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EDITORIAL

Editorial

The COVID 19 vaccine: Fear it not!

Simon Attard Montalto

As a paediatrician I see children and speak to parents, who frequently recount how the pandemic has adversely affected their lives and livelihood, with many describing 'hard times' in relation to their family, job, travel, income, disposable wealth, etc., etc. Invariably, the question *"How will it all end?"* crops up and directs the discussion toward vaccination. Despite having just described the 'hit' that they have sustained, medically or economically or both, and even before any discussion on the rationale and benefits of a vaccine, I am repeatedly surprised by many parents' immediate comment that *"They fear and will not take the vaccine"* and, equally concerning, that they *". . . will be reluctant to give the vaccine to their child"*.* This position is by no means exceptional, and stems from an inherent fear of something new that is relatively untried, and is compounded by misunderstanding from or confusion within the general and social media (less so in the regulated and mainstream channels), as well as unsubstantiated claims from anti-vaxxers.

Interestingly, many parents who raise concerns regarding the COVID vaccines, have very few problems with the anti-meningococcal vaccines, even though the diseases covered are significantly less common than COVID infection, kill far fewer patients over a given period and,[1,2] in some cases (e.g. Men B vaccines), these vaccines carry a much greater adverse event profile.[3] The word 'meningitis' appears to generate an all-encompassing fear that justifies everything whilst, inexplicably, 'COVID' does not!

So, should we fear the COVID vaccines? Certainly, for those vaccines developed by large international companies who have been involved in this work for decades, and have published their data for general and expert scrutiny, the answer is no. Efficacy rates of between 70-90% and very low risks of reported adverse events and allergic reactions (for the AstraZeneca and Pfizer vaccines, for example),[4-5] makes these amongst the most promising and safe when compared with numerous vaccines

Cover Picture:

'Meersburg am Bodensee, Germany (1991)'

Watercolours

By Mario Borg

Mario Borg, Read Pharmacy at Bachelor's level (1982-86) and later read History of Art at both Bachelor's & Master's levels (1994-2001)

He has been practicing art in several of its techniques since a long time ago with watercolours, assemblage, acrylics and collage being my preferred media.

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already established and in routine use for other diseases. The fact that the development of these vaccines was fast-tracked, reflects the seriousness and adverse impact on a global level of COVID-19, and does not mean that short-cuts have been taken. Again, for those vaccines where detailed published data is available, established or advanced vaccine technology has been applied, clinically and scientifically sound methodology adhered to, and pre-licencing rigorous checks and scrutiny enforced as with any new medication, including vaccines.[5] Indeed, together with a postgraduate PhD student, we have been personally involved in a multi-centre meningococcal C vaccine coordinated by the Oxford Vaccine Research Group over a number of years,[6] and can reassure readers that the standards set were unequivocally 'world-leading'. There is absolutely no reason why this *modus operandi* would be altered in any way for the development of a COVID vaccine.

Let us be clear: Fact 1: The COVID 19 pandemic has created a pan-global health crisis with severe impact on individuals, society, business and national economies. Fact 2: Social distancing measures mitigate and control spread of the virus but do not eliminate the pandemic, and Fact 3: In 2020, only a vaccine that is safe AND effective AND is widely distributed to the vast majority of a given population, can suppress the pandemic. The conclusion, therefore, has to be mass population vaccination, with at least 75% (but possibly nearer 90%) of the population vaccinated to achieve effective herd immunity.[7,8] All those in a position to influence public sentiment, have a duty to promote COVID vaccination at every given opportunity. Only with a supportive and concerted effort will any reasonable doubt relating to COVID vaccines be addressed, fears dispelled and the public encouraged to take this on, '*en masse*' (or staggered, as supplies permit).

*Note that the current vaccines have been trialled on adult subjects and, initially, will be licenced for adults. Trials on children are on-going but a COVID19 vaccine(s) for children are not expected till late 2021.

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ORIGINAL ARTICLE

Analysis of risk factors for Helicobacter pylori infection in the Maltese population

Darryl Pisani, Michael Caruana Dingli, Benedict Axisa

Background

To assess risk factors for Helicobacter Pylori Infection in the Maltese population.

Methods

A total of 138 patients undergoing OGD investigation were contacted by telephone and asked a series of questions relating to their H.pylori status, demographics, and the various risk factors under investigation. The main variables under consideration were as follows; smoking status, alcohol status, and socioeconomical status. Data for H.pylori positive and negative individuals was analysed for significance using Chi Squared.

Results

From the 138 respondents 50 were found to be CLO positive whilst 83 were found to be negative. From the positive cohort 62% were found to be non-smokers whilst 38% were found to have previously smoked, and 16% were found to be alcohol consumers (>=3 drinks a week), whilst 84% were non-drinkers. The percentages in the negative cohort were as follows; 59.5% non-smokers and 40.5% smokers, whilst 21.4% were alcohol consumers and 78.6% were not. The cohort was divided into six geographic districts (northern harbour, southern harbour, south east, northern, western, and Gozo) with the % of positives being 18%, 30%, 24%, 14%, 14% and 0%, whilst the negatives were 27.4%, 19%, 16.7%, 14.3%, 21.4%, and 1%. Socioeconomic status was assessed based on government pay scales for occupation. Of the positives 79% were >= to grade 10 whilst 21% were < grade 10. For negatives the percentages were 77.8% and 22.2% respectively.

Conclusion

Thus, it can be seen that there was no significant difference in the incidence of the aforementioned risk factors in the positive and negative cohorts.

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Introduction

The purpose of this study was to assess the potential risk factors for *Helicobacter Pylori* in the Maltese population. To this end a cohort of patients who underwent endoscopy in Mater Dei Hospital were all assessed for; smoking status, alcohol intake, socio-economic status, and geographic location and gender, and these were compared against their *H.pylori* status.

Methodology

Participants were recruited from the endoscopy lists of a General Surgeon practicing at Mater Dei Hospital. All participants had undergone oesophago-gastroduodenoscopy between July 2018 and January 2019. Patients were contacted via telephone and asked regarding the following criteria;

- Age
- Locality
- Job
- Diagnosis following OGD
- Smoking status
- Alcohol intake over a week
- Alcohol type

The data collected was split into unmatched negative and positive lists, and assessed for significant differences using the Chi Square test. Localities were grouped into 6 standardised statistical districts. Jobs were classified according to the 20 Government Pay Scales and grouped into above or equal to grade 10, and below grade 10. Individuals who were listed as housewives were omitted from analysis based on the fact that other sources of income (e.g. partner income) would have been difficult to account for.

A total of 72 females and 66 males were contacted, of whom 28 and 22 were positive respectively. Smoking status was divided into non-smokers, ex-smokers, and smokers. Alcohol status was classified as drinker (at least 3 drinks a week or weekend binge) and non-drinkers. 3 drinks a week were used as this would represent a drink/day for at least half the week, whilst a weekend binge was assumed to represent a similar amount of alcohol intake. As respondents were unable to exactly quantify their intake, this measure has been taken to account for this fact. It should be noted that alcohol type was not analysed as the vast majority of respondents claimed mixed intake with no particular preference.

Results

From the 50 participant positive cohort we found that 31 were non-smokers, 8 were ex-smokers, and 11 were current smoker. On the other hand, from the 84 participant negative cohort we found 50 non-smokers, 20 ex-smokers and 14 current smokers. This resulted in a P value of 0.491 at a confidence interval of 95%. (Figure 1)

With respect to alcohol intake, in our positive cohort we had 8 drinkers as opposed to 42 non-drinkers, whilst in our negative cohort there were 18 drinkers and 66 non-drinkers, resulting in a P value of 0.442. (Figure 2)

The cohort was divided into six geographic districts (northern harbour, southern harbour, south east, northern, western, and Gozo) with the positive and negative participants being distributed as follows. In the northern harbour district; 9 positives and 23 negatives, southern harbour district; 12 positives and 16 negatives, south east district; 12 positives and 14 negatives, west district; 7 positives and 12 negatives, and in Gozo 0 positives and 1 negative. The P value for the above data was

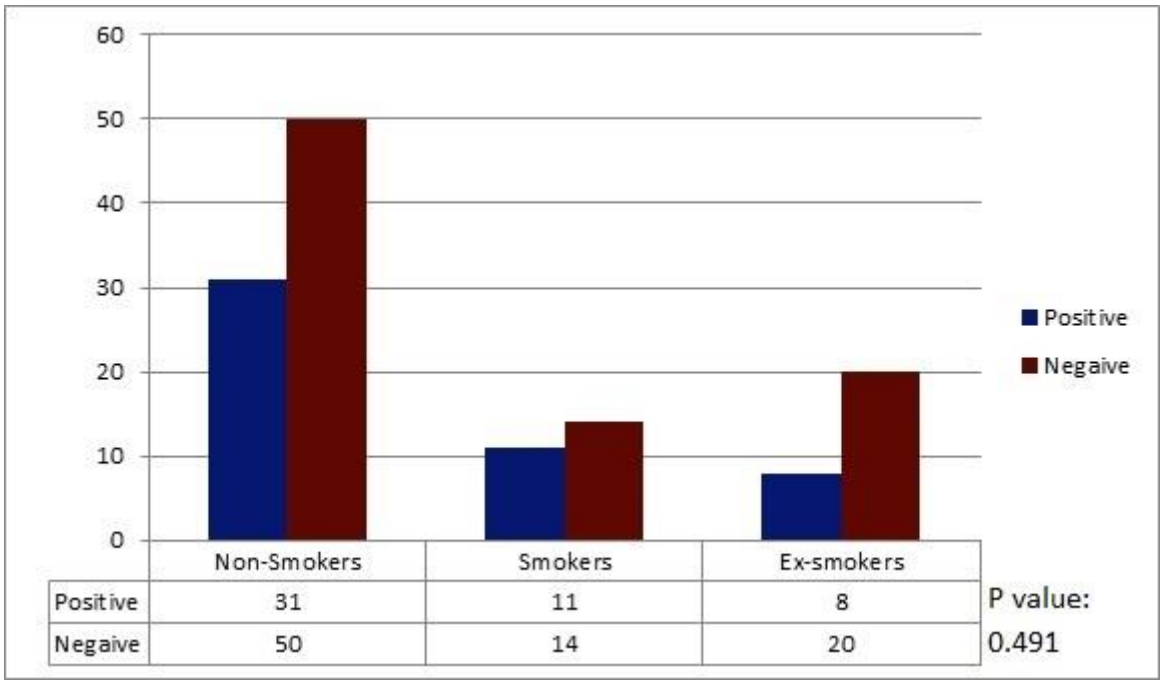
found to be 0.395. It is worth noting that the number of respondents from Gozo was very small due to the fact that the majority of Gozitans elect to undergo OGD at Gozo General Hospital. (Figure 3)

Socioeconomic status was assessed based on government pay scales for occupation. Of the positives 29 were >= to grade 10 whilst 8 were < grade 10. For negatives the percentages were 49 and 14 respectively, resulting in a P value of 0.944. (Figure 4)

From the individuals called 28 females and 22 males were in the positive cohort, whilst 44 females and 40 males were part of the negative cohort. Consequently the P value concerning the association of gender and *H.pylori* risk was found to be 0.684. (Figure 5)

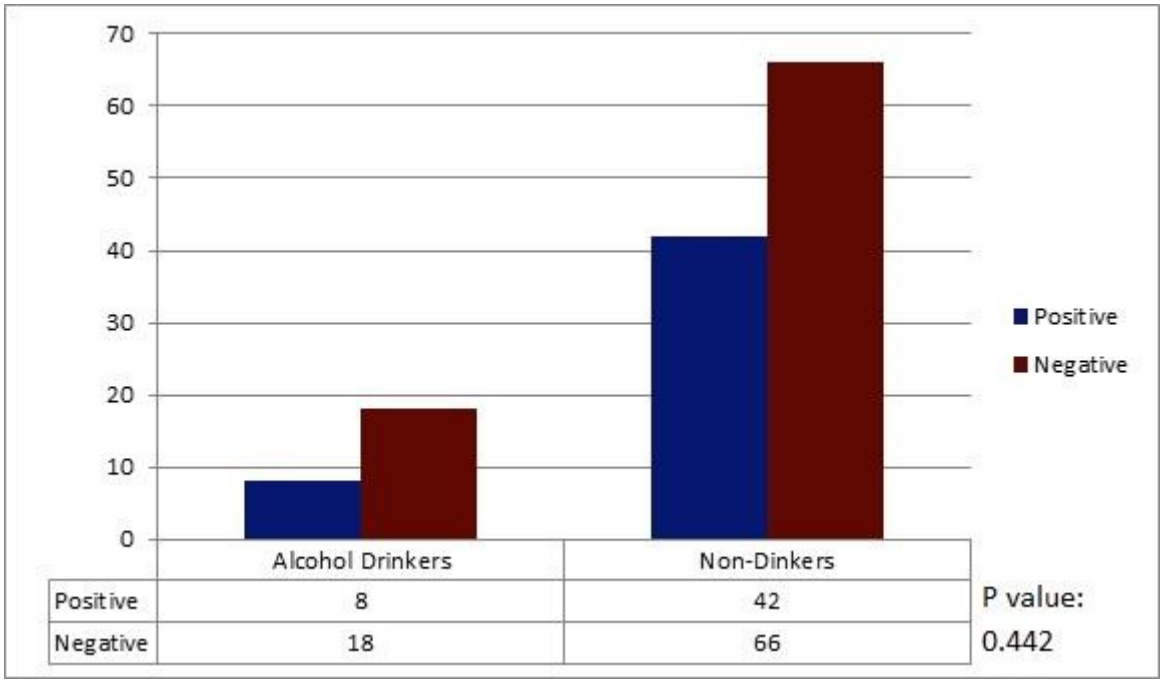
The total sample was split into various age groups, with the positive and negative members being as follows; 16-25 (2,4), 26-35 (6,5), 36-45 (4,13), 46-55 (7,12), 56-65 (18,20), 66-75 (9,22), and 76-85 (4,7). The P value for the association between age and the incidence of *H.pylori* was found to be 0.181. (Figure 6)

Figure 1 Non-Smokers *vs* Smokers *vs* Ex-smokers



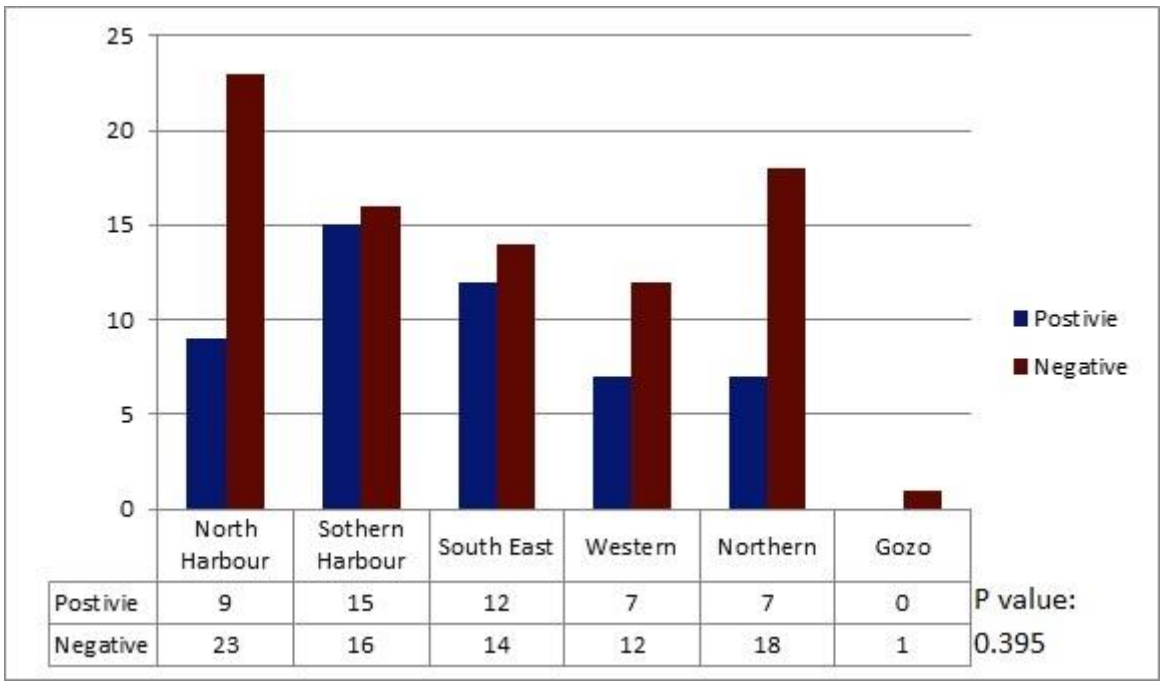
	Non-Smokers	Smokers	Ex-smokers	
Positive	31	11	8	P value:
Negaive	50	14	20	0.491

Figure 2 Alcohol Drinkers *vs* Non-Drinkers



	Alcohol Drinkers	Non-Dinkers	
Positive	8	42	P value:
Negative	18	66	0.442

Figure 3 Geographic Distribution



	North Harbour	Sothern Harbour	South East	Western	Northern	Gozo	
Postivie	9	15	12	7	7	0	P value:
Negative	23	16	14	12	18	1	0.395

Figure 4 Socioeconomic Status

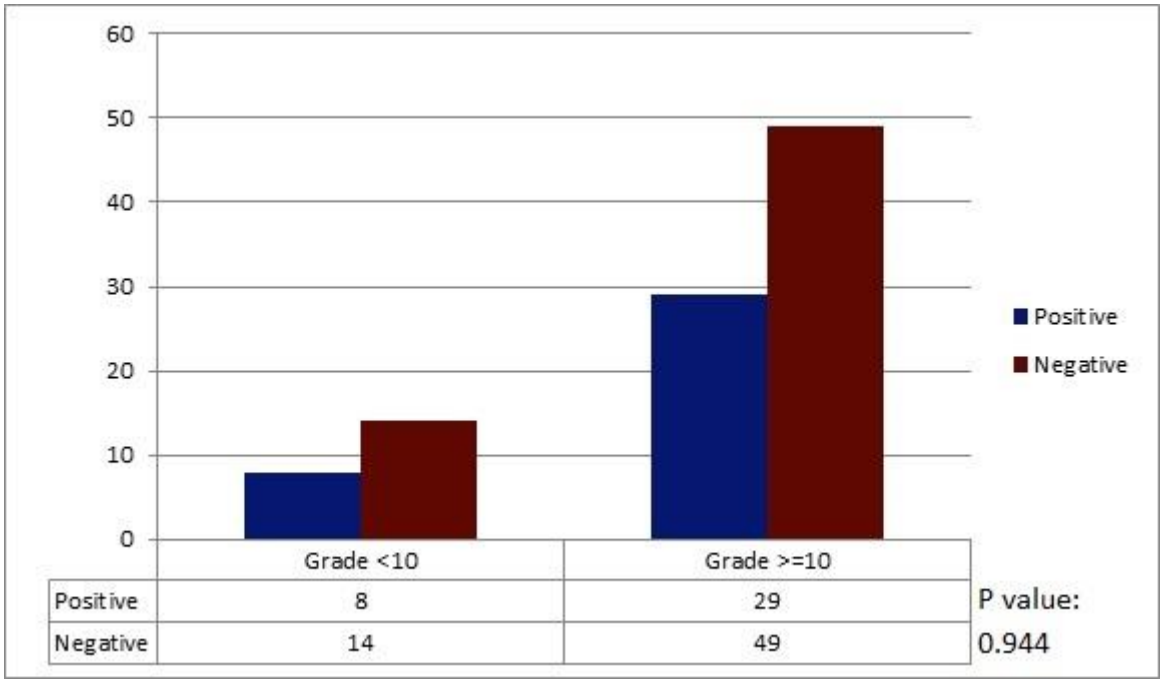


Figure 5 Male *vs* Female

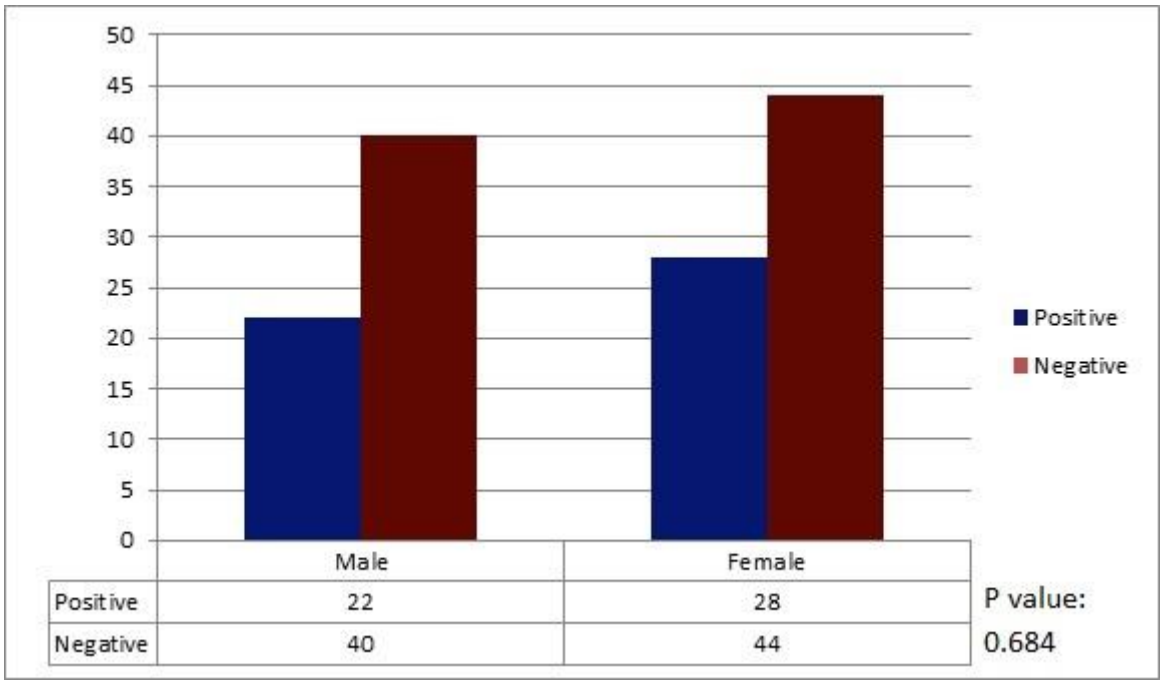
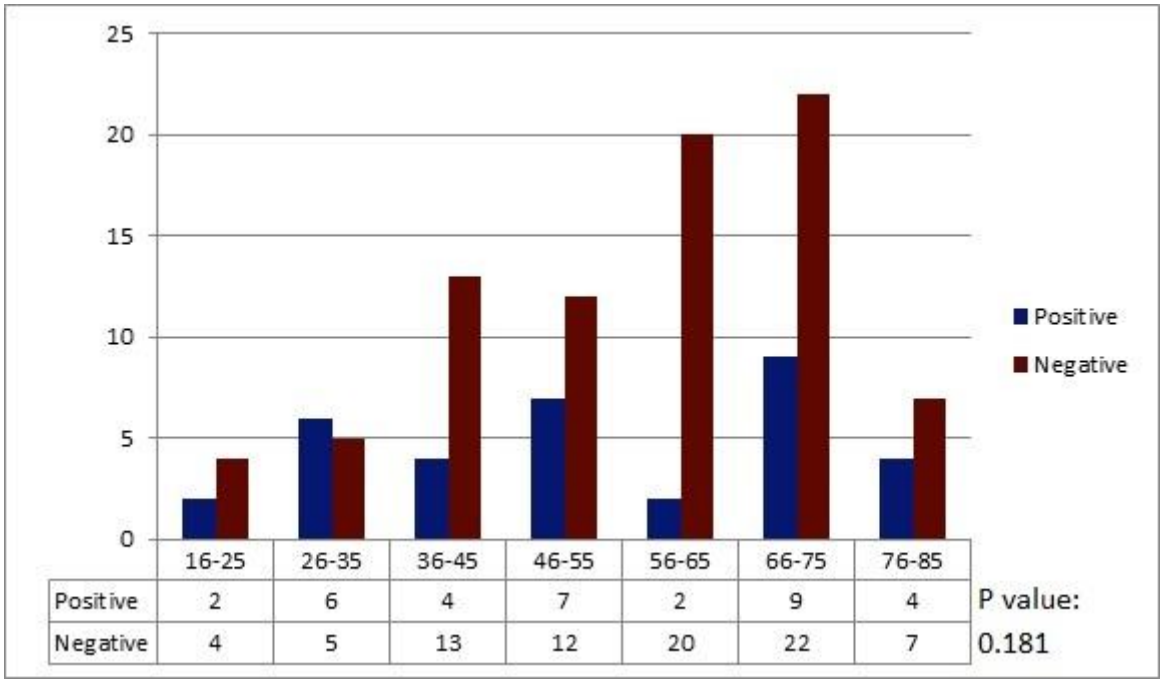


Figure 6 Age Groups



	16-25	26-35	36-45	46-55	56-65	66-75	76-85	
Positive	2	6	4	7	2	9	4	P value:
Negative	4	5	13	12	20	22	7	0.181

Discussion

As stated above no relationship was found between smoking and *H.pylori* infection, however various other studies have been performed which found either a positive relationship, negative relationship or no relationship at all. [1-3] The low number of smokers overall, and the minimal difference in numbers between the positive and negative cohort, made it difficult to ascertain the effects of quantity. The number of cigarettes consumed per day has been previously been shown to have a negative association with *H.pylori* infection.[2] We were also unable to assess the amount of potential second hand exposure to cigarette smoke. It is thus wholly possible that there exists interplay between these factors that masks the effects of smoking on the prevalence of infection. Therefore it stands to reason that further more in-depth study is merited to assess the exact relationship between various forms of smoking, smoke exposure, cigarette consumption and *H.pylori* risk.

With respect to alcohol consumption the results are largely the same as those for smoking, with various papers both being concordant with our results whilst others quote possible positive or negative relationships with *H.pylori* infection.[4-6] An interesting variable mentioned in other papers was the effect of the type of alcohol consumed on the protective effects of alcohol.[7] In this study we were unable to accurately assess the effects of alcohol type due to limitations of sample size and the lack of variation in alcohol preference between respondents. A larger sized study may be merited to look into whether or not alcohol type influences the potential negative or positive relationship with *H.pylori*.

Socioeconomic status is a commonly quoted potential risk factor for *H.pylori* infection in numerous studies.[8-9] However in this study, we

were unable to find any link between income, geographical distribution and CLO positivity. The reason for this may lie in the fact that Malta hosts a densely packed population, where the differences in income, housing conditions, and education may be less pronounced than in the larger countries. In these countries the difference of poverty and wealth are far more pronounced, and there is a greater likelihood that groups of individuals of similar socioeconomic status will reside within the same geographical areas. Consequently, one finds discrepancies in the quality of life, and social determinants of health, within these areas.[10]

Conclusion

From the above data it can be concluded that there is no relationship between *H.pylori* infection and age, gender, locality, socio-economic status, alcohol use and smoking status within the Maltese population. This is in keeping with the limited and conflicting studies performed thus far into *H.pylori* risk factors, and thus further highlights the need for large scale studies encompassing a broader range of potential risk factors for *H.pylori* infection.

Summary Box

Known about this subject:

- *H.pylori* infection inferred to be linked to alcohol and smoking as all three are often related to the development of gastrointestinal ulcers.
- Socioeconomical status is a known risk factor for infection
- Contradicting evidence regarding the link between *H.pylori* and cigarette smoking and quantity of alcohol intake
- Some evidence exists regarding a protective effect of certain forms of alcohol

Findings:

- No socioeconomic discrepancy could be found in this study
- No relationship between smoking and *H.pylori*
- No effect of alcohol quantity on the risk of *H.pylori* infection
- No geographical discrepancies in the rate of *H.pylori* positivity at OGD

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ORIGINAL ARTICLE

Post-operative nausea and vomiting prophylaxis in adult day case surgery: did it justify a local protocol?

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Background

Post-operative nausea and vomiting (PONV) is common following surgery and results in complications. The Society of Ambulatory Anaesthesia (SAMBA) published internationally established guidelines for its prophylaxis. Our aim was to investigate whether guidelines were being followed locally. We also assessed incidence of PONV, delay in discharge or unplanned admissions in adult surgical cases at Day Care Unit. This study was repeated after five years to assess the impact of establishing local guidelines in Mater Dei Hospital in the same year.

Methods

In this retrospective study, we collected information between August and September 2012 and then in 2017. Data regarding vomiting, delayed discharge or unplanned admission due to PONV was documented. Local guidelines were implemented in 2013. Educational measures to raise awareness were carried out, followed by a re-audit in 2017.

Results

195 patients were eligible in the first study and 173 in the second cycle. No statistically significant decrease was found between patients having PONV (12.4%and 10% in the re-audit - $p<0.01$). One in ten patients (1%) had an unplanned admission due to PONV during the first audit with no admissions in the second study. Number of risk factors for PONV did not correlate with anti-emetics given.

Conclusion

The incidence of PONV in adult day cases at our day care unit justifies the use of protocol for better prophylaxis. However, local protocols are not being followed. Education and emphasis of local guidelines can improve the compliance rate.

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Introduction

Post-operative nausea and vomiting (PONV), defined as occurring during the first 24 to 48 hours after surgery is the most frequent side effect after general anaesthesia. It is the least desirable outcome following surgery.[1] The incidence of vomiting and nausea is approximately 30% and 50% respectively, and this may be as high as 80% in high risk patients.[2]

PONV is also linked with an increase in health care cost. The increased expenditure is due to the treatment, delay in discharging of patients both in the acute recovery period and at day care unit and any unplanned admissions due to PONV.[3-6] Parra Sanchez et al. established in 2012 that PONV incurred an extra cost of 75 US dollars per patient in ambulatory day case surgery.[7] Another study, also in 2012, by Dzwonczyk et al. demonstrated that PONV prophylaxis yielded more profits for the hospital than treatment of patients who returned to hospital following day case surgery due to symptoms of PONV.[8] The concept of PONV incurring extra costs to both patients (mainly due to missed wages) and hospitals was already being studied in 1994 when Sanchez et al. published a study about these economic considerations in the Journal of Clinical Anaesthesia.[9]

In 2002, a multidisciplinary international panel of experts from the Society of Ambulatory Anaesthesia (SAMBA) was set up to review medical literature on PONV and to produce guidelines for management of PONV. The aim of these guidelines was to be reliable, clear and above all clinically applicable. The panel based their recommendations on the evidence regarding the prevention and the minimization of PONV. Their primary goals were to identify the primary risk factors both in adults and children, and to recognize the best approach to prevent PONV. A literature review helped to identify a list of the strongest risk factors, and this list was categorized into three groups; patient, anaesthetic and surgical- specific. For patients in whom the risk for PONV was low, the advice is just to watch; moderate risk necessitates 1 or 2 anti-emetics and a high risk would require 2 or 3 anti-emetics. Figure 1 below demonstrates these guidelines.[10]

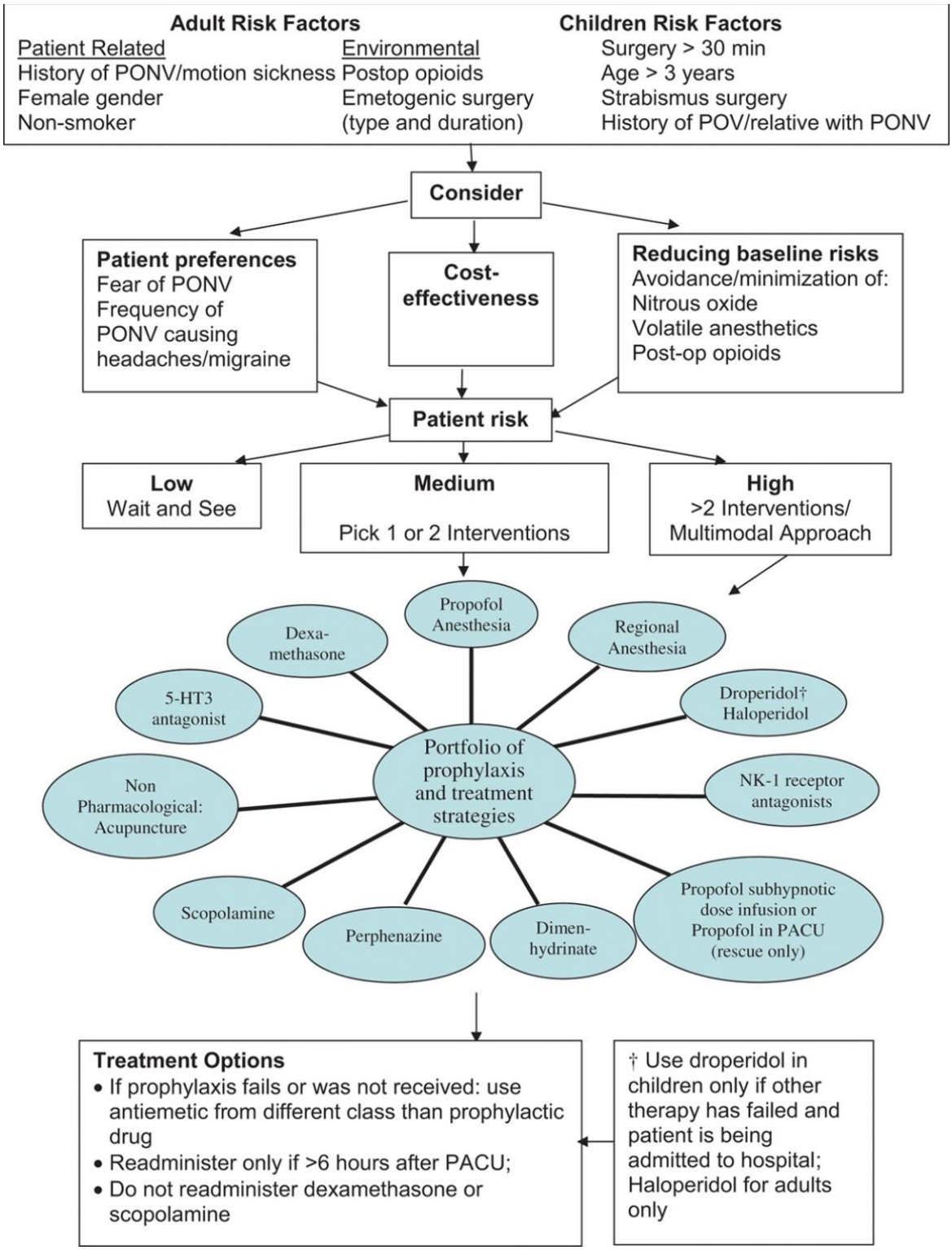
Local practice, at the time of the first cycle, did not follow any strategy both in the prevention and in the treatment of PONV. It was hence felt necessary to offer guiding principles for both prophylaxis and treatment of PONV, and in May 2014, a Guideline Development Group (GDG) produced evidence-based guideline for the management of PONV in patients undergoing Day Surgery procedures.

