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EDITORIAL

Editorial

Early antibiotic exposure linked to childhood obesity

Simon Attard Montalto

Childhood obesity is a predisposing factor for adult obesity and both are major health problems in most countries, including Malta.[1-3] Moreover, the widespread and, often inappropriate, use of antibiotics has also long been cited as another health problem in Malta,[4-5] usually in association with the increasing risk of antibiotic-resistance and the potential emergence of 'superbugs'. Yet both these problems - obesity and the overuse of antibiotics – are interlinked, whereby early exposure to antibiotics increases the risk of those children becoming overweight or obese. This association, although previously documented in various large studies overseas,[6] is under-appreciated locally. Yet the same association was reported in a smaller local study on 3-7 year olds in 2020, by Dr Marwa Khaled Grada at the University of Malta.[7] Dr Grada showed a significant association between antibiotic use and increased childhood BMI (*p=0.001*), and, in this study, the use of antibiotics during infancy was found to be the best predictor of BMI.[7]

The pathophysiological link between early antibiotic exposure and obesity occurs through a mechanism arising from the alteration in gut microbiota,[8-10] and subsequent alteration of the digestive mechanisms of the bowel with, for example, an increase in the absorption of short-chain fatty acids.[11] These alterations, if enacted during infancy, are then imprinted within the gastrointestinal working milieu and established for the remainder of childhood. In effect, children whose bowel microflora is repeatedly 'altered' by antibiotic exposure, are significantly more likely to change their bowel function to one that is obesogenic.

Although there is absolutely no doubt whatsoever that, when used appropriately, antibiotics save lives, there is equally no doubt that they are harmful if used inappropriately.

Cover Picture:

'Fear in Ukraine'

Acrylic on Canvas

By Stephanie Mizzi

Stephanie is a freelance writer and professional photograher. After her mother's sudden passing in 2018 she felt the urge to try her hand at painting. It helped her get through the grief and pain following her demise. She is also a qualified Personal Trainer and Spinning Instructor. In April 2022 she founded Artists for Ukraine, 20,000 Euros were collected in aid of Ukrainian Refugees in Malta. Following its success, she is now working on another project called Artists Inc. which will unite established artists along with new talent both to exhibit their work for charity and to promote new talent. She is also mother to 15-year-old Matthew.

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Malta, like many Mediterranean (and other) countries has a society *and* doctor-driven penchant for antibiotic over-use, mostly in the context of viral infections and as spurious 'prophylaxis' without any evidence-base.[5,12,13] In 2022 in Malta, antibiotic prescriptions for children with simple colds/snuffles, viral infections, minor ailments, and to healthy individuals without a fever and *"just in case"* are routine and the *modus operandi* of many practitioners. Sadly, by encouraging obesity, this over-reliant 'blanket' practice is creating more harm than is appreciated and harm that goes well beyond the encouragement of antibiotic resistance alone. Improved prescribing and a reduction in the injudicious use of antibiotics to small children will help reduce obesity later in life, presently the greatest nutritional and one of the greatest health care problems in the 'modern' era. Indeed, any measure taken to reduce obesity can only be welcome.

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ORIGINAL ARTICLE

Influence of knee osteoarthritis on physical function, quality of life and pain in elderly people

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Objective

Osteoarthritis is the most common age-related joint disease, affecting more than 80% of the elderly, and it is one of the main reasons for outpatient visits elderly in the hospital. Data about physical function and its correlation to quality of life (QoL) and some clinical variables in knee osteoarthritis (KOA) in Iranian elderly is limited.

Method

A cross-sectional study composed of 332 patients with KOA was conducted. KOA were diagnosed based on the clinical criteria of the American College of Rheumatology. Demographic and clinical variables were recorded. QoL, disability, and pain were assessed using the SF-36, the Western Ontario and McMaster (WOMAC) index, and VAS scale. For statistical analysis we used X^2, Independent t-test and Pearson's correlation.

Results

The mean age of the patients was 68.35±5.51 years, of which 213 (64.2%) were women. QoL domains were significantly associated with disability in all three domains of pain, stiffness and function (p<0.001). A significant negative correlation was also found between the QoL domains and the VAS pain (p<0.001). QoL was lower and the disability and pain intensity was higher in women than in men. A correlation was shown between BMI, comorbidity and polypharmacy with some QoL domains. Age, sedentary leisure, and duration of KOA symptoms were correlated with all eight domains of QoL.

Conclusion

Individual differences in predictors of QoL and physical function suggest KOA management strategies should be individualized based on patient characteristics.

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Introduction

Knee osteoarthritis (KOA) is a progressive disease with subsequent limitations in range of motion and loss of the ability to walk.[1] As the disease progresses, patients' functional ability deteriorates. Therefore, due to the limited range of joint and pain, the daily activities of these people are endangered, which causes damage to work, leisure, and social relationships, and as a result, a significant reduction in their quality of life (QoL) is created.[2-3] QoL is an important consequence of health status and evaluating treatment measures.[4]

The prevalence of symptomatic KOA is reported to be 13.1% -71.1% in various Asian countries.[4] A few studies in Iran found that the prevalence of KOA in the general population ranged from15.5 to 47.7 by age.[5] Many studies have been done on pain and physical disability in osteoarthritis[6-7] and there is a great interest in measuring the impact of such diseases on QoL, mainly KOA in the elderly.[8-10] To our knowledge, this is the first study to assess health-related QoL in the elderly with KOA in Iran.

This study aimed to evaluate QoL in elderly people with KOA based on gender, as well as to examine the correlation between QoL domains with disability domains and personal data as potential risk factors for KOA.

Materials and Methods

In a cross-sectional study, 332 people aged 60 and over were enrolled from January 2019 to August 2020. The participants were those who had been referred to the physiotherapy clinic of Yahyanejad Hospital affiliated to Babol University of Medical Sciences, Iran, with a previous diagnosis of KOA and complained of unilateral or bilateral knee pain without a history of knee surgery, significant hip or spinal arthritis and a recent serious illness. All participants met the ACR (American College of Rheumatology) clinical classification criteria for KOA, including knee pain with at least three of the following criteria: age> 50 years, morning stiffness < 30 minutes, crepitus on knee motion, bony tenderness, bony enlargement, and no palpable warmth.[11]

Data collection tools included personal and clinical characteristics questionnaire, QoL, disability and Iranian Short-Form McGill Pain Questionnaire (SF-MPQ). The Questionnaires were completed by the researcher with a face-to-face interview on the first day of the patient's visit to the physiotherapy clinic.

Weight was measured by SECA Digital Scale. Height was determined by a stadiometer in standard conditions. Body mass index (BMI) was calculated as weight (in kg) divided by height in meters squared. Age, gender, symptom duration, marital status, comorbidity, polypharmacy, dependence, sedentary leisure, exercise, use of walking aid devices were recorded. Sedentary behavior was measured based on the average time spent sitting or lying down during the day. Independence was defined as a good memory and the ability to do all daily and semi-independent work as a person in need of help with some daily tasks. Comorbidity is determinded as the concurrence of at least 2 chronic diseases and polypharmacy of taking at least 4 drugs prescribed by a doctor per day.

QoL was assessed using the SF-36 generic tool with two general dimensions of physical health and mental health and each with 4 domains; respectively included physical function (PF), role physical (RP), bodily pain (BP), general health (GH), and vitality (VT), social function (SF), role emotional (RE), and mental health (MH). Scores range for every domain was from 0 (worst) to 100 (best) with higher scores indicating better health status.[12]

Self-reported disability was assessed using the WOMAC with 24 items on three domains: pain (5

items), stiffness (2 items), and physical function (17 items) and an overall score of 0-96 in a Likert form. A score of 0 represented the absence of symptoms and 4, the worst symptoms.[13]

The SF-MPQ consists of three parts (13). The first part evaluates 15 descriptive attributes (11 sensory and four affective) according to their intensity on a four-point scale from zero (0) to intense (3). The second part is VAS to describe the severity of pain from painless to worst pain in centimeters on a horizontal line. The third part is the verbal ranking of pain intensity from none (0) to very painful (5). The ethics committee of Babol University of Medical Sciences approved the study (NO.:MUBABOL.REC. 1394.350).

SPSS version 23 software (SPSS Inc., Chicago, IL) was used to analyze the data. Continuous variables were summarized as mean±SD and categorical variables as n (%). Comparison of continuous variables in two groups after checking normal distribution was done using the student t-test. The Chi-square test was designed to analyze categorical data. Pearson correlation coefficients were used to determine the relationships between variables. The level of significance was set at $p<0.05$.

Results

The study sample consisted of 213 elderly women and 119 men. Table 1 shows the personal and clinical characteristics of the participants. 16% of patients reported having KOA in only one knee and 55% in both knees and the rest did not have accurate information. Of the participants, 51.5% did not use any medication for KOA, 22% used one medicine, 16% used two medicines, and 10.5% used three medicines. Assessment of the QoL dimensions showed that the physical health dimension score was far lower than the mental health dimension score. The mean overall WOMAC score was 47.89±15.63 (out of 15-90), indicating moderate disability severity.

Table 2 shows the mean scores of QoL and disability domains, SF-MPQ's principle components and VAS pain by gender. There was a significant statistical difference in six SF-36 domains between male and female patients. The overall physical health dimension score of QoL was significantly worse in women than men ($p<0.01$), while there was no difference in the mental health dimension score between them. WOMAC analysis showed that the pain and physical function domains score were higher in women than men ($p<0.001$); it means more disability in women. Figure 1 also confirms the above finding regarding the severity of pain based on SF-MPQ ($p<0.001$). Men reported more mild and uncomfortable pain, while more severe pain, such as disturbing, terrible and onerous was experienced by women.

Table 3 shows that all domains of QoL had a significant negative correlation with age, symptom duration, sedentary leisure, VAS pain, and WOMAC in all 3 domains pain, stiffness, and physical function ($p<0.001$). This means that with increasing age, disease duration, sedentary leisure time, VAS pain, and WOMAC score, the QoL decreased. BMI, comorbidity, and polypharmacy only showed a significant correlation with some domains of QoL.

Table 1: Personal and clinical characteristics of the participants

Age (year)	68.35±5.51
BMI	28.36±3.89
Symptom duration (years)	9.01±5.63
Gender	
Female	213 (64.2)
Male	119 (35.8)
Marital Status	
Married	270 (81.3)
widowed/divorced/single	62 (18.7)
Comorbidity	
< Three disease	259 (78.01)
≥Three disease	73 (21.99)
Polypharmacy	
≤ 3 drugs	237 (71.4)
>4 drugs	95 (28.6)
Diabetes	
Yes	77 (23.2)
No	255 (76.8)
Hypertension	
Yes	96 (28.9)
No	236 (71.1)
Cardiovascular disease	
Yes	89 (26.8)
No	243 (73.2)
Sedentary leisure (hours/d)	7.23±1.56
Exercise (30min/d)	
Yes	37 (11.1)
No	295 (88.9)
Walking aid devices	
Yes	46 (13.9)
No	286 (86.1)
Dependence	
Independent	300 (90.4)
Semi-independent	32 (9.6)
QoL dimensions	
physical health	186.71 ± 56.9
mental health	223.75 ± 47.6
WOMAC score	47.89 ± 15.6

-Numbers are mean±SD or frequency (%)

-Comorbid conditions were asthma, chronic bronchitis, chronic obstructive pulmonary disease, hypertension, diabetes, cardiovascular disease, migraine, chronic gastrointestinal condition, depression, rheumatoid arthritis, kidney disease.

Table 2: Comparison of mean scores of QoL and disability domains and VAS pain by gender

	Female	Male	P value
SF-36 domains			
Physical function(PF)	35.45±20.41	45.17±21.40	0.001
Role physical (RP)	60.18±27.59	51.86±33.57	0.025
Bodily pain (BP)	41.84±25.12	51.44±25.83	0.001
General health (GH)	32.23±22.56	39.43±22.47	0.006
Vitality (VT)	32.66±14.52	37.45±13.81	0.004
Social function (SF)	47.55±26.03	57.41±26.61	0.001
Role emotional (RE)	65.89±38.89	55.79±44.25	0.033
Mental health (MH)	65.26±11.18	67.93±10.56	0.035
Physical health dimension	180.89±55.60	197.19±58.33	0.014
Mental health dimension	221.45±47.58	227.83±47.88	0.250
WOMAC domains			
WOMAC-pain	10.75±3.23	9.66±3.66	0.006
WOMAC- stiffness	5.15±3.33	4.55±1.71	0.065
WOMAC-function	34.36±11.06	29.83±12.91	0.001
WOMAC-total	50.03±14.8	43.82±16.26	0.001
Principle component of SF-MPQ			
Sensory	11.23±2.45	10.89±2.31	0.784
Affective	2.12±0.012	2.23±0.010	0.868
VAS pain (0–10)	6.48±0.89	4.67±0.65	0.006

Figure 1: Percentage of pain intensity based on SF-MPQ in the participants by gender (*P*<0.001)

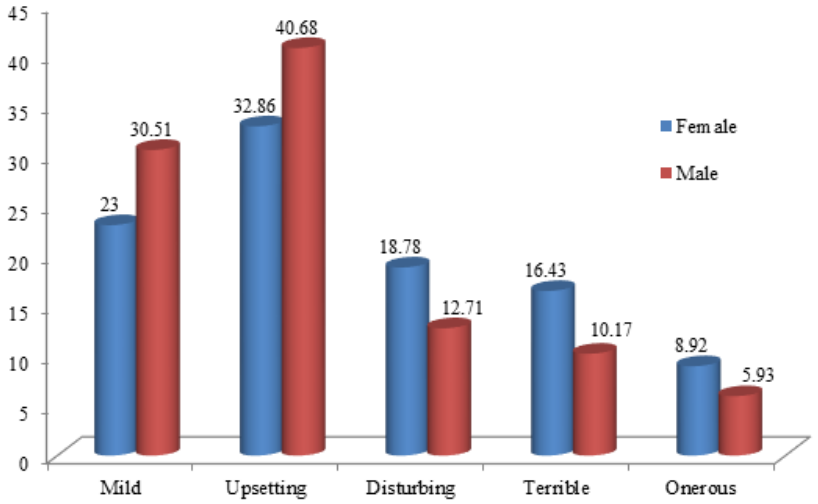

Table 3: Correlation between QoL domains with disability domains and personal data

	PF	RP	BP	GH	VT	SF	RE	MH
***R* value** **Age, *P* value**	-0.445***	-0.222***	-0.422***	-0.261***	-0.376***	-0.411***	-0.195***	-0.276***
Symptom duration	-0.519***	-0.298***	-0.517***	-0.380***	-0.493***	-0.467*** 0.001	-0.271***	-0.360***
BMI	-0.117*	-0.122*	-0.080	-0.106	-0.062	0.051	-0.128*	-0.093
Sedentary leisure	-0.215***	-0.184***	-0.259***	-0.446***	-0.176***	-0.371***	-0.382***	-0.521***
Comorbidity (diseases number)	-0.322***	-0.276***	-0.186*	-0.428***	-0.345	-0.268	-0.276	-0.189*
Polypharmacy (drug number)	-0.436***	0.296	-0.324	-0.338***	-0.188	-0.245	0.412**	-0.231
VAS pain	-0.536***	-0.436***	-0.478***	-0.238***	-0.256***	-0.382***	-0.179***	-0.321***
WOMAC-pain	-0.816***	-0.344***	-0.738***	-0.586***	-0.636***	-0.680***	-0.272***	-0.485***
WOMAC- stiffness	-0.318***	-0.126*	-0.327***	-0.281***	-0.261***	-0.332***	-0.110*	-0.261***
WOMAC-function	-0.852***	-0.351***	-0.794***	-0.622***	-0.668***	-0.741***	-0.276***	-0.495***
WOMAC total	-0.851***	-0.251***	-0.801***	-0.627***	-0.668***	-0.743***	-0.479***	-0.510***

*p>0.05, **p>0.01, ***p>0.001

Discussion

The results showed that the QoL domains of the elderly with KOA were significantly associated with disability in all three domains of pain, stiffness, and function. A significant negative correlation was also found between the QoL domains and the VAS pain variable. In general, the physical health dimension of QoL showed a higher correlation with VAS pain than the mental health dimension. The lower scores in the physical health dimension compared with mental health are consistent with other studies.[7,10-11,14-15] KOA is a chronic disease that can cause significant functional limitations associated with pain. As a result, these two elements can explain the reduction in QoL in patients with KOA.[16] The majority of authors agree that pain and disability are the main predictors of QoL, regardless of the severity of OA radiographs.[17-18] QoL has been linked to the impact of treatment decisions on patients with KOA. Relieving pain, restoring function, and improving QoL have been identified as indicators of efficiency and effectiveness in treating patients with severe illness, as part of the OA assessment.[4,19]

A comparison of QoL and WOMAC domains by gender indicated that the QoL was lower and the disability was higher in women than in men. The severity of the pain was also shown to be more severe in women. Most studies have shown that women reported more severe pain, lower QoL, and more disability than men, even after controlling confounding variables.[1,4,10-11,20-21] A possible explanation for the worse clinical symptoms in women compared to men is that women are inherently more likely to be more sensitive to pain and functional limitations than men. Other potential explanations include more prevalence of obesity in women and differences in daily physical activity between the gender groups. Finally, women in our society need kneeling and squatting postures in daily activities more often than men. Such activities cause more discomfort in women.

In the present study, there was a significant negative correlation between all QoL domains and age. The highest correlation was observed with the physical function domain. Recent studies have shown that this domain worsens as patients get older.[4,16] The link between aging and QoL was shown,[16,22] however, Nobrega et al (2009) reported that the QoL mean did not reduce with age.[23] One of the reasons for this discrepancy may be that when older people define their health as good and reasonable, they do not see themselves as without disease; however, they believe that even with their illnesses, they can function well in their environment.[16]

In this study, some of the QoL domains did show a poor correlation with BMI. The Gomes-Neto study found no difference in QoL domains among overweight and normal people.[24] The association between increased BMI and KOA risk has also been described in other studies.[6,16] Recent studies have shown that both underweight and overweight/obese individuals are more likely to experience function limitation, disability, and mortality, as compared to persons whose weight is in a healthy range.[6,25] These findings identify a subgroup that may be at risk for poor outcomes and show the importance of targeting a healthy BMI.

Comorbidity and polypharmacy were associated with lower QoL scores in this study. This is consistent with some studies.[2,12,26] Polypharmacy over a long time due to common chronic diseases and pain can endanger the health and QoL of the elderly. Therefore, non-pharmacological measures or the use of fewer drugs in low doses can reduce the adverse effects and maintain adequate pain control. Also, early detection of chronic diseases is

essential to develop prevention strategies to help improve their health.[19,27-30]

Another finding of the present study was a significant negative correlation between QoL and sedentary leisure time. This is similar to other studies related to the elderly.[31-32] These results can be explained by the fact that age is associated with reduced mobility and cognitive functions, which has a direct impact on sedentary and self-efficacy activities, and self-efficacy in turn can affect the psychological QoL.[31] Accordingly, sedentary time should be integrated into the guidelines for older people's movement behavior, so that the elderly benefit from less sitting, breaking up their sitting time, and more movement.

The limitations of this study include the analysis of a single group that leads to problems in comparing the results in the study; The inability to assess patients soon after medical counseling, which would have enabled data analysis with less influence of drug treatment or non-pharmacological treatment by the physician; heterogeneity in disease time distribution among participants; and the inability to control conservative treatments previously performed by other health care providers. The strength of the study is the acceptable sample size, well-defined study design and implementation, and also taking into account many factors influencing knee-related QoL.

Conclusions

The results contained several important messages. Poorer knee-related QoL in women than men of the same age suggests that treatments should place a greater emphasis on pain management and improving function, particularly in women with KOA. Week correlation between QoL and BMI also suggests that even underweight people may be at risk for KOA. This demonstrates the importance of targeting a healthy BMI in KOA management. Finally, comorbidity, polypharmacy, and sedentary lifestyle were among the factors affecting the reduction of KOA-related QoL in the elderly. Treatment planning for KOA in the elderly should focus on reducing the number of medications, treating chronic diseases, and improving mobility. In conclusion, individual differences in predictors of QoL and physical function suggest KOA management strategies should be individualized based on patient characteristics.

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MMJ

ORIGINAL ARTICLE

Suitability and uptake of vaccines in the last 4 weeks among child participants of a health screening campaign

Navin Kumar Devaraj

Introduction

Vaccine can be described as a tool available to parents to protect their infants and children from potentially deadly diseases. It can prevent deaths and save lives at the same time. This study was aimed at the suitability and uptake of vaccines in the last 4 weeks among child participants of a health screening campaign.

Methods

A cross-sectional, prospective observational study was conducted at two communities through health campaign. A validated and self-administered questionnaire that includes two sections on socio-demographic details and a section on child vaccination practices was used. Statistical Package for Social Sciences v26.0 was used for data analysis.

Results

The mean age is 50.1±22.7 years. Majority were females (68.3%), of Chinese ethnicity (21.7%), married (73.3%) and not employed (75.0%). Majority had none or primary level of education only (60.0%). Majority of the children were suitable to receive vaccine i.e. 58/60 or 96.7%.

Conclusion

The uptake of children in receiving vaccine is high. This augurs well for a nation keen to have healthy citizens that can spur the economy.

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Introduction

Over the years, vaccines have caused some controversy over its safety but there are no convincing proof of harm that has been found. In Malaysia, vaccines such as Hepatitis B and Haemophilus influenzae are compulsory for infants and children up to 15 years old by the Ministry of Health. Vaccine can be described as a tool available to parents to protect their infants and children from potentially deadly diseases.[1] A vaccine is a weaker version or part of the germ that is causing the disease. It contains the same antigen as the disease. When the infection in vaccine form is inserted in children, their immune system is triggered to make antibodies that protect them from catching the disease when they are exposed to the actual disease in question.[2]

The main use of vaccines is that they protect children against common deadly diseases such as polio, measles, diphtheria and so on. They stimulate the immune system to synthesize antibodies, thus enhancing immunity and providing protection to the child.[3] Immunization is considered as the most cost-effective public health intervention, preventing an estimated 2 to 3 million deaths yearly.[4] Vaccination also helps in the case of newborn babies. Babies receive antibodies from their mother but after a year of life, immunity wears out. Therefore, vaccines boost their immunity. Unvaccinated kids are at higher risk and more vulnerable to the disease than the accinated ones.[5]

In Malaysia, the WHO Expanded Programme on Immunisation provides free vaccination to children since birth up to fifteen years of age. Notwithstanding the huge success of increased immunization coverage rates (>90%) in Malaysia, the hesitancy for vaccine uptake prevails as a rising concern denoted by increasing number of diseases that can potentially be eliminated by vaccines.[6] A ten-fold spike in measles was observed in 2013 to 2018 by the Malaysian Health Ministry from 125 to 1467 respectively. Even though vaccine coverage has been more than 95% consistently, vaccine uptake for measles indicated a decrease in 2017 to 88.8%.[7] Few reasons behind vaccine refusals are religious exemptions, philosophical disapproval like desiring a natural living or overstated concerns for vaccine safety such as relating autism to childhood vaccination. However, no such link regarding autism has been proven by reputed studies.[8] Furthermore, lack of knowledge about vaccinations causing misconceptions, or impact of wrong information shared online as well as former unpleasant incidents regarding vaccination are other reasons.[9] This hesitancy could develop into refusal leading to more unvaccinated children, resulting in outbreaks of vaccine-preventable diseases.[10] Therefore, the suitability and uptake of vaccines among children in a health screening campaign are further explored in this study.

Materials and Methods

A cross-sectional, prospective observational study was conducted at two communities through health campaign. Ethical approval was sought with the Medical Research Ethics Committee, Universiti Putra Malaysia. All participants provided their written informed consent. The inclusion criteria were Malaysian parents aged 18 years and above who were attending the health campaign and who could understand and complete the questionnaires in English or Malay version. The exclusion criteria comprise of those who has mental health issues.

Universal sampling was used to recruit respondents in this study. Those who fulfilled the inclusion criteria was taken as respondents in this study. A validated and self-administered questionnaire that includes two sections on socio-demographic details

and a section on child vaccination practices was used.

The respondents need to take approximately about 10 to 15 minutes to complete all the questions in the questionnaires. A written informed consent will be taken before the process of data collection started. All information of the respondents remains confidential and is solely for research purpose.

Operational Definition

The independent variables for this study are:

1. Sociodemographic characteristics which include age, gender, ethnicity, educational status, marital status and occupation of the parent

Dependent factors are:

Child vaccination practices

For data analysis of the raw data this study, Statistical Package for Social Sciences v26.0 was used. Descriptive analysis was used to analyze the data distribution normality, frequencies, means and standard deviation.

RESULTS

The mean age is 50.1±22.7 years. Majority were females (68.3%), of Chinese ethnicity (21.7%), married (73.3%) and not employed (75.0%). Majority had none or primary level of education only (60.0%). Majority of the children were suitable to receive vaccine i.e. 58/60 or 96.7%. (Table 1)

Table 1: Socio-demographic characteristics of the participants (N=60)

Variable	Frequency	Percentage
Age, years mean ± standard deviation	50.1±22.7	
Gender		
Male	19	31.7
Female	41	68.3
Ethnicity		
Malay	16	26.7
Chinese	30	50.0
Indians	13	21.7
Others	1	1,7
Marital Status		
Married	44	73.3
Never married/divorced	16	26.7
Occupation		
Employed	15	25.0
Not employed	45	75.0
Educational level		
None	8	13.3
Primary	28	46.7
Secondary	15	25.0
Tertiary	9	15.0

Discussion

Immunization in children has been a great success in the public health sector for a long time. However, the suitability and uptake of vaccines during childhood has raised concerns whether acute diseases decrease the efficiency or elevate the adverse reactions of vaccines. Vaccine comprises an active ingredient which is the antigen that gives rise to the immune response, along with other components including preservatives, additives and adjuvants. Some children are prone to allergies to these components, mainly foods such as eggs (60% at 6 years).[11]

Several vaccines produced on embryonated chicken eggs contain egg proteins, mainly ovalbumin with high amounts present in influenza, yellow fever and rabies which are embryonated chicken eggs vaccines while reduced amounts in Measles-Mumps-Rubella (MMR) or tick-borne encephalitis vaccines which are chicken embryos or fibroblasts of chicken embryos vaccines. However, children with mild allergies can uptake any influenza vaccines or MMR vaccine safely without hospital admission while children with severe allergies require a medical setting intervention or hospital admission for vaccination.[12] Moreover, hidden milk proteins may be present in a few vaccines to avoid virus degradation. Allergic reactions have been observed following MMR vaccine in children with milk and egg allergy.[13] In OPV (Oral Polio Vaccine) and DPT (diphtheria, pertussis and tetanus) vaccine, existence of milk proteins is suggested and therefore, children with allergic reaction history are recommended on a 60 min observation following vaccination.[14]

Although anaphylactic reaction to yeast is considered rare, those who have such allergy are suggested to take only yeast-free vaccines such as bivalent human papillomavirus vaccine, over vaccines that has yeast proteins including quadrivalent human papillomavirus vaccine or hepatitis B vaccine.[15] Furthermore, gelatin which acts as a stabilizer in many vaccines is responsible for major allergic events including IgE as well as non-IgE induced reactions.[16] However, a reduction in allergic events is noticed with greater hydrolysed porcine gelatin in use within these vaccines.[17] The risk group includes children allergic to red-meat like bovine, pork or lamb where pork-meat sensitive children (38%) already have particular IgE towards gelatin thereby increasing the risk of anaphylactic reactions during vaccination.[18] In order to avoid bacterial or fungal contaminants in vaccines, small amounts of antibiotics are used, like neomycin, streptomycin etc. However, few adverse events from case reports have been outlined.[19] Moreover, some children are allergic to latex which is found in the vial or syringe of vaccines. However, hypersensitivity events are uncommon in the case of vaccine contaminated by latex. Latex free vaccines are available at present.[13]

In the case of adverse reactions to vaccines in the past, future doses are contraindicated. However, there are circumstances where benefits are more than the risks like the event of an outbreak.[20] Blood disorders such as thrombocytopenia or thrombocytopenic purpura could be a precaution for MMR as well as MMRV vaccines.[21] How safe the live attenuated influenza vaccines (LAIV) in children with lung, heart, kidney or metabolic diseases such as diabetes or any blood disorder is not confirmed yet. However, children from the age of 5 undergoing these disorders, as well as asthma should be carefully dealt with prior to vaccination with LAIV.[22] Moreover, Inactivated Influenza Vaccine is recommended for children on long-term aspirin therapy as well as children who have had wheezing or asthma in the past 12 months from 2 to 4 years of age while use of LAIV is advised against. However,

there is no proof of increased wheezing following LAIV vaccination in those who have had previous wheezing or asthma history and it has not been identified if wheezing would have taken place without LAIV immunization.[23]

Children with epilepsy are known to develop fever and infection that can potentially trigger seizures. Some vaccines such as measles-mumps-rubella (MMR) vaccines, trivalent inactivated influenza vaccines have been linked to febrile seizures in young children in the past.[24] After immunization in children having epilepsy, the risk of seizure is not known. A study was done to determine the risk of seizure after immunization in children (less than 7 years old) with epilepsy.[25] From the results obtained, it was seen that parents can be at ease as immunization does not appear to cause an increase of seizure in children with epilepsy. However, further studies are required to confirm these findings.

Together with its role in boosting the immune system, vaccination has also been seen as a potential modifier of the risk of childhood leukaemia. According to a study carried out by Xiaomei et al, it was seen that vaccinations such as diphtheria and tetanus are not associated with the risk of leukaemia and that Hib vaccination has the ability to reduce the risk of childhood leukaemia.[26] In the case of HIV, most children who are born to women are already infected with human immunodeficiency (HIV) do not get infected but some acquire the virus at the time of delivery or shortly after. Nevertheless, it was seen that immunization is usually safe and beneficial for HIV-infected children, despite the fact that HIV-induced immune suppression diminishes the benefit compared with that received in HIV-uninfected children.[27] But it should be noted that some complications can happen after immunization in the case of severely immunocompromised children but there is no evidence that immunization accelerates the course of HIV infection.[28]

As for children taking anticancer medication or are under chemotherapy, vaccination should be put to a halt. Cancer chemotherapy is known to suppress the immune system.[29] The decrease is most noticeable during the induction and consolidation chemotherapy. After the completion of all therapies, immune functions take months to recover to normal. Primary immunization responses are more affected by immunosuppression than booster responses.[30] Hence, vaccination should not be conducted during induction and consolidation chemotherapy. Other vaccinations options exist in the period of maintenance therapy. Killed vaccines are used in immunosuppressed children as they are less risky but they may not be as effective as the live viral vaccines. Live bacterial vaccines such as the Bacille Calmette-Guérin, oral typhoid should also be avoided.[31]

As for those who are receiving a blood transfusion or blood products, it is better to delay vaccines for a certain period of time. Immunoglobulins have the ability to inhibit the immune response to some vaccines.[32] However, according to the CDC, a blood transfusion at the age of 3 days should not have a great impact on the routine immunization schedule. The varicella and the MMR vaccine would not be due for one year and the precautions associated with blood transfusion are usually for the previous eleven months infants only. As for the whole blood is concerned, the wait to administer MMR or varicella-containing vaccine is around 6 months.[33]

Strength of the study lies in the important data collected which indicate that majority of parents are adhering calls for their child to be vaccinated. Limitation lies in the fact that this is a cross sectional study which may limit causality and the small sample size which may limit its generalisability.

Conclusion

The uptake of children in receiving vaccine is high. This augurs well for a nation keen to have healthy citizens that can spur the economy.

Acknowledgement

We would like to thank the participants of this study.

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MMJ

ORIGINAL ARTICLE

Management of acute relapses of Multiple Sclerosis in Malta

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Introduction

The lack of Multiple Sclerosis (MS) specialist nurses and an increasing prevalence of MS in Malta has raised questions as to whether MS patients are receiving appropriate treatment. The quality of care for patients with MS in Malta has not been previously described in the literature. This audit aims to establish a baseline and improve the quality of management of acute relapses of MS in Malta.

