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EDITORIAL

Artificial Intelligence and Medicine

Simon Paul Attard Montalto

Currently, a 'hot' debate circulating throughout the more serious international media platforms focuses on the downside – or potential downside – of artificial intelligence (AI). The doomsday view warns that AI will become smarter than mankind and, essentially, become uncontrollable and take over the planet! Indeed, one AI expert has suggested that, since AI-driven processes will be far more accessible and will be put to nefarious use with relative ease by erstwhile crooks, it will become more dangerous than nuclear weapons where access and safeguards against their injudicious use is so great. In stark contrast, the use of AI-based methodology to identify Abaucin, a potentially highly effective antibiotic against acinobacter bauinaemii, was recently heralded on BBC radio as a groundbreaking advance in the fight against superbugs.[1] Certainly, by using rapid gene sequencing, AI speeded up the selection process of this antibiotic from amongst hundreds of other potential contenders and curtailed the pre-clinical trial research period that would otherwise have taken several years.[1] Clinical trials have yet to start and will still be required to verify the efficacy of this promising drug. Similar areas where AI-based technology has been applied include vaccine research (e.g. for RSV, Ebola),[2] management and prediction in type 1 diabetes,[3,4] diagnosing retinal disorders[5] and increasing early detection of sepsis by up to 20%.[6]

Simon Paul Attard Montalto
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COVER PICTURE

'Escaped rabbit in Maltese countryside monochrome violet in the style of Van Gogh'

Watercolour A3 size (29.7 x 42 cm)

By Chris Camilleri

Chris Camilleri uses Artificial Intelligence to generate images that are used for reference. He paints watercolour paintings of figures, portraits, animals and battle scenes. He likes traditional Chinese art, Tibetan thangkas and high fantasy. His favourite painters are Otto Dix, J.W. Waterhouse and Frank Frazetta. Chris works as an anaesthetist. He is married to Georganne and lives in Qormi.

Artificial Intelligence describes the use of computers and/or technology to simulate intelligent and critical thinking/processing comparable to human beings, a notion pioneered by Alan Turing in 1950 and first coined by John McCarthy in 1955.[7] In reality, AI has since been applied in medicine for several decades and generally uses computer-based 'virtual' data processing essentially centred around smart algorithms/databases/pattern recognition, and 'physical' machine-based interventions and robotics.[7] Both have already been widely applied in radiological imaging and tumour detection, diverse robotic interventions, routine workflows and equipment maintenance, screening and risk assessment programmes (e.g. in mammography), including early alert systems based on symptomatology and early detection of metastases.[7-9] This exponential increase in the application of AI in medicine has resulted in a substantial increase in submissions in AI-related domains, such that dedicated Journals on AI in Medicine and AI in Healthcare already exist and the New England Journal of Medicine (NEJM) plans to launch a sub-journal aptly named NEJM-AI in 2024.[8]

AI programmes have significantly reduced the burden of day-to-day health administration and patient care including early clinical diagnoses and identification of non-compliance in treatment.[10] AI is excellent in performing arduous and repetitive tasks that humans find tedious and rapidly lose interest, concentration and performance. Nonetheless, development of AI needs to follow clearly accepted guidelines, be aware of commercial interest and bias, avoid secrecy whilst safeguarding confidentiality, and ensure transparency. Issues relating to insurance, liability and responsibilities still need to be defined.

Undoubtedly, AI has already proven to be extremely helpful in numerous medical applications. But is it equal or better than doctors? Sometimes, the answer to this question is "yes": one study reported that AI outperformed 17 from 18 physicians in detecting cancer on chest X-rays, but this is certainly not always the case.[11,12] Will AI make doctors redundant?[11] Unlikely. Can it free up quality time for doctors to perform hands-on clinical work? Definitely.11Hence, the medical fraternity should view this expanding modality as an integral and extremely useful adjunct. AI should be introduced at undergraduate level where, in all probability, already-computer-savvy students will embrace it seamlessly.

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ORIGINAL ARTICLE

Restorative Dentistry Considerations in the Geriatric Dentistry: Systematic Review

Mahdi Rahbar, Mojtaba Pourtarrah, Elaheh Tahmasbi, Afsaneh Bakhtiari, Mohsen Yazdanian, Emran Hajmohammadi

Background and aim

As the number of elderly people visiting dental clinics increases, it is essential to have sufficient information on the correct treatment as well as the appropriate treatment plan for these patients. Therefore, the present study aimed at reviewing the most important restorative considerations for the elderly.

Method

In this systematic review study, databases such as Pubmed, Embase, Web of Science, Scopus, ProQuest, Google scholar, as well as Iranian databases were searched with the keywords of elderly dentistry and restorative considerations. Inclusion criteria were original articles and reviews related to restorative dentistry considerations for the elderly without a time limit and being written in either English or Persian. In order to combine the results of the research, a thematic content analysis method was applied.

Results

The total number of documents recovered was 4208, the number of duplicate documents was 2042, and the number of documents reviewed was 17. The most important considerations related to the elderly included giving due attention to medical and social conditions, medication use, type of restorative teeth, level of restoration involved, use of dentures, age and gender, oral cancer screening, tooth decay education and prevention, and oral hygiene. The most important considerations related to restorative methods and materials were applying minimally invasive methods such as ART, more durable restorative materials, and giving due attention to the aesthetic and non-aesthetic needs of the elderly in choosing restorative materials. The most important considerations related to dentists were the differences in applying restorative methods and materials by experienced dentists in comparison younger dentists and the rate of referral of elderly people to dental centers.

Conclusion

The most important dental considerations of the elderly are using minimally invasive methods and restorative materials with easy maintenance which are washable according to their social, economic, medical, gender, and age conditions. It is also necessary to consider the prevention of tooth decay and provide the required training for families and their caregivers in nursing homes. The elderly people are also required to avoid change their dentists frequently to maintain their oral health.

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INTRODUCTION

The world population is ageing, transforming societies from youth-dominated age profiles to age profiles where over 20% of the population are aged above 65 years. The global ageing population has been related to the recent socioeconomic development through falling fertility rates and increased life expectancy at birth. The multimorbidity of these populations increases the difficulty of maintaining oral health for frail older adults.[1] Lack of oral health increase morbidity in this population.[2] Importance of oral health in elderly causes to educate geriatric dentistry in dental faculties in the world.[3,4]

The global burden of oral problems in elderly patients has shifted from complete tooth loss to periodontitis and untreated decays. One of the most common problems among the elderly is caries. Tooth decay has remained a major public health problem worldwide, with untreated permanent tooth decay being the most common chronic disease among the 291 diseases investigated from 1990-2010 with a global prevalence of 35% for all age groups.[5] The rate of tooth decay in the elderly is higher due to increased dental retention, and other risk factors such as gum erosion exposed to root surfaces, decreased salivation (dry mouth) and physical limitations to maintain oral hygiene.[6] Moreover, old age reduces the number of visits to the dentist for routine care.[7] This leads to untreated disease, pain and tooth loss, and reduced quality of life in the elderly.[8] In addition, access to conventional dental treatment is more difficult for poor individuals or the elderly living in nursing homes. Therefore, providing appropriate and cost-effective dental treatment for these people can be challenging. Hence, governments, policymakers, and society at large are looking for appropriate solutions to improve oral health and thus the quality of life of the elderly.[9]

Advances in periodontics and endodontics have also promoted the dentists' ability to preserve natural teeth, so that for most people today, especially the elderly, the loss of teeth isn't a complicated issue. The advent of implants in the late 1970s was another restorative solution to help dentists.[10] One study indicated that more than 60% of restorations are conducted to replace the existing fillings, especially in the elderly. Nearly 19.1% of restorations performed on the anterior and posterior teeth of people over 60 years of age are due to primary caries. Whereas, in 17-to-19-year-old individuals, this figure is 65.8%.[11] Hence, primary caries, secondary caries, concerns about tooth beauty, restorative fractures, cost, and insurance coverage are other reasons for restorations.[12]

Studies have indicated that the prevalence of oral diseases is more common among the residents of nursing homes owing to social and economic conditions and poor oral hygiene. The severity of oral disease can lead to respiratory diseases and eventually death among the elderly.[13] Given the increasing growth of old people in the world and their care and treatment needs, especially in the field of dental care, there is a growing need for cost-effective approaches and methods of treatment fitting their social, economic, and medical conditions. Therefore, recognizing restorative considerations for these people can be effective in making desirable clinical decisions and promoting oral health in the elderly. Accordingly, the researcher's search for dental literature indicated a lack of comprehensive study on restorative dentistry considerations for the elderly. Various review studies have focused more on one aspect of restoration and more frequently on the type of minimally invasive restoration.[10,14-16] Combining a set of restorative dentistry considerations and approaches proposed for the elderly in the existing texts can be effective in improving the clinical practice of dentists in order to provide desirable restorative services for the elderly community. Therefore, the present study aimed at answering this question "What restorative dental considerations are required to be taken into account for the elderly?"

METHODS

Data searches

This is an applied study conducted as a systematic review in 2021. For this purpose, the researchers have searched non-Iranian databases including Web of Science, Scopus, PubMed, Embase, Proquest, Google Scholar search engine as well as the Iranian databases such as Scientific Information Database (SID), Magiran, and Irandoc with keywords like elderly dentistry, restorative considerations, and synonymous words extracted from MESH and EMTREE.

Keyword searches

All searches were conducted in March 2021 without time and location limitations. An example of a search strategy in the Pabmed is as follows:

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(Aged[tiab] OR elderly[tiab] OR "old people"[tiab] OR geriatric[tiab]) AND (("Atraumatic Restorative Treatment"[tiab] AND Dental[tiab]) OR "Dental Atraumatic Restorative Treatment"[tiab] OR "restorative consideration"[ALL] OR "restorative considerations"[ALL] OR "dental restoration"[tiab] OR "dental restoration failure"[tiab] OR "dental restoration repair"[tiab] OR ("dental restoration"[tiab] AND permanent[tiab]) OR ("dental restoration"[tiab] AND temporary[tiab]) OR "dental restorative procedure"[tiab] OR "dental tissue conditioning"[tiab] OR "denture repair"[tiab] OR "permanent dental restoration"[tiab] OR "regenerative
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dental therapy"[tiab] OR "reparative dental service"[tiab] OR "restorative dental care"[tiab] OR "restorative dental procedure"[tiab] OR "restorative dental services"[tiab] OR "restorative dental treatment"[tiab] OR "temporary dental restoration"[tiab] OR "tissue conditioning"[tiab] OR ("tissue conditioning"[tiab] AND dental[tiab]) OR "tooth restoration"[tiab] OR "restorative care"[tiab] OR "extended care"[tiab] OR "post-acute care"[tiab] OR "skilled care"[tiab] OR "sub-acute care"[tiab] OR "subacute care"[tiab])

Sample searches in other databases and the number of search results are provided in the Appendix 1. Inclusion criteria were as follows: studies and review studies are related to restorative considerations for old people, the studies have been written in either English or Persian, there is an access to the full text of the article, and there was no time and locations restrictions. Exclusion criteria also include books, theses and dissertations, letters to the editor, editor articles, conference papers, and articles of poor quality in terms of reported findings (data are reported as incomplete) and articles in languages other than English or Persian. The quality of the articles was not evaluated due to scoping review.[17] In order to extract the restorative considerations of the elderly, a thematic content analysis method was applied.

RESULTS

The results of a systematic review of restorative considerations for the elderly are reported in Table 1. Figure 1 also shows the process of selecting studies to enter the study.

Most of these studies were conducted as clinical trials, literature reviews, and retrospective descriptive studies. Moreover, most of these studies were related to Ireland accounting for four studies, the United States with three studies, and Hong Kong. The Netherlands, Iran, Australia, Finland, Saudi Arabia, Colombia, and Singapore each accounted for one study. In general, restorative considerations in the elderly fall into three categories, which are be discussed below.

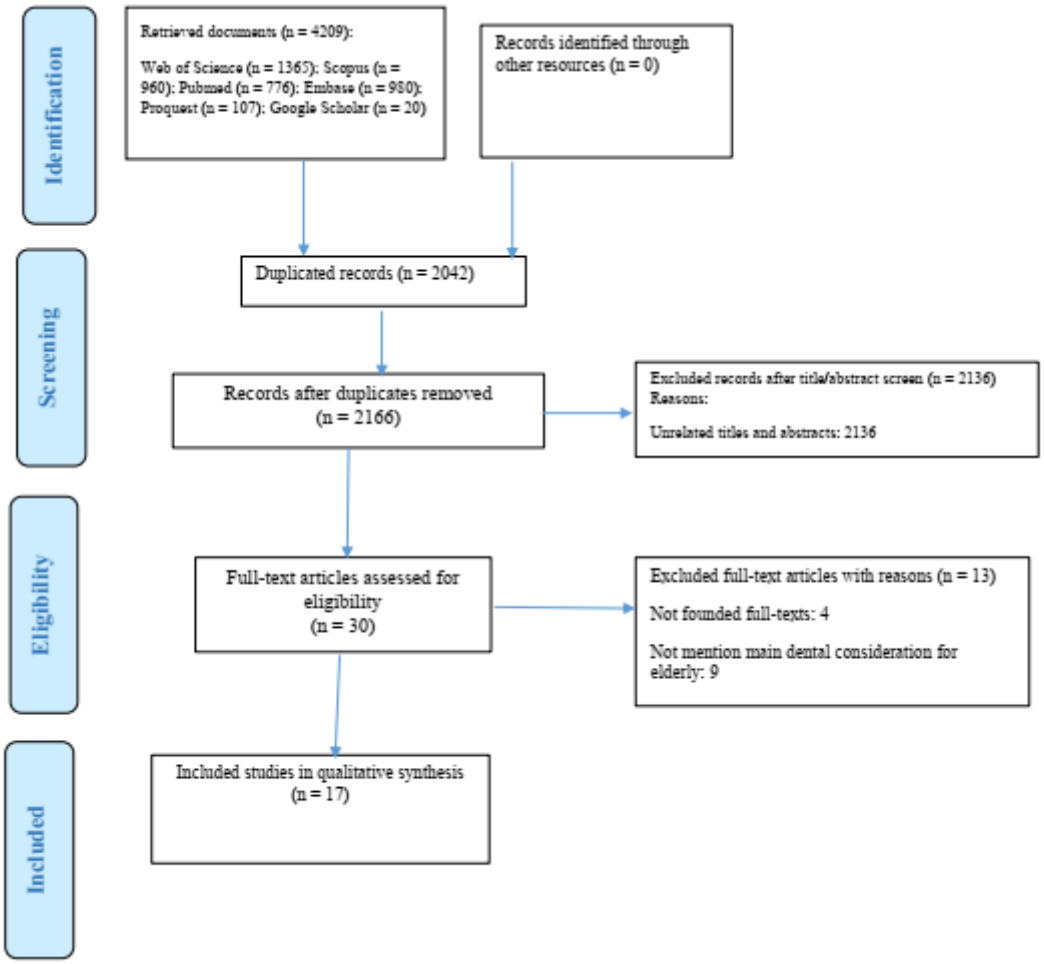

Figure 1 *PRISMA diagram of search and selection process*

Considerations related to the elderly themselves

The most important considerations that dentists are required to consider regarding the condition of the elderly include: the level of restoration involved and the type of tooth being restored[18]; presence of systemic diseases in the elderly and decreased salivation[9,19]; bone, tooth tissue, and periodontal deformities, oral cancer screening in the elderly, the elderly with lung and heart diseases, Parkinson's disease, diabetes, depression, osteoporosis, dementia, stroke, hypertension, Alzheimer's disease, dementia, medications, insomnia;[9,10,19,20] treating and eliminating dry mouth and improving salivary gland function with fluoride, treating dental diseases before radiotherapy, effect of bisphosphonate on jaw osteonecrosis, increased incidence of bruxism in the elderly, using chlorhexidine brush and sponge in patients suffering from ventilator-associated pneumonia, determining the appropriate time to remove teeth in middle age[10]; using dentures;[10,18,20] the elderly's social conditions, the elderly's unfavorable past experience in dental treatment[20]; applying a preventive approach instead of treatment, observing oral hygiene and not consuming carbohydrates, fluoride consumption, repair conditions,[10,13,20,21] age, gender, paying costs, dental arch[11,22]; the presence of a tooth opposite the restored tooth.[13]

Considerations related to restorative materials and methods

The most important considerations related to restoration methods and materials include durability of restoration, type of restoration material and size of restoration;[11,18,21] using implants for the elderly and the preference of non-invasive therapies (ART) over major surgeries;[10,19,20] applying composite and glass ionomer (longer durability of composite resin compared to amalgam), ozone therapy, lack of using implants in patients with bone necrosis[10]; conservative restoration (oral hygiene and prevention and topical fluoride)[10,23]; lack of using indirect composite resin, lack of using ceramic inlay and onlay in people with poor oral or bruxism, lack of using all-ceramihygiene c crowns in cases where beauty is not a priority for the elderly, using implant prostheses only at very old ages, lower jaw implants compared to the upper jaw implants[10]; restoration of crowns and tooth surfaces in people aged 65 to 74 years; the effect of posterior re-restoration on bone erosion, especially in men and the elderly; lack of using amalgam and composite resin in cases of advanced lesions and hard tissue loss, use of washable restorative materials, combination of restorative materials with composite resin for beauty purposes or sandwich technique, use of full veneer crowns as a preservative, not using welded joints, using high hardness castings, limited adhesive porcelain to non-pressure areas, combination of Maryland bridge and resin porcelain veneers[24]; using crown and ionomer in the elderly for restoration[22]; using ART and glass ionomer, glass ionomer modified with composite resin, using caries detection tools when using ART[13,20]; economical use of ART with amalgam[14]; using easy-to-maintain restorations, lack of using dental implants to support removable partial dentures, using SDA shortened dental arch restorative approach compared to RPD removable partial dentures[20]; more frequent use of amalgam, composite and GIC restoration materials, less frequent use of crowns or bridge holders, placement of intra-cavity restorations with initial restoration, higher crown and bridge sensor rate than other intra-cavity restorations, success of composite over amalgam and GIC in intra-cavity restorations, using bridges as the most common root canal restoration, the higher the number of restoration surfaces the shorter the shelf life, a longer shelf life of amalgam in anterior and premolars[15]; using ionomer glass in ART and ioner glass resin in conventional method, complete removal of rotten tissue before ART restoration, using ART restoration in the elderly, especially in nursing homes due to lack of local anesthesia, no pain, and using hand tools[25]; using cost-effective ART compared to CT in the restoration of elderly teeth[9,26]; the importance of controlling the moisture and the size of the cavity in the restoration and repairing rather than restoring.[9]

Considerations related to the dentist's performance

The most important considerations related to dentists include differences in dentists' restorative performance (lack of proper diagnosis, improper use of restorative materials, insufficient removal of decayed lesions, and failing to control moisture), dentist experience, and the constant change of one's dentist.[13,18,22]

DISCUSSION

The present study aimed to determine the most important geriatric restorative considerations in the geriatric dentistry through a systematic review. Most of the identified studies had been conducted by literature review and clinical trials in the United States and Ireland. The most important restorative dentistry considerations for the elderly were related to the elderly themselves, considerations related to restorative methods and materials, and considerations related to dentists.

Regarding the considerations related to the elderly themselves that dentists are required to give due attention, different authors have expressed relatively similar opinions about the health and social conditions of the elderly. Root and periodontal caries are common dental diseases in the elderly. People aged 65-74 need more crown and tooth restorations than people over 74. Re-restorations are also more likely to occur due to recurrence of caries, especially

Table 1:The features of the entered studies

Main author (Year)	Country	Population	Method	Dentistry considerations
M Laske (2016)	Netherlands	50-95 year individuals	Descriptive retrospective	- Durability of restoration - Differences in the restoration performance of dentists - The use of dentures - The amount of surface involved in restoration - Type of tooth to be restored - Type of restoration material
M Rabi'ei (2016)	Iran	-	Review	- The Existence of systemic diseases in the elderly and decreased salivation - Deformation of bones and dental and periodontal tissue - Use of implants for the elderly - Oral cancer screening in the elderly - Elderly with lung and heart diseases, Parkinson's Disease, diabetes, depression, osteoporosis, dementia, stroke, and hypertension - Preference of non-invasive therapies over major surgeries
CG Murray (2015)	Australia	-	Review	- Prevention or reduction of root canal caries in the elderly - Treating and eliminating dry mouth and improving the function of salivary glands with fluoride - Application of minimally invasive methods - Application of composite and ionomer glass - Ozone therapy - Giving due attention to systemic diseases, dementia, Alzheimer's Disease, and medications - Treatment of dental diseases before radiotherapy - The effect of bisphosphonate on osteonecrosis of one's jaw - Lack of applying implants in patients with bone necrosis - Increased incidence of bruxism in the elderly - Using chlorhexidine brush and sponge in patients with ventilator-associated pneumonia - Educating patients and their families - Using dentures - Determining the right time to remove teeth in middle age - Conservative restoration - Durability of composite resin compared to amalgam - Lack of using indirect composite resin - Lack of using ceramic inlay and onlay in people with poor oral hygiene or bruxism - Lack of using all-ceramic crowns in cases where beauty is not a priority for the elderly - Using implant prostheses only at very old ages - Lower jaw implants compared to the upper jaw implants
C.M Pine (2001)	England	16-65 individuals and older	Descriptive	- Paying attention to the conditions of tooth filling - Durability of restoration - Observing oral hygiene and nutrition in the elderly - Educating the required cares for restored teeth
GP Barnes (1986)	United States	>60 years old	Descriptive	- Restoring crowns and tooth surfaces in 65-74year-old individuals
K Hakkarainen (1980)	Finland	43 patients aged 27-45 and 42 patients aged 46-64	Observational	- The effect of posterior restoration on bone erosion, especially in men and the elderly

Main author (Year)	Country	Population	Method	Dentistry considerations
CA Wilson (2014)	Saudi Arabia	-	Review	- Conservative restoration (oral hygiene and prevention and topical fluoride) - Not using amalgam and composite resin in cases of advanced lesions and hard tissue loss - Using washable restorative materials - Combining washable restorative materials with composite resin for aesthetic purposes with a sandwich technique - Using fully veneered crowns as a holder - Not using welded joints - Using casting alloys with high hardness - Limited use of adhesive porcelain to areas lacking pressure - Combining the use of Maryland bridge and resin porcelain veneers
WS Hawthorne (1996)	Hong Kong	29 - 79 years	Retrospective study	- Use of crown and ionomer in the elderly for restoration - Dentist experience and its constant change - Patient's age and gender
AC Cruz Gonzalez (2016)	Colombia	75 elderly individuals	Semi-experimental	- Using ART and glass ionomer - Using glass ionomer modified with composite resin - Dentist performance (lack of proper diagnosis, lack of proper use of restorative materials, lack of adequate removal of decayed lesion, and lack of moisture control) - Use of caries detection tools when using ART - Lack of observing hygiene - Existence of teeth opposite the restorative tooth
C da Mata (2015)	Ireland	99 elderly, aged 65-90	Randomized Clinical Trial	- Minimal Invasive Dentistry (ART)
C da Mata(2014)	Ireland	82 elderly, aged 65-88	Randomized Clinical Trial	- Economical application of ART with amalgam
ECM Lo (2006)	Hong Kong	>60 years old	Clinical trial	- Restoring with ART and conventional methods both cause high durability of the restoration - Using ionomer glass in ART and ionomer glass resin in conventional method - Complete removal of decayed tissue before conducting ART restoration - Applying ART repair in the elderly, especially in nursing homes due to lack of local anesthesia, lack of pain, and using hand tools
P Finbarr Allen (2019)	Singapore	Non-Iranian studies	Review	- Social and medical conditions of the elderly - Adverse past experiences of the elderly in dental treatment - Dentistry with the minimal invasion - Using caries risk assessment tools - Using restorations with easy maintenance - Not performing surgical intervention - Applying a preventive approach instead of treatment (observing oral hygiene and not consuming carbohydrates, fluoride consumption, restorations conditions and the presence of dentures) - Not using dental implants to maintain a partial removable denture - Applying SDA shortened dental arch restorative approach to RPD partial removable dentures
DJ Caplan (2018)	United States	65 - 104 years	Descriptive retrospective	- More frequent use of amalgam, composite and GIC restorative materials.
C da Mata (2015)	Ireland	65 - 90 years	Clinical trial	- Applying cost-effective ART compared to CT in the restoring elderly individuals' teeth - Early diagnosis and prevention of root caries in the elderly - The importance of moisture control and cavity size in restoration - Repairing instead of restoring
C da Mata (2019)	Ireland	> 65 years old	Clinical trial	- Applying cost-effective ART compared to CT in the restoring elderly teeth
TS Ghazal (2018)	United States	> 85 years old	Descriptive retrospective	- Elderly-related factors (age, gender, paying costs, dental arch, underlying disease, medication use, salivation deficiency, insomnia, poor or lack of observing oral hygiene) - Factors related to restoration (type and size of restoration)

in the roots.[22] Among the factors affecting most tooth decay in the elderly, along with reduced salivary flow, changes in the oral flora, reduction of caries-inhibitory contents, including proline-rich proteins, exposure to more cement in the oral environment for several reasons, one's desire for salty and sweet foods, the presence of dentures, and poor oral hygiene, and the need for restoration in the elderly.[19] Murray has stated that there are many causes for dry mouth, most of which occur with aging and include dehydration, damage to the salivary glands owing to autoimmune diseases (Sjogren's syndrome) and radiation. Simultaneous use of several drugs as well as taking drugs related to dry mouth such as anticholinergic drugs have significant effects on dry mouth.[10]

Studies have indicated that older people suffer from a variety of systemic diseases and other complications of aging, such as diabetes, cancer, dementia, Parkinson's disease, depression, gnashing of teeth, bruxism and lung and heart diseases. Thus, they are required to take various medications to improve their health conditions. This leads to dry mouth and the occurrence of oral diseases, especially the fungal ones. This exacerbates tooth decay, especially in nursing home residents due to poor oral hygiene. Regarding restorations that require surgery or anesthesia, using anesthetic drugs has adverse effects on the elderly with neurological diseases such as Alzheimer's Disease.[10]Therefore, the condition of the disease and medication are required to be considered in choosing the appropriate restoration approach for the elderly.[10,19,20] Other side effects of aging include changes in hard tooth tissue, decreased facial height, and dental erosion, especially in the lower anterior teeth where the pulp of the tooth usually appears. Secondary dentin stiffness protects the tooth pulp. However, pulp changes make endodontic treatments difficult.[19]

Another important point is regular oral cancer screening for the elderly. This is especially necessary in toothless people, with or without dentures.[19] Oral malignancies increase with aging, along with tumors in other parts of the body. Treatment of malignant tumors of the head and neck with radiation and drug use leads to destruction of the salivary glands. Dry mouth causes rapid tooth decay and alveolar vascular changes, leading to osteoradionecrosis and osteonecrosis, resulting in a catastrophic lower jaw fracture. The incidence rate of osteoradionecrosis in patients with teeth is almost twice higher than the rate for patients without teeth. Thus, it is necessary to treat dental diseases before radiation to oral tissues.[10,23,27] One of the most important points in the restorative treatment of the elderly is providing the required training to observe oral hygiene and prevent tooth decay. Oral bacteria can lead to ventilator-associated pneumonia if hygiene is not properly observed, in such cases advising and educating elderly's family or caregivers to maintain oral hygiene and using chlorhexidine brushes and sponges is the best way to prevent the consequences of this disease. In addition to observing good oral hygiene, having a diet free of sugars and acids, as well as fluoride, can help prevent or reduce caries. This approach is called conservative restorative dentistry, aiming to maintain the health of natural teeth and selectively extract damaged teeth. Moreover, dentists need to provide the necessary training for the care of restored teeth to the elderly and their families or caregivers in nursing homes.[10,21,23] In addition, the study conducted by Laske et al indicated that there is no difference in terms of gender between the annual failure rate (AFR); however, it is higher in people over 65.[18] Women under the 75 years old usually have a longer restoration life through better oral hygiene and less functional damage. Thus, older age is associated with greater failure of restoration. Patients who use Medicaid insurance have poorer oral health and more restorative failures than those who go to private clinics. Residents of private nursing homes also have better oral hygiene and durability than others.[11] Also, the presence of dentures due to caries and periodontal problems causes less durability of the restoration. Moreover, restoration in molar teeth compared to anterior teeth (annual failure rate of 4.4%) and premolars (annual failure rate of 0.4%) indicates a lower survival rate (annual failure rate of 5.2%). The first molar needs more restoration than other teeth, however, it also accounts for the highest annual failure rate of restoration. In surface restorations, the maximum rate of restoration failure depends on the amount of surface involved.[18]

Evidence shows that the risk of root decay decreases every 3 to 6 months with a non-invasive method, a combination of oral hygiene guidelines and professional application solutions (SDF = 38%; NAF 22,500; CHX = 40%) every 3 to 6 months. The evidence also shows that using chlorhexidine, fluoride, calcium phosphate, amorphous calcium and fluoride (diamine silver) are quite effective in reducing the incidence of root decay in the elderly.[18] Also, the timing of tooth extraction in middle age and providing the necessary training to use dentures are other important considerations.[10]

Regarding the considerations related to the methods and restorative materials, studies have indicated that for the elderly, root surface filling is used more frequently. Moreover, one of the most important considerations in restoring its durability is especially in patients who take several medications at the same time or have a specific medication regimen. This is because taking several medications can cause salivary gland dysfunction and tooth decay. Despite the inability of people in their 70s and 80s, the durability of restoration along with oral hygiene leads to healthy teeth in such people.[21] Regarding the condition of hard tooth loss, using amalgam and composite resin is limited. In these cases, washable

restorative materials with composite resin called sandwich technique can be used, which has both a higher adhesion and a more acceptable beauty. Moreover, in the face of common dental caries, dentists are required to use the conservative cavity design method proposed by Elderton and Mclean, which is both biocompatible and less psychologically harmful to the elderly.[23] Moreover, bulging posterior restorations are associated with approximate destruction of the surrounding bone, which is more commonly observed in men at higher ages due to periodontal disease, more plaque, and more bone erosion.[27]

Another important consideration regarding restoration methods and materials is using caries assessment tools such as Cariogram and CAMBRA to reduce dental caries and periodontal disease in the early stages. Meanwhile, the Cariogram is more successful in assessing the risk of caries in the elderly. However, in general, there is little evidence of the ability of these methods to predict the future course of the disease. Also, using easily maintained restorations prevents damage to the teeth around removable dentures, conventional fixed bridges, and implant restorations in medium and long terms.[20] At present, applying fixed dentures is not contraindicated for the elderly. If the elderly patient has good periodontal support, a single restoration method can help the elderly person without teeth with Maryland bridge and resin porcelain veneers both mechanically and aesthetically. Using removable partial dentures according to the covered surface of the tooth and the degree of hygiene observed by the elderly may cause damage to the surrounding teeth due to the presence of implants for its maintenance. For patients who have lost some of their teeth, the best approach is using a shortened dental arch (SDA), which was proposed by Kayser in 1984. Shortened dental arch includes 12 anterior teeth and 8 premolars in people over 45 years of age.[23] In general, SDA is a more appropriate approach than RPD in terms of reducing costs and preventing oral diseases in the elderly.[20]

Also, the type of restoration material affects its durability. Hawthorne has stated that crown and ionomer are mostly used for restoration in the elderly and there is no difference between men and women in terms of using restorative materials.[22] While Murray introduced amalgam as a suitable material for use in the posterior teeth of the elderly, so that despite the fracture, the restoration is still useful after 100 months and its replacement is usually unnecessary for the elderly. [10]Composite resin restorations are about 2.5 times more durable than amalgam and are recommended in cases of patient beauty requests. Glass ionomer restorations for the elderly and RACF patients are a useful alternative restoration material to tooth color because they are cariostatic and use minimally invasive dentistry. Using indirect composite resins is contraindicated for elderly patients because its failure rate is similar to direct restoration and takes longer to be manufactured.[10]

Clinical and technical challenges of providing a fixed crown and bridge for the elderly, especially those living in nursing homes, prevent them from being selected in most cases. The metal and ceramic crowns have a success rate of 94%, the bridges are expected to survive more than 87% by 10 years, though. All-ceramic crowns are usually preferred over ceramic and metal crowns for their beauty; however, in posterior regions, they have higher fractures and, therefore, it is recommended not to use ceramic and metal crowns in patients for therapeutic purposes than for beauty ones.[10] Laske introduced composite as the most commonly used restorative material for the elderly. The failure rate of 10-year restoration was for composite restorations (4.4%), amalgam (5.1%), compomers (7.5%), and glass ionomer cement (11.1%).[18]

Caplan's study indicated that amalgam, composite, and GIC restorations are among the most widely used restorations in the elderly; crowns or bridge holder were less commonly used.[15] In general, in-cavity restorations are often primarily replaced by the same type of restoration. Among intercoronal restorations, amalgam and GIC restorations fail due to more tooth extraction than composite restorations, and bridges are the most common type of root canal restoration. For amalgam restoration, the average survival time is similar for anterior and premolars; however, it is shorter for mill teeth. For composite restorations, the average survival time for anterior teeth is worse than that of premolars and molars, and for GIC restorations, the average survival time is the same for all types of teeth. Regardless of the restorative material, the life of larger restorations (at larger levels) is shorter than that of smaller restorations (one level). In a given tooth, initial restorations are more durable than subsequent restorations.[15]

On the other hand, one of the appropriate treatment approaches for the elderly is minimally invasive intervention/dentistry, including the diagnosis and treatment of caries as soon as possible and with minimal invasiveness. This means prioritizing prevention, providing the necessary information and guidance to empower patients to maintain oral hygiene, and conducting conservative intervention to minimize tooth loss during surgery. Conservative restorative techniques such as ART and using the concept of shortened dental arch can improve the condition of the elderly teeth and improve the quality of life associated with their oral health. The results of the study conducted by Mata show that minimally invasive methods such as ART and conventional restorative technique (CT) are equally effective in improving the oral health of the elderly and improving their quality of life.[28] The time and cost of ART is less due to non-surgical intervention and anesthesia.[20] The best restoration material is using

glass ionomer.[13] If ART is used with amalgam, it increases its cost-effectiveness.[14]

The combination of glass ionomer and composite resin together causes more coverage and adhesion. This will make the restoration more successful with ART. The width of the root surface of a decaying lesion affects the success of the restoration. ART failure is more likely to be caused by secondary caries. This is more common in nursing home residents due to poor hygiene. Failure to completely remove the decayed lesion, especially with hand tools, increases the severity of the aforementioned failure. The presence of dental plaque is an important factor in the occurrence of secondary caries. Therefore, it is required to identify and completely remove decayed tissue before performing ART restoration with the help of identification tools. The presence of a tooth opposite the tooth receiving the restorative material affect the prolongation of the restorative process resulting from the concentration of tensile forces in that area, causing the failure to maintain and the formation of marginal cracks.[13] Moreover, the moisture content and adhesion of glass ionomer should be controlled in both ART and CT methods for having more successful restorations.[25]

Moreover, in the case of the elderly, if some parts of the restorations are damaged, it is best to repair it before the complete loss of the restoration.[9]Also, Enamelon as a calcium phosphate-based remineralization technology combined with fluoride therapy, and Carisolv as a minimally invasive method that removes only necrotic tissue can be other effective methods of removing root caries in the elderly. Glass ionomer and composite resin are used to restore the intended part. Laboratory evidence has also shown the effective use of ozone on the surface of decayed teeth, but clinical evidence is insufficient to ensure its effectiveness and cost-effectiveness.[10] Moreover, the larger the repair and the more levels it covers, the more likely it is to fail.[11]Owing to the complications of implants that are difficult to manage, its application is not recommended for the elderly, especially for individuals living in nursing homes. Implants must not be used in patients with bone necrosis.[10]

Other factors associated with dentistry that affect the success of restorations include inadequate diagnosis in order to adopt the appropriate clinical approach, inadequate removal of decayed lesion, inadequate use of restorative materials, and inadequate moisture management.[13] The constant change of one's dentist can also affect the amount of restoration work and leads to more restoration work to be conducted. Older people who visit the dentist more often or change their dentist regularly will face more expensive restorations and more crown and ionomer glasses. Experienced dentists use amalgam, especially ionomer, for further restoration, and as for the elderly, they use more crowns and glass ionomers. While younger dentists use more composite resin. This is mainly due to the importance of restorative aesthetics for women who use more composite resin in their anterior teeth.[22] The failure rate of restorations conducted in individual methods (one dentist) or small groups (2 or 3 dentists) is lower than that of the methods conducted by a larger group (several dentists); the size of the treatment has no effect on the durability of the restoration.[18] One of the limitations of this study was the lack of access to the full text of some of the studies. It was attempted to have access to the full texts of such studies by sending emails to the corresponding authors and searching on social networks such as Research Gate.