Why were local guidelines developed?

It is well known that PONV is a particularly challenging issue which has a bearing on both patient satisfaction and appropriate patient discharge. The goal of the recent local guidelines is to provide an easy and inclusive guide to anaesthetists, foundation doctors, anaesthetic and day care unit nurses in order to prevent and treat PONV in Adults undergoing day surgery effectively.

Figure 1 Society of Ambulatory Anaesthesia Guidelines for PONV Prophylaxis, 2002

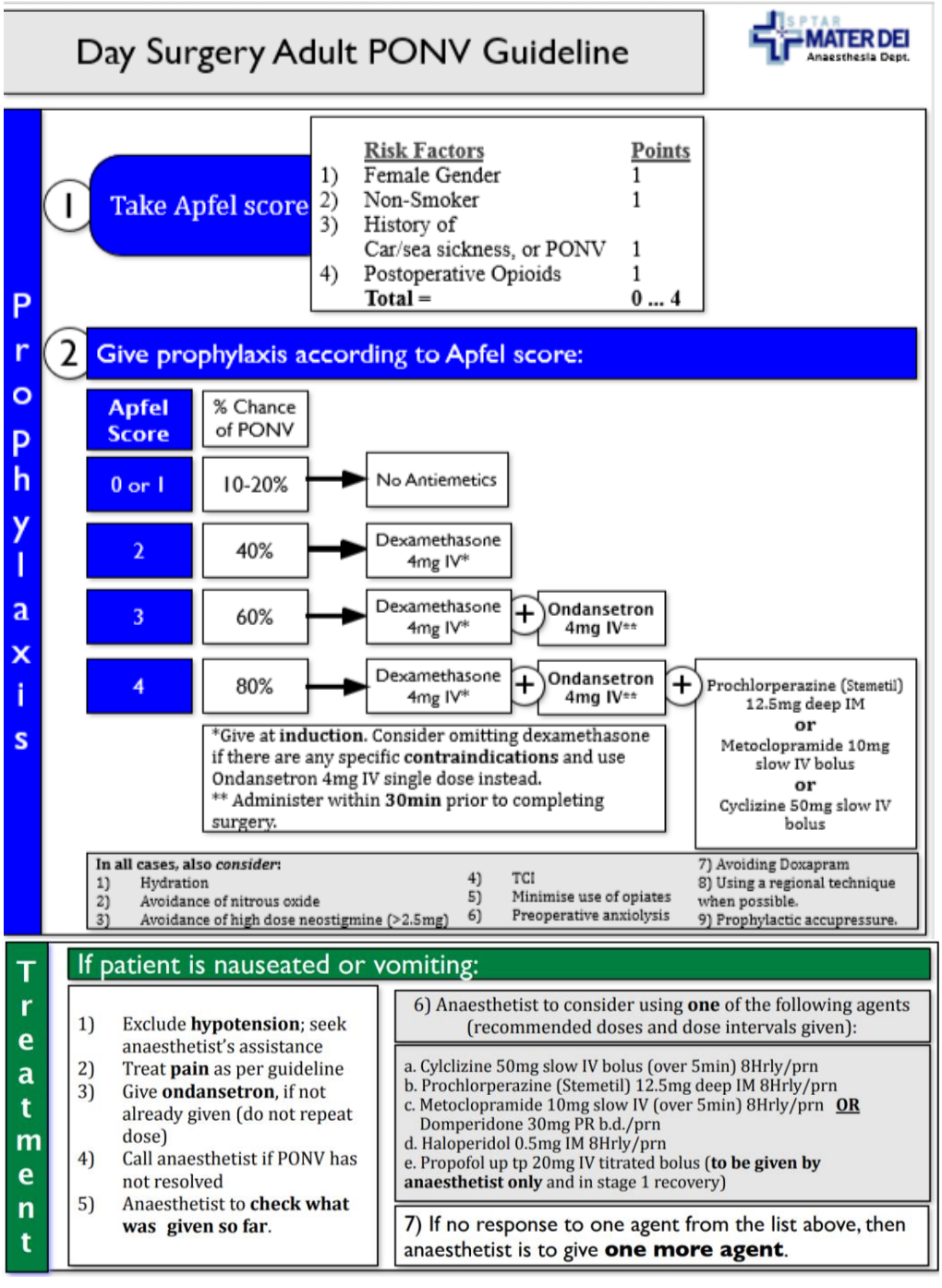
Why were local guidelines developed?



How does the local guideline differ from the existing guidelines issued by the SAMBA?

The SAMBA 2007 guidelines stratify the risk and management according to a rather complex flowchart. On the other hand, the local guidelines were simplified. These consist of two sections, with the first section stratifying patients depending on the Apfel score.[11] The prophylactic treatment is then given according to this scoring system, as per Figure 2 below. The second part addresses treatment of any postoperative nausea and vomiting which may occur in stage 1 recovery or DCU.

Figure 2 Local Guidelines for prophylaxis and treatment for PONV.



It was felt that it would be ideal to re-assess the situation before and after the introduction of the guideline, hence the purpose of this observational study

The objectives of the first audit done in 2012 were primarily to assess the local practice pattern of PONV prophylaxis and compare this with established international guidelines. Following the introduction of the local protocol for the prevention of PONV, the audit was repeated in 2017 to assess such local guidelines and their influence on PONV incidence. The local incidence of PONV, any delay in discharge or unexpected admissions secondary to PONV were also assessed.

METHODS

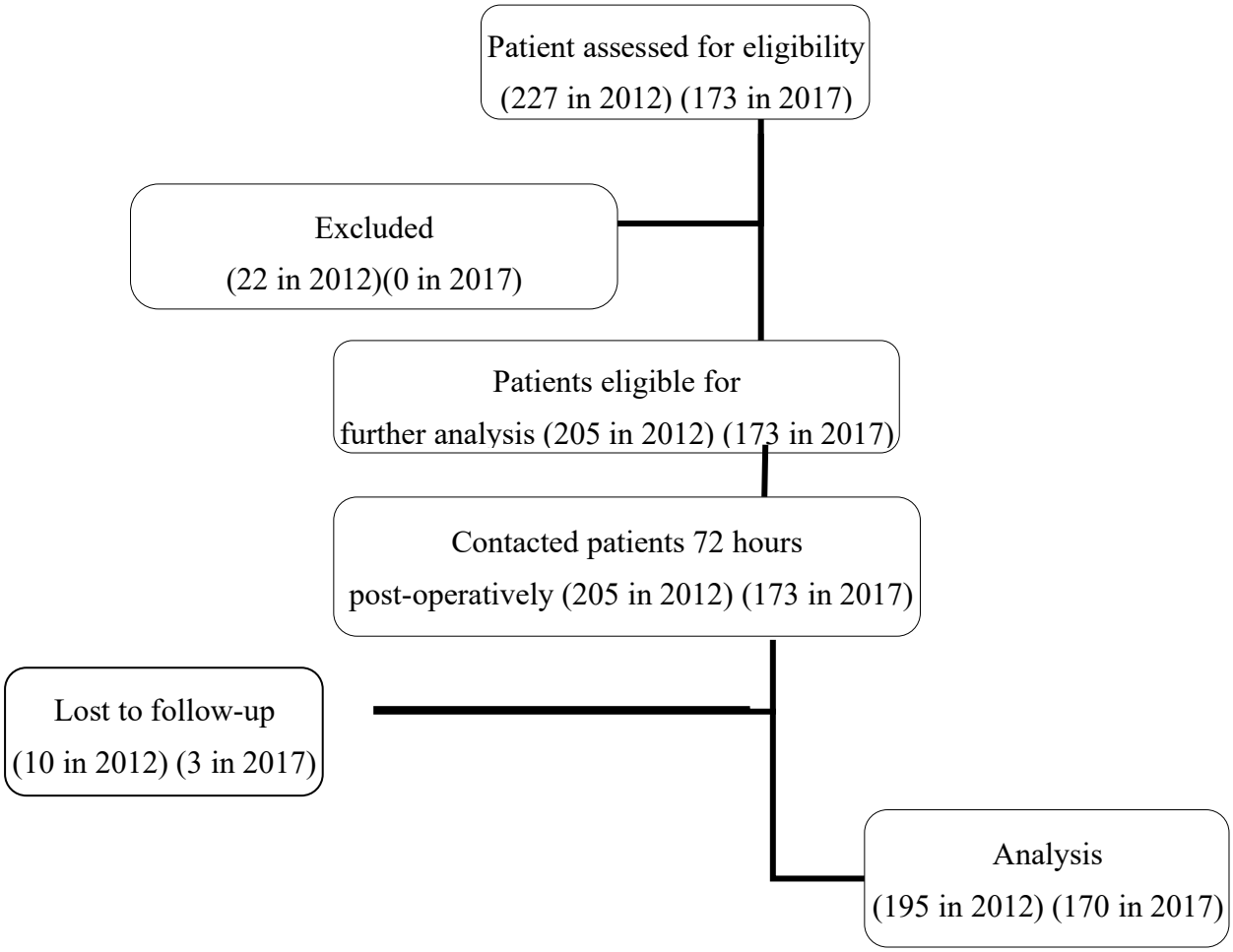
A retrospective audit of adult day care surgical procedures was performed at the Surgical Day Care Unit at Mater Dei Hospital. This was done over a period of 6 weeks between August and September 2012 and again between August and September 2017 Patients were included if they were older than 18 years of age, classified as ASA1 or 2, and were scheduled for elective surgical procedure under general anaesthesia.

Data collected included demographic information, which is depicted in Table 1. Any relevant notes in the patients' files including episodes of nausea or vomiting in recovery stay or at day care unit or any unplanned admissions were noted. Patients were also contacted by telephone 72 hours following surgery in order to confirm any post-operative nausea and vomiting. Data was collected on Microsoft Excel® (Microsoft, US), and analysed using IBM SPSS version 24 (IBM, US).

Table 1 Demographic data of patients included in this observational study

		Frequency		Percentage	
		2012	2017	2012	2017
Surgical Procedure	Gynaecology	96	64	44.1	37.6
	Hernia Repair	32	26	16.4	15.3
	Breast Surgery	6	6	3.1	3.5
	Orthopaedics	41	35	21	20.6
	Other	30	44	15.4	25.6
Age Group	36-45	50	32	25.6	18.8
	46-55	61	47	31.3	27.6
	56-65	31	37	15.9	21.8
	66-75	13	11	6.7	6.5
	75 and over	3	13	1.5	7.6
Gender	Female	135	113	69.2	66.5
	Male	70	60	30.8	33.5
Smoking	Yes	65	42	28.2	22.9
	No	140	131	71.8	77.1

Figure 3 Data collected and analysed in both audit cycles



Results

In total, 400 patients were assessed for eligibility, with data from 365 patients being analysed as shown in Figure 3 overleaf.

Demographic data for the two groups is shown in Table 1, with most of the patients being middle aged, female non-smokers. Most patients had risk factors for PONV. The incidence of PONV in 2012 was 12.8%. In 2017, this incidence was 10%. There was an overall use prophylactic anti-emetics in 51.1% of the total cohort.

Table 2 exhibits the number of patients receiving anti-emetic prophylaxis. Dexamethasone was the commonest drug used as prophylaxis, followed by Ondansetron, which had only been recently introduced in 2012. In all, the total number of doses of antiemetics given was 193.

The use of prophylactic drugs for the prevention of PONV was compared to the number of risk factors, especially for previous episodes of PONV. Overall, those patients who did have previous PONV received an antiemetic in 79.4% of cases, whereas 66.1% of cases received an antiemetic even if there was no history of PONV.

Local guidelines based on Apfel score were used as the audit standard for the second cycle of the audit.

Table 2 Anti-Emetic Doses given as prophylaxis

Anti-Emetic Drug	Number of Patients Given Prophylaxis	
	1st Cycle *n*=205	2nd Cycle *n*=173
Dexamethasone	40	105
Metoclopramide	5	9
Prochlorperazine	6	0
Ondansetron	16	12

Differences between the two cycles

As shown previously in Table 1, there were no particular differences in the demographic data for patients in the two groups.

The number of patients suffering PONV in the first cycle was 25 (12.8%), whereas that in the second cycle was 17 (10%). This was not statistically different.

The use of an antiemetic was much more common in the second cycle, than in the first: a total of 126 doses of an antiemetic were given in 105 patients (62%), compared to 67 doses in 53 patients (27%). Details of the use of antiemetics in each group is shown in Table 2.

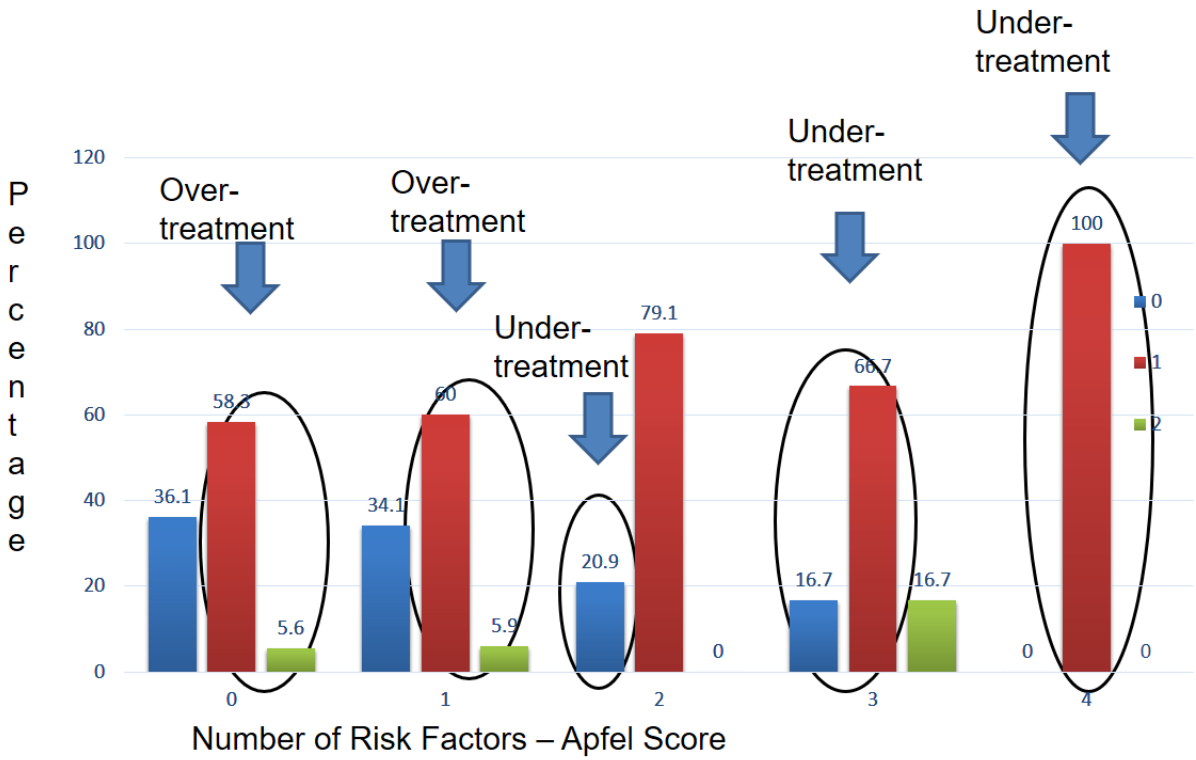
In the second cycle, despite the recommendations, 58% of patients still received an antiemetic, despite having an Apfel score of 0 or 1. A small fraction (6%) of these patients even received two antiemetics. This should be considered as inappropriate treatment, as the guidelines do not recommend anti-emetic prophylaxis for these patients. In total, 225 patients were over-treated. The total extra cost for said overtreatment was calculated at 184.34 euro, using procrurement prices for the antiemeitcs used.[12]

In groups of patients with Apfel score of 2, 79.1% of patients were given one anti-emetic and nobody was given two anti-emetics. Patients with an Apfel score of 3 were given one anti-emetic agent in 66.7% of cases and 16.7% received two anti-emetics.

All the patients with Apfel score of 4 were given one anti-emetic. These were supposed to receive more than one class of antiemetic, so these patients were undertreated.

In the second cycle, 9 patients were found to have no risk factors for PONV. A total of 17 patients (10%) experienced post-operative nausea and 11 patients (6.5%) actually vomited. Of these, 5% were given rescue anti-emetics in the recovery area (most common agent used being ondansetron) and 1% were given rescue treatment in day care unit (0.5% ranitidine and 0.5% ondansetron).

Figure 4 Overtreatment and Undertreatment of Patients based on Apfel Score



Discussion

Our study shows that the lack of local guidelines allowed for a variety of practices which were not based on evidence. However, the introduction of such local guidelines do not significantly improve adherence to established international guidelines.

The overall rate of PONV in our cohort of patients was 11%. This compares to other studies, such as by Gan et al, which quotes a figure of up to 30% in the US.[15]

The use of dexamethasone as an antiemetic is well-established.[16] It is considerably cheaper than ondansetron, and it also seems to improve analgesia.[17] This might have contributed to dexamethasone use being so prevalent, and to the overuse of this drug even if there was no specific indication.

It is disheartening to see that despite the introduction of a local policy, adherence after a year was so poor. A lot of patients received anti-emetics when not indicated, but a lot of patients also received too little when this was indicated. However, such an effect is not new.[19–21] Kooij et al studied PONV prophylaxis being prescribed preoperatively for patients with 3 or more risk factors. Only 35% of these patients were appropriately prescribed prophylaxis. They recommended that electronic alerts included in the preoperative system may improve these results.[19] Brampton et al carried out a yearly audit about incidence of PONV in their centre and the best rate of adherence to PONV prophylaxis guidelines was reported in 2012 when it was 67%.[20] In a multicenter observational study in 2013, White et al showed that maximal drop was obtained in PONV rates when more than three anti-

emetics were given to patients, however less than 70% adherence to hospital guidelines was noted.[21]

A number of limitations were identified related to this study. Firstly, ophthalmic and ENT surgery patients were not included since they do not attend day care unit even for day case procedures. These operations are generally known to carry significant risk of PONV. In our study, we did not differentiate between early or late PONV. Patient satisfaction with anti-emetic prophylaxis was not noted.

Pain scores were not taken into account during this study. Pain, especially if severe, can influence the perception of nausea and vomiting, and can also increase use of opiates.[22] Patient's overall satisfaction with their experience was also not included.

Improved awareness and education regarding PONV guidelines will help improve adherence. In some centres, computer systems are used in anaesthesia with automated reminders regarding PONV prophylaxis, and this has been shown to improve compliance.[23] These automated reminders may even be customized to request a reason for non-adherence to guidelines, and this has also improved compliance in itself.[24] Having guidelines in place for specific types of surgery which are considered high risk, such as breast and gynaecological surgery, may also help to improve outcomes.[25] Simplifying algorithms for PONV prophylaxis and treatment as much as possible has also been shown to help[26], however our local guideline is already quite simple at present.

This study highlighted the fact that locally, despite the introduction of new guidelines regarding prophylaxis and management of post-operative nausea and vomiting, adherence is still relatively poor and improvement is needed to avoid both over-treatment with its attendant costs as well as under-treatment with resulting morbidity.

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ORIGINAL ARTICLE

Screening in-patients for risk of malnutrition

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Introduction

Malnutrition is used to define an imbalance in nutrition and is seen in hospitalized patients. The aim of this study was to assess the risk of malnutrition in patients admitted to the acute medical wards. The 'Malnutrition universal screening tool', was used as a gold standard.

Material and Methods

Data was collected from adult patients from acute medical wards. The data collected included the identification number, age, gender, reason for admission, comorbidities, weight, height, unplanned weight loss in the last 3-6 months and the number of days of no nutritional intake. By means of the MUST, the overall risk of malnutrition score was obtained and its management was recorded.

Results

Fifty patients were recruited and 18% were found to be at medium risk of malnutrition while 36% were found to be at high risk. Only 2% of such patients had a dietician referral and/or adherence to the guideline. Despite 58% of patients were found to have a Body Mass Index score of 0, 21% of these had a BMI score of >30kg/m^2, with 14% of which were admitted secondary to a cardiovascular or respiratory cause.

Discussion

Skills and time are required to diagnose a patient with malnutrition. However, the MUST screening tool, enables this to be done quickly and appropriately. Moreover, implementation of mandatory nutritional screening on admission will allow an increase in dietician referrals and the correct management of this along with the patient's illness, leading to a faster recovery, shorter hospital stay and better long term prognosis.

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Introduction

Malnutrition is commonly used to define an imbalance in nutrition, mostly seen in hospitalized patients at an approximate rate of 25-40%, as reported by European studies.[1] This broad term includes over-nutrition, mostly seen in developed worlds, to under-nutrition in developing countries, as well as in hospitals and residential care facilities in developed countries.[2-4] Malnutrition is related with a negative outcome in patients. Higher rates of infections, muscle loss, delayed wound healing and a longer stay in hospitals are seen in malnourished patients thus increasing the morbidity and mortality rates.[5-11]

In hospitalised patients, malnutrition is often a combination of disease-related cachexia, characterised by extreme loss in body weight, muscle and fat and inadequate nutrient intake.[12]

Obesity, measured by body mass index has become prevalent in both men and women worldwide, resulting in hazardous health implications. Obesity is influenced by genetic, environmental and behavioral factors[13] and more commonly it is associated with Type 2 diabetes mellitus,[14] cardiovascular disease,[15] obstructive sleep apnea,[16] osteoarthritis,[17] hepatobiliary disease[18,19] and a shortened life span.[20]

Originally, the Malnutrition Screening Tool (MST), a three-question tool which assessed recent appetite and weight loss in general medicine, surgical and oncological patients was designed to be used by non-nutrition-trained staff. This tool made use of a scoring system which identified patients at high risk of malnutrition and hence referred for further management by dieticians.[21-23]

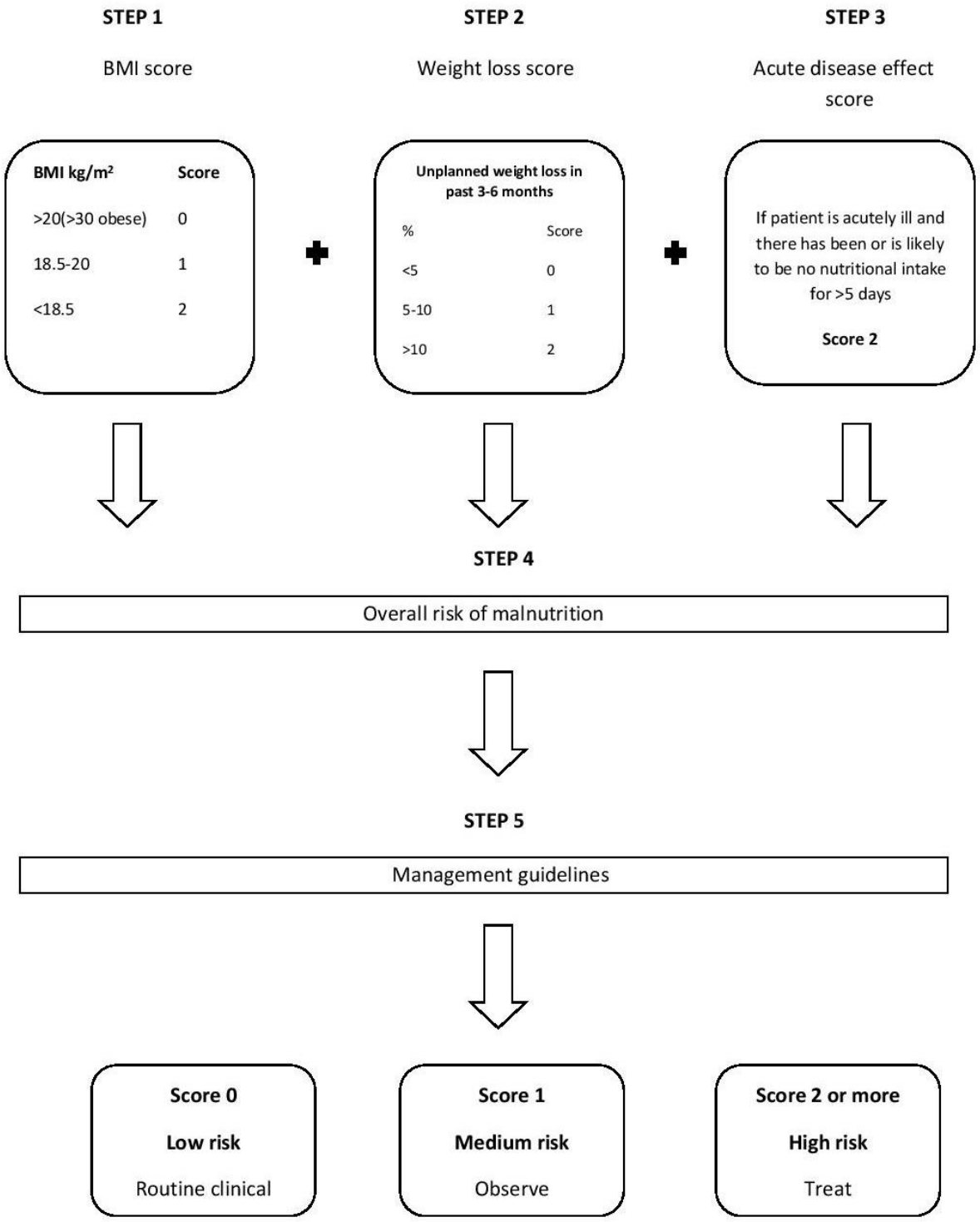
Corresponding to the MST, the Malnutrition Universal Screening Tool (MUST), is a five-step screening tool to identify adults, who are malnourished, at risk of malnutrition (under-nutrition), or obese. It also includes management guidelines which are useful to develop a care plan depending on the score obtained (Figure 1). The design of this tool allows for it to be used in multiple settings including hospitals, nursing homes, the community and can be easily used by all healthcare workers. The MUST, has been shown to give reliable results, however limitations include not being validated in children and renal patients or to be used to detect deficiencies or excessive vitamins and minerals intake.[24-26] The aim of this study was to assess the risk of malnutrition in patients admitted to the acute medical wards.

Materials and Methods

Adult patients (defined as above 16 years of age) admitted in the acute medical wards at Mater Dei Hospital between April and May 2019 were recruited. The identification number, gender, age and reason for admission were noted.

Patients diagnosed with an active cancer during the study were not included in the data collection, hence the terms anorexia, cachexia and sarcopenia were not used. The reason for this being that measurement of muscle is more complex and the ideal tests for measurement of sarcopenia are DEXA scanning and CT or MRI.[27] Furthermore, the MUST score, which is a standard validated tool, was used. Other exclusion criteria including the clinical evidence of fluid overload such as ascites, pleural effusions and lower limb oedema secondary to fluid overload.

Figure 1 Patient's risk of malnutrition and management pathway



Patients had their weight and height measured as to measure their Body Mass Index (BMI). In those patients who were not able to get out of bed or stand up, they had the BMI calculated by measuring the mid upper arm circumference (MAUC).

The patient was asked to bend the left arm at the elbow at 90 degrees angle. The upper arm was held parallel to the side of the body and the distance between the acromion and the olecranon process was measured to obtain the mid-point. The circumference of the mid upper arm was then measured in centimeters at the mid-point obtained earlier. If MUAC is 23.5 cm, the BMI is likely to be <20 kg/m^2 and if the MUAC is 32.0 cm, the BMI is likely to be >30 kg/m^2.

Other data that was collected was:

- Unplanned weight loss. This was scored according to tables that were provided (Table 1). The patient is asked if he/she experienced any weight loss in the last 3-6 months, and if so by how much.
- Establish acute disease effect and score (Patients who are acutely ill or the likelihood/no nutritional intake for more than 5 days results in a score of 2)
- Documentation of dietary intake, referral to a dietician, repeat nutritional screening,

The patient's risk of malnutrition and management pathway were then assessed using the flow chart in Figure 1.

Table 1 Patient cohort and MUST Score

	Score of 0	**Score of 1**	**Score of 2**
Step 1 (BMI score) %	BMI >20 kg/m^2	BMI 18.5-20 kg/m^2	BMI < 18.5 kg/m^2
	58%	36%	6%
Step 2 (weight loss score) %	<5%	5-10%	>10%
	68%	28%	4%
Step 3 (Acute disease score) %	90%	6%	4%
Overall Risk of Malnutrition (Addition of Steps 1-3)			
	Low Risk	Medium Risk	High Risk
Step 4	46%	18%	36%

RESULTS

Total number of patients recruited were 50. Their mean age was 73.04 year (range 34-92 years), the majority being female (66%).

Overall, 46% of patients were not at low risk of malnutrition, 18% were at medium risk of malnutrition and 36% were considered at high risk (Table 1).

Out of 54% of patients who were at medium or high risk of malnutrition only 2% had a dietician referral and/or adherence to the guideline.

More than half of the patients (58%) had a BMI assessment score of 0. However, it is important to note that 21% of these patients had a BMI score >30 kg/m^2 and 14% of which were admitted with a cardiovascular or respiratory diagnosis.

All patients had at least 1 co-morbidity. Figure 2 outlines the number of co-morbidities that patients had, where more than a third of patients had more than 3 co-morbidities. The most common co-morbidities were Hypertension (42%), ischemic heart disease (22%), congestive heart failure (16%) and chronic obstructive pulmonary disease (COPD) (12%). Other co-morbidities included renal impairment and dementia.

The most common clinical indication for hospital admission were respiratory tract infections, presenting as pneumonias (24%), Infective asthma (2%) or COPD exacerbation (8%). The other clinical reasons for admissions are listed in table 2.

Figure 2 The number of co-morbidities

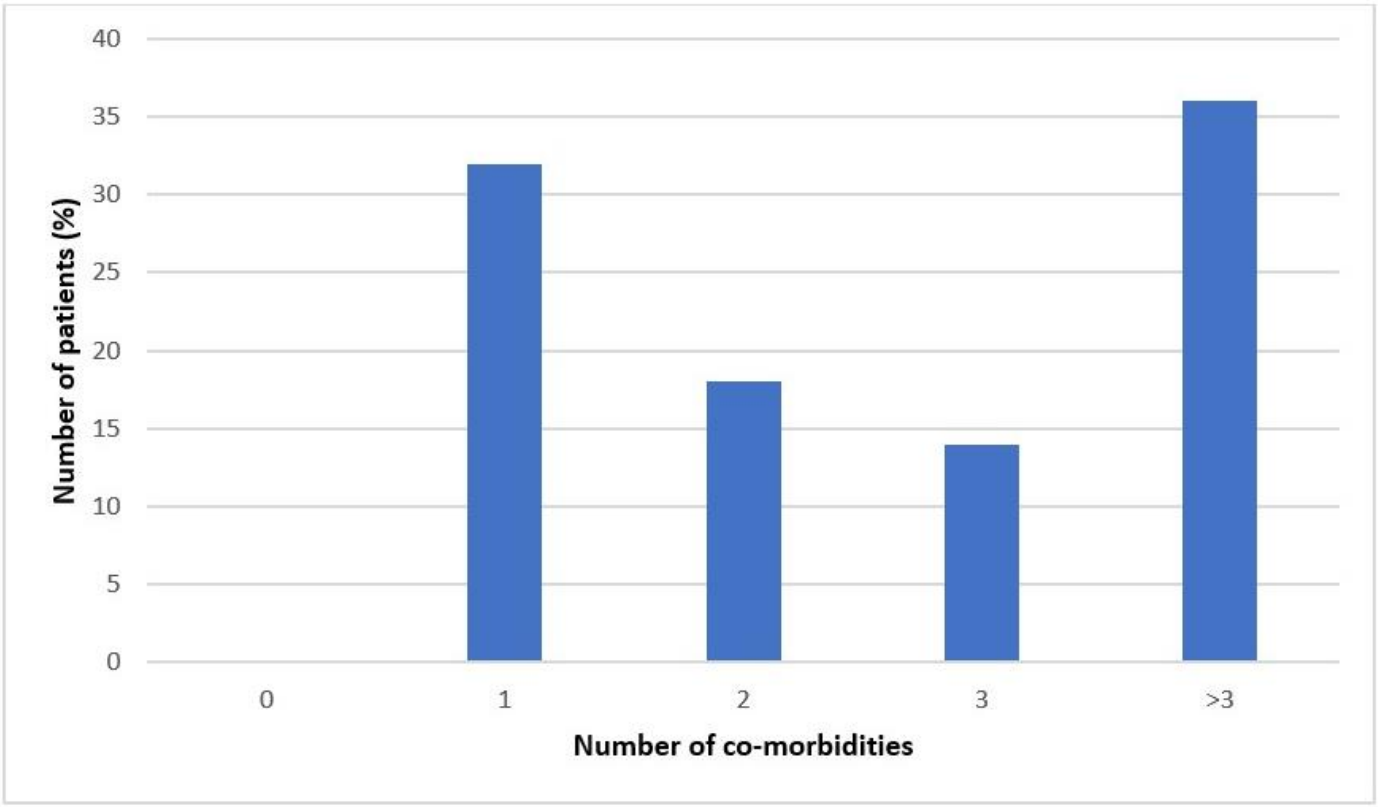


Table 2 Diagnoses with which patients were admitted to hospital

Diagnosis	%
Pneumonia	24
Chest pain	16
Fall	10
CHF exacerbation	10
Infective COPD exacerbation	8
UTI	6
Endocrine disorders/Uncontrolled diabetes	6
Thromboembolic events	4
Headache	4
Constipation	4
Confusion	4
Infective asthma exacerbation	2
Anemia	2

Discussion

This analysis involved 50 patients and was carried at Mater Dei Hospital in Malta. The majority of patients (54%) in this study were found to be at risk of malnutrition, which according to the guidelines require observation and/or referral to the dietician for treatment. Unfortunately, only 2% of patients' malnutrition was treated as per guideline.

The presence of comorbidities is a known risk factor for malnutrition. Approximately a third of the patients (36%) of the patients were noted to have more than 3 comorbidities, thus demonstrating that approximately a third of the patients were chronically ill despite exclusion of patients with malignancy. A limitation in this study was the number of patients involved. However, considering the diagnosis, this is representative of the population.

Assessing the nutritional status of the patient requires skills and time. Patients are often referred to a dietician by the medical and nursing staff in view of this matter. This leaves little time for the dietician to screen other patients for malnutrition. Furthermore, malnourished patients in the acute setting are missed to be identified and are therefore not referred for nutrition assessment and optimisation.[28] This causes a window of missed opportunity to treat and prevent

consequences on both the patients and the healthcare system.