Methods

A standardized questionnaire based on the NICE guidelines for the management of MS was formulated and completed during a one-on-one interview. 35 patients diagnosed with Relapsing Remitting Multiple Sclerosis (RRMS) were recruited from outpatient clinics and in-patients stays with a mean patient age of 39. All participants recruited were diagnosed with MS after 2004. Only the data of latest acute relapse episode was collected. The data was collected across a 9-month period in 2015 and analyzed using SPSS.

Results

34% revealed a delay in presentation and access to treatment, 11% exhibited poor recognition of acute relapses and 47% admitted to lack of awareness of treatment side-effects.

Conclusion

A significant proportion of patients with an acute relapse in the Maltese population require better education and access to be available for more prompt presentation and management. A better-informed patient and a dedicated specialist nurse service may improve the quality of care.

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Introduction

Multiple Sclerosis (MS) is a complex, progressive and lifelong neurological disorder defined by demyelinating lesions within the brain and spinal cord, these lesions are characteristically disseminated in time and place. Formation of such lesions may coincide with a clinically apparent "acute relapse", in essence, a sudden deterioration in neurological function.

Prevalence of clinically probable Multiple Sclerosis (MS) in Malta has grown from 4.2/100,000 in 1978 to 16.7/100,00 in 1999. It is currently estimated that approximately 320 people suffer from MS in Malta.[1-2]

The purpose of this audit was to assess whether acute relapses of MS are being treated in accordance to the recommended NICE October 2014 guidelines, with the ultimate aim being improvement of the quality of care experienced by MS patients in Malta. Furthermore, the lack of a Multiple Sclerosis specialist nurse within the multidisciplinary team has raised questions on the current clinical care is prompt and adequate for acute relapses of Multiple Sclerosis

Materials and Methods

Data collection was carried out prospectively over a period of 9 months in 2016. Patients were recruited from the Multiple Sclerosis Clinic and the Medical Therapy Unit at Mater Dei Hospital. Patients who were recruited to the study attended a one-on-one interview with a single assigned medical doctor equipped with a standardized questionnaire.

The Questionnaire used was based on the "NICE Guidelines: Management of Multiple sclerosis in primary and secondary care" issued in 2014 as best practice. The area of the NICE guidelines we focused on in our audit was section 1.7 (Relapse and Exacerbation). We used this section to produce a questionnaire that was used as framework for the interview. This questionnaire and quoted section from guidelines are demonstrated below the references in the boxes below.

Patients were also given the freedom to add their personal comments and feedback during the interview. Patients included in the study were recruited opportunistically provided that they met the inclusion criteria below.

Information letter for patients in both English and Maltese language were distributed, in addition, Consent was obtained from each patient. Ethical Approval was sought from the local Ethics committee.

Inclusion criteria

We included patients meeting the McDonald criteria for the diagnosis of MS.[3] Only patients who were diagnosed with MS after 2004 were included, and only those who had presented with an acute relapse from 2008 to 2016. Patients below 18 years of age were excluded. In order to minimize recall bias, data collection was carried out for the single latest relapse, *Figure (1)* illustrates the date of relapses selected. Data analysis was carried out using SPSS.

Results

A total of 35 Patients met the inclusion criteria. The mean age of patients recruited was 39. The male to female ratio was 2:3, and the majority of patients (29) had a Relapsing Remitting MS Course, while the remainder (6) had a Clinically Isolated Syndrome (CIS).

Recognition of Relapse

A true acute relapse is defined as neurological deficit lasting for >24 hours in the absence of

infection, as stipulated in the 2010 McDonald Criteria. [3]

Of all the patients interviewed, 86% of them met the appropriate diagnostic criteria of an acute MS relapse. Most relapses assessed occurred in 2016 as shown in *Figure (1).*

Table (1) summarizes the results of the relapse awareness from our questionnaire. Clinically isolated syndrome refers to patients diagnosed with MS after a single episode of acute MS relapse.

Over 34% of patients showed a delay of more than 14 days in the time to treatment from the initial onset of symptoms as illustrated by *Figure (2).*

For the patients who received IV steroids, *Figure (3)* shows the total duration of treatment given. The most common duration was 5 days, a maximum of 7 days and a minimum of one day. only 2 patients did not receive methylprednisolone.

Figure 1: Histogram of relapses measured

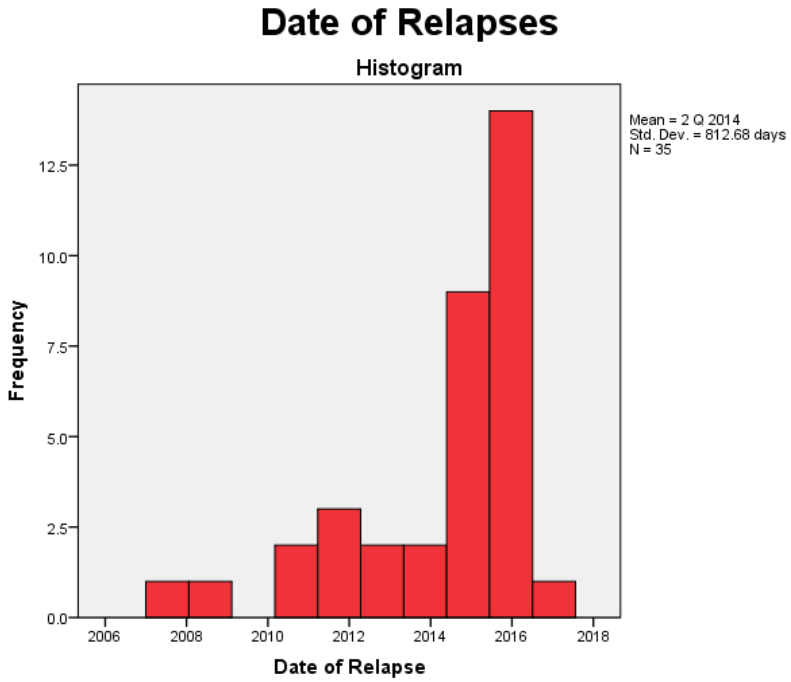


Table 1: Recognizing a Relapse

	Yes	No
Duration of symptoms >24 hours	30(86%)	5(14%)
Symptoms in the absence of infection and fever	30(86%)	5(14%)
Significant impact on ADLs*	24 (68%)	11(32%)
Developed New or Worsening of existing symptoms	30(86%)	5(14%)
Clinically Isolated Syndrome	6(17%)	29(83%)

**ADL: Activities of Daily Living

Figure 2: Time from onset of symptoms to treatment

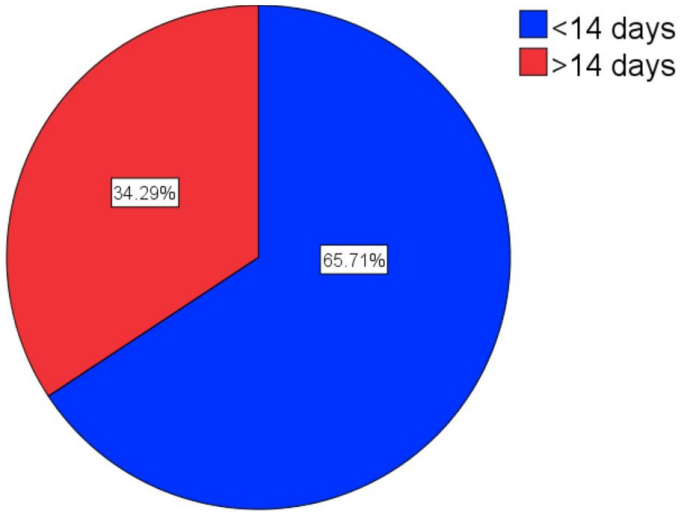
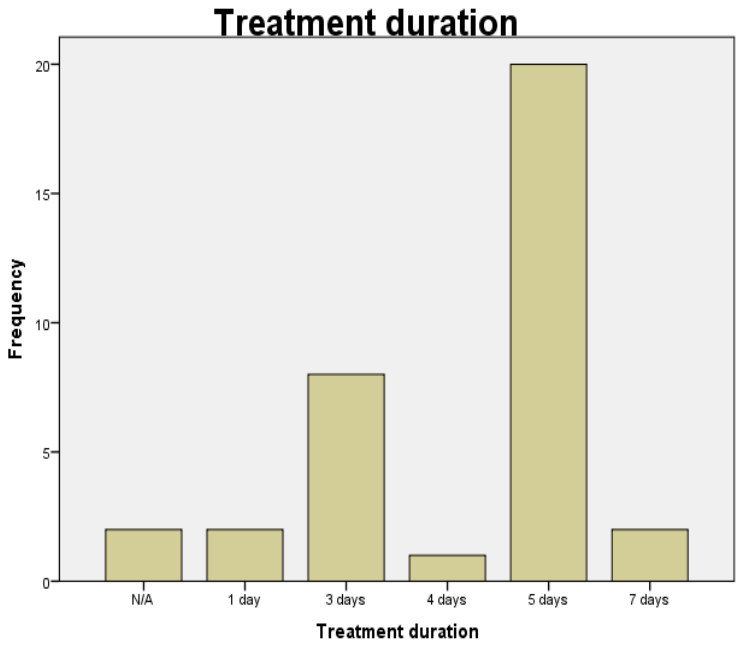


Figure 3: Total duration of IV methylprednisolone given during relapses



Treating a Relapse

89% (31) of patients received IV Methylprednisolone as treatment for their relapse. Treatments given, including doses and duration are shown in Table (2). The remaining 11% (4) of patients did not receive any treatment for their relapse.

Almost one third of patients required inpatient treatment, the breakdown of length of stay and reason for admission is shown in Table (3). Patient are usually admitted in view of a severe disabling relapse, monitoring of a medical or psychiatric condition, or due to poor social support.

Table 2: Summarizes patients characteristics

○ Total number of Patients recruited:	35
○ Received treatment as outpatient	23
○ Received treatment as inpatient	12
- Severe Relapse	9
- Monitoring of Medical condition	3
○ Average Length of Stay	3.9 days

Table 3: Results from treatment section of questionnaire:

○ Lack of Awareness of adverse effects	47%
○ Lack of Focused Patient - Doctor discussion	50%
○ Lack of Formal patient information provided	74%

Information about treating a relapse

We aimed to appraise the basic knowledge of patients on steroid treatment. 47% of patients reported lack of awareness of potential drug adverse effects. 50% claimed that they did not receive any formal discussion with a health care professional regarding risks and benefits treatment. 74% did not receive any formal patient information (e.g. leaflets, website sign-posting) regarding the recognition of relapse.

Medical, therapy and social care needs at time of relapse or exacerbation

33% of patients were referred to a rehabilitation facility (Physiotherapy, Occupational therapy, Speech Language Pathology).

Discussion

At the outset of this audit, we wanted to assess whether the current practice in Malta meets the quality standards set out by NICE guidelines for the management of MS in 2016. [6]

Results show that the overwhelming majority of patients are referred for first line treatment once they are recognized as having an acute relapse. However, it has been identified that service provision can be optimized in, but not limited to, the following areas:

1. It is clear that among some patients there is a delay in access to treatment, thus more timely recognition of those patients in an acute relapse is required. This study demonstrates that of all patients receiving first line treatment, 34% of them received treatment outside the recommended 14-day window suggested by the guidelines. Therefore, identification of the barriers to access in a manner medical attention is an area for further study.
2. MS relapses maybe overlooked by patients and can be confused with symptom fluctuation, as our study showed that 11% of patients did not receive any treatment for their clinically significant relapse symptoms. this highlights the importance of patient education especially with regards to MS relapses. This aspect of MS care is not well documented in the research literature, however, a nursing qualitative study Ross AP et al.[4] recognizes this overlooked issue.

3. This study further elucidated that 47% of patients reported no recollection of a discussion about the potential advantages and disadvantages of commencing steroid treatment and hence constitutes the second area identified for optimization. It is of paramount importance for patient safety that patients are made aware of the most relevant risks and benefits of steroid treatment. However, it is sometimes impractical to have lengthy discussions regarding risk benefit. Patients who receive timely steroid treatment do not necessarily improve, in fact, almost one third perceive the outcomes to be worse on account of the treatment, according to a large-scale observational study carried out by Nickerson et al. [5]

The limitations of this audit included a small sample size and retrospective data collection. A larger sample size and prospective data collection will provide us with stronger evidence to further support the findings. Furthermore, data collected depended on the recollection of relapses by patients, prospective collection and review of clinical notes may provide a more accurate information and minimize recall bias.

Recommendations

As a result of the qualitative findings, we are proposing 3 recommendations to improve patient care in accordance with best practice as set out by NICE guidelines [6] in the management of MS:

1. To improve patient knowledge in recognizing relapse and to expedite access to treatment. Patients could be provided with a 'MS Passport' listing most common symptoms, well as including contact details of a named individual, e.g., MS nurse specialist, to contact if such symptoms occur.
2. To provide adequate and comprehensive information on the risks and benefits of steroid treatment and that these should be made available to patients in an accessible format at the earliest point of contact, ideally prior to acute flares. This could be in the form of patient information leaflets.
3. To introduce a MS Specialist nurse to the Multi-disciplinary team in order provide vital support to patients with MS in Malta.

Summary

What is already known:

1. MS is associated with high levels of morbidity
2. Acute Relapses require prompt assessment and may be mimicked by infection, or chronic symptom fluctuations

What are the new findings?

1. A third of acute MS relapses may go unrecognized or present late
2. Patient education and access to specialist nurse is recommended in Malta

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6. Multiple sclerosis in adults: management. NICE Clinical guideline Published: 8 October 2014 www.nice.org.uk/guidance/cg186

Below is the Multiple Sclerosis Questionnaire used for data collection derived from MS NICE guidelines [6]

Multiple sclerosis acute relapse questionnaire

based on Multiple Sclerosis NICE guidelines 2014

Name: ID number:

Gender: Date of Birth:

Year of diagnosis: Date of Relapse:

Recognizing a Relapse

- Developed new symptoms or worsening of existing symptoms [1.7.3]

☐ Yes ☐ no

- Duration of symptoms: [1.7.3]

☐ <24 hours ☐ >24hours

- Infection ruled out: [1.7.4]

☐ Yes ☐ no

If yes: ☐ UTI ☐ RTI ☐ GI ☐ Other _____

- Signs and symptoms discriminated from Disease progression or fluctuation [1.7.4]

☐ Yes ☐ no

-Time from onset of symtpoms to treatment: [1.7.5]

☐ <14 days ☐ >14 days

-Impact on Activities of Daily living [1.7.5]

☐ Yes ☐ no

-Symptoms present for longer than 3 months: [1.7.5]

☐ Yes ☐ no

Treating a Relapse

- Treatment prescribed: [1.7.7; 1.7.8]

	Dose	Frequency	Duration
☐ Methylprednisolone IV			
☐ Prednisolone PO			
☐ Other_____			

-Treatment as In-patient : [1.7.8]

☐ In-patient Length of stay_____ ☐ No

- If treated as In-Patient, what is the indication for admission [1.7.8, 1.7.9, 1.7.10]

□ Severe Relapse.

□ Monitoring of medical condition

□ Monitoring of psychological condition

□ Poor social support

□ Other _____

-Extra-supply of steroids prescibed for self adminstration [1.7.10]

☐ Yes ☐ no

Information about treating a relapse of steroids

-Benefits and risks of treatment discussed: [1.7.11]

☐ Yes ☐ no

-Potential Side Effects of treatment discussed: [1.7.12]

☐ Yes ☐ no

- Information of Potential Side Effects of treatment given: [1.7.13]

☐ Yes ☐ no

-Multidisciplinary team informed: [1.7.14]

☐ Neurologist ☐ Occupational therapy

☐ Social worker ☐ GP ☐ Physiotherapy

Medical, therapy and social care needs at time of relapse or exacerbation

- □ Rehabilitation Referral
- □ Social worker referral
- □ In-patient treatment offerred if deficient medical or social care needs at home
- □ Patient informed of short term cognitive effects of relapse
- □ Symptom management

Boxes below from Multiple sclerosis in adults: management NICE guidelines Published: 8 October 2014 [6]

1.7 Relapse and exacerbation

Treating acute relapse of MS with steroids

1.7.1 Develop local guidance and pathways for timely treatment of relapses of MS. Ensure follow-up is included in the guidance and pathway.

1.7.2 Non-specialists should discuss a person's diagnosis of relapse and whether to offer steroids with a healthcare professional with expertise in MS because not all relapses need treating with steroids.

Recognizing a relapse

1.7.3 Diagnose a relapse of MS if the person:

- develops new symptoms or
- has worsening of existing symptoms and these last for more than 24 hours in the absence of infection or any other cause after a stable period of at least 1 month.

1.7.4 Before diagnosing a relapse of MS:

- rule out infection – particularly urinary tract and respiratory infections and
- discriminate between the relapse and fluctuations in disease or progression.

1.7.5 Assess and offer treatment for relapses of MS, that affect the person's ability to perform their usual tasks, as early as possible and within 14 days of onset of symptoms.

1.7.6 Do not routinely diagnose a relapse of MS if symptoms are present for more than 3 months.

Treating a relapse

1.7.7 Offer treatment for relapse of MS with oral methylprednisolone 0.5 g daily for 5 days.

1.7.8 Consider intravenous methylprednisolone 1 g daily for 3–5 days as an alternative for people with MS:

- in whom oral steroids have failed or not been tolerated or
- who need admitting to hospital for a severe relapse or monitoring of medical or psychological conditions such as diabetes or depression.

1.7.9 Do not prescribe steroids at lower doses than methylprednisolone 0.5 g daily for 5 days to treat an acute relapse of MS.

1.7.10 Do not give people with MS a supply of steroids to self-administer at home for future relapses.

Information about treating a relapse with steroids

1.7.11 Discuss the benefits and risks of steroids with the person with MS, taking into account the effect of the relapse on the person's ability to perform their usual tasks and their wellbeing.

1.7.12 Explain the potential complications of high-dose steroids, for example temporary effects on mental health (such as depression, confusion and agitation) and worsening of blood glucose control in people with diabetes.

1.7.13 Give the person with MS and their family members or carers (as appropriate) information that they can take away about side effects of high-dose steroids in a format that is appropriate for them.

1.7.14 Ensure that the MS multidisciplinary team is told that the person is having a relapse, because relapse frequency may influence which disease-modifying therapies are chosen and whether they need to be changed.

Medical, therapy and social care needs at time of relapse or exacerbation

1.7.15 Identify whether the person having a relapse of MS or their family members or carers have social care needs and if so refer them to social services for assessment.

1.7.16 Offer inpatient treatment to the person having a relapse of MS if their relapse is severe or if it is difficult to meet their medical and social care needs at home.

1.7.17 Explain that a relapse of MS may have short-term effects on cognitive function.

1.7.18 Identify whether the person with MS having a relapse or exacerbation needs additional symptom management or rehabilitation.

MMJ

ORIGINAL ARTICLE

A retrospective study on the radiographic evaluation of the tibial component alignment in total knee arthroplasty and its postoperative significance

Glenn Costa, Francesca Mercieca, Matthew Aquilina, Raymond Gatt

Background

The goal of tibial component positioning in total knee arthroplasty is to achieve neutral tibial alignment. Malalignment of the tibial component alters the distribution of tibial loading, resulting in increased wear. The purpose of this study was to correlate two radiological parameters (mechanical and anatomical axis) of the tibial component in total knee arthroplasty with patient related outcome measures at 5 years.

Method

91 primary total knee arthroplasties were considered in this study. Tibial component alignment was assessed using post op radiographs. All x-rays were taken immediately post operatively. The Oxford Knee Score was used to quantify the patient's pain and function following the total knee arthroplasty. Patient follow up at Orthopaedic outpatients and date of discharge were also considered. The radiographic outcome was then correlated with the patient reported outcome over 5 years. Correlation was measured using either the parametric Pearson correlation coefficient (testing for a linear correlation) and its non-parametric counterpart; the Spearman's rank correlation coefficient.

Results

There is a very weak correlation between the Oxford Knee Score and the varus angle of deviation. The correlation is stronger in the valgus position, but still not statistically significant. There is also a weak negative correlation between the angle of deviation and the number of follow ups at Orthopaedic outpatients.

Conclusion

From our study, we can conclude that an angle of deviation of $\leq 6^{o}$ in both varus and valgus did not have a negative prognostic effect on patient outcome.

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Introduction

Total knee replacement is an increasingly common procedure; the number of procedures performed in the last two decades has increased by 162% in the US.[1] It is projected that the number of revisions will have increased by 600% from 2005 to 2030.[2]

Implant malalignment following primary Total Knee Replacement (TKR) has been reported to be the primary reason for revision in 7% of revised TKRs.[3] It has also been linked to a decrease both in implant survival[4] as well as inferior patient reported outcomes.[5]

The main objectives of knee arthroplasty surgery are attainment of anatomical knee alignment and soft tissue balancing. The analysis of the post-operative x-rays is a helpful adjunct to ascertain whether these objectives have been achieved and thereby improve future results.[6]

The anatomic axis of the tibia is created by a line drawn proximal to distal in the intramedullary canal. This bisects the tibia in half and determines the entry point for tibial medullary guide rod. The mechanical axis of the tibia on the other hand is a line from the centre of the proximal tibia to the centre of the talus. On anteroposterior evaluation, the mechanical and anatomic axis of the tibia commonly correspond exactly to one another.

Serial radiographs can indicate potential failures well before they manifest clinically. Therefore, radiography plays an important role in both the immediate postoperative period and during long term follow-up. The purpose of this study was to correlate two radiological parameters (mechanical and anatomic axes of the tibia) with patient related outcome measures at 5 years. Outcomes were quantified through the Oxford Knee Score (OKS),[7] a patient centered measurement tool that is widely regarded for its reliability, validity and high response rate when measuring patient outcome after TKR, and through number of patient follow-ups required in the 5 years after the TKR procedure.

Materials and Methods

A cohort of 92 primary TKRs carried out by an orthopaedic firm in 2015 was considered in this study. This consisted of all the primary TKRs carried out in that year excluding revision TKRs and any deceased patients. The list of patients was obtained from the inpatient records at Mater Dei Hospital (MDH). Seven different operators were involved in the TKRs carried out in this study. 51% of the procedures were carried out by a consultant orthopaedic surgeon while 49% were carried out by resident specialists in orthopaedics.

Tibial component alignment was assessed using post op radiographs on the MDH Universal Viewer (internal hospital software used to view and assess radiological imaging). Placement of the tibial component was measured using the angle between the line across the base of the tibial plate and the tibial shaft axis using the angle measurement function on the MDH Universal Viewer.

An angle of 90^0 corresponds to neutral placement; an angle $>90^0$ corresponds to valgus placement of the tibial component; an angle $<90^0$ corresponds to varus placement of the tibial component. All x-rays used in this study were taken immediately post operatively.

The OKS was used to quantify the patient's pain and function following the TKR. Patients were contacted and asked the 12 questions from the score between the months of March and April 2021. These were translated into the final score (from 0 to 48, where 0 indicates the worst possible symptoms and 48 indicates the least amount of symptoms). For 10 patients, the OKS score could not be established.

The number of follow-ups in each case was not pre-determined by the firm. Prior to discharge, patients were advised to contact the firm for an outpatient's appointment only if they had any concerns. This policy applies to the firm under study.

Details regarding patient follow-up at Orthopaedic outpatients (OOP) and date of discharge were obtained from the Mater Dei electronic patient database.

The radiograph findings (alignment, angle, varus/valgus), OKS (0 to 48) and follow-up records were documented and tabulated. The radiographic outcome was then correlated with the patient reported outcome over 5 years.

Statistical analysis

Statistical analysis for any possible correlation between salient attributes (90° deviation of the tibial component, OKS and number of follow-ups (F/Us) was carried out). Correlation was measured using either the parametric Pearson correlation coefficient (testing for a linear correlation) or its non-parametric counterpart; the Spearman's rank correlation coefficient.[8] Correlation significance was confirmed using a two-tailed t-test with a significance level of 0.05.

The cohort sample size required to show a Pearson correlation coefficient of 0.32 with a statistical power of 80% and a significance level of 0.05 is 73 (as calculated in a similar study by Slevin et al[9] and confirmed in).[10] Thus, we are able to draw statistically significant conclusions on correlation within our cohort, both for F/Us (92 cases) and OKS score (82 cases).

Results

From a cohort of 92 patients, 60.9% had a varus placement of the tibial component (0.1° – 7° deviation) while 38.0% had a valgus placement (0.3° - 7.3° deviation). One of the patients had the tibial component in the neutral position (1.1%).

The average OKS for patients with the tibial component in varus was 41.06 while patients in valgus had an average OKS of 40.87. The patient with the tibial component in the neutral position had an OKS of 48.

The average number of F/Us for patients with the tibial component in varus was 4.20 while patients in valgus had an average of 3.97 F/Us (*Table 1*).

The F/Us and OKS scores for each patient against their corresponding tibial component deviation are plotted in Figure 1 for the entire dataset, in Figure 2 for varus datapoints and in Figure 3 for valgus datapoints. The dataset contains a number of outliers both for the OKS results (only two sub-20 OKS scores) and for the F/Us (only two patients requiring 20 or more F/Us). Thus, both the Pearson correlation coefficient and the Spearman's rank coefficient were calculated in order to measure the effect of the outliers on the correlation results. Correlation values and statistical analyses are provided in Tables 2-3 for the entire cohort, Tables 4-5 for patients with the tibial component in varus and Tables 6-7 for patients with the tibial component in valgus.

For all cases, no significant correlation was obtained between either F/Us or OKS and the angle of deviation (null hypothesis was not rejected in any case considered). Some minor discrepancies between the Pearson and Spearman coefficients were obtained, mostly caused by the presence of the afore mentioned outliers and the lack of a linear relationship between the variables considered. Additionally, the Pearson correlation between F/Us and angle of deviation was very close to being significant (Table 2) – it is possible that more data samples could continue to reinforce the weak negative correlation in the data.

Table 1: Key metrics computed from our patient cohort.[1]The OKS for 82 patients out of the total of 92 were available.

Patient Statistics				
	Varus	**Valgus**	**Neutral**	**Total**
Number of patients	56	35	1	92
Average Age	69.66	67.57	79.00	68.96
Percentage (%)	60.87	38.04	1.09	100
Average OKS[1]	41.06	40.87	48.00	41.07
Average number of F/Us	4.20	3.97	6.00	4.13

Figure 1: Scatter plot of OKS and F/Us against tibial component angle of deviation for all patients considered.

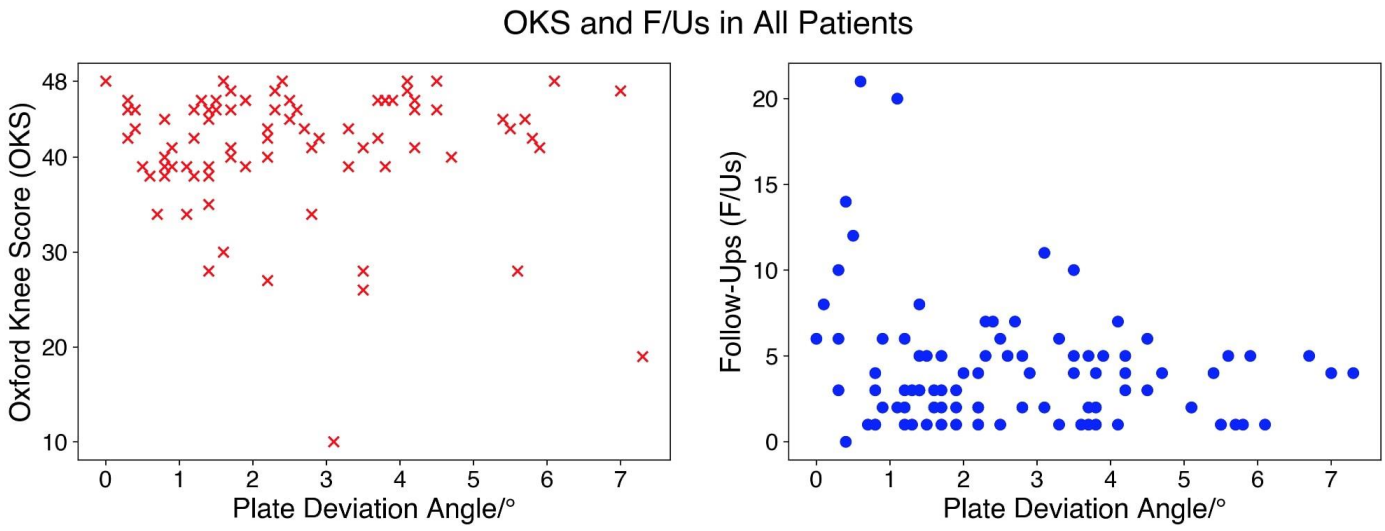

Figure 2: Scatter plot of OKS and F/Us against tibial component angle of deviation for varus patients.

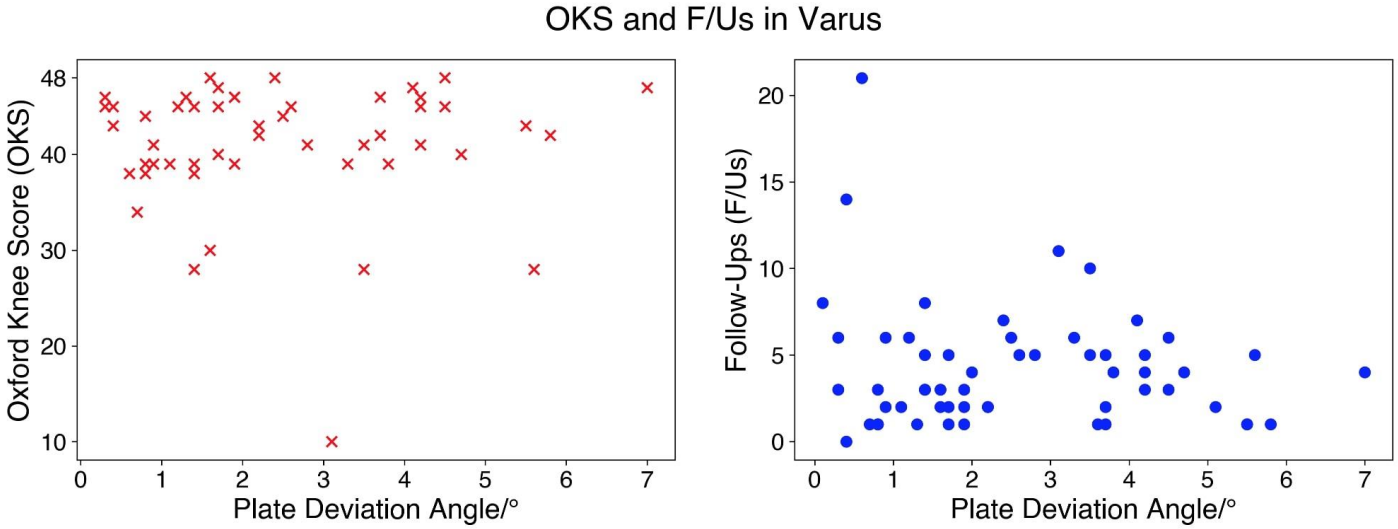

Figure 3: Scatter plot of OKS and F/Us against tibial component angle of deviation for valgus patients.