CONCLUSION

The most important restorative dentistry considerations for the elderly were identified at three levels of considerations related to the elderly themselves, restorative materials and methods, and the dentist's performance through reviewing the related literature. It is, thus, recommended that dentists consider the medical and social conditions of the elderly, age and gender, medications used, type of restorative tooth, level of restoration involved, appropriate timing of tooth extraction in middle age, oral cancer screening, giving due attention to caries prevention approach, and providing the necessary training to the elderly, their families, and their caregivers in nursing homes. Moreover, selecting a suitable durable restoration material and comfortable and washable storage conditions according to the patient's social and economic conditions, using conservative care methods and minimally invasive restoration by identifying and eliminating caries with the help of appropriate tools, controlling moisture and the size of the restoration, aesthetic and non-aesthetic considerations are other suggestions. The elderly people are also required to avoid frequent changes of dentist to observe their oral and teeth health and carefully follow the educational recommendations provided to them. Moreover, due to the special conditions of the elderly and their care and treatment needs, it is recommended that further studies be conducted to evaluate the desired effect of new materials and methods.

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ORIGINAL ARTICLE

Community-acquired pneumonias in SARS-CoV-2 negative patients admitted at Mater Dei Hospital and their subsequent follow-up

Etienne Ceci Bonello, Denise Gatt, Emma Mifsud, Darlene Mercieca Balbi, Peter Fsadni

Background

Community-acquired pneumonia refers to an acute infection of the lung parenchyma acquired within the community, and its management depends on the severity of symptoms and method of presentation. The aim of this audit is to evaluate community-acquired pneumonias in SARS-CoV-2 negative patients admitted at Mater Dei Hospital and their subsequent follow-up.

Methods

In this observational audit, demographic data was collected from 200 patients between June and September 2020. Follow-up of these patients was audited to assess whether local current practice is being adhered to as per British Thoracic Society recommendations.

Results

From our sample of 200 patients, 25.5% who were being treated for community-acquired pneumonia passed away during their admission. The age range of our patients varied from 18 to 99 years with the majority being over the age of 75. 31 out of 149 surviving patients (20.8%) had both imaging and medical outpatient follow-up booked, 18 patients (12.08%) had only a chest x-ray follow-up whilst 19 patients (12.75%) had medical outpatient follow-up only. In total 68 patients (45.63%) had imaging or medical outpatient follow-up, or both.

Conclusion

Any patient admitted and treated for a community-acquired pneumonia should receive a follow-up appointment to assess for resolution of symptoms, and/or follow-up imaging to assess for resolution of changes. Non-resolution of these changes may necessitate discussion at a multi-disciplinary level to conclude how to further investigate such a patient.

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INTRODUCTION

Community-acquired pneumonia (CAP) refers to an acute infection of the lung tissue. This is acquired outside of the hospital setting within the community as the name implies, and management depends on the severity of symptoms and method of presentation. Patients may be treated within the community itself by their general practitioner or may require admission to hospital for further intensive care.

There are several risk factors which make patients more likely to acquire a CAP and which may increase the morbidity and mortality rate. These include: age >65 years, multiple co-morbidities including chronic lung disease (CLD), active malignancy, immunosuppression and smoking.

Assessing severity and identifying which patients require hospital-based care is crucial. Local and current practice involves using the CURB-65 score which is based upon five factors. These include confusion (based upon a specific mental test or new disorientation to person, place, or time), urea 7 mmol/L (19 mg/dL), respiratory rate ≥30 breaths/minute, blood pressure (systolic <90 mmHg or diastolic ≤60 mmHg) and age ≥65 years. One point is assigned for each criterion that is met. For patients with a score of 1 or 2 (unless the score of 1 is due to age ≥65 with no major co-morbidities), hospital admission may be warranted. Scores higher than 3 will require hospitalisation, and scores higher than 4 may need admission to a high dependency unit (HDU) or intensive care unit (ICU).[1] This wide spectrum of presentation and the number of complications resulting from such an infection makes CAP a leading cause of morbidity and mortality worldwide.

Current recommendations as per the British Thoracic Society (BTS) guidelines for the management of CAP issued in 2009, (annotated 2015), suggest that once patients finish their treatment, whether it is within the community or within the hospital setting, a clinical review should be arranged around 6-8 weeks post-treatment. This review can be either with the patient's own general practitioner or in a hospital outpatient clinic.

This practice is well known and has been practiced for a number of years both locally and internationally. In addition, previous guidelines also suggested that repeat imaging should be performed as non-resolving pneumonias may be the first presentation of a primary or secondary malignancy, infection with an atypical pathogen, or subsequent complications from the original pneumonia.

MATERIAL AND METHODS

Approval to carry out this audit was obtained from the Data Protection Office at Mater Dei Hospital (MDH). A search was performed on the medical admissions list between the months of June and September 2020 for the following keywords; shadowing, opacity, pneumonia, lower respiratory tract infection (LRTI) and consolidation/s.

200 patients with a confirmed consolidation on chest radiography were included in this audit. The imaging together with their reports were reviewed using iSOFT Clinical Manager® (ICM®) and Universal Viewer® to obtain this information.

Data collection involved taking into account several factors including: age, gender, active malignancy, CLD, smoking history and a negative SARS-CoV-2 real time polymerase chain reaction (RT-PCR) nasal swab test - taken on all patients admitted to MDH as per local protocol. The CURB-65 score was calculated as well from the emergency documents and investigations which were found on ICM®. Whenever the respiratory rate (RR) was not documented on the admission notes, an oxygen saturation below 94% was taken into account and given a point accordingly instead.

Furthermore, ICM® was used to check any microbiology cultures from blood, sputum and respiratory screens, and whether the patient was given follow-up imaging and/or a follow-up medical outpatient (MOP) appointment. All this data was collected from Universal Viewer®, ICM®, and electronic case summary® (ECS®).

RESULTS

From our sample of 200 patients, 53% were male and 47% were female. A total of 51 patients (25.5%) who were being treated for CAP passed away during their admission at MDH. The age range of our patients varied from 18 years to 99 years. The majority of patients admitted with this pathology (106 patients; 53%) were over the age of 75 (Figure 1).

44 patients (22%) had a history of CLD. CLDs that were taken into account were asthma, chronic obstructive pulmonary disease, bronchiectasis and interstitial lung disease. In addition, 47 patients (23.5%) were known cases of active malignancy.

196 patients had a chest x-ray (CXR) on admission whilst the other 4 patients underwent a computerized tomography (CT) scan in the first instance. 47% of patients (94 patients) had a CT performed after a CXR which confirmed a consolidation. In 20 of these patients, a CT was performed after their initial CXR did not show any evidence of consolidation, but was later confirmed on CT imaging. The remaining 102 patients (51%) did not have a CT during their admission but only a CXR.

The CURB-65 score was calculated using the emergency admission documents and investigations. Whenever the RR was not documented or assessed, an oxygen saturation less than 94% was assumed to

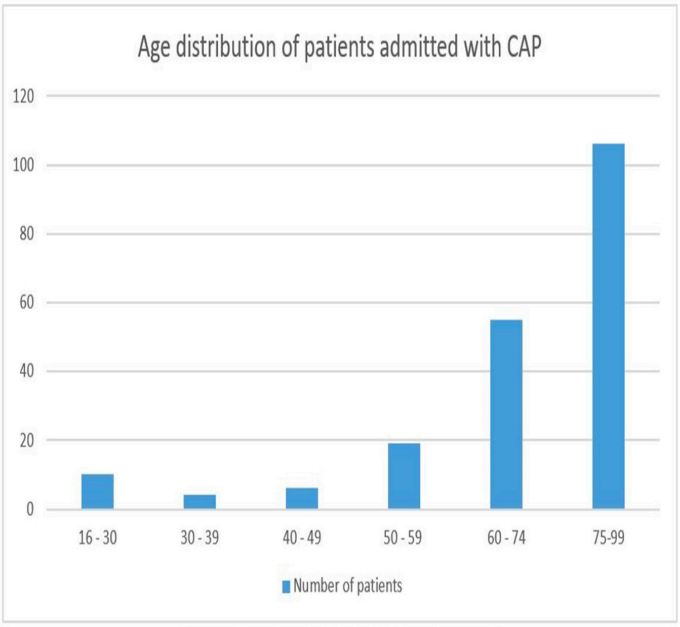

Figure 1 *Age distribution of patients admitted with CAP*

be equivalent to an elevated RR with the patient needing oxygen requirements. 17.5% and 21.5% of patients had a CURB-65 score of 0 and 1 respectively. A larger proportion of patients had a score of 2 (38.5%). Only 8.5% of patients had a score of 4 or higher (Figure 2).

With respect to follow-up imaging and/or MOP, the results showed that 31 patients out of 149 surviving patients (20.8%) had both imaging and MOP follow-up booked, 18 patients (12.08%) had only a CXR follow-up whilst 19 patients (12.75%) had MOP follow-up only. In total 68 patients (45.63%) had MOP or imaging follow-up, or both (Figure 3).

Microorganisms cultured from different media were also noted. Blood cultures, respiratory screen and sputum for microscopy, culture and sensitivity were assessed and the pathogens grown taken into account. 22 patients had negative sputum cultures whilst 9 patients had positive growth on their samples. 169 patients did not have any sputum samples taken. One main reason for such samples not being taken could be the lack of sputum production by the patient or not ordered in the first place by their caring physicians. Blood cultures were taken in 94 patients, positive in 9 of them only, with *Staphylococcus aureus* being the most prominent bacterium cultured. In 97 patients, blood cultures were not taken. Lastly, 15 positive respiratory screens from a total of 86 samples were yielded. In Figure 4 one can find the different pathogens cultured on the different mediums mentioned.

DISCUSSION

For hospitalized patients with a negative CXR and suspected CAP, the Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) guidelines consider it reasonable to initiate empiric antimicrobial therapy and repeat a chest radiograph in 24 to 48 hours.[2] Alternatively, a CT scan may be performed as it provides further radiographic detail and information. CT imaging should not be used routinely due to its high costs, additional radiation exposure and risk of contrast-induced kidney injury. Thus, a chest radiograph is the preferred method of initial imaging.[3-4]

The CURB-65 score should be used as a guideline to assess whether the patient can be treated within the community, or guide the caring physician whether to admit the patient to a normal ward or HDU/ICU. Our data showed that 35 patients (17.5%), were admitted with a CURB-65 score of 0. Retrospectively, it is difficult to assess if the patient needed admission or not whilst in the emergency department, however one might argue that the results show a substantial

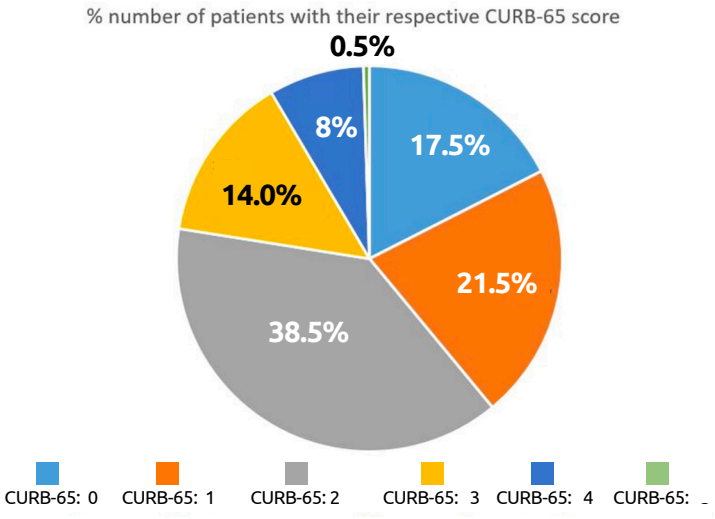

Figure 2 *Percentage number of patients with their respective CURB-65 score*

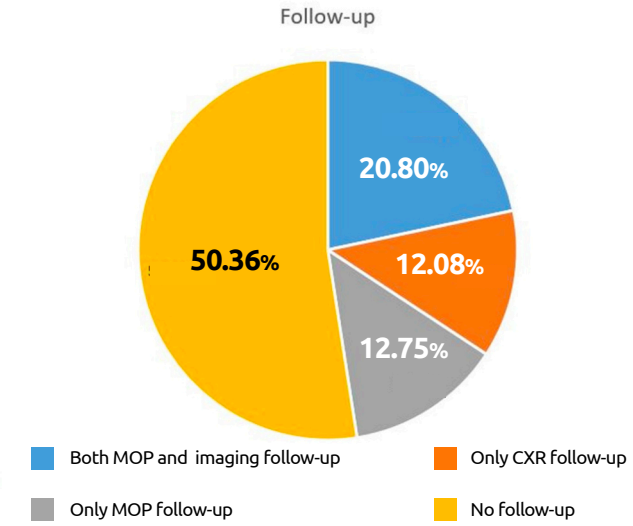

Figure 3 *Follow-ups at MOP and/or imaging*

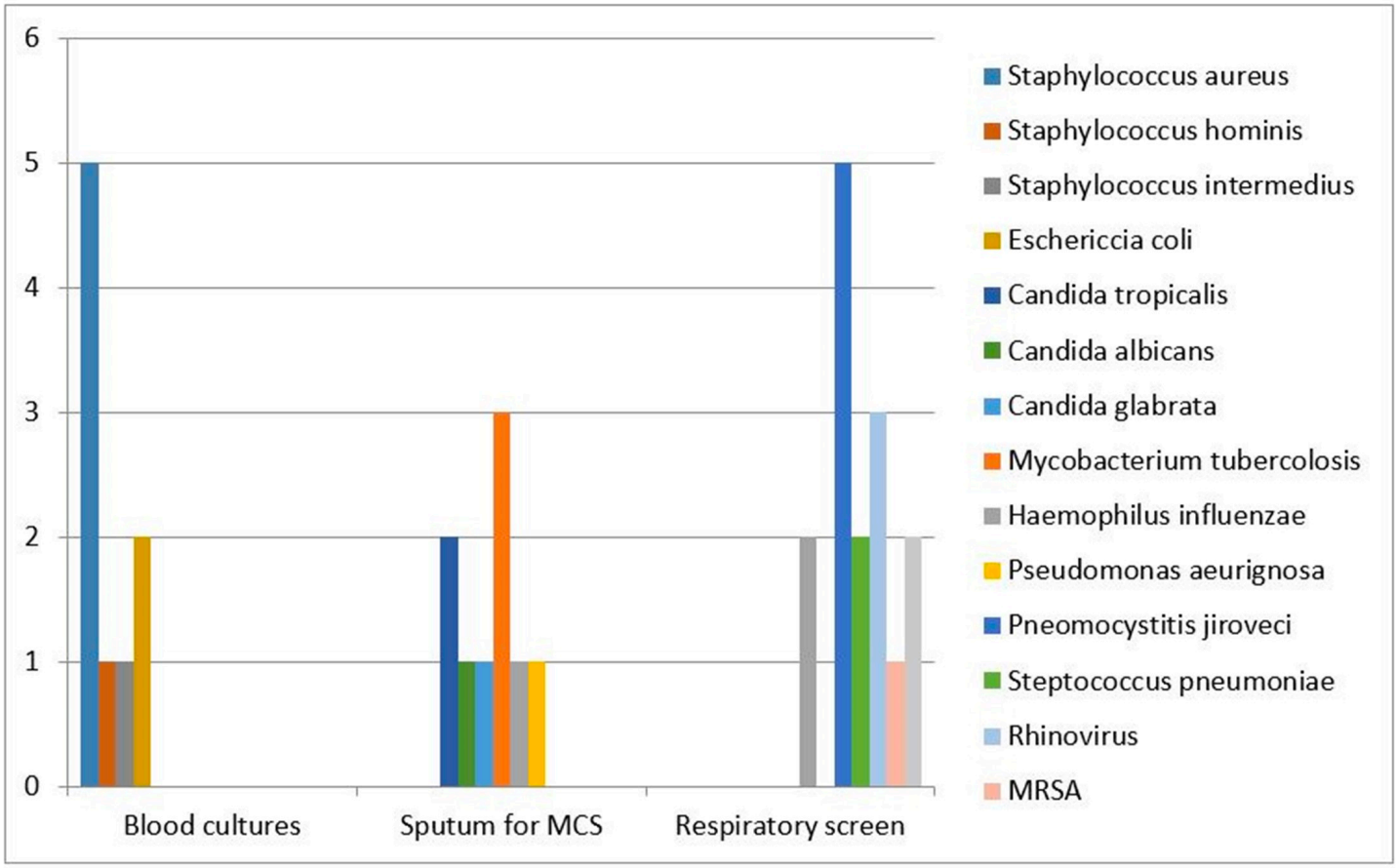

Figure 4 *Pathogens cultured on different mediums*

number of admissions which may have been prevented, and hence decreasing health care related costs and health care related adverse events. The CURB-65 score also does not take into account radiographic severity of CAP.

Data collected showed out of 16 patients with a CURB-65 score of 4, 50% (8 patients) passed away during their admission, and 1 patient with a score of 5 that did not survive. This correlates well with the fact that patients with a score of 4 or higher, require HDU/ICU admission if possible due to their poor prognosis and higher risk of mortality. The majority of patients that did not survive were over the age of 65, making age a strong risk factor to the outcome of such a condition.

Literature shows that in many patients with CAP, even up to 62%, no pathogen is actually detected despite extensive microbiological testing. The most commonly identified causes of CAP can be grouped into typical bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, Group A streptococci, Aerobic gram-negative bacteria such as Klebsiella spp or *Escherichia coli*, microaerophilic bacteria and anaerobes (associated with aspiration). The next group includes the atypical microorganisms such as Legionella spp, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia psittaci*, and *Coxiella burnetii*. These organisms are termed atypical in view of their inability to be visualised on Gram stain, or cultured using traditional techniques. Respiratory viruses include Influenza A and B, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and others such as rhinoviruses, parainfluenza viruses, adenoviruses, respiratory syncytial virus, human metapneumovirus and human bocaviruses. The prevalence of these pathogens varies with geography, pneumococcal vaccination rates, risk factors for CAP, seasonal changes, and pneumonia severity. While the list above details some of most common causes of CAP, more than 100 bacterial, viral, fungal, and parasitic causes have been reported.[5-6]

Follow-up of CAPs is essential for the detection of non-resolving pneumonias and associated complications. Persistence of consolidation on imaging should prompt the caring physician to investigate further. Additional investigations such as bronchoscopy might shed light onto the root cause of a non-resolving pneumonia. Our data shows that only 68 patients from a total population sample of 149 surviving patients were followed up. Follow-up as suggested by previous and current recommendations should be done at 6-8 weeks, to allow for complete resolution of the consolidation on imaging. This time frame should be adhered to, as literature shows that follow-up imaging earlier than recommended provides little to no additional information.[7] Follow-up should also be done to assess for symptom resolution. It is well known that symptoms such as cough and sputum production may persist for some

weeks. Studies show that as many as 87% of hospitalised patients suffer from persisting pneumonia related symptoms within 30 days of the original infection. These results are in keeping with the time frame mentioned above, to allow for resolution of these persisting complaints.[8-9]

LIMITATIONS OF THE AUDIT

Mortality rate could not be attributed solely to complications from CAP as patients may have had other co-morbidities and other non-CAP related complications.

Most patients are over the age of 75, making follow-up for these patients difficult to set up especially if they reside in long-term care facilities or are dependent in their activities of daily living.

The large number of blood cultures, sputum samples and respiratory screen not taken could have been due to multiple factors, such as sputum not being available, or samples not ordered by the caring firms.

When a respiratory rate was not recorded in the patient's notes, an SpO2 less than 94% was used instead to calculate the CURB-65 score. This was not necessarily accurate.

SUMMARY BOX

- We recommend that any patient admitted and treated for a CAP should receive a follow-up appointment to assess for resolution of symptoms, and/or follow-up imaging to assess for resolution of CXR or CT changes. Further efforts should be made in this regard.
- Non-resolution of these changes may necessitate discussion at a multi-disciplinary level to conclude how to further investigate such a patient.
- The CURB-65 score is an important tool which helps the general practitioner or the emergency physician with the management plan.
- Risk factors need to be taken into account when admitting a patient and one should not rely on the CURB-65 only, as age and other risk factors will undoubtedly increase the mortality rate and affect prognosis.

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ORIGINAL ARTICLE

Diagnosis and Growth dynamics of Adrenal incidentalomas: a 6-month retrospective analysis

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Introduction

Adrenal incidentalomas are adrenal masses discovered incidentally on imaging studies originally not performed for suspected adrenal disease.

Aim

To characterise a cohort of adrenal incidentalomas found on CT imaging the adrenal region.

Methods

This was a retrospective analysis, taking into account all the adrenal incidentalomas discovered on CT between July and December 2014 at Mater Dei Hospital. Only lesion greater than 1cm were included in the study. These were then classified according to their radiological features. Previous CT scans and any CT scans done after the study period were also reviewed to establish any change is size of the lesions.

Results

A total of 9100 CT scans were reviewed and adrenal incidentalomas were identified in 296 patients. 216 incidentalomas could be adequately classified and included in the study; 80.1% were confirmed adenomas, 12.9% metastasis, 5.6% myelolipomas and 1.3% ganglioneuromas. 49.1% of patients with an adenoma were males as opposed to 71.4% in the metastasis group. Bilateral lesions were commoner in the metastasis group (9% in adenoma vs 18% in metastasis group). Longest median radiological diameter was 18mm (IQR 14.0-24.0) in the adenoma group and 26.0mm (IQR 16.0-36.0) in the metastasis group (P<0.001). Median follow up in the adenoma group was longer in the adenoma group 20.9 months (IQR 4.5-39.0) vs 11.2 months (IQR 0-29.3) in the metastasis group (P<0.001). Median change in size was also statistically significant: 0.0mm (IQR -1-0.8) in the adenoma as compared to 22.5mm (IQR 12.5-30) in the metastasis group (P<0.001).

Conclusion

This study continues to confirm that adrenal adenomas are the commonest adrenal lesion encountered in clinical practice and the majority, by far remain stable in size over time.

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INTRODUCTION

Adrenal incidentalomas are adrenal masses detected on imaging studies, carried out for reasons other than suspected adrenal pathology. The widespread use of abdominal imaging in recent years has led to a steep increase in the discovery of such lesions. Although most of these lesions are benign and hormonally non-functional, there is a small proportion which are malignant or associated with hormonal excess.

In keeping with trends internationally, the Endocrine Department at Mater Dei Hospital, is coming across an increasing number of referrals for patients with adrenal incidentalomas, with the aim of excluding malignancy and hormonal excess. The aim of this study was to perform an analysis on a cohort of adrenal incidentalomas discovered locally.

SUBJECTS AND METHODS

This was a retrospective study taking into account all the adrenal incidentalomas discovered during a six-month period. All CT scans, imaging the adrenal region, performed at Mater Dei Hospital between July and December 2014 were reviewed. These included all CT scans of the abdomen, pelvis, and thoracic region, CT scan of the kidney/ureter/bladder (CT KUB), CT intravenous urogram (IVU), CT pulmonary angiography and CT colonoscopy. Those reported to have any adrenal pathology were singled out. The actual scans of those singled out were closely re-reviewed, after been reported by radiologist in routine clinical practice.

In line with other studies,[1-2] all adrenal lesions greater than 1cm were included in the study, irrespective of reason of referral. Patients under the age of 18 years were excluded. Data collected included; indication for the CT scan, size (mm) and side of lesion (left/right), homogeneity, unenhanced density (HU), early enhanced density (HU) and 15min delayed density (HU), where indicated. This allowed us to calculate the relative or absolute washout where appropriate.

Imaging characteristics typical of adrenal adenoma included unenhanced density of less than 10HU, relative or absolute washout of 40% or 60% respectively[3] and in the absence of appropriate imaging study, CT imaging following a 12 month period showing unchanged mass characteristics were also considered as a surrogate criterion and included as an adenoma. Previous CT scans, when available, and consecutive scans were also reviewed. The size and radiological features of the lesions present on such scans were also documented in detail as outlined above. In this way, any change in size or characteristics of adrenal lesions were identified.

The adrenal lesions were then classified according to these radiological features into benign adenoma, myelolipoma, adrenal cyst, ganglioneuroma, malignant carcinoma, and indeterminate.

STATISTICAL ANALYSIS

The Kolmogorov Smirnov test was used to assess whether the data collected is normally distributed or not. As predicted, in this study, most of the data was not normally distributed and therefore non-parametric statistics were required to explore the relationship between the variables. The non-parametric statistics included Chi-squared, Mann-Whitney test and Kruskal-Wallis test. Results were expressed as a P value, and a value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 9100 CT scans were reviewed. Adrenal incidentalomas larger than 1cm were identified in 296 patients, a frequency of 3.3%. 80 (27.0%) adrenal lesions could not be classified, this was because they either had only 1 scan (with no unenhanced imaging available) or washout calculations were unavailable. Of the remaining 216 incidentalomas, 173 (80.1%) were confirmed adenomas (Hounsfield units <10, relative or absolute washout values of >40% or 60% respectively or no increase in size over 12 months), 28 (12.9%) were metastatic lesions, 12 (5.6%) myelolipomas and 3 (1.3%) ganglioneuromas (Figure 1).

The mean age of all patients was 65.8 years (±12.2SD). 52.3% of all patients were males. The median longest radiological diameter of all incidentalomas at 1st scan documented was 19.0mm (IQR 15.0-25.0). 81.5% of patients had more than one scan carried out, therefore change in size of the

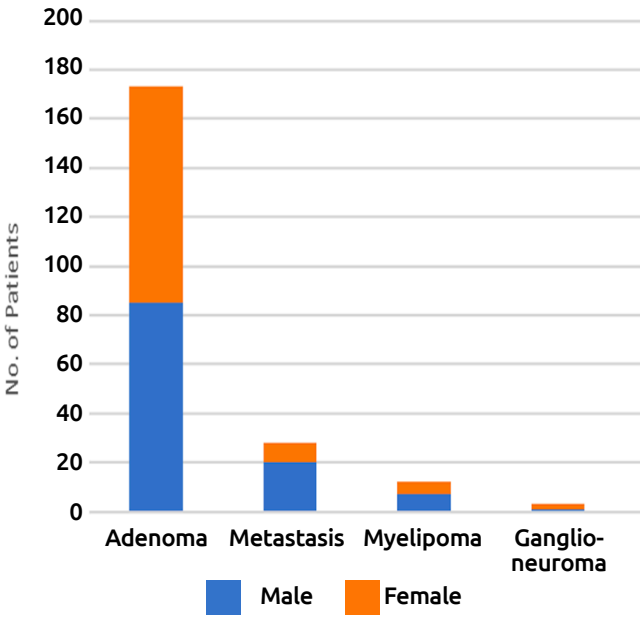

Figure 1 *Characterisation of incidentalomas*

Table 1 *Basic characteristics of all adrenal incidentalomas (Kruskal-Wallis test used)*

	All characterised incidentalomas	Adrenal adenomas	Adrenal metastasis	Myelolipoma	Ganglioneuroma	p-value
Number (%)	216	173 (80.1)	28 (12.9)	12 (5.6)	3 (1.3)	
Age mean (±SD)	65.8 (12.2)	65.2 (12.4)	69.3(11.1)	64.8 (11.1)	70.3 11.8)	NS
Males number (%)	113 (52.3)	85 (49.1)	20 (71.4)	7 (58.3)	1 (33.3)	NS
Longest radiological tumour diameter at 1st scan (mm) median (IQR)	19.0 (15.0-25.0)	18.0 (14.0-24.0)	26.0 (16.0-36.0)	24.0 (17.5-42.5)	25.0 (25.0-41.0)	<0.001
Change in tumour size (mm) median (IQR)	0.0 (-1.0 – 1.0)	0.0 (-1.0 – 0.8)	22.5 (12.5 – 30.0)	0 (0-0)	-5.0 (-6.0 – -2.5)	<0.001
Follow up period (months) median (IQR)	18.0 (2.9-38.6)	20.9 (4.5-39.0)	11.2 (0-29.3)	21.3 (3.9-38.3)	7.1 (3.8-11.2)	<0.001

lesions could be assessed. The median change in tumour size for all incidentalomas was 0mm (IQR -1.0 – 1.0) with a median follow up time of 18.0 months (IQR 2.9-38.6) (Table 1).

Reasons why the CT scan was carried out in the first place varied, with gastrointestinal symptoms being the commonest reason (34.1%) (Figure 2). Interestingly, out of all patients who had a CT scan because of an underlying malignancy and found to have an adrenal incidentalom∑a (63 patients), 33 patients (52.4%) were found to have an adrenal adenoma, 26 patients (41.3%) had metastasis and 4 (6.3%) patients had a myelolipoma.

