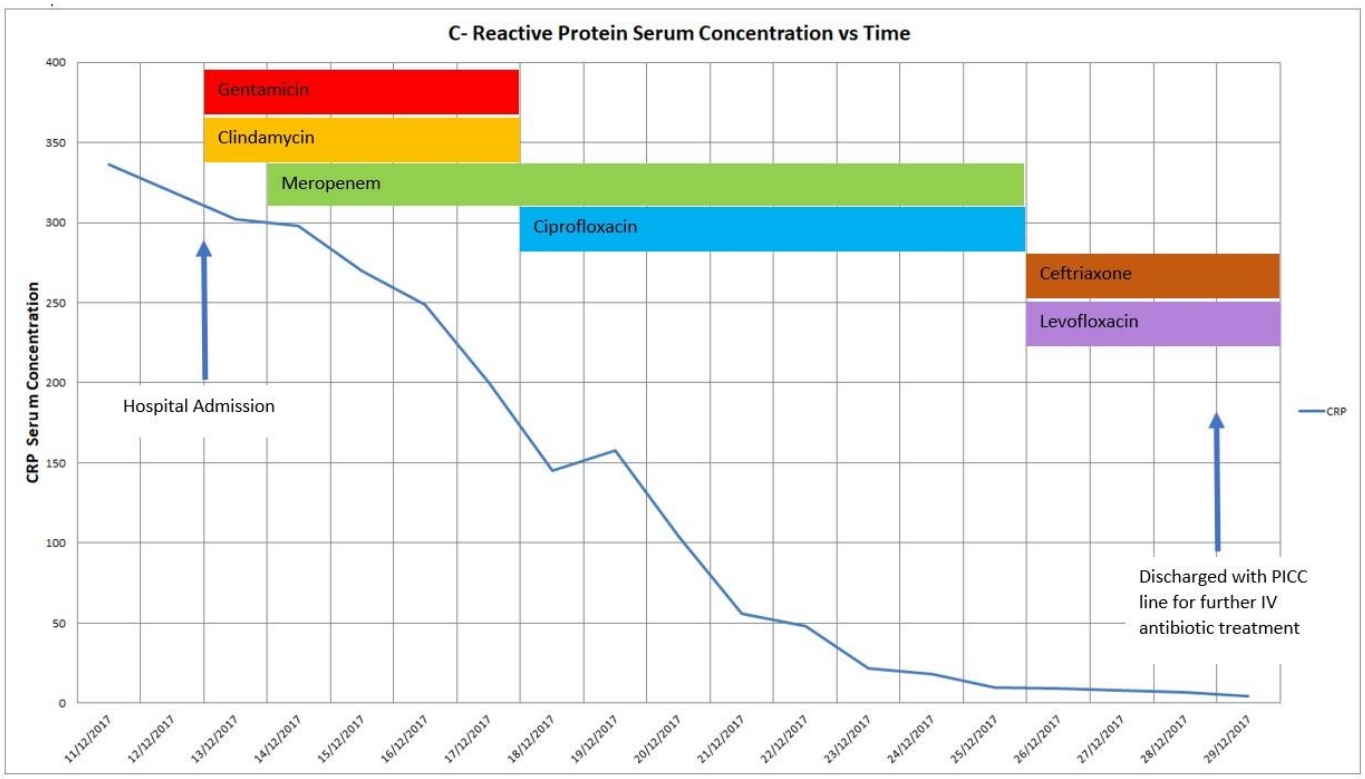


Figure 4 Graph showing relation between Time (x-axis) and C-reactive protein serum levels (Y-axis). Superimposed by the date of onset and termination of Intravenous antibiotics



This was associated with septic arthritis of the sacroiliac joints. The patient was treated with Gentamicin, Meropenem and Clindamycin. One large collection extending to the gluteal region was amenable to surgical drainage and cultures grew positive for *Escherichia coli* and *Streptococcus gallolyticus*. A further intrapelvic collection was drained by a CT guided aspiration and a drain was left in situ. Antibiotics were switched to Levofloxacin and Ceftriaxone and were given for another 3 weeks post-discharge via a PICC line (Figure 4). The patient was deemed fit for discharge after 16 days of intravenous antibiotics. Rehabilitation at the physiotherapy department was organised and she was followed up regularly at outpatients by the obstetricians, orthopaedic surgeons and the infectious diseases team.