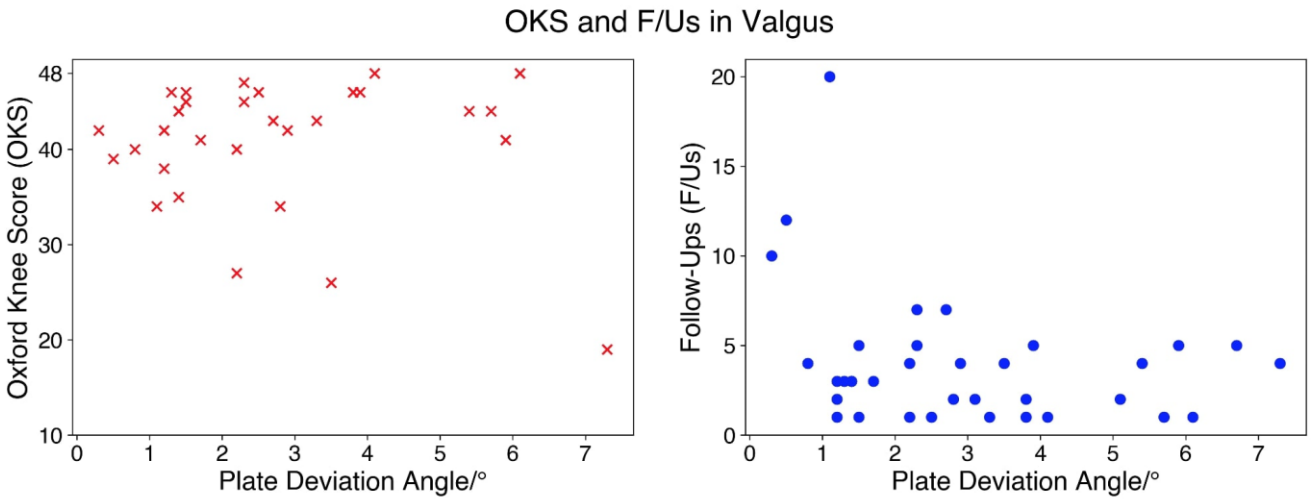

Table 2: Statistical analysis of follow-ups vs angle of deviation in all patients. In both cases, t-statistic is less than the critical value (0.05), which means we cannot reject the null hypothesis (i.e. the two quantities are uncorrelated).

Statistical Analysis of F/Us vs angle of deviation (all patients)		
	Pearson	**Spearman**
Correlation coefficient	-0.208	-0.101
Degrees of freedom (DF)	90	90
T-statistic	2.018	0.959
Critical value (0.05)	2.035	2.035

Table 3: Statistical analysis of OKS vs angle of deviation in all patients. In both cases, t-statistic is less than the critical value (0.05), which means we cannot reject the null hypothesis (i.e. the two quantities are uncorrelated)

Statistical Analysis of OKS vs angle of deviation (all patients)		
	Pearson	**Spearman**
Correlation coefficient	-0.058	0.124
Degrees of freedom (DF)	80	80
T-statistic	0.518	1.115
Critical value (0.05)	2.035	2.035

Table 4: Statistical analysis of follow-ups vs angle of deviation in patients with the tibial component in varus. In both cases, t-statistic is less than the critical value (0.05), which means we cannot reject the null hypothesis (i.e. the two quantities are uncorrelated).

Statistical Analysis of F/Us vs angle of deviation (Varus)		
	Pearson	**Spearman**
Correlation coefficient	-0.140	-0.021
Degrees of freedom (DF)	54	54
T-statistic	1.042	0.154
Critical value (0.05)	2.035	2.035

Table 5: Statistical analysis of OKS vs angle of deviation in patients with the tibial component in varus. In both cases, t-statistic is less than the critical value (0.05), which means we cannot reject the null hypothesis (i.e. the two quantities are uncorrelated)

Statistical Analysis of OKS vs angle of deviation (Varus)		
	Pearson	**Spearman**
Correlation coefficient	0.004	0.122
Degrees of freedom (DF)	48	48
T-statistic	0.026	0.853
Critical value (0.05)	2.035	2.035

Table 6: Statistical analysis of follow-ups vs angle of deviation in patients with the tibial component in valgus. In both cases, t-statistic is less than the critical value (0.05), which means we cannot reject the null hypothesis (i.e. the two quantities are uncorrelated)

Statistical Analysis of F/Us vs angle of deviation (Valgus)		
	Pearson	**Spearman**
Correlation coefficient	-0.285	-0.199
Degrees of freedom (DF)	33	33
T-statistic	1.705	1.167
Critical value (0.05)	2.035	2.035

Table 7: Statistical analysis of OKS vs angle of deviation in patients with the tibial component in valgus. In both cases, t-statistic is less than the critical value (0.05), which means we cannot reject the null hypothesis (i.e. the two quantities are uncorrelated)

Statistical Analysis of OKS vs angle of deviation (Valgus)		
	Pearson	**Spearman**
Correlation coefficient	-0.102	0.270
Degrees of freedom (DF)	29	29
T-statistic	0.552	1.513
Critical value (0.05)	2.035	2.035

Discussion

A successful TKR is the result of several factors. Patient related characteristics such as age, gender and body mass index play an important role in operative outcome.[11-13] Other factors relate to the surgical technique: restoration of limb alignment, correct component positioning as well as satisfactory ligament balance.[14-15] The cohort of patients we selected for this study included all the primary TKRs carried out in the same year by the same orthopaedic firm. This served to eliminate confounding factors such as changes in the prosthesis used and the surgeon's skill and experience.

The radiological definition of "normally" aligned TKA knees is debated,[16-17] but most papers on implant survival and radiological alignment have used some deviation of 3° from a neutral alignment as a threshold for what is acceptable for good long-term results.[18-20]

The goal of tibial component positioning is to maximize coverage to prevent settling,[21] and to achieve a neutral tibial alignment. The latter is achieved by a proximal tibial cut 90° to the mechanical axis.[22] Malalignment of the tibial component alters the distribution of tibial loading, which can lead to increased shear forces at the tibiofemoral interface, resulting in increased wear. Tibial malalignment of > 3° of varus has been reported to increase the risk of medial bone collapse.[20]

Such a 3° threshold has also been chosen in numerous other studies investigating results after TKA,[5,23] and an alignment within 3° of the mechanical axis has been considered to be the gold standard.[24]

The study by Kim et al. (2014)[25] showed an increased failure rate of 3.4% in TKAs with a tibial component alignment other than neutral, compared to 0% failure in neutrally aligned tibias. In our study, only 1 TKA had the tibial component in the neutral position (1.1%). One possible reason for this is that different patients may have different rotational axes and the aim of TKR is to replicate these axes and place the knee into the alignment it was in prior to the development of arthritis or deformity. The OKS of this patient was 48 (maximum score) implying the best outcome in terms of pain and function. However, the patient also required 6 F/Us

which is higher than the average number of follow-ups in both varus (4.20) and valgus (3.97). In the rest of the cohort, no statistically significant correlation between the angle of deviation and our two patient outcome metrics was found.

Postoperative varus alignment has been associated with lower knee scores and increased failure rates [(26)]. From our study, there was no statistically significant difference in outcome between tibial components in varus, in neutral and in valgus.

One of the main limitations in this study was the sample size. A larger sample size with more examples of tibial component placement in the neutral position would have possibly provided more insight into whether there is a significant difference between the outcome of a netral placement *vs* varus/valgus placement. Additionally, 66% of cases had the tibial component with an angle of deviation $\leq 3^{o}$ from the neutral axis. A larger sample of cases with a higher angle of deviation would have also helped provide more representative results.

In our study, we did not consider any possible preoperative varus or valgus knee deformities which could also have influenced the final outcome. Obtaining neutral alignment can be challenging in patients with substantial preoperative deformity [(26)]. Knees with substantial preoperative varus alignment are more likely to have postoperative varus alignment.[27-28]

When compared to other scores, the OKS is easier to use and has a higher response rate. However, it does not take into consideration the patient's comorbidities. Patients undergoing total knee replacement are generally elderly and it is rare to find patients without either comorbid medical conditions or arthritis affecting other joints.[29]

Other scores which could have been used in the study and which are commonly found in the literature include the Hospital for Special Surgery Knee Score (HSS Knee Score) and the Knee Society Score (KSS). These scores include pain and function but also consider other parameters like range of motion, muscle strength, flexion deformity, instability, and subtractions.[30]

Only AP views of the knee joint were considered in this study and the tibial shaft length was not uniform in the post op radiographs. Radiographs of the whole tibia or the use of CT scanograms could have given more reliable results.[31]

Most studies carried out considered both the femoral and tibial components of the knee joint. The femoral component was not considered in our study. This could have influenced the final results.

Gromov et al. (2014)[17] state that tibial components should be placed in neutral alignment (90^{o}). Most studies show that a deviation of 3^{o} from the neutral alignment is acceptable for good long-term results. From our study, we can conclude that the angle of deviation does not seem to have any negative correlation with patient outcome, both for varus and valgus TKRs.

Summary

- The goal of tibial component positioning in total knee arthroplasty is to achieve neutral tibial alignment.
- Malalignment of the tibial component alters the distribution of tibial loading, resulting in increased wear.
- Most studies show that a deviation of 3^{o} from the neutral alignment is acceptable for good long-term results.
- This study correlated two radiological parameters (mechanical and anatomical axis) of the tibial component in total knee arthroplasty with patient related outcome measures.

- From our results there was no statistically significant difference in outcome between tibial components in varus, in neutral and in valgus.
- In our study, the angle of deviation in both varus and valgus does not correlate with patient outcome following TKR, as measured by OKS and number of F/Us.

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MMJ

ORIGINAL ARTICLE

Surveillance of bladder management in a local cohort of neuro-urology patients

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Background

Several neurological conditions, including multiple sclerosis and spinal cord injury, can give rise to a neurogenic bladder. Without proper management and regular surveillance, the sequelae of a neurogenic bladder can be devastating, including recurrent urinary tract infections, urolithiasis, and worst of all, renal failure, all of which continue to negatively impact these patients' quality of life. There are two main guidelines available, developed by the European Association of Urologists (EAU) and National Institute of Clinical Excellence (NICE), to aid clinicians in the management of these patients. While both guidelines promote patient risk stratification into high and low risk categories for renal complications, there are several areas of discordance between them.

Method

In this retrospective audit, 58 neuro-urology patients who underwent video-urodynamics within a 6-year period were included, to determine whether they were properly followed-up, according to their risk category, as per the NICE guidelines.

Results

Surveillance rate in the local cohort of neuro-urology patient was low. This could be attributed to the differences between the two guidelines, creating doubt and hesitancy in decision-making in the caring urologists, thus making their application in clinical practice more difficult. Other contributing factors include the lack of proper registries, and the lack of international evidence-based literature in the field.

Conclusion

Through this audit, we aim to emphasise the importance of further international research, as well as, creating a neuro-urology patient database within the local National Healthcare System (NHS) to ensure an optimal surveillance process.

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Introduction

Neuro-urology lower urinary tract symptoms (LUTS) secondary to a Neurogenic bladder may occur due to a number of underlying neurological diseases or events including Spinal Cord Injury (SCI), Spina Bifida (SB) and Multiple Sclerosis (MS), with the type of symptoms depending on the level and extent of the lesion.[1] Renal failure is one of the main mortality factors in patients with Neurogenic bladders, with for instance around 13% of SCI patients dying as a consequence of urological complications.[2] Therefore, maintaining what is known as a safe bladder is a top priority in the treatment of patients with a Neurogenic bladder.[1] A safe bladder refers to a bladder with detrusor pressures during both the filling and voiding phases within safe limits, and with normal compliance; and therefore, a bladder which does not put the patient at high risk of renal function deterioration.

There are a number of international guidelines which aim to guide the caring team in the management of the neurogenic bladder including the European Association of Urology (EAU) guidelines on Neuro-urology[1] and the National Institute for Clinical Excellence (NICE) CG148 guideline entitled Urinary Incontinence in Neurological Disease.[3] Both of these guidelines give guidance on initial assessment, management and surveillance of patients with Neurogenic bladders. However, whilst the EAU guidelines advise that Video Urodynamics (VUDs) should be performed in the assessment of all patients with neurogenic LUTS, the NICE guidelines suggest stratifying patients into those with a low risk of renal deterioration, and those with a high risk of renal deterioration. The latter group should be assessed with VUDs, whilst the former does not.

The NICE guidelines define patients as being at high risk of renal deterioration if there is at least one definite risk factor or two probable risk factors. Definite risk factors include a duration of MS of more than 15 years, presence of an indwelling catheter, high detrusor pressure on VUDs, and ample uninhibited contractions of the detrusor. The probable risk factors include detrusor sphincter dyssynergia (DSD) on VUDs, age over 50 years, and male sex. Patients with hydronephrosis on imaging, a febrile urinary tract infection or evidence of acute urinary retention should also be classified, or re-classified as high risk.[3]

When it comes to surveillance, there is once again some discord between the guidelines. Whilst both guidelines advocate stratification into high and low risk groups for renal deterioration, the EAU guidelines leave the method of stratification at the discretion of the clinician. The EAU guidelines go on to advise lifelong follow-up with clinical review annually, and Ultrasound (US) of the Urinary Tracts at least once every six months in the high risk for renal deterioration group, together with regular urinalysis and annual blood chemistry. Whilst, in the low-risk group the EAU guidelines advise lifelong follow-up with clinical review at least every two years, and regular urinalysis, they also advise that any significant clinical change should prompt investigation and intervention.[1]

Aims

The aim of this audit is to review local adherence rates to the EAU guideline surveillance protocols,[1] with risk stratification as suggested by the NICE guidelines,[3] in a local cohort of neurogenic bladder patients.

Materials and Methods

This retrospective audit includes data on 58 patients who underwent VUDs at Mater Dei Hospital during a 6-year period. Data protection clearance was

obtained prior to the start of data collection. All data was anonymised in a spreadsheet.

The data was collected by analysing all VUDs reports written between March 2015 and March 2021 by the performing Urology trainee or specialist on the local VUDs software. All patients above the age of 18 referred for VUDs in view of neuro-urology LUTS were included in the study. Patients which were deceased by March 2021 were excluded. Patient demographics, urodynamic parameters, imaging and serum or urine biochemistry results, and clinical follow-up appointment dates were manually retrieved from iSoft Clinical Manager and from the local VUDs software accordingly. The Maltese MS registry was also used to retrieve demographic data for patients with an underlying diagnosis of MS.

Patients were stratified into high and low risk for renal deterioration categories based on their demographics, imaging results and VUD findings. Patients were classified into the high-risk category as per the NICE guidelines protocol defined previously, or if their VUD findings indicated that the bladder was unsafe. A patient was categorised as having an unsafe bladder if there was VUD evidence of Vesico-ureteric reflux (VUR), poor bladder compliance or a leak point pressure (LPP) of >40cmH20.

Local adherence to surveillance protocol guidelines was then analysed by calculating percentage adherence to each recommendation, as mentioned previously, for the patients in the high risk and low risk categories. In this regard, data was collected from the date of the VUD study up to March 2021. For patients who underwent multiple VUD studies in the study period data was collected from the date of the most recent VUDs up to March 2021. Microsoft excel® software was used for statistical analysis tests. The standard referred to for surveillance protocol is the EAU Neuro-Urology guideline.[1]

Baseline demographics results

59 patients were initially included, 1 patient had passed away in October 2018 and was excluded from the study. The 58 patients included had undergone a total of 68 VUD studies in the 6-year period, with 48 patients having undergone one study, 5 patients having undergone 2 studies and 3 patients having undergone 3 studies in the study period. 22, 18, 2, 7, 9 and 10 studies were performed in the first to the sixth study period respectively, with each period being taken as 12 months starting from March 2015 and ending March 2021.

The age of the patients recorded, was the age at the time of their last VUD study in the study period. The mean age of the patients included was 46.8. The youngest patient included in the study was 18 at the time of the VUD study and the oldest 79 years.

36.2% (*n*=21) of the patients included were female, whilst 63.8% (*n*=37) of the patients included were males. This lack of balance may reflect the fact that many underlying conditions for neurogenic bladders having a higher prevalence in the male population. For instance, spinal cord injury is around 3 to 4 times more common in males than females.[4]

The frequency of the various underlying conditions in the group is illustrated in table 1. The most common underlying conditions in the group were SCI, SB and MS which represented 24.1% (*n*=14), 22.4% (*n*=13) and 13.8% (*n*=8) respectively.

46.5% (*n*=27) of the patients were classified as high risk based on their demographic factors, imaging results or previously known urodynamic parameters. 15.5% (*n*=9) patients were classified as high risk based on the urodynamic parameters from the VUD study reports reviewed. This left 37.9% (*n*=22) of the patients in the low risk for renal deterioration category.

Table 1: Frequency of Underlying Neurological Conditions or Events resulting in Neurogenic LUTS

Underlying Neurological Condition or Event resulting in Neurogenic Bladder	*n*=	%
Post Abdominoperineal Resection	**1**	**1.7**
Cauda Equina Syndrome	**2**	**3.4**
Cerebellar Ataxia	**1**	**1.7**
Chronic Inflammatory Demyelinating Polyneuropathy	**1**	**1.7**
Disc Prolapse/Cord Compression	**7**	**12.1**
Cerebral Vascular Accident	**2**	**3.4**
Decompression Sickness	**2**	**3.4**
Devic's Syndrome	**1**	**1.7**
Diabetic Neuropathy	**1**	**1.7**
Post Laminectomy/Discectomy	**2**	**3.4**
Multiple Sclerosis	**8**	**13.8**
Spina Bifida	**13**	**22.4**
Spinal Cord Injury	**14**	**24.1**
Spinal Cord Infarct	**1**	**1.7**
Transverse Myelitis	**1**	**1.7**
Wolfram Syndrome	**1**	**1.7**

Outcome results

For the high risk for renal deterioration group, adherence to 5 recommendations put forward by the EAU neuro-urology guidelines was audited. These surveillance recommendations are that high risk patients should undergo lifelong follow up, clinical review annually, US every 6 months, regular urinalysis (which was taken to mean urinalysis annually), and annual blood chemistry (creatinine). Adherence rates to these recommendations were found to be 69.4%, 69.4%. 8.3%, 25% and 66.7% respectively. Table 2 illustrates these adherence rates graphically.

For the low risk for renal deterioration group, adherence to 3 recommendations put forward by the EAU neuro-urology guidelines was audited. These surveillance recommendations are that low risk patients should undergo lifelong follow up, clinical review every 2 years, and regular urinalysis (which was taken to mean annually). Adherence rates to these recommendations were found to be 63.6%, 72.7% and 18.2% respectively. Table 3 illustrates these adherence rates graphically.

Table 2: Adherence rates to EAU Surveillance Recommendations for High-Risk for Renal Deterioration Neurogenic Bladder Patients

Total High-Risk Surveillance *N*= 36			Adherence
Lifelong Follow Up	No	11	
	Yes	25	0.694
Clinical Review Annually	No	11	
	Yes	25	0.694
US every 6 months	No	33	
	Yes	3	0.083
Urinalysis every 6 months	No	27	
	Yes	9	0.25
Annual Blood Chemistry	No	12	
	Yes	24	0.667

Table 3: Adherence rates to EAU Surveillance Recommendations for Low-Risk for Renal Deterioration Neurogenic Bladder Patients

Total for Low-Risk Surveillance N= 22			Adherence
Lifelong Follow Up	No	8	
	Yes	14	0.636
Clinical Review every 2 years	No	6	
	Yes	16	0.727
Urinalysis Regularly	No	18	
	Yes	4	0.182

Discussion

Continuous surveillance of bladder function in neuro-urology patients is imperative as disease progression may occur in a very short period of time.[5] In addition, there is very little correlation between disease severity and symptomatology.[6] Through regular surveillance, the effect of any intervention or change in management can also be assessed and other treatment options considered according to new findings.[7]

Even though the importance of surveillance is highlighted in most literature, the specific methods, timing and frequency are not clearly identified. This

is attributed to a lack of international evidence-based research on the subject, as most of the available information is derived from retrospective studies and expert opinion.[8-9] The same issue applies to the local situation, whereby, to the authors' knowledge, there have been no local studies and audits on the management of neurogenic bladders up till now. This can also be related to the absence of registries compiling data on patients with neurogenic bladder according to their specific cause, therefore making patient follow-up very difficult. To date, the MS register is the only pertinent register available in this regard in Malta, and this was utilised in this audit to determine the year of MS diagnosis, for risk stratification purposes. Encouragingly, a new guideline on the bladder management in patients with spinal cord injury has recently been developed and published on the local clinical guideline database. This aims to guide the multidisciplinary team in the acute and long-term management of patients with neurogenic bladders secondary to spinal cord pathology.

The lack of surveillance in the local population could possibly be related to the discordance between the available international guidelines, leading to hesitancy from the clinician's point of view. Furthermore, in both the NICE and EAU guidelines, there are several areas of ambiguity, resulting in further uncertainty in clinical practice. One example is that both guidelines mention regular urinalysis as part of the surveillance protocol. However, neither define accurately the interval period. Subsequently, the interval was taken to be equivalent to 1 year in this audit, without any actual scientific basis. This, once again, can be attributed to lack of research on the subject. Another point to consider is that given the limited data available, clinicians are likely to adapt their surveillance method, frequency and duration according to the national healthcare system in which they practice. Although NICE is the more cost effective of the two guidelines, given that it is based on the British NHS, their actual clinical application is still limited by funds and resources available to the caring urologist.[10]

There were several limitations in this study. The most obvious one was the small number of patients involved in this audit, especially in the last 3 years of the study period. One reason for this could be that since VUDs is an invasive investigation, patients might not be willing to undergo the procedure. In addition, in view of the ongoing Covid-19 pandemic, many of the elective procedures, including VUDs were cancelled or postponed. Furthermore, in Malta, patients might be followed-up by Urologists outside the National Healthcare system (NHS), leading to patient loss from the database and missing surveillance data.

Another limitation was that in Malta, air-charged catheters are used during VUDs, while the ICS Standardised Urodynamic Protocol is based on water-charged protocols, leading to possible risk stratification errors. Additionally, since patient information and selection were taken largely from VUD reports, which are heavily operator-dependent, possible documentation errors could arise, again leading to inaccuracies in risk stratification. Another possible issue is that the indication for regular serum creatinine, urinalysis and ultrasonography might have been completely unrelated to the surveillance process, given that such patients have several co-morbidities, requiring multiple hospital admissions and follow-ups from other specialties.

Conclusion

Although both EAU and NICE guidelines are very useful aids to the caring Urologists for proper bladder management in neuro-urology patients, the

discordance between the two bodies, as well as, the overall lack of randomised controlled studies, results in problems with surveillance in this patient cohort. Other possible attributing factors to the low surveillance in the local population include the lack of patient registries and evidence-based literature.

In the Maltese NHS, the first step forwards towards better surveillance and hence the prevention of further complications in neuro-urology patients, has been the introduction and piloting of a "Bladder Management in Spinal Cord injury guideline". However, much more work needs to be done in the field, both locally, through the introduction of specialised registries, as well as internationally, through good-quality randomised control studies.

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MMJ

ORIGINAL ARTICLE

Axilla management in sentinel node positive breast cancer patients at Mater Dei Hospital – An audit and literature review

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Background

Surgical axillary clearance and axillary radiation therapy (ART) provide comparable loco-regional control and survival in patients with sentinel node positive breast cancer. Specifically, ART is associated with less post-therapeutic complications, such as lymphoedema. Our objective is to review the current axillary management for patients with positive SLN breast cancer, within our local hospital, and assess whether this therapeutic protocol complies to the international criteria as highlighted in 10-year follow-up of the large European Organisation for Research and Treatment of Cancer (AMAROS) trial. Ascertaining a safe and minimally invasive oncological therapeutic strategy, without compromising its efficacy, may improve long term morbidity in patients with breast cancer.

Methods

A retrospective and quantitative analysis of 329 patients with breast cancer who underwent an axillary SLN procedure at Mater Dei Hospital (MDH) between January 2019 and 2020 was performed. The inclusion criteria were patient demographics, pre-/post-operative staging, tumour size, and treatment given. Data was analysed and compared to International randomised trials. The San Matteo Criteria based on the AMAROS trial, were reviewed, and used as a standard and compared to local practice.

Results

329 patients were analysed, of which 284 patients fulfilled the inclusion criteria. 70 patients had a positive SLN with 74% having one SLN positive, of which 40% underwent ALND, 6% had ART, 2% refused ART and 52% received no treatment. 26% had 2 positive SLNs of which 44% underwent ALND, none received ART and 56% received no treatment in those with two positive SLN. Patients with more than 2 positive SLNs were excluded.

Conclusion

We have determined that ALND is the accepted management for breast cancer patients with positive SLN in MDH. ART should be considered as a more favourable treatment option in patients with positive SLN being treated as it provides comparable results with significantly lower morbidity than ALND.

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Introduction

Breast cancer is a leading oncological diagnosis in women worldwide. Despite the incidence for breast cancer before the age of 50 in Western countries being 35%, and 5% occuring at a younger age,[30] the overall morbidity and mortality has decreased over the years due to the advent of breast cancer screening programmes, and the introduction of effective management protocols.

The diagnostic work-up of breast cancer involves a 'Triple Assessment' including a physical examination of the breast and locoregional lymph nodes (axilla, supraclavicular fossa), imaging (mammography, ultrasound, Magnetic Resonance Imaging), and pathological assessment of breast tissue or lymph nodes (core needle biopsy, Fine Needle Aspiration).

Following histological analysis of breast tissue, and lymph nodes respectively, staging of the tumour follows the 'tumour-node-metastases' (TNM) classification.

In the management of early breast cancer nodal status is the single most important prognostic factor. Nodal status is important because it serves as a marker of tumour metastatic potential, which translates to survival advantages of up to 40% at five years. Other factors such as grade, size of the tumour and hormonal receptor status (ER, PR, HER2), are of secondary importance as they are both less concerning in the absence of nodal involvement.[6,25]

Studies have shown that accurate staging of the axilla and assessment of lymph node status is an essential component of breast cancer management.[7,13] The TNM staging classifies the extent of metastasis in lymph nodes as follows: isolated tumour cells (<0.2mm), micro-metastases (tumour deposits 0.2-2mm), or macro-metastases (tumour deposits >2mm). Involvement of the axillary nodes has an adverse effect on prognosis of breast cancer with a ten-year survival reduced from 75% to 25%.[2] In fact, level three lymph node involvement carries the worst prognosis.[24] Historically, management of the axilla ranged from limited level 1 axillary node excision through to full level three axillary nodal clearances.

Attempts to minimise the morbidity of axillary node clearance led to targeted operations including axillary nodal sampling and sentinel lymph node biopsy (SLNB). The sentinel lymph node (SLN) is the most likely lymph node to harbour metastasis from the breast tumour. It is identified, biopsied and surgically removed by using tracers that mimic the route of cancer cells from the tumour site through the lymphatic vessels towards the nodes. To assess the pathological status of the axillary lymph nodes (ALNs), in patients with clinical stage I/II breast cancer and without cytohistological evidence of metastatic axillary metastases, SLN mapping and concomitant resection during surgery is highly recommended for diagnosis.[5,22] SLNB is an accurate way of determining further adjuvant treatment and prognosis.[8]

Our current practice of identifying the SLN during breast cancer surgery involves an injection of methylene blue dye around the tumour directed towards the axilla and pre-operative radiological-assisted administration of radioactive labelled technetium-99m colloid around the area of the tumour. The latter is a gamma-emitting colloid commonly used in the scintillation scanning of the reticulo-endothelial system. This will be confirmed clinically during surgery using a gamma probe which detects technetium-99m decay. The SLN will be the first to take up both methylene blue and technetium-99m colloid, and hence have a higher uptake.[14,15]

Treatment options for breast cancer include local and systemic treatment. Local treatment involves surgery (to the breast and to the axilla) and radiotherapy. Randomised clinical trials have shown that survival rates were similar for women treated by mastectomy or breast conservation surgery (BCS).[3,11] Currently, 60-80% of newly diagnosed breast cancers in Western Europe are amenable to BCS (wide local excision and radiation therapy).

Adjuvant systemic treatment involves endocrine therapy in all patients with detectable ER expression i.e., pre-menopausal are treated with nonsteroidal anti-oestrogen such as tamoxifen, and post-menopausal with aromatase inhibitors.

In contrast, chemotherapy is recommended in most patients with triple negative hormone receptors, HER2-positive breast cancers and in high-risk HER2-negative tumours. The benefit from chemotherapy is more pronounced in ER-negative tumours.

Management of Axillary Metastasis: ALND vs ART vs no treatment

The optimal management of micro-metastatic spread and isolated tumour cells is the subject of ongoing research. Based on the results of the IBCSG 23–01 trial, further axillary treatment does not seem to be required when a sentinel node has micro-metastasis.[15,16] The presence of macro-metastatic spread in the sentinel node traditionally mandated conventional axillary lymph node clearance. Thus, patients with isolated tumour cells (ITC) (<0.2 mm) in the sentinel node and patients with limited involvement of the sentinel lymph node undergoing tangential breast irradiation may not need to have any further axillary procedure.[12]

Aim

This audit will review the clinical practice of axillary management of breast cancer patients in Malta, following identification of positive SLN. The data retrieved through MDH databases will be compared to international criteria. We will assess whether the possibility of de-escalating therapy might improve the morbidity of our patients without compromising their outcomes.

Materials and Method

Audit Design

Data protection approval was obtained from the Data Protection Office at Mater Dei Hospital (MDH). Permission to access patient data from the MDH database was obtained via written consent form the three breast cancer consultant surgeons operating at our local government hospital. Furthermore, access to the histology reports of such patients was retrieved from histopathologists and their databases. A list of breast cancer patients who underwent an axillary sentinel lymph node procedure at the Agatha Breast Unit at Mater Dei Hospital, during the period of January 2019 to January 2020 was obtained from the Clinical Performance Unit at MDH with the approval of the consultants. Data was collected in a retrospective manner.

Every patient was assigned an individual numerical code and was included in a data sheet shared among the researchers and assistants. This data was stored for two months. Patient demographic data and information relating to preoperative imaging and histology, size, grading, lymph node involvement of the breast malignancy was gathered and further substantiated through online software systems including iSoft Clinical Manager® and Electronic Case Summary®. No Health Ethics Committee

Approval was required for this initiative as this was a retrospective study with no patient contact.

Inclusion and Exclusion criteria

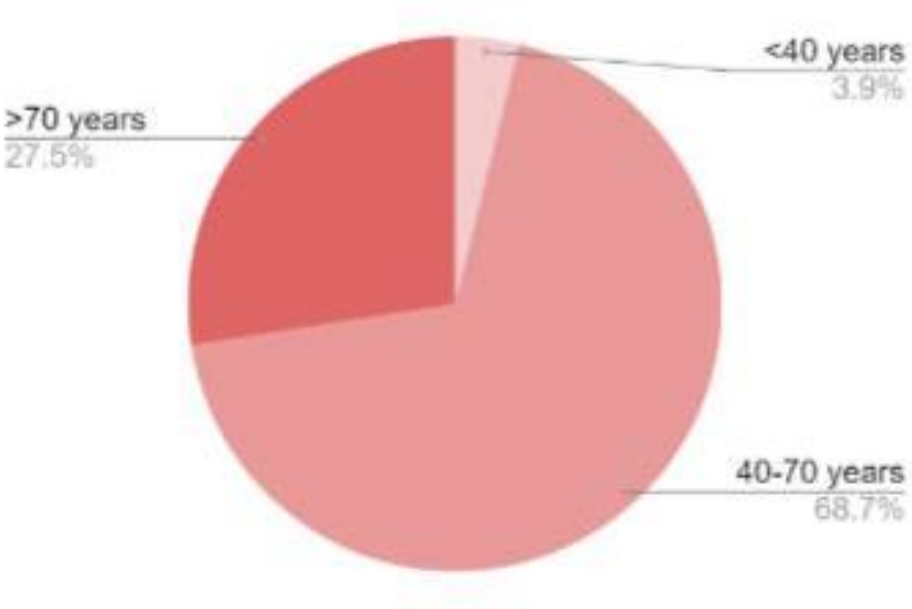
A sample of 284 patients were included in this audit who appropriately fit the inclusion criteria. This cohort consisted of patients with a tumor size of pT1 and T2, had a Wide Local Excision (WLE) or Mastectomy, had a SLNB performed, and/or had no neoadjuvant chemotherapy.