Unpleasant results of malnutrition include the increased risk of pressure ulcers, infections, delay in wound healing, alteration in thermoregulation and impairment of renal function.[2, 10, 11, 29] It also causes loss of muscle and fat mass, a reduction in the respiratory and cardiac function along with atrophy of visceral organs.[7,10,29] On a psychological level malnutrition causes fatigue and apathy which causes a delay in recovery. It has been reported in literatures that malnutrition increases the length of hospital stay and imposes further stress on the acute health care facilities. As malnourished patients have higher rates of infections pressure ulcers and are less independent, the need for a greater nursing care and medications increases.[30-33]

An important missed opportunity in screening patients for malnutrition on admission is referring obese patients for the management of weight loss. In this analysis, 21% of patients were found to have a BMI >30kg/m2, 14% of which required admission due to cardiovascular or respiratory disease. Obesity, an imbalance in nutrition due to over nutrition, is associated with an increase in multiple comorbidities which can involve multiple systems such as the cardiovascular, neurological, musculoskeletal and the reproductive system.

Obesity also imposes stress on the healthcare system through higher emergency room and doctor visits, admission to hospitals, investigations, medications and sick days. Limitations of this study include the relatively small sample. However, from routine clinical practice we believe that these results mirror the actual clinical occurrence and referrals.

In conclusion, the introduction of a simple tool, that does not take a long time to perform and that can be done jointly between the caring physician and an allied health care professional can result in both the identification and management of this common problem.

Summary Box

What is already known about this subject:

- Identification of malnutrition is fundamental for its treatment
- Many malnourished patients in the acute settings are not identified and hence not referred for assessment and treatment
- Malnutrition is known to cause impairment at the cellular, physical and psychological level. It also places additional stress on health care facilities with a longer hospital stay and increase in hospital costs

What are the new findings:

- Lack of use of the 'MUST' score in the referral and management of malnutrition
- A third of malnourished patients are chronically ill
- Lack of weight loss referral for obese patients is secondary due to lack of screening on admissions

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ORIGINAL ARTICLE

Student and doctors' handwriting and transcription skills: how great is the potential for medical error?

Yimeng Zhang, Nicole Marie Zerafa, Simon Attard Montalto

Illegible handwriting and prescription errors within healthcare settings have consistently been shown to affect patient wellbeing. The aim of this study was to analyse the handwriting and transcription skills in cohorts of undergraduate students and doctors or varying levels of experience, and assess the impact of these skills as a potential for prescription errors. Students and doctors were asked to copy and complete a pre-prepared prescription including five medications onto a standard hospital prescription chart. Every participant's handwriting was graded using a standard score, cross-checked by two researchers and a further three independent assessors.

166 prescriptions were completed by 137 students and 29 doctors, of which 15 had some prior handwriting training. Handwriting quality was of 'print quality' in 25% of the participants, legible in 50% and poorly legible in 25%. Transcription and prescription errors were made by 92% of all participants, with a mean and median of 2 errors per participant. 111 errors made in the writing of patient's name, identification, age, height, weight and allergies. 422 errors were identified in the prescriptions of the 5 given medications, including the omission of drug details (53%), incorrect dosage (49%) and incorrect instructions for administration (47%). Although some of these errors were relatively minor, all could have resulted in serious consequences if extrapolated to real patients.

78% of participants admitted to being concerned with poor handwriting and would take appropriate action, 22% reported that they would choose to ignore illegible texts. Undoubtedly, the causes of prescription errors are multifactorial secondary to a combination of individual and organisational factors and there are no standardised methods to ensure error-free prescriptions. A concerted effort to address this problem at undergraduate level, and ongoing emphasis during and after medical training is essential if medical errors and subsequent patient morbidity and medico-legal costs are to be averted.

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Introduction

Illegible handwriting and prescription errors within healthcare settings have consistently been shown to affect patient wellbeing. Mistakes may cause delayed treatment, unnecessary tests and inappropriate/incorrect prescriptions and doses, which can all ultimately lead to decreased quality of patient care causing significant morbidity and mortality.[1-2] This issue has also been demonstrated to have adverse medico-legal implications, as well as affecting the efficiency of those working in healthcare, leading to frustration and wasted time.[3]

The Institute of Medicine in the United States (IoM) reported that medical errors cause approximately 44,000-98,000 preventable deaths annually, of which, 7,000 deaths are attributable to illegible handwriting alone.[2] Indeed, doctors are known to have poor handwriting, possibly due to their time constraints and demands for multi-tasking.[4-5] In the workplace, poor handwriting and related practices should be brought to attention without delay and remedial steps taken to implement change and prevent unnecessary patient harm in the future. Therefore, it is crucial to assess the legibility of handwriting within the medical profession at all levels from student level, at the start of doctors' careers and after some years working in the field.[6]

The aim of this study was to analyse the handwriting of, as well as identify prescription errors made by both medical students and doctors working in a large, busy National General Hospital. This is to determine any characteristics within these two populations that may influence the quality of handwriting.

Method

Subjects

The study was conducted at Mater Dei Hospital, an 800-bedded National General Hospital and incorporating the only State-run Medical School in Malta. Students in the third year through to fifth (final) year of the medical course where recruited to take part in the study. Students were selected by contacting every third student within the class list of each of the three student cohorts. Doctors ranging from junior doctor through to consultant level were randomly selected to take part in the study. These included junior doctors in the first and second year of their foundation programme, basic and higher specialists in training, resident specialists and consultants within a number of departments, including Medicine, Surgery, Paediatrics, Psychiatry and Anaesthesia. Other doctors who delivered tutorials to the co-authors, according to a pre-set rota prepared by the Medical School of Malta, were also invited to participate. The randomly selected students and doctors were briefed and invited to participate. All were free to decline or opt out without reservation at any stage of the study.

Questionnaire

The handwriting of participants was assessed by asking participants to complete a brief questionnaire and copy a pre-set list of medications onto a routine-issue Mater Dei Hospital prescription chart. The questionnaire, summarised in Figure 1, was divided into three sections: the first requested simple participant demographic data, including age, gender, and current training/job level. The second part consisted of the handwriting task: a fictional patient admitted to hospital for treatment was presented. He required five medications that varied in the complexity of their generic name,

route of administration, dose and frequency of administration. An example of a correctly completed drug chart is shown in Figure 2. The participants were asked to transpose the five medications from the narrative provided onto the standard treatment chart, as a theoretical exercise (not on the wards) and without any time constraints. Participants were asked not to sign the drug chart to maintain anonymity.

The final part of the questionnaire requested self-reflective feedback from participants in order to gauge their own attitude toward legible handwriting. Participants were also asked what action would they take when encountering poor-to-decipher handwriting. All participants were asked whether they had had any prior training in handwriting skills, or not.

Figure 1 Summary of Questionnaire

Part 1: Basic Information

Age:

≤ 20	
21-30	
31-40	
41-50	
51-60	
≥ 61	

Gender: M / F

Position: Student Year: 3, 4, 5 / FY1 / FY2 / BST / HST / SR / Consultant

Department: _____

Part 2: Case Scenario

A 60-year gentleman, Mr Mario Borg, ID 079165(M), 80Kg, DOB (4.2.1963) was admitted to MS7 ward, MDH. He was allergic to penicillin and NSAIDS. He was prescribed the following medications: Paracetamol, five hundred milligrammes by mouth, as required for fever; Ipratropium bromide, five hundred microgrammes by nebulizer, six hourly; Gentamicin naught point three per cent eye drops, three times a day; Mogamulizumab one milligramme per kilogram intravenously, once a week for eight doses; Gliclazide sixty milligrammes slow release, by mouth, once daily.

Please transcribe the above information of the case into the prescription sheets on pages 3 and 4.

Part 3: Questions

Before completing this part of the questionnaire, please fill in part 3, beginning overleaf.

1. Taking what you have written in the prescription on the next page, how would you rate what you have written in terms of legibility when compared to your usual handwriting?

Much Worse	Worse	Same	Better	Much Better
1	2	3	4	5

2. How much are you bothered by illegible text in this hospital?

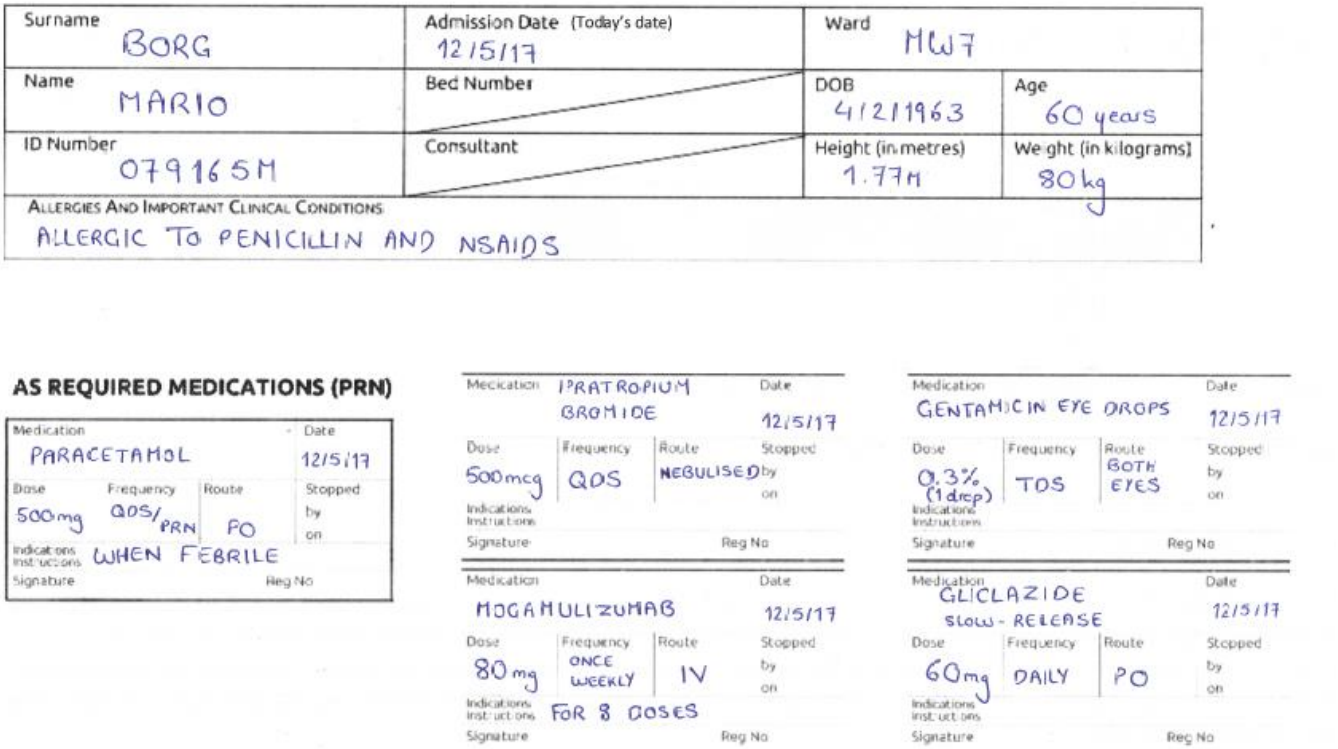
Very Bothered	Quite Bothered	Somewhat Bothered	Hardly	Not At All
1	2	3	4	5

3. What do you normally do when you encounter something which you could not read clearly in any hospital documentation? *(Tick one or more from the following)*

i.	Ask a colleague for help	
ii.	Call / speak to the person who wrote it to clarify	
iii.	Try and find more information elsewhere	
iv.	Ignore the text	
v.	Other *(please specify)*	

4. Have you ever had any formal training in handwriting/calligraphy? YES / NO

Figure 2 Example of correctly filled in Drug Chart



Data Analysis

Each aspect of the completed treatment chart was independently scored by two authors. The drug name, its route, dose and frequency of administration, as well as the date of the prescription were assessed for legibility and whether any errors were made on the prescription. The list of errors reviewed is shown in Table 1.

A rating scale for grading the degree of legibility of the handwriting was designed. This used a Likert-score from one to five, ranging from: *Print quality (=1); Clearly Legible (=2); Moderately Legible (=3); Barely Legible (=4) and Completely Illegible (=5)*. If a discrepancy was noted between the score awarded by each of the two authors, the better of the two scores was taken as the final grade.

Inter-assessor variability and any potential bias was minimised by asking independent assessors to review and grade every tenth prescription. To this end, three independent assessors who were fluent in English and acquainted with the study investigators but from outside of the field of Medicine were invited to independently score treatment charts. The scores awarded by these three independent assessors: a fourth year English student, a third year Psychology student and a newly graduated lawyer, were then compared with those awarded by the authors.

Anonymous data was collected and analysed using unpaired t test, comparisons were made between the results obtained from different grades of students and doctors. A p value of ≤ 0.05 was taken to represent a significant association or difference.

Table 1 List of errors analysed by medication

Drug	Error
Paracetamol	Spelling
	Dosage
	Dose Units
	Frequency
	Route
	Indication
Ipratropium Bromide	Spelling
	Dosage
	Dose Units
	Frequency
	Route
Gentamicin	Spelling
	Dosage
	Dose Units
	Frequency
	Route
Mogamulizumab	Spelling
	Dosage
	Dose Units
	Frequency
	Route
	Stop Date
Gliclazide	Spelling
	Dosage
	Dose Units
	Frequency
	Route
	Slow Release

Table 2 Data on questionnaires returned

Position	
Student Year 3	49
Student Year 4	49
Student Year 5	39
Foundation Doctor	8
Specialist Trainee	6
Senior Registrar	5
Consultant	9
Job Title Missing	1
Total	**166**

RESULTS

A total of 150 students and 50 doctors were invited to participate over a six-week period, from March to April 2017. A total of 200 questionnaires were distributed and 166 (83%) questionnaires were completed, 137 by medical students and 29 by doctors. 15 (9%) of the participants admitted to have had previous handwriting training. The breakdown of the results from the questionnaires collected is shown on Table 2.

Handwriting quality

There were a total of 25 (15%) instances where the grades awarded by the two authors did not match. In those cases, the lower (better) grade awarded was accepted for analysis. The third party independent assessors reviewed 17 questionnaires, and in all cases awarded the same grade as those given by the two authors.

In total, 41 participants (25%) had print-quality handwriting, 84 (50%) were clearly legible, 36 (22%) moderately legible, five (3%) barely legible and none were completely illegible. Figures 3 and 4 show the breakdown of the handwriting grades between the different training levels with no statistical difference noted between the student and doctor groups (p=0.35).

Errors in transcribing patient information

When transcribing the patient data onto the 'Patient Information' section of the Drug Chart, participants recorded a total of 111 mistakes or omissions. 37 participants (22%) failed to complete or inputted incorrect information relating to the section on allergies. 28 (17%) recorded an incorrect age for the patient, 18 (11%) incorrect height, 9 (5%) incorrect weight, and 13 participants (8%) made mistakes in the transcription of the patient's name, surname or identification number.

Errors in prescription

The questionnaire required the participants to transcribe five drugs into a drug chart using their generic name, dose and frequency. A total of 422 prescribing errors were made by the 166 participants. 14 (8%) participants handed in a faultless drug chart, 37 (22%) committed a single error, 44 (27%) made two errors, 31 (19%) three errors, and 49 (30%) of participants made between four to nine prescription errors (Figure 5). The most common errors included: omitting the term 'slow release' for Gliclazide in 53% of cases, not calculating the correct dose of Mogamulizumab (49%), and omitting or recording the incorrect indication 'as required' (PRN) for Paracetamol (47%), as shown in Figures 6 and 7.

Figure 3 Breakdown of handwriting quality by participant grade

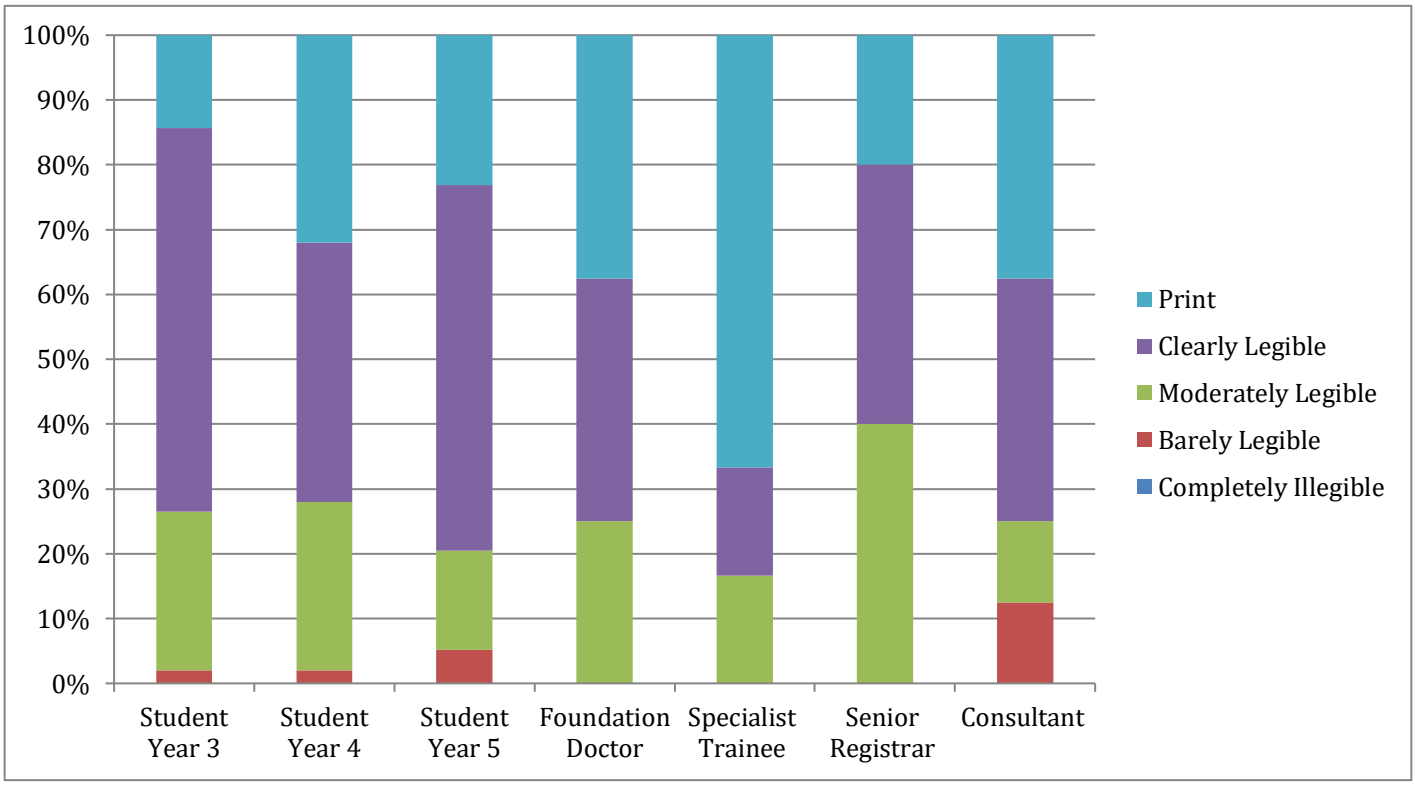


Figure 4 Comparison of handwriting between students and doctors

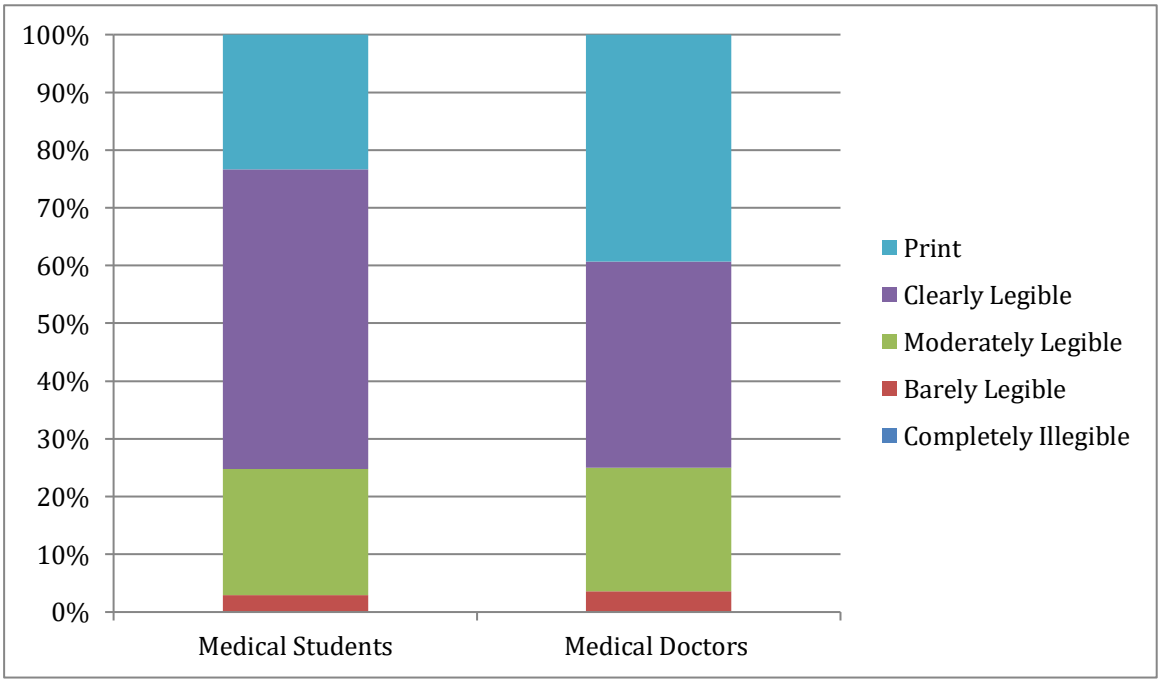


Figure 5 The number of prescription errors made per person

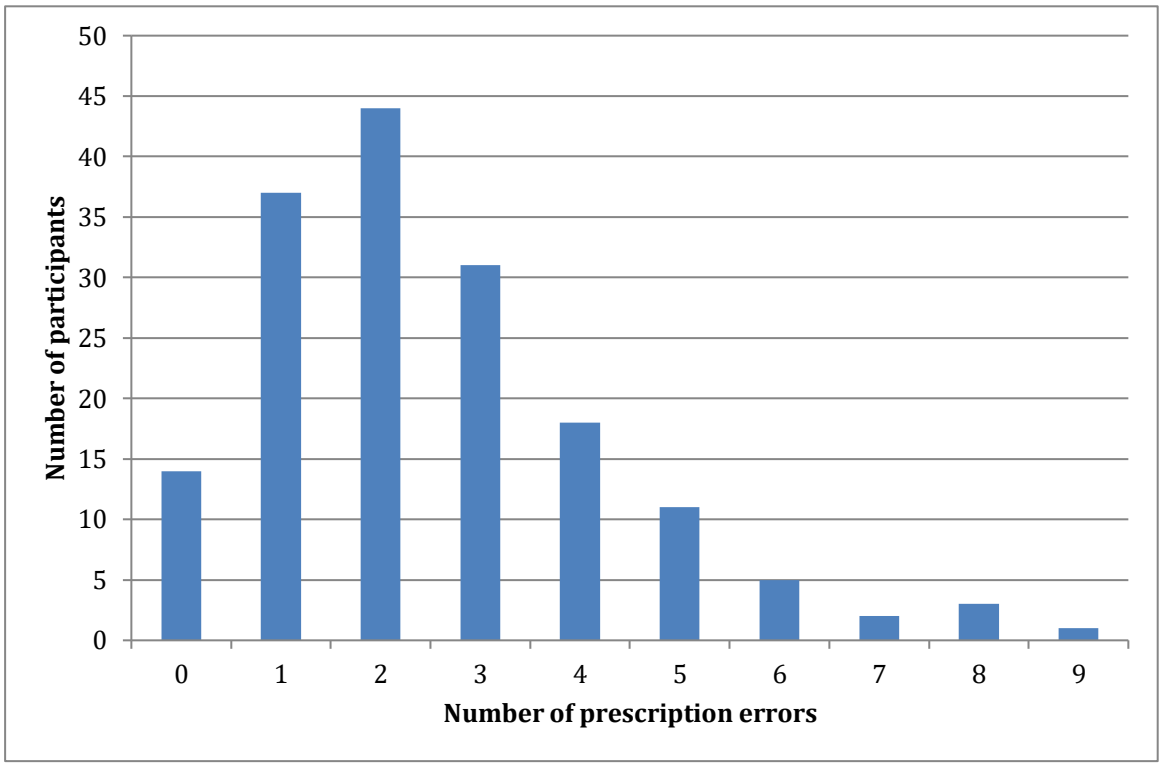


Figure 6 Breakdown of prescription errors

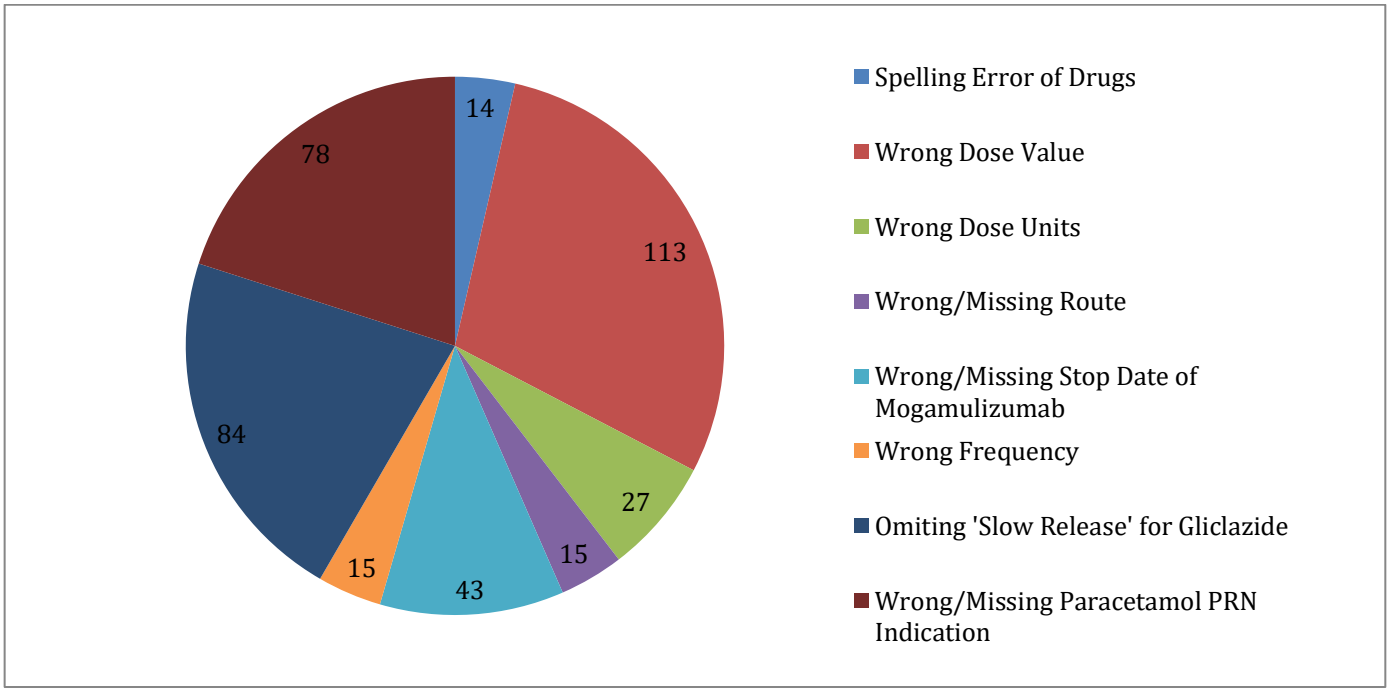


Figure 7 Prescription errors according to training grade (number per participant)

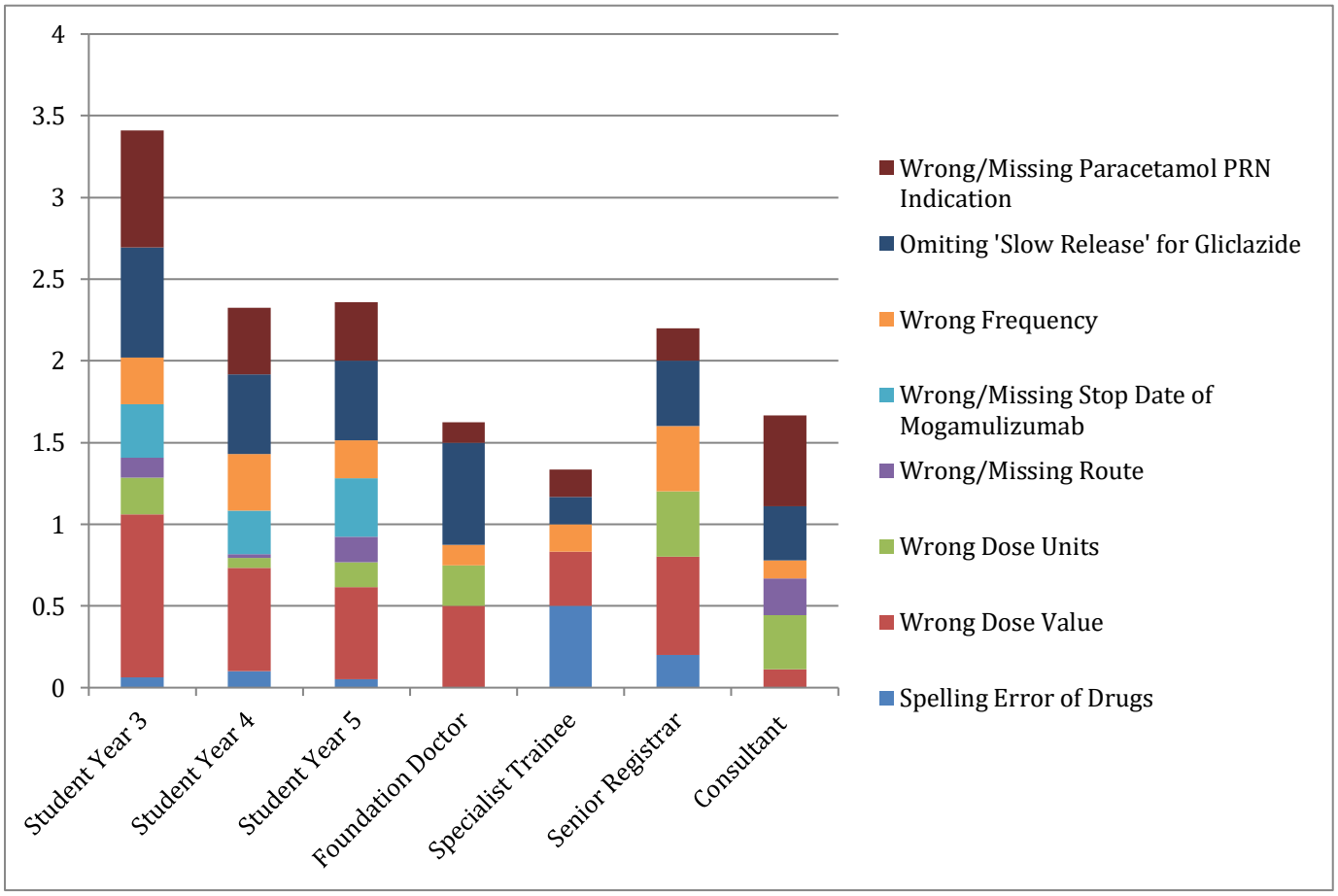
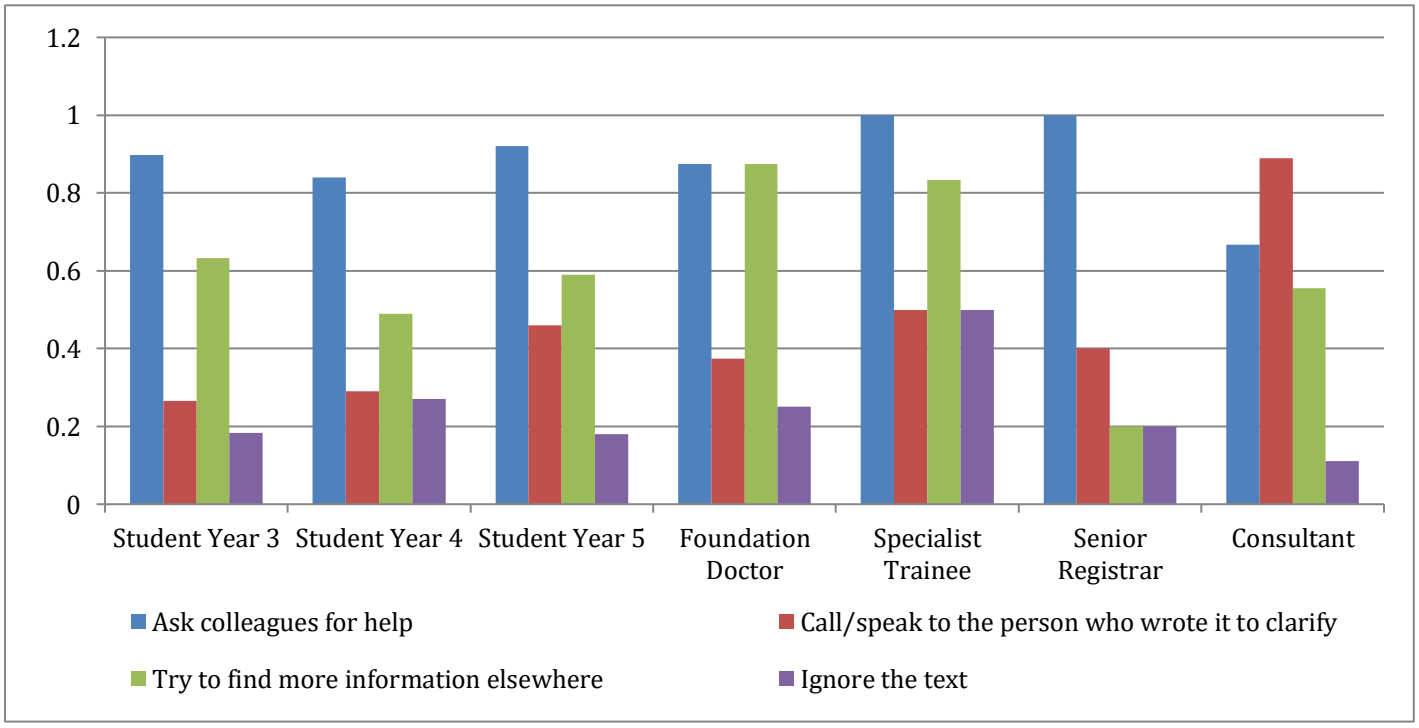


Figure 8 Result of self-directed feedback



Self-reflective feedback

65% of the participants stated that their handwriting in this exercise was similar to their usual standard of handwriting. 23% of participants perceived their handwriting as "better" or "much better" during the exercise, whereas 12% thought their handwriting was "worse than usual". The majority of participants reported being "very" (36%) or "quite bothered" (42%) by the legibility of colleagues' handwriting, with 6% reporting that they were "hardly bothered" or "not bothered at all". There was no statistical difference between the responses obtained from the medical students and doctors (p=0.93).