Background

Pyomyositis is a purulent infection affecting originally skeletal muscle arising via hematological spread, usually associated with abscess mass formation. This infection may occur in children aged two to five years, but more commonly in adults, with males being predominantly affected. There is a tendency of increased incidence in immunocompromised individuals such as those suffering from Human Immunodeficiency Virus, diabetes mellitus, malignancy and individuals being treated with immunosuppressants. Recent literature notes an increased preponderance of cases in individuals residing in temperate and tropical climates. Other predisposing factors include trauma, concurrent infection and malnutrition. In the cases reported in literature common factor was muscle injury

due to exercise or trauma. As yet the mechanism of the pathophysiology of pyomyositis is poorly understood.

Multiple cased based presentations repeatedly noted pyomyositis following vigorous exercise. They postulated that this may be due to increased muscle perfusion due to trauma providing additional iron to the muscle bed favoring bacterial growth. An alternative hypothesis could be related to hematoma formation.

The first mention of pyomyositis occurring secondary to vaginal delivery was first noted in 2011 by Gaughan et al., whereby they noted that the patient's vaginal delivery was a causative factor that instigated the process of bacteremia.

Discussion

Anatomy

The iliopsoas compartment is extraperitoneal and contains the psoas muscle and the iliacus. The psoas muscle extends from the lateral margin of the 12th thoracic vertebra to the 5th lumbar vertebra and inserts at the lesser trochanter of the femur. Its muscle fibers blend with the iliacus and together form the major flexors of the hip. It is innervated by L2, L3 & L4 nerve roots. It has a large blood supply and is in close proximity to other organs such as sigmoid colon, appendix, jejenum, abdominal aorta, ureters, kidneys, pancreas, spine and iliac lymph nodes. This makes it more prone to abscess formation which can be either primary or secondary (Mallick et al., 2004).

Aetiology

An iliopsoas abscess refers to a collection of pus in the iliopsoas compartment. This was first described by Mynter in 1881. Iliopsoas abscess can be primary following haematogenous spread of infection (Walsh et al., 1992). This is more common in young males, diabetics, intravenous drug users, immunocompromised or malnourished individuals, or those who have renal failure or hematological malignancies. Secondary psoas abscess results from direct spread of infection from the adjacent organs such as diverticulitis, appendicitis, urinary tract infection, septic arthritis, vertebral osteomyelitis or infected abdominal aortic aneurysm (Ricci et al., 1986).

In a case series Ricci et al. (1986), noted worldwide difference in the aetiology of iliopsoas abscesses. Primary iliopsoas abscess is more common in Asia and Africa while secondary abscess formation is more common in Europe and North America (Ricci et al., 1986).

Despite the patient being of Maltese origin, her iliopsoas abscess appeared to be primary. We postulate that in this case observed locally, the muscle trauma and inflammation related to the normal vaginal delivery might have increased blood perfusion with iron deposits feeding bacterial growth. Muscular hematoma formation with superseding inflammation may also have played a role in this case.

Microbiology

Various pathogens can lead to the formation of iliopsoas abscess with *Staphylococcus aureus* being most common in primary cases. *Streptococcus and Eschericae coli* are more common in secondary abscess formation (Agrawal et al., 2002). Some cases also reported the presence of *Proteus* (Gruenwald et al., 1992), *Bacteriodes* (Melissas et al., 2002), *Clostridium* (Wells et al., 1985), *Yersinia enterocolitica* (Kahn et el., 1984), *Klebsiella* (Change et al., 2001) and *Mycobacterium kanasii* (Simms & Musher, 1998). In the past iliopsoas abscess was a known complication of

spinal tuberculosis also known as Pott's syndrome (Mallick et al., 2004).