SUBTYPE CLASSIFICATION

ADRENAL ADENOMA

Of the 173 patients with an adrenal adenoma, 49.1% were males with a mean age of 65.2 years (±12.4). The

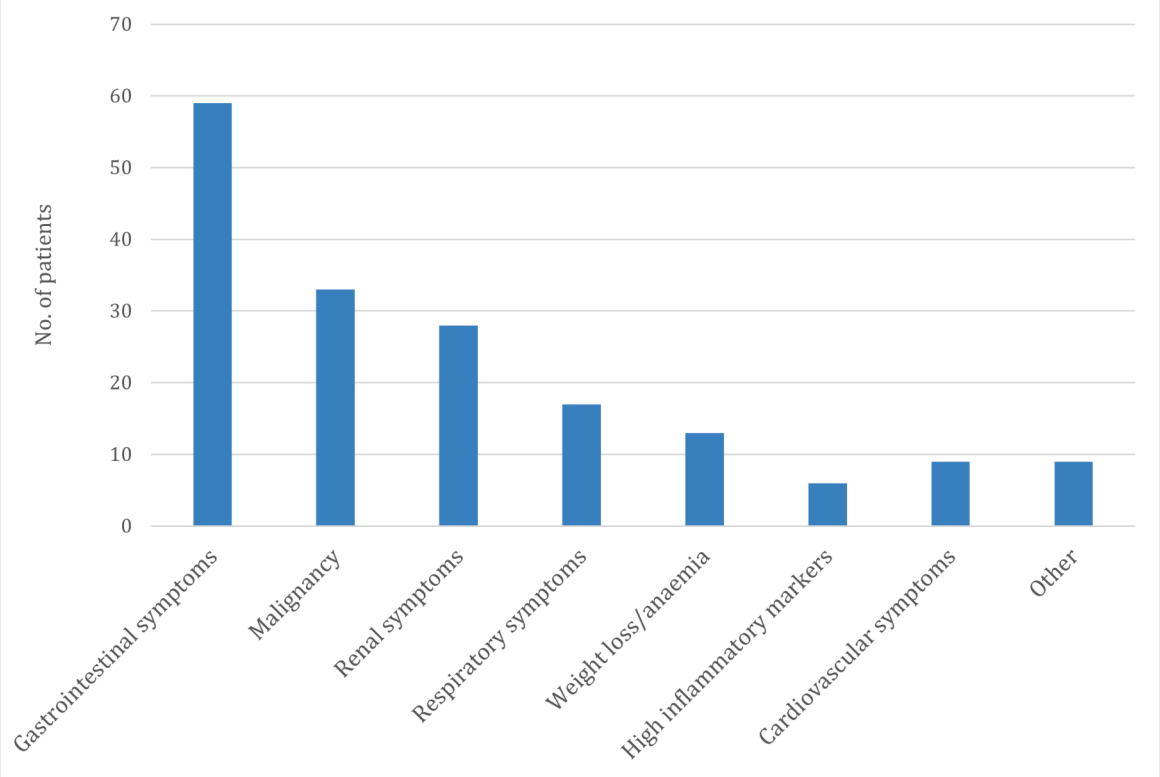

Figure 2 *Reason for CT in patients with adrenal adenoma*

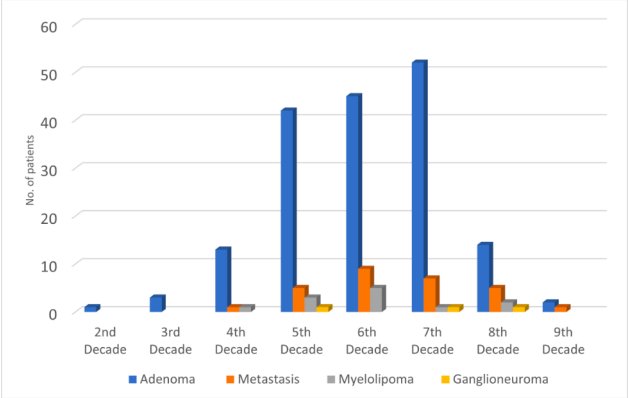

Figure 3 *Adrenal incidentalomas according to decade of presentation*

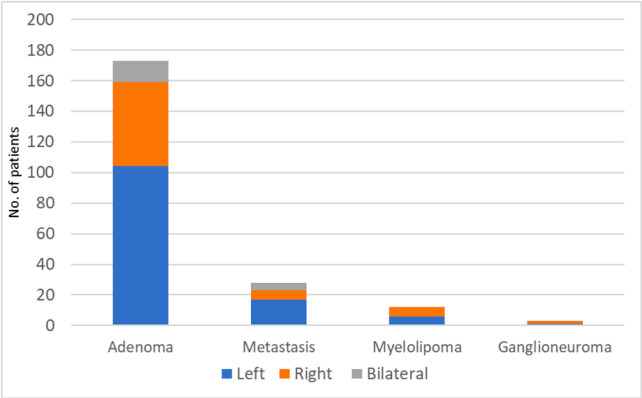

Figure 4 *Laterality of adrenal lesions*

7th decade was the commonest decade for presentation (30.0%), followed by the 6th (26.6%) (Figure 3). 59.5% had a left-sided lesion (Figure 4).

Laterality of adrenal lesions

The longest median radiological diameter was 18.0mm (IQR 14.0-24.0) in the adenoma group (Table 1). In the whole adenoma group, during a median follow up of 20.9 months (ICR 4.5–39.0) the median change in size was 0.0mm (IQR -1.0 – 0.8) (Table 1).

Adrenal Metastasis

In the metastasis group (28 patients), 71.4% were males (Table 1). The mean age was 69.3 years (±11.1SD). In this cohort, most patients presented in the 6th decade (32.1%), (Figure 3). 60.7% had left sided lesions (Figure 4). The longest median radiological diameter was 26.0mm (IQR 16.0 – 36.0) in the metastasis group. Median follow up for this group was 11.2 months (ICR 0-29.3) whereas the median change in size was 22.5mm (IQR 12.5 - 30.0) (Table1).

The commonest primary malignancy was lung cancer (9 patients) (Figure 5). None of the patients required biopsy for the confirmation of the diagnosis of metastasis.

Comparing Different Subtypes

When comparing the different groups described above, there was an appreciable statistically significant difference in change in size ($p<0.001$), with median change in size in the adenoma group being

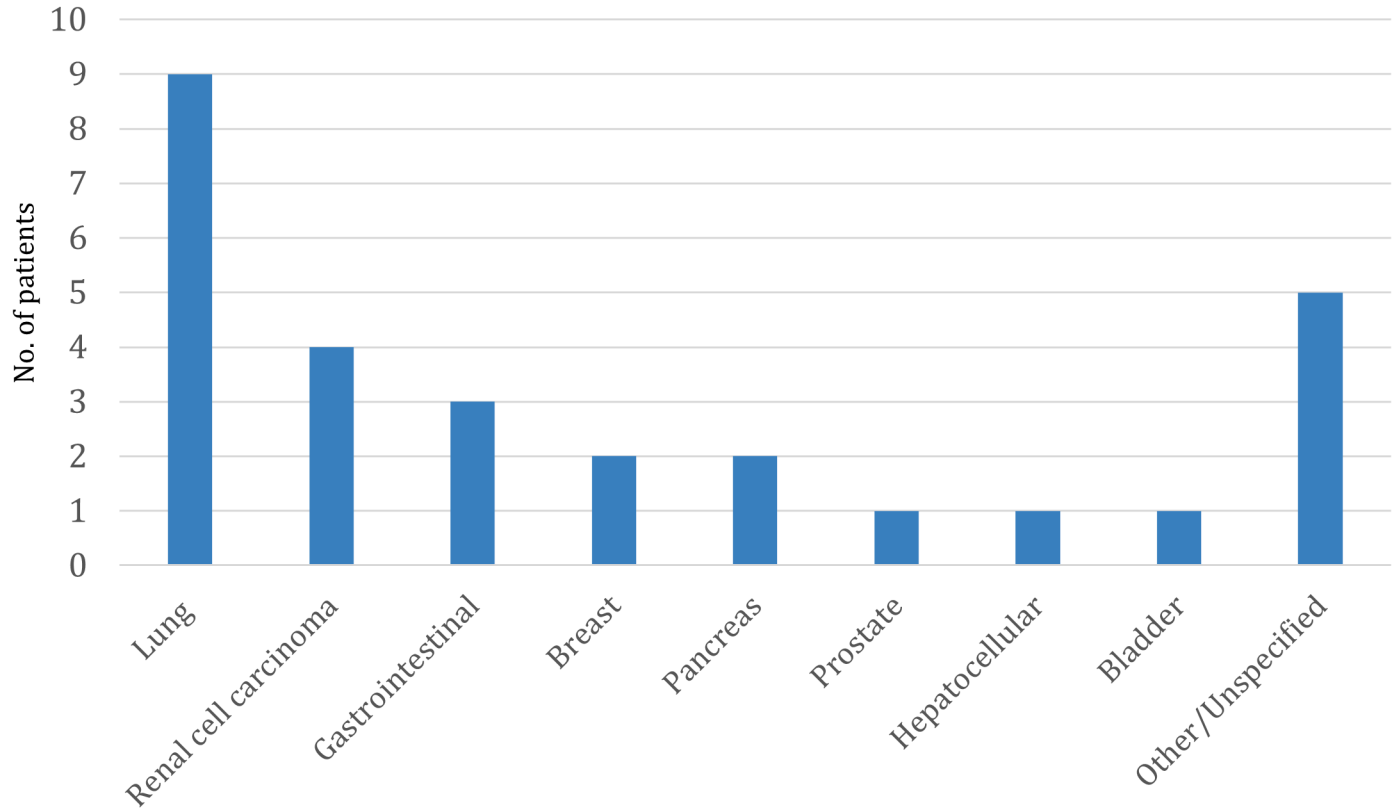

Figure 5 *Primary malignancy in patients with adrenal metastasis*

Table 2 *Comparing frequency of adrenal incidentalomas from this study with that published in the literature*

Authors	Type	Date	n	Age (years) *mean (±SD) **range	Tumour size (mm) mean (±SD)	Subtype classification (%)							
						Adrenal Adenoma			Phaeochromocytoma	ACC	Adrenal metastasis	Myelo-lipoma	Other
						Non functional	Cortisol excess	Mineralo-corticoid excess					
Kloos et al	Meta-analysis	1995	86,842				36-94		0-11	0-25	0-21	7-15	
Mantero et al	Retrospective study	2000	1,004	*56 (12.9)	36 (25)	85.1	9.2	1.6	4.2	4.7	0.7	8	15
Barzon et al	Meta-analysis	2003	3,868	*56.9	30-35 (range 5-250)	71.2	7.9	1.2	5.6	4.4	2.1		
Mansmann et al	Meta-analysis	2004	3,648	*57	34		5-47	1.6-3.8	5.0	4.7			
Cawood et al	Meta-analysis	2009		*58	32		6.4	0.6	3.1	1.9	0.7		
Young Cho et al	Retrospective analysis	2013	282	*57.15 (10.49)	23 (14)	78.0	9.9	1.8	2.1	0.7	0.4	2.8	
Goh et al	Prospective study	2017	228	**20-86	21	83.3	7.9	0.4	0.9	1.3		0.9	
Current study	**Retrospective**	**2019**	**216**	***65.8 (12.2)**	**22 (11)**		**80.1**		**0**	**0**	**12.9**	**5.6**	**1.3**

0.0mm (IQR -1.0 – 0.8), in the metastasis group being 22.5mm (12.5-30.0) and in the myelolipoma group that of 0mm (IQR 0-0). In the ganglioneuroma group there was a median decrease in size of 5mm (IQR -6.0 – -2.5). The most significant change in size can be observed in the metastasis group, and this holds true despite the statistically shorter (P<0.001) follow up period in this group (median follow up of 11.2 months IQR 0-29.3) when compared to the adenoma group (median follow up of 20.9 months IQR 4.5-39.0), the myelolipoma group (median follow up of 21.3 months IQR 3.9-38.3) and the ganglioneuroma group (median follow up of 7.1 months IQR 3.8-11.2) (Table 1).

Left sided lesions were also found to be statistically more common than right sided lesions (P<0.001), with 58.8% of all lesions being left sided; 59.5% of patients having a left sided adenoma, 60.7% of metastasis being left sided metastasis, 50% of myelolipomas being left sided and 33% of the patients with a ganglioneuroma having a left sided lesion (Figure 4).

Comparing Adrenal Adenomas With Adrenal Metastasis

When comparing the adenoma group with the metastasis group alone, change in size remained significantly different (P<0.001) despite no statistically significant difference in the duration of follow up in the adenoma group (median 20.9 months ICR 4.5–39.0) vs the metastasis group (median 11.2 months ICR 0-29.3) (P=0.084) (Table 1).

Unenhanced density was also significantly different (P=0.002) with the median unenhanced density of the adenoma group being 5HU (IQR -3 – 11) and 34HU (IQR 28 – 35) in the metastasis group. More males had adrenal metastasis (71.4%) as opposed to the adenoma group (49.1%) (P=0.028).

DISCUSSION

From a total of 9100 CT scans, 216 incidentalomas were identified, with a frequency of 3.3%. The frequency of adrenal incidentalomas in the general population, as calculated from radiological series is suggested to be around 2-3% in those around the age of 50 years and increases to 10% in the elderly.[1,4]

From the identified 216 incidentalomas, 173 (80.1%) were confirmed adenomas, 28 (12.9%) were metastasis, 12 (5.6%) were myelolipomas and 3 (1.3%) were noted to be ganglioneuromas. These compare well to results from similar studies (Table 2). No phaeochromocytomas or adrenocortical carcinomas were detected during the study period. This could be attributed to the fact that the incidence of such conditions is low and we reviewed a finite amount of CT scans.[9100] Our rate of metastasis was higher than that reported in the literature (Table 2). In most of the quoted literature, patients with previous or concurrent history of malignancy which are known to metastasize to the adrenal gland were excluded.[2,5-6] The authors argue that patients with

malignancies of the lung, breast, stomach, kidney, melanoma and lymphoma, which are known to metastasize to the adrenal gland, should be excluded from the definition of a true incidentaloma.[6]

Our study demonstrated no major male to female difference in the adenoma group (49.1% males), however, this cannot be extrapolated for the metastasis group; where a male preponderance of 71.4% was noted. Most studies report a higher female to male ratio.[7-8] In the meta-analysis by Barzon et al., there was a higher female to male ratio in the overall analysis including radiological, autopsy and surgical series, but when taking autopsy studies independently, this female preponderance was lost. This could be ascribed to a higher rate of imaging performed in females than in males.[6] In the study by Comlekci et al.,[2009], there was also a female:male ratio of 2.9 in the adenoma group, with a ratio of 0.07 in the metastasis group, with 93% of patients with adrenal metastasis being males (n=14 patients; 3.7% of whole cohort).[9] The reason as to why more male patients were noted to have adrenal metastasis could be explained by the fact that most patients with adrenal metastasis in our cohort, and in the study by Comlekci, had primary lung cancer (39% in our cohort and 57.1% in the other cohort). Previously published data shows that lung cancer, internationally, has a higher prevalence in males rather than in females.[10]

More lesions were discovered on the left side and this was found to be in concordance with other studies where left sided tumours were more prevalent.[11-12] Older studies had shown a right sided predominance[2] but this may have been attributed to the predominant diagnostic modality used in these studies. Ultrasonography (US) was the diagnostic technique used in most cases and the right adrenal gland is known to be better visualised than the left adrenal gland by ultrasonography.

The mean age at presentation was 65.8 years (±12.2SD). This age distribution might not be representative of the whole population as more diagnostic procedures are usually carried out in ageing patients.[2] Still, it is well documented that adrenal adenomas are more prevalent with increasing age.[13-14] Our cohort revealed an older mean age at presentation when compared to most meta-analyses. Once again, this could be attributed to the fact that in most published data, patients with metastasis were excluded and these tend to be older patients. In the study by Muth et al., patients with a history of extra adrenal malignancy, but no evidence of active disease at time of study were included in a separate arm of the study.[15] The mean age of those with no extra adrenal malignancy was 67 years, whereas the mean age of patients with a history of extra adrenal malignancy was 68 years. This compares better to our results, possibly because the cohort of patients included in the study was similar to our cohort. In the same study, the commonest reason for performing the initial CT scan was for investigation of gastrointestinal symptoms (38% of patients). Similarly, in our cohort, gastrointestinal symptoms were the commonest trigger factor for the initial CT scan (34.1% of patients).

In the large Italian multicentric retrospective study published in 2000, including 1004 patients, the median size of adrenal incidentalomas was found to be 36mm[2] whereas in more recent studies performed in New Zealand[12] and Korea,[11] the median diameter was 21mm (IQR 10-83mm) and mean of 23mm (±13SD) respectively. The latter figures are increasingly similar to our data, where the mean longest radiological tumour size at first scan was found to be 22.4mm (±11.6SD). This may be attributed to increased awareness by reporting radiologists on adrenal incidentalomas reporting even smaller lesions and better imaging techniques leading to improved resolution of adrenal lesions.[12]

Our study revealed that half of the patients being followed up for malignancy were found to have an adrenal lesion consistent with an adrenal adenoma whilst being followed up for their primary malignancy. This may potentially justify the inclusion of all patients who had imaging of the adrenal region, including those with a history of malignancy, when characterising adrenal incidentalomas. Most studies in the literature exclude patients with underlying malignancy, on the basis that this cohort is at increased risk of harbouring adrenal metastasis.[2,5] However, given the high prevalence of adrenal adenomas in our study even in this cohort of patients, it effectively illustrates that patients with current malignancy may still have an adenoma irrespective of their malignancy.

We detected no malignant transformation in the 173 patients diagnosed with an adrenal adenoma, followed up for a median of 20.9 months (IQR 4.5-39.0). The mean change in size was that of 0.1mm (±2.1SD) over a median follow up of 20.9 months in the adenoma group. In a recent systematic review, the natural course of an apparently benign adrenal incidentaloma developing malignancy was found to be very low at 0.2% (95% CI:0.0-0.4).[1] Out of the 906 patients included in the systematic review, only 2 patients were identified and the transformation was dubious in both scenarios; one patient had non-Hodgkin lymphoma and the initial radiological images were not consistent with benign characteristics in the first place, whilst in the second case there was a history of renal cell carcinoma and it was unclear whether the incidentaloma was found during the follow up of cancer or discovered incidentally.[5] Importantly, in the other 904 patients, there was no evidence of malignant transformation in a presumably benign adrenal incidentaloma. Based on these findings, the recently published guidelines suggest against repeated imaging if the lesion is confirmed to be a benign adrenal mass smaller than 4cm at diagnosis[1] because even a small increase in size does not seem to have significant clinical

implications. The cut-off of 4cm was based on clinical experience by panel members on the basis that repeated imaging might risk false positive results together with significant financial burden on the health system and psychological stress on patients. This data has been recently confirmed in a retrospective study including 1149 patients where the mean change in size was 14mm over a median of 4 years (IQR 2.0-6.0). The optimal cut-off value for diagnosing a benign lesion based on size was 3.4cm in the latter study, with a sensitivity of 100% and specificity of 95.0%. When using a cut-off value of 4cm to distinguish benign from malignant lesions, the sensitivity and specificity were 90.0% and 97.9% respectively.[16]

A larger mean change in size in the metastasis group was noted over a shorter median follow up period when compared to the adenoma group (p=0.001). Since most data in the literature excludes patients with extra adrenal metastasis it was rather difficult to compare our results with published data. In light of the fact of this significant difference, our data can therefore be useful in clinical practice when assessing incidentalomas, highlighting the possibility of a lesion being sinister if there is a significant increase in its size. Our finding that 52.4% of patients with underlying malignancy found to have an incidentaloma, had in fact a radiologically confirmed adenoma, proves the consistent rate of adenoma, thus highlighting the consistent rate of picking up incidentalomas in the course of imaging.

LIMITATIONS

There is always a finite number of borderline cases when it comes to classification. This was the case when classifying adrenal incidentalomas into subtypes. To mitigate this all cases were re-reviewed, after been reported by radiologist in routine clinical practice, by the same team. Furthermore, equivocal cases were discussed by members of the research team.

CONCLUSION

In conclusion, a snapshot of adrenal incidentalomas in Malta has been established together with the frequency of each subtype over a 6-month period. An important finding was that patients with underlying malignancy do indeed have a higher probability of being diagnosed with adrenal metastasis as expected. However, they may still be harbouring an incidental adrenal adenoma as half of our malignancy cohort had in fact an incidentaloma with radiological features consistent with an adenoma.

SUMMARY BOX

- Adrenal incidentalomas are a common occurrence in abdominal imaging.
- Adrenal adenomas are the commonest adrenal lesion encountered in clinical practice and the majority, by far remain stable in size over time.
- Patients with underlying malignancy who present with an adrenal incidentaloma may still harbour an adrenal adenoma, rather than metastasis.

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ORIGINAL ARTICLE

The Impact of appointment interruptions due to COVID-19 in patients being treated with phototherapy

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The phototherapy unit in Malta, previously located at Sir Boffa Hospital in Floriana, had an annual turnover of around 11 thousand visits. Many of these patients suffer from moderate-to-severe psoriasis (plaque, guttate and palmo-plantar), but other indications include eczema, mycosis fungoides, morphea and others.

In view of the current COVID-19 pandemic this phototherapy unit was closed and treatment of patients receiving light therapy was forced to cease. The aim of this short study was to follow up patients previously receiving phototherapy, to assess the effect of the abrupt halt in treatment on their clinical condition and their quality of life.

In summary, closure of the service has led to a general worsening of patients' clinical condition, with 54.21% of the patients interviewed having felt worse whilst off treatment when compared to being on treatment 3 months prior, and 4 of the 83 individuals (4.8%) having to be placed on systemic immunosuppressant agents.

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INTRODUCTION

The 2019 novel coronavirus (COVID-19) was initially identified in Wuhan, China, back in December 2019[1] and announced as a pandemic by the World Health Organization (WHO) in March 2020.[2] The first COVID-19 case in Malta was recorded on the 7th March 2020,[3] with lockdown measures starting as of the 12th March 2020 and elective outpatient clinics at the National Health Service Hospital being halted on the 15th March 2020.[3]

Prior to the COVID-19 outbreak, Malta's national Dermatology services were based at Sir Paul Boffa Hospital. However, from the start of the pandemic back in March 2020, this hospital was reassigned as a facility to house COVID-19 positive patients who could not self-quarantine in their households; with dermatology services eventually moved to the island's main hospital, Mater Dei Hospital (MDH). As a result of the new COVID-19 measures and the eventual logistic relocation, phototherapy services in Malta were interrupted between March 2020 up until November 2020.

The main objective of this study was to assess patients' self-reported clinical condition and its effect on their quality of life following the abrupt halt in phototherapy treatment.

MATERIALS AND METHODS

Phototherapy unit records from the month of January 2020 up until the last day of treatment in March 2020 were obtained. A total of 118 patients received phototherapy in this time. Very few patients had been referred for granuloma annulare, vitiligo and unspecified pruritus, and thus were excluded, leaving a total of 83 patients.

The following information from these phototherapy unit records were obtained: age, gender, indication for phototherapy, type of phototherapy (narrowband UVB vs PUVA), session number (since start of current phototherapy course until last session), and improvement seen with current course. Patients were contacted in June 2020 via telephone and asked a range of questions via a 'modified' Dermatology Life Quality Index (DLQI) score, simplified to target a telephone questionnaire (Table 1). Additionally, patients were asked if their condition worsened since the closure of the phototherapy unit. For those in whom worsening of their general condition was observed, the time taken for the relapse to occur was noted. It was also documented if the patient was started on a systemic therapy to replace the phototherapy.

RESULTS

A summary of the results can be found in Table 2. From the 83 participants questioned, 55.4%[46] were males and 44.57%[37] were females, with an average age of 51.35 years. The average total number of sessions from the start of 2020 until March 2020 was 44.08 with most sessions being for UVB (86.75%) as opposed to 13.25% undergoing photochemotherapy with PUVA; 69 of the 83 individuals (83.13%) stated that they saw an improvement with phototherapy after their last session, whilst 14 stated that they did not see any improvement with from their phototherapy sessions. 57.8%[48] stated that they 'relapsed' after closure of the unit, whilst 42.1%[35] stated that they did not. For those that did relapse, the average time it took to note a change in skin condition was 2.23weeks (15 to 16days). Figure 1 demonstrates the time taken for relapse when comparing different skin diseases. The greatest indication for phototherapy was psoriasis at 66.77%, followed by mycosis fungoides at 13.25%, eczema at 9.64% and the sclerosing skin conditions (localized scleroderma at 3.61% and unspecified scleroderma at 1.2%). A score of percentage of patients affected by their skin condition at the time of questioning was obtained from the combination of scores in the modified DLQI score; 25.3% of patients were greatly affected by their skin condition, in comparison to 12.04% who were not affected at all. When comparing the overall modified DLQI score at the time of questioning to how they felt whilst on therapy, 54.21% felt they were overall worse.

DISCUSSION

The DLQI score is a validated tool/outcome measure that can be used to assess the physical, psychological and social wellbeing of patients being treated in a phototherapy unit. A modified version of this score was used to assess the impact of the patient's current skin condition off therapy, as compared to whilst on therapy back in March 2020. Data gathered highlighted that 42.16% described their skin as sore/itchy/painful; with 42.16% stating that it was more so than when on UV therapy. When asked, 55.41 % felt embarrassed/self-conscious about their skin, although 51.80% stated that it was comparable to when on treatment. This highlights the impact of skin disease on the psychological well-being of individuals. When asked about the effect their skin had on their work, home, and leisurely activities, 39.3% noted a considerable impact, with 60.24% stating that this is comparable to when on therapy.

In Malta, comparable to the UK,[4] psoriasis is the greatest indication for phototherapy. In this study 66.77% of patients receiving phototherapy had psoriasis (including plaque, palmoplantar and guttate psoriasis). Mild plaque psoriasis is usually managed with topical therapy alone, with the addition of narrowband UVB phototherapy and PUVA in patients whose symptomatology and rising Psoriasis Area and Severity Index (PASI) score cannot be controlled by topical therapy alone.[5] Phototherapy is also beneficial in the management of other skin diseases including eczema, cutaneous T-cell lymphoma, vitiligo, prurigo and others.

Phototherapy provides many dermatology patients with an effective treatment option that does not involve use of immunosuppressants. With no global guidelines for the safe treatment of patients, many phototherapy centres limited their services or stopped treating patients completely. In a similar study conducted on a phototherapy unit in Brazil, the disease severity of patients after cessation of therapy was evaluated using questionnaires during a medical appointment.[6] Prior to cessation of therapy, a plan of action recommending whether each patient should continue phototherapy had been taken. 81% of patients stopped phototherapy; 33.7% of their own accord and 47.7% on medical recommendation. 95% of patients who stopped phototherapy (for whichever reason) reported a worsening of their disease.

This sudden cessation of phototherapy coupled with an increase in stress brought about by the pandemic, has caused these chronic dermatoses to become poorly controlled. In our study, 4 of the 83 (4.8%) individuals contacted took systemic agents after closure of the service. The use, including both discontinuation and initiation, of biological therapy and systemic agents during the pandemic has been a matter of much debate, with institutions concerned on the possible increase in morbidity and mortality from an underlying COVID-19 infection, especially in a co-morbid patient.[2] At the time of data collection, recommendations were unclear and vague. To date, there has been no evidence that patients on immunosuppressants are at a greater risk of contracting COVID-19 or develop a more severe form of the COVID-19 infection.[7] Whilst it has been recommended to continue immunosuppressants in patients who are well, starting patients on a biological agent or other systemic agents should be considered on a case-by-case basis.[7]

In view of the small sample size, we were unable to obtain statistically significant results. Further to this, we were unable to include an objective measure of severity and extent of psoriasis via a PASI score, as the patients were contacted via telephone. For a better understanding of the severity and relapse rate, comparison with similar data obtained from (ideally the same) patients having previously received the full prescribed course of their therapy is needed. In our data collection, we had not specified if phototherapy had been halted at the start or towards the end of the treatment course. Lastly, outpatient records were not obtained. It is possible that in addition to the four individuals who were started on systemic agents, others had been advised to do so by their dermatologist.

In conclusion, the 9-month suspension of the phototherapy service in Malta led to a general worsening of patients' clinical condition, with 54.21% of the patients interviewed having felt worse whilst off treatment, and 4 of the 83 individuals (4.8%) having to eventually be placed on systemic immunosuppressant agents.

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ORIGINAL ARTICLE

The Impact of first wave of COVID-19 on referrals to Mtarfa Mental Health Clinic and evaluation of service response

Roberto Galea, Martha Anne Apap Bologna, Catherine Dimech, Anton Grech

Background

The COVID-19 pandemic necessitated social distancing measures to curb the spread of disease. This disrupted daily activities and social interaction with attendant impact on mental well-being, as well as mental health service provision.

Method

The study aims to investigate first contact community psychiatry referrals to the Mtarfa mental health clinic before and after the onset of COVID -19 and the adequacy of the service response. Following necessary approvals an index of new case appointments was constructed from the register at Mtarfa MHC from 11 March 2019 to 31 December 2020. This was cross referenced with eMR. The imposition of social distancing on 12 March 2020 was used to separate the date into before and after the onset of COVID-19.

Results

A total of 236 new case appointments were identified, 92 of these records preceded the onset of COVID-19 and 144 records followed. The date of referral was available in 105 of the 136 appointments attended. The waiting time could be calculated in 77.2% of these appointments, 76.4% before the onset of COVID-19 and 77.8.% after. The mean number of new case referrals received per month increased from 7.4 before the first wave to 21.2 after, a three-fold increase. Mean waiting time was 21.6 weeks prior to the onset of COVID-19 which decreased to 7.4 weeks when a steady state was observed after the first wave.

Conclusion

The COVID-19 pandemic posed significant challenges to community mental health services resulting in major service restructuring. These challenges were met through staff redeployment and increased clinic frequency. The service increase successfully met a threefold increase in new case appointments at the clinic and decreased waiting time by two thirds.

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INTRODUCTION

The onset of the Coronavirus disease 2019 (COVID-19) pandemic necessitated social distancing measures to curb the spread of disease. These measures disrupted normal patterns of daily activities and social interaction, as well as mental health service provision.[1] Isolation has added to the psychological burden of living through the pandemic, with resulting impact on community mental healthcare demand in Malta.[2-3]

BACKGROUND

The first wave of the COVID-19 pandemic hit Malta between 6 March and 24 April 2020.[4-5] On 12 March 2020, public health measures were announced including: closure of all schools, university and childcare centres; closure of day centres for the elderly; cessation of religious activities unless mandatory; suspension of social gatherings including sport and political activities.

During the first wave, between March and June of 2020, psychiatry outpatient clinics at Mater Dei Hospital were suspended and telepsychiatry services provided. A resident specialist and trainee psychiatrist provided telepsychiatry consultations through the Mtarfa Mental Health Clinic (Mtarfa MHC). Significant restructuring of community mental healthcare services occurred in response to the pandemic. Prior to the onset of COVID-19, Mtarfa MHC accommodated 12 specialist clinics quarterly (just under one clinic per week). Following the first wave, clinics at Mtarfa were resumed on a daily basis, a five-fold increase in clinic frequency.

Aim

This study aims to investigate and compare the number of first contact community psychiatry referrals to the Mtarfa MHC before and after the onset of COVID-19 and the adequacy of the response to the increased demand.

METHOD

Outline

Appointment data from the time leading up to the initial announcement of public health measures effecting social distancing at the onset of the first wave of COVID-19 in Malta (12 March 2020) was used to establish baseline demand. Following the end of the first wave regular clinics were resumed in July 2020. Appointment data from the period following resumption of regular clinics was then used to determine the increased demand secondary to COVID-19 imposed social distancing plus the concomitant COVID-19 related nation-wide psychiatry outpatients restructuring.

Methodology

Permissions: Approval for this study was obtained from the head of the department of psychiatry, and subsequently from the data protection officer. Ethical approval was facilitated as no patient or relative contact was required.

Workflow analysis: The Mtarfa MHC workflow was established through personal experience of the authors and interviewing the nursing officer in charge of the Mtarfa MHC.

Index: An index of first contact referrals to community psychiatry services assigned to Mtarfa MHC were identified through the clinic's register. The period chosen was between 11 March 2019 and end December 2020.

Capture: Subsequently, the respective files were consulted and analysed. Only data pertaining to this analysis was collected. Cross referencing with Electronic Medical Records (eMR) was performed to confirm attendance, further follow-up and residence locality. All data was then anonymised.