On questioning, 78% admitted to being concerned with poor handwriting in the healthcare work environment. In the event that participants had difficulty reading a prescription due to poor handwriting, 146 (88%) of participants reported that they would ask colleagues for help, 96 (58%) would try to find the information elsewhere and 37 (22%) stated that they would ignore the text completely (Figure 8).

Discussion

Poor handwriting is a well-recognised problem within healthcare settings despite being described as "the dinosaur that is long overdue for extinction".[6] It results in patient morbidity and mortality,[1-4] and leads to unnecessary health costs and medico-legal expenses.[7] One area where poor handwriting is particularly problematic within hospital settings relates to the writing of prescriptions and medication errors, and these may result in significant lawsuits and penalties, where both doctors and pharmacists have been found guilty of serious negligence.[8-10] Prescription errors occur on average 52 times per 100 admissions and 24 times per 1,000 patient days.[4] The financial implications of prescription errors have been difficult to evaluate, with a systematic review demonstrating the economic impact of one prescription error to range from €2.58 to €111,727.98.[7] This study assessed the handwriting skills of medical students and doctors, as well as their own perceptions of this problem.

In order to obtain a representative overview of the problem, medical students from the three clinical years of their training and doctors of various grades were invited to participate in the study. Handwriting was assessed according to a pre-determined grading system, was cross-checked for reproducibility by two of the researchers, and further assessed by three independent assessors who were not otherwise involved in the study. In practice, a difference in the handwriting grade awarded by the two researchers occurred in just 15% of 166 questionnaires and prescriptions. The final grade was verified in all cases when graded by independent assessors who, unlike the researchers, did not have the benefit of knowing what the prescriptions read beforehand. Furthermore, participants were themselves asked to adjudicate their own handwriting and 23% admitted to having made an effort and filled in the study forms using handwriting that was superior to their norm, whereas 12% felt that they writing was worse than usual. Overall, therefore, the handwriting as presented in this study was deemed representative of that of the participants on a daily basis.

Unfortunately, recruitment of doctors was suboptimal and the resulting doctor subgroups were too small for effective statistical comparisons. Nevertheless, for all groups, handwriting quality was deemed to reach 'moderately legible' or 'barely legible' in

as many as 25% of participants. Others have reported similar results with up to 15% of medical and 37% of surgical case notes being illegible, with just 24% having 'excellent' handwriting.[11-12] Interestingly, 15 participants (9%) admitted to having some form of prior training in handwriting and, on analysis, these scored higher grades (26% 'print quality', 53% 'clearly legible' and 20% 'moderately legible').

Overall, prescription errors were commonplace and found in an alarming 92% of all participants. Although third year students made more errors compared with fourth and final years, there was no statistical difference within student groups and doctor grades.

Only 14 participants (8%) returned a perfect questionnaire, whilst one individual made 9 errors. Indeed, this study reported an average of 2 errors per participant (Figure 5), with no difference in those who have had previous handwriting training. Simple transcription of patient details included 111 mistakes, all of which could potentially be linked to subsequent medication errors. Omissions relating to allergies included two cases documenting "No known allergies" when these were clearly stated in the patient's information given to participants that, in the real world, could prove very dangerous. Of more concern, there were 422 errors in the actual prescriptions of the five given medications, including the omission of drug details in 53% of cases, incorrect dosage in 49% and incorrect instructions for administration in 47% of prescriptions. Although some of these errors were relatively minor, all could have resulted in serious consequences if extrapolated to a real patient.

The majority of participants (78%) admitted to being concerned with poor handwriting in the healthcare work environment and the majority would take appropriate action in an attempt to circumvent any illegible script. Nevertheless, 22% still reported that they would ignore the illegible writing, an attitude that could potentially increase the risk of medication errors.

This study was limited by a low recruitment rate particularly with doctors that negated any meaningful comparisons within this subgroup. No account was taken for level of experience although, interestingly, third year students made more errors than their colleagues in Final year. Sources of error were not limited to handwriting alone and, indeed, transcriptional and other prescribing variables also contributed to many of the errors identified. A real-life study focusing on actual drug prescriptions in the workplace would go some way to circumventing these limitations. Despite these limitations, and although this study comprised a theoretical 'paper' exercise, if extrapolated into real life, the findings would amount to a significant and worrying level of errors on every prescription chart.

Traditionally, doctors have a reputation for poor handwriting and some have argued that this is secondary to the nature and pressure of the job.[5,13] Others have reported that doctor' handwriting is no better or worse than non-medics.[14-15] Either way, all typographical errors carry a significant financial burden and, for example in the UK, the cost to online business from such errors has been estimated to run in the millions.[16] This burden is, however, considerably greater when medical or prescription errors are concerned due to the added sequelae on health, adverse events and, in some cases, mortality. The need, therefore, to eradicate this preventable problem with all its implications, cannot be understated. A comprehensive approach to a solution is required.[5] This may include penmanship

classes, the use of self-inking stamps to heighten prescriber' awareness and traceability,[5,17-19] use computer generated prescribing, voice activating systems and, as this study would support, routine training for medical students.[3,5,18,20] Some countries and states have gone one step further and have introduced legislation for good handwriting and impose fines if errors result.[21-22]

Conclusion

The Medical Defence Union lists "Thou shalt write legibly" top of their 'things to do' list.[23] Therefore, the aim should be to achieve legible handwriting of near-print quality at all times, but particularly when it comes to areas that are susceptible to medical errors that may result in harm to the patient with medico-legal implications. This study has shown that this ideal is clearly not being reached and, moreover, the lack of concern for illegible handwriting is worrying. Undoubtedly, the causes of prescription errors are multifactorial secondary to a combination of individual and organisational factors and there are no standardised methods to ensure error-free prescriptions. A greater emphasis on correct and safe prescribing during formative medical education and training is required, and should also address issues relating to the quality and clarity of handwriting.

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MMJ

ORIGINAL ARTICLE

Vitamin D in the older population: a study of Maltese doctors' knowledge and management

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Background

Vitamin D deficiency is reaching pandemic levels in Europe. It is important for musculoskeletal health, and doctors are a crucial source of information to their patients. International studies have suggested that there is a knowledge gap amongst doctors with regards to this vitamin that can impact their management of its deficiency. In its attempt to assess the knowledge and management of Maltese doctors with regard to vitamin D in older adults, this study is the first of its kind in Malta.

Methods

Cross-sectional survey of 847 Maltese doctors. A questionnaire assessing attitudes, practices, and knowledge about vitamin D was adapted and distributed. Descriptive statistics were used, and knowledge and management scores were devised from the literature. The relationship between knowledge and management scores was correlated, and the mean scores were compared between several independent groups clustered by gender, speciality, training, work experience, and the extent of their confidence in their knowledge of vitamin D.

Results

The final recruited population was of 138 participants (7.4% margin of error assuming 95% confidence level). The mean knowledge and management scores were 33.22 (one can achieve a minimum score of -24 to a maximum of 68 points) and 23.64 (one can achieve a minimum of -9 to a maximum of 46) respectively. A positive correlation was found between the both of them (p <0.05), and doctors who felt very confident in their knowledge tended to score higher (p =0.010).

Conclusions

This study identified there is room for improvement regarding knowledge and management of vitamin D amongst Maltese doctors. Doctors that scored higher in their knowledge and management scores subjectively felt more confident in their knowledge of vitamin D. The majority of doctors (90.6%) believe there is a lack of awareness and acknowledge that more guidance is needed. Further research is required to explore whether clinical guidelines and post-graduate lectures can address this gap in knowledge of this important vitamin.

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Introduction

Vitamin D deficiency is reaching alarming levels in Europe.[1-2] This vitamin is critical to musculoskeletal health; its deficiency causes rickets in children, osteomalacia, osteopaenia, osteoporosis, muscle weakness and risk of falls in older adults. Vitamin D receptors are found in many other tissues in the body, and among others, it has been linked to an increased risk of common cancers, type 1 diabetes, osteoarthritis, cardiovascular heart disease, hypertension, depression and schizophrenia. However, literature regarding its benefits for other non-musculoskeletal medical conditions is mixed.[3-4] In spite of conflicting evidence, it continues to be a very important area for investigation, especially where older adults are concerned[5], as they are at higher risk of vitamin D deficiency. Older adults have a decreased production of this vitamin and they might be more prone to experience limited sun exposure and a decrease in dietary intake. This is found especially in those that are institutionalised.[5]

Since doctors are a crucial source of information to older adults, and are likely to visit patients who are at risk of vitamin D deficiency,[6] it is important to assess their knowledge and management of this essential vitamin. Only a few international studies were conducted to assess knowledge on vitamin D amongst healthcare professionals, and in most of them it was found that there is a knowledge gap.[7–10] This study is the first of its kind in its attempt to assess knowledge, practices and attitudes of Maltese medical practitioners with regard to vitamin D in older adults.

Materials and Methods

Population

The methodology is centred on a cross-sectional survey of all Maltese medical practitioners, excluding doctors that do not come into frequent contact with older adults (supplementary table), and doctors who were not currently practising or residing in Malta at the time of the study. All 847 medical practitioners were selected from the 'Medical and Dental Specialist Register' and the 'Principal Register' which can be found online and are regularly updated.[11] In order to construct a 95% confidence interval with a margin of error of 5%, the minimum sample should be 384 and therefore all 847 doctors were included in the study.

Information to Participants

An information letter on specifying the aims of the survey was sent by post, and included a link to the online questionnaire. Completion of the questionnaire implied consent. To increase recall,[8] participants were given the opportunity to participate in a lottery with the chance of winning a weekend break for two on a bed and breakfast basis. Information on how to take part in the lottery was provided at the end of the online questionnaire. A collective email was sent via the Maltese Ministry of Health personnel to all medical practitioners working with the government. This e-mail contained the same information as the letter and was disseminated at the beginning of data collection as well as one month later.

Ethical Approval

Ethical approval was sought from the Maltese "Health Ethics Committee", and permission to send a collective email to governmental doctors was sought from the "Ministry of Health". With permission from the authors, the

questionnaire used by Bonevski *et al.*, 2012 [8] was adapted for the purpose of this study.

Survey Instrument

The original questionnaire was developed to assess general practitioners' (GPs') attitudes, practices and knowledge about vitamin D. This study specific survey was reviewed by 11 key stakeholders in the medical field (including endocrinologists, dermatologists, vitamin D specialists, behavioural scientists, cancer experts and members of the local GP research interest groups), and then it was pilot tested.[8] The questionnaire contains 28 questions about the following domains: demographics, training and medical experience; knowledge on vitamin D; management of vitamin D insufficiency/deficiency; and doctors' opinion on if there is lack of vitamin D awareness among medical practitioners and how this could be improved. The final questionnaire takes 15 minutes to complete. Face validity of the adapted questionnaire was done by a geriatrician, GP, and a medical academic, and the online questionnaire was tested by five medical doctors who were not part of the included specialities. These were randomly selected from the medical register.

Data Analysis

The software used for data analysis was SPSS version 23. All data was of a categorical type and descriptive statistics were used to describe doctors' demographics, medical and training experience, self-reported practices, knowledge, management and attitudes on vitamin D. The questions on the domains of knowledge and management of vitamin D deficiency were given a score. Total scores for each respondent were worked out for knowledge-based and management-based questions. Knowledge-based questions assessed the understanding of groups at the most risk of vitamin D deficiency, its symptoms, and the main sources of vitamin D. On the other hand, management-based questions assessed knowledge on vitamin D supplementation in terms of pharmacotherapy and investigations required. Scores for questions were weighted depending on the perceived importance of the question as evidenced by literature. The maximum knowledge and management scores were 68 and 46, and the minimum knowledge and management scores were -24 and -9 respectively. The Pearson correlation coefficient was used to measure the strength of the relationship between the two scores, and the One-Way analysis of variance (ANOVA) test was used to compare the mean knowledge scores between several independent groups clustered by gender, speciality, training, work experience and level of confidence. The normality assumption was checked by the Kolmogorov-Smirnov test.

RESULTS

Respondents' characteristics

Of the 847 doctors, 143 completed the questionnaire. Five of these met the exclusion criteria and the final sample was of 138 doctors. This gives a response rate of 16.9% and a maximum margin of error of 7.4% assuming a 95% confidence level. There were almost equal amounts of male (*n*=65) and female (*n*=73) doctors. The majority of doctors were either GPs (*n*=72) or medical physicians (*n*=49), and almost half of the participants were still in training (47.8%) (Table 1).

Knowledge of vitamin D and Management of its deficiency

Most of the participants believe that the higher risk groups of vitamin D deficiency are older adults (87.7%), people in institutional

care (81.9%), persons suffering from malabsorptive conditions (80.4%), and those taking medications that increase vitamin D metabolism (78.3%). 34.1% of the participants defined vitamin D insufficiency as a level between 21-29 ng/ml, and 52.2% define vitamin D deficiency as a level less than 20 ng/ml.

Doctors think that vitamin D deficiency can be prevented by the adequate intake of vitamin D fortified food (83.3%) and daily vitamin D supplements (85.5%). The majority of doctors (82.6%) believe that exposure to outdoor sunlight is the main source of vitamin D in Malta. With regard to food, participants believe that fish (73.9%), cod liver oil (62.3%), milk (60.1%), and cereal (58%) have a high vitamin D content. 58% managed vitamin D insufficiency/deficiency by prescribing both vitamin D and calcium supplements, 50% by prescribing only vitamin D supplements, and 44.2% by giving advice to receive more natural sunlight.

Table 1 The gender, training status and specialty of participants.

		Sample (*n*=847)	Percentage (%)	Sample (*n*=138)	Percentage (%)
Gender	**Male**	536	63.3	65	47.1
	Female	311	36.7	73	52
Training status	**In-training**	211	24.9	66	47.8
	Not in training	636	75.1	72	52.2
Specialty	**General Practitioners**	392	46.3	72	52.2
	Medical Physicians	291	34.4	49	35.5
	Emergency Medicine	47	5.55	8	5.8
	Gynaecologists	75	8.85	5	3.6
	Orthopaedics	42	4.96	4	2.9

Note: The 1st two columns represent the original population of 847 doctors, and the last two columns represent the actual respondents of the questionnaire with the number of 138 participants. n=number; %=percentage.

The mean vitamin D knowledge and mean vitamin D management scores were 33.22 (out of 68), and 23.64 (out of 46) respectively. The Pearson correlation coefficient (0.517) is positive, indicating that knowledge and management scores are positively related (Figure 1). This relationship can be generalised as the *p* value is 0. There was no statistical difference between mean knowledge scores, and gender, training status, work experience and different specialties (Table 2).

Extent of confidence in knowledge and management

In a separate question, participants were asked how confident they feel in their knowledge of vitamin D. 10.1% (*n*=14) of doctors felt very confident, and these scored an average of 35 (SD=4.946) in their knowledge score and 30.29 (SD=5.483) in their management score. 66.7% (*n*=92) of doctors felt somewhat confident, and these scored an average of 34.36 (SD=8.542) in their knowledge score and 24.11 (SD=8.686) in their management score. 23.2% (n=32) of the participants felt not confident at all and these scored an average of 29.19 (SD=9.320) in their knowledge and 19.38 (SD=9.022) in their management score. Participants who responded as feeling somewhat confident on their knowledge of vitamin D scored significantly higher on the knowledge score than their counterparts who are not at all confident (p=0.010) (Figure 2). Participants who felt very confident scored significantly higher on management score than those who were somewhat confident (p=0.033), who in turn scored significantly higher than those who were not confident (p=0.021, see Figure 3).

Source of Information

31.2% obtained their vitamin D knowledge through online sources, 29% through medical training, 26.1% through medical journals and 21% from other medical colleagues. 90.6% of participants believe that Maltese doctors do not have enough knowledge of vitamin D, and the majority suggest further education via post-graduate lectures (61.6%) and a clinical practice guideline (61.6%).

Figure 1 The Pearson correlation coefficient (0.517) showing a positive relationship between the knowledge and management scores.

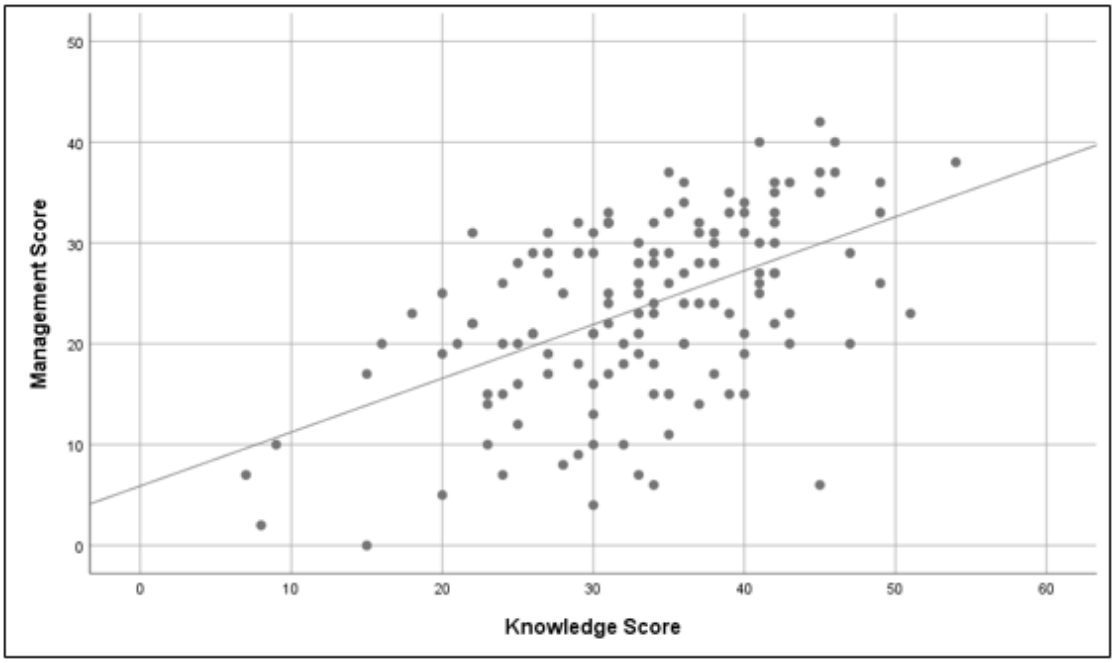


Table 2 The knowledge scores grouped by gender, training status, work experience and specialty

		Sample Size	Mean	Std. Dev	P-value
Gender	**Male**	65	32.4	9.091	
	Female	73	33.96	8.301	0.297
Training Status	**In-training**	66	33.8	8.016	
	Not in training	72	32.69	9.281	0.456
Work Experience	**<5 years**	47	32.38	9.532	
	5-10 years	24	35.25	5.666	
	11-20 years	16	35.25	7.206	
	>20 years	15	32.41	9.288	0.385
Specialty	**Medicine**	49	34.41	8.684	
	General Practice	72	33.19	8.48	
	Emergency	8	26.63	11.928	
	Gynaecology	5	34.8	4.207	
	Orthopaedic Surgery	4	30.5	5.26	0.192

Note: Std. Dev= Standard Deviation.

Figure 2 Showing the mean participants' extent of confidence in their knowledge of vitamin D deficiency. Participants who felt somewhat confident in their knowledge scored significantly higher than their counterparts who were not at all confident. Error bars represent the standard deviation. The asterix (*) represents the *p* value of <0.05.

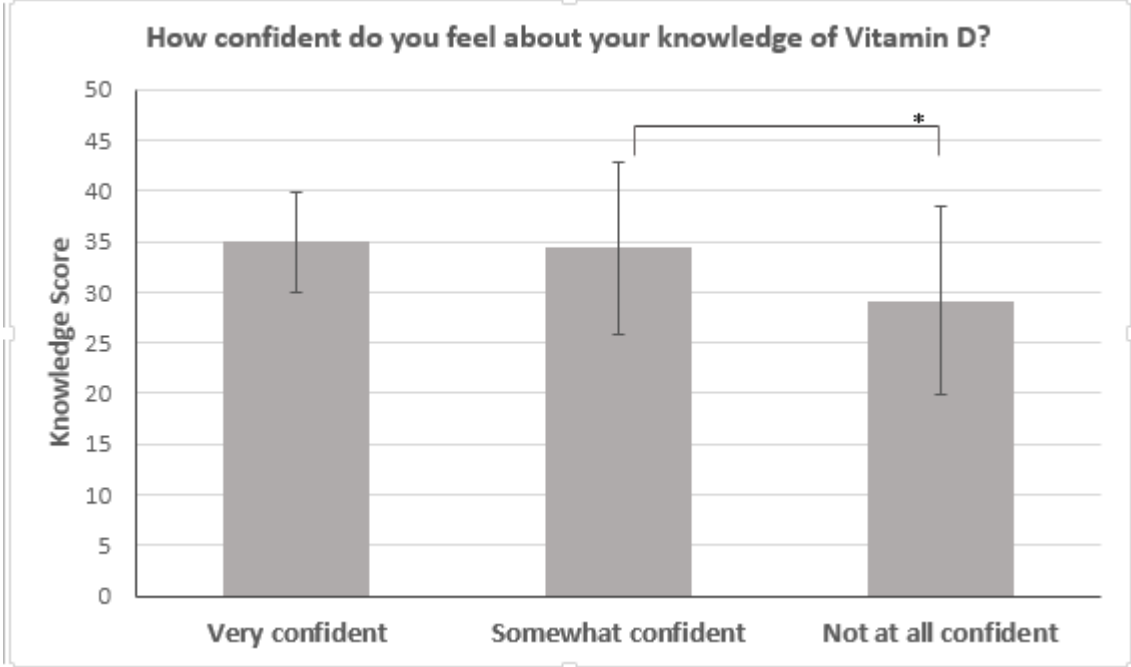
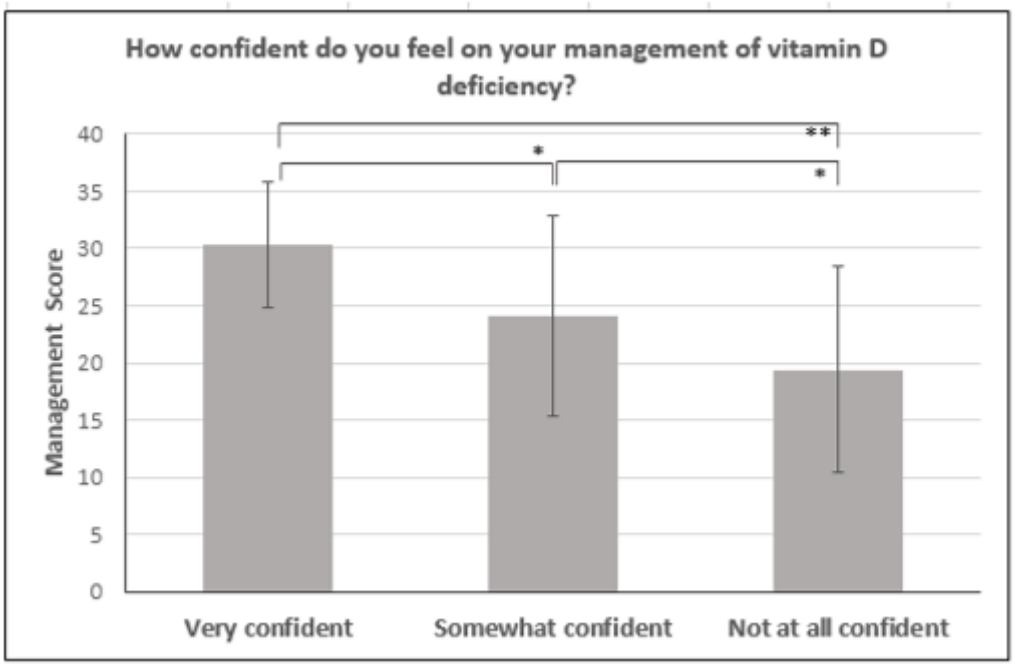


Figure 3 Showing the mean participants' extent of confidence in their management of vitamin D deficiency. Participants who felt very confident scored significantly higher on management than those who felt somewhat confident and also significantly higher than those not confident at all. Participants who felt somewhat confident also scored significantly higher than those not confident at all. Error bars represent standard deviations. The asterix (*) represents the p value of <0.05. The double asterix (**) represents the p value of <0.0001.



Discussion

Knowledge on vitamin D

This study identified that there is still room for improvement in knowledge and management of vitamin D deficiency, which is similar to other studies carried out on GPs in New Zealand[12] and Australia,[8] and on doctors working in the UK[10] and Saudi Arabia.[9] In the current study, no statistical differences were found in knowledge by gender, speciality, training status, or work experience. The reason for this could be due to the small sample size. This is in contrast to a study done in the UK where it was found that being a consultant or a GP was a significant predictor of superior knowledge of vitamin D.[10] On the other hand, in a study in Saudi Arabia, it was found that doctors in training had higher knowledge scores than consultants and resident doctors.[9]

Similar to other surveys,[8,12-13] most doctors managed to correctly identify that older adults and those in institutional care are at an increased risk of vitamin D deficiency. A fewer number of doctors recognized that individuals who are obese,[14] and/or dark-skinned individuals,[15] are also at a higher risk of vitamin D deficiency. Dark skin colour is considered to be a major contributor to vitamin D deficiency but respondents usually fail to identify this.[8]

There is some controversy about what is the optimal serum 25-hydroxyvitamin (OH) D concentration for skeletal and extraskeletal health with a general consensus to keep the concentration between 20 and 40 ng/ml.[16] The Institute of Medicine (IOM) suggests that serum 25(OH)D levels above 20 ng/ml are adequate for the general population,[17] while The National Osteoporosis Society similarly proposed that plasma levels of 25(OH)D of <10 ng/ml is considered deficient, 10-20 ng/ml inadequate, and levels of more than 20 ng/ml sufficient. However, the Maltese serum 25(OH)D reference range follows the Endocrine Society guidelines where they consider levels above 30 ng/ml to be adequate, levels between 20-30ng/ml to be insufficient, and levels less than 20ng/ml to be deficient.[18] The majority of Maltese doctors classify the deficiency as less than 20ng/ml. In most international studies the definition of adequate/insufficient and adequate vitamin D levels varied broadly.[18–20] In the discussions by Tarn *et al.*,[20] about the definition of vitamin D deficiency, most doctors failed to follow society guidelines, and some doctors used laboratory cut-off points to guide their discussions. This might be what is happening in Malta as well.

Management of vitamin D deficiency

Maltese practitioners believe that vitamin D deficiency can be prevented by an adequate intake of vitamin D fortified food and daily vitamin D supplements. Their strategy to manage deficiency is by prescribing calcium and vitamin D supplements or vitamin D supplements only. Despite this approach, there is still room for improvement, especially with regards to lifestyle advice regarding sunlight exposure and nutrition. The results are similar to the UK healthcare survey by Fallon *et al.*,[10] where lifestyle advice to have sunlight exposure and nutritional intake were recommended respectively by 50% and 47% of the survey population. There is limited evidence of benefits from daily supplementation in the general population. Bischoff-Ferrari *et al.*,[21] showed that vitamin D supplementation between 700-1000 IU reduces the risk of falling among older adults. Doses of less than 700 IU or serum 25(OH) D levels less than 20 ng/ml, may not have this effect. The combination of calcium and

vitamin D supplementation was found to better reduce falls and fractures amongst older adults.[4] There is still controversial evidence that supplementation of vitamin D lowers the risk of falls and fractures among the elderly.[22-23]

Extent of Confidence in knowledge and management of vitamin D

Maltese doctors believe that more awareness and knowledge regarding vitamin D is needed among doctors. Only a small proportion of doctors felt very confident about their knowledge of vitamin D and this is similar to the survey conducted on Australian GPs,[8] in which 13.5% felt very confident. Despite this, there were fewer Maltese doctors than Australian doctors who felt somewhat confident (66.7% vs 77.3%), in their knowledge, and a higher number of participants who did not feel confident at all (23.2% vs 9.2%).[8] In contrast, the survey conducted in Saudi Arabia showed a high number of confident participants (73%).[9] The results in context of the Maltese doctors, were not surprising, as at the time of this study, no post-graduate conferences/updates on vitamin D were conducted in Malta, and there was no national clinical guideline. When compared to a similar international survey on vitamin D knowledge,[9] this study also shows that doctors who feel more confident tend to score higher in knowledge and management scores. On the contrary, there were also studies that found no relationship[24] or an inverse relationship[25] between doctors' self-reported level of confidence and performance levels.

Sources of information

Maltese medical practitioners, similarly to those in Saudi Arabia, stated that their primary sources of information about vitamin D were obtained from online sources, medical journals and continuous medical education.[9] Therefore, this emphasizes the need for more accessible online clear guidelines in identifying risk factors and management of vitamin D deficiency. Some studies found a significant beneficial clinical outcome when doctors use clinical guidelines to help them in their practice, whilst other studies showed unclear or no benefits.[26] Newer research also shows mixed results, but a study done in 2017[27] suggests that clinical guidelines have a positive effect on individual knowledge and management behaviours.

Study Limitations

To increase the sample population, all doctors in the chosen specialities were included, with the link to the online questionnaire sent by both post and email. There may have been some participation bias, as the tool was only available online and there might have been doctors who had limited access to online services or found it more difficult to fill in due to limited information technology literacy. Moreover, doctors who were more engaged in the importance of vitamin D deficiency might have been more likely to complete the questionnaire, further creating a participation bias. A larger population would have been more ideal, as the extent to which these results can be generalised is debatable. Medical physicians, GPs, and emergency medicine physicians were well represented, but there was over-estimation in the female respondents and in doctors who are still in training (Table 1). On a positive note, participation was voluntary and it was not targeted towards doctors based on their prior knowledge or competence of vitamin D deficiency.

Conclusions and Future Recommendations

Despite that the majority of Maltese doctors correctly identified the common risk factors for vitamin D deficiency, there is still room for improvement as indicated from the mean knowledge and management scores obtained. Moreover, the extent of their confidence in their knowledge positively reflected their obtained knowledge and management scores which might indicate that improving education might boost their confidence in the subject and vice versa, but more research is needed to look into this. The majority of Maltese doctors would like to gain more knowledge on vitamin D, and therefore further research is required to explore whether clinical guidelines and the implementation of lectures in the post-graduate educational curriculum can address this knowledge gap.

Summary Box

- International studies on healthcare professionals show that some knowledge gap on vitamin D is present. This is also present among medical doctors practicing in Malta.
- This study indicates that a positive correlation exists between knowledge on vitamin D and adequate management of vitamin D deficiency.
- No difference found between mean knowledge scores and gender, training status, work experience and different medical specialties.

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Supplementary Table showing Included and Excluded Doctors by Specialty

Included Doctors by Specialty	Excluded Doctors by Specialty
General Practitioners	Paediatricians
Emergency Physicians	Haematologists
Gynaecologists	Occupational Medical Doctors
Orthopaedic surgeons	Microbiologists/bacteriologists
Medical Physicians (including oncologists and palliative care physicians)	Radiologists
	Anaesthetists
	Psychiatrists
	All other surgeons

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REVIEW ARTICLE

Autism spectrum disorder

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Autism spectrum disorder (ASD) is a complex heterogeneous condition that is characterized by impairments in social interaction, communication, and behaviour which mostly co-exist with several comorbidities. The current prevalence of ASD in the general population is estimated to be that of 1 in every 54 children in USA. The accurate diagnosis involves detailed assessments at age specific intervals and finally a comprehensive evaluation by specialists. Although genetic and environmental factors contribute to cause ASD, the precise mechanisms underlying ASD are poorly understood. Concerning management, early interventions are always recommended, as they lead to better outcomes. However, despite the availability of multiple medications, no definitive cure currently exists and the management of the disease remains poor, posing significant problems to life perspectives. Therefore, further studies are required to fully understand the pathogenesis and the possible resultant identification of more effective treatment options for ASD. This overview on autism covers its causes, presentation and therapies.

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Introduction

ASD is a complex and heterogeneous neurodevelopmental disorder, which manifests itself with a variety of signs and symptoms.[1] The *Diagnostic and Statistical Manual of Mental Disorders* (DSM V) defines ASD as an incessant neurodevelopmental disorder that exhibits poor social skills, essentially in terms of social-emotional reciprocity, verbal and non-verbal communication along with restrictive and repetitive behaviour which are present from early developmental age. According to DSM V, several related diseases such as Asperger's disorder, childhood disintegrative disorder also known as Heller syndrome or pervasive developmental disorder, which are not otherwise specified and, others are now diagnosed as ASD. However, the notion that mental disorders can be classified into distinct, discrete categories has been challenged and scientists are re-examining the theories underlying brain illnesses, significantly. Indeed, it appears that these disorders shade into each other, as there are no hard dividing lines and, changes in the brain's decision-making systems could be involved in many different conditions. This new perspective is further supported by genetic evidences showing that the same genes are associated with seemingly distinct disorders, such as autism and schizophrenia.[2-3]

It has been proposed that the use of new diagnostic criteria could be responsible for the rise in the number of cases of autism, rather than a true rise in the prevalence of the disorder.[4,5] However, it seems unlikely that this assumption could account for the diagnosis of a child with autism with every 54 new-born in US[6] and the higher incidence rates reported in distinct countries such as Hong Kong and Japan. Psychiatrists have long observed differences also between women and men in terms of their susceptibility to certain brain disorders. Autism is among those, as boys are more affected than girls (4:1 ratio)[7] and females are diagnosed with ASD at later age compared to males.[8] Interestingly, it has been reported that estrogens can rescue ASD phenotypes in animal models of autism supporting the "*female protective theory*".[9]

To address ASD-related issues and compile this review we selected the literature published from 1995 till 2020 using the PubMed, Scopus and Google Scholar databases and the keywords autism spectrum disorder, etiology, diagnosis and treatment. Particular emphasis was given to the evaluation of evidence based research and clinical practice trough systematic review of high quality publications.

Presentation

The presentation of ASD tends to vary from one individual to another. This variation in the clinical symptoms could be explained by alterations in the heritable background, epigenetics, and environmental factors.[10] The following three main core symptoms should be observed to enable one to properly diagnose ASD in a subject: (a) continuous difficulty in communication and interaction which are social and reciprocal; (b) difficulty in using or understanding language, tending to focus attention and conversation on a limited number of topics, frequently repeating phrases, and have very limited speech ability; (c) restrictive and repetitive behavior. The severity of ASD can be graded from Level 1 to Level 3 in two domains: social communication and restrictive stereotyped behaviour. Regarding communication, severity ranges from problems with starting social interactions to verbal and non-verbal communication

resulting in impaired functioning. Concerning behavioural deficits, the phenotype can range from the inflexibility of behaviour in one context to extreme difficulty in coping with changes in daily routine, significantly interfering with proper functioning in all spheres.[11] Autism coexists with other disorders in nearly 95% of the cases and its occurrence alone is rare. Indeed, several comorbidities are often associated with ASD such as epilepsy (up to 30%), intellectual disability (~40%), sleep disorders (50–80%), gastrointestinal problems (up to 70%) and motor deficits (~80%).