A sample of 48 patients were excluded. The following exclusion criteria were applied based largely on the San Matteo Criteria 2019: patients who had large tumors (pT3 and over), patients who had >2 positive SLN, patients who had complete primary axillary clearance, patients who received neoadjuvant treatment, and patients whose histological result was not invasive ductal or lobular carcinoma. The latter criterion included patients diagnosed with ductal carcinoma in-situ (DCIS), papillary carcinoma and phyllodes tumours.

Data Analysis

The 284 eligible breast cancer patients who met our inclusion criteria were divided into two categories as follows: patients with a positive SLN (*n*=70) and patients with a negative SLN (*n*=214). The patients with a positive SLN were further subdivided into two categories: patients with one positive SLN (*n*=52), and patients with two positive SLN (*n*=18). In addition, these latter groups were analysed based on the presence of micro- vs macro-metastases. A flow diagram outlines the structure of the study (Reference of the flow chart i.e. Figure 1)

Figure 1: Demographic Data



RESULTS

329 patients were included in this audit. Out of these, 45 patients (13.68%) were excluded since they did not meet the inclusion criteria. These patients were as follows:

- 8 patients (2.43%) had more than two positive SLN.
- 10 patients (3.04%) had a pT3 primary lesion.
- 17 patients (5.17%) had a postoperative histology report showing DCIS.
- 5 patients (1.52%) had a postoperative histology report showing Papillary Carcinoma.
- 1 patient (0.30%) had a postoperative histology report showing Phyllodes Tumor.
- 7 patients (2.13%) received neoadjuvant chemotherapy.

Demographics

The overall mean age of subjects was 61 years. Breast cancer patients were categorised according to the age as follows (shown in Figure 1):

- Less than 40 years of age, of which there were 11 patients (3.87%).
- Between 40-69 years of age, of which there were 195 patients (68.66%).
- More than or equal to 70 years of age, of which there were 78 patients (27.46%).

Procedure

Out of 284 patients, 264 patients (92.96%) underwent a Wide Local Excision (WLE) and 20 patients (7.04%) underwent a mastectomy. Patients who underwent a mastectomy have a lower representation rate and do not represent a large tumor size.

Post-operative histological grade and type

Out of 284 patients, 223 patients (78.52%) had an invasive ductal carcinoma (IDC), 44 patients (15.49%) had an invasive lobular carcinoma (ILD), one patient (0.35%) had tubular carcinoma, four patients (1.41%) had a mucinous tumour, two patients (0.70%) had a micropapillary cancer and one patient (0.35%) with an apocrine carcinoma. Nine patients (3.17%) had a mixed histology result.

The histological grade of these carcinomas was as follows (shows in Figure 2):

- 87 specimens were Grade 1 (30.63%)
- 132 specimens were Grade 2 (46.48%)
- 62 specimens were Grade 3 (21.83%)
- 2 specimens were Grade 1/2 (0.70%)
- 1 specimen was Grade 2/3 (0.35%)

Post-operative Tumor Size (pT)

Out of 284 patients, 197 patients (69.37%) had a tumor size of </=2cm i.e., T1. 87 patients (30.63%) had a tumor size of >2 cm but </=5cm i.e., T2 as per TNM staging classification (shown in Figure 3). Most of the subjects had small to medium sized tumors. The cut-off size in this research was 5cm.

Lymph node involvement: Amount and presence of micro- or macro-metastasis

Out of 284 patients, 214 patients (75.35%) had no lymph nodes involvement, and 70 patients (24.65%) had a positive SLN as shown in Figure 4.

52 patients (74.29%) out of the 70 breast cancer patients had one positive SLN, of whom 17 patients (32.69%) had micro-metastasis and 35 patients (67.3%) had macro-metastasis. From the 17 patients who had micro-metastasis in one positive SLN, 16 (94.12%) received no treatment to the axilla, while 1 patient (5.88%) had axillary clearance and none of the patients received radiotherapy as seen in Table 1

Figure 2: Post-operative Histological Grade data

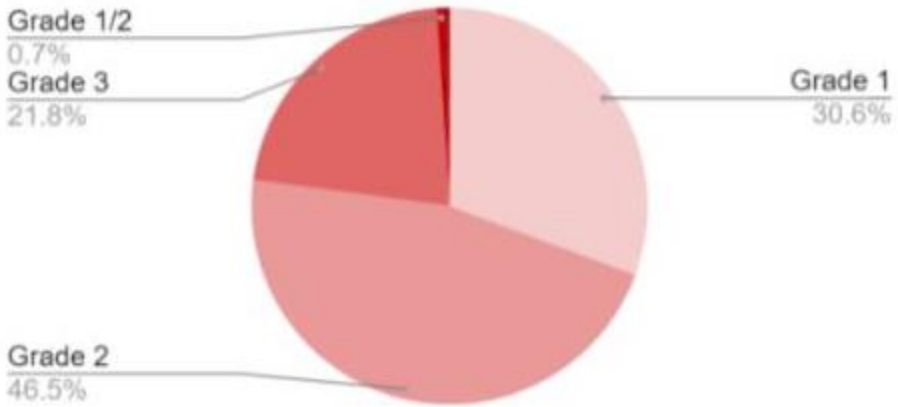


Figure 3: Post-operative Tumor Size (pT)

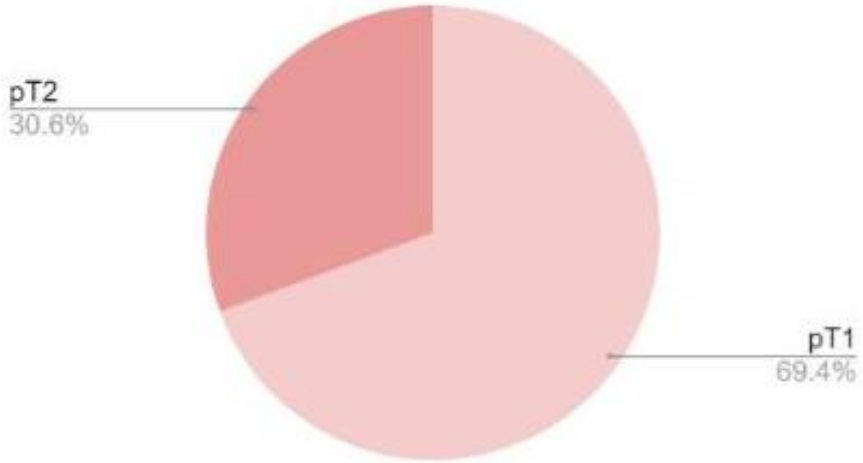


Figure 4: Number of eligible patients with positive and negative SLNB.

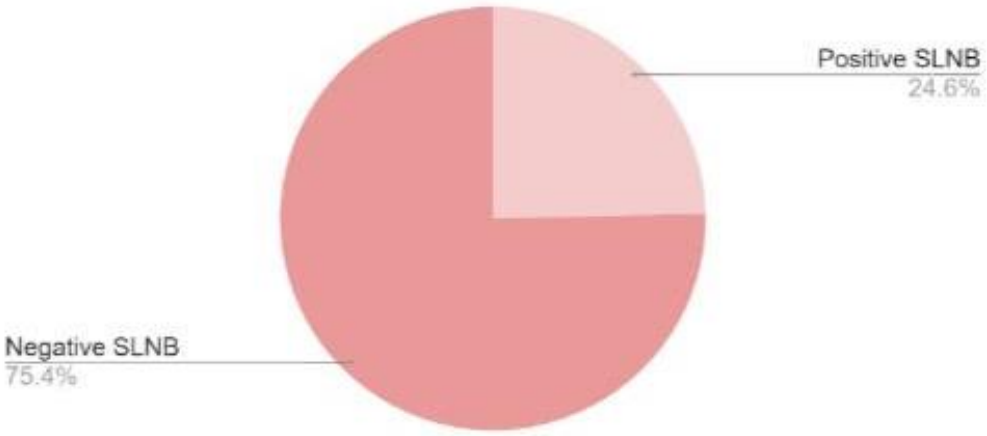


Table I: Result table of patients with one positive SLN.

1 Sentinel lymph node positive: 52 patients (74.29%)	
Micro-metastasis: 17 (32.69%)	**Macro-metastasis: 35 (67.3%)**
Axillary clearance: 1 (5.88%)	Axillary clearance: 20 (57.14%)
Radiotherapy: 0 (0%)	Radiotherapy: 3 (8.57%) Radiotherapy refused: 1 (2.86%)
No treatment: 16 (94.12%)	No treatment: 11 (31.43%)

Out of 35 patients who had macro-metastasis in one positive SLN, 11 patients (31.43%) received no treatment to axilla (2 of which had distant metastasis), 3 patients (8.57%) received radiotherapy to the axilla, 1 (2.86%) refused radiotherapy to axilla and 20 patients (57.14%) had axillary clearance (1 of whom had distant metastasis) as seen in Table 2.

Out of the 70 patients with positive SLN, 18 (25.71%) had two positive SLNs; of whom three patients (16.67%) had micro-metastasis and 15 patients (18.33%) had macro-metastasis. Out of the 3 patients with micro-metastases; one patient (33.33%) (pT2) received no treatment, none received radiotherapy and two (66.67%) (pT1) had axillary clearance. Out of the 15 patients with macro-metastasis, six (40%) had axillary clearance, nine (60%) received no treatment. From the nine who received no treatment, two (22.22%) were diagnosed with distant metastasis and another two patients (22.22%) were above the age of 70.

Table 2: Result table of patients with two positive SLN.

2 Sentinel lymph nodes positive: 18 patients (25.71%)	
Micro-metastasis: 3 (16.67%)	**Macro-metastasis: 15 (18.33%)**
Axillary clearance: 2 (66.67%)	Axillary clearance: 6 (40%)
Radiotherapy: 0 (0%)	Radiotherapy: 0 (0%)
No treatment: 1 (33.33%)	No treatment: 9 (60%)

Discussion

The focus on SLNB has led to more detailed pathological evaluation of excised lymph nodes e.g., the use of immunohistochemistry, allowing for more detailed analysis of axillary nodal micro-metastases. Tumor nodal burden is a continuous variable. The size of LN metastasis i.e., whether it is ITC (<0.2mm), micro-metastasis (0.2-2mm) or macro-metastasis (>2mm) has a proportional effect on the survival outcome in early breast cancers. Therefore, the smaller the metastasis the less effect on the patient's outcome, which in turn means that further axillary management will not be beneficial.[23]

Clinically apparent axillary disease is treated as for advanced breast cancer. On the other hand, breast cancer patients with negative clinical examination undergo SLNB. Patients with clinically node negative but positive SLNB, have historically been managed with ALND following the rationale that this has a better prognostic outcome. However, this surgery has side effects as mentioned above without improving survival.[16-22]

The advantage of ALND is that it optimizes regional control, provides additional prognostic information, and potentially improves overall survival (OS). However, some patients do not need ALND because of a low risk of residual disease or recurrence.[16-17]

If the sentinel node is negative, then patients do not need to proceed with ALND. This recommendation is supported by results of multiple randomized clinical trials which show that in 15–20% of cases, an ALND leads to persistent and troublesome complications such as impairment of shoulder function, shoulder pain, paresthesia over the inner aspect of upper arm and axilla due to intercostobrachial nerve injury or lymphoedema.[11,29] Additionally, studies have shown that there is no difference between SLNB or Level I and II dissection in determining the metastatic status of axillary nodes if an experienced team performs such a procedure.[10]

The presence of micro-metastasis and its impact on survival is debated. In some studies, it seems to confer an increased risk of locoregional recurrence[4] and a reduction of disease-free survival[19], whilst in others it shows no overall impact.[6] It is important to distinguish between micro-metastasis and isolated tumour cells, as the latter do not have an adverse impact on prognosis.[25]

The need for definitive treatment of the axilla in breast cancer patients with positive sentinel nodes was addressed by the ASCOG Z0011 trial. In this trial, women were randomised to undergo axillary lymph node clearance or to observation without surgery. Groups were further adjusted for other prognostic factors and treatments. The investigators found no survival benefit in routinely undertaking axillary node clearance, where axillary nodal disease was limited in its extent. Regardless of the options in women with a low-risk axilla, those individuals who have overt evidence of axillary nodal involvement either through positive SLNB or preoperative ultrasound and fine needle aspiration, should still receive complete axillary treatment be it clearance or radiotherapy.[16-17]

75.35% of the patients who satisfied the inclusion criteria had a negative SLNB. These patients did not need any further axillary treatment as the recurrence risk is very low. In contrast, 24.65% of the patients in our study had a positive SLN, which were further categorized as highlighted in the 'Results' section. In this category of breast cancer patients, a cut-off of two positive SLN was used as per recommendations listed in the *'San Matteo Criteria'*.

Recent clinical trials also suggest that ALND may be omitted safely in selected patients who are clinically

node negative, with metastatic carcinoma limited to one or two SLNs.[23] SLNB is equivalent to ALND for staging of the axilla in patients with clinically node-negative (cN0) disease as proven in many studies. This also offers the advantage of significantly less morbidity, most notably lymphoedema and shoulder pain.[23]

Our audit showed that 94.12% of breast cancer patients with one positive SLN with micro-metastasis had no further treatment to axilla and only 5.88% underwent axillary clearance. On the other hand, 66.67% of patients who had two positive SLNs with micro-metastasis, an axillary clearance was performed, while 33.33% had no treatment. No radiotherapy to the axilla was performed in both these groups. The St. Gallen Consensus Panel (2009) did not recommend ALND to three distinct groups of breast cancer patients as follows: those with SLN detected micro-metastasis, patients with isolated tumour cells, and other with well-differentiated and small tumours. It was agreed that axillary radiotherapy would be a better alternative to ALND, as it had the same outcome with less morbidity.[30] More than half of the patients (57%) with one positive SLN with macro-metastasis underwent ALND, 8.6% received axillary RT while 31% received no treatment to the axilla. In contrast, 60% of patients who had two positive SLN with macro-metastasis, received no treatment to the axilla. Reasons for this included the presence of distant metastasis, underlying multiple comorbidities and age above 70 years. 40% of patients who had two positive SLN with macro-metastasis received ALND and none received ART. This shows that various factors may affect the decision to treat the axilla and which modality of treatment is chosen. Studies have shown that not performing a SLNB in patients with cN0 and aged 70 years or older may reduce morbidity associated with such a procedure due to similar outcomes and better quality of life. The reasoning behind this is that treatment recommendations were unlikely to be altered based on the SLN status. Elderly patients were more susceptible to dying of alternative causes other than breast cancer, thus SLNB did not affect their survival. In fact, the NCCN guidelines suggest that in the lack of data showing superior survival, SLNB for axillary staging may be optional in patients with serious comorbidities and the elderly.[23]

Recent results of the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial from the EORTC (European Organisation for Research and Treatment of Cancer) compared the locoregional control and survival of patients who had clinical T1–T2 cN0 invasive breast cancer and 1 to 2 sentinel lymph nodes containing metastases. This trial showed that there were no significant differences in 10-year (10y)-OS, 10y-axillary recurrence and 10y-DMFS (Distant metastasis-free survival) and between patients who underwent Breast Conserving Surgery (BCS) with surgical lymph node dissection and tangential adjuvant Whole Breast Radiotherapy (WBRT) or Mastectomy randomised to axillary radiotherapy (ART) against ALND.[7,11]

Conclusion

We have determined that ALND is the preferred management option for breast cancer patients with positive SLN at MDH, even though the AMAROS trial has shown that ART is not inferior to ALND. The trial did not find any significant difference between ART and ALND in treating this category of breast cancer patients. However, such findings cannot be applied to all groups of patients, as in some groups (distant metastasis and elderly) no treatment was commoner.

Limitations

While performing data collection it was noted that there was missing information relating to the booking of the 'Radiotherapy Planning CT scan' on iSoft Clinical Manager®. Oncologists failed to specify the area of breast to be irradiated, and whether such radiotherapy was adjuvant treatment to the breast or ART. Furthermore, oncological follow up information on breast cancer patients is documented and stored separately in files at the Sir Anthony Mamo Oncology Centre. Therefore, crucial information such as management plans, could have been missed. Secondly, breast cancer patients in Malta are seen by different oncologists with their own preferred approaches to managing breast cancer, specifically axillary treatment which influences management of patients. Also, missing data relating to radiological or histological investigations performed at private institutions were not uploaded on the online software systems, which in turn resulted in untraceable data. Lastly, 284 breast cancer patients fulfilled the inclusion criteria for our study. Out of this cohort only 70 patients had positive SLN, which is not significant and not representative. A prime example is the demographic data. Like other international studies the younger cohort are under-represented, where only 3.87% were less than 40 years of age at the time of diagnosis. This was a result of the natural history of the disease and selection bias. Mastectomies were also underrepresented in this audit, with only 7.04% of eligible patients who underwent such a procedure.

Suggestions and Recommendations

Over the years, there have been international changes in practice guidelines which are shifting away from the management option of ALND. Several randomised controlled trials have shown that in terms of outcome both ART and ALND are similar, however ALND carries a greater morbidity risk towards the patient. As we discussed earlier, the preferred management option at Mater Dei Hospital is ALND. We recommend that another study in the form of a questionnaire should be carried out amongst the Maltese breast cancer specialists (surgeons, oncologists, radiologists) to try to understand why the majority prefer ALND to ART.

We suggest that better documentation should be given priority, especially when it comes to writing the indication of ART, and the area of therapy through the online request forms and on the oncology notes. Documents from SAMOC should be made available and accessible to MDH staff through online software systems to allow better continuity of care within a multi-disciplinary team environment.

Although our audit included 284 breast cancer patients, only 70 patients had a positive SLN. Thus, we recommend that the data collected through this study is re-audited at a later stage and larger sample size should be considered.

Finally, ART should be considered as a more favourable treatment option in patients with positive SLN at MDH, as it provides comparable results with significantly lower morbidity than ALND, in terms of causing significantly less lymphoedema, shoulder pain and stiffness than the surgical management alternative.

SUMMARY

- The size of the LN metastasis has a proportional effect on survival outcome in early breast cancers.
- ALND is preferred management option for breast cancer patients with positive SLNB in MDH.

- Patients with positive SLNB managed with ALND have significant side effects.
- Various factors may affect the decision to treat the axilla and which modality of treatment is chosen.
- AMAROS trial has shown that ART is not inferior to ALND in breast cancer patients with positive SLNB.
- Findings cannot be applied to all groups of patients as in cases with distant metastases and elderly no treatment was commoner.

Acknowledgements

We would like to express sincere gratitude to the staff of the Department of Histopathology, MDH and Medical Records SAMOC respectively, for their support and assistance during the retrieval and collection of data for the purposes of this audit.

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MMJ

ORIGINAL ARTICLE

A local study of radiological findings in children diagnosed with urinary tract infection

Nadine Anne De Battista, Valerie Said Conti

Background

Urinary tract infection (UTI) is a common cause of morbidity in children, requiring investigation to avoid complications. This study aims to:

describe the microorganisms grown on culture according to age at presentation

look for a relationship between abnormal US and/or MCUG results and age and clinical presentation

explore whether an abnormal MCUG was associated with abnormal US

explore whether a DMSA provides additional information to that already given by an US and/or MCUG

Methodology

All children less than 16 years of age hospitalised for upper or lower UTI, from the 1st January 2019 up till 31st December 2019 were included. Demographics, urine culture and imaging results were collected through the hospital clinical system.

Results

A total of 96 children were included. *E. Coli* was the commonest causative organism across all ages. 30 children underwent both US and MCUG, whilst 14 underwent US, MCUG and DMSA. Age and clinical presentation did not highlight a statistically significant relationship with abnormal findings on US and/or MCUG. 20% of children had a normal US but an abnormal MCUG. There were no abnormal DMSA results for children with normal combination US and MCUG.

Conclusion

MCUG is still warranted in cases of normal baseline US, irrespective of age and gender. Given that our study was not powered enough, it was not possible to ascertain whether DMSA adds additional information in children with a normal US and MCUG. Further studies with larger cohorts are warranted with the aim of reducing DMSA referrals, radiation, and costs.

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Introduction

Urinary tract infection (UTI) is one of the commonest presentations of children to medical services and can be a significant cause of morbidity. Although most children recover fully with no further sequelae following treatment, a minority, especially those presenting with atypical or recurrent episodes, will require further investigation and follow up in order to avoid long-term complications of chronic kidney disease and hypertension.[1]

Treatment with fluids and antibiotics and performing radiological studies to elucidate any underlying abnormality are mainstay in managing children presenting with a UTI. The age of presentation and type of infection, which can be classified as typical or atypical, and/or recurrent, help guide further investigation using different imaging modalities. First-line imaging investigations usually involve a renal ultrasound, a non-invasive modality that can be very useful to detect anatomical abnormalities of the renal tract such as abnormalities of kidney size and structure, evidence of obstruction or reflux (presence of hydronephrosis and/or hydroureter) and significant renal scarring. When indicated, this is then followed by more invasive imaging such as micturating cystourethrography (MCUG), which further confirms or excludes the presence of reflux, delineates the bladder outline and excludes ureterocoeles or posterior urethral valves in boys; and 99mTc-labeled dimercaptosuccinic acid (DMSA) renal scintigraphy for split kidney function evaluation and detailed mapping of any renal scarring. Other radiological investigations include diethylene triamine pentaacetic acid (DTPA)/ mercaptoacetyltriglycine (MAG3) renal scintigraphy, a dynamic modality that determines relative kidney function, blood flow and obstruction of the kidneys and, more recently, magnetic resonance urography to delineate the anatomy of the renal tract. One or more of these modalities may be used depending on the issues that need to be addressed.

Although UTI is a common infection in childhood, it is estimated that only 4% of cases will have renal scarring which is visible on DMSA scans. An even smaller proportion of these cases will develop long-term complications.[2] Invasive radiological imaging techniques can be psychologically traumatic to both children and carers alike, with complications including exposure to radiation and introduction of infection via catheterisation in the case of MCUG. Therefore, guidelines and local protocols [3,4] have been established to put forward recommendations for use of different modalities of imaging, with various studies examining the findings of ultrasound, MCUG and DMSA to determine the respective efficacy of each in predicting abnormalities in structure and function of the urinary tract.[5-6]

Objectives

The aims of this study are:

1. To describe the pattern of microorganisms grown on culture according to age at presentation.
2. To look at whether there is any relationship between the presence of abnormal findings on US and/or MCUG vs age and clinical presentation of UTI.
3. To explore whether an abnormal MCUG was associated with abnormalities on US, for a cohort of children who had both an US and an MCUG performed.
4. To explore whether performing a DMSA scan adds more information to that already given by an US and/or MCUG.

Methodology

Permission was obtained from the chairman of the Department of Adolescent and Child Health, the Data Protection Office and CEO office at Mater Dei Hospital.

A list of children up to 16 years of age admitted for management of UTI was obtained from departmental handover sheets, in keeping with the following inclusion criteria.

Inclusion criteria

- All children less than 16 years of age hospitalised for urinary tract infection (both upper and lower) from 1st January 2019 up till 31st December 2019.
- Only positive urine cultures obtained through clean-catch and catheter collection were considered.

Exclusion criteria

- Positive urine cultures obtained via bag collection.
- Positive urine cultures from children discharged from the Paediatric Emergency Department.

The following data was collected through the hospital electronic clinical manager system:

- Age at time of admission
- Gender
- Typical *vs* Atypical infection
- Culture results
- First episode of UTI vs recurrent UTI
- Result of any US – abnormal/normal
- Result of any MCUG
- Result of any DMSA

For the purpose of this study, atypical infection was defined as the presence of one of:

- Presence of an abdominal or bladder mass
- Poor urine flow
- Raised creatinine levels
- Septicaemia and serious illness
- Non-E. Coli infection on final culture
- Poor response to initial antibiotics after 48 hours

This data was collected through analysis of information documented on online investigation request forms and departmental handover sheets. Results for creatinine levels and culture results were obtained through the online hospital clinical manager system.

Recurrent infection was defined as per local protocol, that is:

- Two or more episodes of upper UTI OR
- One episode of upper UTI + one/more episodes of lower UTI OR
- Three/more episodes of lower UTI

All the above data collected was analysed using Microsoft Excel software. Chi square/Fisher test were used for interpretation of some of the results obtained.

Results

Demographics

A total of 96 children were admitted during the study period. 88 (91.6%) had a UTI confirmed on urine culture analysis whilst another 8 children were treated for UTI on clinical grounds, despite this not being confirmed on culture.

Table 1 below shows the sex and age distribution of the population studied. The commonest age group requiring admission was that below 6 months of age (42.7%), with a male predominance (70.7%). On the other hand, a female predominance was observed above 6 months of age.

Table 1: Age and sex distribution of population studied

		No (%) of patients	
Age group	**Total (%)**	**Male**	**Female**
< 6 months	41 (42.7)	29 (70.7)	12 (29.3)
6 months - 3 years	40 (41.7)	18 (45)	22 (55)
3 years +	15 (15.6)	4 (26.7)	11 (73.3)
Total (%)	**96 (100)**	**51 (53.1)**	**45 (46.8)**

Culture Results in different age groups

Figure 1 below demonstrates culture results across the different age groups. E. Coli was the commonest causative organism across all age groups (61.5%). This was followed by Klebsiella in children less than 6 months of age (7.3% of infections within this age group), Enterococcus in the 6 months to 3year age group (10% of infections in this age group), and ESBL-positive E. Coli in children older than 3 years (13.3% of infections in this age group).

Correlation of Imaging Findings with Age and Presentation of UTI

A total of 96 renal ultrasounds, 31 MCUGs and 24 DMSA scans were performed. The commonest abnormality reported on US was unilateral hydronephrosis (11.5%), that on MCUG was bilateral vesicoureteral reflux (19.4%) and that on DMSA was bilateral renal scarring with a smaller left kidney (12.5%).

Table 2 summarises the data collected for imaging results for different presentations of UTI across the different age groups. The first column shows the number of abnormal ultrasounds (irrespective of MCUG results for a particular child), whilst the second column represents the number of abnormal MCUGs (irrespective of US result for a particular child). The third column represents the total number of normal US and MCUG results for the sample population studied.

Not included in the table are 3 cases for which ultrasound was performed in view of UTI being diagnosed on clinical grounds (culture result contaminated/negative) and therefore, could not be categorised into the groups below. All ultrasounds for these latter 3 cases were normal.

Figure 1: Figure showing culture results for the different age groups. “Mixed” refers to contamination in sampling, “Negative” refers to children treated as UTI based on history and clinical symptoms despite negative culture, and “Multiple” refers to more than one organism being recorded in the laboratory culture report.

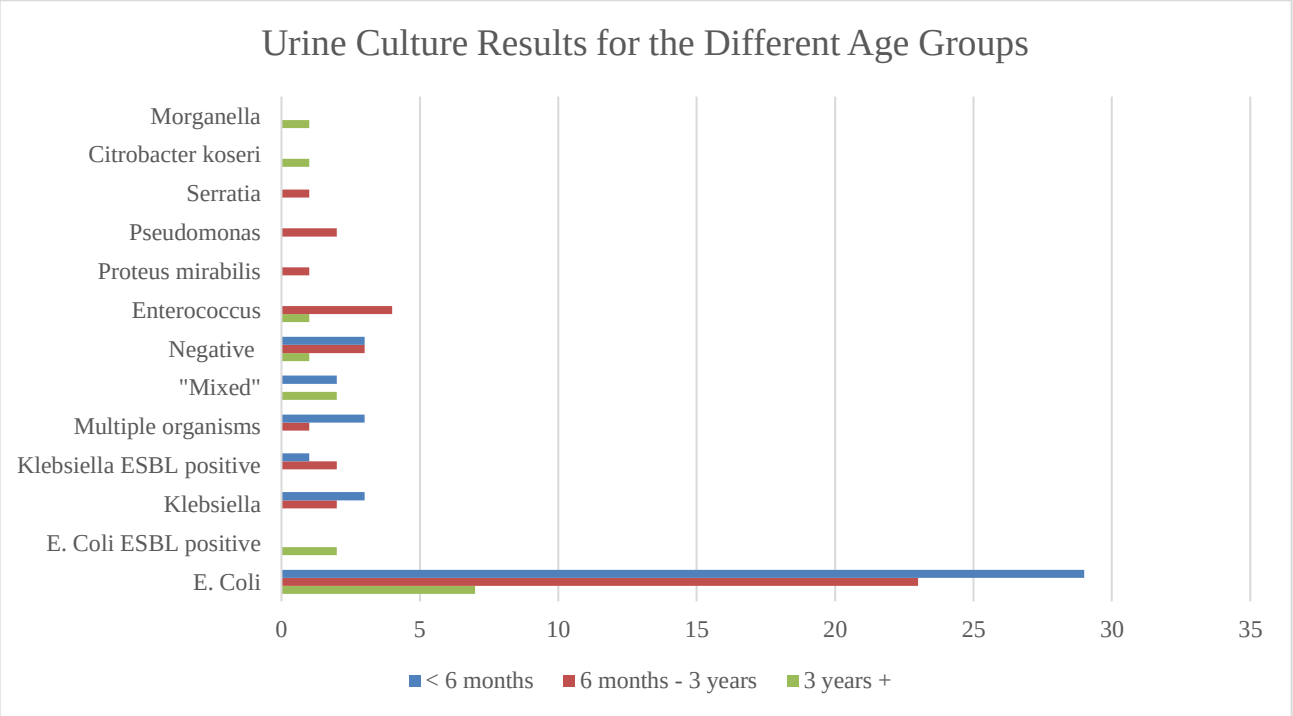

Table 2: Summary of Data Collection

	Abnormal US Number (%)	Abnormal MCUG Number (%)	Normal US + MCUG Number (%)	Total US and MCUG performed
Typical				
< 6 months	5 (10.4)	4 (8.3)	39 (81.2)	48
6 months - 3 years	6 (23)	2 (7.7)	18 (72)	26
3 years +	3 (42.9)	0 (0)	4 (66.7)	7
Atypical				
< 6 months	0 (0)	1 (14.3)	6 (85.7)	7
6 months - 3 years	0 (0)	0 (0)	3 (100)	3
3 years +	1 (33.3)	0 (0)	2 (66.7)	3
Recurrent				
< 6 months	1 (16.7)	1 (16.7)	4 (66.7)	6
6 months - 3 years	7 (35)	4 (20)	9 (45)	20
3 years +	1 (25)	0 (0)	3 (75)	4
Total	**24 (19.4)**	**12 (9.7)**	**88 (71)**	**124**

General Observations

The highest number of ultrasounds and MCUGs were performed for children presenting below 6 months of age, accounting for 49.2% of all investigations performed. 35% were performed for children between 6 months to 3 years of age and 11.3% for children aged 3 years and above.

Table 3 below allows for a more clarified description of patterns observed during analysis. Imaging studies performed in cases of typical infection yielded most abnormal results in children less than 6 months of age, very closely followed by the 6 months – 3 years age group, whilst imaging performed for recurrent infections, yielded most abnormal imaging results for children falling within the 6 months to 3 years category. Of note, for children above 3 years of age presenting with first episode typical UTI, ultrasound revealed newly diagnosed PUJ stenosis for one child and hyperechoic bladder with debris or possibly a blood clot for another child. There were no abnormal MCUG results within this category.

Abnormal Findings on US and/or MCUG vs Age

The highest number of abnormal imaging results were reported for the 6 months to 3 years age group at 54.3%. This was followed by 34.3% for children less than 6 months of age and 11.4% for children above 3 years of age. However, further analysis of such data showed that there was no significant statistical association between the presence of abnormal imaging findings on US or MCUG and age at presentation, with a p value of 0.07 (Table 4).

Table 3: Total number of abnormal US and MCUG results (irrespective of individual results for a particular child) for different ages according to UTI presentation type. Shaded boxes indicate the highest number of abnormal results for the respective age group.