Incidence

Iliopsoas abscess formation is a rare phenomenon with an incidence of 0.4 in 100,000. It is three times more common in males. Due to its insidious presentation, iliopsoas abscesses lead to increased morbidity and mortality. Mortality complicates 2.4% of primary and 18.9% of secondary abscesses (Melissas et al.,2002). Mortality can be as high as 100% if the abscess is not diagnosed and drained on time (Thongngarm & McMurray, 2001).

Clinical Features

The clinical presentation of iliopsoas abscess includes a triad of fever, back pain and limp. However, this presents in only 30% of cases. Back pain is the most commonly encountered symptom in these cases with a mean duration of 10 days prior to presentation (Chern et al., 1997). Other symptoms include flank or abdominal pain, malaise, weight loss and lump in the groin. The presentation of these abscesses is usually vague and non-specific making them more difficult to diagnose. Thus, they can be easily confused with other conditions such as arthritis, vertebral osteomyelitis, lumbar strain, femoral hernia, tumour or inguinal lymphadenopathy (Bar-Dayan et al., 1997).

Investigations

Blood investigations are non-specific for iliopsoas abscess. Routine CBC, CRP and ESR are indicated in cases of sepsis as they can help to assess response to treatment. Blood cultures and urinalysis are also important to identify the source of infection and causative micro-organism. Blood cultures are positive in 50% of cases. Leucocytosis is the most common feature. However, anaemia and pyuria can also be present (Riyad et al., 2003).

Imaging includes ultrasonography. However, this is highly operator dependent and is diagnostic in only 60% of cases (Isdale et al., 1994). The gold standard investigation is a IV contrast-enhanced spiral CT scan with 90% sensitivity. Magnetic resonance imaging is occasionally preferred as it can help to discriminate between soft tissues and enhances the abscess walls without using contrast. The ultimate diagnosis is achieved by CT guided percutaneous drainage and fluid culture (Perez-Fernandez et al., 2006).

Management

The management of iliopsoas abscess requires a multidisciplinary approach from orthopaedic surgeons, nursing staff, microbiologists, radiologists and physiotherapists. The use of empirical broad-spectrum antibiotics is essential to prevent further dissemination of the infection. This would need to be adjusted according to the pathogen and sensitivities obtained through culture of samples. These should be continued for at least two weeks after drainage. Drainage of the abscess is the ultimate treatment for these cases. It can be done surgically through incision and drainage or CT-guided percutaneous drainage (PCD). The latter is the gold standard especially in primary abscess as it is less invasive (Dinc et al., 1996). However, surgical drainage can be used if there is any contraindication to PCD or an abdominal pathology is present which also requires intervention. Thus, surgical intervention is more commonly used in secondary abscess formation (Procaccino et el., 1991).

Complications

If not treated iliopsoas abscess can lead to sepsis, disseminated intravascular coagulation

and death. It can also lead to long term disability including femoral nerve damage, hydro nephrosis secondary to compression on the ureters, deep vein thrombosis affecting mainly the iliac veins (Simms et al., 1998) and septic arthritis with hip joint damage as the infection tracks down along the iliopsoas bursa which connects with the hip joint in 15% of cases (Arai et el., 1999).

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CASE REPORT

The longest ocular axial length ever recorded?

James Vassallo, Thomas Fenech

This is a brief report of a case of possibly the longest ocular axial length documented in the literature. Contact a-scan ultrasound gave a mean AL of 38.34mm. To the best of our knowledge, this is the longest reported AL of a human eye. 15mls of silicone oil were needed to fill the vitreous cavity during surgery for retinal detachment.