Screening and diagnosis

The *American Academy of Pediatrics* (AAP) policy recommends surveillance and screening to identify children who are at a risk of ASD at an earlier stage to ensure implementation of the effective interventions. The guidelines recommend developmental surveillance at 9, 15 and 30 months of age and specific screening for autism at 18, 24 and 30 months of age.[12-13] Surveillance includes: *a*) maintaining a developmental history; *b*) making accurate and informed observations of the child; *c*) eliciting and attending to parents' concerns; *d*) identifying the presence of risk and protective factors; *e*) documenting the process and findings. It should be performed at every preventive visit throughout childhood. Further standardized developmental tools should be used for screening if surveillance raises concerns. Notably, the AAP recommends that all children should be screened during visits to a primary care provider in an outpatient setting with the same time schedule, regardless of whether any concerns have been raised or not. The screening of the general pediatric population is essential to the timely identification of children at risk or exhibiting signs suggestive of ASD. In addition, AAP recommends using a standardized autism-specific screening tool on all 18-month old children at a preventive care visit with repeated evaluations for those who regress after the initial screening.[14] Selection of the autism-specific screening tool is done according to the age of the child. If the screening raises concerns, a referral specialist (pediatric neurologist, developmental-behavioural pediatrician, child psychiatrist, licensed child psychologist) should be consulted for a definitive diagnosis and comprehensive assessment.[15] The comprehensive examination includes: *a*) detailed pediatric history along with parental concerns; *b*) physical examination including assessment for dysmorphic features, head circumference, Wood's lamp examination of the skin (tuberous sclerosis) and full neurologic examination; *c*) direct observation of the child's current cognitive, language, and adaptive functioning by a clinician experienced with ASD according with the DSM V criteria.[16] However, making an ASD diagnosis is just the beginning. Further in-depth evaluations should be performed to understand the child's unique strengths and challenges. This evaluation is crucial for defining what kinds of medication, educational programs and behavioral therapies would be most beneficial. Usually, this process involves a number of specialists, such as child neurologists, developmental behavioral pediatricians, speech-language pathologists, child psychologists and psychiatrists, nurse practitioners, educational specialists and occupational therapists.

Genetic factors

Over the last few decades, it has been shown that the genetic component of ASD can range

from 40 to 80%.[3,17] Large variation in the genetic mechanism underlying ASD exists depending on the inheritance pattern, chromosomal aberration and mode of action.[18-20] The advanced paternal age has been implicated in neurodevelopmental disorders due to increased mutation occurrence in spermatogenesis at a later age.[21-22] A seminal study performed by Filstein and Rutter showed that monozygotic twins had a concordance of 36% meaning that over a third of both pairs had autism while no concordance was found between dizygotic twins. More recently concordance of ~60% has also been reported.[3] A Swedish study demonstrated that monozygotic co-twin always had another neurodevelopmental disorder disconcordant for ASD.[23] It is proposed that more than half of the risk of developing ASD is linked with genetic variability that is evident by an increased prevalence of ASD in families of individuals with autism.[24] Notably, these genes are also found in other neurodevelopmental and psychiatric disorders.[25] To date, hundreds of risk genes have been identified by means of large-scale genetic screenings of ASD patients and their family members.[3] The majority of reproducible hits point to proteins involved in synapse pathology (synapse formation and transmission), transcriptional regulation, chromatin-remodeling pathways and neural network formation (*e.g.* neuroligins, cadherins, synaptic vesicle cycling proteins synapsin-1 (SYN1), synapsin-2 (SYN2), *MeCP2, UBE3A, FMRP, FXRP1, SHANK3*, *GABRG3, etc*). Genetic defects in sodium, calcium and potassium channel types plays an important role in the pathogenesis of autism (*e.g. SCN2A, CACNA1E, KCNJ10, KCNQ3, KCNQ5, KCND2*)[26]. Investigations carried out at the University of Malta showed that dysfunction of the inwardly-rectifying potassium channels Kir4.1 results in autism associated with epilepsy (*autism-epilepsy phenotype, AEP*) [26-29]. Indeed, an international collaborative research team identified germline heterozygous variants in some affected children where epileptic spasms were major issues emphasizing the role of variants in *KCNJ10* (Kir4.1) and *KCNJ2* (Kir2.1) in AEP.[30-32] In the previous seminal studies the functional properties of Kir4.1 mutant channel were characterized demonstrating that the identified mutations produced gain of channel function.[31] In another study on monozygotic twins with autism and short QT interval on ECG as a comorbidity, it was demonstrated the presence of a novel *KCNJ2* variant that increased the surface expression of Kir2.1 channels (*gain of function*). This study pointed to the involvement of Kir2.1 channels in AEP and the necessity to perform neuropsychiatric assessments in patients with short QT syndrome (SQT3) to identify the presence of subtle autistic traits.[32] Recordings from surgical specimens of patients with intractable epilepsies showed a remarkable reduction of Kir conductance in astrocytes, impairing their ability to perform potassium clearance. It could be inferred that either the enhancement or the reduction of Kir4.1 activity leads to epilepsy possibly causing an alteration in the excitatory-inhibitory balance in the brain. Nevertheless, the mechanisms involved in this apparently contradictory dual effect is unclear.[33] Scientists from the Department of Physiology & Biochemistry at the University of Malta have contributed prominently to these discoveries and are currently clarifying the mechanisms responsible for the development of AEP that may render valuable benefits to autistic individuals. Indeed, a genetically modified mouse model of autism was generated and is currently under investigations in the above mentioned

laboratories to further understand the pathogenic relevance of *KCNJ10* mutations, clarify the underlying mechanisms and identify potential treatments.

Environmental factors

The possibility that the environment contributes to the causation of autism has arisen from our current understanding of the exquisite vulnerability of the developing human brain to toxic substances in the environment and studies that specifically linked autism to prenatal exposures to environmental factors or medicines.[34] The antiepileptic medication Valproic acid represents the typical example of drug-induced autism which does so through different mechanisms.[3] Hallmayer and colleagues showed that a moderate genetic component combined with considerable environmental factors may cause ASD.[35] In terms of maturity, preterm infants are at greater risk of adverse neurodevelopmental outcomes in comparison to the full term infants. Thus, it is recommended that premature individuals should be closely observed in order to implement effective interventions if the need arises.[36] The proposed factors that may play major roles include hypoxia, oxidative stress, inflammation, endocrine disturbance and immune activation. Several autoantibodies such as anti-MAP_2, anti-MBP, anti-NFP, anti-MAG and anti-Tau were found in higher levels in children exhibiting ASD with their mothers having similar levels. In contrast, control children and their mothers had negligible amounts of auto-antibodies against neuronal and glial proteins, implying the involvement of the maternal immune system in the development of ASD in offspring.[37] Maternal intake of folic acid during perinatal period reduces the risk for the development of ASD. Also, maternal intake of polyunsaturated fatty acids decreases the risk for ASD, whereas, very low levels of Omega 3 fatty acids increase the risk for ASD.[35,38] Heavy metals may else play an important role in autism. Indeed, newborns from mothers exposed to high levels of mercury, lead, nickel, and manganese were at higher risk of developing autism.[39] The risk for ASD was doubled by gestational exposure to nitrogen dioxide (NO_2), particulate matter less than 2.5 (PM 2.5) or 10 (PM 10) micrometers in diameter.[40] In Malta, high concentrations of airborne PM are reported particularly in heavy-traffic areas with the consequent relevant health implications.[41] Organochlorine exposures in the first trimester of gestation showed a strong association with ASD. Whereas, exposures to pyrethroid or bifenthrin during the overall gestational period showed moderate association.[42] The observed heterogeneity in symptoms severity and prognosis of ASD patients also suggests that a combination of genetic predisposition, gut microbiota (GM) dysbiosis and, the alteration of metabolites produced by microbes may represent a critical "environmental factor" impacting brain function and behaviour, thus potentially promoting the development of autism.[1] Several observations strongly support the role of GM in ASD, such as the high occurrence of gastrointestinal (GI) abnormalities in ASD patients, the amelioration of symptoms upon short-term treatment with antibiotics and probiotics and the improvement of GI function and behaviour in autistic children after Fecal Microbiota Transplant (FMT).[43-48] Abnormal GM composition has been widely reported both in animal models with behavioral traits relevant to autism and in human pre-clinical investigations of autistic patients.[49-52]

Treatment

In spite of considerable economic costs caused by autism, there are limited treatment options to ameliorate the typical symptoms associated with ASD, and the relevant comorbidities known to exacerbate the severity of the phenotype. There are numerous challenges for the identification of effective treatments for ASD. Systematic reviews highlighted the possibility that the high heterogeneity in the genetic, environmental, cognitive, social and ASD phenotype reduce the overall validity and efficacy of potential interventions.[53] Anthropological differences, which propose the deviation from typical behaviour in one culture but not in another culture, further contribute to obscure treatment strategies.[54] Aripiprazole and Risperidone are the most widely studied medications used to manage behavioral symptoms. Aripiprazole, is an atypical antipsychotic drug.[55] The US FDA particularly indicated aripiprazole and risperidone for children and approved them for the treatment of behaviours associated with ASD.[56] Such medications control irritability, aggressive and self–injury behaviours.[57-58] Despite some beneficial effects, these drugs present with adverse effects such as extrapyramidal symptoms, tremors and sedation.[59] Parents and health care professionals must closely monitor a child's progress and reactions while he or she is taking a medication to be sure that any negative side effects of the treatment do not outweigh the benefits. Apart from medications, early intensive behavioral therapy is considered to be beneficial for school-aged children diagnosed with ASD.[60] Behavioral interventions can be classified as early intensive behavioral and developmental interventions, social skills interventions, parent training, play/interaction-focused interventions, interventions targeting symptoms commonly associated with ASD such as anxiety, and other general behavioral approaches. The Agency for Healthcare Research and Quality (United States) reviewed several studies reporting statistically significant evidence and showed that early intensive behavioral therapy over extended timeframes was associated with improvement in cognitive functioning and language skills of young children with ASD. A notable treatment approach that is used in many schools and treatment clinics for people with ASD is called *applied behaviour analysis* (ABA) which uses principles and techniques to understand, treat and prevent challenging behaviors such as anxiety and to promote new, desired behaviors. There are different types of ABA: A) Discrete Trial Training (DTT) that uses a series of trials to teach each step of a desired behavior or response. Lessons are broken down into their simplest parts and positive reinforcement is used to reward correct answers and behaviors. Incorrect answers are ignored; B) Early Intensive Behavioral Intervention (EIBI) that is used for ASD children younger than five, and often younger than three; C) Pivotal Response Training (PRT) that aims to increase a child's motivation to learn, monitor his own behavior, and initiate communication with others; D) Verbal Behavior Intervention (VBI) that focuses on teaching verbal skills. The interventions used in the early intensive behavioural therapy are outlined in the University of California, Los Angeles (UCLA)/ Lovaas-based approach, the Early Start Denver Model (ESDM), and parent training approach.[61] The UCLA/ Lovaas-based approach applies ABA procedures that focus on teaching new skills and reducing interfering behavior in children with ASD. It relies on one-on-one therapy sessions where a trained therapist adopts discrete teaching trials with a

child to practice target skills. The therapy is tailored to each individual in order to benefit the needs of the child.[62] The ESDM is an approach for preschool-aged autistic children that incorporate ABA with developmental and relationship-based approaches. This therapy is delivered by trained therapists and parents.[63] The Building Block program provides early interventions for young children with autism and their families. The Building Block model includes various approaches such as positive behavior support, naturalistic play-based intervention, assessment of sensory processing issues, and extensive use of visual supports, behavioral and developmental theory, structured teaching and the development of functional communication skills.[65,66] Notably, children attending this program showed significant improvements on some social and communication skills. A randomized control trial involving parent training was conducted in Australia[64] and compared two variations of Building Block program that was performed at home or center based. This trial showed that children receiving centre based intervention had greater improvement in language comprehension.[64] Social skill training improves social interaction in school-aged children.[61] A meta-analysis of early intensive behavioral intervention for children with autism supported that this should be an intervention of choice for children with autism. Regrettably, the costs are excessive, require several resources to be implemented and not all patients may benefit from these interventions.[67] Other approaches include occupational therapy that teaches skills to help the person live as independently as possible. Skills might include dressing, eating, bathing, and relating to people. The speech therapy helps to improve the person's communication skills. Some people are able to learn verbal communication skills. For others, however, using gestures or picture boards is more realistic. Indeed, the Picture Exchange Communication System (PECS) uses picture symbols to teach communication skills. The person is taught to use picture symbols to ask and answer questions and have a conversation. Some dietary treatments have been developed by reliable therapists, although these treatments do not have sufficient scientific support needed for widespread recommendation. Complementary and alternative treatments (e.g. special diets, chelation of heavy metals from the body, secretin treatment, deep pressure, etc.) are used by some parents and health care professionals despite the fact that they are outside of what is typically recommended by pediatricians.

Concluding remarks

ASD is a complex disorder that has several etiologies involving genetic and environmental factors. Remarkable advances in the discovery of factors leading to autism have been achieved in the past years. However, the different types of modifiers that may exacerbate or ameliorate disease severity have not been identified, clearly. Such modifiers could include epigenetics, sex-linked modifiers, or environmental factors. Furthermore, the key architecture of ASD development which could be targeted for treatment remains still an uncharted territory. A better understanding and awareness of autism by the general population and health care professionals is also essential as it allows prompt diagnosis and early interventions that influence positively the development of the child affected by this invalidating disease. New hopes for children with ASD may result from the accomplishment of the Research Domain

Criteria project by the National Institute of Mental Health that aims to explore the biological and psychosocial causes of ASD and identify new treatments strategies for autism.[68] Thus, further work is imperatively needed to broaden the horizons on the causes and accomplish new therapeutic options for ASD.

Abbreviations

Autism spectrum disorder (ASD), Diagnostic and Statistical Manual of Mental Disorders (DSM V), American Academy of Pediatrics (AAP), autism-epilepsy phenotype (AEP), inwardly-rectifying potassium channels (Kir4.1), microtubule-associated protein-2 (MAP-2), myelin basic protein (MBP), neurofilament triplet proteins (NFP), myelin-associated glycoprotein (MAG), particulate matter (PM), gut microbiota (GM), gastrointestinal (GI), Fecal Microbiota Transplant (FMT), applied behaviour analysis (ABA), University of California, Los Angeles (UCLA), Early Start Denver Model (ESDM)

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REVIEW ARTICLE

Potential biomarker of neutrophil extracellular traps in venous thromboembolism: a systematic review

Eka Prasetya Budi Mulia, Ivana Purnama Dewi, Mohammad Budiarto

Background

Neutrophil extracellular traps (NETs) are a network of extracellular DNA produced by activated neutrophils to trap and disarm microbes. NETs increase the formation of thrombus by forming a network frame that activates platelets and initiates coagulation. NETs were involved in the thrombogenic process and have been reported in various animal models. However, the evidence of NETs' role in venous thromboembolism (VTE) development in humans is still scarce. This review aims to discover the relationship between NETs and VTE risk.

Methods

We performed literature search to identify relevant available articles from PubMed, Cochrane Library, MEDLINE, EMBASE, Clinical Key between October 2009 until October 2019. The inclusion criteria were: clinical trials published in English, involving humans as subjects, conducted within the past ten years, and had available and accessible full-text. In addition, Newcastle Ottawa Scale (NOS) was used to assess evidence quality.

Results

Four studies with a total of 1,430 patients, i.e. three case controls and one cohort, met our eligibility criteria. All four studies' quality was good. One study of cancer patients demonstrated that NETs increase VTE risk, two other studies demonstrated NETs correlate with deep vein thrombosis (DVT), and another study demonstrated there were increasing NETs in residual vein obstruction (RVO) and increased D-dimer. All four studies found a significant association of NETs and VTE occurrence (p=0.003; p=0.018; p<0.01; p<0.001, respectively).

Conclusions

NETs are associated with an increased VTE risk. Further studies are necessary to determine the NETs' role in VTE as a diagnostic biomarker or target of therapy

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Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a common cause of morbidity and premature mortality worldwide, but our knowledge in diagnosing and treating these diseases is limited.[1] A recent study estimated that in the United States, total annual VTE cases reached more than 900,000, by which more than 250,000 were fatal.[2] The average yearly attack rates of VTE related and unrelated to hospitalization were 282 and 8 per 10,000 person-years, respectively. A multicenter study in Europe involving six countries reported an estimated annual 465,715 DVT cases, 295,982 PE events, and 370,012 VTE-related deaths.[2] In Asia, the incidence of VTE ranging from 14 to 57 cases per 100,000 patient-years.[3–6] Despite advances in vascular biology and medicine, VTE's incidence has not declined in the last 25 years.[2]

The standard protocol for the diagnosis of patients with VTE is to use a D-dimer biomarker to exclude VTE diagnosis, while compression ultrasound has been the gold standard for diagnosing DVT and Computed Tomography (CT) angiography for PE diagnosis.[7,8] However, all of these diagnostic modalities have limitations such as being less specific, require a long time, uneven availability, and are quite expensive. Thus, an investigation of new diagnostic biomarkers to function as early identification of patients at low or high risk of first diagnosed and recurrent VTE is needed to enable immediate diagnosis and assessment of therapy.

Venous thromboembolism is epidemiologically related to inflammatory diseases, such as infections, cancer, and autoimmune disorders. Acute infections and autoantibody against prothrombin 11 and phospholipid are risk factors for PE and DVT.[9] The incidence of malignancy and venous thrombosis also has been described in the 19th century. More recently, VTE and mortality risk is associated with an increase in neutrophils in cancer receiving chemotherapy.[10] Neutrophils are the most numerous inflammatory cells and have recently emphasized their significance in DVT in animal studies.[11–13]

Neutrophils are the first leukocytes that came to the site of infection and neutralized phagocytic bacteria.[14] In phagosomes, microbes are killed by reactive oxygen species (ROS) and high concentrations of antimicrobial proteins. Neutrophils produce neutrophil extracellular traps (NETs) to trap and neutralize microorganisms in extracellular space. NETs are whole chromatin fiber scaffolds with antimicrobial proteins, ideal for maintaining large numbers of microbes.[15] NETs also encourage the formation of thrombus by serving as a network frame to activate platelets and initiate coagulation.[16]

Neutrophil extracellular traps productions had been studied in thrombosis models of inferior vena cava in baboons' iliac veins and Peptidyl arginine deiminase-4 (PAD4)-knockout mice. Studies revealed higher levels of plasma deoxyribonucleic acid (DNA) and NETs in venous thrombi, greater thrombus size/rate with higher von Willebrand factor (vWF) activation recruitment of platelet. Of note, histone infusion accelerates the thrombosis process while cleavage of NETs by Deoxyribonuclease 1 (DNase1) or heparin reduces the process.[17-18] The thrombogenesis role of NETs has been documented in animals with various settings of thrombosis. However, evidence of NETs' role in the risk of developing VTE in humans is still scarce. This review aims to discover whether NETs are correlated with VTE risk.

Methods

This systematic review was conducted using a predetermined protocol following "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines.[19] 1). The review was carried out in a series of steps: (i) searching the database for published articles, (ii) quality assessment for each obtained articles, (iii) extraction of data from tables and graphs, and (iv) interpretation and summary of findings. A meta-analysis of the data obtained could not be carried out because of the heterogeneity and broad diversity of study settings across the included literature. Thus, we provided the synthesis and findings of our review as a narrative summary.

Database search for identification of relevant studies

We performed a literature search to identify relevant available articles from PubMed, Clinical Key, MEDLINE, EMBASE, Cochrane Library using subject terms "neutrophil extracellular traps", "NETS", "venous thromboembolism", "VTE", "pulmonary embolism", "PE", "deep vein thrombosis", and "DVT. Search parameters were limited to a clinical trial, within the last 10 years (October 2009 to October 2019), and full-text availability. Only English language was included. Manual searches of bibliographies and references were conducted. All three authors independently conducted searches. Abstracts for all results were reviewed, and relevant studies were selected for further review. Any disagreement in screening, extraction, and analysis of data was resolved by discussion.

Review methods and study selection

We included all studies enrolling the general population whose study participants had undergone an examination of NETS or biomarker of NETS formation with VTE incidence as an outcome. This review excluded review articles, descriptive studies, non-English language articles, commentaries, letters, studies with non-human subjects, incompatibility of biomarkers with NETS formation, and studies with outcomes without VTE. Our search resulted in 108 articles, and ten more relevant articles were added from the bibliography, reference lists, and related citations of the primary articles, with a total of 128. Of the citations received, 82 duplicates were issued, leaving 46 articles, as illustrated in figure 1. All articles were screened by two independent reviewers (EPBM and IPD) based on inclusion and exclusion criteria.

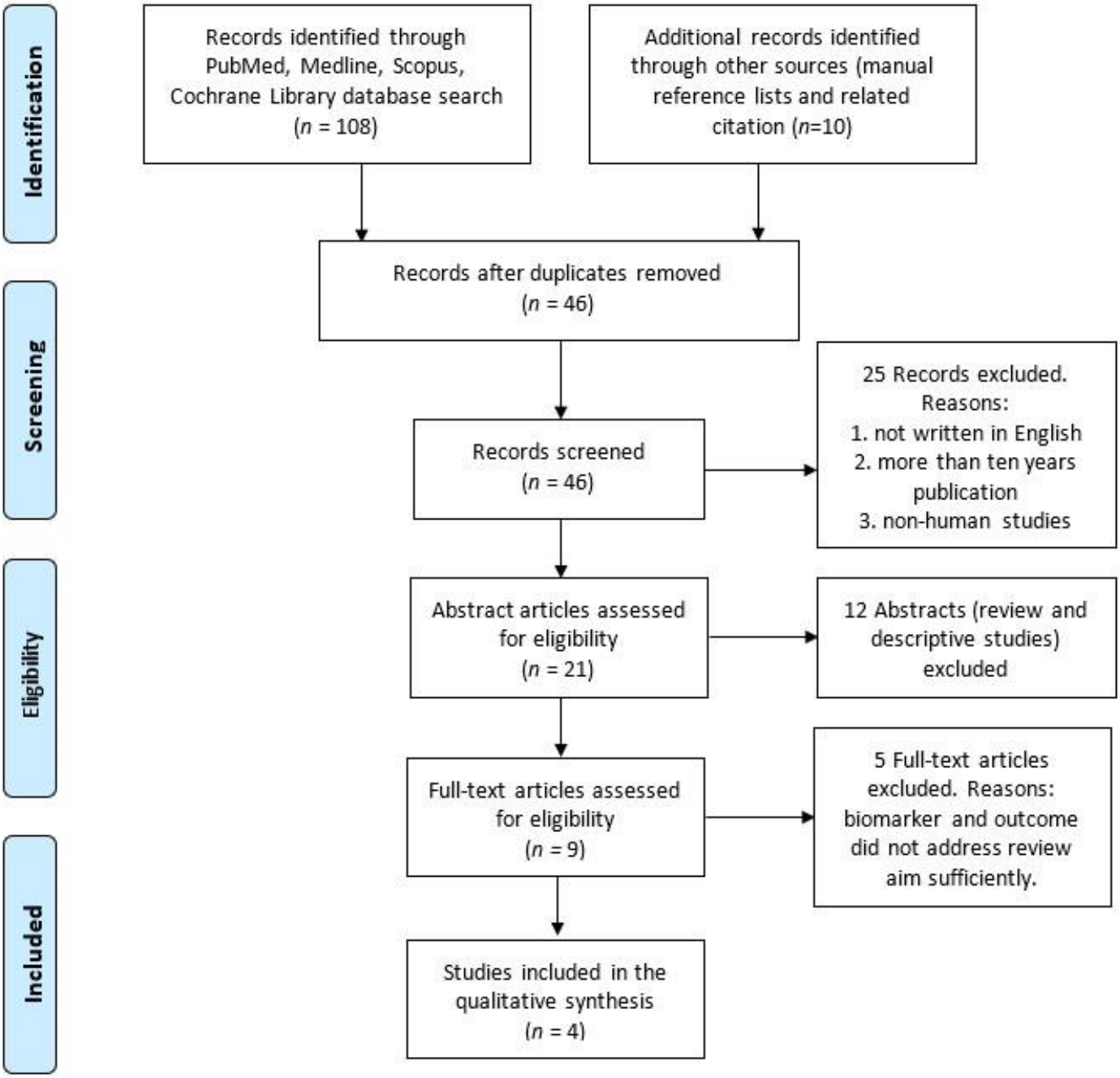
Of the 46 records after the removal of duplicates, the examination of titles and abstracts of the latter according to eligibility criteria resulted in the removal of 37 additional articles, leaving nine articles. A complete reading of the entire contents of the last number of papers further excluded five additional articles because biomarkers and outcomes did not address the review's aim sufficiently, thus, leaving four studies for consideration.

Data extraction and quality assessment

Data were extracted by two authors (EPBM and IPD) independently, then reviewed and validated by the third author (MB). All four studies were classified according to author/year, country/setting, the methodology of the study, sample size, statistical analysis, and outcome. The authors also conducted an assessment of the quality of each research article. We assessed the quality of the methods and research of studies by using Newcastle Ottawa Quality Assessment Scale (NOS) using predefined criteria, namely:

selection (representativeness of population), comparability (adjustment for confounders), and ascertainment of the outcome. The NOS allocates a maximum of four points for selection, two points for comparability, and three points for the outcome. Nine points of NOS reflects the highest study quality.

Figure 1 Flowchart of study selection



RESULTS

Four studies with a total of 1430 patients met all inclusion and exclusion criteria. Three were of case-control and one was a prospective cohort study. The sample size varied between studies. The setting of research was well described in all publications. In Table 1, the research setting was either classified as a hospital or academic medical center (utilizing laboratory). The outcome of the studies was the incidence of VTE (Table 1).

In spite of the fact that all of the articles were published in peer-reviewed journals in this review, we still carried out the examination of the methodological quality using NOS. The four qualifying reports good quality in all of the studies, as shown in table 2.

There are several biomarkers of NETS formation that are different from each study, namely: citrullinated histone H3,[20] circulating nucleosome and activated neutrophils,[21] plasma DNA,[22] and neutrophil adhesion with inflammatory cytokines.[23] All biomarkers were measured at baseline only, with no longitudinal measurements reported. One study used a specific population of cancer patients,[20] while 3 others did not mention special populations.[21–23] One study of cancer patient demonstrated that NETs increase VTE risk,[20] two other studies demonstrated NETs correlate with DVT,[21-22] and one study demonstrated there is increasing NETs in residual vein obstruction (RVO) and increased D-dimer.[23] Table 3 showed that all four studies found a significant association of NETs and VTE occurrence (p=0.003; p=0.018; p<0.01; p<0.001). Two studies used DVT as an outcome; one study used VTE in general as an outcome, while the rest used residual vein obstruction and increased D-dimer as an outcome. Increased biomarkers of NET formation were correlated with a threefold risk of DVT and biomarker of NETs formation is increased in DVT patients and correlates with DVT biomarkers.[21–23]

Table 1 Description of the studies

Author (year)	Country/Setting	Method	Subject (n)	% VTE
Mauracher et al. (2018)[20]	Austria/ Medical University	Cohort	946	9.4
Zapponi et al. (2014)[23]	Brazil/ Medical University	Case Control	58	50
Diaz et al. (2013)[22]	Switzerland/ Medical University	Case Control	94	50
van Montfoort et al. (2013)[21]	Netherlands/ Academic Medical Center	Case Control	332	45

Table 2 Quality assessment of studies using NOS

Author (year)	Selection	Comparability	Outcome/Exposure	Summary
Mauracher et al. (2018)[20]	4	2	3	9
Zapponi et al. (2014)[23]	4	2	3	9
Diaz et al. (2013)[22]	4	2	2	8
van Montfoort et al. (2013)[21]	4	2	3	9

Table 3 Study Results

Author (year)	NETs biomarkers	OR; 95% Confidence Interval (CI); *P*-value	Outcome
Mauracher et al. (2018)[20]	citrullinated histone H3	1.13; 95%CI 1.04–1.22; p=0.003	Biomarker of NETs formation is associated with VTE development in cancer patients.
Zapponi et al. (2014)[23]	neutrophil adhesion with inflammatory cytokines	24.68 vs 19.29 *vs* 18.23**; p=0.018	Increased biomarkers of NETs formation profile among patients with RVO and increased D-dimer.
Diaz et al. (2013)[22]	plasma DNA	57.7±6.3 vs 23.9±2.1 *vs* 17.9±3.5*; p<0.01	Biomarker of NETs formation is increased in DVT patients and correlates with DVT biomarkers.
van Montfoort et al. (2013)[21]	circulating nucleosome and activated neutrophils	3.0; 95%CI 1.5–3.9; p<0.001	Increased biomarkers of NETs formation were correlated with a threefold risk of DVT.

data are expressed as
*mean ± SD
** median % adhesion

Discussion

Significant correlations between NETs and the incidence of VTE were demonstrated in all included studies. Citrullinated histone H3 (H3Cit) has been proposed as a target biomarker, which reflects the formation of NET.[24,25] Mauracher et al. mentioned cancer patients with elevated H3Cit levels experiencing higher cumulative VTE events than patients with H3Cit levels under this limit with a 2-year risk of 14.5% and 8.5%, respectively. Competing-risk regression analysis showed that for each increase in H3Cit levels of 100 ng / mL, there is a relative increase of 13% in the risk of VTE (subdistribution hazard ratio [SHR] 1.13; 95% CI 1.04-1.22). This relationship remained after adjustment for tumor site with very high VTE risk and high VTE risk, dissolved P-selectin levels, and D-dimer levels.[20]

Histones are the most abundant protein in NETs. Histones are positively charged proteins that have the function to wrap DNA in the nucleus. This helps regulate the activation of platelet and thrombin in a dose-dependent manner.[26] Platelets reveal several characteristics associated with activation such as aggregation, phosphatidylserine presentation, and P-selectin surface expression after treatment with histones.[27] Importantly, the compilation of histones complexes with DNA (such as those encountered in NETs), their ability to support platelet and generation of thrombin is strengthened.[27] It has also been proposed that histone contributes to thrombin activation by isolating protein C and thrombomodulin and preventing the activation of thrombomodulin-dependent protein C.[28] Varied experiments in animal models showed that intravenous histones promote DVT risk in the context of inferior vena cava in mice.[7]

The population used in the study by Mauracher et al. is cancer patients.[20] Cancer populations have an increased risk of VTE. A review by Horsted et al. stated that each year, VTE develops in more than 1% of cancer populations, but it differs significantly by time since diagnosis, type of cancer, stage of the disease, and treatment modality. Horsted et al. also stated that brain and pancreatic cancer had the highest risk of VTE.[29] Tumor cells release cell-free DNA, growth factors, and procoagulant factors, which increase VTE. These factors include tissue factor (TF)-positive microvesicles, granulocyte-colony stimulation factors (G-CSF), thrombopoietin (TPO), and IL-6. The release of G-CSF enhances the release of NETs from neutrophils and the expression of tissue factors by monocytes. Other drugs, including chemotherapy used to treat cancer, can also injure the endothelium and increase the level of plasma cell-free DNA, which may contribute to the mechanism of cancer-related thrombosis.[30]

Van Montfoort et al. explore the relationship between elastase complex - α1-antitrypsin (EA) and nucleosomes, and the presence of DVT. Activation of neutrophils consequently leads to the NETs formation and nucleosome exposure to NETs contributes to in vivo coagulation activation and DVT development. Activated neutrophils were measured by EA. Patients with nucleosome levels more than 80th percentile from controls had an increase in DVT risk compared to patients with levels less than equal 80th percentile (OR 3.0; 95% CI 1.5-3.9). Besides, patients with EA complex levels more than 80th percentile from controls had an increase in DVT risk compared to patients with levels less than equal 80th percentile (OR 2.4; 95% CI 1.5-3.9). Increased levels of EA complex

and circulating nucleosomes are associated with a threefold DVT risk, and the relationship remains the same after adjusting for potential confounders (smoking, malignancy, recent hospitalization, and recent immobilization). This risk increased with a higher level of EA and nucleosomes, showing a relationship between circulating nucleosomes, activated neutrophils, and DVT in a dose-dependent way.[21]

Diaz et al. showed that circulating DNA (a surrogate marker for NETs) was increased in patients with DVT significantly, compared with patients without DVT (57.7 ± 6.3 vs. 17.9 ± 3.5 ng/mL; $p<0.01$) and controls (57.7 ± 6.3 vs. 23.9 ± 2.1 ng/mL; $p<0.01$). Strong positive correlations were found with D-dimers, C-reactive protein, vWF, myeloperoxidase/MPO, and Wells scores, and also strong negative correlations with disintegrin and metalloproteinase with type 1 thrombospondin motifs, member 13 (ADAMTS13) and ADAMTS13/vWF ratio. A strong relationship between plasma DNA and the presence of DVT was showed in logistic regression analysis (receiver operating characteristics/ROC curve 0.814).[22]

Plasma contains circulating DNA (cDNA) and is increased in cardiovascular, inflammatory, and thromboembolic disorders. In vivo and in vitro data showed the vital role of cDNA in thrombosis and inflammation. DNase infusion reduces tissue inflammation and prevents thrombus formation in murine models by decreasing cDNA.[12,31] Circulating DNA may be produced from dead cells and release of NETs from neutrophils, which is described as DNA fibers that contain enzymes released from neutrophil granules and histones. A study by Jiménez-Alcázar et al. showed that cDNA levels increased in patients with VTE compared with healthy controls. However, the relationship of cDNA to VTE level and outcome is poorly understood. They measured cDNA and nucleosomes as well as plasma circulating NETs from acute VTE patients. Their study suggested that cDNA levels but not NETs showed the level of inflammation and may function as a biomarker for stratification of patients with VTE who are at risk of death.[32]

Fibronectin (FN) is a high molecular weight plasma glycoprotein produced by hepatocytes from the extracellular matrix that binds to integrins (membrane-spanning receptor proteins). Fibronectin plays a vital role in many cellular processes, including tissue repair, embryogenesis, cell migration/adhesion, and blood clotting. Because fibronectin is on the surface of endothelial cells and is secreted into the cell matrix, the adhesive properties of FN are modulated and enhanced by cell retaining to collagen or proteoglycan substrates.[33] Similar neutrophil adhesive properties of fibronectin (FN) between VTE and control patients were demonstrated in a study by Zapponi et al. Subgroup evaluation of patients who showed high D-dimer levels and residual venous occlusion (RVO) (n = 15; 51%), a significant increase in neutrophil adhesive properties when compared with the controls and the remaining patients could be observed, respectively (24.68%, 19.29%, 18.23%, p = 0.0179).[23]

For average-risk studies, the prevalence of VTE varied between 9.4%[20] to 50%[21,22]. Some studies use case-control designs that usually use case and control with almost the same comparison; therefore, three studies showed a VTE prevalence of around 50%. One cohort of cancer patient showed that NETs increase VTE risk (9.4%), two case-controls showed NETs correlate with DVT (45% and 50%),[21,22] and one case study showed there is increasing NETs in

RVO and increased D-dimer with 50% prevalence.[23]

Several limitations of our study include non-random trial assignments, various populations, and small sample sizes. Four included studies also using various biomarkers in NETs measurement and having various study outcomes.