Processing: Anonymised data from the initial capture spreadsheets was entered into a rapid application database, checked for errors and consistency and normalised. The flat field data was then restructured into a relational database. This period was divided into two sections: prior to the 12 of March 2020 as the time prior to COVID-19 and from the 12 March 2020 onward. This date was chosen as it was the first announcement of public health measures effecting social distancing.

Querying: All subsequent queries were performed through structured query language (SQL).

RESULTS

Number of Appointments

Index and allocation: A total of 236 records were identified through the register at Mtarfa MHC between 11 March 2019 and 31 December 2020. On 12 March 2020 initial public health measures effecting social distancing were announced. This was taken as the onset of COVID-19. 92 of these records preceded the onset of COVID-19 and 144 records followed. (Figure 1)

Attendance: Of 236 register entries, 38 did not have an entry on eMR and a further three died before the appointment date leaving 195 attenable appointments. 46 patients did not attend (DNAd) and 13 appointments were cancelled. 136 appointments were attended in the whole study period according to eMR. (Table 1).

Analysis of Files Not Found

The original referral for an outpatient appointment (with date of referral when available) is kept in the

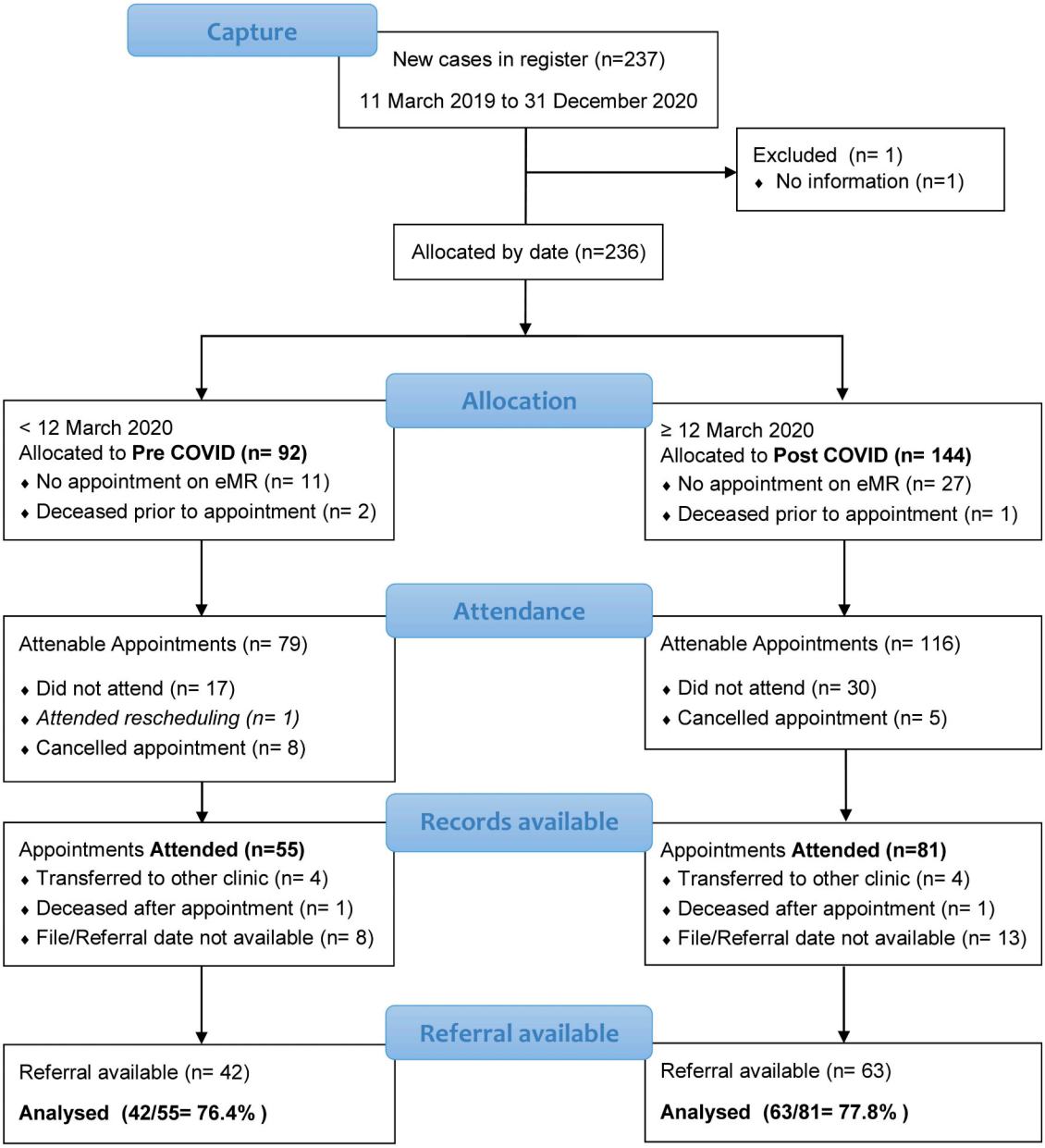

Figure 1 *Audit flow diagram giving number of appointments analysed*

patient's clinical notes. A date of referral was available in 105 of the 136 appointments attended. The waiting time could be calculated in 77.2% of these appointments. Referral dates were available for 76.4% of the pre COVID group and 77.8.% of the post COVID-19 group, a 1.4% difference. This difference is not statistically significant (Chi squared = 0.036, df = 1, 95% CI *P*=0.849). In 31 cases a date of referral was not available. 8 cases were transferred to another clinic after the visit and 2 cases died after the appointment, making the clinical files unavailable – thus unable to ascertain cause of death. In a further 21 instances either the file or the date of referral were not available at the time of writing, six of these DNAd subsequent appointments at Mtarfa MHC and a further two had eMR registered locality outside the Northern Region. Five of 21 were foreign nationals.

Patients having More than One Referral

Two patients had more than one entry in the register in the period of study. One had the initial appointment cancelled, the reason for this is not recorded in eMR; however, the patient then did not attend the second appointment given and subsequent appointments at Mtarfa MHC following the end of the study. The second patient had two appointments within a month, the patient passed away in this short interval and is likely to have been too unwell to attend the first.

Analysis of Impact of Covid-19 Onset on number of New Case Appointments, Waiting Time & Service Changes

The mean number of new case referrals received at Mtarfa MHC was 7.4 cases per month in the period

Table 1 *Number of appointments analysed for frequency and wait time*

	Pre COVID	Post COVID	Total
Register	92	144	236
Appointment in eMR	81	117	198
Deceased before appointment	2	1	3
Attenable	79	116	195
DNA (attended rescheduling)	17 (-1)	30	46
Cancelled	8	5	13
Attended	55	81	136
Transferred to other clinic	4	4	8
Referral date or File not available	8	13	21
Deceased after appointment	1	1	2
Referral date available	42	63	105
Proportion	*76.4%*	*77.8%*	*77.2%*

from 11 March 2019 to 11 March 2020 prior to the onset of the COVID-19 pandemic. This increased to 21.2 cases per month after the first wave, that is between first August 2020 and end December 2020, effectively a three-fold increase. See figure 2 below. The mean waiting time from referral to appointment was 21.6 weeks prior to the onset of COVID-19. This increased gradually to a maximum of 27 weeks during the first wave and subsequently decreased to 7.4 weeks after the number of clinics increased. Figure 2 below suggests that a steady state may have been achieved in August 2020 following the resumption of clinics in July. The mean number of patients and waiting time for the interval August to December 2020 was taken to represent a steady state. Further audit following the time window investigated, would add confidence to this estimate. The institution of the second lock down in March 2021 would mark the end this steady state period.

Interim Telepsychiatry

The telepsychiatry service set up at Mtarfa MHC was dealing with an average 6.3 new cases per month up to a maximum of 13 new cases in June 2020 at the

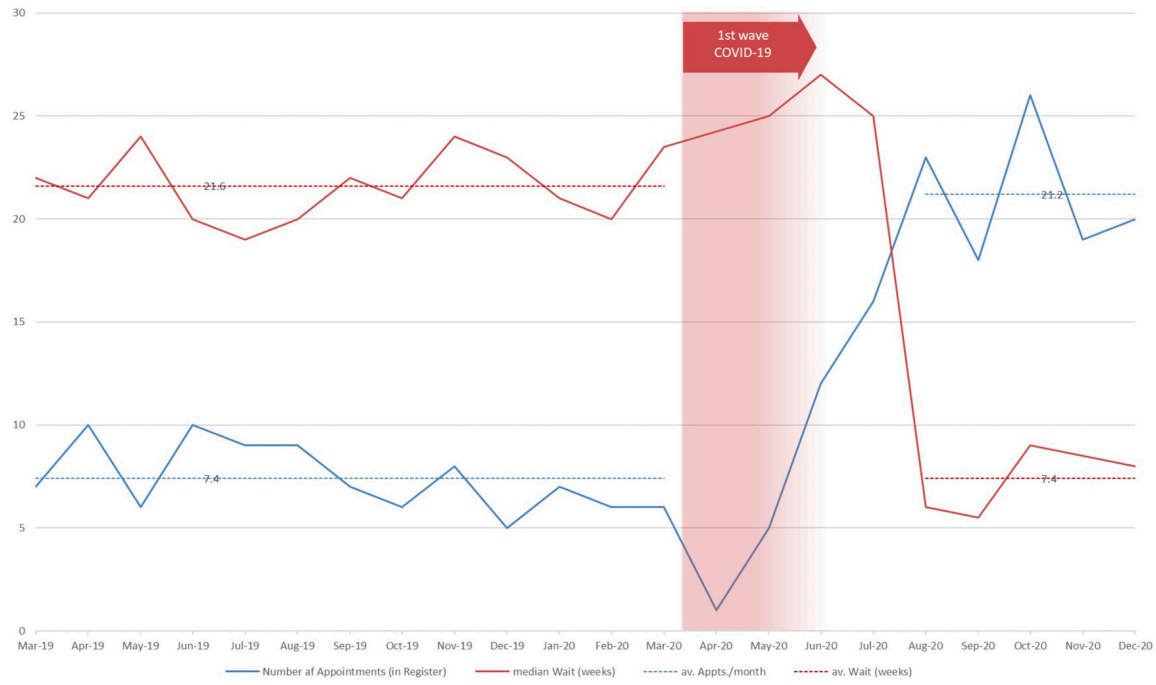

Figure 2 *Number of new case appointments and median wait from referral at Mtarfa MHC*

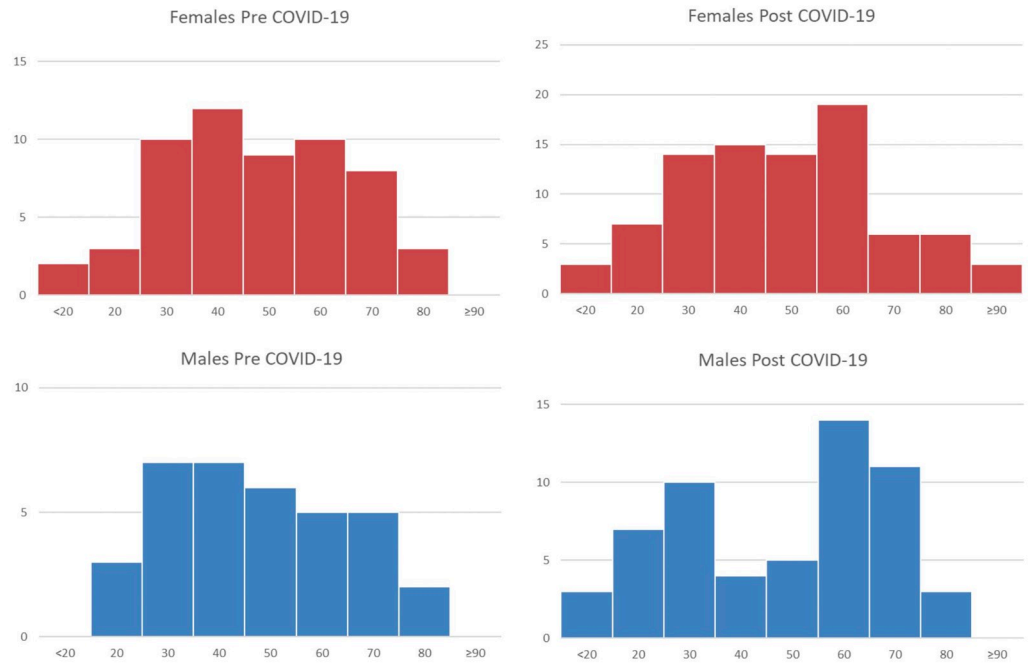

Figure 3 *Gender age distribution before and after COVID-19*

end of the first wave. The median waiting time for new cases in June 2020 rose from a median of 23.5 weeks to 27 weeks. While the number of new cases seen effectively doubled, only a 13 % increase in waiting time was observed for this period. This interim effort appears to have largely contained the waiting time burden; indeed a steady state appears to have been achieved by the increased service provision (daily clinics) within the space of a month.[6]

Demographic Analysis

Age

The ages of patients referred to Mtarfa MHC during the study period are analysed separately for both sexes prior to and following the onset of COVID-19. The proportion of new case referrals for men aged 60-80 appears to have increased; a similar change is observed for 60–70-year-old females. (Figure 3)

This observation could reflect the anxieties of health risk and isolation in older persons.[7] The expected rise in working age adults is not seen. This may be due to a lag and would be scope for further audit. Coincident with the onset of the first wave, referral practices changed, resulting in additional patients being referred to Mtarfa MHC. This and the different intervals studied are confounding issues that do not allow direct comparison of numerical values. Hence normalised histograms are presented below to facilitate comparison of distributions rather than absolute number.

Nationality

The majority of referrals to Mtarfa MHC are Maltese nationals, both before and after the onset of COVID-19. The proportion of referrals of individuals from central and eastern Europe (Serbia, Poland, Romania, Albania, Hungary, Slovakia, Ukraine and Bosnia and Herzegovina) decreased by more than half following the onset of the pandemic, while the proportion of referrals of persons originally from the UK remained unchanged. Referrals also included other nationals from Italy and Germany, Egypt and South Africa. The numbers are too few for meaningful analysis. In view of changes in referral practices as well as different time intervals studied, proportions are being represented to facilitate comparison.

These results are in keeping with expectations. Central and Eastern Europeans tend to be younger/ middle aged workers who would return home if their

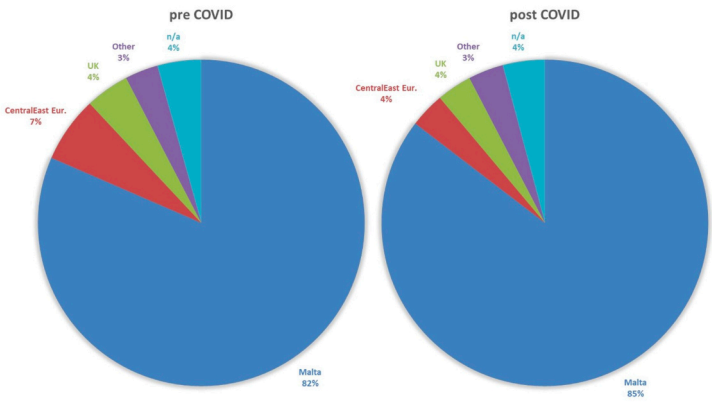

Figure 4 *Proportion of referrals to Mtarfa MHC by nationality*

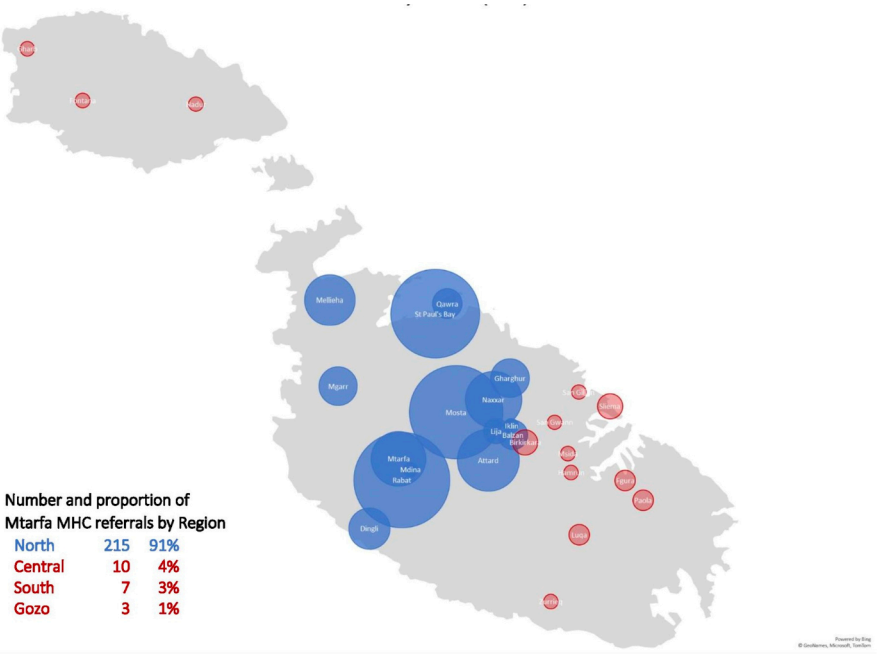

Figure 5 *Referrals to Mtarfa MHC by location (eMR)*

job security is threatened while UK citizens tend to be longer term residents in Malta. (Figure 4)

Locality Of Referrals

Locality of referrals was obtained through the registered address on eMR for all 236 entries in the Mtarfa MHC register. In one entry the locality was not forthcoming. Localities were then analysed for appropriateness to clinic catchment area. (Figure 5)

Referrals to Mtarfa MHC by location (eMR)

It appears that the vast majority of referrals to the clinic are region appropriate, allowing for interim change of address and patient preferences. A separate analysis before and after the onset of COVID-19 found no relevant change in this pattern. This is to be expected as these regional divisions are service imposed and as such arbitrary, with no association to the locality background excepting convenience to patients and workload distribution.

SOURCES OF REFERRAL TO MTARFA MCH

Referrals to Mtarfa MHC are primarily made by General Practitioners working in the community. Referrals from Mater Dei Hospital (Medicine and Surgery) as well as directly from the Accident and Emergency department are also encountered. See

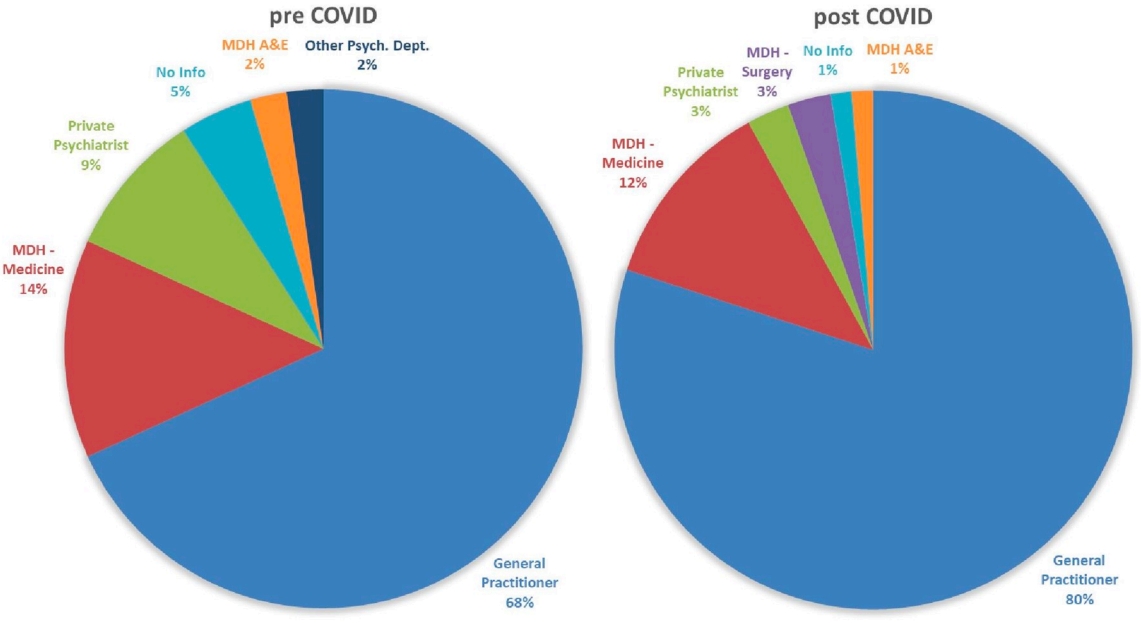

Figure 6 *Proportion of referrals to Mtarfa MHC by source*

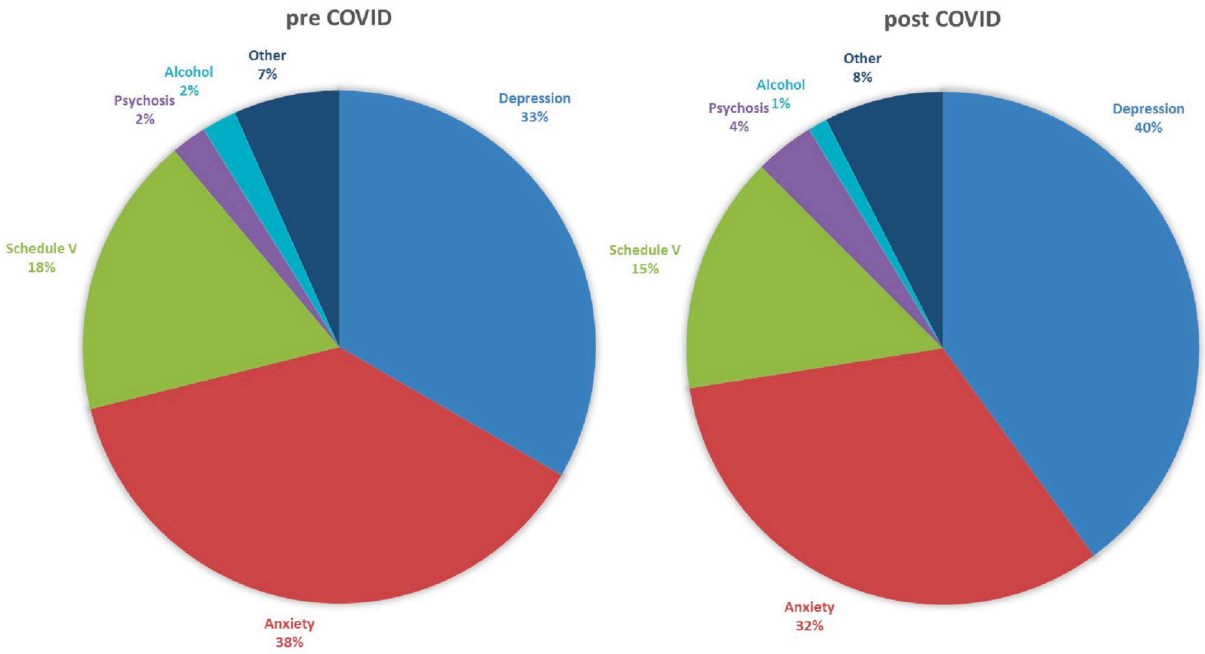

Figure 7 *Presenting complaints cited on referral*

figure 6. The available sample size did not allow these observations to reach statistical significance at 95% confidence interval. It would have been significant with the initial sample size.

Pathologies

The relative proportions of presenting complaints cited on referrals to Mtarfa MHC during the study period are represented in Figure 7.

The most frequent presentation before the onset of COVID-19 was anxiety accounting for 38% of presentations. This dropped to 32% after the onset of COVID-19. The proportion of depression has increased from 33% to 40% after the onset of COVID-19. Similarly, psychosis has doubled from 2 to 4%. Alcohol misuse has dropped by half. This may have been the result of social distancing measures. Available sample size did not allow these observations to reach statistical significance at 95% confidence interval. It would not have been significant even with the initial sample size.

DISCUSSION

This audit comprises three phases – a one year period leading up to the onset of the COVID-19 pandemic, the first wave of the COVID-19 pandemic in Malta and the six months thereafter. Following closure of the Psychiatric Outpatients Department (POP) at Mater Dei Hospital, patients were redistributed to community mental health clinics. This simultaneously achieved better social distancing, limiting the potential for COVID-19 transmission and allowed better provision of services to patients in their community. The combined effects of the POP closing down and probable increased demand for psychiatric community services secondary to the psychological impact of the COVID-19 pandemic has resulted in a median fivefold increase in demand at Mtarfa MHC. This has been met with an increase in clinic frequency and staff allocation, that increased the monthly number of new case appointments from 7 to 20 cases.

Disruption of services secondary to clinic closure and pandemic-mandated isolation measures contributed to a backlog of new cases during the first wave, with attendant increase in wait time, to a maximum median wait of 27 weeks. Telepsychiatry services rapidly increased their workload to address this, seeing 16 new cases in the month of June. A threefold increase in new case appointments has increased the burden of the clinic that was met through a fivefold increase in clinic frequency. Waiting time has decreased from a mean of 21.6 weeks before the onset of COVID-19 to 7.4 weeks in the last five months of 2020. In effect this constitutes a 66% drop in waiting time despite a threefold increase in workload. The increased referral of retirement age patients to Mtarfa MHC may reflect health anxiety and adverse impact of isolation in this age group. This age group is likely to pose greater resistance in adapting to telepsychiatry.

Referrals in other ages remained relatively stable during this period. The expected rise in mental health burden in the younger age groups may not have been observed due to a lag in effect or because of the change in demographics that may have accompanied the above closures.[7-9]

General Practitioners are the primary source of referrals made to Mtarfa MHC, and the majority of cases seen are Maltese nationals. The proportion

referred by private psychiatrists has decreased substantially following the first wave. This may be due to changes in clinical practice following the onset of COVID-19 or changes in the altered referral base. Analysis of presenting complaint revealed a relative increase in depression and a drop in anxiety. The latter deficit may be obscured by the imposed proportional analysis and/or the changing case mix after the onset of COVID-19.[10]

CONCLUSION

The COVID-19 pandemic posed significant challenges to community mental health services at the Mtarfa MHC. Major service restructuring through decentralisation, such as the termination of psychiatric out-patient services at Mater Dei Hospital and respective shift into community MHCs increased the demand at this mental health clinic. These challenges were met through staff redeployment and increasing clinic frequency fivefold, from weekly to daily. The service increase successfully met a threefold increase in new case appointments at the clinic and decreased waiting time by two thirds.

This study focuses on the early stages of the COVID-19 pandemic, and it is likely that mental health burden will continue to increase with time. Further studies would be well-placed to assess longer-term effects. Separating the effects of decentralisation from increased demand secondary to the COVID-19 pandemic would merit separate study. This study would need to evaluate the previous central versus peripheral workloads, the redistribution of the central workload to community mental health centres and adherence to agreed catchment areas.

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ORIGINAL ARTICLE

Retrospective Review of the Diagnostic Pathway of Suspected Prostate Cancer in Mater Dei Hospital

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Background

A well-established prostate cancer diagnostic pathway is used in Europe[1] to increase early diagnosis of clinically significant prostate cancers. This retrospective review was aimed to assess the efficiency and accuracy of this pathway within the department of urology at Mater Dei Hospital.

Method

Data collected included demographic data, digital rectal examination (DRE) findings prior to magnetic resonance imaging (MRI) and prostate specific antigen (PSA) values preceding MRI. PSA doubling time and PSA velocity were calculated. The cohort was divided into three groups according to the MRI result - negative, positive or equivocal for prostate cancer. Prostate gland volume, Prostate Imaging-Reporting and Data System (PI-RADS) score, TNM stage and histology results were documented and compared.

Results

41% of the cohort had a DRE suggestive of cancer. The cohort had a mean PSA value of 4.912 ng/ml, mean PSA density of 0.152 ng/ml, mean PSA velocity of 0.306 ng/ml/year and mean PSA doubling time of 64 months. The mode PIRADS count was 2. Most cancers were staged at T3a . The mean prostate size was 61.46 cubic centi-metres. 93.4% of patients with an MRI of the prostate suggestive of cancer had a prostate biopsy. 79.5% provided samples suggestive of cancer. The most common grade of cancer was Gleason 7 disease.

Conclusion

Allowing for limitations of a retrospective review and a small cohort, this study has shown that using the European pathway for diagnosis of prostate cancer increases diagnosis of significant prostate cancer.

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INTRODUCTION

A well-established prostate cancer diagnostic pathway is used in Europe[1] to increase early diagnosis of clinically significant prostate cancers. This retrospective review was aimed to assess the efficiency and accuracy of this pathway within the department of urology at Mater Dei Hospital.

MATERIALS AND METHODS

A cohort of patients was selected for a retrospective review of the diagnostic pathway for prostate cancer. All individuals who underwent a multi-parameteric magnetic resonance imaging (MRI) of the prostate in 2019 were included. Patients who were on active surveillance or were previously assessed for prostate cancer were excluded. MRIs performed for reasons other than prostate cancer diagnosis were also excluded.

Demographic data pertaining to date of birth and age was collected from digital records. Clinical findings acquired from a digital rectal examination prior to MRI were noted. Prostate Specific Antigen (PSA) values preceding the MRI were collected and used to calculate PSA Doubling Time and PSA velocity.

Every MRI was interpreted by a single experienced urology radiologist. The cohort was divided into three groups according to the MRI results - negative, positive or equivocal for prostate cancer. The prostate gland volume, the Prostate Imaging-Reporting and Data System (PI-RADS) score and the TNM stage were collected.

The definitive diagnosis is based on histopathological assessment of tissue samples obtained using traditional trans-rectal systematic ultrasound guided prostate biopsy or MRI trans-rectal ultrasound guided fusion prostate biopsy.[1]A significant prostate cancer was defined as a cancer with a minimum Gleason score of six and a tumour volume of at least 0.5 cubic centi-metres.[4]

Electronic case summaries of patients who required a prostate biopsy were analysed and any biopsy related complications were noted. The complications were graded according to the Clavien-Dindo Classification system (Clavien et al, 2009).

Statistical analysis was performed using Chi-squared test for categorical variables. Independent sample t-test and one-way ANOVA analysis for continuous variables. Results were considered significant if $p < 0.05$. IBM SPSS Statistics (Version 26) was used for data analysis. Clearance was obtained from the data protection office.

Table 1 *Reasons for Exclusion*

Reason for Exclusion	Total
On active surveillance	38
Previously investigated	352
MRI for non-cancer disease	63
Others	8

RESULTS

The cohort was made up of 1180 patients. 720 patients were included. 460 patients were excluded. The most common reason for exclusion was previous investigation for prostate cancer (Table 1). The mean age of the cohort was 68 years old.

PSA values at referral ranged from 0.47 ng/ml to 19.54 ng/ml with a mean of 4.912 ng/ml. Figure 1 illustrates the most common PSA values. 41% of the cohort had a digital rectal examination suggestive of cancer, 34% of the cohort had no documented digital rectal exam and the rest had a normal digital rectal examination.

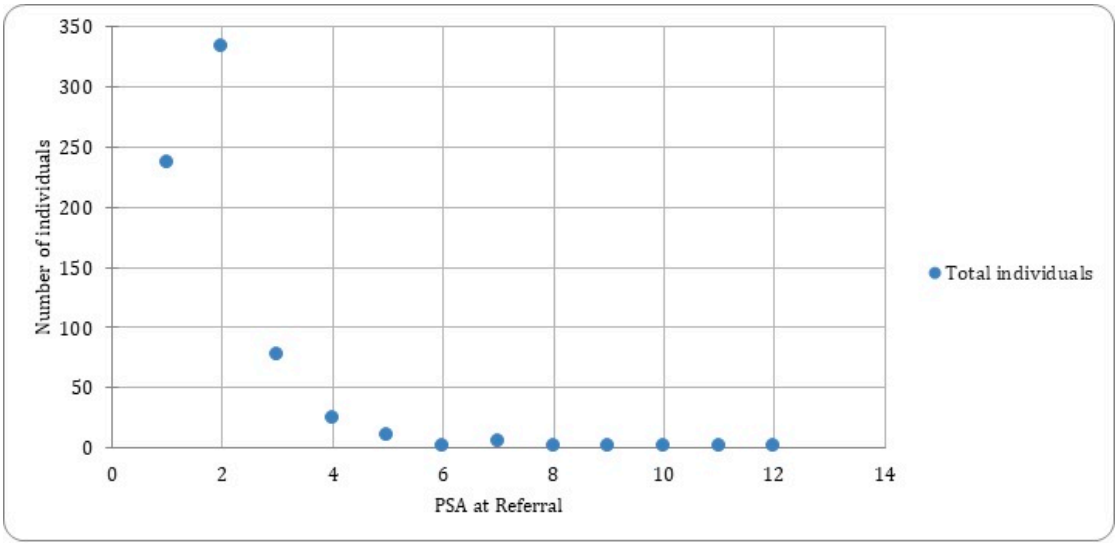

Figure 1 *PSA value at referral*

The mean PSA density for the whole cohort was 0.152 ng/ml, mean PSA velocity was of 0.306 ng/ml/year with a mean PSA doubling time of 64 months. In the prostate cancer group PSA density was 0.23ng/ml and a mean PSA velocity of 1.91 ng/ml/year. In the non-prostate cancer group the mean PSA density is 0.11ng/ml and a mean PSA velocity of 0.36 ng/ml/year.