	Number of abnormal US and/or MCUGs		
Age	**Typical**	**Atypical**	**Recurrent**
< 6 months	9	1	2
6 months – 3 years	8	0	11
3 years +	2	1	1
Total No. all ages	**19**	**2**	**14**

Table 4: Summary of the total number of abnormal and normal results (irrespective of individual results for a particular child) according to the different age groups

Age Groups	Abnormal US/MCUG Number (%/age group)	Normal US/MCUG Number (%/age group)	Totals
< 6 months	12 (19.7)	49 (89.3)	61
6 months - 3 years	19 (38.8)	30 (61.2)	49
3 years +	4 (28.6)	10 (71.4)	14
Total all ages	**35 (28.2)**	**89 (71.8)**	**124**

Abnormal Findings on US and/or MCUG vs Presentation

Table 5 below summarises results categorised solely according to clinical presentation. Analysis of the total number of abnormal results obtained on US or MCUG (grouped together), irrespective of individual results for a particular child, showed that:

There was no statistically significant association between the presence of abnormal imaging findings in children presenting with atypical infection when compared with those presenting with typical infection (p=0.73).

On the other hand, a statistically significant association could be ascertained for the presence of abnormal imaging findings for children presenting with recurrent infection vs those with typical infection (p=0.026).

However, when both the atypical cohort and the recurrent cohort were analysed together, no statistically significant association with the presence of abnormal imaging findings (p=0.13) could be ascertained.

Moreover, when the number of abnormal US and the number of abnormal MCUG results was analysed separately against UTI presentation type, there was no statistically significant correlation between the two, with a resulting p value of 0.63 for both imaging modalities.

Analysis of US vs MCUG results for children with both modalities performed

30 children had both an US and MCUG performed (1 child did not have a recent US performed despite a recent MCUG). Table 6 below summarises data for this cohort of children, comparing the results of these two modalities. Analysis shows that 20% of children (6 / 30) in this cohort had a normal US result but a significant abnormal MCUG result - 2 children had bilateral high-grade reflux, 1 had bilateral reflux with grade not reported, 2 had unilateral grade I/II reflux and 1 child had bladder wall thickening raising the suspicion of posterior urethral valves. This represents a rate of 26.67% with a lower confidence interval of 12.98 and an upper confidence interval of 46.17.

Moreover, further detailed analyses showed that there was no statistically significant relationship between findings on US and MCUG irrespective of age and gender.

Table 5: Summary of imaging results vs UTI presentation type irrespective of age

UTI presentation	Abnormal US/MCUG	Normal US/MCUG	Totals
Typical	20 (23.52%)	61 (57.48%)	**81**
Atypical/Recurrent	16 (37.2%)	27 (62.8%)	**43**
Totals	**36 (29%)**	**88 (71%)**	**124**

Table 6: Number of children categorised according to their MCUG and US result

	US Abnormal	US Normal	Totals
MCUG Abnormal	2	6	**8**
MCUG Normal	7	15	**22**
Totals	**9**	**21**	**30**

Analysis of DMSA results for children who had DMSA performed in addition to US and/or MCUG

14 children had all three imaging investigations performed (US, MCUG and DMSA). Table 7 describes the data obtained for the cohort of children who had a DMSA performed in addition to an US and/or MCUG. Imaging results were available for a total of 22 children; 2 DMSA results were not available during time of data collection despite being performed. 63.6% had a normal DMSA result despite an abnormal US and/or MCUG result, with a 95% CI 0.43 - 0.80. Moreover, there were no cases for which an abnormal DMSA was obtained on a background of a normal US and MCUG. Despite this, given the small cohort of children studied, this represents a rate of 75% with an upper confidence interval of 0.75, and therefore, no statements can be made as to whether a DMSA can be avoided in such cases.

Table 7: Number of children categorised according to their US/MCUG and DMSA result

	Abnormal US or MCUG	Both US & MCUG Normal	Totals
DMSA Abnormal	4	0	4
DMSA Normal	14	4	18
Totals	**18**	**4**	**22**

Discussion

Radiological imaging studies have an important role in the investigation and management of children admitted with urinary tract infection. Such imaging studies in many countries generally include renal ultrasound in the first instance, followed by MCUG and DMSA when indicated. Various studies have been performed attempting to predict the yield of renal scarring and its associated morbidity using different imaging modalities, alone or in combination, for different clinical scenarios, with the aim of advocating against the use of invasive imaging techniques such as MCUG and DMSA in certain instances. [7,8.] The aim of this study was to explore whether similar proposals can be put forward for our local centre, with the aim of reducing unnecessary referrals, burden of radiation and costs.

General Demographics

A total of 96 children were included in this study, for which biochemical data, urine culture results and imaging reports were reviewed. The commonest age group requiring admission during the study was children less than 6 months of age. This was expected given that such children are more susceptible to being clinically unwell and require the administration of intravenous antibiotics and urgent imaging as per local and international guidelines. A predominance of male children was observed in this age group, similar to other studies performed in centres abroad, and this can also be explained by the higher prevalence of congenital renal tract anatomical abnormalities such as posterior urethral valves in males. [9] Circumcision, which is known to reduce urine infections in certain cohorts, is not prevalent in our culture and only performed for specific indications, commonly for posterior urethral valves. It is also well known that there is then a marked female preponderance beyond the 6-month age group, explained by the presence of a shorter female urethra and therefore, a higher incidence of ascending infection, as also demonstrated in this study. [10]

Pattern of Culture Results

E. Coli infection was the commonest causative organism across all ages, followed by *Enterococcus faecalis* and *Klebsiella pneumoniae*. This pattern in culture results is also mirrored throughout the literature in various studies performed in other centres, as highlighted by Kaufman *et al*.[11] Interestingly, in our study, children between 6 months to 3 years of age had most atypical infections compared to the other age groups. Given that a relationship between the presence of underlying renal tract abnormalities and atypical presentation is well-established and reported, including in studies previously performed locally, this would also explain why the number of abnormal US and MCUGs were highest within this age group accounting for 54.3% of abnormal imaging results obtained. [12]

Imaging results according to age and presentation of UTI

In this study, as also widely reported in the literature, the commonest abnormality on ultrasound was found to be unilateral hydronephrosis, that on MCUG was found to be bilateral high-grade reflux, whilst that on DMSA was found to be bilateral renal scarring with a smaller left kidney.[13]

Children between 6 months and 3 years of age were reported to have the highest number of abnormal imaging results, which could also be related to the increased prevalence of atypical and recurrent infection within this age group. This was followed by children less than 6 months of age, mainly for typical infection. Children above 3 years of age had the lowest number of abnormal imaging results, as

expected, given that the majority of UTIs within this age group are usually due to secondary factors such as constipation or potty training. [14]

For children above 3 years of age, ultrasound and/or MCUG (only 1 MCUG was performed within this age category for a 12 year old girl presenting with findings suggestive of acute right focal pyelonephritis on ultrasound) were performed for 86.7% of cases with 69.2% being normal. 30.8% of ultrasounds performed within this age category were abnormal, however, further in-depth analysis revealed that only one child had a newly diagnosed underlying renal tract anomaly (newly diagnosed PUJ stenosis) whilst the others were already known cases (known case of left duplex kidney with new onset mild to moderate hydronephrosis) or had an incidental acute presentation suggestive of upper UTI, requiring further imaging investigation in order to confirm this (right sided pyelonephritis).

However, despite these patterns, no statistically significant relationship could be ascertained between the presence of abnormal imaging findings on US and/or MCUG, presentation of UTI and age, and therefore, despite various guidelines highlighting consideration to age and/or presentation type to guide further investigations for most cases, vigilance is always encouraged in order to avoid missing out important underlying abnormalities that might lead to avoidable complications and increased morbidity.

Comparison of different imaging modalities used in parallel

In this study, three different imaging modalities, namely US, MCUG and DMSA were compared. When analysing abnormal imaging results for the cohort of children who had both an US and MCUG performed, 20% were found to have a significantly abnormal MCUG result (2 children had bilateral high-grade reflux, 1 had bilateral reflux with grade not reported, 2 had unilateral grade 1/2 reflux and 1 child had bladder wall thickening raising the suspicion of posterior urethral valves, despite a normal US result. Therefore, despite various centres advocating avoiding MCUG in cases of a normal baseline US, the same cannot be said for our local centre, irrespective of age, gender and presentation of UTI. [9]

This study also aimed to explore whether performing a DMSA scan adds additional information to that already given by an US and/or MCUG. Various centres are recommending the combined use of US and MCUG to safely exclude renal scarring, with a false negative risk of 3.0%.[9] In our study, there were no abnormal DMSA scan results for children with previously normal US and MCUG results. Moreover, 63.6% of children had a normal DMSA result despite abnormal US and/or MCUG result/s. In view of the small cohort of children studied, no statistically significant statements could be made as to whether a DMSA can be avoided in cases of combined normal US and MCUG. However, given these results, studies with larger cohorts of children are encouraged with the aim of exploring whether DMSA can be avoided in such cases locally similarly to centres abroad.

Limitations of the study

The main limitation of this study is the small number of children studied. Moreover, further studies with larger cohorts, spanning a longer time span, with more in-depth analysis of the past medical history and clinical information of the children being investigated, might highlight additional confounding factors that might be affecting the results being presented.

Conclusion

Invasive radiological imaging techniques such as MCUG and DMSA can be psychologically traumatic

to both children and carers alike, with complications including exposure to radiation and introduction of infection via catheterisation in the case of MCUG. The results of this study suggest that in our local centre, MCUG is still warranted in cases of normal baseline US, irrespective of age, gender and presentation of UTI. Moreover, in view of the small cohort of children studied, it was not possible to ascertain whether performing a DMSA can be avoided in cases of normal baseline US and MCUG. However, given that in our study, all children with normal US and MCUGs had normal DMSA scans and 63.6% of children had normal DMSA scans despite abnormal US and/or MCUG, further studies with larger cohorts of children are warranted with the aim of reducing referrals for DMSA, unnecessary radiation burden and costs.

Summary

What is known about the subject

1. Urinary tract infection is a common cause of morbidity in children.
2. Investigation of UTI in children often involves imaging including ultrasound, MCUG and DMSA scans.
3. Various guidelines have been put forward to guide imaging investigations in children depending on age and clinical presentation of UTI.
4. Various centres advocate avoiding MCUG in case of normal baseline US and avoiding DMSA in cases of normal combination US and MCUG results.

New findings

1. E. Coli infection was the commonest in our studied cohort, similar to studies performed abroad.
2. In our local centre, MCUG is still warranted despite normal baseline US irrespective of age, gender and type of presentation.
3. Further local studies with larger cohorts are warranted in order to ascertain whether a DMSA can be avoided for children with normal combination US and MCUG.

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MMJ

ORIGINAL ARTICLE

The effect of tocilizumab on procalcitonin and other biochemical and clinical markers in severe COVID-19 infection: Time to rethink our interpretation of results?

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Background

Tocilizumab (TCZ) is an interleukin-6 (IL-6) inhibitor approved for use in patients severely affected by COVID-19, which has been shown to reduce mortality but has as yet undetermined effects on procalcitonin (PCT) and C-reactive protein (CRP).

In Malta, TCZ started being administered to COVID-19 patients who experience worsening symptoms or increased oxygen requirements over a period of hours in January 2021. This study aimed to assess the effect of TCZ on PCT primarily, and white cell count (WCC), lymphocyte and neutrophil counts, neutrophil to lymphocyte ratio (NLR), CRP and PaO2/FiO2 (P/F) ratio as secondary measures.

Methods

Fifty patients who received tocilizumab were recruited to the treatment group along with a matched control group of 50 patients who did not receive the drug. Serum PCT and other biochemical markers were recorded daily for both groups and differences in the values for the two groups extracted. Outcome measures included differences between the biomarkers at 5, 10 and 15 days.

Results

PCT and CRP were significantly lowered by administration of TCZ on Day 5. WCC, lymphocyte and neutrophil counts and P/F ratios were not affected. There was no difference in positive blood culture results between the two groups.

Conclusion

PCT and CRP may not be reliable indicators of bacterial superinfection in severe COVID-19 pneumonia patients who have been given TCZ.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has swept across the world since 2019, with thirty thousand cases and 462 recorded deaths in Malta at the time of writing.[1-2]

Risk factors for developing severe infection include advanced age, male gender, diabetes, obesity, a history of heart disease, immunosuppression, smoking and substance abuse – these risk factors are very common in many populations.[3]

One of the commonest complications of COVID-19 is adult respiratory distress syndrome (ARDS),[4] which involves diffuse alveolar inflammation and viral particles within type II pneumocytes.[5-6] A cytokine storm, in which interleukin-6 (IL-6) is believed to play an important role, is believed to underly the pathogenesis of ARDS in COVID-19.[7-8]

Tocilizumab (TCZ), a well-established treatment in rheumatoid arthritis, has emerged as a potential treatment for severe COVID-19, being a monoclonal antibody against the IL-6 receptor with the potential to modulate the cytokine storm.[9-10] Early in 2020, small studies demonstrated the survival advantages of TCZ in severe COVID-19.[9,11]

The largest trial to date was the REMAP-CAP trial published in late February 2021, which aimed at assessing the efficacy of TCZ when compared to sarilumab (another IL-6 receptor inhibitor) or to no anti-interleukin treatment.[12-13] Patients given IL-6 receptor inhibitors fared better than the control group, with 10 fewer median organ support-free days in the TCZ group and 11 fewer days in the sarilumab group. An analysis at three months also demonstrated improved survival in treated patients compared with controls.[14]

The TOCIVID-19 trial is another large phase 2 single arm trial involving multiple centres, dedicated to assessing the effects of tocilizumab in critically ill COVID-19 patients.[13] This trial is still underway and expected to be completed in December 2022.[15] Primary outcomes will be mortality at fourteen and at thirty days post-administration. Secondary outcomes will include time to death, time to initiation of mechanical ventilation, time to extubation, time until invasive ventilation was no longer necessary, duration of hospital stay, and trends in clinical and biochemical markers such as IL-6, C-reactive protein (CRP), SOFA score, lymphocyte counts, radiological evidence of response to treatment and PaO2/FiO2 (P/F) ratio.[13]

As studies continue to be published confirming the positive effect of TCZ on survival, clinicians turned their attention to potential harm from TCZ. Known side effects include neutropenia, thrombocytopenia, immunosuppression and liver damage.[16] However, we suggest another indirect effect on clinical management might be more significant and should be studied in more detail.

Bacterial coinfection on admission was detected in early samples taken from approximately 20% of COVID admissions; during the weeks on intensive care up to 50% of COVID admissions could also suffer from hospital-acquired sepsis.[17-18] There was some data before the pandemic that TCZ can independently lower all markers of infection used by clinicians to monitor bacterial sepsis onset and prognosis and decide on escalation or de-escalation of antimicrobial therapy.[19-21] An interesting question regarding the use of TCZ in the management of severe COVID-19 infection is related to its effects on biochemical and clinical markers of infection. Common infection markers used include CRP, procalcitonin (PCT) and white cell count (WCC).[22-24] There is even less data available on how TCZ affects infection markers in a population on regular corticosteroid therapy given this only became standard therapy for COVID disease after June 2020.[25]

Vu et al[26] reported an increase in P/F ratio after administration of single dose TCZ in a group of sixty patients. A reduction in CRP was observed for 10 days following drug administration, subsequently rising again. The team postulated that this may indicate the need for further doses of TCZ. It is worth noting that in this study 32 out of 60 patients were treated concomitantly with glucocorticoids.[26]

Neutrophil to lymphocyte ratio (NLR) has been discovered to be a predictor of COVID-19 severity. Elevated NLR has been associated with poorer outcomes in terms of disease progression and mortality.[27] In a study by Hartog et al[28] patients who were administered TCZ in the setting of severe COVID-19 and whose NLR did not immediately show a downward trend were found to have poorer outcomes compared to those who responded swiftly to anti-IL6 treatment. Elevated NLR may therefore also indicate a likelihood for resistance to TCZ therapy.[28] This study did not compare the effect of TCZ on WCC or NLR to a control group.

Finally, Hariyanto and Kurniawan[29] published a short review including 9 studies and 577 patients in which they considered the effect of TCZ on multiple biochemical infective markers. CRP, ferritin and D-dimer were reduced following the administration of TCZ and lymphocytes were increased. This review did suggest that PCT was also found to decrease after TCZ was given.[29]

Following UK guidance on TCZ in COVID disease issued in January 2021, local infectious disease physicians in Malta started prescribing TCZ to patients who exhibit a sudden deterioration in condition after being diagnosed with COVID-19 pneumonia.[30-31] Sudden deterioration was determined by an acute increase in oxygen requirements and intensive care admission. Patients in whom the deterioration was more gradual or patients who have a serum alanine aminotransferase level 5 times above the upper limit of normal, were not considered for TCZ therapy. In suitable candidates, TCZ is given as a single dose of 8mg/kg intravenously up to a maximum dose of 800mg.[31-32]

The main objective of our study is to monitor effects of TCZ on PCT levels, CRP, WCC, neutrophil and lymphocyte specific counts, NLR and P/F ratio from day of admission until discharge from intensive care in a population of patients admitted for COVID pneumonia receiving regular dexamethasone.

Methods

This was a retrospective single centre study, in a general intensive therapy unit (ITU) in a tertiary University-affiliated hospital, with over 1,000 admissions per year. Data protection and ethical approval were obtained from the relevant authorities. This trial was registered on the clinicaltrials.gov (NCT05035589).

The first 50 consecutive COVID-19 patients admitted to ITU given TCZ were recruited to the treatment group. The control group for this study consisted of 50 patients, all admitted to ITU due to COVID-19, who were not given TCZ. They were matched with the treatment group for gender, age, length of stay in ITU and type of respiratory support (high flow nasal oxygen (HFNO) or mechanical ventilation) required.

Blood panel results for PCT, CRP, WCC, neutrophils, lymphocytes and the P/F ratio at 6am each day were recorded from the day on which TCZ was given until twenty days post-administration, or until discharge from the ITU or death if this occurred earlier. The first set of parameters recorded in this group were generally taken on admission and just before the dose of TCZ is administered.

Statistical Analysis

Results were analysed statistically using R Studio (version 1.4.1106) with R statistical package (version 4.0.4). The data was checked for normality and skewness using visual methods and using Shapiro-Wilk normality tests. When appropriate, t-tests, Mann-Whitney U tests, Kruskal-Wallis test and chi-squared tests were used for univariate analysis. With a p-value of 0.05 or less, the result was taken to be significant.

The main outcome of the study was difference of PCT on Day 5, 10 and 15 between the two groups, using univariate tests. A linear mixed model was also used to compare the trajectories of individual patients in the two groups. The same methodology was then repeated for CRP, WCC, Neutrophil and Lymphocyte counts and the P/F ratio.

Furthermore, the incidence of positive blood cultures, and the date of first positive culture was compared between the two groups.

Results

The demographic data of the two groups are shown in Table 1. Given the small sample size, and that there were high levels of skewness in the data, median values with interquartile ranges are shown. There were no statistical differences between the two groups at baseline.

Table 1: Baseline demographic characteristics of the two groups of patients. Results reported as median values [IQR].

	Control Group	Treatment Group	p-value
n	50	50	
Age (years)	68.5 [63.0 - 74.0]	66.0 [60.0 - 72.0]	0.22
Male (n)	40 (80%)	41 (82%)	1.00
Respiratory support			
- HFNO	18 (36%)	17 (34%)	1.00
- Intubation	32 (64%)	32 (64%)	
- Non-rebreather mask	0 (0%)	1 (2%)	
WCC	10.2 [7.9 - 12.5]	9.6 [7.3 - 12.6]	0.46
Neutrophils	9.1 [6.9 – 10.9]	8.5 [5.4 – 10.9]	0.36
Lymphocytes	0.6 [0.4 – 0.7]	0.6 [0.5 – 0.8]	0.55
N/L Ratio	15.7 [9.3 – 21.1]	13.0 [8.7 – 18.5]	0.26
PCT	0.4 [0.1 - 0.9]	0.4 [0.2 - 1.6]	0.48
CRP on Day 0	127 [77.9 - 227.3]	140 [80.1 – 224]	0.99
P/F Ratio	144 [112 - 192]	137 [104 - 195]	0.91
Survived (n)	30 (60%)	38 (76%)	0.13

Table 2 summarises the differences observed in the values of all biochemical and clinical markers studied at day 5, day 10 and day 15, along with the p-values obtained in order to determine statistical significance. Below is a breakdown of the findings from data analysis for each biochemical and clinical marker.

Procalcitonin

On univariate analysis, the PCT level was influenced by TCZ administration, on Day 5 with PCT values for the treatment group being 0.18 in the treatment group and 0.37 in the control group. The p-value obtained for this data was 0.19. On day 10 and day 15, there still was a marked difference, but this was not statistically significant since the p-values were 0.06 and 0.08 respectively. The values obtained for the two groups on these days were 0.31 for the treatment group on day 5 compared to 0.76 in the control group, and 0.37 in the treatment group at day 15 versus 0.77 in the control group,

Table 2: Difference in biochemical and clinical markers observed between the two groups at Day 5, 10 and 15, with corresponding p-values

Parameter	Day:	Treatment Group	Control Group	p-Value
PCT	5	0.18 [0.10 - 0.41]	0.37 [0.15 - 1.22]	**0.019**
	10	0.31 [0.11 - 0.72]	0.76 [0.23 - 1.12]	0.08
	15	0.37 [0.26 - 0.47]	0.77 [0.31 – 1.7]	0.06
CRP	5	15.4 [9.0 - 22.9]	107.0 [51.3 - 181.0]	**<0.001**
	10	8.9 [3 - 33.8]	109.2 [65.1 - 178.7]	**<0.001**
	15	31.4 [11.9 - 65.1]	215.6 [84.8- 260.3]	**0.0011**
WCC	5	9.6 [7.4 - 13.1]	11.3 [9.1 - 14.3]	0.20
	10	11.7 [9.5 - 18.7]	12.0 [9.9 - 14.5]	0.92
	15	8.4 [7.8 – 17.0]	10.4 [8.6 - 12.92]	0.49
Neutrophils	5	7.7 [6.2 - 10.8]	9.7 [7.3 - 11.3]	0.16
	10	9.9 [7.4 - 15.2]	9.9 [8.7 - 13.0]	0.96
	15	6.8 [6.3 - 13.4]	8.4 [6.9 – 10.9]	0.34
Lymphocytes	5	0.70 [0.40 - 0.93]	0.53 [0.40 - 0.79]	0.22
	10	0.80 [0.46 - 1.37]	0.74 [0.41 - 0.95]	0.32
	15	1.09 [0.54 - 1.39]	0.68 [0.55 - 1.14]	0.30
NLR	5	11.0 [5.4 - 26.2]	17.3 11.5 – 26.9]	0.11
	10	11.1 [5.9 - 21.52]	14.7 [9.7 - 27.8]	0.21
	15	6.3 [5.2 - 14.3]	10.5 [7.7 - 18.4]	0.11
P/F ratio	5	189 [131- 219]	158 [138 - 193]	0.20
	10	187 [158- 240]	169 [136- 219]	0.071
	15	195 [174- 251]	186 [135- 232]	0.34

Following TCZ administration, the median levels of PCT decreased until day 6, and started to increase again by day 7.

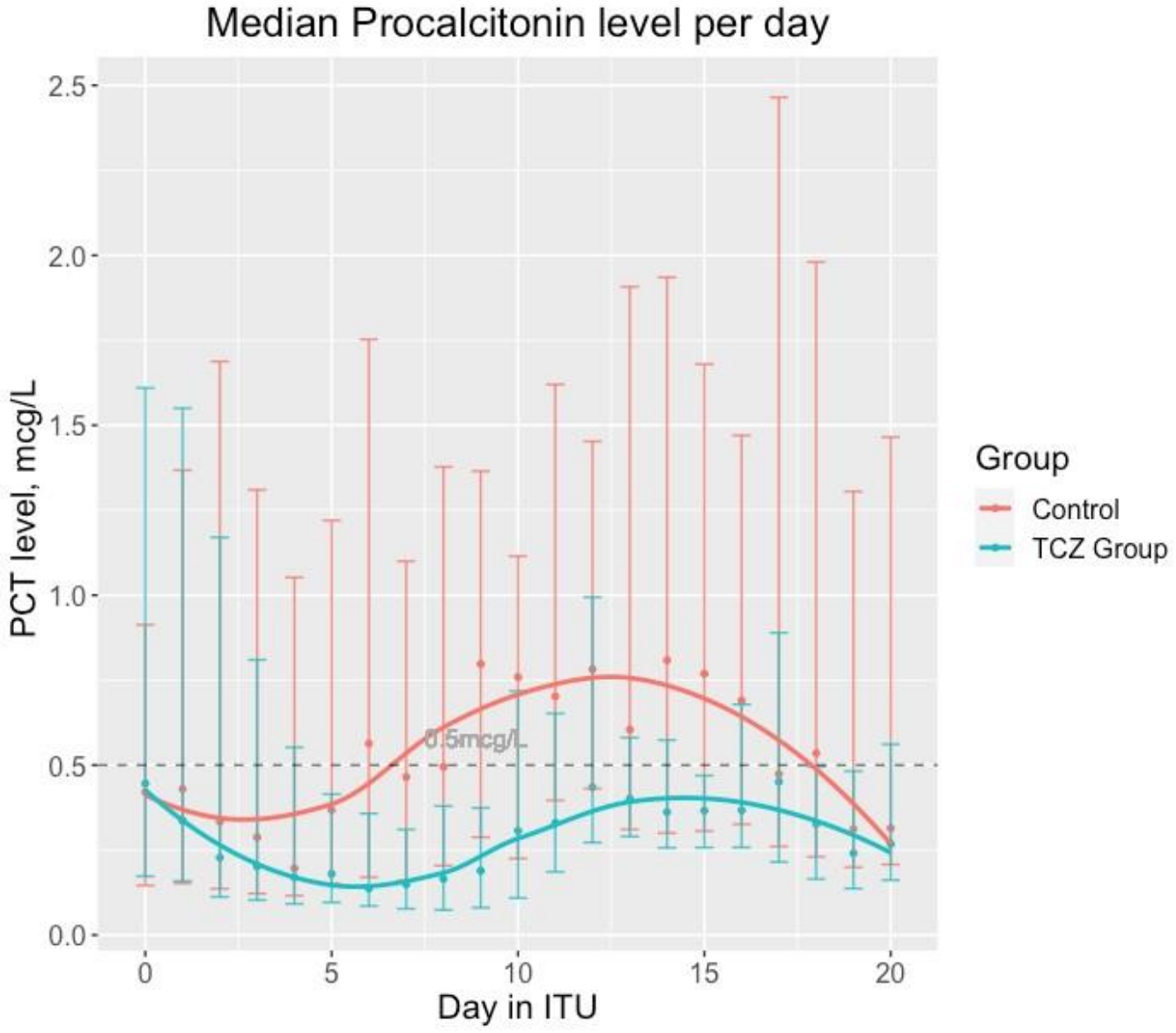
A linear mixed effects analysis, to account for the repeated measures, showed that the TCZ administration affected the trajectory of PCT levels (Estimate -1.93, p-value 0.03).

In fact, throughout the observed period, the median levels of PCT in the treatment group never exceeded 0.5mcg/L, which is the cut-off level suggestive of infection.[33]

Five patients (10%) who received TCZ had an increase in their PCT after the initial decrease. This started after an average of 5.2 days (range: 3 – 10 days).

Figure 1 depicts the described variations in PCT levels following administration of TCZ when compared to the control group.

Figure 1: PCT variation over twenty days in ICU admission, difference between tocilizumab test group and control group. Data presented as median values, with error-bars indicating IQR.



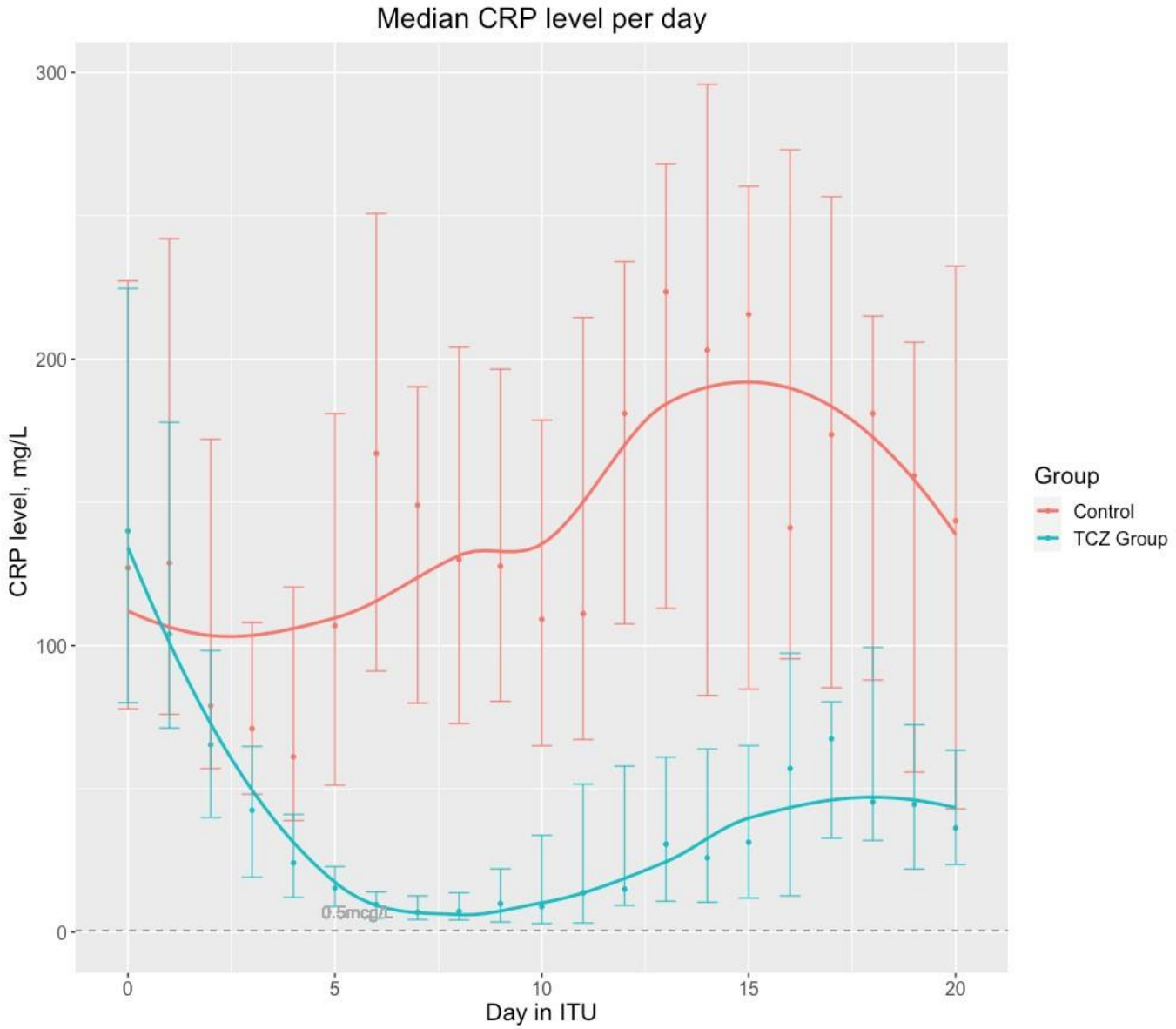
C-Reactive Protein

As seen in Table 1, CRP was significantly higher in patients who had not received TCZ at all points investigated. On day 5, the CRP in the treatment group was 15.4 compared to 107 in the control group. On day 10, the CRP in the treatment group dropped to 8.9 but that in the control group increased marginally to 109, and on day 15, the CRP value for the treatment group was 31.4, and that for the control group was 215.6. The p-values for all this data were below the 0.05 cut-off.

The median levels of CRP decreased significantly over 8 days in the treatment group, then started to rise slowly again, but remained lower than 75mg/L. This is depicted in figure 2.

Analysis using a linear mixed effect model confirms the above, with a marked effect of TCZ on CRP levels (Estimate: -63.8, p<0.0001).

Figure 2: CRP variation over twenty days in ICU admission, difference between tocilizumab test group and control group.