Conclusions

Neutrophils' role in thrombogenesis is the recent advances in understanding VTE. Neutrophils are unique and essential; NETs formation has been shown to have a causative role in increasing VTE risk. More research is necessary to determine the NETs' role in VTE as a diagnostic biomarker or target of therapy.

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REVIEW ARTICLE

Approach to adrenal incidentalomas: a review

Miriam Giordano Imbroll, Josanne Vassallo, Mark Gruppetta

Adrenal tumours are nowadays most often discovered incidentally, on imaging not performed for suspected adrenal disease that are termed adrenal incidentalomas. There are two questions clinicians need to explore: whether the lesion is benign or malignant (relying mostly on radiology) and whether it is functional or not (relying on biochemical tests).

An unenhanced CT scan (CT without contrast) or MRI is the imaging modality of choice. However, if an incidentaloma is discovered on a CT with contrast, done for other reasons than suspected adrenal pathology, contrast washout may be helpful in diagnosing a benign lesion.

Functional analysis in patients confirmed to have an adenoma or rarely an adrenal carcinoma should include tests to exclude cortisol excess, and in patients with hypertension, mineralocorticoid excess. The production of subtle amounts of cortisol, not enough to cause classical clinical features of Cushing syndrome, but enough to cause metabolic disturbances and, possibly increased mortality, has over recent years gained more attention. In those patients with suspected phaeochromocytoma, plasma free metanephrines or urinary fractionated metanephrines should be checked.

This review, based on recent literature, discusses the evidence based suggested algorithms for investigating adrenal incidentalomas.

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Introduction

In clinical practice, tumours are the most frequently encountered pathologies of the adrenal gland. Such tumours may be either discovered incidentally or present with symptoms of hormonal excess.[1] In recent years, the increasing use of abdominal imaging has resulted in a steep rise in the incidental discovery of adrenal lesions. These masses, detected by imaging studies originally not performed for suspected adrenal disease, have been coined 'adrenal incidentalomas'.[2]

The aetiology of adrenal incidentalomas varies and includes both benign and malignant lesions arising from the adrenal cortex or medulla. Metastatic deposits may also present as adrenal incidentalomas. The majority of primary adrenal lesions are hormonally non-functional, however, a small proportion produce one or more adrenal hormone/s in excess.[3] This excess production may occur irrespective of whether the lesion is benign or malignant.[1] Over the last decade, there has been increasing awareness that those with apparent non-functional tumours, that is, no classical signs and symptoms of hormonal excess, might exhibit mild autonomous cortisol hypersecretion without overt symptoms of Cushing syndrome.[4] These patients possibly exhibit increased cardiovascular risk related to cortisol excess such as arterial hypertension, type 2 diabetes mellitus, insulin resistance, hypercholesterolaemia, obesity,[5-9] increased vertebral fractures[10] and increased mortality.[11]

Adrenal incidentalomas raise challenging questions for both patients and their caring physicians. The aim of this review is to explore the latest evidence based approaches to adrenal incidentalomas and understand the pathway of investigations to be carried out when such an incidentaloma is discovered. The questions to be answered in the following review are:

1. What are the imaging modalities of choice when dealing with adrenal incidentalomas? How often should imaging be carried out?
2. How is a sinister lesion distinguished from a benign lesion?
3. What functional tests should be carried out?

Characterisation of adrenal tumours

Once an adrenal lesion is incidentally discovered, there are two questions the clinician should consider (Figure 1):

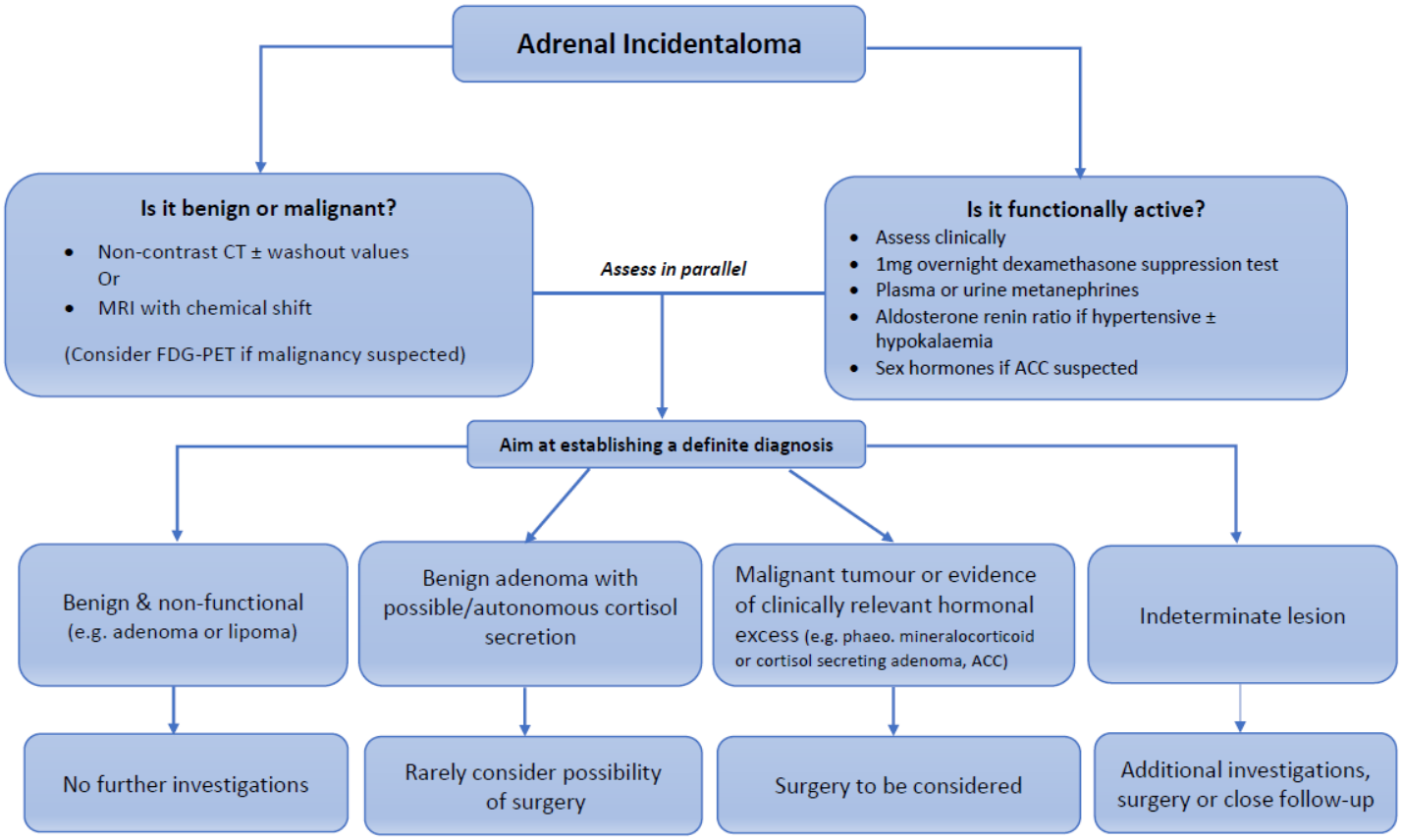
whether the lesion is benign or malignant (relying mostly on radiology) and,

whether it is functional or not (relying on biochemical tests).

Assessing for malignant potential: adrenal radiology

Generally, 80-90% of adrenal incidentalomas are benign.[1] Current morphological imaging modalities with computed tomography (CT) or magnetic resonance imaging (MRI) have proven to be a reliable means of excluding adrenal malignancy. Conversely, fluorodeoxyglucose (FDG)- positron emission tomography (PET)/CT is mainly used for detection of malignant disease.[12]

Figure 1 Algorithm for management of adrenal incidentaloma (Adapted Fassnacht et al.,[17]) (ACC: Adrenocortical carcinoma)



Non-contrast CT

CT has a high spatial and quantitative contrast resolution. By measuring X-ray absorption of tissues, an assessment of tissue density can be made. This is measured in Hounsfield units (HU) which is an objective quantification of X-ray absorption of tissues compared with water (HU value of 0). The threshold density for diagnosing a lipid rich, benign adrenal adenoma on a non-contrast CT is a density of less than 10HU (Figure 2).[13] However, approximately 30% of benign lesions are considered lipid poor adenomas and therefore have an attenuation of >10HU on non-contrast CT. Other lesions such as malignant lesions and phaeochromocytomas also have high density on non-contrast CT, creating an area of overlap with lipid poor adenomas.[14-16] A density of >10 HU on non-contrast CT of the tumour has a high sensitivity of 100% (95%CI 91-100%) but poor specificity of 72% (95%CI 60-82%) for detecting malignancy.[12] In other words, an incidentaloma discovered on non-contrast CT is deemed to be benign if density is ≤10HU.

Figure 2 A right sided adrenal lesion (arrowed) measuring 32 x 27mm with characteristics in keeping with a typical lipid rich adrenal adenoma:

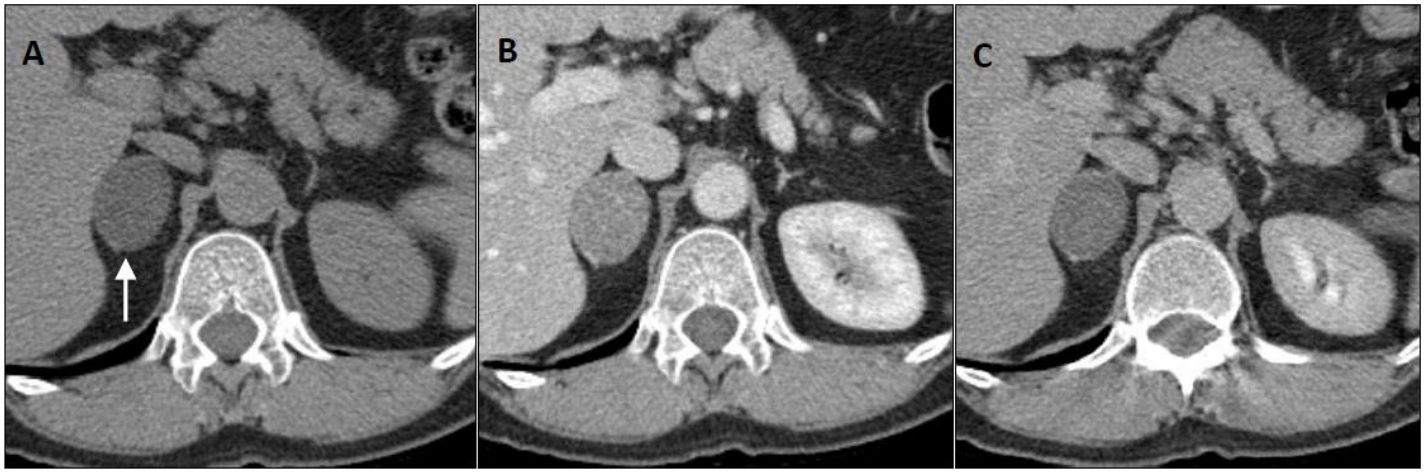
a. CT pre-contrast showing a density of 3HU

b. CT at 60 seconds after contrast: 67HU

c. CT at 15 minutes after contrast (delay): 27HU

Absolute washout 63%

Relative washout 60%



Contrast enhancement CT with washout

Adenomas are unique in their perfusion pattern. They take up intravenous CT contrast quickly but also lose contrast rapidly; a phenomenon termed 'contrast enhancement washout'.[13-15] On the other hand, malignant lesions and phaeochromocytomas, usually demonstrate washout of contrast medium at a slower pace. Adrenocortical carcinomas demonstrate heterogenous enhancement with predominance at the periphery, and centrally there are often areas of cystic changes or necrosis. About 30% demonstrate intra-tumoral calcification.[13] Phaeochromocytomas are usually characterised by areas of degeneration, necrosis, fibrosis, calcification and cystic changes. Adrenal metastasis show overlapping features with adrenocortical carcinoma and phaeochromocytoma. Hence in a patient with a history of extra-adrenal malignancy, metastasis should be included in the differential diagnosis, especially if lesions are bilateral or have shown rapid growth in size.[15]

'Contrast washout values' utilise this unique property to further characterise adrenal lesions which on non-contrast scans have a density of more than 10HU. Attenuation measurements are done in the following three phases: before injecting contrast (unenhanced density (HU)), at 60 seconds following contrast injection (early enhanced density (HU)) and after 15 minutes of injecting contrast (delayed density (HU)). This allows for the calculation of the relative contrast enhancement washout and absolute contrast enhancement washout according to the following formulae: relative washout = (early enhanced density of lesion (HU) – delayed density of lesion (HU)) / (early enhanced density (HU)) x 100%. Absolute

washout = ((early enhanced density (HU) – delayed density (HU)) / (early enhanced density (HU) – unenhanced density (HU)) x 100%.[13] A relative washout of >40% and an absolute washout >60% is suggestive of a benign adrenal adenoma (Figure 2), whereas a relative and/or absolute washout value of less than 40% and 60% respectively is suggestive of malignancy, including metastasis or phaeochromocytoma.[15-16] Sensitivity of CT contrast enhanced washout was found to be 100% (95% CI 75-100%) and specificity 92% (95% CI 62-100%), in patients with no history of underlying malignancy.[12]

MRI scan

Chemical shift imaging is an MRI technique used to identify adenomas from other adrenal lesions.[16] Within magnetic fields, protons in water vibrate at a slightly different frequency than protons in lipid, thus fat and water protons oscillate in and out of phase with respect to one another. Lipid rich adrenal adenomas usually lose signal intensity on out-of-phase images compared with in-phase images, whereas malignant lesions and phaeochromocytomas (and lipid poor adenomas) remain unchanged. The advantage of this modality over CT is that it avoids radiation exposure and iodine based contrast, together with its better tissue resolution. According to the same meta-analysis by Dinnes et al., sensitivity is 86% (95%CI 31-99%) and specificity is 85% (95% CI 73-93%).[12]

18F-FDG-PET

18F-FDG-PET is a nuclear medicine modality that provides quantitative tomographic images after intravenous injection of a beta-radiation-emitting radiotracer (18-Fluorine) used to label 2-deoxy-D-glucose rendering fluoro-deoxyglucose (18F-FDG). Both glucose and deoxyglucose enter cells via glucose transporters, but while glucose undergoes further enzymatic breakdown, deoxyglucose does not and becomes trapped inside the cells. Cancer cells have an increased requirement for glucose, so they take up more glucose and deoxyglucose, which can then be measured, giving a standard clinical measurement index; the standardised uptake index (SUV).[16] This test has a sensitivity of 100% (95%CI 78-100%) and specificity of 96% (95% CI 57-100%) for detecting malignancy in those patients without previous extra-adrenal malignancy. In those with previous malignancy, sensitivity drops to 82% (95% CI 41-97%) whereas specificity is similar to that in patients without previous malignancy.[12]

Assessing for hormonal excess

Hormonal evaluation is recommended to be performed on all incidentally found adrenocortical adenomas, suspected adrenocortical carcinomas and phaeochromocytomas (Figure 1). A detailed clinical evaluation including history and examination might help to detect signs and symptoms of hormone excess.[17] The most frequent lesion is a non-functional adrenal adenoma; comprising 85% of all lesions.[18] These lesions do not need further interventions.[17] Functional adrenocortical adenomas include those producing excess cortisol and mineralocorticoid, and phaeochromocytomas which are characterised by excess metanephrines and catecholamines secretion. Adrenocortical carcinomas may produce glucocorticoids, mineralocorticoids and/or adrenal androgens.

Cortisol excess

In recent years further interest has centred on those adrenal adenomas which produce subtle amounts of cortisol which are not enough to manifest clinically with overt features of

cortisol excess (round plethoric complexion, acne, hirsutism, centripetal obesity, proximal muscle weakness, mood disturbance and menstrual disturbance). This phenomenon, labelled 'autonomous cortisol secretion', in fact, is the most frequent endocrine dysfunction in adrenal adenomas,[17] ranging from 1 to 29%. Various thresholds to diagnose cortisol excess have been quoted,[1,19] but according to recent European guidelines, a 9am serum cortisol level of less than 50nmol/l, after 1mg dexamethasone (overnight dexamethasone suppression test (ODST)) given at 11pm the night before, excludes the diagnosis of autonomous cortisol secretion. A level between 51 and 138nmol/l suggests 'possible autonomous cortisol secretion' whilst a level of >138nmol/l supports the diagnosis of 'autonomous cortisol secretion'. Overt Cushing syndrome is defined as a level of cortisol following dexamethasone of >138nmol/l plus classical clinical manifestations of Cushing syndrome.[17]

Patients with Cushing syndrome have increased multisystem morbidity and mortality, and surgery should therefore be considered in the first instance (Figure 1).[17] In a study by Dekkers *et al.,* patients with Cushing syndrome (including both ACTH dependent (pituitary) and ACTH independent), mortality was twice as high in the Cushing syndrome group when compared to controls (HR 2.9, 95%CI 1.8-2.9). The risk was also increased for venous thromboembolism (HR 2.6, 95%CI 1.5-4.7), myocardial infarction (HR 3.7, 95%CI 2.4-5.5), stroke (HR 2.0 95%CI 1.3-3.2), peptic ulcers (HR2.0 95%CI 1.1-3.6), fractures (HR 1.4, 95%CI 1.0-1.9), and infections (HR 4.9, 95%CI 3.7-6.4). These risks were similarly increased, irrespective of whether they had pituitary or adrenal source of cortisol excess.[20]

Studies have also demonstrated that low grade autonomous cortisol secretion might be associated with certain comorbidities, including hypertension, glucose intolerance and type 2 diabetes,[6] ischaemic heart disease and dyslipidaemia,[9] obesity,[8] osteoporosis[10] and increased mortality.[11] However, a recent meta-analysis, showed only low-to-moderate-quality evidence pointing in favour of adrenalectomy in patients with autonomous cortisol secretion, on the cardiovascular risk factors, when compared with conservative management.[21] Therefore, surgery, in patients with autonomous and possible autonomous cortisol secretion, should be done on an individual basis taking into account age, degree of cortisol excess, general health, comorbidities and patient's preference (Figure 1).[17]

Mineralocorticoid excess

Primary aldosteronism is characterised by an inappropriately high level of aldosterone in proportion to sodium status, relative autonomy from the regulators of its secretion, namely angiotensin II and plasma potassium concentration, and no suppression on loading with sodium.[22] Patients with an adrenal incidentaloma and hypertension are recommended to undergo a 3-step process which includes screening, confirmatory testing, followed by subtype classification for detection of an aldosterone secreting adenoma.[22] Plasma aldosterone/renin ratio (ARR) is the screening test proposed in the guidelines. When primary aldosteronism is suspected based on the ARR, a confirmatory test (oral sodium loading, saline infusion, fludrocortisone suppression test or captopril test) will further enhance the diagnosis in those contemplating surgery. In these patients, subtype classification with the help of imaging and possibly adrenal vein sampling

(AVS) might be indicated to identify unilateral as opposed to bilateral disease. Surgery is the preferred option in patients with unilateral disease and who are fit for surgery, with the rest being treated with a mineralocorticoid receptor antagonist.[22]

Patients with primary aldosteronism have a higher cardiovascular morbidity and mortality, compared to age- and sex-matched patients with the same degree of hypertension, unrelated to mineralocorticoid excess.[23] They have increased target organ damage and cardiovascular events than patients with essential hypertension who have similar risk profiles.[24] There is also an ongoing debate on whether treatment with adrenalectomy is superior to treatment with mineralocorticoid receptor antagonists. Recent studies have shown that in a unilateral aldosterone secreting adenoma, surgery is superior in reducing left ventricular mass, as it reverses the ventricular wall thickening as well the general enlargement of the left ventricular cavity.[25]

Combined glucocorticoid and mineralocorticoid excess

Some case reports have reported co-secretion of excess glucocorticoids and aldosterone.[26] A recent study by Arlt *et al.,* showed that a large proportion of patients do in fact co-secrete these two hormones.[27] In this study, mass spectrometry steroid metabolome was used on a 24 hour urine collection and this technique detected that glucocorticoid metabolite excretion, in patients with primary aldosteronism, is a frequent occurrence ($P<0.001$) with levels as high as in patients with overt adrenal Cushing syndrome. This might shed light as to why treatment with adrenalectomy is superior to mineralocorticoid receptor antagonists in patients with presumed isolated aldosterone excess.

Catecholamine excess

Phaeochromocytomas form part of a broad group of tumours derived from the neural crest of the sympathetic or parasympathetic nervous system, collectively termed phaeochromocytoma/paragangliomas (PPGL). These tumours commonly secrete one or more of the following catecholamines: adrenaline, noradrenaline and dopamine. Surgical resection of PPGLs is recommended in the first instance.[28]

Untreated excess catecholamine secretion is associated with increased cardiovascular morbidity and high mortality.[29] To prevent the morbidity and mortality associated with this tumour and because there are cases of 'silent' phaeochromocytomas, where catecholamine secretion may be intermittent, any adrenal incidentaloma, especially those not having characteristics of an adenoma on CT or MRI, should be screened for a possible phaeochromocytoma. Screening with plasma free metanephrines or urinary fractionated metanephrines is recommended.[28] In phaeochromocytomas, a diagnosis of malignancy is only established with the detection of extra-adrenal metastasis.

Another reason why phaeochromocytoma detection is actively sought is, that at least one third of cases, have a disease-causing germ-line mutation. Therefore, detecting a phaeochromocytoma might result in earlier diagnosis and possibly screening of other family members. Genetic studies are recommended in all patients with phaeochromocytoma.[28] Some forms of phaeochromocytomas, especially those associated with the gene succinate

dehydrogenase sub unit B (SDHB) have a higher malignant potential (40%).[30]

The latest guidelines on adrenal incidentalomas[17] recommend measuring plasma-free or 24-hr urine fractionated metanephrines, in all patients with adrenal incidentaloma, but point out that it may be reasonable to avoid such biochemical testing in patients who have an adrenal incidentaloma with unenhanced attenuation of less than 10HU. A recent study by Canu et al. further supports this. Out of 376 phaeochromocytomas for which unenhanced attenuation data were available, 99.5% had an attenuation of >10 HU (374 patients). The two exceptions (0.5%), were found to have an unenhanced attenuation of exactly 10 HU, which lies just within the range of ≤10 HU that would suggest a diagnosis of adrenocortical adenoma. In this study, however, assessment with contrast washout was unreliable for ruling out phaeochromocytoma.[31]

Androgen excess

The adrenal cortex also secretes androgens, however screening for androgen excess is not recommended in patients with an adrenal adenoma on a routine basis.[17] The only recommended instance when measurement of adrenal androgens (dehydroepiandrosterone sulphate (DHEA-S), androstenedione, 17-hydroxyprogesterone and testosterone in women and oestradiol in men and postmenopausal women) is suggested, is when suspecting adrenocortical carcinoma (Figure 1).[17]

Follow up of adrenal lesions

Current recommendations by the European Society of Endocrinology Clinical Practice guidelines, in collaboration with the European Network for the Study of Adrenal tumours, suggest against repeat imaging in patients with an adrenal incidentaloma less than 4cm which on initial assessment had benign features on imaging studies.[17] Before these guidelines were issued, common practice was that if a lesion was thought to be benign at baseline, further follow up investigations were recommended to detect the occurrence of malignancy in an adrenal incidentaloma displaying typical features of adrenocortical adenoma at initial imaging studies. Hormonal evaluation was suggested to be carried out annually for 4 years.[1] This reasoning was challenged, because amongst more than 2,300 patients included in follow up studies, there was nearly no report of adrenal malignancy occurrence in those incidentalomas thought to be benign at initial evaluation.[17] However, most patients with adrenal incidentalomas >4cm in diameter have undergone adrenalectomy in the past, and the literature on follow-up of non-operated large adrenal incidentalomas is scarce. Thus, some experts argue that at least one follow up imaging after 6-12 months might be considered in lesions not operated upon and, thought to be benign at diagnosis, but are >4cm.[17]

Change in size of adrenal lesion

One of the main dilemmas in managing patients with adrenal incidentalomas is when there is an increase in size in a lesion which was deemed to be benign on initial imaging. In the consensus statement by the Italian Endocrine Association (AME), it was concluded that in a group of patients with adrenal incidentalomas followed up for an average of 4 years, 5-20% showed mass enlargement >1cm and/or appearance of a mass in the contralateral adrenal gland. Mass enlargement was generally limited to 1-2 cm increase in diameter over a period of 1-3 years. However,

even in those tumours which exhibited a pattern of slow growth, malignant transformation was still very low (<1 out of 1000).[1] The presence or absence of endocrine abnormalities at the time of diagnosis cannot be used as a predictor of possible increase in tumour size during follow-up, because even non-functional adenomas were documented to have increased in size.[32] Moreover, shrinkage, or even complete resolution of a mass was reported in around 4% of cases, most often those with a cystic component, haematomas or adrenal pseudo-tumours.[32]

Focus on Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) is a rare malignancy with an estimated incidence of 0.7-2 cases/million/habitants/year.[33] Most often it presents with either steroid hormone excess or an abdominal mass, although in 15% of cases, ACC is discovered incidentally. Prognosis in patients with ACC is poor.[34]

Urine steroid metabolomics in the context of ACC and beyond

Despite the numerous tests and imaging procedures proposed to distinguish benign from malignant and functional from non-functional tumours, definite diagnosis is sometimes difficult to ascertain, especially in those tumours presenting in an atypical way. Mass spectrometry based steroid profiling is also being proposed for detecting adrenocortical malignancy.[35] This steroid metabolomic approach is based on the fact that, although theoretically most (60-70%) of adrenocortical carcinomas are biochemically active, conventional hormonal detection is negative in most cases. This may be explained by the inefficient steroid production in adrenocortical carcinoma. This novel technique has proven to be efficient in detecting these steroid precursors in urine. The top nine most discriminatory markers have been identified and may be used in clinical practice in the future.[35]

Conclusion

With the advent of newer imaging modalities, there has been a steep rise in the pick-up rate of adrenal incidentalomas over recent years. Lately, strong evidence has emerged on the workup of such lesions focusing on two main areas: assessing for malignancy by relying mainly on radiology and assessing functionality (relying on biochemical tests) in a parallel fashion as outlined in Figure 1.

Since adrenal incidentalomas are encountered by clinicians across different fields, in this article we have provided a succinct account on the management of such incidentally discovered lesions, keeping in mind that malignancy and functionality are two characteristics which need to be sought out independently, by following the recently elaborated evidence based approaches discussed above.

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CASE REPORT

Symptomatic extra-macular traumatic pigment epitheliopathy

Alastair David Bezzina, Eve Warrington, Elaine Buttigieg

To describe the evolution and diagnosis of post-traumatic pigment epitheliopathy (TPE) in a young male following blunt trauma to the globe as well as discuss the histopathological and optical coherence tomography (OCT) features of TPE.

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Clinical Case

A 17-year-old male presented to the ophthalmic casualty clinic after being hit in the right eye by a football. The patient complained of profound blurring of vision from his right eye associated with photophobia and bulbar pain. No symptoms were reported with regards the left eye. The patient and his accompanying relative both excluded any relative past ophthalmic history which could contribute to the loss of visual acuity.

Initial examination revealed a right visual acuity of 6/36 (Snellen) which did not improve on using pinhole. Left eye visual acuity was 6/6 unaided. Ecchymoses of the right superior palpebra was noted on inspection. The right pupil was dilated and non-reactive to light but produced pupillary constriction in the left eye on reverse relative afferent pupillary defect testing. Extra-ocular movements appeared to be unrestricted and there was no globe displacement. Slit-lamp examination of the right eye revealed a diffuse corneal haze, linear epithelial defect and a hyphema was noted in the anterior chamber with active bleeding originating from the supero irido-corneal angle. Intra-ocular pressure in the right eye was 9mmHg. Traumatic mydriasis was noted. No fundal view could be obtained at the time of presentation, but B-scan ultrasonography did not reveal any abnormalities in the fundus. The patient was admitted for strict bed rest and started on topical chloramphenicol ointment, high-frequency dexamethasone eye drops and topical cyclopentolate.

On the second day following admission the corneal haze cleared and a fundal view was obtained. Retinal pallor just superior to the macula could be observed with loss of the foveal reflex (Figure 1). Scattered intra-retinal haemorrhages were observed in the periphery. OCT revealed diffuse retinal oedema across all the retinal layers with a central macular thickness of 440µm. Topical nepafenac was prescribed and the patient was discharged after 4 days once the hyphema resolved. After one week, vision from the right eye improved to 6/18 and the central macular thickness reduced to 223µm.

On the fourth week following presentation the patient started complaining of difficulty fixing on a target when closing his left eye. Repeat examination revealed a visual acuity of $6/9^{+3}$ in the right eye and the pupillary diameter came down to 4mm with a normal photic response. On Amsler grid evaluation the patient could not see the grid inferior to the central target. Fundoscopy revealed an area of mixed hypo-pigmentary and hyper-pigmentary changes superior to the macula which exhibited hypo-autofluorescence (Figure 2). An inferior para-central scotoma, corresponding to the depigmented area on fundoscopy, was confirmed on Humphrey visual field testing (Figure 3). The diagnosis of TPE was made. The patient was advised that the visual field defect should not affect his activities of daily living as it will be compensated for by the binocular field and his left eye was the dominant eye of the two. Yearly follow-up was advised then after.

Figure 1 Fundal photo of the right eye demonstating pigmentary changes superior to the macula.

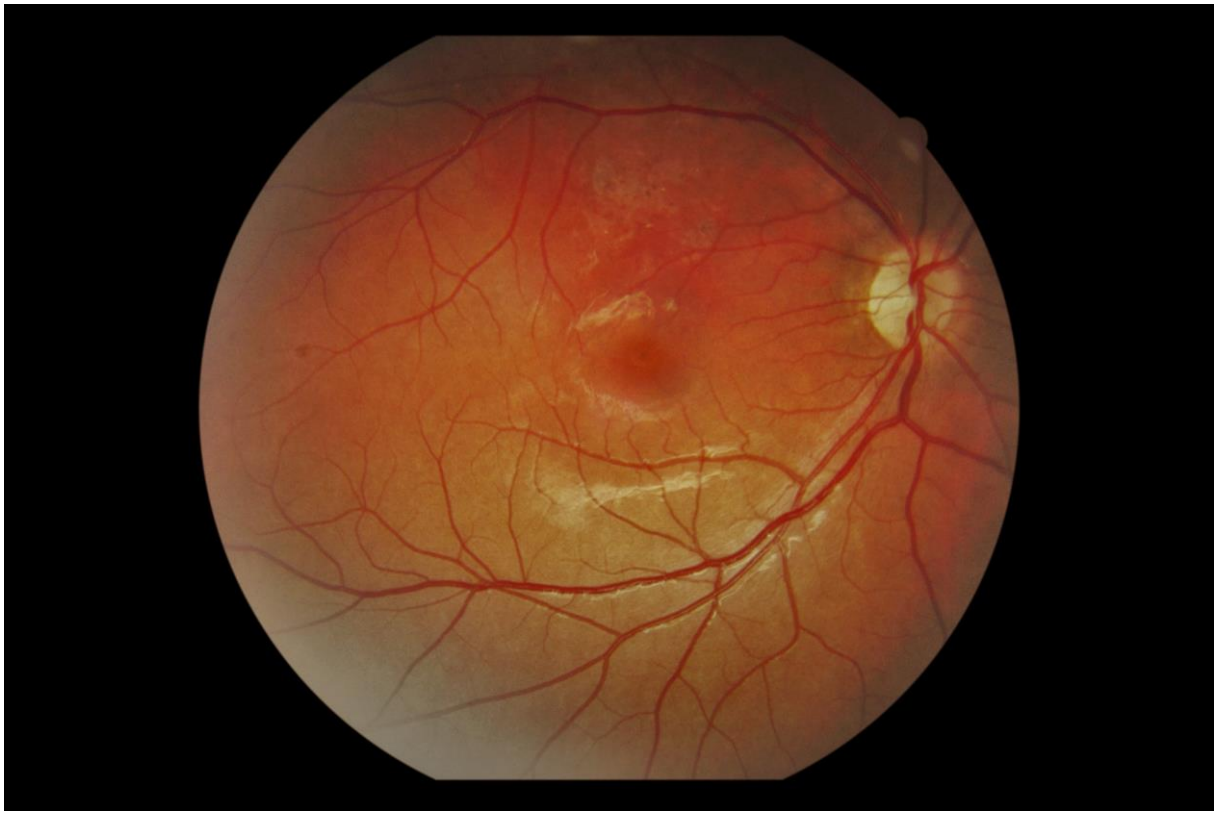


Figure 2 Fundal Auto-Fluorescence photograph of the right eye showing hypo-autofluorescence superior to the macula denoting RPE loss.