From the 720 MRI prostate reviewed, 261 suggested prostate cancer, 336 were not suggestive of prostate cancer and 126 were equivocal. The mode PIRADS count was 2. Most cancers were staged as T3a according to the TNM staging system.[1] The mean prostate size was calculated to be 61.46 cubic centi-metres, ranging from 13 to 369 cubic centi-metres.

From the cohort selected 244 individuals (33.8%) were further investigated using a prostate biopsy. This means 93.4% of patients with a MR of the prostate suggestive of cancer. Most common biopsy performed was targeted trans-rectal ultrasound guided systematic biopsy. Prostate cancer was diagnosed in 194 out 244 men undergoing prostate biopsy (79.5%). The most common grade of cancer was Gleason 7 disease (Figure 2).

Eleven patients out of 244 men suffered a complication related to their biopsy, post biopsy sepsis in 10 patients and haematuria in one patient. According to the Clavien-Dindo classification, 7 out of 11 patients were noted to have a grade 2 complication whilst the rest were not documented.

A statistically significant correlation was made between increasing age and the incidence of significant prostate cancer ($p<0.001$). Similarly, patients with a higher PSA value at referral were more likely to have a significant cancer ($p<0.001$. MRI derived PIRADS score was also correlated to histological results, with a higher PIRADS score represented a higher risk for a significant cancer ($p<0.001$).

DISCUSSION

Prostate cancer is the second most common cancer in males.[9] An accurate universal diagnostic pathway is essential to reduce the morbidity and mortality related to prostate cancer. Screening has been a crucial tool in the latter for most cancers but screening for prostate cancer is a controversial topic. Studies have shown that screening increases diagnosis of less advanced disease but does not increase the overall prostate cancer specific survival benefit.[8]

This retrospective study included individuals who were referred urgently for investigation of an elevated prostate specific antigen result. The cohort was investigated according to guidelines published by the European Association of Urology.[1] The aim was to diagnose significant prostatic cancer[4] and eliminate insignificant prostate cancer according to Epstein's criteria. This is essential to prevent over treatment.

In this study, it was noted that higher PSA velocity and PSA doubling time values were associated with significant prostate cancer. However, these values do have a prognostic value[10-11] following treatment of prostate cancer. As serum PSA is influenced by many factors, there is no universal value that is diagnostic of prostate cancer. Nonetheless, the higher the value, the greater the likelihood of prostate cancer.[1] The latter consolidates the importance of monitoring the PSA velocity and PSA doubling time of patients.

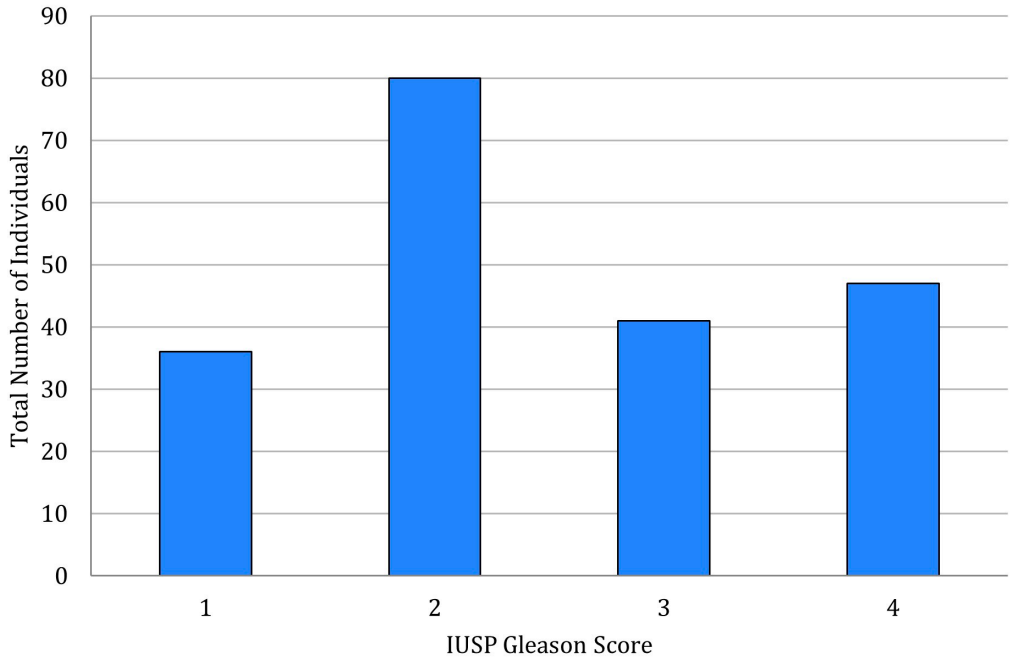

Figure 2 *IUSP Gleason score on first biopsy*

Multiparametric MRI is central to the diagnosis of prostatic cancer with a sensitivity and specificity of 95% according to a Cochrane meta-analysis.[11] This imaging modality has increased the amount of significant prostate cancers diagnosed. In this cohort, most patients were found to be in stage T3a according to the TNM staging system on MRI. The locally advanced stage may reflect delays in referral and investigation of suspected prostate cancer in the local scenario. Despite the great benefit of using MRI, it is inaccessible to patients with MRI incompatible devices. Also, MRI is relatively contra-indicated in patients who are claustrophobic, have a high body mass index or suffer from kidney disease if Gadolinium contrast is required.[12]

Most patients in the cohort who were referred for biopsy underwent a targeted prostate biopsy. The local urology department has strived to shift towards this sampling method as it has been shown to be more accurate and less invasive compared to other methods.[7]

CONCLUSION

Allowing for limitations of a retrospective review and a small cohort, this study has shown that using the European pathway for diagnosis of prostate cancer increases diagnosis of significant prostate cancer.

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ORIGINAL ARTICLE

Knowledge, Attitude, Practice and Awareness on Hypertension among Students and Staffs in Faculty Of Medicine and Health Sciences (Fmhs), Universiti Putra Malaysia

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Introduction

The number of patients diagnosed with hypertension among the population is rising rapidly. Its inherent risk of mortality is a grave cause of concern. Therefore, this study aims to determine the level of knowledge, attitude, practices and awareness on hypertension and associated factors among students and staff in the FMHS, Universiti Putra Malaysia.

Methods

A cross sectional study was done at the FMHS, Universiti Putra Malaysia for 17 weeks duration in 2020. Through stratified random sampling, students and staff selected from the faculty answered a questionnaire distributed in Google Documents form via Whatsapp. The data was analyzed using the SPSS v25.

Results

340 students and 87 staff participated in our study. Overall, majority of the students and staffs demonstrated a good level of knowledge, attitude, practice and awareness of hypertension. In multivariate analysis, ethnicity shows a significant association with awareness among students. There was significant association between age with the level of practice of hypertension among staff, and between the field of staff with the level of practice and awareness of hypertension among the staff in multivariate analysis.

Conclusion

Majority of the students and staffs demonstrated a good level of knowledge, attitude, practices and awareness among both staffs and students. This augurs well for this current and future health professionals in their battle in reducing the prevalence of hypertension.

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INTRODUCTION

The World Health Organization (2019) stated that hypertension can be defined as a systolic blood pressure reading ≥140 mmHg and a diastolic blood pressure reading ≥90 mmHg on each occasion when blood pressure measurementswas taken on two or more separate occasions. There are two types of hypertension, which are essential hypertension and secondary hypertension. High blood pressure wheresecondary causes such as renal failure, renovascular disease, hyperaldosteronism, pheochromocytoma or other causes of secondary hypertension or Mendelian forms (monogenic) are absent are known as essential or primary hypertension. Secondary hypertension is high blood pressure due to another condition or disease such as chronic kidney disease, obstructive sleep apnea, primary hyperaldosteronism, pheochromocytoma, Cushing syndrome, acromegaly, and drug related causes such as birth control pills consumption.

According to the World Health Organization (2019), unhealthy diets like a diet rich in saturated fat and trans fats, excessive intake of salt, tobacco and alcohol consumption, lack of physical activity, and an overweight or obese condition are some of the modifiable risk factors for hypertension. Non-modifiable risk factorsmeanwhile, may comprise of a family history of hypertension, presence of existing diseases such as diabetes, ethnicity and an age of 65 years or above.

Knowledge can be defined as the comprehension of a community on any topic that is being studied among them, which in the case of this research, is hypertension.[1] Attitude can be defined as the community's outlook on the topic being studied together with any predetermined notions about it.[1]Practice, on the other hand, is the method by which the community shows their knowledge and attitude by their activities.[1] Awareness can be defined as the community's understanding of a topic or subject in the contemporary period founded on facts or experience.[2]

In this day and age, the number of patients diagnosed with hypertension is rising rapidly. The World Health Organization (WHO) has stated that Malaysia had the highest rate of obesity and overweight cases among the nations in Asia with both 64 percent and 65 percent of the male and female population, respectively being obese or overweight cases. The National Health and Morbidity Survey of 2015 by the Ministry of Health Malaysia showed that the participants aged 18 years and above in that survey had an overall prevalence of hypertension (known and undiagnosed) of 30.3% (95% CI: 29.3, 31.2). An overall rising trend in prevalence with age was observed, from 6.7% (95% CI: 4.7, 9.4) in the age group of 18-19 years, to achieving a peak of 75.4% (95% CI: 70.5, 79.7) for participants in the 70-74 years age group. The low knowledge level on the clinical practice guidelines among the people will further aggravate these phenomena, particularly since hypertension can be asymptomatic. Despite the advancements of modern technology for the diagnosis and treatment of hypertension, the rate of detection of hypertension remained poor. For every one patient who was diagnosed with hypertension, two were not diagnosed with it. Similarly, for every three hypertension patients undergoing treatment, only one patient was successfully treated for hypertension and its coherent risk of cardiovascular events[3]

In addition, there was a lack of research conducted into the degree of knowledge, awareness, attitude and practice on hypertension among medical students and staff, who make up the current and future health personnel. As the prevalence of the disease increases, it is crucial to assess the degree of knowledge of future and current health personnel who will be disseminating information to the patients and providing care for them as well. The objective of the research was to determine the level knowledge, attitude, practices and awareness on hypertension among students and staff in the Faculty of Medicine and Health Sciences (FMHS), Universiti Putra Malaysia. This research also aimed to determine the factors associated with the level of knowledge, attitude, practice and awareness on hypertension among students and staff of FMHS, Universiti Putra Malaysia. It wastherefore crucial to assess the level of knowledge, attitude, practice and awareness on hypertension among students and staff of FMHS, Universiti Putra Malaysia to determine their degree of readiness to handle the rising number of hypertension cases in the country as well as to provide quality care to the hypertension patients.

MATERIALS AND METHODS

A cross sectional study was carried out at the FMHS, Universiti Putra Malaysia for a 17 week's duration. The total number of staff and students of FMHS, Universiti Putra Malaysia was 2585 consisting of 537 staffs and 2321 students, respectively. Based on this numbers, it was concluded that the total number of staff was almost a quarter from the students; therefore, from the sample size, total respondent was ¼ from staff and ¾ from students. The estimated sample size was calculated using the formula for sample size estimation in cross sectional study to compare proportion between two groups, giving a required sample size of 426 respondents to cover for both students and staffs considering a 10% non-respondent rate.

Through stratified random sampling, the name list of medical students from the first to fifth year, students from other courses from the first to fourth Year and staffs working at the FMHS, Universiti Putra Malaysia was prepared. The questionnaire was distributed in

Google Documents form via WhatsAppfor the respondents to answer. The questionnaire consisted of a consent form, followed by Section A where it provided information on socio-demographic characteristics of the respondents. Section B was divided into four parts consisting of knowledge, attitude, practice and awareness respectively. Each part consisted of eight questions and the total marks of each part was calculated for every respondent. The questionnaire was obtained from a previously similar study that was conducted by a group of researchers consisting of lecturers from the Faculty of Medicine and Defense Health, National Defense University of Malaysia and Kuliyyah of Allied Health Sciences, International Islamic University Malaysia.[5] Approval to use the questionnaire was obtained through email to. Face and content validation was done for the questionnaire. Face validation was done with 10% of the intended study population. Content validation was done with an expert panel of 5 experts including 2 family physicians, 1 internal medicine specialist, 1 public health specialist and 1 statistician.

Table 1 *Socio-demographic distribution of students' respondents in Faculty of Medicine and Health Sciences, Universiti Putra Malaysia*

Variables	Frequency (%)
Age	
19	1(0.3)
20	131(38.5)
21	126(37.1)
22	38(11.1)
23	22(6.5)
24	18(5.3)
25	2(0.6)
30	1(0.3)
34	1(0.3)
Gender	
Male	96(28.3)
Female	244(71.7)
Ethnicity	
Malay	227(66.8)
Chinese	45(13.2)
Indian	58(17.1)
Others	10(2.9)
Year of study	
Year 1	129(37.9)
Year 2	139(40.9)
Year 3	34(10)
Year 4	24(7.1)
Year 5	14(4.1)

Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 25 software. First, normality was checked by using Kolmogorov-Smirnov method. Next, descriptive analysis was used to obtain the frequency and percentage of the obtained data followed by multiple logistic regression test that was used to determine any association between the independent and dependent variables which werethe domains of knowledge, attitude, practice and awareness on hypertension among students and staffs in FMHS, Universiti Putra Malaysia. The level of significance was set at $p < 0.05$.If these domains were normally distributed, those participants scoring ≥ the mean scores of these domains were classified as having a good score and those otherwise as poor scores. If these domains were not normally distributed, those participants scoring ≥ the median scores of these domains were classified as having a good score and those otherwise as poor scores.

Approval from JKEUPM (Ethic Committee for Research Involving Human Subject) Universiti Putra Malaysia had been obtained prior to proceeding with the research. Data and information from respondents were kept confidential. All the respondents were instructed to fill in the consent form so that they are aware of their participation in research.

RESULTS

A total of 427 respondents answered the questionnaire that consisted of 340 (79.6%) students and 87(20.4%) staff. Table 1 shows the distribution of the student respondents by their socio-demographic characteristics and year of study. The majority of the respondents were between the ages of 20-21 (75.6 %), were female (71.7 %), were of Malay ethnicity (66.8 %), and were 1st year or 2nd year students (78.8 %). Table 2 shows the distribution of the staff respondents by their socio-demographic characteristics of staff. The majority of the respondents were of the ages 36 and 43 (18.4 %), were female (70.1 %) were of Malay ethnicity (83.9 %), had tertiary education (98.9 %) and were academic staffs (71.3%).

The score obtained by respondents for each section which is knowledge, attitude, practice and awareness were categorized into good or poor based on median score respectively. Table 3 shows total of good scores obtained for each of the dependent variable for both the students and the staff. As for knowledge, median score was 7 for both students and staff. There were more students 274(80.6%) and staff 72(82.8%) with good scores. In terms of attitude score, the median score was 7 and majority of respondents obtained a good score on attitude questions where 183(53.8%) students and 55(63.2%) staff obtaineda good score.

Table 2 *Socio-demographic distribution of staff respondents in Faculty of Medicine and Health Sciences, Universiti Putra Malaysia*

Variables	Frequency (%)
Gender	
Male	26(29.9)
Female	61(70.1)
Ethnicity	
Malay	73(83.9)
Chinese	7(8.0)
Indian	6(6.9)
Others	1(1.1)
Educational level	
Secondary and below	1(1.1)
Tertiary	86(98.9)
Field of staff	
Academic Staff	62(71.3)
Non-academic staff	25(28.7)

#The median age (interquartile range, IQR) was 40.0(10.0) years.

Similarly, most of respondents had a good score for both the practice and awareness sections. Median score for practice and awareness was 11 and 6, respectively. As for practice, 206(60.6%) of students and 67(77.0%) staff obtained good score while 202(59.4%) of students and 68(78.2%) of staff got a good score on awareness. There was no significant difference in the domain scores of knowledge, attitude, practice and awareness between this two categories of staff and students (p>0.05).

There was no significant association between socio-demographic factors (age, gender, ethnicity, year of study for student, educational level and field of staff for staff) with knowledge for both students and staff in both univariate and multivariate analysis. Likewise, there was no significant association between socio-demographic factors (age, gender, ethnicity, year of study for student, educational level and field of staff for staff) with attitude for both students and staffs both univariate and multivariate analysis.

Nevertheless, Table 4 that shows the practice level of hypertension among staff noted that there was a significant association between age and level of practice on hypertension for staff (p-value = 0.002). In the multivariate analysis, it was found that older staffs had a 10.426 higher odd of having poor level of practice as compared to younger staffs (p-value = 0.001). In terms of field of staff, non-academic staffs hada 0.237 lower odd of having poorer practice as compared to academic staffs (p-value = 0.046).

In terms of awareness, Table 5 and 6 showed the association between socio-demographic factors with awareness on hypertension among students and staff, respectively. It was found that there was no association between socio-demographic factors (age, gender, ethnicity and year of study) and the level of awareness among students. In the multivariate analysis in which variables that had a p value of less than 0.25 were entered into the multiple logistic regression model, Chinese students had a 0.454 lower odd of having poor awareness level as compared to Malays (p=0.028). Meanwhile, among staff, there was an association between field of staff and level of awareness (p-value = 0.012) in univariate analysis. Following multivariate analysis, in terms of field of work, it was found that non-academic staffs hada 3.666 higher odd of having poorer level of awareness as compared to academic staffs (p-value = 0.019).

DISCUSSION

The majority of students (78.8%) who participated were from preclinical years (Year 1 and Year 2). There were a smaller number of clinical year students (Year 3 to Year 5) participated as they were having an examination during data collection period. Meanwhile, there was a huge different in educational level among the staffs. Among the participants, there was only one staff with secondary and below

Table 3 *Distribution of good and poor score on knowledge, attitude, practice and awareness*

Dependent Variables	Median (IQR)	Category	Students (%)	Staff (%)	p-value
Knowledge	7(1)	good	274(80.6)	72(82.8)	0.239
Attitude	7(1)	good	183(53.8)	55(63.2)	0.334
Practice	11(2)	good	206(60.6)	67(77.0)	0.789
Awareness	6(2)	good	202(59.4)	68(78.2)	0.277

Table 4 *Association between socio-demographic factors with level of practice among staff*

Variables	Practice level		Univariate Analysis			Multivariate Analysis		
	Poor (n=20) (%)	Good (n=67) (%)	Odds Ratio	Confidence Interval	p-value	Odds Ratio	Confidence Interval	p-value
Age Median (IQR)	36 (6%)	43 (11%)	0.84	2.24 - 31.45	0.002	10.43	2.68 - 40.60	0.001
Gender								
Male	7 (27%)	19 (73%)	1.00 (reference)					
Female	13 (21%)	48 (79%)	0.74	0.25 - 2.13	0.57			
Ethnicity								
Malay	17 (28%)	56 (77%)	1.00 (reference)					
Chinese	2 (22%)	5 (78%)	1.14	0.23 - 7.41	0.75			
Indian	0 (0%)	6 (100%)	0.00	0.00 - 0.00	1.00			
Others	1 (100%)	0 (0%)	>0.05	0.00 - 0.00	1.00			
Educational level								
Secondary & below	0 (0%)	1 (100%)	0.00	0.00 - 0.00	1.00			
Tertiary	20 (23%)	66 (77%)	1.00 (reference)					
Field of staff								
Academic staff	17 (27%)	45 (73%)	1.00 (reference)			1.00(reference)		
Non-academic	3 (12%)	22 (88%)	0.36	0.10 - 1.36	0.13	0.24	0.058 - 0.98	0.046

#As the practice domain was not normally distributed, those participants scoring ≥ the median score of this domain were classified as having a good score and those otherwise as poor scores.

Table 5 *Association between socio-demographic factors with level of awareness among students*

Variables	Awareness level		Univariate Analysis			Multivariate Analysis		
	Poor (n=138) (%)	Good (n=202) (%)	Odds Ratio	Confidence Interval	p-value	Odds Ratio	Confidence Interval	p-value
Age Median (IQR)	21 (1%)	21 (2%)	0.82	0.68 - 0.98	0.32			
Gender								
Male	38 (40%)	58 (60%)	1.00 (reference)					
Female	100 (41%)	144 (59%)	1.06	0.66 - 1.72	0.81			
Ethnicity								
Malay	103 (45%)	24 (55%)	1.00 (reference)			1.00 (reference)		
Chinese	13 (29%)	32 (72%)	0.49	0.24 - 0.98	0.044	0.45	0.22 - 0.92	0.028
Indian	19 (33%)	39 (67%)	0.59	0.32 - 1.08	0.09	0.57	0.31 - 1.07	0.08
Others	3 (30%)	7 (70%)	0.52	0.13 - 2.05	0.35	0.51	0.16 - 2.05	0.34
Year of study								
Year 1	54 (42%)	75 (58%)	2.64	0.70 - 9.92	0.15	3.15	0.83 - 11.97	0.09
Year 2	64 (46%)	75 (54%)	3.13	0.84 - 11.71	0.09	3.59	0.95 - 13.55	0.06
Year 3	14 (41%)	20 (59%)	2.58	0.60 - 10.92	0.20	2.74	0.64 - 11.77	0.17
Year 4	3 (13%)	21 (88%)	0.52	0.09 - 3.04	0.47	0.60	0.10 - 3.52	0.57
Year 5	3 (21%)	11 (79%)	1.00 (reference)			1.00 (reference)		

#As the awareness domain was not normally distributed, those participants scoring ≥ the median scores of this domain were classified as having a good score and those otherwise as poor scores.

Table 6 *Association between socio-demographic factors with level of practice among staff*

Variables	Practice level		Univariate Analysis			Multivariate Analysis		
	Poor (n=19) (%)	Good (n=68) (%)	Odds Ratio	Confidence Interval	p-value	Odds Ratio	Confidence Interval	p-value
Age Median (IQR)	39 (15%)	42 (10%)	2.59	0.88 - 7.61	0.08	2.34	0.77 - 7.16	0.13
Gender								
Male	6 (23%)	20 (77%)	1.00 (reference)					
Female	13 (21%)	48 (79%)	0.90	0.30 - 2.71	0.86			
Ethnicity								
Malay	18 (25%)	55 (75%)	1.00 (reference)					
Chinese	0 (0%)	7 (100%)	0.00	0.00 - 0.00	1.00			
Indian	1 (17%)	5 (83%)	0.61	0.07 - 5.58	0.66			
Others	0 (0%)	1 (100%)	0.00	0.00 - 0.00	1.00			
Educational level								
Secondary & below	1 (100%)	0 (0%)	>0.05	0.00 - 0.00	1.00			
Tertiary	18 (21%)	68 (79%)	1.00 (reference)					
Field of staff								
Academic staff	9 (15%)	53 (86%)	1.00 (reference)			1.00(reference)		
Non-academic	10 (40%)	15 (60%)	3.93	1.35 - 11.42	*0.012*	3.66	1.24 - 10.85	0.019

#As the awareness domain was not normally distributed, those participants scoring ≥ the median score of this domain were classified as having a good score and those otherwise as poor scores.

educational level while the rest had tertiary educational level. It is understandable as staffs working in university must have higher educational qualification.

Association between sociodemographic factors with knowledge, attitude, practice and awareness on hypertension.

Firstly, age had no association with level of knowledge, attitude, practice and awareness among students but there was a significant association between age and the level of practice of hypertension for staff. In contrast, a study stated that age was associated with the level of knowledge about hypertension. It shows that participants between 36 to 45 years old had 3.6 times better knowledge as compared to those from 76 to 85 years old.[4] In the same study, it shows that age was not associated with the level of attitude of participants which similar as findings in this research.[4] Another study observed that there was a strong association between age and the level of knowledge, attitude and practice regarding hypertension.[5] It stated that an increase in age will also increase the level of knowledge, attitude, practice and awareness about hypertension, thereby disagreeing with our study as many and frequent exposures to continuous medical education on hypertension over the years would have led to a better practice among the staffs regarding hypertension. However, for our study the results were contrary as possibly some of the respondents were not involved in clinical work i.e., working as basic medical sciences lecturer, and therefore contributing to a poorer practice level.

Moreover, gender showed no significant association with knowledge, attitude, practice and awareness for both students and staff. However, a study stated that there was an association between gender and the level of knowledge, attitude, practice and awareness of hypertension.[6] Another study done in public universities also found that there was an association between the level of knowledge, attitude, practice and awareness with gender.[7] Both studies stated that females had better attitude and practice than males. However, our study finding is contradictory with the previous study. Possibly this means that students and staffs of both gender in these faculty are well versed in hypertension related knowledge and skills due to emphasis during undergraduate study and frequent continuous medical education on this disorder.

As for ethnicity, there was no association between ethnicity and the level of knowledge, attitude, and practice of hypertension. However, it was noted that there was a significant association between being a Chinese and the level of awareness among students. In terms of staffs, it was observed that there was no association between the ethnicity and the level of knowledge, attitude, practice and awareness of hypertension. A study reported that there was an

association between ethnicity and the level of knowledge, attitude, practice and awareness. Based on that study, it was found that being Chinese and Other ethnicity have better practices than those who are Malays(8). In other studies, it was shown that Malays had a better knowledge on cardiovascular diseases as compared to other ethnicities.[9] However, our findings did not meet the similarities with the past study probably because students and staff of all ethnicities in our faculty were equally exposed on hypertension related knowledge.

In addition, there was no significant association between year of study with knowledge, attitude, practice and awareness on hypertension. There was a study done among students in local university regarding knowledge, attitude and practise on risk factor of cardiovascular disease concluded with same findings as well[7]

There was no association between educational level and knowledge, attitude, practise and awareness among staff. A study in largest state in Malaysia, Selangor reported no significant association between educational level and KAP on hypertension(5). However, in Iran, a study stated that there was a significant association between educational level with knowledge but no association with attitude and practice.[10] The result was different from our study, with possible reasons of uneven distribution between those with secondary and below educational level and those with a tertiary educational level.

There was a significant association between field of staff with practice and awareness but no association with knowledge and attitude. A study in Isfahan State Institution, Irna stated that there was a significant association between institutional positions which are teacher, student and staff with the level of awareness. The result found out that prevalence of hypertension was higher among staff as compared to teachers and students.[11]However, a study in Ethiopia reported that there was a significant association between occupation and level of knowledge on hypertension.[12] Possibly our finding agrees with the known fact that academics working in a medical based faculty are well versed with hypertension related knowledge and skills, and therefore shows a significant association with practice and awareness on hypertension.

Our study had a few limitations. Our study only focused on the students and staff at the FMHS, so the validity and reliability of our study was only limited to the students and staff at the faculty. Secondly, our study was a cross-sectional study, which has disadvantages of unable to determine a causal and temporal relationship. Furthermore, there was also a non-respondent bias as some students and staff did not participate in our study due to personal reasons.

CONCLUSION

Overall majority of the students and staffs demonstrated a good level of knowledge, attitude, practices and awareness among both staffs and students. In our study done on 427 students and staff in the FMHS, Universiti Putra Malaysia, there was no significant association between age, gender, ethnicity and year of study with the level of knowledge, attitude, practice and awareness of hypertension among the students. As for the staff, there was no significant association between the socio-demographic factors of age, gender, ethnicity and level of education with the level of knowledge, attitude and awareness of hypertension among the staff. However, it was found that there was a significant association between age and the level of practice of hypertension among the staff, showing a p-value of less than 0.05. Meanwhile, the field of staff was significantly associated with practice and awareness but not associated with knowledge and attitude.

Based on the research we conducted, we would like to suggest to other researchers to extend their research to students and staff in other faculties of Universiti Putra Malaysia. The research could also be extended to the medicine and health sciences faculties in other universities as well.

In addition, information regarding hypertension, its negative effects and how to overcome it should be widely disseminated among the students and staff. The faculty can organize interesting activities such as campaigns, put up posters and have exhibition to educate and persuade this category of the population to join in the battle against this great silent killer.

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ORIGINAL ARTICLE

Evaluation of HbA1c using High Performance Liquid Chromatography and Capillary Electrophoresis in Type 2 Diabetes Mellitus patients suspected to have haemoglobin variant

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Background

High-Performance Liquid Chromatography (HPLC) is widely used for HbA1c measurement. However, it is prone to haemoglobin (Hb) variant interference. Capillary electrophoresis (CE) is believed to have better performance in patients with Hb variant. This study aimed to compare HbA1c level between HPLC and CE among Type 2 Diabetes Mellitus (T2DM) patients suspected to have Hb variant, determine the type of Hb variant among those patients, and evaluate the agreement between both methods.

Methods

A cross-sectional study conducted at Endocrine Laboratory, Hospital Universiti Sains Malaysia, from June till December 2020. HbA1c results of adults T2DM from HPLC with suspected Hb variant were re-analysed using CE. The comparisons of HbA1c were made using paired t-test and Wilcoxon Signed Rank Test. The correlation and method comparison were made using Pearson correlation, Bland Altman (BA) and Passing-Bablok (PB), whereas the agreement using Intraclass Coefficients Correlation (ICC).

Results

250 patients were included with a median (IQR) age of 52.19 (11.11) years. For reportable results (?3.8% to ?18.5%), both methods showed no difference (p=0.382) whereas the results were difference for HbA1c >18.5% (p=0.048). 26 patients had Hb analysis with majority having Hb E trait 14 (5.6%). HPLC overestimated HbA1c in patients with Hb J and alpha Hb variant while CE able to report. Pearson correlation and PB regression analysis showed good correlation (r=0.987, p<0.001) and good agreement [slope of 1.0 (95% CI: 1.00 to 1.03); intercept of -0.3 (95% CI: ?0.61 to 0.30)]. BA plot revealed a mean difference of 0.30% (95% CI:0.00 to 0.50) with limits of agreement from ?0.54 to +1.14. ICC showed excellent reliability (0.983 (p<0.001).

Conclusion

HPLC and CE can be used interchangeably for HbA1c analysis across the measurement range. CE is the preferred in T2DM with certain Hb variant.

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INTRODUCTION

Haemoglobin A1c (HbA1c) is the major form of all glycated haemoglobin (Hb) species produced by the non-enzymatic addition of glucose residues to valine moieties at the N-terminal end of the β- chain of the Hb.[3]

HbA1c can be measured by various methods and all are based on the principle of Hb fraction separation and quantification. The methods include those based on charge differences (ion-exchange high-performance liquid chromatography [HPLC], electrophoresis, and isoelectric focusing), structural differences (affinity chromatography and immunoassay), or chemical analysis (photometry and spectrophotometry).[7]

HbA1c measurement is subjected to the interference by Hb variant and this is method dependent. Hb variant is abnormal forms of Hb, caused by variations in the genetics. It is defined as Hb with single amino acid substitutions in its globin molecules. It can cause modification in Hb structure and biochemical functions that leads to either insignificant alteration of physiological effects or severe disturbances.[10]

In order to overcome the limitation of HPLC, capillary electrophoresis (CE) has been developed and adapted to the analysis of HbA1c.[13]

This study aims to determine the level of HbA1c in T2DM patients suspected to have Hb variant in Hospital Universiti Sains Malaysia (USM) using ion-exchange HPLC and CE as well as to determine the type of Hb variant among those patients. This study is also to evaluate the agreement of HbA1c results between the two methods. The awareness regarding the interference by Hb variant during HbA1c analysis is crucial in ensuring optimum management of diabetic patient. Concurrent detection of Hb variant can give additional value to routine HbA1c reports and further advice can be given accordingly.

MATERIALS AND METHODS

A cross-sectional study was conducted at Endocrine Laboratory, Department of Chemical Pathology, Hospital USM from June till December 2020. This research has been granted ethical approval by the Human Research Ethics Committee USM (HREC) (USM/JEPeM/19120945).

All HbA1c samples of T2DM patients in Hospital USM sent to the laboratory, which fulfilled the eligibility criteria based on the patient's record, were selected. The inclusion criteria were all samples from patients aged above 18 till 65 years old. The exclusion criteria were samples with Hb F > 10% and urea ≥ 30 mmol/L. Urea level of at least ≥30 mmol/L contributes to carbamylated Hb (cHb) production and cHb ≥3.5% is reported to chromatographically interfere with HbA1c measurement.[14] The largest sample size was obtained with calculation for the agreement objective. After considering 20% anticipated dropout rate, the number of patients required is 250. These samples were selected using the random sampling method.