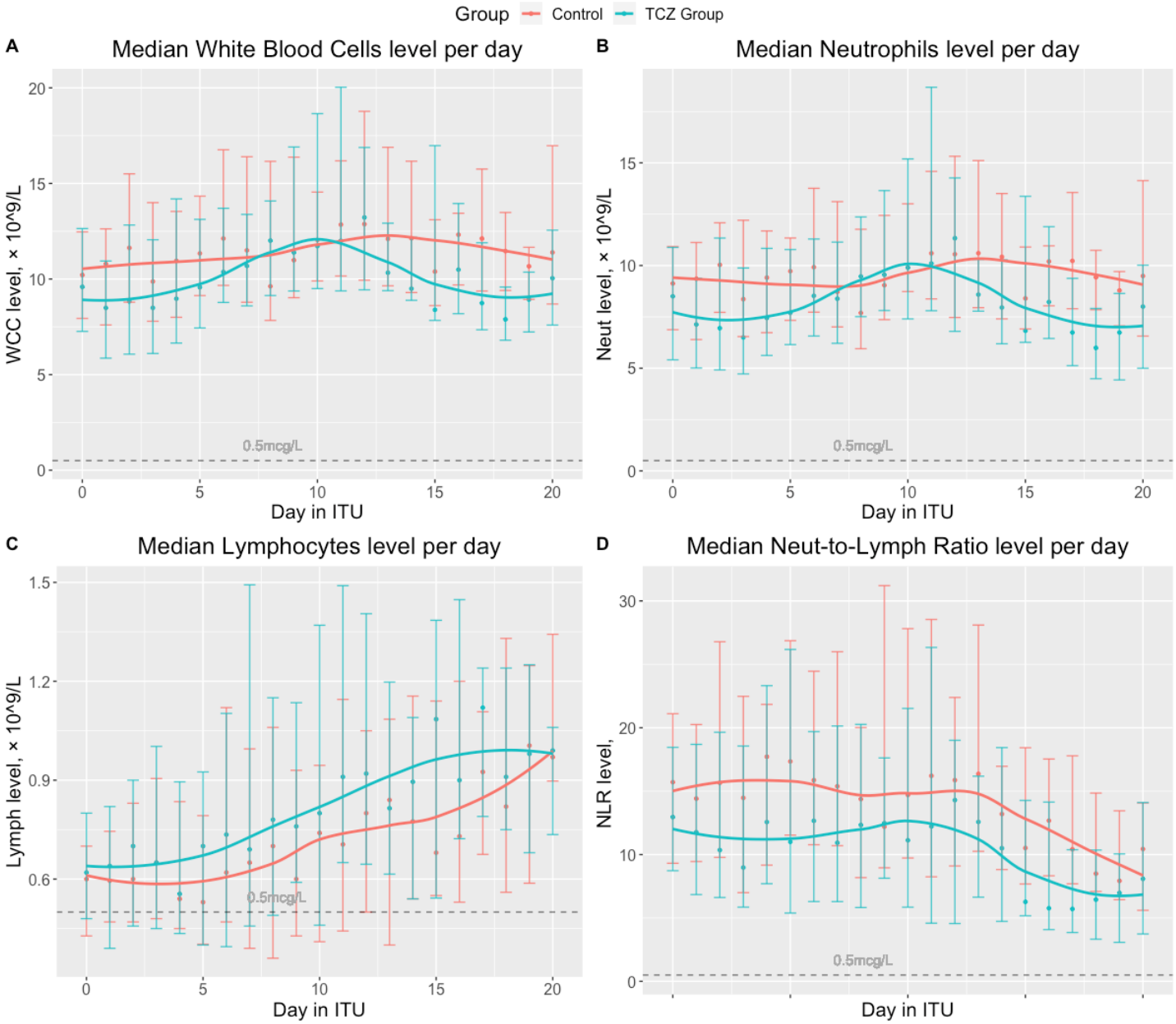
White Cell Count, Neutrophil Count, Lymphocytic Count

Figure 3 shows the median counts for White Cells, neutrophils, lymphocytes and the NLR.

Although on Day 5 and 15, the total WCC and the neutrophil counts were higher in patients in the control group, this was not statistically significant. This was confirmed with analysis by a linear mixed effects model.

Lymphocyte counts and the NLR were not different between the two groups.

Figure 3: WCC variation over twenty days in ICU admission, difference between tocilizumab test group and control group.



PaO2 / FiO2 ratio

As shown in Figure 4, there was no difference between the median P/F ratio in the first 20 days between the two groups. This was confirmed on a linear mixed model analysis.

Microbiology

Table 3 provides details of blood culture results for both bacterial and fungal cultures in the TCZ group as well as the control group, with the corresponding p-values.

There was little difference in the number of patients who had a positive blood culture (excluding contaminants) between the two groups (tocilizumab group: 48% vs Controls: 40%, p-value= 0.55). Positive cultures tended to occur earlier during the ITU stay in patients treated with TCZ, but this was not statistically significant (TCZ group: 6.5 days vs Controls: 9 days, p-value=0.16). This is shown in Table 2.

There was no difference in the incidence of fungal cultures in either group.

Figure 4: P/F ratio variation over twenty days in ICU admission, difference between tocilizumab test group and control group.

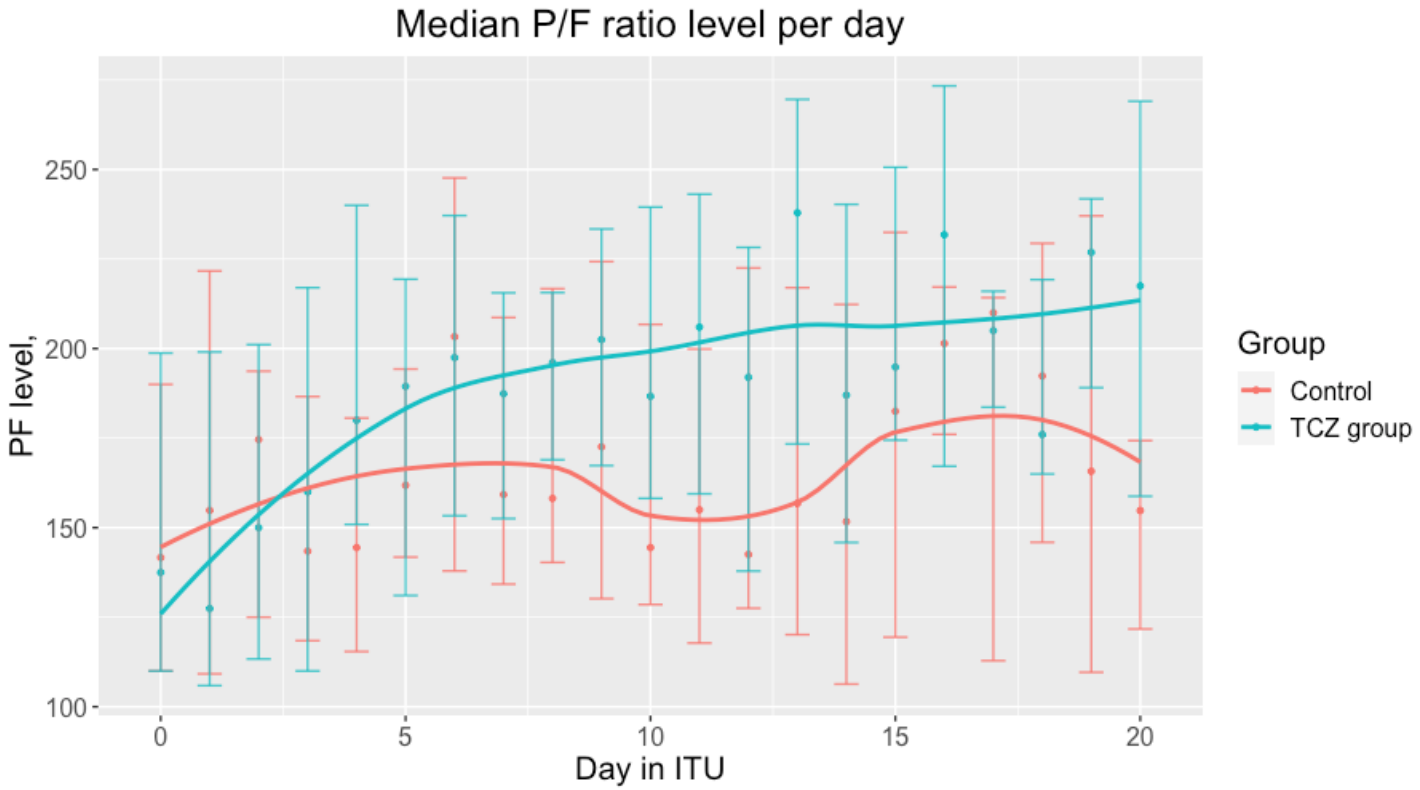


Table 3: Number of positive Blood culture results in both groups, median day of occurrence, and number of positive Mycology results. These values are excluding cultures thought to be due to contamination.

	Control Group	Treatment Group	p-value
n	50	50	
Any positive blood culture	20 (40%)	24 (48%)	0.55
Day of occurence	9 [6 - 11.3]	6.5 [4 - 9]	0.16
Fungal cultures	14 (28%)	10 (20%)	0.48

Discussion

The primary aim of this study was to investigate whether the administration of TCZ in critically ill patients with COVID-19 pneumonia had a significant effect on PCT levels as well as on other commonly recorded clinical and biochemical markers in subsequent days.

Our results show that PCT is significantly lowered following TCZ administration until the sixth day following dosing. After this point, the median PCT tended to be lower, but the difference was not statistically significant.

Secondary aims of this study were the assessment of TCZ effects on other biochemical markers, namely CRP, WCC, lymphocytes and neutrophils, NLR and finally P/F ratio and positive blood cultures as clinical markers.

CRP is lowered to a significant extent following TCZ administration. This decrease is sustained throughout all twenty days included in this study. Other parameters, mainly WCC, neutrophil and lymphocyte count, NLR were not significantly affected by the use of TCZ therapy, although they tended to be lower at all times during the study. P/F ratios and the rate of positivity of blood cultures (excluding contaminants) were also found to demonstrate no statistically significant difference between the treatment group and the control group.

Some international studies have already hinted at results similar to those obtained from our cohort. PCT and CRP have been significantly lowered with TCZ administration, including in. patients who did not require mechanical ventilation, as was reported in the COVIDOSE trial.[26,34-35]

With regards to other parameters, these are less extensively studied and conflicting reports seem to exist. An Indonesian study showed that NLR was improved in patients treated with TCZ.[36] Rana et al[37] reported improvement in the P/F ratio of patients treated with TCZ.[37] Salvarani et al[38] found no benefit of TCZ treatment in patients with mild ARDS with regards to P/F ratio and CRP.[38] Other studies described in the introductory section of this paper demonstrated various effects on inflammatory markers such as a lowering of PCT and D-dimer,[29] as well as an overall positive effect on survival outcomes and weaning off mechanical ventilation.[14]

Studies that focus on PCT response in TCZ treatment are few and far between.

The significance of this study is that it demonstrates that PCT and CRP may no longer be reliable markers of superinfection in the setting of severe COVID-19 pneumonia in patients treated with TCZ.

TCZ itself is still associated with a risk of bacterial infection, although in COVID-related ARDS the benefits of its use seem to outweigh the risk in most cases.[39] However, when monitoring for the development of infection, other markers such as WCC and bacterial cultures may have a more important role to play than the commonly used PCT and CRP values. Whether prophylactic antibiotics should be administered with TCZ in order to reduce the possibility of undetected superinfection is still a topic for ongoing discussion, since microbial resistance must be considered.[40]

Limitations of this study include the relatively small sample size and the fact that only one centre was included. All patients received dexamethasone, so this could be a confounding factor that might have minimised bigger differences between the two groups.

Further studies are required into the consequences of TCZ administration and the best way to prevent complications of bacterial superinfection in these patients. Larger trials and more prolonged studies are needed to better elucidate the exact effects and mechanisms of TCZ function in severe COVID-19, prior to officially encouraging a change in clinical practise.

SUMMARY

What is Currently Known about the Subject:

- Tocilizumab, an interleukin-6 inhibitor often prescribed for rheumatoid arthritis, has shown survival benefit and a reduction in ventilation time in patients with severe COVID-19 pneumonia.
- In Malta, this treatment started being used in January 2021 for patients with COVID-19 pneumonia that exhibited a sudden deteriorated in condition, as indicated by rapid increase in oxygen requirements and need for admission to intensive care.
- Little data is available in the literature about the effect tocilizumab has on common biochemical and clinical markers of infection in this population of patients, and how the interpretation of these values may need to be altered in patients who have received the drug.

The New Findings in this Study:

- Tocilizumab significantly lowers the levels of procalcitonin and C-reactive protein in severely ill COVID-19 patients in the days following its administration.
- This demonstrates that caution is required when relying on these inflammatory markers to diagnose a secondary or worsening infection, since they may be falsely low.
- Other markers such as white cell count, neutrophil and lymphocyte count and PaO2/FiO2 ratio, as well as results of blood cultures are unaffected by this drug, and can therefore still be used as accurate markers for infective conditions.

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MMJ

ORIGINAL ARTICLE

Family screening and the psychosocial implications of coeliac disease

Zachary Gauci, Abigail Attard, John Schembri, Pierre Ellul

Background

Screening of first-degree relatives of patients with coeliac disease is recommended, though evidence on the frequency of repeat screening is lacking. Diagnosis of a chronic condition can have psychosocial implications. The aims of this study were to determine the proportion of first-degree relatives of patients who were screened and diagnosed with coeliac disease, as well as to determine the impact of the condition on their quality of life.

Methods

Patients diagnosed histologically at Mater Dei Hospital in Malta, between May 2009 and December 2018, were asked regarding family screening and a questionnaire was used to assess the effects of coeliac disease on their quality of life (n=96, 79% female, mean age: 46, 29.2% asymptomatic).

Results

11.4% of tested first-degree relatives were diagnosed with coeliac disease, despite only 31.7% (165/520) of first-degree relatives having undergone routine screening at least once and only 3.1% (16/520) having undergone multiple screening tests.

77% of index cases felt that other people do not understand their dietary needs. 38.5% avoid social activities because of their dietary requirements. 76% experience difficulty in finding something suitable to eat when not at home. Importantly, 83.3% claimed significantly increased costs.

Conclusion

The prevalence of CD in first-degree relatives of index CD patients is higher than that of the general population. However, a greater emphasis needs to be employed in ensuring serological screening of the at-risk groups.

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Introduction

Coeliac disease (CD) is a chronic autoimmune condition precipitated by the intake of gluten, a protein present in wheat, barley and rye. CD occurs in approximately 1% of the Western population. The availability of serological investigations testing for CD, as well as awareness of potential complications of the condition, contribute to this increasing prevalence as a result of improved diagnosis.[1] Despite this, due to the paucity of symptoms in some patients, which if present may be non-specific, CD is likely to be under-diagnosed and the true prevalence of the condition is probably higher.

The prevalence of CD in first-degree relatives is around 10%, with significantly greater prevalence values in monozygotic twins, families with multiple members affected, or siblings who have the same HLA susceptibility alleles.[2]

The British Society of Gastroenterology (BSG) and the National Institute for Health and Care Excellence (NICE) guidelines recommend active case finding in certain clinical situations, including in first-degree relatives of patients with CD.[2-3]

Lifelong adherence to a gluten-free diet (GFD) can affect the patient's quality of life (QOL) including psychologically, socially and financially.[4]

The aims of this study were:

- To identify the proportion of first-degree relatives of patients previously diagnosed with CD who were screened and found to be affected by CD
- To determine the patients' perception of the effects of CD on their life

Materials and Methods

Patients diagnosed with CD at Mater Dei Hospital in Malta, between May 2009 and December 2018, were recruited. The patients were identified through the histopathology department. The inclusion criteria were age above 16 years and a histological confirmation of CD. Patients who did not have biopsy-proven CD were excluded from the study.

Patients were contacted during the year of 2019 and were consented for participation in the study. Patients were interviewed. They were asked about the clinical symptoms or pathway that led to investigations for CD. In those who were asymptomatic, the reason for CD screening was ascertained. The patients' clinical case notes were reviewed.

The next part of the questionnaire focused on family screening of first-degree relatives (parents, siblings and offspring). The number of first-degree relatives was ascertained, as well as whether any of them were known to suffer from CD and whether they underwent opportunistic screening via serology and subsequent endoscopy. For those in whom family screening did take place, the year of initial screening and whether a positive result was obtained was recorded for each first- degree relative. For those family members who were screened and initially tested negative, it was enquired whether screening was ever repeated at a later date and if so, the year during which subsequent screening was carried out was noted. First-degree relatives who underwent opportunistic screening in view of their positive family history were included. It was also enquired if any first-degree relatives had undergone coeliac serology testing in view of gastrointestinal symptoms and if any of them were diagnosed with CD.

The second part of the unvalidated Quality of Life (QOL) questionnaire focused on assessing the patients' perception of some of the psychosocial effects of CD on their life.

The following four questions were asked:

1. Do you feel that people don't understand your dietary needs or think that you're exaggerating?
2. Have you ever avoided social activities or felt less able to integrate with others because of your dietary requirements?
3. Do you find difficulty in finding something suitable to eat when you are not at home?
4. Do you feel that you have significantly increased expenses due to coeliac disease[4]?

The patients` response was graded on a 5-point Likert scale (never, rarely, sometimes, often, always).

RESULTS

Index Cases

One hundred and eight patients (108) met the inclusion criteria. Twelve of these patients were excluded because they have since become deceased (*n*=2), or because they could not be contacted (*n*=10). The majority of the patients diagnosed with CD were female (79%).

The current mean age of the patient population was 46 years (range: 18-80 years). The time that had elapsed from diagnosis varied between 6 months and 10 years (Figure 1).

The majority of patients (70.8%) that were diagnosed were symptomatic. The most common symptoms that patients complained about were abdominal pain (29.2%), diarrhoea (21.9%) and bloating (20.8%). Figure 2 demonstrates the various symptoms that the patients experienced.

Figure 1: Time elapsed from initial coeliac disease diagnosis of index case

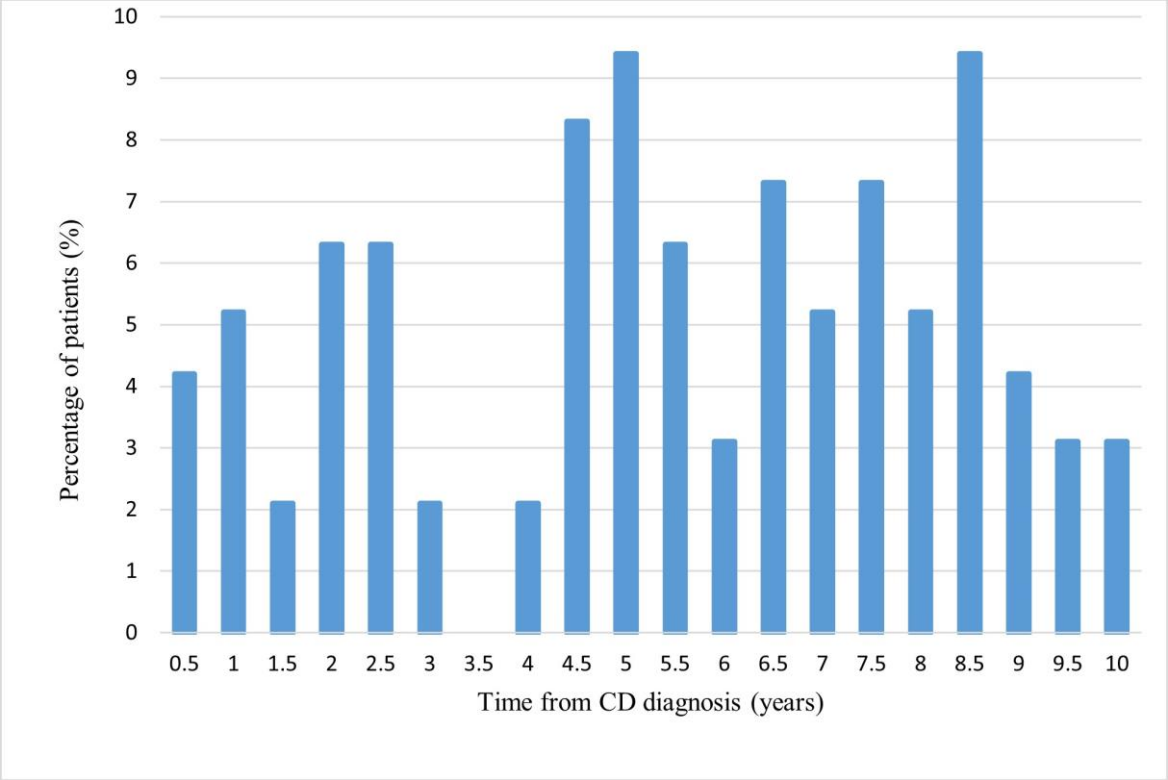
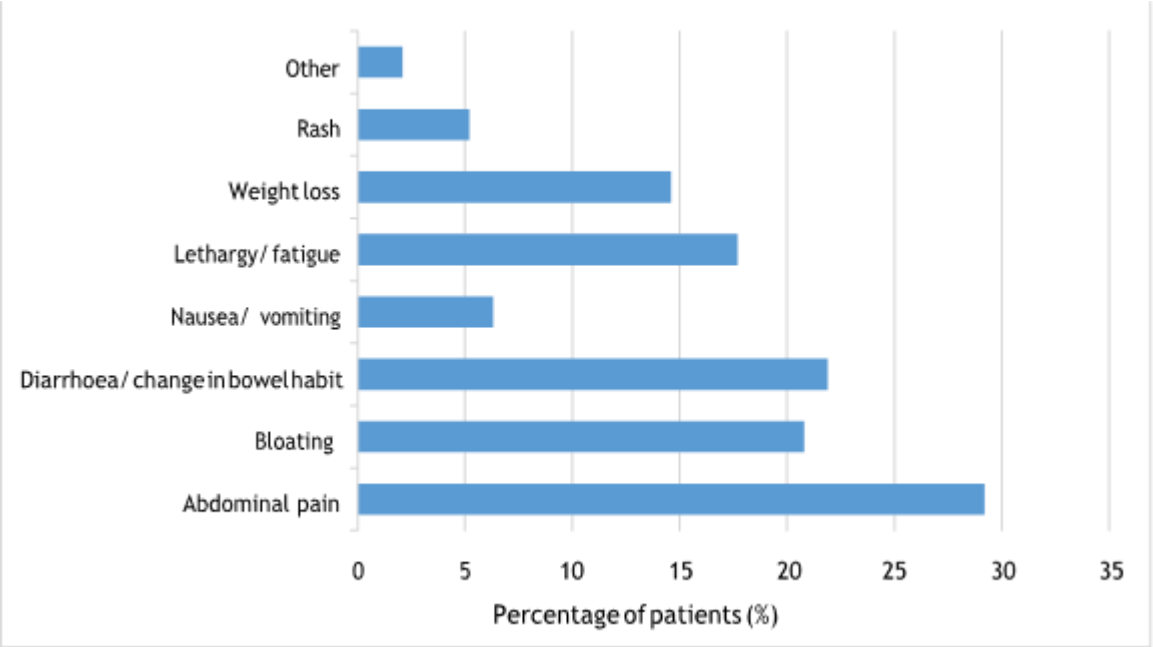


Figure 2: Symptoms reported by index cases



In the asymptomatic group, the reasons for performing serological blood investigations for CD were:

- Screening in view of a family history (14.3%) or other autoimmune conditions (7.1%),
- Osteoporosis diagnosed on dual-energy X-ray absorptiometry (DEXA) scanning (17.9%)
- Investigation of asymptomatic iron deficiency anaemia (60.7%).

The serological blood test that was performed was an anti-tissue transglutaminase antibody (anti-TTG Ab) which also included routine IgA levels as to identify those with IgA deficiency. Histology confirmed the diagnosis in all patients. The majority of patients had a histological classification of Marsh 3 (96.9%) (Table 1).

Screening of Relatives

The total number of first-degree relatives of index cases was 520 and 31.7% (165/520) of these were screened by means of a serum anti-TTG at least once in their lives. In this sub-group, 9.7% (16/165) of the individuals screened, were tested more than once. Thus overall, only 3.1% (16/520) of all first-degree relatives had multiple screening tests for CD following diagnosis of their first-degree relative.

The total number of relatives diagnosed with CD was 20. This accounts for 11.4% of all first-degree relatives who were tested, half being diagnosed prior to our index case due to gastrointestinal symptoms and /or anaemia (*n*=10) and the rest being diagnosed through routine screening after the index case was diagnosed (*n*=10/165; 7 female). Two families had 3 affected members in all, including the index case. In the screened group, the majority (90%; *n*= 9/10) were found to be positive the first time they were screened. Similarly, from the first-degree relatives who had already been previously diagnosed (i.e. before the index case) with CD, 7 out of 10 patients were also female.

The majority of patients undergoing screening (72.7%), underwent screening by means of anti-TTG antibody testing within 12 months from the diagnosis of the index case. Within the next 2 years, 12.7% were screened while the rest (14.6%) were screened more than 4 years after the index case.

Table 1: Marsh Classification of the index cases

Marsh Type	Percentage of study population (%)
1	2.1
2	1.0
3a	35.4
3b	37.5
3c	24.0

Table 2 shows the time interval between each screening for those individuals who were screened more than once (*n*=16). From those who were found to have CD upon initial screening, 60% (*n*= 6/10) were screened within the same year of diagnosis of the index case while 30% (*n*=3/10) were first screened 2 years following diagnosis of the index case. The remaining patient (*n*=1/10, 10%) initially tested negative when screened the first time but was then found to have CD 6 years from diagnosis of the index case when she was screened for the second time.

There was no statistical difference in the type of first-degree relatives that had undergone screening between parents (34.3%; *n*=48/140), siblings (24.6%; *n*=64/260) and children (44.2%; *n*=53/120).

Table 2: Time interval between each screening for those patients screened more than once

Time interval between each screening	Percentage of people screened more than once (%)
Yearly screening	25.0
2-year	18.8
3-year	31.3
4-year	6.3
5-year	0.0
6-year	12.5
Other*	6.3

**Initially screened after 2 years, then on a yearly basis*

Patient Response to Questionnaire

The patients' responses to the four questions asked in our questionnaire are summarised in Table 3.

In response to our first question, the majority of patients felt that at least sometimes, people did not understand their dietary needs or thought they were exaggerating (77%).

Similarly, more than a third of patients (38.5%) often or always avoided social activities or felt less able to integrate with others because of their dietary requirements.

Quite importantly, 76% of patients expressed at least some kind of difficulty in finding something suitable to eat when not at home.

With regards to economic terms, a significant proportion of patients (83.3%) stated that their expenses have significantly increased due to CD.

Table 3: Patient responses to questionnaire

Question (Q)	Never (%)	Rarely (%)	Sometimes (%)	Often (%)	Always (%)
Q1. Do you feel that people don't understand your dietary needs or think that you're exaggerating?	15.6	7.3	30.2	26.0	20.8
Q2. Have you ever avoided social activities or felt less able to integrate with others because of your dietary requirements?	22.9	9.4	21.2	17.7	20.8
Q3. Do you find difficulty in finding something suitable to eat when you are not at home?	10.4	13.5	25.0	26.0	25.0
Q4: Do you feel that you have significantly increased expenses due to coeliac disease?	7.3	9.4	19.8	22.9	40.6

Discussion

CD is a relatively common, chronic autoimmune condition estimated at occurring in approximately 1% of the population. There is a significant genetic basis for the development of the condition with a strong association with the HLA-DQ2 and HLA-DQ8 gene loci with more than 95% of affected individuals expressing the HLA-DQ2 or DQ8 haplotype.[5] This explains the high prevalence in family members of the affected individuals, particularly in first-degree relatives with HLA DQ2/DQ8 positivity and especially so if they are HLA-DQ2 homozygous.[6-7]

A significant proportion of these patients are asymptomatic or have symptoms secondary to, as of yet, clinically undetected CD. Due to the high prevalence of undiagnosed CD in first-degree relatives of affected individuals, routine screening of this cohort is routinely advised by various guidelines.[3,8-9]

A systematic review and meta-analysis reported a pooled prevalence of CD of 7.5% amongst first-degree relatives and 2.3% in second-degree relatives.[10] In studies, known familial tendencies usually vary from 4 to 15%[11-19] though a recent retrospective study quoted a higher proportion with 44.4% of screened first-degree relatives having been diagnosed with CD.[20]

In our study, less than a third of relatives had undergone screening (31.7%). Screening was done through anti-TTG IgA antibodies, which also included routine IgA levels to identify those with IgA deficiency. Subsequently, CD was confirmed by means of duodenal biopsies. In our study group, from those relatives who were tested, 11.4% of them were diagnosed with CD. Recall bias might be a source of error. Patients might have forgotten if their relatives had been screened and/or tested and furthermore, they might not be fully aware of their relatives' screening or their relatives might not have divulged the results to them. The relatively small community might act against this as most families are very close together. However, our first-degree relatives' rate of CD is consistent with international data. When screened, most of the first-degree relatives were screened within a year of diagnosis of the index case (72.7%). This might be due to the fact that patients and relatives tend to be more concerned at diagnosis. Furthermore, patients are usually advised to inform relatives about screening at diagnosis and not subsequently. Another limitation to our study was the inability to contact patients either due to lack of contact details or the patients not answering their phone despite multiple attempts.

The majority of index patients with CD (79%), as well as their relatives diagnosed with CD (70%), were female. Amongst all first-degree relatives, the highest proportion screened was that of the index cases' children (44.2%) followed by parents (34.3%) and siblings (24.6%). Some patients with young children expressed the intention to screen their sons and daughters at a later date as they were deemed to be too young to be screened at the time of this study. It is not generally recommended to use IgA anti-TTG antibody screening for children younger than four years old due to immaturity of the immune system.[21]

Evidence suggests that screening of high-risk groups such as relatives of the index case is beneficial.[22] However, evidence for the frequency of repeated testing in those who are initially negative is limited. Some institutions carry out repeat screening via anti-TTG testing every two years.[17] The 2019 European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other

gluten-related disorders recommends that it would be reasonable to screen at-risk family members every 3 to 5 years though acknowledging that testing frequency has not been clearly defined.[23]

In this study, only 3.1% of all first-degree relatives were screened more than once, though most patients were diagnosed during the first screening episode.

HLA typing, which has not been routinely performed in this cohort of patients, has previously been suggested as an option in order to determine those family members with initially negative anti-TTG who have predisposing DQ2/DQ8 alleles and focus on follow-up screening for them.[17] HLA typing has a relatively high negative predictive value for CD. Therefore, CD is very unlikely to develop in those patients with negative anti-TTG and negative HLA typing. However, positive HLA typing is also present in patients who will never develop CD and this might lead to unnecessary fear and anxiety of developing CD.[24-25]

This study also sought to obtain information on the impact of a diagnosis of CD on the patient. The accredited Coeliac Disease Assessment Questionnaire (CDAQ) was used as a reference in order to guide us in adapting questions to include in the questionnaire.[4,26] A total of 4 focused questions were chosen in order to keep the interview brief and keep the patients focused. The 4 questions dealt with the psychological, social and financial impact of the condition on their daily lives. Thus, though we made use of an unvalidated questionnaire that we developed, the questions that we asked were all obtained from the accredited CDAQ.

The first question focused on the psychological effect of the disease due to the patients' perception of stigma or lack of understanding by other people. The results show that the majority of Maltese CD patients felt that this is still an issue and that awareness and understanding of the condition is poor among the general public. In fact, 20.8% replied that they always feel that the general population does not understand their dietary needs and believes that their dietary needs are an exaggeration. Only 22.9% reported that they either rarely or never felt this way.

The second and third questions assessed the effects of the condition on the affected individuals' social lives. A significant proportion of patients claimed that their dietary needs drive them to avoid social activities and make them less able to integrate with others. More than a third of them avoided social activities on a regular basis and 76% of patients expressed at least some kind of difficulty in finding something suitable to eat when not at home.