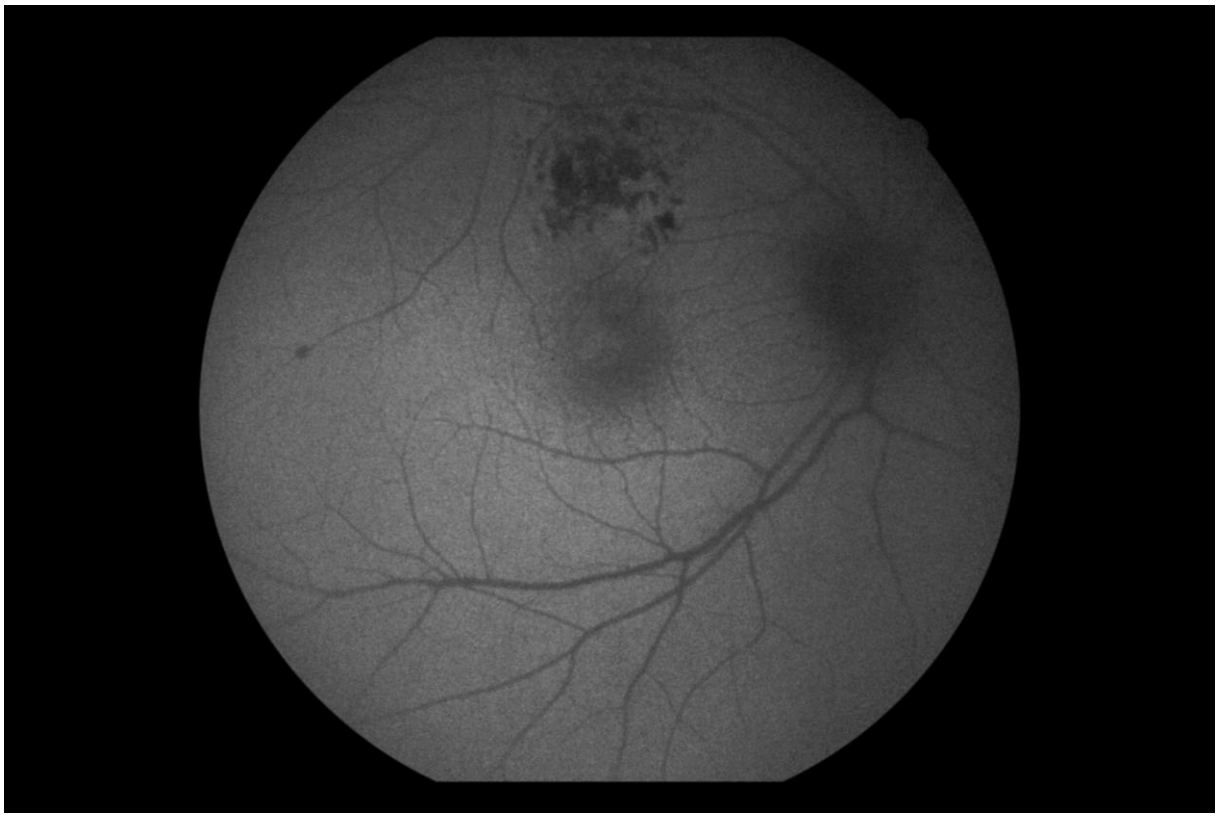
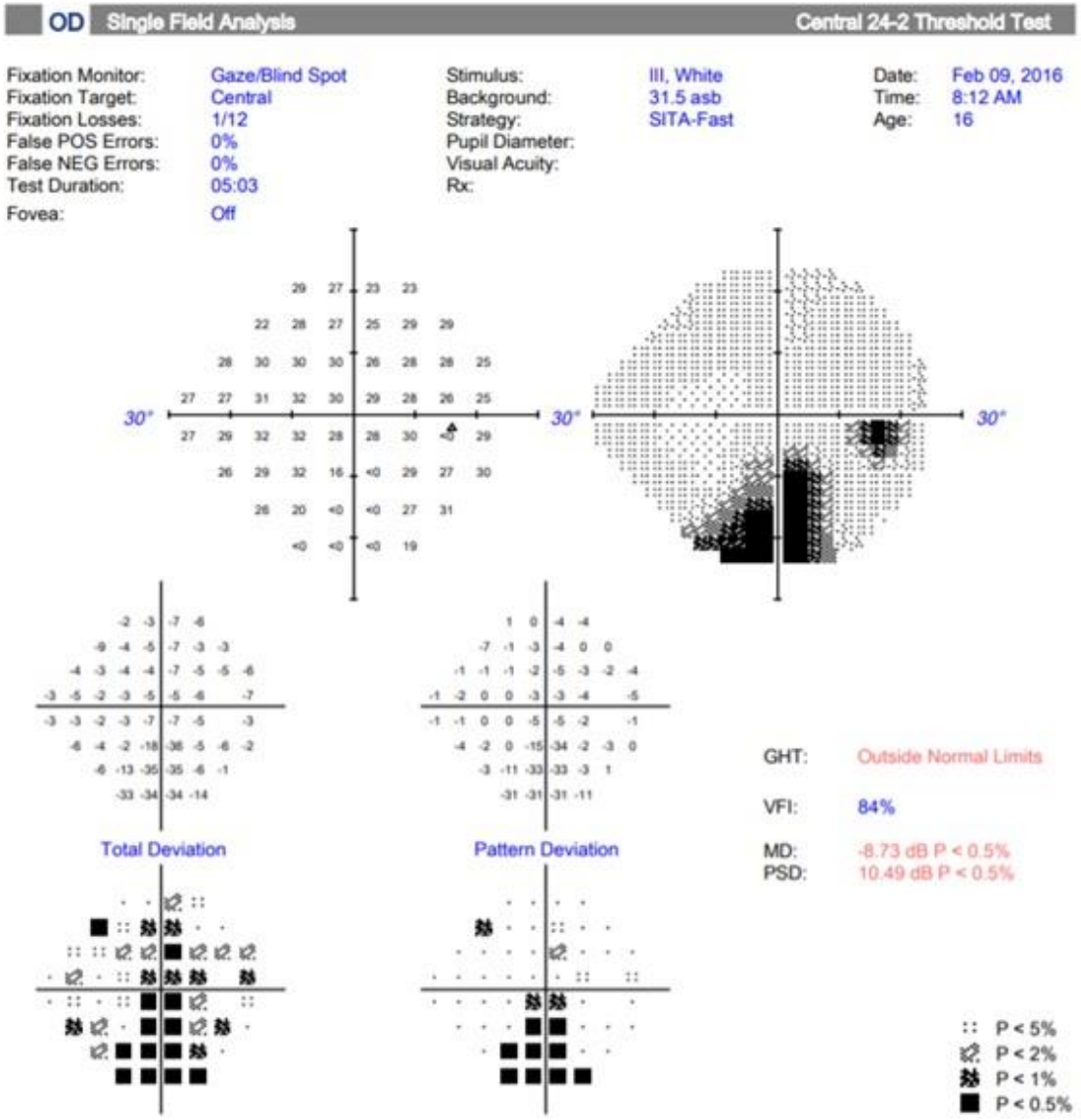


Figure 3 24-2 Humphrey visual field test confirming the inferior para-central scotoma in the right visual field corresponding to the superior-lying are of RPE loss secondary to TPE.



Discussion

Blunt trauma to the eye is characterized by acute globe deformation followed by reformation resulting in stretching of the intraocular contents. Vitreous deformation, caused by the transmission of kinetic energy, results in stretching of the retinal tissues, particularly the outer retinal layers which lack the structural support of Müller cells offered to the inner layers[1], resulting in a condition known as commotio retinae (CR). This condition is clinically characterised by a white-yellow opacification of the affected retinal tissue, as noted on dilated fundoscopy, and can be classified as macular or extra-macular CR with the former having the highest risk of visual loss due to the development of central or para-central scotomata.[2] The development of these scotomata may be due to irreversible damage to the outer retinal tissues resulting in ~~a~~ fragmentation of the photoreceptor outer

segments and retinal pigment epithelium (RPE) apical process loss.[1] Permanent disruption of the aforementioned structures has been coined as traumatic pigment epitheliopathy (TPE), a late complication of CR.[3]

Lavinsky *et al.* described the evolution of TPE in 2 patients following a closed globe injury secondary to blunt trauma which was preceded by CR over the same fundal area 1-3 months before the diagnosis of TPE was made.[3] On fundoscopy, TPE was described as an area containing mixed atrophic and hypertrophic RPE changes, the latter being characterised by scattered loci of hyperpigmentation. The RPE changes noted on fundoscopy corresponded to the patterns seen on fundal autofluorescence imaging demonstrating a high degree of heterogeneity[3] which could be attributed to foci of RPE cell loss (hypo-autofluorescence) and areas of metabolic substrate accumulation (hyper-autofluorescence) from photoreceptors and RPE cell degeneration.[4] The prognosis of TPE depends on the location involved, hence involvement of the macular area carries the highest risk of functional visual deficit due to the formation of a central scotoma although symptomatic para-central scotomata, as in this case, have been documented in the literature.[2] To date there is no effective therapy which can aid in the resolution of this condition.

Histopathological reviews on the formation of CR and its progression in animals[5] and humans[1] have been published in the past. Blight and Hart carried out sequential retinal biopsies in animal subjects following blunt ocular trauma over a period of 2 months.[5] The latter experiment determined that the immediate changes following trauma, including the characteristic opacification of the retinal tissue, was not an ischaemic phenomenon but was due to the formation of intracellular oedema, primarily in the outer retinal layer. The formation of intracellular oedema was accompanied by the fragmentation of the photoreceptor OS layer as well as the loss of apical processes of the RPE cells[5] which would explain the acute symptomatology in macular CR should the posterior pole be involved. Similar changes were noted in the report published by Mansour, Green and Hogge who carried out a histological examination of an enucleated eye obtained from a patient involved in a motor vehicle accident.[1] Examination of retinal biopsies 2 months following trauma showed re-organisation of the photoreceptor OS layer in animal subjects accounting for the symptomatic improvement noted after the resolution of CR.[5] There is no published literature on the histopathology of TPE or its progression from CR, although the findings noted on examination and imaging in this case suggest that when subjected to more severe trauma, loci of RPE cells may be lost (accounting for the hypo-auto-fluorescence noted on fundal autofluorescence photos) with subsequent metabolic damage to the outer retinal layers, which would have also been subjected to mechanical disruption, resulting in permanent visual field defects.

Despite the lack of direct observation of the histological changes that occur in TPE, OCT has allowed researchers to gain more insight on the pathophysiological process leading from CR to TPE in a non-invasive manner.[6] In a case series consisting of 13 patients investigated using spectral-domain OCT during their follow-up following blunt ocular trauma, Souza-Santos et al. noted immediate post-traumatic changes on OCT in TPE patients which differed from the early changes noted in CR patients.[6] Hyper-reflectivity across all the retinal layers,

as opposed to hyper-reflectivity noted below the inner-segment/outer-segment junction in CR patients, was associated with disease progression (p=0.002), namely outer nuclear layer and photoreceptor layer thinning[6] which could be attributed to RPE cell loss and secondary photoreceptor cell death.

To date there is no established treatment to interrupt the evolution of TPE and current management is limited to regular clinical examination and the use of ophthalmic imaging for the purpose of prognostication.

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CASE REPORT

Adenolipomas: a case series of 16 patients over 5 years

Juanita Parnis Luca Borg, Francis X. Darmanin

Introduction

An adenolipoma is a benign, rare variant of a lipoma and is histologically very similar to a lipoma but contains eccrine glands amongst the mature adipose tissue. According to our knowledge, this case series of adenolipomas, is the largest one in the literature. The aim is to increase awareness about this variant of lipoma.

Method

The data was collected retrospectively from the histopathology department and patients' notes.

Results

We had a total of 16 cases of adenolipomas between 2013 and 2017 in our hospital. 75% of the patients were being managed by General Surgeons. 88% of them occurred in female patients and the patients' age varied between 15 and 64 years. The most common location of adenolipomas was the thighs and the largest diameter of the histology specimen varied between 15 and 100mm. 31% were encapsulated, 25% had apocrine glands present and 6% had myxoid changes. None of them had mast cells present. No recurrences were documented.

Conclusion

It is a benign lesion and awareness amongst pathologists is imperative so that it can be identified histologically.

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Introduction

An adenolipoma is a benign, rare variant of a lipoma and is histologically very similar to a lipoma but contains eccrine glands amongst the mature adipose tissue.[1] It was initially described by Hitchcock et al in 1993.[2] This was followed by another case series by Ait-Ourhrouil and Grosshans in 1997 where they disagreed about the name. They recommended using the term "per-sudoral lipoma" instead, because it originated from the adipose tissue itself without proliferation of the eccrine glands.[3] According to our knowledge, this case series of adenolipomas, is the largest one in the literature. The aim is to increase awareness about this variant of lipoma.

Method

The data was obtained retrospectively from the histopathology department at Mater Dei Hospital, Malta, after approval from the Data Protection Department. All the adenolipomas from the year 2013 to 2017 were included. The data was obtained from the histopathology reports and patients' notes and inputted into an excel sheet.

Figure 1 The location of the adenolipomas excised

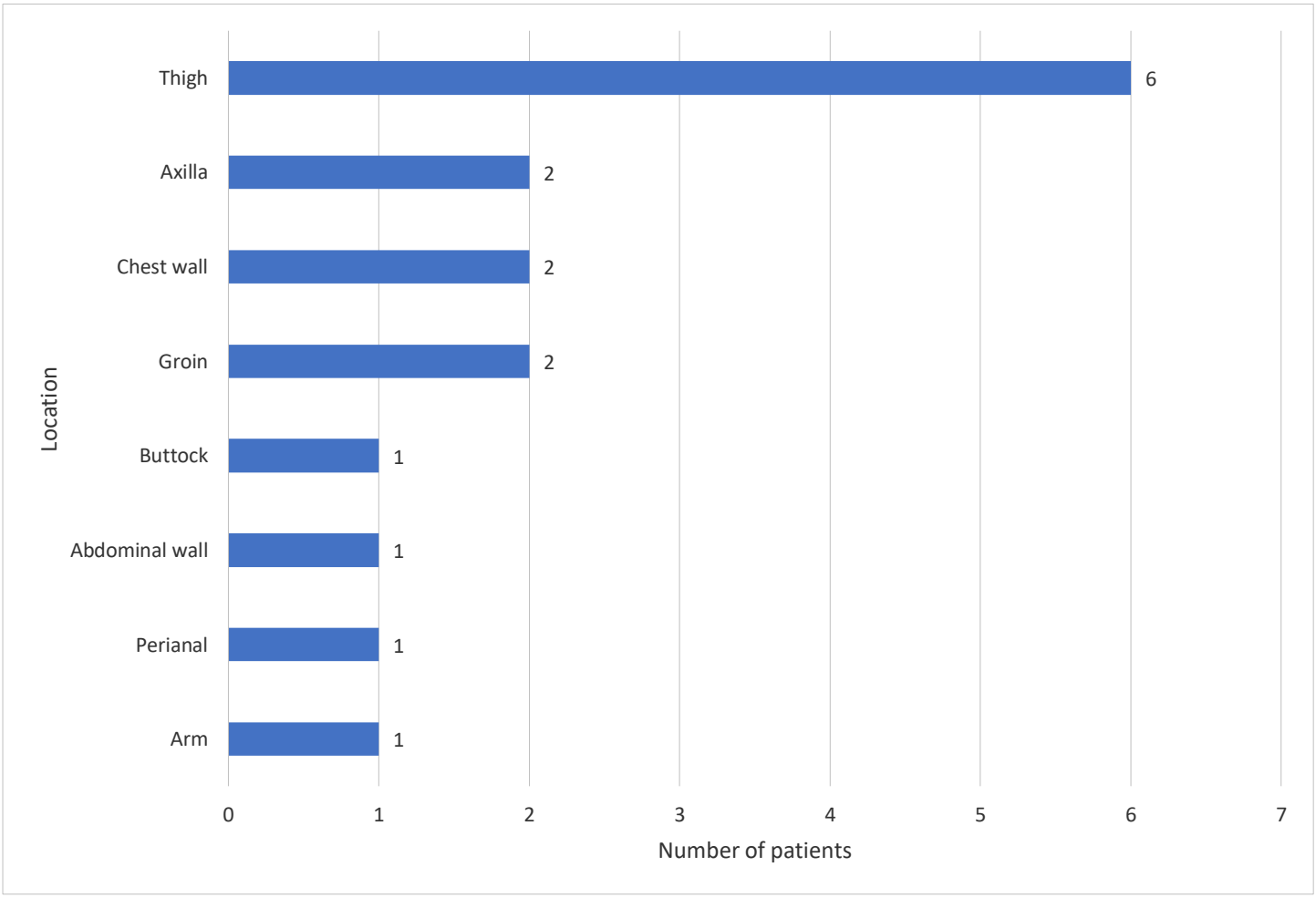


Table 1 Summary of the data for the 16 cases of adenolipoma

	Year	Age	Gender	Site	Size	Encapsulation	Myxoid changes	Mast cells	Apocrine glands	Specialty
1	2013	15	F	Anterior Abdominal Wall	100 x 17 x 10 mm	No	No	No	No	Paediatric Surgery
2	2015	40	M	Left arm	60 x 40 x 20mm	Yes	No	No	No	General Surgery
3	2014	40	F	Right buttock	55 x 30 x 25mm	No	Yes	No	No	General Surgery
4	2015	61	F	Perianal area	45 x 45 x 10mm	No	No	No	No	General Surgery
5	2013	36	F	Left chest wall	45 x 45mm	Yes	No	No	No	General Surgery
6	2014	41	F	Right chest wall	40 x 39 x 12mm	Yes	No	No	No	General Surgery
7	2014	50	F	Thigh	40 x 35 x 15mm	No	No	No	No	General Surgery
8	2013	48	F	Right axilla	35 x 25 x 10mm	No	No	No	Yes	General Surgery
9	2016	36	F	Left thigh	30 x 15 x 15mm	No	No	No	No	General Surgery
10	2013	61	F	Right thigh	25 x 25 x 5mm	No	No	No	No	Vascular Surgery
11	2013	51	F	Left thigh	26 x 18 x 5mm	No	No	No	No	General Surgery
12	2014	33	F	Right axilla	25 x 20 x 5mm	No	No	No	Yes	General Surgery
13	2014	38	F	Left groin	20 x 13 x 8mm	Yes	No	No	Yes	Plastic Surgery
14	2014	64	M	Left groin	15 x 10 x 6mm	No	No	No	Yes	General Surgery
15	2014	28	F	Thigh	15 x 10 x 3mm	No	No	No	No	Plastic Surgery
16	2017	37	F	Right thigh	N/A	Yes	No	No	No	General Surgery

Results

In 5 years, we had a total of 16 histology proven adenolipomas in our hospital. 75% of them (*n=12*) were diagnosed in 2013 and 2014. 88% (*n=14*) of adenolipomas were in female patients and 12% (*n=2*) were in male patients. 75% of the patients (*n=12*) were being managed by General Surgery, 13% (*n=2*) were managed by Plastic Surgery, 6% (*n=1*) was under the care of Vascular Surgery and the last 6% (*n=1*) was being managed by Paediatric Surgery. The age of the patients varied from 15 to 64 years. 38% (*n=6*) of the adenolipomas occurred in the thighs. Other areas included the axillae, arms, trunk, groin, buttock, perianal area as shown in figure 1. The largest diameter of the histology specimen varied from 15mm to 100mm. In one specimen, the size was not specified in the histology report. 31% (*n=5*) of the adenolipomas were encapsulated, 25% (*n=4*) had apocrine glands present, 6% (*n=1*) had myxoid changes and none had mast cells present. No recurrences were documented. A summary of the data is shown in table 1 in decreasing adenolipoma size.

Discussion

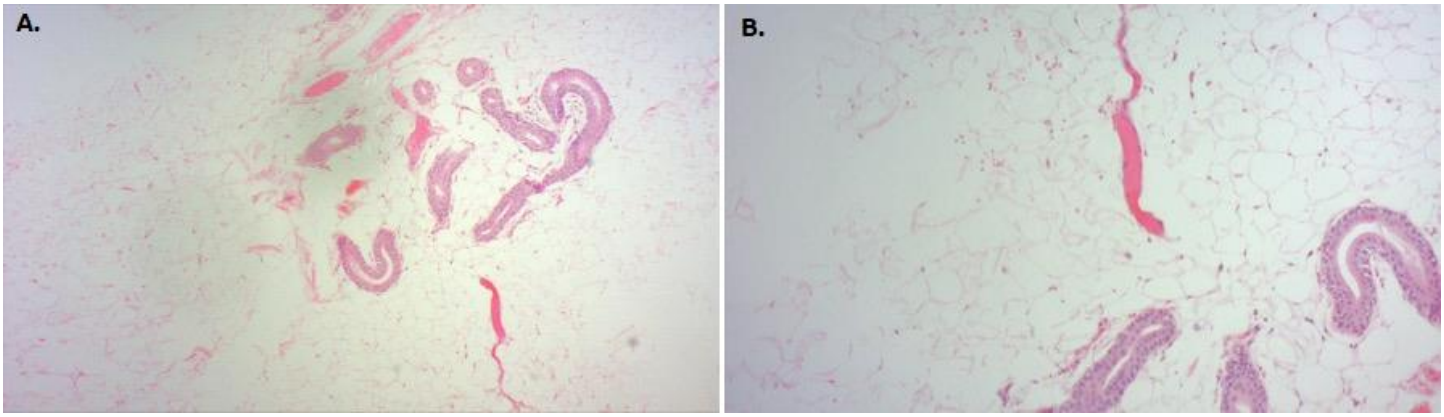
Adenolipomas typically present as a soft, slow-growing, painless lump, commonly arising in the thighs, as shown in our case series, where 6 of our 16 patients had an adenolipoma in the thigh. However, it is also documented that they can arise in the thyroid gland, parathyroid, bronchus, colon, lip, liver, nose, female external genitalia and breast.4-13 The management and prognosis of an adenolipoma mirrors that of a typical lipoma.

The age range is said to be between 25 and 75 years of age but our case series shows a wider spectrum ranging from 15-75 years.14 We document the size range to be between 1.5 and 10cm compared to the case series by Amir et al where they found it to be between 1 and 6cm.1

Macroscopically, they appear to be soft, lobulated, yellow masses. Microscopically, they consist of lobules of adipose tissue that are larger than those of subcutaneous tissue. Dispersed amongst these adipocytes, are eccrine glands and ducts which may show epithelial hyperplasia, cystic duct dilatation and squamous or clear cell metaplasia, as shown in figures 2(a) and 2(b).15 Amir et al document that apocrine glands are rarely seen.1 In contrast, 25% of our lesions had apocrine glands present histologically. Most reported cases of adenolipomas are encapsulated.1 However, in our series, only 31% of the lesions had a capsule when compared to the 9% of encapsulated adenolipomata described in a case series by Amir et al.1

Misdiagnosis of adenolipomas is possible because specimens are usually presented to the Histopathologist in a fragmented manner. This makes it more difficult to determine the location of the eccrine glands. Eccrine glands in the periphery of the lesion, makes it more challenging to distinguish between glands originating from the tumour itself and normal glands lying adjacent to the tumour. It is also important that pathologists are aware that this variant exists, to be able to identify it as such.1 The incidence of adenolipomata may be underestimated as not all lipomata are sent for histological analysis once they are removed.

Figure 2 Both photos show sheets of mature adipocytes with occasional embedded glandular structures lined by a bilayer of epithelial cells, in keeping with eccrine glands. H&E stain. (a) x100 and (b) x200 magnification.



Conclusion

An adenolipoma is a rare variant of a lipoma that contains eccrine glands surrounded by mature adipose tissue. It is a benign lesion and awareness amongst pathologists is imperative so that it can be identified histologically.

Acknowledgements

We would like to thank Dr Alexandra Betts, Consultant Histopathologist at Mater Dei Hospital, Malta, for her time, in order to obtain the data for this case series.

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CASE REPORT

Joints, bones and congenital heart disease… A forgotten association?

Rachel Xuereb, Maryanne Caruana, Michela Frendo

A 20 year old Caucasian male, with a history of uncorrected cyanotic congenital heart disease, presented with a one year history of bone pains in his thighs, legs and forearms. The diagnosis of hypertrophic osteoarthropathy (HOA) was picked up on bone scintigraphy. HOA is usually associated with lung disease and the link with congenital heart disease has become a less frequently encountered association.

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Introduction

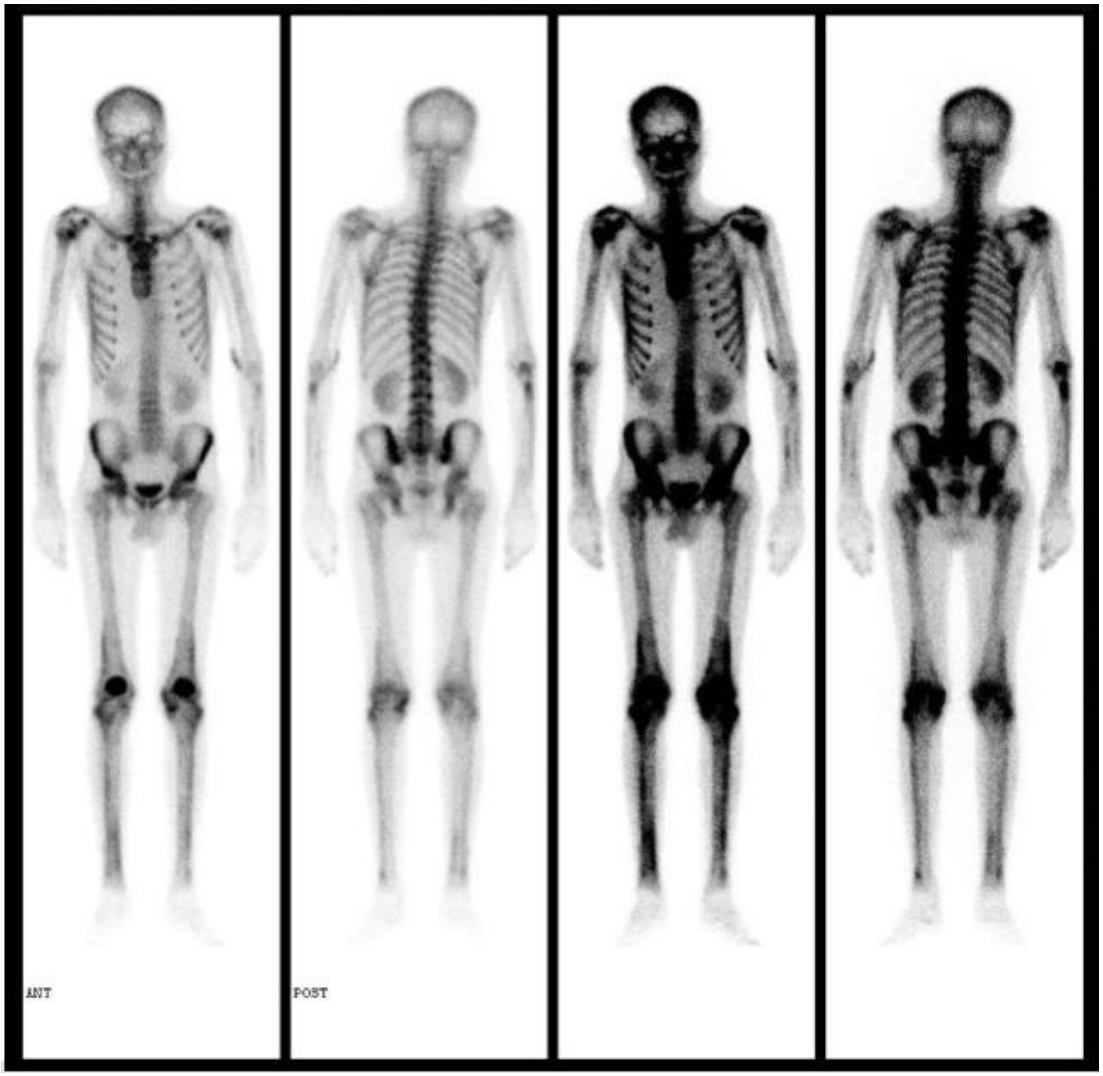
Gout, as a result of increased red cell turnover and hyperuricaemia, is the most commonly recognised cause of joint disease in patients with cyanotic congenital heart disease. We describe a case of hypertrophic osteoarthropathy (HOA), a far less common cause of bone disease in patients with congenital heart disease. It is now becoming increasingly rare to see HOA in these patients, as surgical correction of most congenital heart defects is now successfully being performed earlier on in life.

Case presentation

A 20 year old male was referred to the Rheumatology Department complaining of bone pains in the upper thighs, legs and forearms over the past year. The pain was present throughout day and was not affected by activity. He denied nocturnal pain, joint swelling, systemic upset, rashes, fever, mouth ulcers or sicca symptoms.

Figure 1 Whole body bone scan

Increased tracer uptake along the diaphyseal and metaphyseal surfaces of the femoral bones and tibiae and to a lesser degree the radius and ulna bilaterally.



He was born with complex congenital heart disease, in the form of dextrocardia, double outlet right ventricle and subvalvular pulmonary stenosis. At the age of one year, he underwent a palliative Blalock-Taussig shunt in view of worsening cyanosis but over time developed pulmonary vascular disease and subsequent Eisenmenger syndrome. He had been established on advanced pulmonary vasodilators for several years.

On examination, the patient had an oxygen saturation of 62% on room air. He had clubbing of the digits and central cyanosis. There was no evidence of synovitis or joint deformities, but thickening of the distal part of both tibiae was noted. There was no overlying erythema or tenderness. Blood investigations were normal, apart from a high haemoglobin of 20.2 g/dL (14.1 - 17.2 g/dL) with a high haematocrit level of 59.3% (40.4 - 50.4%), slightly elevated uric acid of 507 umol/l (202 - 416 umol/l) and high alkaline phosphatase of 225 U/l (40 - 104 U/l). Autoimmune screen including antinuclear antibody, rheumatoid factor and anti-cyclic citrullinated peptide antibody was negative. Plain X-rays of hands and lower legs showed no abnormalities. Whole body bone scan, Figure 1, showed increased tracer uptake along the diaphyseal and metaphyseal surfaces of both femoral bones and tibiae and to a lesser degree the radius and ulna bilaterally. These findings are in keeping with HOA. The patient was treated with paracetamol and non-steroidal agents. He is being followed up regularly at rheumatology out-patient clinic for evidence of progression of disease.

Discussion

HOA is characterised by triad of severe disabling arthralgia and arthritis, digital clubbing and periostosis of tubular bones with or without synovial effusion. HOA was first described by Eugen von Bamberger and Pierre Marie in 1890.[1] In rare cases it is inherited as an autosomal dominant condition, known as pachydermoperiostosis. In 95-97% of cases, it is secondary to pulmonary or extrapulmonary diseases, Table 1. The majority of these cases are of pulmonary origin, when it is known as hypertrophic pulmonary osteoarthropathy (HPOA). 90% of these are associated with malignancy. Non-small cell lung cancer (NSCLC), specifically adenocarcinoma, is the most common cause (0.7-17%). Although lower in absolute incidence, a higher percentage of pleural tumours result in HPOA, 22% of solitary fibrous tumours of pleura as compared to 5% of NSCLC.[1]

Three pathways for the mechanism of development of HOA have been proposed:

1. Vascular pathway due to secretion of vasoactive agents by the tumour or due to arteriovenous shunting within the pulmonary circulation,
2. Neurogenic pathway triggered by vagal innervation, resulting in vasodilatation and increased blood circulation to the extremities,
3. Hypoxaemia driven surge of circulating growth factors e.g. platelet-derived growth factor, vascular endothelial growth factor (VEGF) and prostaglandin E2.

The latter is the proposed mechanism in patients with cyanotic congenital heart disease.[2]

Table 1 Causes of generalised HOA

Pulmonary	Cardiac	Gastrointestinal	Hepatobiliary	Miscellaneous
Bronchogenic carcinoma/ metastatic disease	Congenital cyanotic heart disease	Polyposis	Cirrhosis	Thymoma
Mesothelioma	Atrial myxoma	Malignancy	Biliary atresia	POEMS syndrome
Cystic fibrosis	Infective endocarditis	Inflammatory bowel disease	Primary biliary cirrhosis	Myelofibrosis
Pulmonary tuberculosis		Achalasia	Wilson disease	Haematological malignancy
Chronic infections		Laxative abuse	Hepatobiliary carcinoma	
Pulmonary arteriovenous malformations			Primary sclerosing cholangitis	
Sarcoidosis				
Solitary fibrous tumours of the pleura				

POEMS: polyneuropathy, organomegaly, endocrinopathy, myeloma protein and skin changes.

Patients with HOA share common features: pleomorphic platelets, giant macrothrombocytes with aberrant volume distribution curves, glomerular enlargement with entrapped megakaryocytic nuclei and high circulating levels of von Willebrand factor antigen.[2] All these lead to the activation of platelets and endothelial cells, with the subsequent release of growth factors. Electron microscopy shows structural damage to vessel integrity with prominent Golgi complexes, activated endothelia, duplicated capillary basement membranes and perivascular infiltrate. At the level of joints the pathologic changes are dominated by arterial wall thickening.[3]

There are no specific serological markers of HOA and as a result, the diagnosis of HOA is often delayed. Bone formation markers such as alkaline phosphatase, osteocalcin or amino-terminal propeptide of type 1 pro-collagen may be increased.

Imaging is the mainstay of diagnosis. X-rays typically show symmetrical periostosis of the shafts of tubular bones in the absence of cortical destruction or fracture. The tibia, fibula, radius and ulna are most commonly affected sites. Magnetic resonance imaging shows a low to intermediate signal intensity on T1 and T2 weighted images, highlighting periosteal elevation and reaction.[4] There are

cases where HOA was diagnosed on positron emission tomography by increased fluorodeoxyglucose (FDG) uptake, however there is the risk of an erroneous diagnosis of metastatic disease.[5] Bone scintigraphy with technetium 99m (99mTc) methylene diphosphonate (MDP) is the gold standard and is the most sensitive test.

The differential diagnosis of HOA includes thyroid acropachy, hypervitaminosis A and a rare autosomal dominant disease known as Camurati Engelmann disease. Voriconazole has been reported to cause periostitis that mimics HOA.

Management of HOA includes treatment of the underlying cause and appropriate analgesia. Other treatment options described include: unilateral vagotomy, in cases of inoperable primary lung malignancies. The procedure was first carried out in the 1950s and was revisited in 2006, however not many cases have been reported in the literature.[6] Adrenergic blockade with propranolol or phenoxybenzamine was trialled once in 1976.[7] This option has not been used favourably. NSAIDs, currently the most widely used treatment option, work by blocking the prostaglandin pathway. In fact, opioids are less effective. Octeotride, a VEGF inhibitor, has been shown to limit endothelial proliferation and is highly effective in pain relief.[8] There are several case reports regarding the symptomatic and therapeutic effects of bisphosphonates, also VEGF inhibitors.[9] Therapeutic trials are currently being carried out with bevacizumab, a VEGF inhibitor and erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, which could show promising results.[10]

Conclusion

Bone pains in patients suffering from malignancy, chronic lung disease, liver disease or cyanotic heart disease should raise the suspicion for HOA. Likewise, a new diagnosis of HOA should always trigger a search for the primary cause.

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CASE REPORT

Small bowel perforation secondary to intestinal tuberculosis in patient with chronic idiopathic myelofibrosis

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Idiopathic myelofibrosis is a myeloproliferative disorder in which blood cell development is abnormal. It causes scarring and fibrotic changes in the bone marrow. Also known as primary myelofibrosis (PMF), this condition is usually chronic and progressive. The exact causative factor is not clear but scientists found that the condition is typically characterized by the mutations in Janus Kinase 2(JAK2) gene. Clinical features of PMF include progressive anemia, symptomatic splenomegaly, and other constitutional symptoms. PMF is associated with a poor prognosis and a marked reduction in life expectancy, with median survival ranging from 3.5 to 6 years. There have been reports on the coexistence of PMF with other granulomatous diseases such as tuberculosis. It was reported that the incidence of tuberculosis is much higher in patients having PMF compared to the normal population. PMF is commonly treated with JAK2 inhibitor (Ruxolitinib) and prednisolone. Several case reports have shown that PMF treatment may lead to opportunistic infections, such as tuberculosis. We would like to report a case of small bowel tuberculosis flare-up by patients of chronic idiopathic myelofibrosis that leads to bowel perforations.

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Introduction

Idiopathic myelofibrosis is a clonal hematopoietic stem cell disorder due to a mutation in the signaling regulator gene JAK2. The condition is widely treated with Ruxolitinib which is a JAK2 inhibitor along with prednisolone. The only curative treatment available till now is allogeneic haematopoietic stem cell transplant.[1] Ruxolitinib with prednisolone despite promising has been linked with the risk of opportunistic infections and reactivation of tuberculosis.[2]We herein report a patient with chronic idiopathic myelofibrosis who developed small bowel perforations secondary to the flare-up of gut tuberculosis.