HbA1c measurement was initially analysed using a Bio-Rad D-10 analyser based on the HPLC principle (main analyser offers for service). First, HbA1c results from HPLC were screened for the presence of the Hb variant by identifying the variant, S and C windows in the chromatogram. Then, the samples with the suspected presence of Hb variant were re-analysed for HbA1c using Sebia Capillarys 2 Flex Piercing analyser based on CE principle. Finally, the results of these two analysers were compared.

Statistical Analysis

Data entry and analysis was done using Statistical Package for the Social Science (SPSS) Version 26.0. P-value of < 0.05 was taken as statistically significant. Descriptive statistics were used to summarise the socio-demographic characteristics of the patients. All the numerical data were presented as mean and standard deviation (SD) or median and interquartile range (IQR) based on their distribution, while categorical data were expressed as frequency (n) and percentage (%). The comparison of HbA1c level between HPLC and CE was analysed using paired t-test and Wilcoxon Signed Rank Test. Correlation, method comparison, and agreement of HbA1c between HPLC and CE were made for the results within the reportable range of HPLC (≥3.8% to ≤18.5%). The correlation was evaluated using Pearson correlation analysis. The method comparison was made using Bland Altman (BA) analysis to assess the bias, whereas Passing-Bablok (PB) regression analysis was done to determine the systematic error between both methods. PB regression and BA analysis were analysed using method comparison regression in R software version 4.0.3. The agreement was evaluated using two-way random effects, absolute agreement, single rater/measurement of Intraclass Coefficients Correlation (ICC).

RESULTS

250 diabetic patients suspected of having Hb variants were included in this study. The baseline characteristics of the participants are summarised in Table 1. The included patients ranged between 19 to 65 years old with the median (IQR) age of 52.19 (11.11) years. The males predominate (52%), and the

Table 1 *Baseline characteristics of the participants (n=250)*

Variables	Median (IQR)	n (%)	
Age (years)	52.19 (11.11)		
Gender			
Male		130	(52)
Female		120	(48)
Ethnicity			
Malay		231	(92.4)
Chinese		15	(6)
Indian		1	(0.4)
Other		3	1.2)

Table 2 *The availability of haemoglobin analysis and the type of haemoglobin variant of the participants (n=250)*

Haemoglobin analysis	n (%)
Not available	224 (89.6)
Available	
Hb E trait	14 (5.6)
HbE disease	7 (2.8)
Hb J	3 (1.2)
Alpha Hb variant	1 (0.4)
HB C	1 (0.4)

Table 3 *Comparison results of HbA1c between HPLC and CE (n=250)*

	Mean (SD) of HbA1c			
	n	*HPLC method*	*CE method*	p-value
Reportable	238	8.6 (2.6)	8.4 (2.6)	0.382[a]
Non-reportable				
No peak	7	-	-	-
>18.5	5	30.5 (5.3)*	7.5 (1.8)*	0.048[b]

[a] Paired Sample Test
[b] Wilcoxon Signed Rank Test, * Median (IQR)

majority are Malay (92.4%). Of all the participants, only 26 patients had done Hb analyses for a confirmatory test for the Hb variant. The majority of these patients have Hb E trait, 14 (5.6%) with Alpha Hb variant and Hb C were the least (Table 2).

Table 3 shows the comparison of HbA1c results between HPLC and CE. The reportable range for HbA1c results using HPLC in our laboratory is ≥3.8% to ≤18.5%. Therefore, any chromatogram with no HbA1c peak or outside the reportable range will not be reported. The table showed that both HPLC and CE measurements have no significant difference (p=0.382) in those reportable results, whereas for HbA1c >18.5%, a statistically significant difference (p=0.048) was observed. Thus, HPLC was observed to overestimate HbA1c while CE was able to report HbA1c results. Furthermore, both HPLC and CE gave similar results among 7 patients with no HbA1c peaks, suggesting the absence of HbA1c in those patients, leading to the unmeasurable level of HbA1c by both methods.

Table 4 shows the HbA1c results between HPLC and CE, fasting blood sugar (FBS) and the type of Hb variant for the non-reportable HbA1c. The mean (SD) of FBS for the no HbA1c peak is 10.1 (2.3) mmol/L. Those patients were found to have Hb E disease from Hb analysis. In 5 patients with HbA1c >18.5%, HPLC gave a high result of HbA1c compared to CE, which gave reportable results corresponding to respective FBS. In these patients, 3 have Hb J variant, 1 with Alpha Hb variant and 1 with no documented type of Hb variant.

PB regression with correlation coefficient and BA plot are shown in Figure 1. The Pearson correlation analysis showed a strong positive significant linear relationship between the results of these two methods (r=0.987, p<0.001). PB regression showed a good agreement between HPLC and CE method with a slope of 1.0 (95%CI: 1.00 to 1.03) and an intercept of -0.3 (95% CI: −0.61 to 0.30). The BA plot revealed a mean difference of 0.30 % −0.54 to +1.14. The ICC value of 0.983 (p<0.001) showed excellent reliability between both methods in providing an estimated HbA1c value (Table 5).

DISCUSSION

HbA1c is widely used for the diagnosis, monitoring and complication risk predictor of T2DM. It is an indirect measure of average blood glucose level over the most recent 2-3 months.[11]

Table 4 *Distribution of HbA1c (HPLC and CE), fasting blood sugar (FBS) and type of Hb variant among non-reportable HbA1c based on HPLC (n=12)*

	HbA1c (%)			
n	*HPLC method*	*CE method*	FBS (mmol/L)	Type of Hb variant
7	No peak	No peak	10.1 (2.3) [a]	HbE disease
1	30.9	8.4	10.5	Alpha Hb variant
1	30.7	7.5	9.3	Hb J
1	30.5	6.0	7.5	Hb J
1	27.6	8.1	10.2	Hb J
1	23.4	6.8	8.7	Not available

[a] mean (SD)

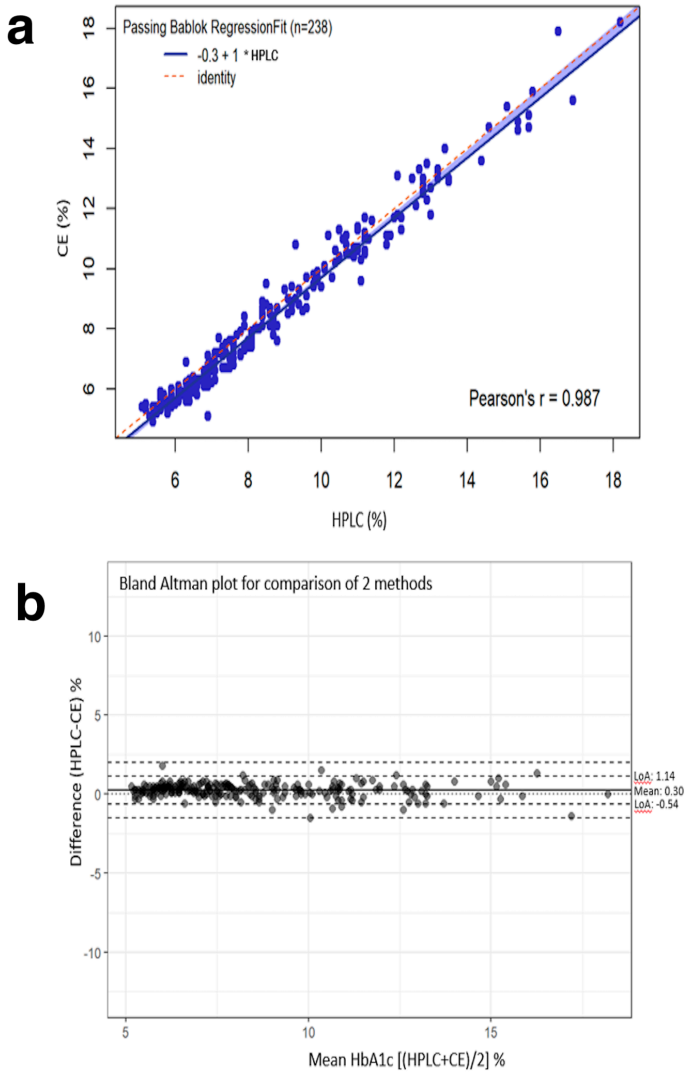

Figure 1 *Method comparison of HbA1c levels between HPLC and CE within the reportable range (n=238) (a) PB regression plot with Pearson correlation coefficient and (b) Bland–Altman plot. The Dotted line represented the 95% limit of agreement.*

The study involved 250 patients with the majority were Malays. This is because in Kelantan, majority of the people are from Malay background (91.3%).[22]

Our study demonstrated most of the patients that undergone Hb analyses are having Hb E variant (trait and disease) followed by Hb J, alpha Hb variant and Hb C. This is in keeping with the study that showed in Malaysia, Hb E is the most prevalent type of Hb variant and it is more commonly seen in Malay with carrier rate of 5% and there are 10 Malays with Hb E to one in Chinese Malaysians.[16]

The HbA1c level within the reportable range showed no significant difference when measured with HPLC and CE. However, inferior performance of HPLC compared to CE can be seen when HbA1c result exceeding linearity limit of HPLC (HbA1c >18.5%) (Table 3, 4). This is attributed to the presence of Hb variant that analytically interfere with measurement of HbA1c using HPLC. For instance, in alpha Hb variant and Hb J, HPLC give misleading result of elevated HbA1c value which significantly different with CE measurement. This is due to this type of Hb variant is carrying similar charge with HbA1c resulted in co-elution of both Hb species thus giving falsely high value of HbA1c with HPLC.[26]

Apart from causing analytical interference, presence of Hb variant may interfere with formation of HbA1c in vivo and this is method independent. Hb variant alters the composition and structure of Hb and resulted in error of measurement HbA1c level. This study found that patients with Hb E disease produced no HbA1c peak both on HPLC and CE (Table 4). It is attributed by the fact that these patients do not have or have very little amount of Hb A and therefore no HbA1c being formed, only the glycated form of the variant can be found, namely HbE1c.[29] This kind of Hb variant impedes the glycation process of Hb in vivo and analytical assay have little influence towards variation of HbA1c result.

This study demonstrated that HPLC has good correlation and agreement with CE for HbA1c values across the measurement range. Pearson correlation analysis showed that the HbA1c level of all 238 patients within the reportable range of HPLC measured by both methods gave a good linear relationship. PB regression proved that there was no significant systematic difference as demonstrated by 95% CI of slope and intercept. The results of the BA analysis showed that the HPLC method measures on average 0.30% more than the CE method with range of agreement between −0.54 to +1.14. However, this difference was not statistically significant given by CI of mean difference which contains 0 (95% CI: 0.00 to 0.50) indicating that HPLC measurement were not

Table 2 *The availability of haemoglobin analysis and the type of haemoglobin variant of the participants (n=250)*

		95% confidence interval		
	Interclass correlation[a]	Lower bound	Upper bound	p-value
HPLC-CE	0.983	0.960	0.991	<0.001

Two-way random effects, absolute agreement, single rater/measurement

[a.] Type A intraclass correlation coefficients using an absolute agreement definition, the value taken of single measure

significantly higher than CE measurements. To further support the good comparability of HPLC and CE, ICC analysis demonstrated excellent reliability of the measurements given by these two methods. This is consistent with reports from previous studies have shown that HbA1c result measured from HPLC and CE methods are comparable and there are no significant different observed.[31]

The clinical laboratory must aware of the effect of locally prevalence Hb variant when choosing the analytical assay for HbA1c measurement. Laboratories personnel must take extra caution on reporting results when the presence of a Hb variant is suspected. As with other laboratory test, any discordant result with clinical finding should be investigated further. In those patients with Hb variant that are not eligible for HbA1c measurement, non-Hb-based methods such as continuous glucose monitoring, serum fructosamine or glycated albumin can be alternative way to access long term glycemic control.

CONCLUSION

The HbA1c levels between HPLC and CE are comparable and have good agreement that can be used interchangeably for the analysis of HbA1c across the measurement range. However, CE has advantages in the presence of Hb variant. Special attention should be given during interpretation of HbA1c in the presence of Hb variant to prevent mismanagement of these patients.

SUMMARY BOX

What is already known?

- HbA1c can be measured by various methods with each method having limitations and advantages.
- HPLC is considered as gold standard for HbA1c analysis. However, it is prone to analytical interference by Hb variant.
- Laboratories personnel must take extra caution on reporting HbA1c results when the presence of a Hb variant is suspected.

New findings from this study

- HPLC and CE showed excellent agreement for the analysis of HbA1c across the measurement range.
- In patients with Hb J and alpha Hb variant, CE showed better performance in the measurement the HbA1c value compared to HPLC. CE was able to report a more accurate result which corresponding to FBS of those patients, meanwhile HPLC overestimated HbA1c value.
- For patients with Hb E disease, the absence of HbA in vivo leading to the unmeasurable level of HbA1c by both methods as indicated by absence of HbA1c peak.

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ORIGINAL ARTICLE

Prevalence and associated factors of true hypertension among primary school children in the Klang Valley: a cross - sectional study

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Introduction

Hypertension is an important risk factor for cardiovascular disease and there is an increasing risk of development of hypertension among children. Our study aims to determine the prevalence of true hypertension and its associated factors among primary school children in the Klang Valley region.

Methods

A self-administered questionnaire was used which explores the socio-demographic background, past medical history, family history & lifestyle characteristics of the participants. Diagnosis of hypertension were based on standard protocol. Data analysis was done using SPSS v26.0.

Results

This study involved 251 respondents. The prevalence of true hypertension among primary school children is 2%. Significant determinant of true hypertension were higher body mass index (BMI), children living with single parent and being of Indian ethnicity. It was found that Indians had 55 times higher odds of having true hypertension compared to Malays (95%CI =1.47-2061.87, p = 0.03). It was also found that children from households with a single parent had 85 times higher odds of having true hypertension compared to households with both parents (95%CI = 2.68-2537.53, p = 0.01). In addition, those with a higher BMI had 1.4 times higher odds of having true hypertension (95%CI = 1.06-1.43, p = 0.018).

Conclusion

The prevalence of true hypertension is similar to the rates reported globally. This provides an insight where regular BP monitoring in children should be advocated amongst healthcare professionals, especially amongst children having risk factors for the development of hypertension.

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INTRODUCTION

Hypertension is an important risk factor for cardiovascular disease. The latest National Health and Morbidity Survey (NHMS) for non-communicable disease (NCD) risk factors in 2019 showed an overall prevalence of raised blood pressure of 30% among adults 18 years and above.\(2013\)1

Arterial hypertension is less common among children compared to adults. However, there is an increasing concern regarding elevated blood pressure (BP) among children due to its close association with the obesity epidemic and cardiovascular dysfunction which often tracks into adulthood.[2] Children with elevated BP are at a two to three fold increased risk of developing essential hypertension in young adulthood.[3-5] Furthermore, there is evidence of adverse outcomes associated with childhood arterial hypertension such as carotid artery thickening, left ventricular thickening, urinary protein excretion and hypertensive retinopathy. The most significant long-term consequence of elevated BP in childhood is the continuation of hypertension into adulthood, therefore causing cardiovascular, cerebrovascular and renal disease in later life.[6-7]

Globally, a systematic review done in 2019 showed that the prevalence of hypertension and pre-hypertension among children aged below 19 years are 4% and 9.6%, respectively.[8] However, in countries geographically closer to Malaysia the figures are much higher. For example, hypertension among adolescents in China and India was reported to be 26.2% and 20.1% respectively.[9-10] There are a few studies that have been done in Malaysia over the last ten years that examined the prevalence of elevated blood pressure among the younger age group population. The first study was carried out in 2008 among seven- and eight-year-old primary school students in Kota Kinabalu by Chong et al to investigate the prevalence of obesity and its association with childhood hypertension. In this study, 13.4% of the students were found to be hypertensive on a single visit.[11] The subsequent study was conducted in 2012 among primary school students in the suburban areas of Selangor by Sreeramareddy et al. The prevalence of elevated blood pressure was 13.4% in this study.[12] The latest study was published in 2019, among children attending pre-schools in Kuching, Sarawak. The results that were based on a single measurement showed that 9.6% of the participants were found to have elevated blood pressure.[13] The results of these three studies in Malaysia may not represent the prevalence of true hypertension among primary school students as they were not done based on standard protocol as defined by the American Academy of Paediatrics.

Therefore, this study aims to determine the prevalence and associated factors of true hypertension among primary school students in the Klang Valley, Malaysia to fill up this important research gap.

METHODOLOGY

DEFINITION OF HYPERTENSION IN CHILDREN

Arterial hypertension in children is defined by elevation of at least three blood pressure (BP) measurements above the 95th centile at different visits, adapted for age, height and sex.[14] In 2017, the American Academy of Paediatrics (AAP) updated its clinical practice guideline for the screening and management of high BP in both children and adolescents.[2] In children younger than 13 years, elevated blood pressure is defined as BP ≥ the 90th percentile for age, height, and sex, and hypertension is defined as BP ≥ the 95th percentile.[2] Stage 1 hypertension is defined as BP ≥ 95th percentile to < 95th percentile + 12 mm Hg, or 130/80 to 139/89 mm Hg (whichever is lower).2 Stage 2 hypertension, meanwhile is defined as BP ≥ 95th percentile + 12 mm Hg, or ≥ 140/90 mm Hg (whichever is lower).[2]

Study Design

This was a prospective cross-sectional study conducted among primary school children attending primary care clinics. Data was collected between November 2020 to March 2021.

Inclusion And Exclusion Criteria

The inclusion criteria were primary school children from Standard 1 to Standard 6 attending primary care clinics. The exclusion criteria were students without parental consent, children with body temperature ≥ 38.0 degrees Celsius, and children with a pain score ≥ 4/10 and very unwell.

Sample Size Calculation

Sreeramaddy et al reported that the prevalence of hypertension was 13.4%.[12] We estimated the sample size using the prevalence of 13.4% by this formula: $n = n(1-n)\ (Z/E)^2$. Where n = prevalence of interest; Z = critical standard normal value for a two-tailed test = 1.96 (95% confidence); E = absolute precision required on either side of the proportion = 0.05%. The required sample size was 267 considering a 50% non-response rate. The higher non-response rate selected for this study was in response to possible difficulty in coming for follow-up or repeat measurements in view of COVID-19 pandemic.

Instrument

A self-administered questionnaire consisting of 5 parts was used. Part A to D was filled in by the parents of the respondents. Part E was a pro forma for the investigators to fill in. The questionnaire was prepared in both Bahasa Malaysia and English and validated by a panel of experts consisting of two

paediatricians, two family medicine specialists, and one statistician. Face validation of the questionnaire was conducted in 30 patients prior to the pilot test. The questionnaire was also subjected to internal consistency analysis, which showed a Cronbach alpha level of 0.80.

Digital oscillometric BP device that were validated for use in children with appropriate cuff sizes was used for screening. Every BP machine was calibrated and validated daily by comparing the measurements to an aneroid sphygmomanometer. Measurements were taken by the investigators. The child was asked to be seated for at least 5 minutes before taking the blood pressure measurement. Height, weight and waist circumferences were also measured using the standard method. BMI was calculated by dividing the weight in kg by the height in metres squared (kg/m^2). BMI was used as the sole measure of obesity.

Data Collection

The participants were selected via convenient sampling. The parent/guardian consent form and patient information sheet were given to the selected students and their parents during the visit to the clinic.

When the mean systolic BP was above the 90th centile, the child's blood pressure was measured again within 2 weeks during the second follow-up visit through the auscultatory method. A subsequent third blood pressure measurement was taken within another 2 weeks during the third follow-up visit if both the first and second blood pressure measurements were above the 90th centile through the auscultatory method. A minimum of three readings with a blood pressure ≥ 95th centile will be required to confirm the diagnosis of true hypertension. All those diagnosed with hypertension were referred to the paediatrician for further management.

Ethical Approval

Ethics approval was obtained from Medical Research & Ethics Committee of Ministry of Health Malaysia on 8th September 2020 (Approval No. KKM/NIHSEC/P20-1290.

Data Analysis

All statistical analysis was done using the Statistical Package for Social Sciences (SPSS version 25.0). The true proportion of those screened and confirmed to have hypertension was computed. Continuous data were described as mean and standard deviation if the distribution was normal. However, when the data has a skewed distribution, median and interquartile range (25-75th percentiles) were used. Categorical data were reported as proportions (percentage) and frequency.

Chi-square test or Fisher exact tests were used for the categories or dichotomous predictors. Factors associated with having true elevated blood pressure were also determined using logistic regression analysis. All analyses were done with 95% confidence intervals (CI), and the level of significance was set at $p<0.05$.

RESULTS

A total of 267 respondents were approached of which 251 agreed to participate, giving a response rate of 94.0 %. Among those, 16 did not come for repeat measurement of blood pressure. Data from these 251 respondents were used for analysis.

Table 1 shows the socio-demographic data of the participants. The mean age was 8.72 +/- 1.75 years (age range 7-12 years). The normality test for age showed a normal distribution. There were more male participants compared to female participants (53.8 % vs 46.2 %). Malay participants formed the highest respondent (86.1 %), followed by Indian (9.2%), Chinese (3.2%), and those from other ethnic groups (1.6%). The majority of the participants' parents were married (87.6%) ; only 12.4% were either divorced,

Table 1 *Socio-demographic profile of participants (n=251)*

Variable	n (%)
Age years (Mean +/- SD)	8.72 (+/- 1.75)
7	94 (37.6%)
8	39 (15.6%)
9	36 (14.4%)
10	30 (12.0%)
11	25 (10.0%)
12	26 (10.4%)
Gender	
Male	135 (53.8%)
Female	116 (46.2%)
Ethnicity	
Malay	216 (86.1%)
Indian	23 (9.2%)
Chinese	8 (3.2%)
Others	4 (1.6%)
Marital status of parents/carer	
Married	219 (87.6%)
Single parent *(divorced/widowed/unmarried)*	31 (12.4%)
Number of children	
1	16 (6.4%)
2-3	145 (58.0%)
4 or more	89 (35.5%)
Gross Income	
Less than RM 5000	149 (60.3%)
RM 5001-10,000	64 (25.9%)
More than RM 10,001	34 (13.8%)
Highest education level in parents	
None - Primary	6 (2.4%)
Secondary	75 (30.4%)
Tertiary	166 (67.2%)

widowed or unmarried. Most of the participants came from a household with three or less siblings compared to 64.4 %with more than three siblings (35.5%). Majority of the participants ,60.3 %, came from lower income households of less than RM 5000 compared to middle gross family income (25.9%) and higher gross family income of more than RM 10000 (13.8%). Only 2.4 % of participants' parents had no or primary education, whereas most parents had secondary education (30.4 %) or more (67.2 %).

Table 2 shows the medical history, family history and lifestyle characteristics of the respondents. The majority of the participants were healthy (94.3%) with only 5.7% of the participants having underlying medical illness. Most of the participants, 87.3 % had never been examined for high blood pressure compared to those who had (5.7%) in the past. Majority of them had a family history of hypertension (58.8 %), followed by heart disease (25.5%), stroke (21.3%), and chronic kidney disease (11.6%).

In terms of lifestyle attributes, most of the participants had inadequate sleep of less than 9 hours (65.2%) compared to those who had normal sleep hours (34.8%). Majority of the participants had a screen time exposure of more than 2 hours (75.1%) compared to 2 hours or less (24.9%). Correspondingly, most of the respondents ,68.1% exercised less than 4 hours weekly compared to those who did (31.9%). About 40% of the participants were exposed to passive smoking in their house. Majority of the participants had consumed fast food in their diet (88.0%). This study found that 5 children out of 251 had hypertension, giving a prevalence of 1.99%.

Table 2 *Medical history, family history and lifestyle characteristics of the respondents (n=251)*

Variable	N (%)
Chronic disease	
Yes	14 (5.7%)
No	234 (94.3%)
Examined for high blood pressure	
Yes	31 (12.7%)
No	213 (87.3%)
Family history of chronic disease	
Hypertension	143 (58.8%)
Stroke	52 (21.3%)
Heart Disease	62 (25.5%)
Chronic Kidney Disease	28 (11.6%)
Adequate sleep	
Less than 9 hours	163 (65.2%)
9 hours or more	84(34.8%)
Exposure to screen time	
2 hours or less	62 (24.9%)
More than 2 hours	187 (75.1%)
Exercise weekly	
Less than 4 hours	171 (68.1%)
4 hours or more	79 (31.9%)
Exposure to passive smoking	
Yes	99(39.6%)
No	151(60.4%)
Regular fast-food consumption	
Yes	221 (88.0%)
No	30 (12.0%)

Table 3 shows the association between socio-demographic characteristics, family history and lifestyle factors of the participants and the presence of true hypertension. Those who were found to be hypertensives were of older mean age (9.40 ± 1.52 years old vs 8.71 ± 1.75 years old, p=0.383). Majority of those found to have true hypertension were males (2.2%, p=1.000) and Indians (13.0%, p=0.016). Most of the children who were found to be hypertensives came from a single parent household (12.9%, p=0.001). Majority of the hypertensive participants came from a family with 2-3 siblings (2.8%, p=0.751) and with parents that had a secondary education level (2.7%, p=0.689). Family history of chronic kidney disease was noted most frequently in participants who were found to have true hypertension (3.6%, p=0.459).

In terms of lifestyle characteristics, participants who were found to be hypertensive had a higher mean body mass index (BMI) (28.40 ± 7.76 kg/m^2 vs 17.25 ± 4.57 kg/m^2, p<0.001). Those who were found to be hypertensive had more sleep of 9 hours or more (3.4%, p=0.345), 2 hours or less exposure time to screen (2.1%, p=1.000) and weekly exercise of more than 4 hours (2.5%, p=0.652). Majority of the participants with true hypertension had exposure to passive smoking (2.6%, p=0.651) and consumed fast food regularly (2.3%, p=1.000).

Therefore in univariate analysis, the only factors that were found to be statistically significant with the presence of true hypertension were ethnicity, parent's marital status & BMI (p value < 0.05) (Table 3).

These 3 significant factors (ethnicity, parent's marital status & BMI) were entered into the multiple logistic regression analysis to determine the determinants of the presence of true hypertension (Table 4). In terms of ethnicity, it was found that Indians had 55 times higher odds of having true hypertension compared to Malays, and this association is statistically significant (95%CI =1.47-2061.87, p = 0.03). It was also found that households with a single parent had 85 times higher odds of having true hypertension compared to households with married parents and this association is also statistically significant (95%CI = 2.68-2537.53, p = 0.01). In terms of BMI, those with a higher BMI had 1.4 times higher odds of having true hypertension compared to those with a lower BMI and this association was also statistically significant (95%CI = 1.06-1.43, p = 0.018).

Table 3 *Association between socio-demographic characteristic, family history & lifestyle of the participants and the presence of true hypertension*

Variable	Presence of true hypertension		T-test/ Chi square or Fisher's Exact test	p value
	Yes	No		
Age	9.40 ± 1.52	8.71 ± 1.75	- 0.87	0.383
Gender			-	1.000
Male	3 (2.2%)	132 (97.8%)	(Fisher's Exact Test)	
Female	2 (1.7%)	114 (98.3%)		
Ethnicity				0.016
Malay	2 (0.9%)	214 (99.1%)	10.379	
Chinese	0 (0.0%)	8 (100.0%)	(Fisher's Exact Test)	
Indian	3 (13.0%)	20 (87.0%)		
Others	0 (0.00%)	4 (100.0%)		
Marital status of parents/carer				0.001
Married	1(0.5%)	218(99.5%)	- (Fisher's Exact Test)	
Single Parent	4(12.9%)	27 (87.1)		
Number of children				0.751
1	0 (0.0%)	16 (100%)	0.68	
2-3	4(2.8%)	141(97.2%)	(Fisher's Exact Test)	
4 or more	1(1.1%)	88(98.9%)		
Gross Income				1.000
RM 5000	4(2.7%)	145 (97.3%)	0.51	
RM 5001-10000	1(1.6%)	63 (98.4%)	(Fisher's Exact Test)	
>RM10001	0(0.0%)	34 (100%)		
Highest education level in parents				0.689
None- Primary	0(0.0%)	6 (100%)	0.98	
Secondary	2(2.7%)	73 (97.3%)	(Fisher's Exact Test)	
Tertiary	3(1.8%)	163 (98.2%)		
Family history of chronic disease				
Hypertension	2(1.4%)	143(98.6%)	- (Fisher Exact test)	0.404
Stroke	0(0.0%)	52(100%)	- (Fisher Exact test)	0.587
Heart Disease	0(0.0%)	62(100%)	- (Fisher Exact test)	0.333
Chronic Kidney Disease	1(3.6%)	27(96.4%)	- (Fisher Exact test)	0.459
BMI	28.40 ± 7.76	17.25 ± 4.57	T Value: -5.320	<0.001
Adequate sleep			-	0.345
Less than 9 hours	2(1.2%)	161 (98.8%)	(Fisher's Exact Test)	
9 hours or more	3(3.4%)	84 (96.6%)		
Exposure to screen time			-	1.000
2 hours or less	4(2.1%)	183 (97.9%)	(Fisher's Exact Test)	
More than 2 hours	1(1.6%)	61(98.4%)		
Exercise weekly			-	0.652
Less than 4 hours	3(1.8%)	168 (98.2%)	(Fisher's Exact Test)	
4 hours or more	2(2.5%)	77 (97.5%)		
Exposure to passive smoking			-	0.651
Yes	1(1.0%)	98 (99%)	(Fisher's Exact Test)	
No	4(2.6%)	147 (97.4%)		
Regular consumption of fast food			-	1.000
Yes	5(2.3%)	216 (97.7%)	(Fisher's Exact Test)	
No	0 (0.0%)	30 (100%)		

DISCUSSION

In this study, we found that the prevalence of true hypertension among primary school students was about 2%. This prevalence was almost similar to the systematic review and meta-analysis done by Song et al in 2018 among Southeast Asian population which was 3.10%.[8] The same study also showed a global pooled prevalence was 4%.[8] The slightly lower prevalence could be due to the location where we obtained our sample, which is Klang Valley, Malaysia's most urban area. Prevalence of hypertension among adults in Malaysia in the past three National Health and Morbidity Surveys has been shown to be higher in the rural areas instead.[15-16]

Body mass index (BMI) has been found to be a significant determinant of true hypertension among primary school children in this study. This has been shown in almost all international systematic reviews and local studies.[8,11-12,17-18] Besides that, being obese was shown to be significantly related to both abnormal systolic and diastolic BP during the first visit in this study as well. This shows that obesity is the one of the main health issues that needs to be addressed to reduce the risk of children developing true hypertension.

Among adults, the prevalence of hypertension in Malaysia is highest among Bumiputeras from East Malaysia followed by the Malays and the Indians.[19]However, in our study, Indian ethnicity has been shown to be a determinant of the presence of true hypertension. The prevalence of obesity in our study was also highest among the Indians, thereby contributing to the excess risk towards developing true hypertension.

Another significant association to true hypertension in this study is children living with single parents. 4 out of the 5 children with true hypertension in our study are living with single parents. Scharte et al have shown there are increased health risk among children living with single parents.[20] In sub analysis of our study, prevalence of obesity was also higher in children living with single parents.

This is one of the few first studies which looks at the prevalence of true hypertension among primary school students and its associated factors in Malaysia, as other previous studies done only focus on elevated BP. The BP measurement was done according to guidelines using a calibrated digital Oscillometric BP device with the appropriate paediatric sized cuff. Children who presented with elevated BP (>90th centile) during the first visit were given appointments on 3 separate occasions, 2 weeks apart, to confirm the diagnosis of true hypertension. This is done in accordance with the 2017 Academy of Paediatrics Guidelines.[2]

In view of the limitations of traveling & recruitment of samples in school during the Covid-19 pandemic, this study only focused on participants around the Klang Valley area and walk-in non acute cases visiting the selected government health clinics. The study was also conducted in clinics located in the urban area only, thereby limiting its generalisability.

We recommend that future studies should include more states nationwide to get a more accurate national hypertension prevalence among these target groups. Regular BP monitoring should be encouraged and advocated amongst healthcare practitioners, especially amongst children with risk factors such as Indian race, living with single parents & higher BMI, which were found to be significant determinants of true hypertension in this study. Targeted intervention strategies should be implemented in children with identified risks which includes health education and risk reduction interventions to reduce serious long-term morbidity and mortality.

CONCLUSION

Prevalence of true hypertension in Malaysia is 2%. Factors found to be associated with the prevalence of true hypertension were Indian race, living with single parents & having a higher BMI.