The last question emphasised the financial implications of their dietary requirements. In Malta, patients with biopsy-confirmed CD are entitled to make use of the National Coeliac Scheme in which patients are entitled to a monthly monetary voucher which can be exchanged for a number of gluten-free products.

Despite this, 63.5% of patients have noted that their diagnosis has substantially increased their financial burden. This concern has also been recently highlighted by a study on the cost and availability of GFF in the United Kingdom.[27]

In conclusion, the prevalence of CD in first-degree relatives of index CD patients is higher than that of the general population. However, our local screening rates are still low and a greater emphasis needs to be done as to ensure adequate screening through serological testing. Future studies should also focus on the frequency of testing of first-degree relatives.

Summary

What is already known about the subject

- The prevalence of coeliac disease (CD) in first-degree relatives is elevated when compared with the general population at about 10%, due to a strong association with the HLA-DQ2 and HLA-DQ8 gene loci.
- Screening of first-degree relatives of patients with coeliac disease is recommended, though evidence on the frequency of repeat screening is lacking.
- Lifelong adherence to a gluten-free diet can affect the patient's quality of life including psychologically, socially and financially.

What are the new findings?

- In our Maltese study group, 11.4% of tested relatives were diagnosed with CD, such a percentage being consistent with international data.
- Less than a third of first-degree relatives of Maltese patients with CD were found to have undergone screening (31.7%) at least once, with only 3.1% having been screened more than once.
- The majority of interviewed Maltese patients felt that living with CD had a detrimental effect on their quality of life including perceived stigma due to lack of awareness of the general population, limitation of social activities and financial burden.

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REVIEW ARTICLE

Prevalence and associated factors of road crash involvement (RCI) among medical doctors: Systematic review and meta analysis

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Background

There have been vague reports on road crash involvement (RCI) affecting medical doctors with limited studies on its' prevalence. The aim of this study is to determine the prevalence and associated factors of RCI among medical doctors.

Methods

Four databases, SCOPUS, PubMed, EMBASE and Medline were systematically searched from their inception date till October 2020. Eligible studies including cross sectional studies, review articles and press reports in English underwent a systematic search to determine which articles reported on the prevalence and associated factors of RCI amongst medical doctors. Two sets of 2 independent reviewers screened the references in two steps: abstract screening, followed by full text review. The checklist Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was used for quality assessment of the studies.

Results

599 articles were retrieved, of which 27 articles were removed after duplicate screening. The remaining 572 articles were further assessed and only 4 articles fulfilled the inclusion criteria. The RCI prevalence among medical doctors worldwide ranged from 7.9%-24.6%. Factors associated with increased risk of RCI include lack of sleep and fatigue related to long working hours. Other associated factors include number of years in residency, number of weekly working hours, weight gain, tendency to fall asleep while driving, hypertension, absence of breaks, inadequate rest facilities, tolerance towards shiftwork, capacity to overcome sleepiness, and quantity of night shifts worked per month.

Conclusion

The prevalence of RCI among medical doctors is high. Further studies are needed to evaluate this emerging public health issue.

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BACKGROUND

A significant number of lives are lost each year due to road traffic crashes causing significant losses to individuals and the economy.[1-2] Road crash involvement (RCI) is an international public health burden involving commuting accidents of workers to and from work as the majority of workers tend to travel by road.[3-4] Commuting accidents comprise 15% of work-related accidents in Europe compared to a much higher rate of 47.6% in Malaysia with an alarming increase in the prevalence over the years.[3]

Healthcare workers are among those that are at risk of such injuries. A study among Japanese nurses reported that, among other work-related injuries, traffic accidents contributed approximately 3%.[5] Work-related accidents were presumed to be due to shift work and lack of sleep.[5-6] Another healthcare personnel that is at risk are ambulance drivers, due to the nature of their work.[7-8] Eksi et al suggested that these occurrences are due to time and speed factors.[8] There are limited published studies on healthcare workers on RCI as a whole. The current focus is on medical doctors, with recent RCI reporting that have raised concerns among the public and medical fraternity.[3,6,9-13]

To compound the issues further, there has been reported shortage of healthcare workers including medical doctors in the workforce and this shortcoming has added new impetus to improve measures to prevent work-related injuries among these healthcare personnel.[14-15] There are many factors predisposing medical doctors towards RCI including fatigue and sleep deprivation in addition to the long working hours and heavy workload.[12-13,16]

Despite these observations, there is still a lack of concerted effort to address this problem. Medical doctors work hard to save the lives of others, but are simultaneously exposed to the dangers of their own jobs. Therefore, the objective of this study was to determine the prevalence and associated factors of RCI among medical doctors.

METHODS

Search strategy

Four databases, SCOPUS, PubMed, EMBASE, Medline were systematically searched from their inception date till October 2020 with the following search terms: (risk OR risk factor OR factor) and (doctor OR physician) and (road accident OR traffic accident) and (prevalence OR incidence). Combinations of expanded MeSH term and free-text searches that were applied are shown in Appendix 1. In addition, reference lists of relevant articles were also screened for its suitability.

Inclusion criteria

Any studies that report prevalence and risk factors for road crash involvement among doctors and fulfilled the following criteria were entered into the analysis: (1) prevalence and risk factors were reported as the primary results; (2) journal articles written in English. The authors also identified other relevant studies through reverse-forward citation tracking and reference lists of the selected articles.

Study selection

We imported the articles identified through the databases into EndNote© X9 version after performing de-duplication. There were two teams of reviewers, one team consisting of two reviewers (KI and AAR) and (NKD and FM) who screened through the titles and abstract of the remaining articles in pairs. If there was a lack of information on the prevalence of RCI in the title and/or abstract, the full text was then retrieved to identify the relevant data. Discussions were also held before reaching a final consensus.

Quality assessment and data extraction

The checklist Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for cross sectional study was used to assess the quality of the retrieved articles by two independent investigators. The tool consists of 22 items that assesses vital components in observational studies. If the information provided was not enough to assist in making a judgement for the items, we agreed to grade the item with a '0'. This means "high risk of bias". Each article's quality was graded as 'good' if the STROBE score is more or equal 14 out of a maximum score of 22 and graded poor if otherwise. Only studies with a STROBE score ≥ 14 were included in the analysis. The scoring of the selected articles is shown in Appendix 2.

One of the reviewers recorded the data from the selected studies into the extraction form in the Excel sheet, while the second reviewer verified its accuracy. The characteristics of the selected studies were extracted as follows: first author, year of publication, title of study, country, study design, study population, gender, mean age, sample size, number of accidents, and the prevalence of RCI. The outcome measures extracted were the prevalence of road traffic accident and its risk factors.

Data analysis

A random-effects (DerSimonian and Laird method) meta-analysis was used to determine the pooled prevalence and odds ratio (OR) from the individual studies and was reported with a 95% confidence interval (CI). Heterogeneity across studies was assessed using the I2 index (low is < 25%, moderate 25–50%, and high > 50%), that indicated the percent of total discrepancy due to variation in the studies. Subgroup analysis based on the study design was also performed. OpenMeta[analyst] was employed for statistical analysis. The prevalence of RCIs worldwide was analyzed by performing subgrouping of the study setting.

RESULTS

Description of included studies

We identified 599 manuscripts in our initial search as shown in Fig. 1. After de-duplication (*n*=27), 572 studies were then retrieved for further review. After evaluation of the inclusion and exclusion criteria, a total of 4 studies that were performed from 1996-2017 and had a STROBE score of ≥14 was included in this systematic review and meta-analysis.

Characteristics of included studies

Out of the 4 included studies, two were cross sectional studies (Marcus et al., 1996, Fruchtman et al., 2011), and the other two were cohort studies (Steele et al.,1999, Barger et al., 2005). 11,17-19 These studies had a population group mean of 910 participants with the mean age of 30.6 years. This includes 2061 males and 1737 females. All the studies involved doctors in different departments. One study involved doctors in the emergency department (Steele et al.,1999), another from the pediatric department (Marcus et al., 1996), and two involved a combination of many departments (Fruchtman et al., 2011, Barger et al., 2005). 11,17-19 Among the four studies, three were conducted in Unites States of America (Marcus et al., 1996, Steele et al.,1999, Barger et al., 2005), and one in Israel (Fruchtman et al., 2011). Overviews of the studies characteristics are shown in Table 1.11,17-19

The overall pooled prevalence of RCI was 12.3 (95% CI=8.1, 16.4, I2=87.54) (Fig. 2). Figure 2 shows the prevalence of RCI across the study population. The pooled prevalence of RCI analyzed by subgroup analysis was 18.9% (95% CI= 6.7, 31.2, I2=73.16%) among cross sectional study and 10.3% (95% CI= 5.8, 14.8, I2=94.43%). The prevalence of RCI by study population was highest in Pediatric residents at John Hopkins Hospital (24.6%). The lowest prevalence of RCI was in Emergency Medicine Residents in the USA (7.9%).

Figure 1: PRISMA flow diagram of the literature screening process

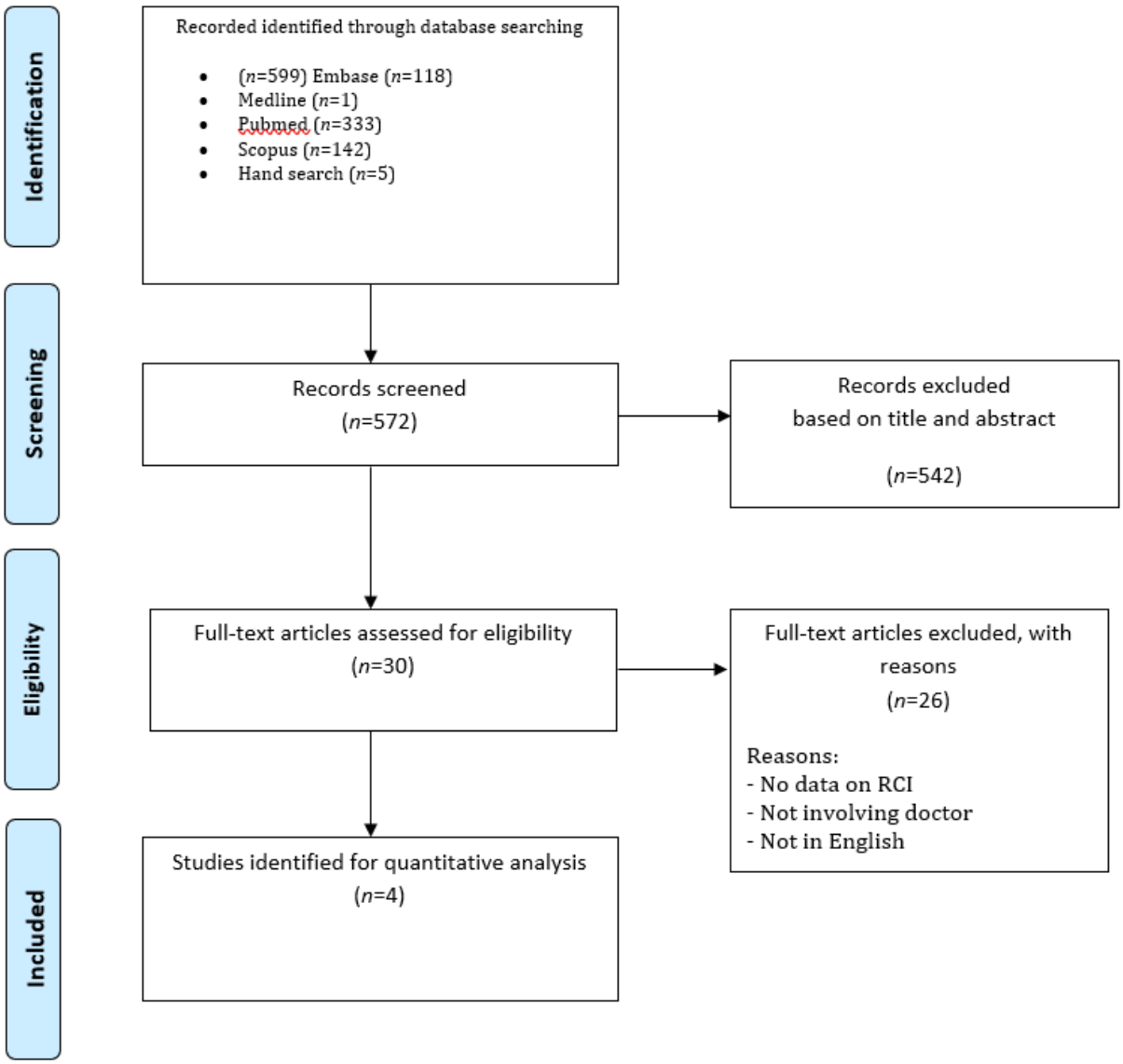

Figure 2: Forrest plot on the prevalence of road traffic accident

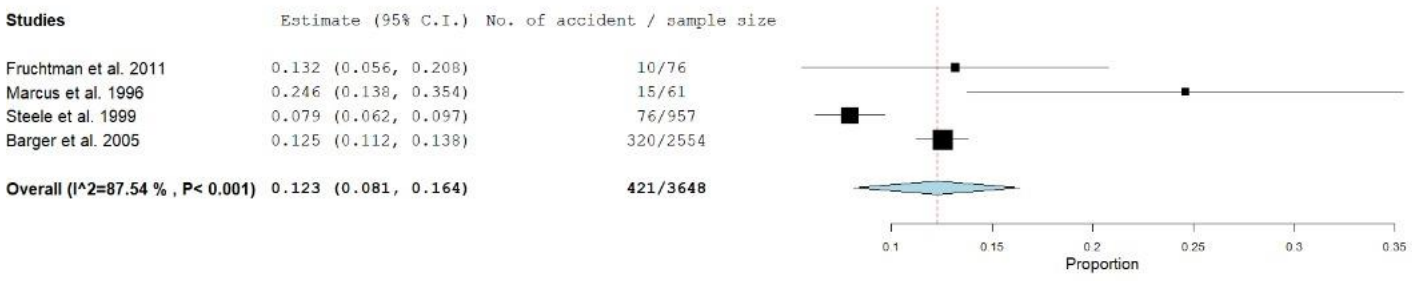

Table 1: Characteristics of included studies

Author	Year	Title study	Study design	Study population	Gender	Mean age	Sample size	No of accident	Pooled Prevalence	Risk Factors
Fruchtman et al.	2011	Fatigue in medical residents--lessons to be learned	Cross sectional	Medical resident from Soroka University Medical Center (SUMC), Israel.	40 males and 36 females	35.5 (±4.8) years	76	10	**13.9%**	Fatigue, number of years in residency, number of weekly working hours, hypertension, weight gain
Marcus et al.	1996	Effect of sleep deprivation on driving safety in housestaff (HS)	Cross sectional	Pediatric HS and faculty members (FAC), USA	17 males and 44 females (HS)	29	61	15	**24.6%**	Sleep deprivation
Steele et al.	1999	The occupational risk of motor vehicle collisions for emergency medicine residents	Cohort	Emergency Medicine Residents, USA	718 males and 239 females	30 (±3) years	957	76	**7.9%**	residents' subjective tolerance of shiftwork, ability to overcome drowsiness
Barger et al.	2005	Extended Work Shifts and the Risk of Motor Vehicle Crashes among Interns	Cohort	First postgraduate year residents (interns) different specialties, USA	1286 males and 1451 females	28 (±3.9) years	2554 (93% of the study cohort [2737] completed at least one monthly survey and were eligible for the analysis of crashes and near-miss incidents)	320 (131 of the 320 crashes occurred on the commute from work)	**12.5%**	Number of night shifts worked per month

Risk Factors

For clarity in terms of describing the risk factors, we divided them according to study design. For the cross-sectional studies, factors associated with RCI among medical doctors are number of years in residency, number of weekly working hours, weight gain, and hypertension. For the cohort studies, absence of breaks, inadequate rest facilities, residents' subjective tolerance of shiftwork, ability to overcome drowsiness, and number of night shifts worked per month, to be the contributing factors for the occurrence of RCI.

DISCUSSION

To our knowledge, this is the first systematic review on the prevalence of RCI among doctors. We report the pooled prevalence rate of 12.6%. Looking into other healthcare profession such as nurses, a study reported that the prevalence of RCI or near miss accidents is approximately 22%.[20] Therefore, there is not much difference between the prevalence of RCI occurrence among doctors and nurses as they usually share the same work-related stresses and environment, causing them to have similar risk factors to the occurrence of commuting accidents, bearing in mind that the data on the nurses also included near miss accidents. In contrast, the number of RCI among ambulance drivers is relatively greater than medical doctors. From a retrospective secondary data analysis conducted by the Ministry of Health (MOH), Malaysia, 129 ambulance accidents per year was reported.[21] Another retrospective analysis study conducted in the United States of America reported the occurrence of 339 RCI among ambulance drivers causing 405 fatalities and 838 injuries.[22] Compared to other hospital staffs such as ambulance drivers, medical doctors have different backgrounds and job specifications, so the risk of RCI also varies. For ambulance drivers, the occurrence of these accidents can be related to the fact that they not only drive vehicles, but also double-up as EMS (Emergency Medical Services) workers. Ambulance drivers are also authorized to exceed the speed limits and proceed past a red or stop signal as they are required to rush critical patients to the nearest health facility.[23] Therefore, RCI among medical doctors and other healthcare workers emerged as an important occupational safety issue which needs to be addressed quickly.

From review of the cross-sectional studies, the number of years in residency is closely related to RCI. Ideally, the more senior the doctor is, the more experienced he or she will be, hence, a more balanced work-life cycle will usually follow. However, a cohort study among 15,271 subjects in France reported that senior skillful workers (managers) had a higher risk of RCI compared to junior staffs.[24] This observation may be due to the higher stress or work pressure among those in higher medical posts and considered to be senior staffs. We also found that extended work hours may be a significant factor among medical doctors with increased tendency to fall asleep while driving and the potential for RCI and near miss. Doctors are known to work long hours, sometimes extending more than 24 hours, resulting in sleep deprivation and fatigue.[19] Fatigue and sleep deprivation have been studied extensively, especially among healthcare professionals, and have been reported to have a negative impact on their work and wellbeing.[17] Shorter sleep durations were associated with greater risks of struggling to stay awake driving home.[20] This often results in reduced clinical function, impaired neurocognitive impairment, and negative effect on mood. Reduced attention and reaction time has been shown to have measurable impact when driving a motor vehicle.[25] Sleep related disturbance, such as obstructive sleep apnea, micro sleep and poor sleep hygiene, have

also been said to affect driving performance. In addition, weight gain has been reported to have a significant effect on RCI based on the cross-sectional studies retrieved. This particular factor is an important feature to develop obstructive sleep apnea (OSA) which has a strong negative impact on RCI. A study by the American Academy of Sleep Medicine (AASM) among 1478 sleep apnea patients reported that obstructive sleep apnea patients were nearly 2.5 times more likely to have RCI compared to a control group of other drivers in the general population.[26] Hypertension, meanwhile, is a disease known for its systemic effects in impairing the cognitive function in patients with suboptimal to poor control of the disease. From the available reviews, we noted that hypertension has a meaningful contribution to RCI. A case control study conducted among 733 injured drivers in France reported that patients suffering from hypertension has a higher significant risk to be involved in RCI (adjusted odds ratio [adjOR] =3.82; 95%CI=[1.42–10.24]).[27]

As for the cohort studies that we reviewed, the number of night shifts worked per month also contributes to the occurrence of RCI. A study reported that shift duties working personnel had a 30% higher risk of traffic accidents while commuting to and from the workplace, compared to office hours only employees.[28] All of these factors are closely related to their role in handling and treating patients. Based on above reasons, working hour regulations are usually unintentionally violated due to major challenges in insufficient number of doctors, that makes the doctors on-call exposed to an intense workload and extended working hours. Moreover, inadequate rest facilities also have a role in RCI. This factor, however, has a close relationship to fatigue and sleep deprivation. Most hospitals fail to have rest facility for on call doctors. Since they have few or none of these facilities, they have no choice but to commute home straight after a long night or on call shift. Moreover, pit stops or Rest & Relax (R&R) centers are only available on major highways. Most doctors will therefore choose to live nearer to their workplaces. Nevertheless, micro sleep is hardly avoidable regardless of the distance between their homes and workplaces. For this reason, they are commuting on main roads where R&R centers are not available. A cross-sectional study among 949 male truck drivers in Italy reported that taking a **rest** break or a nap appear to be protective against RCI.[29] The ability to overcome drowsiness while driving can be considered a miraculous cure that not only doctors but all drivers should implement to promote a safer commutation. However, in a moderate to severely fatigue and sleep deprived person (even doctors), their cognitive functions as well as the decision-making ability are mainly impaired. Hence, they could not make decisions well especially during driving. A study conducted among 13 Australian armies reported that cognitive performance, decision making, self-regulation and self-monitoring declined significantly following a sleepless night.[30]

The main strength of this study was that it is one of the first systematic reviews that look at the prevalence of RCI among medical doctors worldwide. This study also employed a comprehensive search of four major databases in order to capture all the articles related to the study objectives. This study also has a high number of participants. The main limitation is the high heterogeneity noted among these studies due to differences in background and relatively small number of studies.

CONCLUSION

The prevalence of RCI among medical doctors are 7.9%-25.7%. This study shows that the pooled estimation of prevalence was 12.6%. The associated

factors are sleep deprivation and fatigue after long working hours. These factors should be addressed carefully as it has become a major occupational safety risk for doctors and other medical personnel. We recommend larger, nationwide studies looking into the prevalence and factors associated with RCI among doctors involving different specialties and further actions to be taken to reduce these significant and preventable work-related health problems. Table 2 highlights the summary of risk factors and recommendations

Acknowledgments

The authors would like to thank the Ministry of Education Malaysia for funding this study. Fundamental Research Grant Scheme. Grant no: FRGS/1/2018/SKK01/UPM/03/1.

Table 2: Summary of risk factors and recommendations

Risk factors	Recommendations
1. Increased number of years in residency 2. Presence of hypertension 3. Increased number of weekly working hours along with absence of breaks and increased number of night shifts 4. Weight gain 5. Inadequate rest facilities 6. Residents' subjective intolerance of shiftwork 7. Inability to overcome drowsiness	1. The main associated factors are sleep deprivation and fatigue after long working hours. 2. These factors should be addressed, and appropriate actions taken (e.g. shorter working hours and less night shifts) as it has become a major occupational safety risk for the health personnel. 3. We recommend larger, nationwide studies looking into the prevalence and factors associated with RCI among doctors involving different specialties.

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Appendix 1 Search numbers (20191107)

	Search strategy	Embase	Pubmed	Medline	Scopus
#1	Risk OR Risk factor OR Factor		4033638		
#2	doctor OR Physician		680319		
#3	road accident OR traffic accident		52786		
#4	prevalence OR Incidence		3060830		
#5	1 AND 2 AND 3 AND 4	118	333	1	142

#1 prevalence OR Incidence

#2 Risk OR Risk factor OR Factor

#3 road accident OR traffic accident

#4 doctor OR Physician

#5 1 OR 2

#6 5 AND 3 AND 4

Appendix 2: Assessment of risk of bias of included studies by STROBE Checklist (cross sectional studies)

	1a	1b	2	3	4	5	6a	6b	7	8	9	10	11	12a	12b	12c	12d	12e	13a	13b	13c	14a	14b	14c	15	16a	16b	16c	17	18	19	20	21	22	total
Fruchtman et al., 2011	0.5	0.5	1	1	1	1	0.5	0.5	1	1	0	1	1	0.2	0.2	0	0.2	0	0.3	0.3	0	0.3	0	0	1	0.3	0.3	0.3	0	1	1	1	1	0	17.4
Barger et al., 2005	0.5	0.5	1	1	1	1	0.5	0.5	1	1	0	1	1	0.2	0.2	0.2	0.2	0	0.3	0.3	0	0.3	0.3	0.3	1	0.3	0.3	0	1	1	1	1	1	0	18.9
Marcus et al, 1996	0.5	0.5	1	1	1	1	0.5	0.5	1	1	0	1	1	0.2	0.2	0.2	0	0	0.3	0.3	0.3	0.3	0	0	1	0.3	0	0	1	1	1	1	1	0	19.1
Steele et al, 1999	0.5	0.5	1	1	1	1	0.5	0.5	1	1	0	1	1	0.2	0.2	0	0.2	0	0.3	0.3	0	0.3	0	0	1	0.3	0.3	0.3	0	1	1	1	1	0	17.4

MMJ

CASE REPORT

Point of Care Cardiac Ultrasonography in three paediatric arrests

Eugenio Azzopardi, Elizabeth Grech, Victor Grech

Introduction

Point-of-Care Ultrasound (POCUS) refers to bedside ultrasonography in the clinical setting at the site of initial presentation. Few studies have reported the use of POCUS for emergency paediatric echocardiography.

Methods

This paper outlines the utility of POCUS echocardiography in three cases in Malta.

Results

Cardiac POCUS was used with utility and value on three children in the acute resuscitation setting.

Discussion

Echocardiography in children during resuscitation is feasible and it is possible to eyeball contractility and cardiac filling and assess the size of any pericardial effusions. Although the images obtained are inferior to those obtained in an echocardiography laboratory, useful information in real time can be obtained.

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Introduction

Point-of-Care Ultrasound (POCUS) refers to bedside ultrasonography in the clinical setting at the site of initial presentation. This could be a hospital emergency department, an ambulance, or a remote village.[1] Few studies have reported the use of POCUS for emergency paediatric echocardiography.[2] Malta is a small central Mediterranean island with a total population of circa half a million, and one large regional hospital.[3-4]

Methods

This paper outlines the utility of POCUS echocardiography in three cases in Malta.

Results

Case 1

A 3-year-old male presented with a widespread petechial rash together with areas of ecchymosis extending from the forehead to the feet. These were non-blanching, along with an area of sloughing on the dorsum of the left hand and on the chin (figure 1). On initial examination he was also quiet and lethargic but responsive to commands. There was tachycardia with hypotension and rapid clinical deterioration. The working diagnosis was meningococcal septicaemia. A large bore cannula was inserted and a saline bolus was commenced. Despite this, blood pressure became unobtainable, with absent pulses and a 2nd saline bolus was administered together with intravenous ceftriaxone as per local guidelines. Over the next minutes he became bradycardic and his pulses became impalpable. Cardiac massage was commenced and the child was intubated. Adrenaline was given with some improvement of heart rate. Echocardiography was performed initially from the parasternal long axis view, later from the subcostal view. Spontaneous contrast with ventricular dilatation and very poor contractility was evident (figure 2). This indicated that the main cause for shock was reduced myocardial contractility rather than fluid depletion, prompting the decision to administer more inotropes. He was admitted to intensive care and was discharged neurologically intact after 10 days.

Figure 1: Photo of child's hand showing skin loss and petechiae

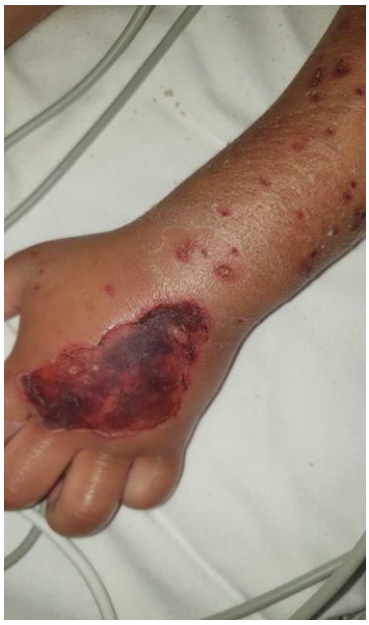
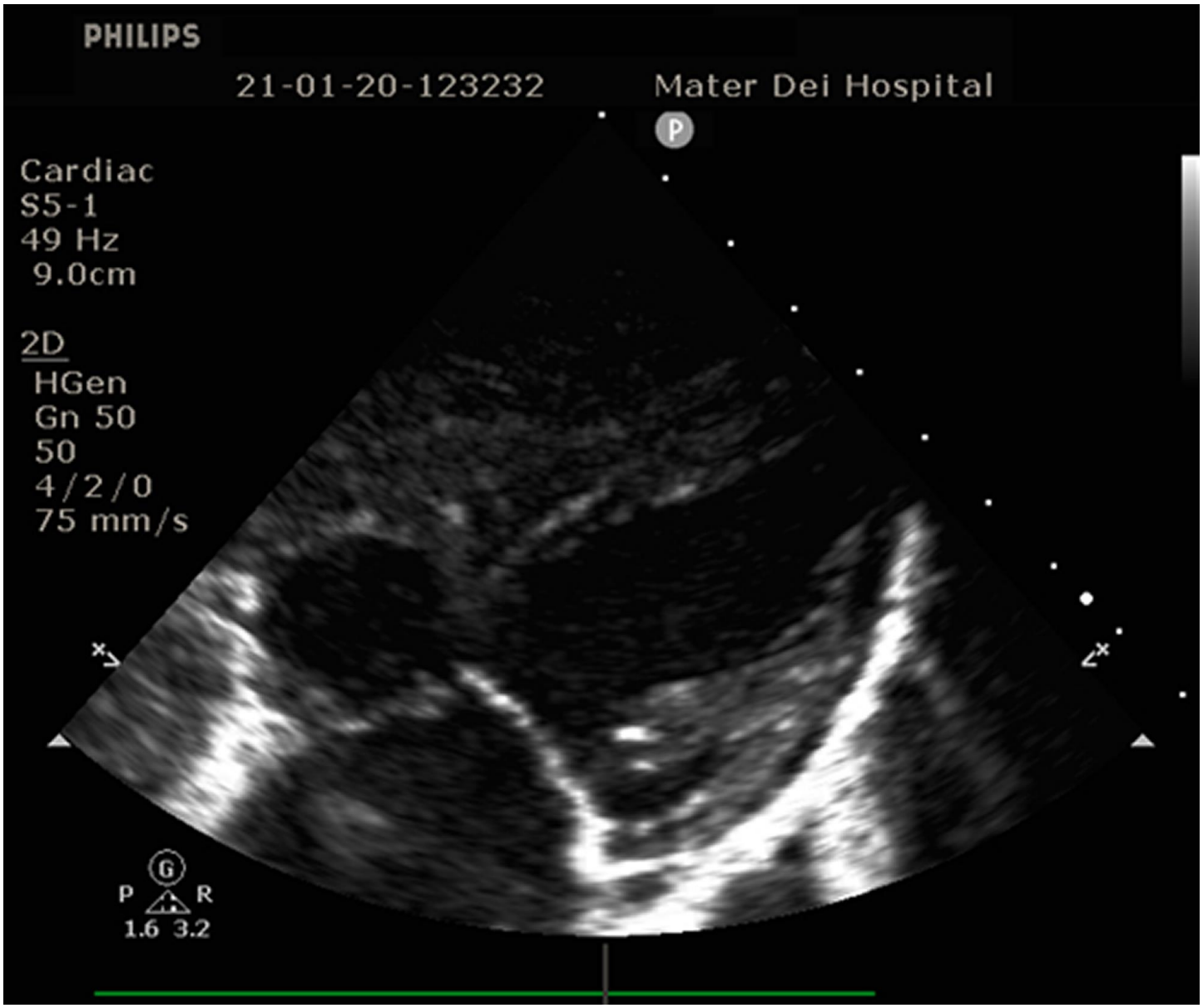


Figure 2: Subcostal view showing biventricular dilatation



Case 2

A 12-year-old girl was admitted with pulseless electrical activity despite eight doses of adrenaline given by the pre-hospital team at home. She was brought to hospital in full cardiopulmonary resuscitation (CPR). In this case a subcostal echo was performed during rhythm checks to confirm persistent cardiac standstill and demonstrate to the understandably distraught parents the lack of cardiac function and hence the futility of continuing resuscitation beyond 30 minutes at hospital.

Case 3

A 6-year-old girl was admitted in cardiac arrest following a 1-day history of high-grade fever accompanied by two episodes of vomiting. The pre-hospital team found her in cardiac arrest, and she was brought to hospital in full CPR. The initial ECG demonstrated cardiac standstill. After two doses of adrenaline, return of spontaneous circulation was established but the initial echocardiogram demonstrated poor contractility of the left ventricle. After three minutes she again went into asystole.