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Introduction

We would like to report a case which may represent the longest axial length (AL) measured in a human eye.[1]

Materials and Method

A case description is provided.

Results

A 47-year-old phakic Maltese Caucasian patient presented with a recurrent rhegmatogenous retinal detachment. This happened two years after removal of a scleral buckling explant which had been in situ for 25 years and had to be removed due to infection. There was very severe posterior chorioretinal atrophy secondary to degenerative myopia (Figure 1). When he presented the retinal detachment, the visual acuity was hand motion, but the posterior extension of subretinal fluid was limited by the posterior atrophy. The very poor visual acuity was thus likely attributable to the state of the macula.

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There was no known history of childhood glaucoma and no systemic disease which was associated with axial myopia, but the patient was very tall. The other eye was non-seeing due to untreated esotropia since childhood. Three-port 23-gauge pars plana vitrectomy was deemed necessary, and pre-operative biometry was performed. The AL was unmeasurable with an optical device (Lenstar LS900, Haag-Streit AG, Koeniz, Switzerland). Contact a-scan ultrasound (Quantel Axis-II, Quantel Medical, USA) gave a mean AL of 38.34mm; the other eye had a similar length (Figure 2). If one outlying AL measurement (#2) of the index eye is excluded, the mean AL would be 38.42+/-0.20mm. During the procedure (TF), excessive scleral indentation was required to reach the posterior pole during aspiration of fluid with a soft-tipped cannula from over the disc on fluid-air exchange; surgical maneuvers were difficult in such an abnormally large eye. With a flat retina and the crystalline lens in situ, 15mls of silicone oil (Siluron 1000; Geuder AG, Heidelberg, Germany) were needed to fill the vitreous cavity at the end of the operation to serve as persistent tamponade. Oil removal (JV) was done 13 months later to optimize his refractive status.

Figure 1 Colour photo of the postoperative appearance of the posterior pole of the right eye with the crystalline lens and silicone oil in situ. Severe chorioretinal atrophy of the macula is prominent.