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Table 4 *Determinants of the presence of true hypertension*

Variable	Odds ratio	95% Confidence interval	p value
Ethnicity			
Malay	ref	ref	ref
Chinese	0.0	0.0	0.999
Indian	55.00	1.467-2061.878	0.030
Others	0.00	0.00	0.999
Marital status			
Married	ref	ref	ref
Single parent	85.187	2.680-2537.531	0.010
BMI	1.433	1.064-1.433	0.018

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ORIGINAL ARTICLE

Symptoms and underlying diseases associated with the hospitalization period of 3,480 Covid-19 patients in Hormozgan, Iran

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Objectives

COVID-19 has a relationship with patients 'demographic characteristics as well as their underlying diseases. This research has been conducted to evaluate factors' effect on Covid-19 patient's hospitalization rate and period in Hormozgan, Iran.

Methods

The inclusion criteria of this retrospective study included all patients diagnosed as COVID-19 patients after PCR who were referred to Covid-19 hospitals from February 2020 to June 2020 in Hormozgan province (3480 patients). The checklist was designed according to COVID-19 guidelines and approved by the World Health Organization and Iran Ministry of Health and Medical Education. These data were analyzed using descriptive (average-standard deviation-percentage) and analytical (including Chi-square, t-test, and regression tests) statistics with SPSS Ver.23 software.

Results

In this study, 1852 male patients (53.20%) with a median age of 43.11±21.72 and 1628 female patients (46/80%) with a median age of 44.86±22.40.The median age of men was significantly lower than the women's median age(P= 0.02). The hospital stay length of male and female patients was reported 2.64±4.14 and 2.76±4.297; the death rate of patients in our study was 6.6%.

Conclusions

The results of this study showed that the hospital stay length of HIV-positive patients and patients with cardiovascular and pulmonary diseases is much longer than other people, which imposes many human and financial costs on the country's health care system. These results can improve health care system planning and improve medical services presented to covid-19 patients.

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INTRODUCTION

In late December 2019, a strange case of pneumonia was reported in Wuhan with similar clinical symptoms to viral pneumonia.[1] The WHO introduced the virus as COVID-19. This virus is from the beta-corona genera with different potential hosts.[2-4] Coronaviruses are single-stranded, enveloped RNA viruses with 120-180 nm diameter. Before the COVID-19, there were only six coronaviruses that could infect humans. Among coronaviruses, four strains, including OC43, 229E, HKU1, and NL63, have less pathogenicity and cause mild respiratory illness. Strains that are SARS-CoV and MERS-CoV have caused two fatal epidemics. The homology and pathogenesis mechanism of COVID-19 is very similar to the SARS-CoV pathogenesis mechanism.[5,6] Based on recent studies, there is a correlation between COVID-19 and demographic characteristics. The highest mortality rate is related to elderly men at the age of 65 years or older[7] with underlying diseases such as diabetes, high blood pressure, chronic respiratory disease, cancer, high interleukin-6 level, or a history of previous surgery. The cellular immune system function- an important immune system feature against viral infections- decreases in the elderly.[2,8-11] The most common clinical symptoms of COVID-19 infection are fever (87.9%), cough (67.7%), fatigue (38.1%). vomiting (5%) and diarrhea (3.7%).[12] Also, confusion, forgetfulness, olfactory dysfunction, neuropathic pain, seizure, and stroke are among the neurological symptoms of this virus that result in hypoxia and inflammation of the brain. Brain inflammation can be indirectly caused by a cytokine storm (autoimmune encephalitis) or directly caused by a broken blood-brain barrier by a virus (viral encephalitis).[13, 14] Besides, Acute Respiratory Distress Syndrome (ARDS) occurs around 90 days after infection. The virus also damages other tissues, including the heart, kidneys, liver, eyes, and nervous systems.[12] A healthy lifestyle, including exercise, good nutrition, a balanced weight, and non-smoking, contributes to a balanced immune system and Covid-19 prevention. Based on recent findings, the most prominent reason for the morbidity and mortality rate caused by Covid-19 in the US is overweight.[15,16] Also, personal hygiene, using the face mask, adequate rest, and proper ventilation are effective ways to prevent infection.[2] Disease occurrence depends on the interaction between the virus and the immune system. Virus-related factors also include the type of virus, mutation, and the number of viruses. Genetics (e.g., HLA gene), age, gender, nutritional status, homeostasis between the immune, nervous and endocrine systems, and physical condition affect a person's immune system. These factors contribute to an individual's infection, the duration and severity, and the recurrence of the disease. Since the exact mechanism of transmission of the disease is not fully understood, and vaccines do not make permanent protection, the most important task now is to interrupt the chain of transmission.[16] People with chronic disease with Covid have 19 more severe symptoms and are more likely to be admitted to the intensive care unit than people without chronic illness.[17]

Therefore, special attention is paid to patients with underlying diseases. This study aimed to identify the underlying diseases and investigate the relationship between these diseases and the length of hospitalization in patients with Covid-19 in 1399 in Bandar Abbas.

MATERIALS AND METHODS

This study was conducted from January 21, 2020, to May 30, 2020, in Hormozgan province (Hormozgan province is one of the 31 provinces of Iran, which is in the south of the country and the capital of the province is the city of Bandar Abbas), Iran (the Islamic Republic of Iran is a country in West Asia and Tehran is also its capital) to analyze the Hospital length of stay) LOS of COVID-19 patients. The research participants of this study were all patients referred to hospitals in Hormozgan parovince with a diagnosis of COVID-19 based on a PCR test.

Inclusion criteria were patients diagnosed with COVID-19 after a Real-time PCR test. Exclusion criteria were patients who did not consent to participate in this study or had incomplete or distorted information. Based on these inclusion and exclusion criteria, 3480 patients were included in the study.

Patients' data has been collected through the interview by MCMC (Medical care monitoring center) personnel in the hospitals after completing the consent form and observing ethical principles. The checklist used to collect information has been designed according to Iran national COVID-19 guidelines and approved by the Iran Ministry of Health and Medical Education and the World Health Organization. The studied variables were gender, age, patients' resident place, history of smoking and drug use, pregnancy, referral type to the hospital (by or without an ambulance), history of contact with COVID-19 patients, early symptoms (including cough, muscular pain, level of consciousness, respiratory, olfactory and taste dysfunction, seizure, headache, dizziness, paresis and limb palsy, chest pain, inflammation, and skin lesions, stomach ache, nausea, vomiting, diarrhea, and anorexia), intubation, Po2 level, history of cancer, chronic liver diseases, diabetes, chronic blood diseases, HIV/AIDS, acquired or congenital immunodeficiency, cardiovascular diseases, chronic kidney diseases and dialysis status, asthma and other chronic lung diseases and chronic neurological disorders. Multinomial logistic regression was used with hospitalization less than one day as the reference group; the baseline model included Cancer, Liver disease, Diabetes, High blood pressure, HIV positive, Immune system defects,

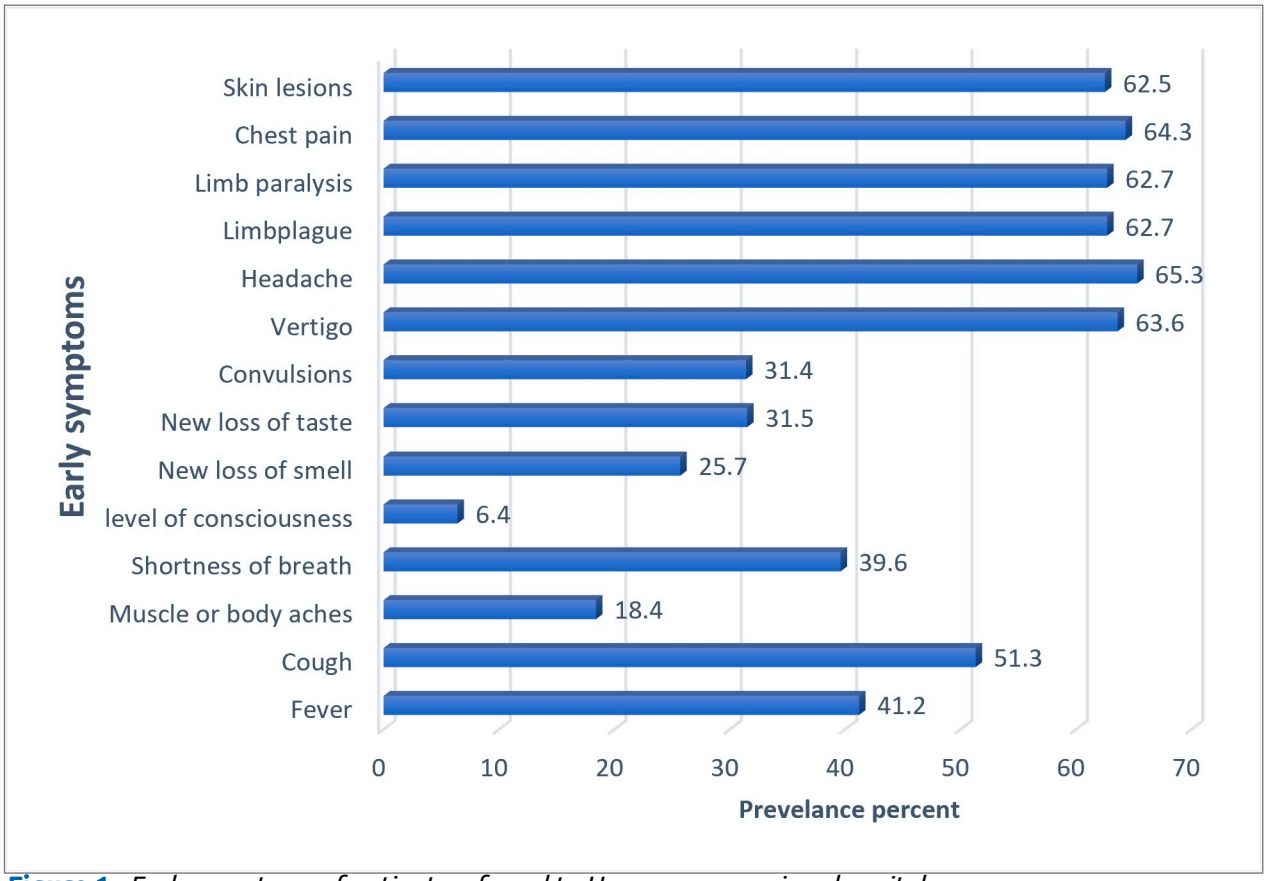

Figure 1 *Early symptoms of patients referred to Hormozgan province hospitals*

Cardiovascular disease, Pregnancy, kidney disease, Asthma, Lung Disease, Nervous disease.

These data were entered into SPSS V.23 software and analyzed using descriptive (average - standard deviation - percentage) and analytical (including Chi-square, t-test, and regression tests) tests.

RESULTS

In this study, 3480 patients referred to hospitals in Hormozgan province with COVID-19 diagnosis have been evaluated. This number includes 1852 male patients (53.20%) with a median age of 43.11±21.72 and 1628 female patients (46.80%) with a median age of 44.86±22.40. The median age of men was lower than women significantly (p=0.02). The hospital LOS of male and female patients has been reported 2.64±4.14 and 2.76±4.297, respectively, without a statistically significant relationship between the hospital LOS between different genders

According to Figure 1, the most prevalent early symptoms in patients were headache (65.3%), chest pain (64.3%), and dizziness (63.6%).

After examining the patients' gastrointestinal symptoms, it was found that the most common symptoms were vomiting (55.7%) and diarrhea (55.6%). Gastrointestinal symptoms are shown in Figure 2.

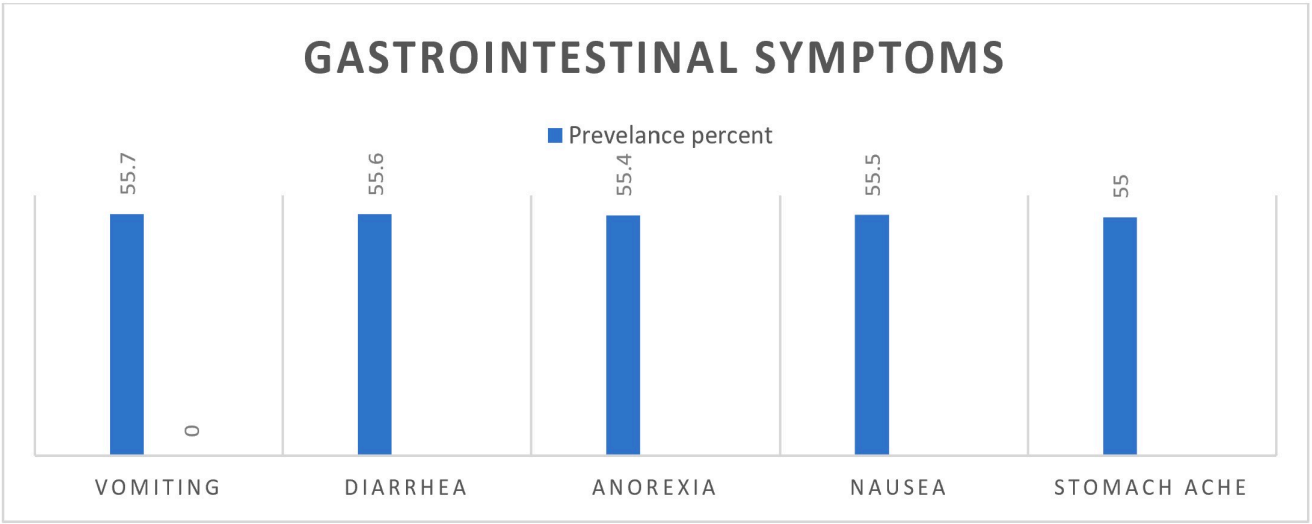

Figure 2 *Gastrointestinal symptoms of patients referred to Hormozgan province*

Table 1 shows the distribution of the variables between men and women. The mean age in men is lower than women and is statistically significant (p=0.020). Liver disease, diabetes, hypertension, cardiovascular disease, and asthma are different between men and women and are statistically significant. (p<0.05 for all). The hospital LOS, cancer, HIV positive, immune deficiency, kidney, lung, and nervous system diseases showed no significant difference between men and women. Statistically, they were not significant (p>0.05 for all).

Table 2 Regression model with time response variable based on hospitalization time grouping (according to the schedule less than one day - one day to the end of 7 days (week) - 8 days to the end of 30 days (one month) - more than 30 days (More) more than a month) has been done with independent variables showed that, diabetic Covid-19 patients have a higher risk of prolonging hospitalization to one-seven days range (OR = 1.445, CI95% = 1.113-1.876, P = 0.006). In addition, Pregnancy increased hospital LOS in Covid-19 patients to one-seven days range (OR = 2.187, 95% CI = 1.245-3.842, P = 0.006). Covid-19 infected patients with cardiovascular disease had more risk of prolonging hospitalization to eight to 30 days range. (OR = 1.581, 95% CI = 1.073-2.331, P = 0.021). Also, our study showed that Covid-19 patients with kidney disease have more risk of prolonging hospitalization to eight to 30 days range. (OR = 2.889, 95% CI = 1.535-5.435, P = 0.001). Besides, cancer can increase the

Table 1 *Percentage number of patients with their respective CURB-65 score*

Variable	Category/Scale	Male1852(%53.20) Mean ± SD or N (%)	Female 1628(%46.80) Mean ± SD or N (%)	p-value*
Age	Years	43.11±21.72	44.86±22.40	0.020
Duration of hospitalization	Day	2.64±4.14	2.76±4.297	0.356
Cancer	Yes	34(%1.80)	33(%2.00)	0.682
	No	1818(%98.20)	1595(%98.00)	
Liver disease	Yes	21(%1.10)	4(%.20)	0.002
	No	1831(%98.90)	1624(%99.80)	
Diabetes	Yes	125(%6.70)	171(%10.50)	<0.001
	No	1727(%93.30)	1457(%89.50)	
High blood pressure	Yes	19(%1.00)	45(%2.80)	<0.001
	No	1833(%99.00)	1583(%97.20)	
HIV positive	Yes	1(%0.10)	1(%0.10)	0.927
	No	1851(%99.90)	1627(%99.99)	
Immune system defects	Yes	4(%.20)	7(%.40)	0.262
	No	1848(%99.80)	1621(%99.60)	
Cardiovascular disease	Yes	187(%10.10)	204(%12.50)	0.023
	No	1665(%89.90)	1424(%87.50)	
Kidney disease	Yes	50(%2.70)	40(%2.50)	0.653
	No	1802(%97.50)	1588(%97.50)	
Asthma	Yes	70(%3.80)	98(%6.00)	0.002
	No	1782(%96.20)	1530(%94.00)	
Lung disease	Yes	52(%2.80)	39(%2.40)	0.447
	No	1800(%97.20)	1589(%97.60)	
Nervous system disease	Yes	21(%1.10)	21(%1.30)	0.674
	No	1831(%98.90)	1607(98.70)	

*p-values have been calculated based on Chi-Square or independent samples t-test.

Table 2 *Factors related to the length of hospitalization period of COVID-19 patients*

Hospitalization period	1-7			8-30			30+		
Variable	**OR***	**95% CI**	**P-value**	**OR***	**95% CI**	**P-value**	**OR***	**95% CI**	**P-value**
Cancer									
No	Ref		1.00	Ref	-	1.00	Ref	-	1.00
Yes	0.88	0.52 - 1.51	0.65	1.507	0.67 -3.418	0.33	26.48	7.69 -91.19	*<0.001*
Liver disease									
No	Ref		1.000	Ref	-	1.00	Ref	-	1.00
Yes	2.08	0.88 - 4.92	0.096	0.154	0.003 - 7.86	0.35	0.54	0.00 - 145.3	0.88
Diabetes									
No	Ref		1.00	Ref	-	1.00	Ref	-	1.00
Yes	1.45	1.11 - 1.88	*0.006*	1.223	0.77 - 1.96	0.40	0.25	0.013 - 4.79	0.38
High blood pressure									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	0.80	0.47 - 1.37	0.41	1.602	0.72 - 3.55	0.25	0.28	0.00 - 189.7	0.70
HIV positive									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	160	0.00 - 0.001	1.00	1141.584	0.00 - 0.001	1.00	3.14	3.13 - 3.13	*<0.001*
Immune system defects									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	0.44	0.10 - 1.87	0.27	1.091	0.16 - 7.49	0.93	0.25	1.44 - 434.8	0.78
Pregnancy									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	2.19	1.25 - 3.84	*0.006*	1.457	0.49 - 4.33	0.50	0.31	1.78 - 547.4	0.85
Cardiovascular disease									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	1.17	0.93 - 1.48	0.18	1.581	1.07 - 2.33	*0.021*	5.54	1.83 - 16.75	*0.002*
kidney disease									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	1.29	0.80 - 2.07	0.29	2.889	1.53 - 5.44	*0.001*	0.32	0.002-42.4	0.65
Asthma									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	0.94	0.68 - 1.30	0.70	0.76	0.39 - 1.48	0.41	0.27	0.005 - 15.7	0.53
Lung disease									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	1.044	0.67 - 1.62	0.85	0.55	0.19 - 1.56	0.26	8.82	2.12 - 36.67	*0.003*
Nervous disease									
No	Ref	-	1.00	Ref	-	1.00	Ref	-	1.00
Yes	1.141	0.61 - 2.15	0.69	0.97	0.28 - 3.32	0.96	0.25	3.07 - 198.7	0.81

* Multinomial logistic regression was used with Hospitalization less than one day as the reference group; the baseline model included Cancer, Liver disease, Diabetes, High blood pressure, HIV positive, Immune system defects, Cardiovascular disease, Pregnancy, kidney disease, Asthma, Lung Disease, Nervous disease

hospitalization period in Covid-19 patients to more than 30 days. (OR = 26.475, 95% CI = 7.687-91.185, p

<0.001). Concurrent HIV and Covid-19 infection increases risk of hospitalization to more than 30 days (OR = 3.136, 95% CI = 3.136-3.136, p <0.001). Compared to patients with less than one day of hospitalization and more than 30 days of hospitalization, people with cardiovascular disease have more risk of prolonging hospitalization. Concurrent lung disease and Covid-19 infection increases the risk of hospitalization to more than 30 days (OR=5.542, 95%CI=1.834-16.746, p=0.002).

DISCUSSION

The Covid-19 disease severity depends on the interaction between the virus and the immune system. Virus-related factors include mutations and the number of viruses exposed. An individual's immune system is also affected by genetics (e.g., HLA gene), age, gender, nutritional status, homeostasis in the immune system, nervous system, endocrine system, and physical condition. These factors contribute to an increased risk of an individual's infection, duration, severity, and recurrence of the disease. Due to the increasing need for covid-19 clinical areas[18], this study was conducted in the Hormozgan province to analyze factors affecting the COVID-19 patients' hospital LOS.

The results of the study showed that the most common early symptoms of the disease include headache, dizziness, sore throat, and cough, which are consistent with other studies.

The most common symptoms of this disease, which have been reported in several articles, are fever higher than 38 degrees (78%), cough (76%), fatigue and muscle pain (44%), shortness of breath (55%), headache (8%), bleeding (5%), and diarrhea (3%).[14, 19-21]

The results of the study showed that among the gastrointestinal symptoms of patients, vomiting and then diarrhea are the most common symptoms among patients. And these symptoms usually appear after the initial symptoms of the disease and are consistent with the results of other studies. In a study conducted by Erika et al., ten patients infected with COVID-19 presented gastrointestinal symptoms such as abdominal pain, nausea, and vomiting. The results indicated that nine of the patients had mild respiratory symptoms and fever before hospital admission.[22] In recent studies, fever and respiratory distress prevalence in Covid-19 patients reported 80.2% and 23.4%, respectively.[23] SARS-CoV-2 can also cause gastrointestinal symptoms such as vomiting, diarrhea, or abdominal pain in the early stages of the disease. Intestinal dysfunction causes changes in intestinal microbes and an increase in inflammatory cytokines.[24]

The present study shows that the relationship between the length of hospitalization of patients with Covid-19 is from high to low, respectively: lung disease, cancer, AIDS, kidney, heart, diabetes, and then pregnancy are at higher risk for long-term hospitalization. Prolonged hospitalization, in addition to mental and physical problems, increases the cost to the patient and the community and the government and is an important problem. The results were consistent with other studies conducted in the world, but no study on this subject was found in Iran.

The study Semenzato, et all showed that with age, the risk of Hospitalization for COVID-19 increased more than fivefold. Almost all chronic diseases were associated with an increased risk of COVID-19-associated hospitalization and in-hospital mortality.[25]

A study by Villapol, et all showed that the severity of COVID-19 is usually combined with a set of comorbidities such as hypertension, diabetes, obesity and / or old age that seriously aggravate the consequences of infection.[24] The study Petrilli, et al. Showed that age, heart problems and obesity were the main reasons for the prolongation of Hospitalization in Covid 19 patients.[26]This results also indicate importance of screening of covid-19 patients with underlying diseases to manage covid-19 pandemic and improve health status of society which is in line with Ardaneh et al. study.[27]

CONCLUSION

The death rate of patients in our study was 6.6%. Although Hormozgan province was categorized in the red zone in COVID-19 spread during this study but had a clearance rate of 96.4%, all of which were in good general condition. This shows the acceptable and valuable performance of health services personnel in this province. This study also showed that the hospital LOS of HIV-positive patients and patients with cardiovascular and pulmonary diseases is much longer than other people, which imposes many human and financial costs on the country's health care system. Therefore, to maintain individual health and help improve the critical condition of the virus, it is better to develop and apply stricter protocols to prevent further outbreaks of the disease and check underlying diseases of people suspected to have Covid-19. These results can improve health care system planning and improve medical services presented to covid-19 patients.

ETHICAL CONSIDERATIONS

The authors declare that the investigations were carried out following the rules of the Declaration of Helsinki of 1975. The ethics committee approved the study protocol of Hormozgan University of Medical Sciences with IR.HUMS.REC.1400.029 code.

ACKNOWLEDGMENT

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SUMMARY BOX

What is already known about this subject:

- Based on recent studies, there is a correlation between COVID-19 and demographic characteristics. The highest mortality rate is related to elderly men at 65 years or older with underlying diseases such as diabetes, high blood pressure, chronic respiratory disease, cancer, high interleukin-6 level, or a history of previous surgery.
- The most common clinical symptoms of COVID-19 infection are Fever (87.9%), cough (67.7%), fatigue (38.1%). Vomiting (5%) and diarrhea (3.7%).
- Disease occurrence depends on the interaction between the virus and the immune system. Virus-related factors also include the type of virus, mutation, and the number of viruses. Genetics (e.g., HLA gene), age, gender, nutritional status, homeostasis between the immune, nervous and endocrine systems, and physical condition affect a person's immune system. These factors contribute to an individual's infection, the duration and severity, and the recurrence of the disease.

What are the new findings:

- The death rate of patients in our study was 6.6%.
- The results of this study also showed that the hospital LOS of HIV-positive patients and patients with cardiovascular and pulmonary diseases is much longer than other people, which imposes many human and financial costs on the country's health care system.
- The results of the study showed that gastrointestinal symptoms such as vomiting (55.7%), diarrhea (55.6%), nausea (55.5%), and abdominal pain (55%) are the most common gastrointestinal symptoms among patients

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ORIGINAL ARTICLE

Retrospective audit for preoperative factors and clinical outcomes in patients undergoing bladder

Zuhair Ahmed, Natalia Wieczorkiewicz, Viktoria Czok, Eren Aslan, Gerald Busuttil, Simon Bugeja

Background

Five percent of urinary tract stones are found in the urinary bladder.[1] Bladder stones are responsible for 8% of urolithiasis related mortalities.[2] We have conducted a study and evaluated the effectiveness, safety and the outcome of transurethral cystolithotripsy using a rigid cystoscope under general anaesthesia.

Methods

A retrospective study conducted at Mater Dei Hospital in Malta, from 2004 until 2020. Information obtained from medical records, information technology hospital system and department theatre list. 201 patients were included who all underwent cystolithotripsy with or without transurethral resection of prostate (TURP) or bladder neck incision (BNI). Approval to conduct the study was obtained after fulfilling all requirements requested by the University Research Ethics Committee of Malta, as well as obtaining approval of the CEO of Mater Dei Hospital in line with applicable hospital protocols.

Results

The mean age was 65 years, ranging between 21 and 89. Overall, the procedure was well tolerated and there were no major peri-operative complications. The hospital stay ranged between 1 to 33 days with an average of 3 days. Follow up average was 4.3 years. The maximum period with bladder catheter was 18 days before a successful trial without catheter. The majority of patients remained catheter free in the long term with a minority still requiring conservative measures for the relief of lower urinary tract symptoms.

Conclusion

Transurethral cystolithotripsy using a rigid cystoscope under general anaesthesia is a safe and effective technique for the treatment of different sizes of bladder calculi.

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INTRODUCTION

5% of urinary tract stones are bladder stones[1] and incidence peaks at 60 years [2] The aetiology of bladder stones is typically multi-factorial.[3] They can be classified as primary, secondary or migratory.[4]

Primary bladder stones can occur in the absence of other urinary tract pathology, typically seen in children in areas with poor hydration, recurrent diarrhoea and a diet deficient in animal protein.[5] Secondary bladder stones occur in the presence of other urinary tract abnormalities, which include bladder outlet obstruction (BOO), neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies (including catheters), bladder diverticula and bladder augmentation or urinary diversion. In adults, BOO is the most common predisposing factor for bladder stone formation and accounts for 45-79% of vesical calculi.[1,6,7,8] The prevalence of bladder stones is higher in males, with a reported male: female ratio between 10:1 and 4:1.[1,2]

Common associated symptoms with bladder stones are urinary frequency, haematuria (which is typically terminal) and dysuria or suprapubic pain, which are worse towards the end of micturition, symptoms may worsen on sudden movement and exercise. Detrusor over-activity is found in over two thirds of adult male patients with vesical calculi, however, recurrent urinary tract infections (UTIs) may be the only symptom.[6,8]

Detection of bladder stones using ultrasound (US) in adults has a reported sensitivity and specificity of 20-83% and 98-100%..[9,8] Computer tomography (CT) and cystoscopy have a higher sensitivity for detecting bladder stones than US in adults [9,10] While cystoscopy allows for direct visualization of bladder stones and possible underlying disease such as bladder tumour, CT scan provides information on presence of upper urinary tract lithiasis..[11,12]

Treatment of bladder stones can be with open, laparoscopic, robotic assisted laparoscopic, endoscopic (transurethral or percutaneous) surgery or extracorporeal shock wave lithotripsy (ESWL).[13] Transurethral cystolithotripsy provides high stone-free rates (SFR) and appears to be safe, with a very low risk of unplanned procedures and major postoperative and late complications.[13]

Typically, bladder stones in men aged over 40 years are related to benign prostatic obstruction (BPO), the management of which should also be considered. Presence of bladder stones were usually an indication for a surgical intervention for BPO. However, this has been questioned by recent studies, in which medical management with an α-blocker with or without 5-alpha reductase inhibitor after successful cystolithotripsy had a lower recurrence rate overall in comparison to the surgical approach including a combination of cystolithotripsy with TURP.[14]

Factors need to be addressed prior and post-surgery to ensure a successful outcome, like relieving obstruction, eliminating infection, meticulous surgical technique, accurate diagnosis, and post-operative care.[1]

MATERIALS AND METHODS

This is a retrospective study conducted at Mater Dei Hospital in Malta, from 2004 until 2020. 201 patients were included who all underwent cystolithotripsy. All patients who underwent a transurethral cystolithotripsy with or without TURP/BNI between were also included.

All procedures were performed under general anesthesia in an operating theatre, with all patients having an overnight stay. Stones were fragmented using a mechanical pneumatic lithotripsy, after which stone fragments are evacuated through the cystoscope sheath, without contact with the urethral urothelium, thus the procedure is associated with a minimal chance of postoperative urethral injury. The use of laser lithotriosy was not intentionally excluded, no patients had laser lithotripsy were within the time period of our audit.

Treatment with an alpha blocker, 5-alpha reductase inhibitor (5-ARI) or a combination of both were administered in case of persisting lower urinary tract symptoms (LUTS).

Patients who had bladder neck contracture were managed, in the same session, by bladder neck incision, while those with benign prostatic hyperplasia were managed with a TURP procedure during either the current or a later organized session. A urinary catheter was inserted at the end of each procedure.

RESULTS

Pre-operative and post-operative data of 201 patients were analyzed. Range of age was between 21 and 89 with a mean of 65 years old. These patients were followed up for an average of 4.3 years.

Prior to cystolithotripsy, 17% of total patients suffered from retention. 3.4% had a pre-operative post void residual (PVR) of more than 500mls. Of these patients, 20 were catheter free at last follow up, 14 required long-term catheter. On average of PVR in patients who had previous TURP/BNI, concurrent TURP/BNI, subsequent TURP/BNI, No TURP/BNI was 200mL, 51mL, 161mL, 173mL respectively.

There is a lack of consensus about what constitutes a significantly elevated post-void residual volume, and there is conflicting data [15,16] This is especially that there is no standard calculation for measuring

Table 1 *Mean age, prostate size, hospital stay, TWOC, residual preoperatively, residual post TWOC, residual at last follow up*

Variables	Values
Mean age (years)	65
Mean prostate size (mL)	51
Mean hospital days (days)	3
Median TWOC (days)	1.19
Median residual preoperatively (mL)	141
Mean residual post successful TWOC (mL)	47
Mean residual at last follow up (mL)	38

Table 2 *Comorbidities of patients at time of presentation*

Diabetes	37
Known prostate cancer	8
CVA with deficit	3
Parkinson's	2
Other neurological disease	7
Diabetes and CVA with deficit	2
Diabetes and other neurological disease	1
Diabetes and known prostate cancer	1
CVA with deficit and other neurological disease	1
Pelvic surgery and other neurological disease	1

bladder volume exists, and measurement modalities produce different bladder volumes.[17,18,19]

PVR in adults less than 50mL is adequate bladder emptying, and over 200mL indicates inadequate emptying.[20] While in elderly, 50-100 ml PVR is considered normal.[21,22]

Patients per-operatively had an average of 86.7mL/min/1.73m^2 of their estimated glomerular filtration rate (eGFR). Of these 7.4% had a eGFR of less than 60mL/min/1.73m^2.

The diagnosis of bladder stones was based on either cystoscopy, or ultrasound or computer tomography findings. Only 126 patients underwent ultrasound prior to surgery, hydronephrosis was evident in 13.5% of the 126 individuals.

Basic characteristics like mean age, prostate size, hospital stay, trial without catheter (TWOC) and mean residual at last follow up are shown in Table 1.

At presentation, one third of patients (31.4%) had one or more of the following comorbidities, diabetes, cardiac vascular accident, Parkinsonism other neurological diseases, known prostate cancer, and pelvic radiation therapy, the rest of the patients had at least one or more of the following as shown in Table 2.

The effectiveness of surgical treatment for bladder outflow obstruction was assess by a successful TWOC and change in uroflowmetry and post-voiding residual volume on bladder sonography. TWOC was successful in 85.5% of patients with an average of 1.19 attempts. Average duration with a bladder catheter postoperatively was 3 days. Preoperative and postoperative average flow rate at uroflowmetry were 8mL/s and 19mL/s respectively.