Resuscitation was continued for 30 minutes and echocardiography was also used to demonstrate to the parents the futility of continuing resuscitation. The post-mortem showed severe myocarditis.

Discussion

In the paediatric age group, both asphyxia and circulatory failure result in bradycardia and hypotension before deteriorating further to a pulseless cardiac arrest.[5] For this age group, the prognosis for survival to hospital discharge is much better than adults (OR of 2.29).[5] Furthermore, children may ultimately recover with excellent neurological function even after cardiac standstill.[6]

Point-of-care cardiac ultrasonography is a goal-directed bedside test that can enhance diagnostic confidence, facilitate clinical decision-making, and aid judicious management in the hemodynamically unstable child within the emergency department.[7] Diagnostic echocardiography is distinct from point of care cardiac ultrasonography as the scope of this investigation is often restricted to addressing the clinical questions raised by the patient's clinical state in order to guide immediate management decisions.[8]

Despite this, the paediatric literature regarding cardiac POCUS is sparse.[9,10,11] A small case series showed that cardiac POCUS is feasible although none of the patients in this series were in pulseless electrical activity secondary to septic shock.[12] However, an expert review has noted the utility of this type of imaging in the setting of cardiac tamponade, myocarditis and infective endocarditis.[12] However, there are no extant recommendations regarding performance of POCUS in the setting of septic shock with respect to fluid responsiveness or cardiac contractility.[13]

Interestingly, a study has shown that the level of skill required to perform cardiac POCUS to identify reversible causes of arrest, such as pericardial effusion, and to assess ventricular function and size, after only two hours of training, is almost on par (>93%) with that of paediatric echocardiographers.[14]

Point of care echocardiography can be employed to identify reversible causes of cardiac arrest as well as predict short-term outcome in these patients. In patients with a low probability for return of spontaneous circulation, the absence of spontaneous cardiac movement on echocardiography can predict a poor prospect of survival and guide the decision of resuscitation termination.[15] This was, in fact how this point of care test was applied in cases 2 and 3 above.

Conclusion

Echocardiography in children during resuscitation is feasible and while it is impossible to perform detailed calculations during cardiac massage, such as shortening fraction, it is still possible to eyeball contractility and cardiac filling and assess the size of any pericardial effusions. A small ventricle indicates the need to administer fluids while poor contractility indicates the needs for inotropic support.

Although the images obtained are inferior to those obtained in an echocardiography laboratory, useful information in real time can be obtained.

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MMJ

CASE REPORT

The danger of inappropriate use of personal protective equipment

Edward Muscat, Rachel Clancy, James Henderson

The coronavirus pandemic is a global health emergency which has had widespread unforeseen mental health consequences. Those diagnosed with borderline personality disorder are predisposed to poor coping strategies to manage such stress and require intense psychological input which was not widely available during the peak of the pandemic. It is likely that the coronavirus outbreak has had a significant impact on the mental stability of such patients which aggravated deliberate self-harm behaviours.

A 20-year old psychiatric in-patient with borderline personality disorder, held under Section III of the mental health act, presented to the adult plastic surgery team in Bristol with localised infection of her right forearm. Foreign bodies were easily palpable and imaging revealed linear metal objects. The patient reported that she had removed metal strips from her collection of face masks and inserted them into her forearm as an act of deliberate self-harm. The patient was taken to operating theatre for removal of these foreign bodies under general anaesthetic. After twenty-four hours of antibiotics she was discharged safely back to the psychiatric ward.

Despite the epilogue of the COVID-19 pandemic facemasks are still mandatory within the hospital setting. Clinicians need to be aware of these unusual circumstances where a form of protective equipment was deconstructed to cause actual bodily harm. The purpose of this report is to promote awareness of this type of injury especially in those suffering from mental illness. The authors would suggest an alternative mask without any form of metal.

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Introduction

On March 11, 2020, the World Health Organization announced the coronavirus disease (COVID-19) outbreak as a global pandemic.[1] Government rules such as isolation, contact restrictions and economic shutdown presented an abrupt change to the psychosocial domain of the general population. Those diagnosed with borderline personality disorder (BPD) are already predisposed to poor coping strategies to manage stress[2] and are likely to have been negatively impacted from this.

The UK government enforced mandatory facemasks for all members of the public when entering indoor public areas. The rationale being that they will prevent spread of coronavirus droplets which is an added protective strategy when considering social distancing and regular hand hygiene. Face coverings are now mandatory within the National Health Service which should be worn by all staff and patients, unless exempted, in hospitals and community care establishments including psychiatric units.

The authors present a case involving a patient with BPD who deliberately inserted metal strips from face masks into her soft tissues whilst in a secure psychiatric unit. We would like to create an awareness of this method of injury especially for patients with psychiatric illnesses during these challenging times which are destabilising the mental health of such vulnerable patients.

Case presentation

A 20-year-old Caucasian lady, with a history of BPD, anxiety and deliberate self-harm (DSH) was referred to the plastic surgery team in Southmead hospital, Bristol, with a soft tissue infection over her right forearm. She was under Section III of the mental health act (MHA) for deterioration of BPD and repeated episodes of DSH. She presented with a three-day history of erythema, pain and swelling over her right forearm. Eventually, it was revealed to staff that she had been inserting metal strips into her forearm from a collection of face masks she had acquired overtime.

During history taking she answered questions appropriately and engaged well. She was accompanied by a member of the psychiatry unit. She had a baseline tachycardia of 90 beats per minute and was apyrexial showing no signs of sepsis. Upper limb examination demonstrated a localized infection of her right dorsal forearm with erythema, swelling and tenderness. These metal foreign bodies were easily palpable with radiographs confirming the location of four metal wires superficially within the forearm and two metal strips in the hand *(Figure 1)*.

After acquiring informed consent, exploration of her right forearm was performed under general anaesthesia. This procedure necessitated the use of mini C-arm fluoroscopic imaging to identify the location of the strips allowing precise planning of surgical incisions with minimum incision lengths. All four metal strips were found buried within the adipose tissue and retrieved successfully with no associated complications (Figure 2). A clinical decision was made to leave the two old metal wires in the hand in situ as they demonstrated no signs of infection. Following the procedure, she remained an inpatient for twenty-four hours for which she experienced a good recovery. She received a period of strict arm elevation along with a course of intravenous antibiotics before being discharged safely back to the psychiatry ward. There was no demonstration of any intent to perform acts of self-harm during her inpatient stay and she cooperated well with the hospital staff. She was discharged on a short course of oral antibiotics and no postoperative follow up was required.

Figure 1: Intra-operative radiograph demonstrating the metal strips in the right forearm

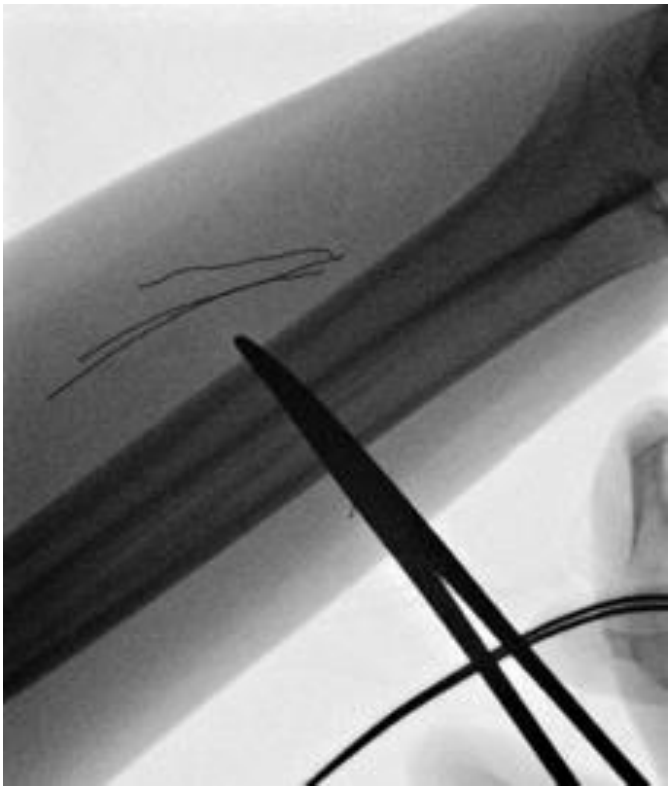

Figure 2: Four metal strips retrieved in theatre

Discussion

The COVID-19 pandemic contributed to a degree of psychosocial impact on every member of society especially those suffering from psychiatric illnesses.[3] An increment in figures of deliberate self-harm (DSH) was observed when social distancing was enforced during the pandemic.[4] However, evidence is lacking regarding its incidence within psychiatric units. This is the first case report which describes a presentation of self-embedding using the metal strips of protective face masks.

Borderline Personality Disorder (BPD) is a significant psychiatric condition described as affect dysregulation, unstable self-image and DSH.[5] Its incidence is approximately 2-6% according to recent epidemiological studies.[6] Prevalence of DSH in the UK has been estimated to be between 4.6-6.6% .[7] BPD symptoms have been revealed to be associated with earlier age of onset and incremental frequency of DSH.[8-9] This patient presented in this report had a recurrent history of DSH originating during her early teenage years and had unfortunately presented with other forms of DSH after this episode. BPD patients share a strong predisposition for emotional and physical proximity with others which was suppressed because of social distancing rules due to the pandemic.[10]

Consequentially, the experience of lockdown was likely to be exhausting for these patients.[11] It is reasonable to believe that such isolation may have precipitated negative feelings about oneself resulting in conflicts secondary to misinterpretation of distance from others, due to preventative health measures, as a sign of neglect or betrayal to these patients. As a result, this misperception of social distancing of others may have encouraged substance misuse as a form of therapy in order to deal with this loneliness.[12] Within the psychiatric unit members of staff and patients were practicing social distancing which mandated face mask use. Despite being under Section III the patient was still able to commit DSH on a few occasions on the psychiatric unit and only presented to staff after developing signs of infection. Clinicians need to be aware of such unusual circumstances were a form of protective equipment was deconstructed to cause actual harm warranting an operation under general anaesthetic. The authors propose an alternative mask using plastic strips for mental health wards as opposed to metal strips.

Conclusion

Measures that were put in place by public health authorities during the coronavirus outbreak such as social distancing and isolation precipitated the feeling of emptiness and aggravated the fear of abandonment in patients with BPD.[3] The purpose of this report is to provide awareness of this method of injury with careful consideration of alternative forms of mask wear. It remains unpredictable as to how individuals with BPD will respond to current mask-wearing rules due to COVID-19 but, as clinicians, we have a shared responsibility to ensure the environment that are patients are treated in is safe.

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CASE REPORT

A rare case of Paediatric Narcolepsy in Malta

Jessica Pace, Stephen Attard, Nancy Formosa, Patrick Sammut

Narcolepsy is a lifelong disorder that is usually diagnosed in early adulthood, however most often symptoms begin in the childhood years. It is characterized by excessive day time sleepiness (EDS) and features of rapid eye movement (REM) sleep. It is under diagnosed in both children and adults due to the clinical heterogeneity. We report a case of a child presenting with excessive day time sleepiness, who was diagnosed with narcolepsy, which although is a rare disease, is very treatable, and early intervention will reduce its psychosocial impact.

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Introduction

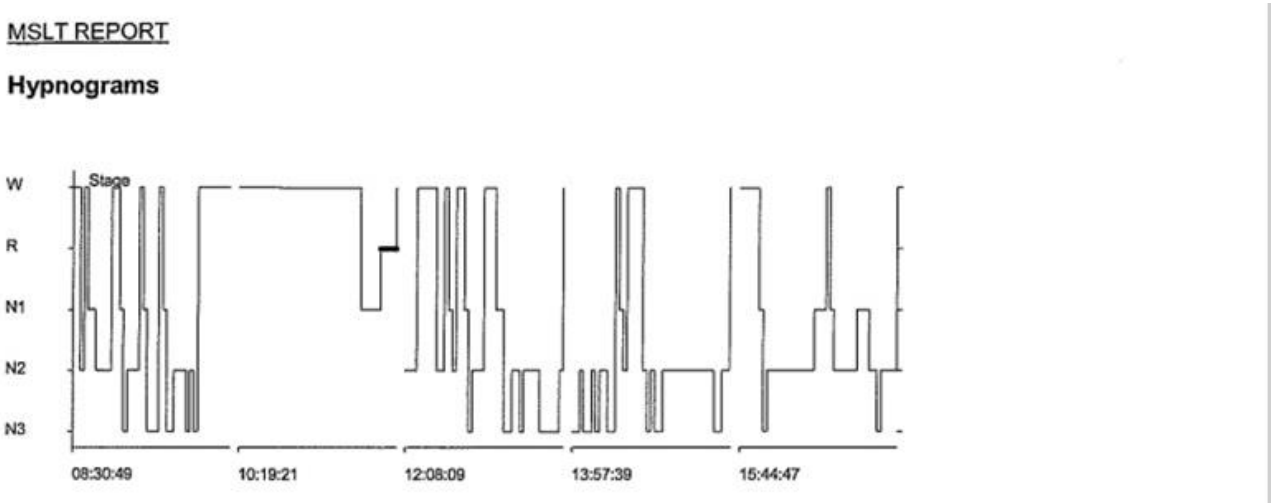
Narcolepsy is a lifelong disorder that is usually diagnosed in early adulthood, however most often symptoms begin in the childhood years.[1]It is characterized by excessive day time sleepiness (EDS) and features of rapid eye movement (REM) sleep. It is under diagnosed in both children and adults due to the clinical heterogeneity. We report a case of a child presenting with excessive day time sleepiness, who was diagnosed with narcolepsy, which although is a rare disease, is very treatable, and early intervention will reduce its psychosocial impact.

Case

A previously healthy nine-and-a-half-year-old girl was referred to the children's outpatient department with a 10-month history of increasing daytime lethargy and sleepiness which started at age 8. She was sleeping well at night for an average of ten hours, but she was still complaining of feeling tired during the day, with frequent episodes of sleeping during school hours. After returning home from school, she would sleep again for another three hours. According to her mother her academic performance and concentration were being affected because of this. She had an Epsworth sleepiness scale of 14.

She was never noted to snore at night or mouth breath. Her systemic examination was unremarkable, and her height and weight were on the 50th percentile with a Basal Metabolic Index (BMI) of 19 kg/m^2. She was investigated thoroughly with blood tests which excluded iron deficiency anemia, and showed normal thyroid, renal and liver function tests, and a normal cortisol response of 958 nmol/L after a short synacthen test. Magnetic Resonance imaging of the brain was reported as normal. A polysomnography study was performed and the patient had a mean sleep latency of 3 minutes 48 seconds, one sleep onset rapid eye movement (SOREM) of 2 minutes 30 seconds on the multiple sleep latency test (MSLT), and at least one SOREM of less than 20 minutes in the preceding overnight polysomnography study (Fig 1). Her oxygen saturation and carbon dioxide levels were normal during sleep. The MSLT and polysomnography findings were suggestive of narcolepsy. HLA-DQB1*06:02 was found to be positive which further confirmed the diagnosis.

Figure 1: Multiple Sleep Latency Test (MSLT)



She was started on low dose methylphenidate at 5 mg twice daily for a week then increased to 10mg in the morning and 5 mg in the afternoon. She improved rapidly, with resolution of her daytime sleepiness, requiring no naps throughout the day, sleeping for ten hours at night, and she also resumed extracurricular activities such as art lessons. She was also referred for psychological assessment and support.

Discussion

EDS and cataplexy, associated with sleep paralysis and hypnagogic and hypnopompic hallucinations, are typical characteristic features of narcolepsy.[2] EDS is the most common presenting feature and may be reported as tiredness or lack of energy by the patient or carers.[3] EDS can be the result of a wide range of sleep disorders and other conditions, and it may affect the child's health and general wellbeing.[4] Causes of EDS include insufficient sleep duration, broken or fragmented sleep, illness which increases sleep requirements and circadian misalignment. When assessing a child presenting with features of EDS it is important to quantify the total sleep time and the impact of EDS on overall function of the child. Whilst narcolepsy is rare in childhood, its incidence has increased since 2009 and this is thought to be due to the administration of adjuvanted H1N1 vaccine and viral infections.[5] The prevalence of narcolepsy in children between ages five to nineteen years is 0.83 per 100,000.[6]

Onset of narcolepsy is described as having a bimodal distribution with 2 peaks at ages 15 and 35. EDS in children may cause change in behaviour of the child, with increased irritability and aggression, and this may lead to delay in diagnosis. Children might find the occurrence of day time sleepiness embarrassing as it might be mistaken for laziness, and the patient might deny their symptoms. Furthermore, since this condition is uncommon in prepubertal children, health care professionals may dismiss these symptoms.[7] The diagnosis of narcolepsy in children is made by a history of EDS, together with nocturnal polysomnography and a multiple sleep latency test. The diagnostic criteria in adults and children are identical. The International Classification of Sleep Disorders, Third Edition, requires two criteria to make a diagnosis of type 1 narcolepsy (NT1): 1) at least a 3 month history of excessive day time sleepiness and 2) the presence of one or both of i) cataplexy and a mean sleep latency of less or equal to 8 minutes and two or more SOREM on an MSLT (A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT); and ii) CSF hypocretin concentration which is less than or equal to 110pg/mL.[8] NT1 is also known as narcolepsy with cataplexy. On the contrary, type 2 narcolepsy (NT2), also called narcolepsy without cataplexy, is clinically distinguished from NT1 by the absence of cataplexy symptoms. However, patients diagnosed at onset with NT2 can be reclassified as having NT1 after development of cataplexy symptoms, usually within 5 years of diagnosis but this can also be delayed by up to twenty years especially among at-risk children for example those with low CSF hypocretin-1 levels.[9]

Use of MSLT is limited in children less than 8 years of age, as baseline MSLT values are not known for this age group. NT1 is a thought to be an autoimmune condition linked to both an underlying genetic susceptibility, and environmental factors in predisposed individuals, precipitating cell loss that destroys the hypocretin producing neurons in the dorsolateral hypothalamus. Hypocretin is a neuropeptide transmitter and is required for wakefulness and it inhibits REM sleep.

There is a strong association between NT1 and HLA-DQ6 (DQB1*06:02) and its presence is sometimes used to support the diagnosis together with

characteristic symptoms and findings of MSLT or polysomnorgraphy.[10] Genetic factors also play a role as there have been reports of familial narcolepsy in the literature. Environmental risk factors that play a role in development of narcolepsy include H1N1 infection or specific H1N1 vaccination (specifically Pandemrix), and upper respiratory tract infections such as *Streptococcal* infection. Other neurological illnesses may also be associated with NT1 such as traumatic brain injury, Guillan Barre syndrome and Multiple Sclerosis.[9]

An association between narcolepsy in prepubertal children and endocrine diseases such as precocious puberty and obesity has been observed in some studies, however the exact causation is unknown. [11]

There is no curative treatment for narcolepsy as destruction of hypocretin producing neurons is irreversible,[12] thus management is symptomatic and includes both behavioral modification and pharmacotherapy. Use of cognitive and behavioural modification therapy is encouraged to decrease the negative impact of this disease on the patient's quality of life, as well as increase adherence to medication. The importance of sleep hygiene must be emphasized, and regular sleep-wake schedules enforced. Children should be encouraged to exercise to increase daytime alertness and decrease day time sleepiness attacks. If the child requires naps, these should be planned at appropriate times, for example after coming home from school. Furthermore, naps should be timed and should not last longer than 30 minutes.[13] It is advisable that the child and parents complete a sleep diary. Teenagers must be counselled about the risks of driving and use of alcohol, which will worsen the symptoms.[6] Cognitive behavioural therapy was found to not only improve patient's quality of life, but also decrease symptoms of EDS[14]. Pharmacotherapy treatment is based on the individual's symptoms. In children with increased daytime sleepiness, wake promoting agents such as Modafinil and Armodafanil or traditional stimulants such as Methylphenidate are recommended. These are used off license, but they are commonly used in split doses in the paediatric population[13]. Split doses have been shown to have an improved effect on EDS. Side effects include headaches, irritability and appetite loss.[6] Low doses are initially started, then they are titrated according to clinical response to allow for effective daytime functioning. Sodium oxybate is used off license to treat cataplexy in childhood and is given in two divided doses at night. Randomised controlled trials on use of sodium oxybate in the paediatric population, with symptoms of both narcolepsy and cataplexy, have shown a similar safety profile to that of adults.[15-16]

This disorder commonly affects the child's behaviour and relationship with their peers, as well as their mental health and academic performance, hence psychosocial support is a crucial part of its management.

Conclusion

Childhood narcolepsy has a major impact on the child's quality of life and academic performance, hence prompt diagnosis and treatment is essential to limit morbidity. Difficulties in diagnosis may arise as the occurrence of EDS can cause embarrassment to the child or may be misinterpreted as laziness and such symptoms can be denied. These issues can be minimized by greater public awareness of the condition. Untreated narcolepsy may affect the child's safety, as well as their social development. This case report highlights the need for further evaluation of EDS in paediatric population and the importance of knowledge of normal sleep development in children.

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CASE REPORT

One-and-a-half syndrome: Its presentation, causes and neuroanatomy

Matthew Azzopardi, David Agius

Background

One-and-a-half syndrome involves a combination of an ipsilateral horizontal gaze palsy and an ipsilateral internuclear ophthalmoplegia. This condition is easily missed due to its presentation, but can be the first sign of serious disease. We aim to increase awareness of this syndrome's presentation and give an insight into the intricate neuroanatomical connections that are affected in it.

Case Presentation

We present a case of a 39-year-old previously healthy female who presented with a one-week history of diplopia and non-vertiginous dizziness. On examination, a left horizontal gaze palsy with deficits in left abduction and right adduction was noted, accompanied by left adduction weakness and right horizontal disconjugate jerk nystagmus in abduction. A diagnosis of OAHS was made, and she was admitted for further tests. An MRI of her brain revealed multiple hyperintensities throughout, along with an enhancing lesion in keeping with active disease. A diagnosis of Multiple Sclerosis was made and she was given a five-day course of methylprednisolone, with which her vision, and ultimately her gait, improved. She was discharged with outpatient follow-up, to further discuss treatment options for her new diagnosis.

Conclusion

Diplopia and vertigo are symptoms that should prompt careful clinical examination with proper attention to ocular motility testing, and subsequent referral to neurology if required. Unnecessary delays in diagnosis and management could ultimately be detrimental to the patient, and being aware of uncommon presentations would go a long way in enhancing patient safety.

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Introduction

One-and-a-half syndrome (OAHS), first described in 1967,[1] presents with a combination of an ipsilateral horizontal gaze palsy (the 'one') and an ipsilateral internuclear ophthalmoplegia (INO) (the 'half').

Here we present a case of this syndrome which presented to Ophthalmic Casualty in Malta, in order to increase awareness of this syndrome's presentation and give an insight into the intricate neuroanatomical connections that are affected in this syndrome.

Case

A 39-year-old previously healthy female presented to ophthalmic casualty with a one-week history of diplopia and non-vertiginous dizziness. These were interfering with her daily life due to multiple falls, as well as with her job as a lifeguard due to a decreased ability to differentiate between different areas of the beach. She denied having other symptomatology such as headaches or nausea. She was prescribed prochlorperazine by her general practitioner, but her symptoms only got worse and she decided to go to the Emergency Department. Her past medical history included occasional sinusitis and myopia, for which she uses glasses. Her only past surgery was a lower segment caesarean section. She denied any smoking, drug use or excess alcohol intake, and was on no regular treatment. Her family history was unremarkable, and she was only allergic to seafood.

On examination, her aided visual acuity was 6/18 in each eye, which improved to 6/12 in either eye using pinhole. Pupils were equal and reactive to light, and no relative afferent pupillary defect was present. On attempted left gaze, there was a left horizontal gaze palsy (ie deficits in left abduction and right adduction) whilst on attempted right gaze, there was a left adduction weakness and right horizontal disconjugate jerk nystagmus in abduction. Convergence of the eyes was intact, and no other significant findings were noted on examination.

In view of her left lateral gaze palsy and left sided internuclear ophthalmoplegia, a diagnosis of OAHS was made. The on-call neurology team assessed her and admitted her for further investigations, to delineate the underlying cause.

Her blood investigations were all within normal limits, and a CT scan of the brain demonstrated no acute intracranial pathology. However, an MRI scan of her brain revealed a midline symmetrical hyperintensity underneath the floor of the fourth ventricle, along with multiple hyperintensities in both the cerebrum and cerebellum in a periventricular and subcortical distribution. An enhancing lesion in the left periventricular white matter was also noted, in keeping with an active plaque. These lesions were highly suggestive of demyelinating plaques, and a diagnosis of Multiple Sclerosis was made. She was given a five-day course of methylprednisolone, with which her vision improved and she started mobilizing independently. Alternating eye patching was also done to help with her vision. Once improved she was discharged with outpatient follow-up, to further discuss treatment options for her new diagnosis of multiple sclerosis.

Discussion

OAHS is a syndrome which manifests only in horizontal gaze. Three main structures are involved in horizontal gaze, namely the paramedian pontine reticular formation (PPRF), the internuclear fibres of the medial longitudinal fasciculus (MLF) and the abducens nuclei in the lower pons. Upon initiating horizontal gaze, an excitatory stimulus is sent from the PPRF to the ipsilateral abducens nucleus.[2] In turn, this trigger both the motor fibres of the

ipsilateral lateral rectus and also the contralateral medial rectus via the interneuronal fibres of the contralateral MLF, which ascend and terminate in the oculomotor nuclear complex.[3]

Since OAHS is purely a combination of ipsilateral horizontal gaze palsy and ipsilateral INO, a combination of lesions giving rise to these two components would need to be present. Firstly, with regards to the horizontal gaze palsy component, there are four theoretically possible lesion locations:

1. Damage to the ipsilateral abducens nucleus and ipsilateral PPRF
2. Damage to the ipsilateral PPRF only
3. Damage to the ipsilateral abducens nucleus only
4. Two separate lesions damaging the ipsilateral abducens nerve root fibre and the contralateral MLF[3]

Furthermore, the pattern of horizontal gaze palsy would also depend on the exact location of the lesion. In situations where ipsilateral PPRF damage is the culprit, both saccadic and pursuit eye movements are lost in addition to the horizontal gaze palsy. However, if the PPRF lesion is rostral to the abducens nucleus, vestibular reflexic horizontal eye movements are preserved, contrasting with PPRF lesions located at the level of the abducens nucleus, in which these reflexes are also lost. All of these voluntary and reflexic eye movements are also lost if the horizontal gaze palsy is due to ipsilateral abducens nucleus damage.[3-4]

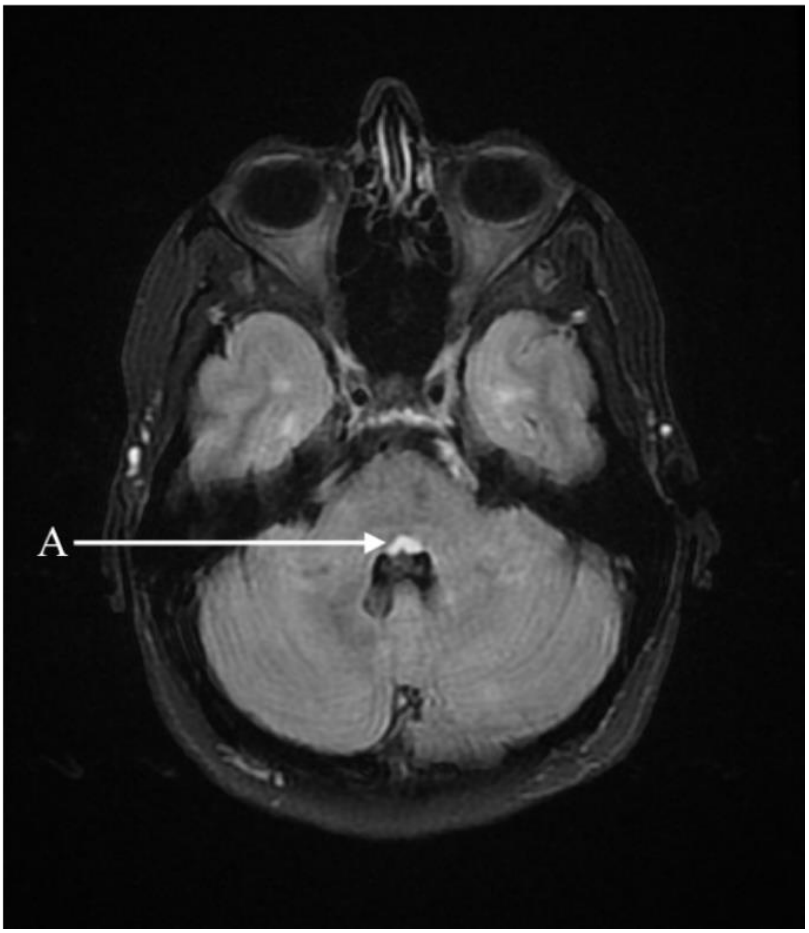
Secondly, the ipsilateral INO component of OAHS occurs due to lesions involving the ipsilateral MLF, in combination with those causing the horizontal gaze palsy. This occurs because of the integral role the internuclear fibres of the MLF play in conjugate horizontal eye movements. Because of this damage, the ipsilateral eye would be unable to adduct, and on abducting the contralateral eye a horizontal jerk nystagmus is observed, giving rise to INO.[3]

In fact, amongst the lesions found on MRI in our patient, a midline symmetrical hyperintensity underneath the floor of the fourth ventricle was noted, corresponding to the location of the colliculus facialis and the abducens nucleus (Figure 1).[5] This lesion was probably the cause of the horizontal gaze palsy component of her OAHS.

The commonest visual symptoms reported in OAHS include diplopia, blurred vision and oscillopsia.[3] However, it often presents with non-visual symptoms which would arise either as a consequence of the underlying pathology or of the visual disturbance itself, such as nausea, vertigo, and unsteadiness.[3] This highlights the importance of not dismissing non-specific symptoms and signs without a proper, thorough examination.

Many different disease pathologies can give rise to the pontine lesions behind OAHS. In our patient, OAHS was the first presenting feature of multiple sclerosis (MS). When one considers ocular presenting features of MS, optic neuritis immediately comes to mind. However, this is not the only possible ocular presenting feature, and in fact there are a number of other cases reported in which MS presented with OAHS.[3] Most OAHS cases are due to vascular causes, such as ischaemic or haemorrhagic brainstem infarction, basilar artery aneurysms and arteriovenous malformations. Other causes such as brainstem malignancies, infiltrative lesions, and infections have also been reported.[6]

Figure 1: Transverse section of the Magnetic Resonance Imaging scan of our patient's brain showing the midline symmetrical hyperintensity underneath the floor of the fourth ventricle corresponding with the abducens nucleus within the colliculus facialis (A)



Treatment of this syndrome is usually aimed at the underlying cause, as in our case. However symptomatic treatment modalities for diplopia, oscillopsia, blurred vision and other symptoms can be employed, such as eye patching or prism use. Botulinum toxin injections in the lateral rectus muscle and surgical extraocular muscle recession have also been used with good effect.[7-8]

Ever since this syndrome was first reported, similar syndromes have been described. For example, eight-and-a-half syndrome refers to one-and-a-half syndrome with ipsilateral facial nerve palsy,[9] whilst sixteen-and-a-half syndrome refers to eight-and-a-half syndrome with ipsilateral hearing loss (VIII cranial nerve).[10]

Conclusion

One-and-a-half syndrome is one of the lesser known ocular manifestations of common diseases such as multiple sclerosis and stroke. Diplopia and vertigo are symptoms that should prompt careful clinical examination including attention to ocular motility testing, with subsequent referral to neurology if required. In many of the pathologies that cause this syndrome, unnecessary delays in diagnosis and management could be detrimental to the patient. Proper examination and early involvement of the relevant specialities could go a long way in helping ensure the best possible outcome for our patients.

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