Case report

A 57-year-old Malay ethnicity male which was diagnosed with primary myelofibrosis since 2014 and under regular haematology follow up was referred to the general surgery department for acute onset of generalized abdominal pain. The patient has an underlying history of Pulmonary Tuberculosis (TB) and has completed treatment about ten years ago. He claimed that he was on anti TB drugs for about six months and was tested negative after completion of the therapy. The rest of the family members were screened negative otherwise. The patient gave a history of loss of weight and appetite with persistent lethargy and poor oral intake for the past two months. He has been receiving treatment from the haematology department ever since he was diagnosed with PMF. His JAK2 status was negative while the peripheral blood film showed borderline bicytopaenia with leucoerythroblastic picture and occasional suspicious mononuclear cells. Bone marrow trephine biopsy confirmed the diagnosis of myelofibrosis (in cellular phase). The patient arrived at the emergency department with signs of hypotension and prompt resuscitation measures were taken while arrangement for an urgent chest and abdominal x-rays were ongoing. The initial chest x-ray showed air under the diaphragm and the patient was rushed to the operating room with the diagnosis of perforated gastric ulcer (Figure 1). Upon entering the abdomen noted that there were copious collections with small bowel adhesions especially at the ileum (Figure 2). A segment of the small bowel (ileum) was noted to have multiple perforations (three perforations each measuring 2-4mm in diameter) with content leakage. Segmental bowel resection (about 10cm in length), double-barrel stoma with peritoneal lavage was performed. The peritoneal collections were sampled for culture and sensitivity and acid-fast staining. Resected bowel segment HPE came out as perforated granulomatous ileitis secondary to mycobacterium infection (figure 3 and 4). Peritoneal fluid acid-fast staining showed negative for Mycobacterium while the culture and sensitivity showed mixed growth. The patient was subsequently started on anti-TB medications and was put under direct supervision therapy. With our latest follow up, the patient was doing well with no further complications since the operation.

Figure 1 CXR showed presence of pneumoperitoneum

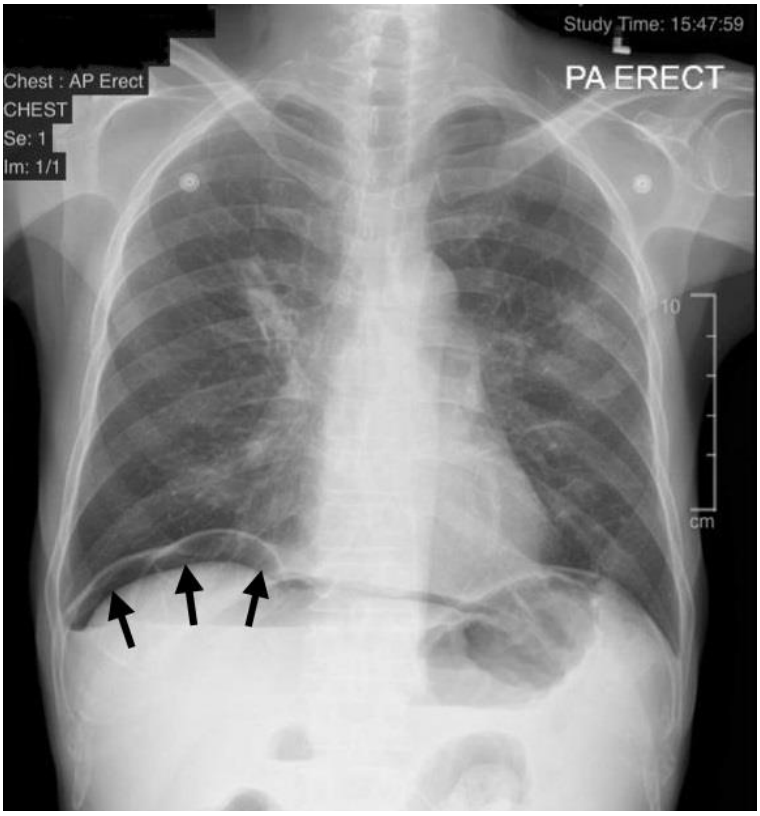


Figure 2 Laparatomy findings of small bowel adhesions

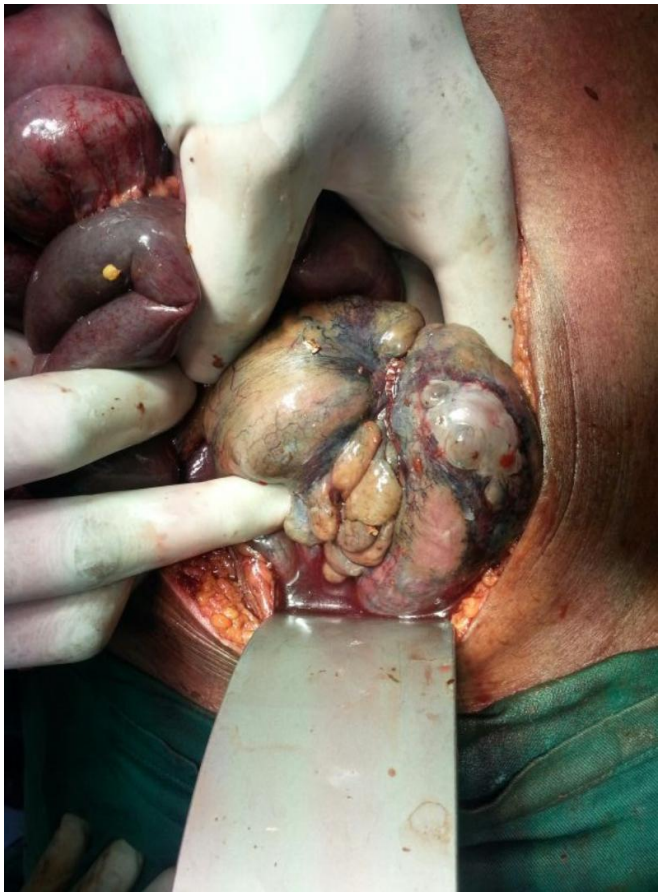


Figure 3 (Hematoxylin and eosin, 40x magnification) showing granuloma formation composed of epithelioid cells (arrowhead) with oval to elongated nuclei and abundant eosinophilic cytoplasm, surrounded by mature lymphocytes and histiocytes collection. Langerhans cells are also seen (circle) and central caseous necrosis (arrow).

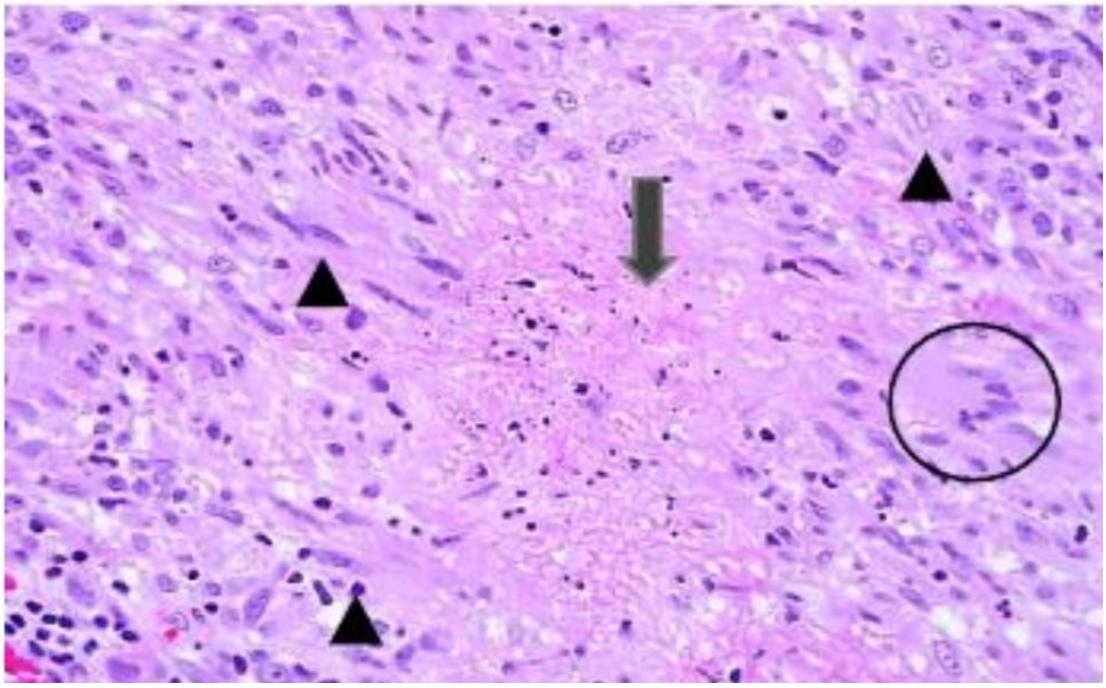
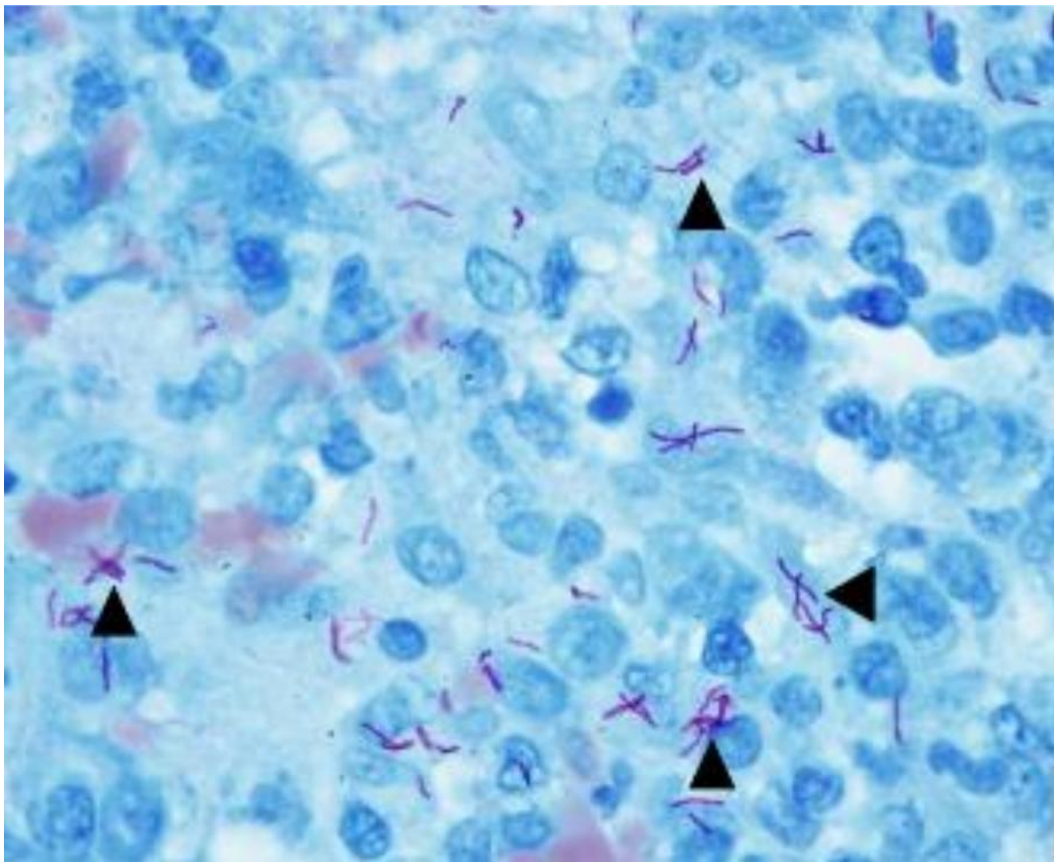


Figure 4 (Ziehl- Neelsen staining 100x magnification) Numerous scattered magenta coloured, beaded acid fast bacilli (AFB, arrowhead) is seen in between the cells



Discussion

Primary Myelofibrosis is a myeloproliferative monoclonal disorder characterized by extensive bone marrow fibrosis. Till the present day, treatment for PMF is using Ruxolitinib, a JAK 2 inhibitor along with other newer drugs.[3-4] Curative treatment is by using allogeneic haematopoietic stem cell transplant with a five-year survival rate.[5] Nonetheless, treatment for PMF has been linked with the risk of weakening host immunity and opportunistic infections.[6] Tuberculosis is a granulomatous infection with the hallmark of caseating necrosis that can be found in both pulmonary and extra pulmonary regions. The case that we encountered showed that patients with PMF on treatment have a high probability to get a flare-up of tuberculosis be it pulmonary or extra pulmonary. Despite being JAK2 negative, the patient has been prescribed with long term steroids since 2014 by the haematology unit. He was offered with allogenic stem cell bone marrow transplant which the patient refused. Asymptomatic patients usually do not need treatment. Treatment is subjected to patients to improve their quality of life and to manage the ongoing complications. We would like to establish a link between PMF and TB and the potential flare-up of tuberculosis that might occur in such patients.[7] Interestingly extra pulmonary tuberculosis flare-up in PMF has never been reported before. The coexistence of PMF and TB has been documented decades ago.[8] Besides myeloproliferative disease itself, the treatment may potentiate granulomatous infection in the host. As per this case, the patient has a history of pulmonary TB some ten years ago. It is well known that mycobacterium may remain dormant for many years in the host before reactivation.[9] We would also like to highlight the importance of strengthening the host immunity once been diagnosed with myeloproliferative disease. As per today, the only curative treatment available is allogeneic stem cell bone marrow transplant.[10] The patient in this case succumbed to the complications of extra pulmonary tuberculosis flare up secondary to the myeloproliferative disease and its treatment. It is a challenge to the treating physician as well as to the patient diagnosed with myeloproliferative disease to endure the uncertainty of the course of the disease. With the reported case above, we should be vigilant in dealing with patients with myeloproliferative disease and the complications of the current treatment modalities and definitely to be aware of tuberculosis flare up both pulmonary and extra-pulmonary.

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CASE REPORT

Back pain as first presentation of Hepatocellular Carcinoma

Anil Kumar, Ikhwan Sani Mohamad, Maya Mazuwin Yahya, Leow Voon Meng, Zaidi Zakaria

Hepatocellular Carcinoma (HCC) is known to be one of the leading causes of deaths globally. In Malaysia HCC is known to be the eight most common cancer in both genders and the fifth most common cancer for males.

The etiological factors associated with HCC are chronic Hepatitis B or C viral infection, liver cirrhosis and nonalcoholic fatty liver disease. Patients with HCC usually present with right upper quadrant pain, jaundice, loss of weight, and a palpable mass over the right hypochondrium.

This case report will describe and discuss about the diagnosis of HCC in a patient with an atypical presentation of back pain which was confirmed with supportive findings of CT scan and MRI liver.

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Introduction

Hepatocellular Carcinoma (HCC) is known to be one of the leading causes of deaths globally. In Malaysia HCC is known to be the eight most common cancer in both genders and the fifth most common cancer for males.[1]

The etiological factors associated with HCC are chronic Hepatitis B or C viral infection, liver cirrhosis and nonalcoholic fatty liver disease. Patients with HCC usually present with right upper quadrant pain, jaundice, loss of weight, ascites and a palpable mass over the right hypochondrium.[2] Hepatocellular carcinoma is commonly diagnosed after the symptoms have presented or usually in intermediate or end stage of HCC. If early diagnosis was done and treatment was received, the survival rate could increase up to 50%.[3]

Case report

A 58-year-old gentleman presented to our hospital with complaint of severe back pain for the past 5 months. The pain was described as dull persistent in nature which was relieved by analgesics and leaning forward. On further questioning the patient also claimed to have significant loss of weight over the past 1 month. The patient had no history of alcohol consumption and family history of malignancy.

Abdominal examination revealed hepatomegaly with an ill-defined liver border. There was no clinical evidence of ascites or other stigmata of chronic liver disease.

The biochemical parameters revealed normal liver function test. Serological findings including of hepatitis B was positive. The alpha fetoprotein was markedly elevated with value of 24 980 ng/ml (N:<8.5 ng/ml) .

The patient was subjected for a CECT Liver 4 phase. The findings included: large ill-defined peripherally enhancing mass occupying segment 5 and 6 measuring 6x13x7cm (Figure 1). Central hypodensity seen within the mass suggestive of necrotic areas. This mass medially involves the head of the pancreas and laterally displays a poor fat plane with the adjacent D2 segment of the duodenum. Filling defect seen within the right posterior portal vein was suggestive of thrombosis. Multiple enlarged matted lymph nodes in the porta hepatis, paracaval, aortacaval and paraaortic areas at the level of the renal veins. Hyperdense lesion was also present at body of Lumbar (L2) Vertebrae (Figure 2).

The case was diagnosed as multicentric advanced hepatocellular carcinoma with nodal, bone (L2) and pancreatic involvement. An ultrasound guided liver biopsy was subsequently done and the results were suggestive of a moderately differentiated HCC.

Figure 1 Coronal cut of arterial phase of CT abdomen showing segment 6 Liver Lesion (arrow).

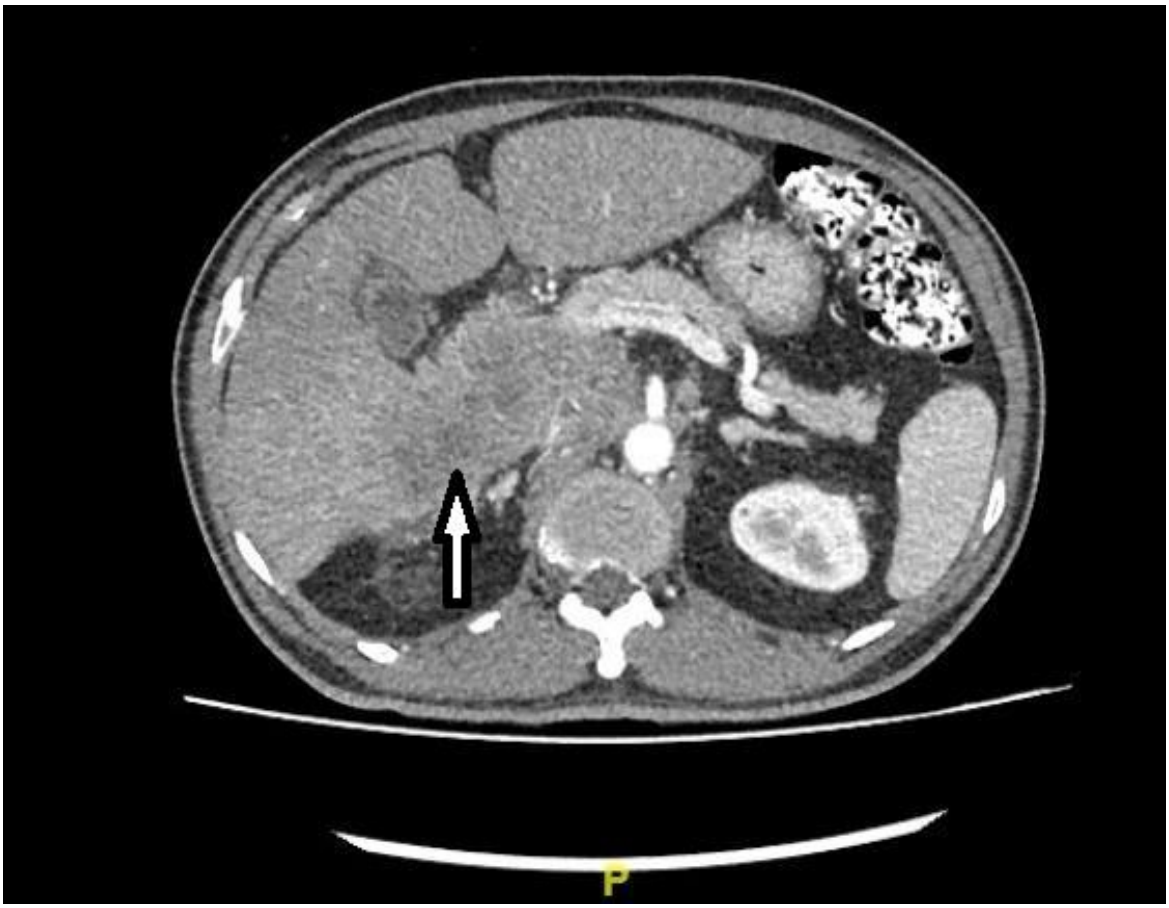
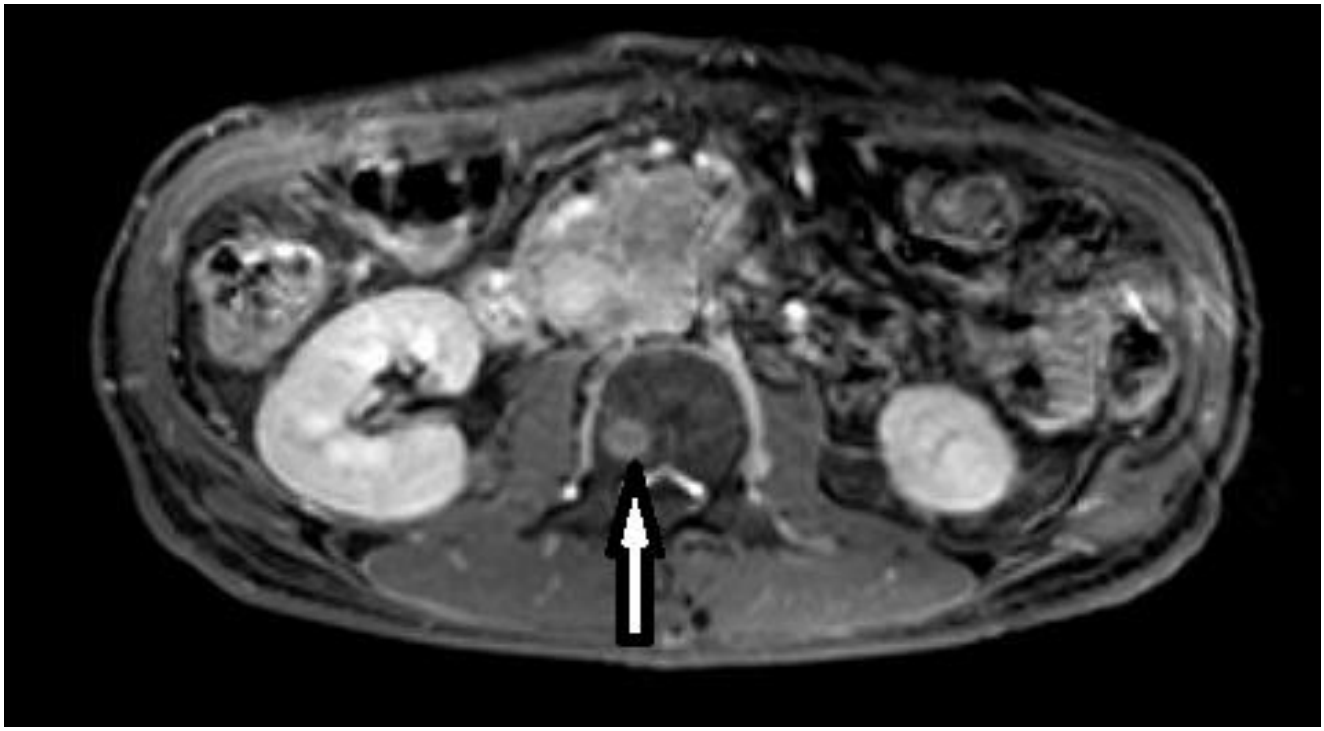


Figure 2 L2 Vertebral body lesion(arrow).



Discussion

In normal circumstances, the prostate, breast, kidney, lung, and thyroid are the most frequently encountered cancers that metastasize to the bone.[4] The bone metastasis from HCC is considered rare unless it is due to local infiltration by adjacent liver mass. In this particular case, the CT Liver 4 Phase, MRI liver and the elevated AFP level were highly suggestive of HCC.

Bone metastasis as the first sign of extrahepatic HCC very seldom occurs. Due to this there has only been a few case reports that has been reported. In one study which included 149 patients with extrahepatic metastasis of HCC, the most frequently involved sites of extrahepatic metastasis were lung, lymph node, musculoskeletal, and adrenal gland in order of frequency.[4]Most of the musculoskeletal involvements (66%) already had multiple other no osseous sites of metastatic disease at the time of presentation of the first documented extrahepatic HCC. However, isolated bone metastasis as the first manifestation was only seen in 14 out of 149 (9.5%) patients. The most frequently involved location was the lumbosacral and thoracic spine.[3,5]

The pathogenic mechanism of spinal metastasis are as follows: (1) The coexistence of pulmonary and brain metastases supports the conclusion of dissemination through the arterial route; (2) the other is spread through the vertebral venous plexus, extending from the pelvis to the cranial venous sinuses, enabling retrograde transportation to the spinal cord; (3) direct invasion from contiguous structures; and (4) intraspinal dissemination.[3]Since symptoms attributable to HCC are usually absent in early stage, liver ultrasonography and serum AFP are used for the surveillance of HCC in high risk group. Positivity for viral markers, larger tumour diameter, multiple tumour nodules, the presence of vascular invasion, and the elevated tumour markers were associated with the development of extrahepatic metastasis. Most of HCC occurs on the background of chronic liver disease including chronic hepatitis B and hepatitis C viral infection and alcoholic liver disease ultimately followed by cirrhosis. However, NAFLD, the hepatic manifestation of obesity and related metabolic disorders, is now a known-risk factor of cryptogenic cirrhosis and HCC.[3]

We presented our experience of a rare case of HCC in a noncirrhotic liver, presenting as chronic back ache with an isolated lumbar vertebrae metastasis as the sole manifestation in patient with well-known risk factor. This case suggests that HCC should be considered as one of differential diagnosis in patient which presents with spine metastasis, even in the absence of liver cirrhosis.

Conclusion

Extra hepatic metastasis of Hepatocellular Carcinoma is not rare. HCC should be included in the differential diagnosis of spinal metastasis because in some cases it may be the initial manifestation of HCC, with or without signs of liver disease as occurred in our patient.

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CASE REPORT

ARDS and systemic sepsis from Actinomycosis related IUCD infection

Kimberley Grech, John Mamo

Six weeks following a reinsertion of a levonorgestrel intrauterine contraceptive device (IUCD), this 43 year old lady was admitted with severe abdominal pain. Radiological investigations indicated fluid collection in the rectovaginal area. The differential diagnosis included pelvic inflammatory disease with a possible pyosalpinx. The condition of the patient deteriorated further developing bilateral pleural effusions and pulmonary edema despite antibiotics. Patient started improving after CT guided aspiration of the pelvic abscess. Further management with antibiotics was administered after blood cultures showed an Actinomycosis infection. This patient presenting with a non-pulmonary cause of sepsis deteriorated rapidly and developed Adult Respiratory Distress syndrome. Although Actinomycosis is detected incidentally on cervical cytology in asymptomatic patients with an intrauterine device, it may present with lethargy, pyrexia and rigors. Prior to removal/re-insertion of an IUCD, cervical smears specifically for *actinomyces* should be done and patients should be treated with antibiotics if positive. The IUCD should then be introduced 6 weeks later. IUCD's should not be left in situ beyond their expiry date.

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Introduction

Actinomycosis in humans is a disease caused either by *Actinomyces israelii*, *A gerencseriae* and *Propionibacterium propionicus*. *Actinomyces Israeli* (principal pathogens) are Gram-positive rods. They are mostly commensals, living in the vagina, mouth and colon. A break in the mucosa for example during the insertion of Intrauterine Contraceptive Device (IUCD) will cause invasion of tissues by this bacterium.

With reference to IUCD related infections, two known mechanisms have been explained by which actinomyces israelii may lead to Pelvic Inflammatory Disease (PID). One mechanism describes how the string of the IUCD acts as a vehicle for ascent of the microbe from the vagina into the uterine fundus.[1]

The second mechanism describes how an IUCD which would have been kept in situ beyond its expected date of change/removal, undergoes calcium encrustation and disintegration. These calcium encrusted plastic fragments migrate through the cervical canal into the uterus providing an ideal surface for colonization and spread of the organism.[1] However this is mostly related to the Lippes loop IUCD which were left in situ for years on end as they did not expire.

We would suggest a third mechanism by which an infection is introduced into the uterine cavity. When removing the IUCD on expiry, you are also removing the "protective" mucous plug which would have been produced by the progestin releasing device. Hence if there is *actinomyces* present within the cervical canal, it can be reintroduced into the cavity upon re-insertion. This argument re-enforces the need to carry out smear tests prior to re-insertion of IUCD.

Actinomycosis detected in cervical smears may be present in symptom free patients. However early symptoms include low grade fever, chills and rigors. Eventually, late presentations include pelvic pain, foul smelling discharge leading to hospital admission with abscess formation.[1] Actinomycosis infection is sensitive to Penicillin.

The Case

A 43 year old athletic lady with a known case of endometriosis was admitted with sudden onset of right iliac fossa pain (RIF). A change of IUCD had been done 6 weeks before admission. Upon examination, tenderness with guarding was present in the RIF. A pregnancy test was negative and a chest X-ray and abdominal X-ray reported no abnormalities beside an IUCD in situ. Eventually a computed tomography scan (CT scan) was done which noted a fluid collection of 55mm in diameter between the uterus and rectum.

A transvaginal gynaecological ultrasound was done which reported an IUCD in situ, a cystic ovary in the right adnexae of mixed echogenicity and a small follicle in the left ovary. The pouch of Douglas was clear.

The patient was given analgesia and started on Piperacillin/Tazobactam and Metronidazole intravenously (IV). During her admission she developed bilateral lower limb pitting edema up to thighs and shortness of breath (SOB). Hypoalbuminaemia was also reported on blood tests. Eventually the SOB worsened, developing bilateral pleural effusions and bilateral lower lobe lung collapse. A Brain Natriuretic Peptide (BNP) was requested as the patient presented with a clinical picture of heart failure. BNP was reported to be high. An echocardiogram confirmed normal left ventricular dimensions, normal wall motions,

left ventricular ejection fraction >60%, normal: left atrium, right atrium and right ventricle excluding heart failure. Bumetanide and Albumin supplements were administered to reduce the extravasation of fluid secondary to sepsis.

The main diagnosis established was systemic sepsis due to PID, with development of Acute Respiratory Distress Syndrome (ARDS) and lower limb edema. The possible cause of PID was a pyosalpinx following IUCD insertion. The IUCD was removed.

A CT guided drainage of abscess was done. Eventually the patient continued to spike fever and antibiotics were switched to Teicoplanin and Meropenam IV. Blood cultures were obtained which cultivated *Actinomyces*. Eventually the patient still continued to experience fluctuating fevers in view of a recollection of the abscess and antibiotics were switched to Benzylpenicillin and Clindamycin IV.

Discussion

The relationship between cervical smears and its association with PID

The presence of actinomyces-like organisms on cervical smears is uncommon (only 7% of smears).[2] Many studies reported that incidence of *Actinomyces*-like organisms in IUCD's is higher. Positive smears are not diagnostic, nor a predictor of pelvic actinomycosis. Therefore most patients are treated conservatively unless symptomatic.

According to Merki-Feld GS et al. levonorgestrel-releasing IUCD users have a lower incidence of actinomyces-like organisms compared to copper-IUCD users. Women who have an IUCD insitu are more likely to develop bacterial vaginosis compared to the general public. This makes an environment favourable to anaerobes within the vagina facilitating actinomyces growth. [3-4]

Removing IUCD's once actinomycosis is detected still remains controversial. Treating conservatively usually results in negative cervical cytology after 4-6 weeks. Merki-Feld GS et al suggested IUCD removal should be done within a period of 3-5 days after starting treatment rather than immediately upon detection. Reinsertion should be done 4-6 weeks later.[3]

Studies by Chatwani. A and Amin-Hanjani. S conducted in Philadelphia showed that negative follow up smears, had a success rate of 100% when the option of IUCD removal combined with antibiotics was considered, 97.4% for IUCD removal alone, and 36.8% for antibiotics therapy alone. Hence it was concluded that the best way to manage actinomycoses is by removal of the IUCD with or without antibiotics. Patients who had multiple antibiotics including penicillin and tetracyclins had a better outcome compared to those patients who were on monotherapy.[5]

Actinomycosis and PID

Patients' with actinomycotic IUCD colonization have a greater risk of developing actinomycotic tubo-ovarian and subphrenic abscesses then those women with no IUCD colonization.[6] A period of at least 4-6 weeks of therapy is usually recommended. Most patients with pelvic masses underwent hysterectomy and bilateral salpingo-oophorectomy in addition to penicillin and IUCD removal; a few were successfully treated with drainage of an intra-abdominal abscess just like in this case.

Fluid extravasation in systemic sepsis leading to ARDS

In this case the initial signs of bilateral lower edema and increased SOB in such a young, healthy haemodynamically stable patient were surprising. Considering the patient's past medical history of intense physical body training; cardiomyopathy induced heart failure was being considered as a differential. A BNP of 457 (high) reinforced the decision to do an echo which excluded such pathology. Other causes of bilateral lower limb edema such as renal failure and liver failure were excluded through normal blood work up.

Upon reviewing the case; the development of pleural effusions, persistent lower limb edema, and hypoalbuminaemia made the final diagnosis of fluid extravasation and ARDS secondary to sepsis more likely. In studies done by Nakamura T et al. BNP levels were positively correlated in septic patients having high CRP levels without echocardiographic evidence of systolic dysfunction or volume overload.[7]

Furthermore, a positive correlation was found between a high BNP in septic shock patients and Sequential Organ Failure Assessment scores and prognosticated survival. Hence one can argue that BNP can be used as an independent prognostic marker in severe sepsis, being higher in non-survivors than survivors up to 72 hours post admission.[8-9]

Acute respiratory distress syndrome is a serious complication of severe sepsis, increasing mortality rates.[10] Underlying mechanisms are characterized by inflammation and endothelial dysfunction. Dysregulation of angiopoietin and Von Willebrand factor in endothelial injury are common findings in indirect causes of ARDS (non-pulmonary causes).[11] 6-7% of adult patients with sepsis in Western countries eventually develop ARDS. Once sepsis sets in, progression to ARDS is rapid. Hence identifying and treating sepsis early will reduce the need for patients to receive mechanical ventilation.[12] Main treatment of ARDS is to maintain adequate tissue perfusion and avoid hypoxia.

Conclusion

The overall learning points of this case including: 1. IUCD's should be removed immediately upon expiring; 2. Cervical cytology smears with specific request to screen for *Actinomyces* should be done prior to removal and/or re-insertion of IUCD's. 3. Removal of IUCD and treatment with antibiotics is the best option for *Actinomyces* positive smears. 4. ARDS secondary to systemic sepsis is an indicator of poor prognosis hence immediate treatment is recommended, BNP can be used as an independent prognostic marker in severe sepsis.

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