Complications were observed in 10%, most of these events occurred within 9 days of the operation. The majority of complications were mild in nature as classified by the Clavien Dindo classification of severity (Figure 1).

There was no perioperative deaths. The two patients who required a transfusion had concurrent TURP. One post-op bladder neck stenosis was recorded. 5.9% of total patients had positive cultures

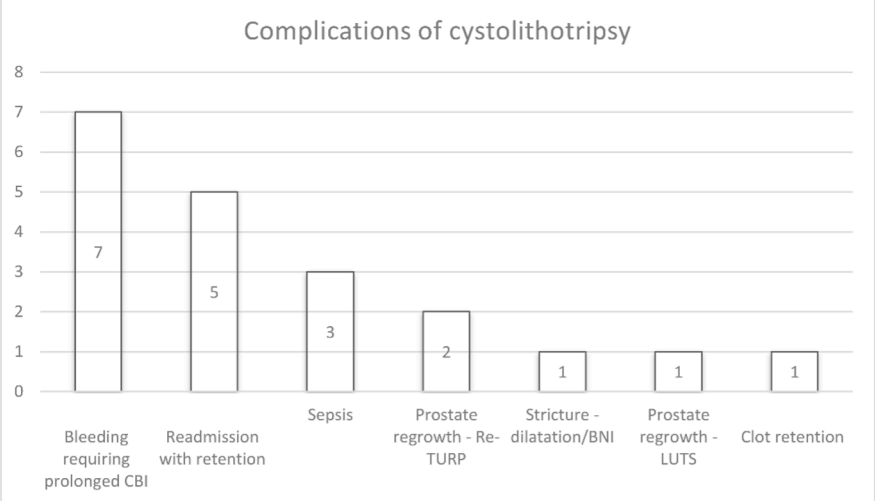

Figure 1 *Complications of cystolithotripsy*

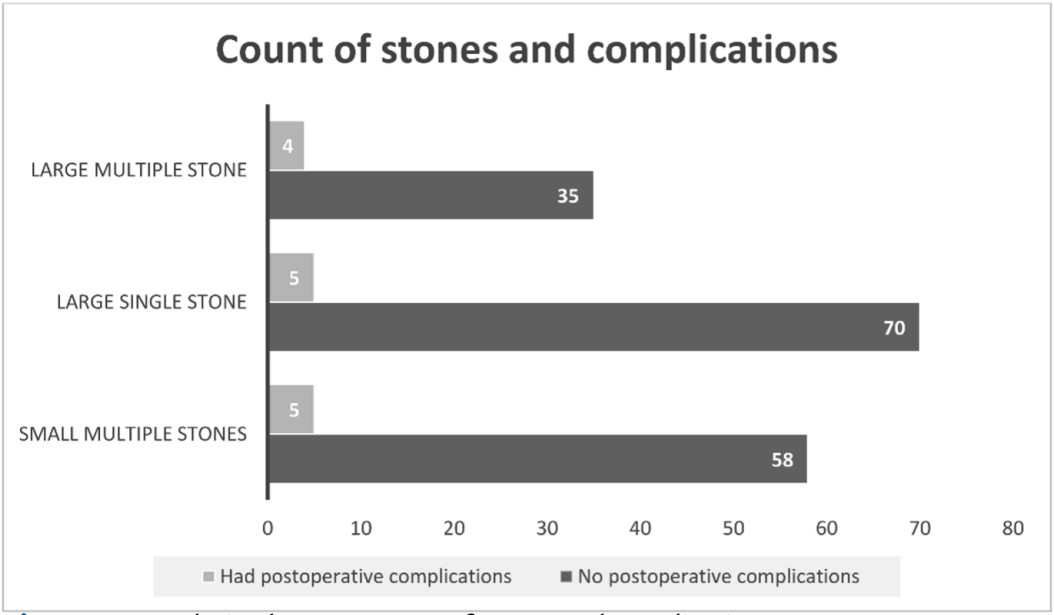

Figure 2 *Correlation between count of stones and complications*

preoperatively, however none had infective post-operative complications. No major intraoperative complications, such as bladder perforation, were detected.

With regards to stone burden, 35.6% had small multiple stones, 42% had large single stones, 22% had large multiple stones. The correlation between stone count and complications are shown in Figure 2. The complication rate was highest in large multiple stone removal: 11.4%, lowest in large single stone: 7.1%, where in small multiple stone percentage was 8.6%.

Recorded findings at operation like enlarged prostate, enlarged median lobe, urethral stricture, and bladder neck contracture are shown in figure 3.59% of patients had these anatomical obstructive findings (Figure 3).

31% of patients received pharmacological therapy preoperatively, while the percentage rises slightly up to 32% postoperatively. Detailed numbers of types of medications used in Table 3.

44% of patients did not undergo a TURP/BNI at any point within the duration of the study, while the rest had a TURP/BNI previously 5.4%, concurrently 28.8% or subsequently 21.3% to cystolithotripsy.

DISCUSSION

The results of this retrospective review of cystolithotripsy for bladder stones carried out at our institution show that this is an effective and safe procedure. Peri-operative complications were uncommon and mostly Clavien grade 1 or 2. Most of these adverse events occurred in patients who also

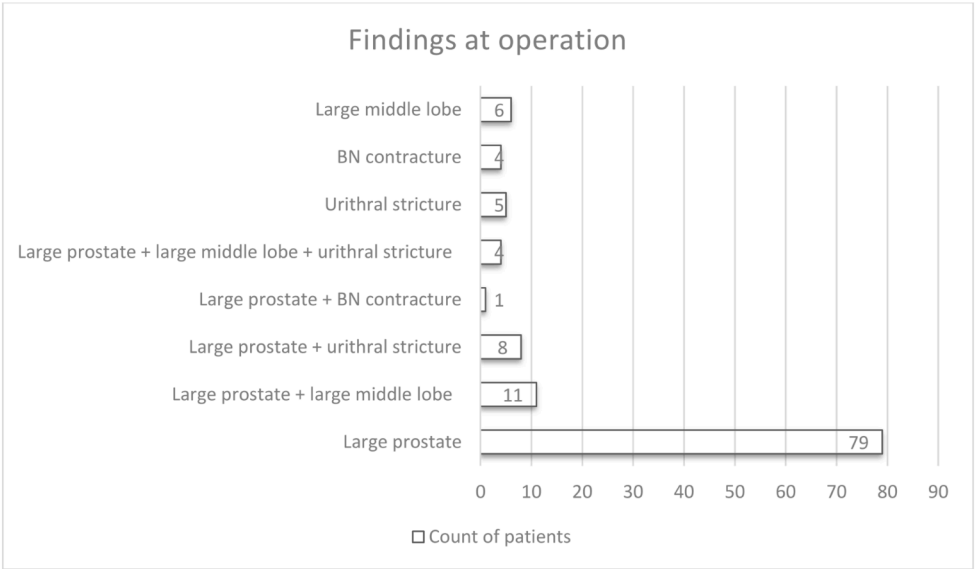

Figure 3 *Findings at operation*

Table 3 *Medications used preoperatively and postoperatively*

Drug	Count of drug pre-op	Count of drug post-op
Tamsulosin + Dutasteride	44	50
Tamsulosin	5	5
Dutasteride		4
Doxazocin	3	4
Alfuzosin	4	2
Finasteride	0	1

underwent resection of the prostate for associated bladder outflow obstruction and can be attributed to this part of the procedure rather the endoscopic removal of bladder stones per se. As expected the complication rate was highest in large multiple stone removal and lowest in large single stone removal.

Cystolithotripsy was associated with short hospital stay and TWOC within approximately 1 day in our subset of patients. In those patients who also underwent bladder outflow surgery, PVR drastically decreased post-operatively This was also mirrored by uroflowmetry, which showed an improvement in lower urinary tract function with maximum flow rate doubling post operatively.

A significant proportion of patients undergoing surgery for bladder stones in our cohort did not present with retention or else had significant chronic retention on pre-operative sonography. This is not in keeping with classical teaching, which attributes bladder stone formation to high bladder post voiding residuals and urinary stasis. Having said that, more than half of the patients were found to have an anatomical abnormality causing obstruction to flow, mostly an enlarged prostate but also bladder neck contractures or urethral strictures. One may hypothesize that intermittent incomplete bladder emptying, which is not always detected on ultrasound, may be the cause for bladder stone formation. Furthermore, patient who underwent cystolithotripsy with TURP and later on diagnosed at cystoscopy with prostate re-growth, were considered for re-intervention.

Our review comes with numerous limitations, mostly a selection bias inherent to a retrospective review, a heterogeneous group of patients (some patients underwent cystolithotripsy alone, others had a combined operation including bladder outflow surgery), incomplete data entry because of poor documentation, and selection bias with regards to long term outcomes as patients who do well after the procedure are not followed up long term.

Despite these limitations, this is the only review of a common urological procedure in a local population and will help with counselling of patients planned to undergo bladder stone fragmentation and removal.

SUMMARY BOX

- Cystolithotripsy, with or without bladder outflow surgery, performed at a local institution is a safe and effective way of dealing with both bladder stones and bladder outflow obstruction if indicated. Although this is not a prospective, randomized controlled trials comparing different treatment options, the data obtained will help proper consenting and decision making in the local urology clinic.

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CASE REPORT

Early Postnatal Genetic Diagnosis for Joubert Syndrome Type 14

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Background

Joubert syndrome is an autosomal recessive condition characterised by a midbrain-hindbrain malformation giving rise to the characteristic "molar tooth sign" on MRI. Common signs and symptoms include neonatal breathing dysregulation, hypotonia and developmental delay. A spectrum of conditions referred to as Joubert syndrome and Related Disorders (JSRD) have also been described, referring to the presence of multiorgan involvement in addition to the neurological signs and symptoms characterising "pure Joubert".

Case Presentation

We report a case of JS type 14 (homozygous pathogenic variant in TMEM237) in a male neonate referred antenatally with a brain malformation and bilateral cystic kidneys on ultrasound and MRI, raising the suspicion of a ciliopathy. Clinical features at birth included hypotonia, hydrocephalus, ocular colobomas and breathing difficulties which required mechanical ventilation.

Conclusion

Antenatal suspicion followed by confirmation of JS in the immediate postnatal period, has enabled early timely intervention by a multidisciplinary team, thus optimising parental counselling, developmental outcomes, and monitoring for potential future complications.

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INTRODUCTION

Joubert Syndrome (JS) results from complex midbrain-hindbrain malformation involving underdevelopment or complete absence of the cerebellar vermis, its hallmark being the characteristic diagnostic "molar tooth sign" on magnetic resonance imaging (MRI).[1] It is mostly inherited in an autosomal recessive manner, though various other patterns of inheritance have also been described.[2]

Presenting signs and symptoms vary, but commonly include neonatal breathing dysregulation and hypotonia, developing into early childhood coordination disorders and oculomotor apraxia. Developmental skills particularly motor and language, tend to be delayed. Distinctive facial features might also be observed such as ptosis, low-set ears, and a broad forehead.[3]

Joubert syndrome related disorders (JSRD) refers to the spectrum of conditions characterised by the presence of multiorgan involvement in addition to the neurological symptoms described above. Over 30 different types have been described to date, with involvement of ocular, renal, hepatic, skeletal and orofaciodigital systems. JSRD are part of the expanding group of ciliopathies, thought to result from gene mutations leading to malfunctioning primary cilia, thus disrupting crucial cell signalling pathways during development. Mutations known to cause JS are found in 60-90% of children with this condition, the remainder of which are still pending a precise genetic diagnosis.[3-4]

A case of JS type 14 is hereunder presented; caused by homozygous or compound heterozygous mutations in the TMEM237 gene on chromosome 2q33. Additional findings which may characterise this type include the presence of renal cysts, eye abnormalities and postaxial polydactyl.[5]

CASE PRESENTATION

A male neonate with an antenatal history of schizencephaly, hydrocephalus and cystic kidneys was delivered at 38^{+6} weeks gestation via emergency caesarean section for foetal distress. He was immediately noted to develop tachypnoea with episodes of prolonged apnoeas, requiring early intubation and mechanical ventilation.

Ultrasound and MRI brain confirmed extensive schizencephaly with dilatation of the lateral and 4th ventricles. He required insertion of a ventriculoperitoneal shunt on day 16 because of increasing apnoeas. Repeat MRI scans showed a persistent infratentorial cyst, with gradual enlargement and extension above the posterior fossa, requiring repeated shunt revisions leading to a reduction in the size of the posterior fossa cyst and improvement in drainage and clinical condition. He required minimal oxygen and despite persistent self-resolving episodes of apnoeas, he was weaned off completely from respiratory support by day 53 of life.

Maximal serum creatinine perinatally was 90umol/l which dropped to 30umol/l by 3 months of age and has been stable since. He was discharged from hospital at 4 months of age with extensive developmental delay, poor head control and axial hypotonia.

Investigations

The presence of a brain malformation and renal cysts on his antenatal scans led to the early suspicion of a ciliopathy, and he was referred to the multidisciplinary team allowing early postnatal intervention with a full workup, to confirm the diagnosis and to actively look for other possible associated anomalies.

Initial MRI showed a Dandy-Walker malformation with enlargement of the posterior fossa and a wide communication between the fourth ventricle and the posterior subarachnoid. Dysgenesis of the cerebellar vermis with only a tiny superior component was observed. Absence of the septum pellucidum, dysgenesis of the corpus callosum with a resultant dorsal cyst (initially thought to be schizencephaly), atresia of the cerebral aqueduct and an enlarged right lateral ventricle in keeping with colpoencephaly were also reported.

EEG (electroencephalogram) and cerebral function monitoring excluded seizures as a cause of the child's apnoeas. An echocardiogram was normal.

Postnatal renal US and MRI confirmed bilateral cystic dysplastic kidneys, measuring 8cm with abnormal morphology and echogenic central parenchyma with scattered predominantly peripheral cysts of varying size in keeping with bilateral cystic cortical dysplasia. Imaging appearances on MRI were suggestive of nephronophthisis.

Ophthalmic review showed bilateral optic disc colobomas.

Karyotype was confirmed to be male. By 6 weeks of age exome sequencing confirmed a homozygous pathogenic variant in the TMEM237 gene, suggestive of JS type 14. Parental carrier testing was also performed.

Differential Diagnosis

Various pathogenic variants in genes that cause JSRD, have been identified in other syndromes with overlapping clinical findings, (Table 1).

Treatment

Treatment for JS is mainly supportive. Respiratory support is commonly required during the neonatal period. Insertion of a ventriculoperitoneal shunt with two subsequent revisions was required for this child, in view of progressively worsening hydrocephalus

Table 1 *Table describing syndromes with pathogenic genetic variants and clinical findings overlapping with JSRD*

Syndrome/Condition	Features
Goldstron syndrome	Polycystic kidneys, Dandy-Walter +/- hepatic fibrosis
Bardet-Biedl syndrome	Retinal dystrophy, renal disease, polydactyly, genital malformation, hypogonadism
Leber congenital amaurosis	Retinal dystrophy, global development delay and neonatal apnoeas
Meckel syndrome	Cystic renal disease, posterior fossa abnormalities, hepatic fibrosis
Hydrolethalus syndrome	Midline brain anomalies, polydactyly, micrognathia
Acrocallosal syndrome	Corpus callosum agenesis, posterior fossa anomalies, hypertelorism, polydactyly

secondary to inadequate drainage of the ventricular systems. Physiotherapy and occupational therapy input were sought early, and he was referred to the local Child Development and Assessment Unit to help improve developmental outcomes and guide educational needs and social support. His parents were trained in basic life support, and domiciliary oxygen and an apnoea monitor were provided for emergency use. Parental carrier testing and genetic counselling was carried out by the genetics team.

DISCUSSION

Pathophysiology And Genetics

More than 200 cases of JSRD have been published since originally described, with mutations in over 30 genes including AHI1, NPHP2 and CEP290, all of which result in malfunctioning primary cilia. The presence of these crucial cell signalling proteins across multiple organ systems, explains the multiorgan involvement in JSRD. Currently, a molecular genetic diagnosis can be established in 60-90% of cases, enabling family counselling and prenatal diagnosis should a specific mutation be found.[4]

Clinical Features And Diagnosis

Heterogenous clinical presentation and lack of awareness explain the wide range of age at diagnosis reported, with an average age of 33 months being reported in one study by Maria et al., and a mean of 6.67 ± 8.10 years in a study by Nuovo et al.[6-7] Prenatal accurate diagnosis using only imaging is very difficult, with genetic testing being required. Diagnostic criteria continue to evolve but are mainly based on the presence of a "molar tooth sign" (combined presence of a deep posterior interpeduncular fossa, prominent superior cerebellar peduncle and vermian hypoplasia) on MRI, in combination with developmental delay, hypotonia and late-onset ataxia.[4]

Developmental delay usually spans across multiple areas but interestingly, developmental outcome is independent of the severity of the intracranial malformations diagnosed on MRI.[8] Moreover, despite breathing dysregulation being considered a classical sign of JS, it is not a consistent feature, reported as being present in 44% to 71% of children.[9]

Treatment And Outcomes

Gene therapy is only available in a research setting. The outcome ranges from mortality in childhood to surviving patients with mild to severe developmental delay.[8] Therefore, recognising JS and related disorders early on in life, remains a key factor in improving developmental outcomes, whilst also allowing for appropriate timely parental counselling.

CONCLUSION

JS is an autosomal recessive ciliopathy, resulting in complex midbrain-hindbrain malformation giving rise to the characteristic "molar tooth" sign on MRI. Signs and symptoms include neonatal hypotonia, breathing dysregulation, developmental delay, and ataxia. Multiorgan involvement characterises JSRD. Treatment is mainly supportive. Heterogeneity in presentation and outcomes, makes early recognition desirable to allow for counselling and early intervention by multidisciplinary teams.

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CASE REPORT

Gullain-Barre' syndrome post-SARS-CoV-2 in Malta: a Case Report

Joseph Saliba, Clarissa Fenech, Adrian Pace

A 70-year-old lady presented three weeks after a mild SARS-CoV-2 infection with a nine-day history of worsening back pain, progressive lower limb weakness and paraesthesia, dysphagia, constipation and difficulty in completing full sentences. Outcome of her investigations were in keeping with a diagnosis of acute inflammatory demyelinating polyneuropathy. The patient made a rapid and full recovery after treatment with intravenous immunoglobulins (IVIG).

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INTRODUCTION

The SARS-CoV-2 virus was first identified as the cause of a new transmissible infectious disease in humans with respiratory complications in Wuhan, China at the end of 2019. The virus spread swiftly throughout China and within weeks emerged in several other countries around the world. On the 11thMarch 2020 the World Health Organization (WHO) declared SARS-CoV-2 a pandemic.[1]

SARS-CoV-2 is known to cause a wide range of symptoms. Most of the time these appear between 2 to 14 days post exposure to the virus. In the acute phase SARS-CoV-2 may cause fever, cough, shortness of breath, fatigue, myalgias, headache, sore throat, runny nose, nausea, vomiting and diarrhoea.[2] Neurological complications secondary to SARS-CoV-2 were also reported. These include hyposmia, ageusia, cerebrovascular accident, encephalitis, Guillain-Barre' Syndrome (GBS) and transverse myelitis.[2-6]

GBS is an acute type of polyradiculopathy which causes flaccid paralysis that commonly presents in a progressive symmetric weakness and areflexia. GBS usually occurs secondary to an immune system-activating event such as vaccination or infections including *Campylobacter jejuni*, cytomegalovirus, Zika virus and Epstein-Barr virus.[7] Other rarer causes of GBS include trauma, surgery, bone marrow transplantation, systemic lupus erythematosus (SLE), Hodgkin's lymphoma and sarcoidosis.[8,9] We report a case of GBS following shortly after infection with SARS-CoV-2 and its clinical outcome.

CASE

A 70-year-old woman presented to hospital with a nine-day history of back pain and a three-day history of progressive ascending paraesthesia which started bilaterally at the toes and progressed up to the groin. This paraesthesia was followed by progressive weakness in her lower limbs, causing unsteady gait, multiple falls and reduced mobility. Moreover, she also complained of progressive dysphagia, fatigability on completing full sentences and constipation. Three weeks prior to these symptoms the patient was diagnosed with SARS-CoV-2 via reverse transcription-polymerase chain reaction (RT-PCR) nasal swab test. At that time, she did not have fever, chills, rigors, cough, or shortness of breath. Her only SARS-CoV-2 related symptoms were a 2-day history of diarrhoea and runny nose.

On admission she was haemodynamically stable, afebrile, alert and oriented. She did not require oxygen supplementation within hospital, and her oxygen saturations on room air remained above 95% throughout her admission. No signs of meningism were noted. Her cranial nerve and upper limb examination were normal. On the other side her lower limb examination was not intact. Tone and muscle bulk were normal but she was noted to have diminished power (MRC) 4/5 across all lower limb muscle groups bilaterally. Reflexes were elicited but appeared diminished bilaterally. Plantars were down going bilaterally. Sensory testing revealed hyperaesthesia and allodynia in her lower limbs, with impaired vibration and proprioception. She was unable to stand independently.

Blood tests on admission revealed a raised white blood cell count of $17.4x10^9$/L and neutrophil count of $12.9x10^9$/L. Erythrocyte sedimentation rated and C-reactive protein were normal at 9mm 1st hour and 4mg/L respectively. An auto immune screen, thyroid function test and vitamin B_{12} were normal. Chest x-ray did not show consolidation or ground glass shadowing. Our two differential diagnoses were transverse myelitis and GBS post SARS-CoV-2 infection. Magnetic resonance imaging of the head and whole spine excluded intracerebral and spinal pathology.

Cerebrospinal fluid (CSF) showed albuminocytological dissociation with a raised protein level of 1068mg/l (Normal range: 150-450mg/l) but no leukocytes. Paired oligoclonal bands in CSF and serum were detected, indicating a systemic immune reaction. Anti-ganglioside profile including anti-MAG, GM1, GM2, GD1a, GD1b and GQ1, was negative.

On day four post admission, the patient complained of bilateral paraesthesia at the tips of her fingers and experienced worsening of the power in her lower limbs (MRC 3/5 in most of the muscle groups), absent ankle reflexes and increased breathlessness. Nerve conduction studies (NCS) identified a severe, generalized, patchy, sensory more than motor, mixed demyelinating, and axonal peripheral neuropathy, consistent with a diagnosis of GBS.

Baseline lung function test revealed a reduced forced expiratory volume (FEV_1) of 1.17 and forced vital capacity (FVC) of 1.47 with a FEV_1/FVC ratio of 0.80. She was treated with 2g/kg of IVIG over two days. Pregabalin 50mg twice daily was prescribed to relieve the neuropathic pain.

After IVIG was administered the progression of her symptoms stopped, and the patient manifested steady signs of recovery. Her shortness of breath, and dysphagia improved after four days. Three weeks post treatment the patient was able to walk independently with a Zimmer frame and was discharged home. A repeat lung function test after four weeks showed an increase in FEV_1 from 1.17 at baseline to 1.56. Two months after the IVIG treatment a follow up nerve condition study showed that the multifocal polyneuropathy had resolved.

DISCUSSION

GBS post SARS-CoV-2 infection was reported in several cases around the world.[3] The mean latency of GBS post SARS-CoV-2 infection was 12.1 days, with most of the patients experiencing their first neurological signs between 7 to 28 days.[10] Although numerous cases of GBS were reported post SARS-CoV-2 infection, it is a rare complication. In fact, Toscano et al. studied 1000-1200 patients between 28th February and 21st March 2020, and found out that only five patients had GBS post SARS-CoV-2 infection. Three of these patients had respiratory failure.[11] It is well known that GBS can cause respiratory muscle weakness and 10 to 30 percent might require ventilatory support.[12] It is important to remember that SARS-CoV-2 can cause GBS since patients which are sedated on ventilatory support might be missed.

In our case report we found that the patient's findings were in keeping with acute inflammatory demyelinating polyneuropathy (AIDP). Abu-Rumeileh et al pointed out that AIDP was reported in 46 patients out of 74 cases, making it the most common GBS variant post SARS-CoV-2 infection.[13] AIDP is an autoimmune reaction directed towards epitopes which are found on the schwann cell surface membrane or myelin.[14] It is known that a small number of patients who have AIDP can develop severe secondary axonal degeneration.[15]

Other subtypes of GBS post SARS-CoV-2 infection include Miller Fisher Syndrome (MFS), which causes ataxia, areflexia and ophthalmoplegia, Acute Motor Axonal Neuropathy (AMAN) which is characterised by sparing of sensory nerves and most of the time it is preceded by *Campylobacter jejuni* infection, and Acute Motor and Sensory Axonal Neuropathy (AMSAN) which is similar to AMAN but effects the

sensory nerves as well.[15] A literature review showed that only seven AMSAN type of GBS and only three AMAN type of GBS were noted out of 74 cases and that 70% of the patients had good recovery with IVIG.[13] They also mentioned that other post-infectious GBS and post-SARS-CoV-2 GBS share most features, raising the question whether they share the same immune-mediated mechanisms.[13]

CONCLUSION

Our case report demonstrated that mild SARS-CoV-2 infection may also cause GBS, in this case our patient had AIDP subtype. GBS may be missed when it disguises itself as a myelopathy. GBS may also be missed in those patients which are sedated in ITU and in those who have SARS-CoV-2 infection which develop respiratory failure secondary to GBS rather than SARS-CoV-2.

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CASE REPORT

Toxic Tea - Case Report

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A young gentleman presents with deliberate unidentified plant ingestion, complaining of abdominal pain and vomiting. He is found to have junctional rhythm at 37 beats per minute. On further questioning, he is noted to have ingested *Nerium oleander* leaf tea extract as part of a ritual. The mechanism of action, diagnosis and management of oleander poisoning is discussed in this case report. Awareness to the common oleander plant and its toxicity in the Maltese islands and around the Mediterranean is emphasized.

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INTRODUCTION

Cardiac glycosides are a group of chemicals naturally occurring in several subtropical plants. They can be found in many plant genera such as *Digitalis*, *Nerium*, *Crochorus* and *Rhodea*.[1] The best known of these plants is the Foxglove plant (*Digitalis*) from which the commonly used drug digoxin is produced. Cardiac glycosides act by inhibition of the sodium-potassium ATPase pump in myocardial cells.[2] This is used as treatment for various cardiac conditions but in excess it has toxic effects.

The oleander plant (*Nerium oleander* and *Thevetia peruviana*) is a common evergreen shrub with long, pointed leathery leaves. It blooms between April-October, portraying bright pink or yellow flowers (species-dependent) and is commonly found around field margins, valley-sides and damp shrublands. It is native to central and east Mediterranean. In suitable habitats, it can grow up to 3.5 meters. In the Maltese islands its popularity grew dramatically in the 1970s and 80s with large populations of oleander being found all over the islands.

Oleander poisoning may occur on minimal ingestion of any part of the tree, including leaves, flowers, stems, twigs, and roots.[3] Its bright-coloured flowers give rise to numerous accidental poisonings. Whilst most accidental poisonings do not give rise to toxic effects, deliberate ingestion of significant quantities, such as in folk medicine practice, cultural rituals, homicides, and suicide, often lead to serious toxicity.

Toxic effects result from cardiac glycosides found in all parts of the plant. As cardiac glycosides are not disrupted by heat, plant smoke from burning can also lead to toxicity. Reports of deaths after eating cooked food over oleander wood fires have been reported.[1] Commonest effects from oleander poisoning include cardiac, gastrointestinal, and metabolic effects, with the former taking up to 12 hours to fully develop.[3]

Below we present a case report of deliberate oleander ingestion.

CASE PRESENTATION

A 23-year-old gentleman was brought to the Emergency Department (ED), in view of multiple episodes of vomiting, abdominal pain and feeling generally unwell. Symptoms began 14 hours after ingestion of self-prepared "olive leaf" tea (100mL). This was ingested to relieve the generalised pain caused by construction work, as part of a ritual.

On assessment, the patient was alert but pale, lethargic and diaphoretic. Chest examination revealed normal vesicular breath sounds and normal percussion notes. The patient had a blood pressure of 101/60mmHg, with a heart rate of 37bpm. Other parameters were within normal limits. ECG revealed a junctional rhythm at 37bpm (Figure 2).

The patient was treated with atropine (0.5mg iv), with almost-immediate resolution of the bradycardia. His heart rate increased to 97bpm within seconds, with recurrence of bradycardia after 30 minutes. This was followed by another atropine administration, with the same outcome.

The clinical toxicologist on-call was contacted in view of possible oleander poisoning and suggested a serum digoxin level, which revealed a digoxin level of 0.8 ng/mL [0.6-1.2 ng/mL], with all other routine blood tests being within normal limits.

Images of olive leaves and oleander leaves where shown to the patient and the patient identified the oleander leaves as the 'olive leaves'. It thus came to light that he had not ingested olive leaf tea but an oleander extract. Treatment with 5 vials (200mg) of digoxin-specific antibody (DigiFab) was initiated. The patient was concomitantly resuscitated with intravenous fluids and intravenous anti-emetics. No further episodes of bradyarrhythmias occurred post DigiFab in the ED.

He was subsequently admitted to hospital and had an uneventful recovery.

Figure 1 Oleander photo

DISCUSSION

Mechanism Of Action

Oleandrin is the main toxin found in the oleander plant. As a cardiac glycoside, oleandrin affects multiple essential cell processes, the most common being inhibition of the sodium-potassium ATPase pump, which in turn has an effect on other transport proteins, including the sodium-calcium exchanger found in cardiac myocytes.[2] This may lead to cardiac arrhythmias. Oleandrin also increases vagal activity of the heart and exhibits a negative chronotropic and dromotropic effect by acting on the SA and AV nodes respectively. Gastrointestinal effects include nausea and vomiting, cramping and bloody diarrhea. Central nervous system symptoms range from mydriasis, visual disturbance, dizziness, and confusion.[4] Metabolic effects include hyperkalemia (associated with poorer prognosis) and metabolic acidosis.[4-5]

Diagnosis And Management

Diagnosis of oleander poisoning will depend on the identification of Nerium oleander ingestion, symptoms and signs exhibited (nausea, vomiting, abdominal pain, lethargy and bradycardia, anorexia, delirium and visual changes) and hyperkalemia.

Management involves general supportive care as well as specific treatment for cardiac glycoside toxicity. Supportive care includes haemodynamic support of bradycardia with atropine administration and arrhythmia management according to latest guidelines, which may include temporary venous pacemaker and cardioversion (chemical or electrical).

The antidote for cardiac glycoside poisoning is digoxin-specific antibody (Fab) fragments, commercially available as DigiFab, notably when signs of instability are present.[7-8] DigiFab rapidly reverses the effect of cardiac glycosides. Non-digoxin glycosides (such as oleander) may cross-react with antibodies found in most radioimmunoassay kits and result in digoxin being reported as present. While a measurable digoxin concentration may confirm

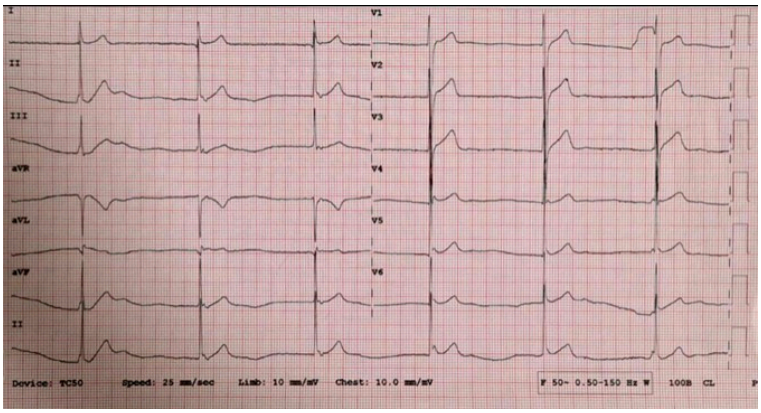

Figure 2 ECG

exposure, the qualitative concentration cannot be used to guide therapy.[6]

Higher doses of DigiFab are used in oleandrin poisoning when compared to digoxin toxicity as DigiFab is less specific to oleandrin.[9] Cardiac glycosides are well absorbed by charcoal; administration of charcoal should be considered in all cases that present within 1 to 2 hours post ingestion. Emesis is not recommended for cardiac glycoside ingestion.

CONCLUSION

Oleander is a common plant around the Mediterranean and other places in the world, and its availability should alert emergency physicians to consider it as a potential poison in toxicology cases where ingestion of a plant is likely. Whilst our case did not lead to fatality, multiple reports of fatal ingestion have been reported. Awareness, early recognition, and management should reduce mortality and morbidity.

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