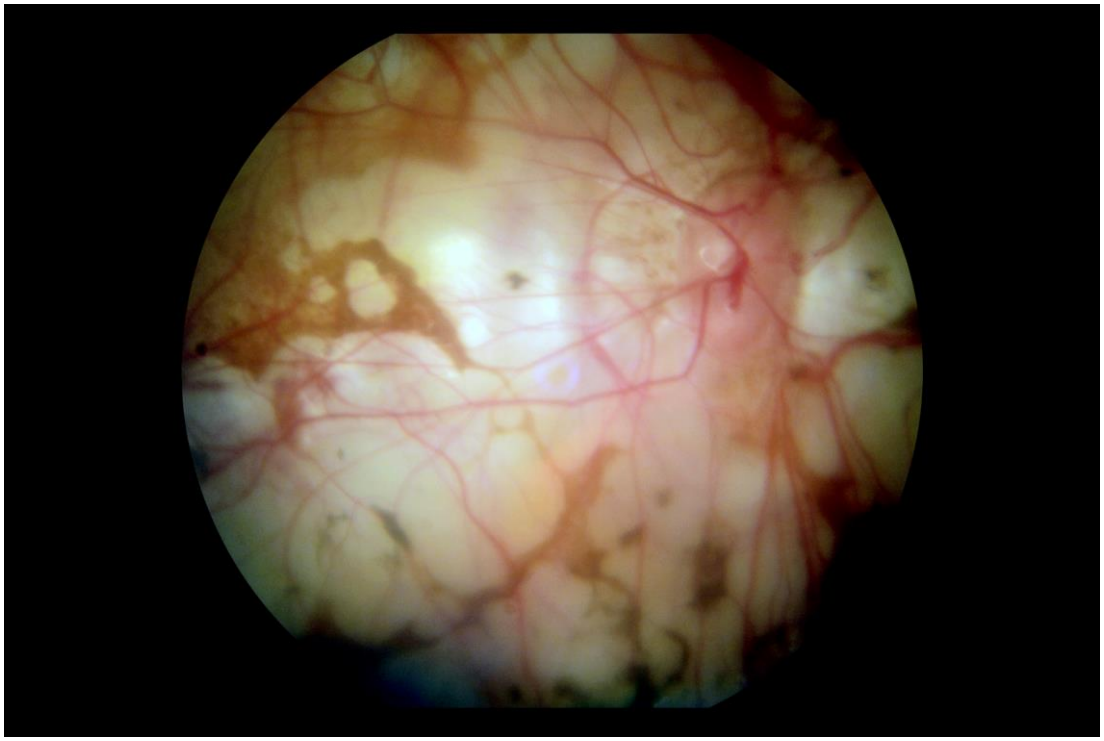
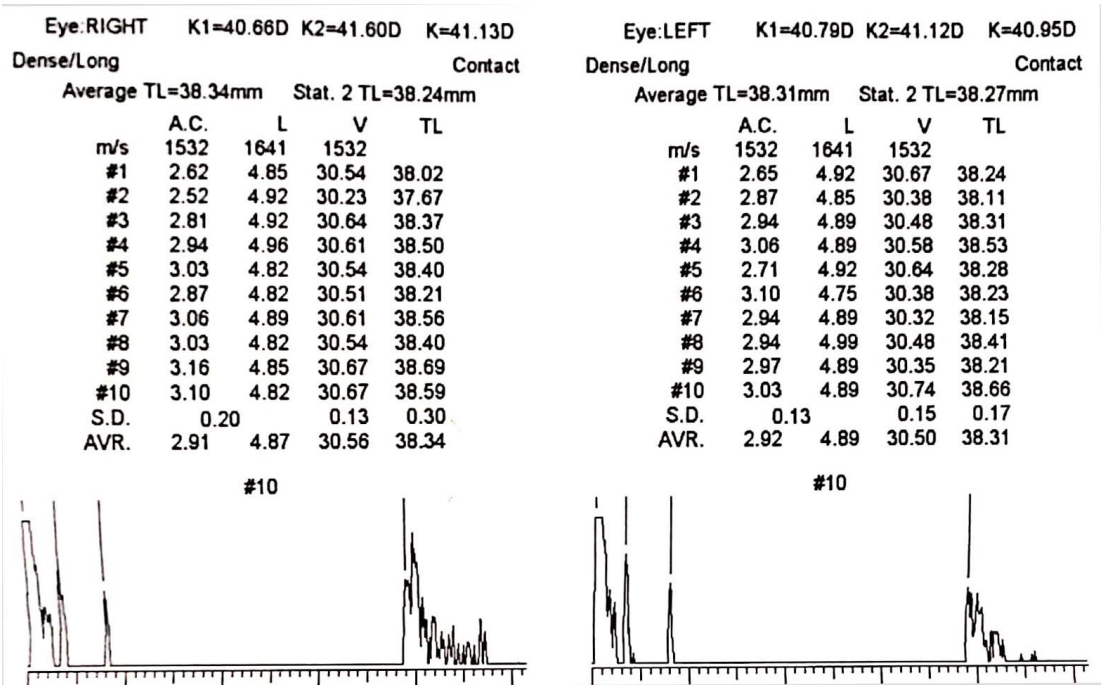


Figure 2 Axial length measurements of both eyes obtained with contact a-scan ultrasound.



Discussion

It may be argued that the longstanding scleral buckle may have contributed to persistent axial elongation; however, this patient's ocular axial length was equally exceptional in the fellow eye which did not have a history of scleral buckling. This case illustrates some of the unique challenges presented by cases of extreme myopia, which may become a more common occurrence in the future.[2] Design of surgical instruments should cater for such long eyes with telescoping probes or extensions.

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