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The MMSC XI: a postscript

Simon Attard Montalto

The XIth Malta Medical School Conference, organised at the Mediterranean Conference Centre in Valletta on the 4-6th December 2025, has come to pass. Incredibly, despite the challenges faced including but not restricted to often unreasonable bureaucracy, apathy, an almost two-year delay and of course spiralling expenses, the Conference was a success. The Malta Mediterranean Conference Centre (MCC) in Valletta is, undoubtedly, an amazing location and elevates 'the whole' by its inherent grandeur and historical splendour. Staff at the MCC, the Conference caterers, as well as the outside support for audiovisual aids for the Republic Hall, our website host, and other farmed-in miscellanea that a conference of this size necessitates, all 'came good' on the day(s)! Certainly, costings were at a premium, but we were not disappointed for having had to pay for quality.

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COVER PICTURE

'The Neolithic'

Pierre mallia has been painting on canvas for the last fifteen years, most of which go for charity and the rest in a personal collection.

He follows in the steps of his father and is inspired by the towers and bastions of Malta but also by the Neolithic sites, views of sunsets on the sea and others. His method is an abstraction of a scene which he adapts from pictures or personal photos.

He is to host an exhibition for Puttinu cares later this year.

The conference stuck to its 'green' mantra and did away with most paper paraphernalia and, as with most modern conferences, presented all posters in electronic format. Despite the slow start with submissions – just over 100 with only 2 months to go – these took off after 2 extended deadlines for submissions to reach almost 600 (a record for any MMSC). The scientific Committee, ably led by Professor Chris Scerri, had to work overtime to prepare an exciting programme in the brief time left after the deadline for abstracts closed. But deliver they did, and the Organising committee was forced to activate the option with the MMC to use all six breakout rooms to accommodate the chosen 350+ oral presentations. These were varied and of a high scientific level, anchored by five superb plenary lectures. Speakers hailed from several countries in Europe and a few from the United States and included eminent experts from august institutes such as The Karolinska Institute in Sweden, MD Anderson in the US, Great Ormond Street Hospital in London, and Gemelli Hospital in Rome, amongst others.

A conference without sufficient registrants is 'empty' regardless of the quality of the scientific content: the MMSC XI did not disappoint, and at the final count, 827 registrants exceeded the numbers who attended all previous MMSC conferences. Although the vast majority of departments and subspecialties supported the conference with

abstract submissions and registrations, there were a few still conspicuous by their absence. This was a shame and is a lacuna that needs to be plugged next time around.

Feedback from guest and invited speakers, participants, exhibitors, and sponsors was uniformly or overwhelmingly positive. The very few dissenters were a minority of habitual moaners or those who were not offered an additional discount to their already heavily discounted registration fee! Amazingly, such individuals still exist! Many participants and exhibitors who had attended previous MMSC conferences declared that this surpassed all others. Praise indeed, but this feedback raises the bar still higher for MMSC XII.

I believe we can declare that the MMSC XI has continued to fly the flag of the Malta Medical School, and offered a platform whereby the work and research carried out by Maltese doctors and allied disciplines was show-pieced. To-date, it remains the largest academic event of its kind organised within this University. Its success is owed to numerous persons including members of the Organising and Scientific Committees and, especially, to all the administrative staff from the Medical School who deserve a special salutation. The XIth MMSC has re-set the bar and has re-defined the challenge for the XIIth MMSC to surpass in three years' time.

Treatment of Symptomatic Intracranial Atherosclerotic Stenosis: A Review

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Intracranial atherosclerotic stenosis (ICAS) is an important cause of ischemic stroke worldwide, accounting for 8-10% of strokes in North America and Europe and up to 50% in some Asian populations. Patients with symptomatic ICAS are at high risk of recurrent stroke, with rates up to 18% at 1 year despite medical therapy. This review discusses current evidence on prognosis, risk factors, and optimal medical and endovascular treatment for symptomatic ICAS. All patients should receive intensive medical therapy focused on antiplatelet agents, blood pressure control, cholesterol management, and lifestyle changes. Short-term dual antiplatelet therapy provides additional benefit for some patients. Endovascular stenting has not shown benefit over medical therapy in clinical trials and is not routinely recommended. However, selected patients who fail medical management may be considered for stenting or alternate endovascular approaches on an individual basis. Further research is critically needed to identify patients at highest risk of recurrence and evaluate novel therapies to improve outcomes. This review provides a framework for prognosis and management of symptomatic ICAS based on current evidence.

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ICAS is defined as atherosclerotic narrowing of major intracranial arteries and is an important cause of ischemic stroke worldwide. Symptomatic ICAS refers to ICAS that has resulted in a transient ischemic attack (TIA) or ischemic stroke attributable to the stenotic artery. Compared to extracranial atherosclerosis of the carotid or vertebral arteries, relatively less is known about the optimal management of intracranial atherosclerotic disease. However, research interest in ICAS has grown over the past two decades given its strong association with recurrent stroke risk.

This review aims to summarize current evidence on the following key aspects of symptomatic ICAS:

- Epidemiology and risk factors for recurrence
- Medical therapies to reduce recurrent stroke risk
- Imaging modalities
- Endovascular treatment approaches
- Identification of patients at high risk of recurrence
- Future directions for research

Understanding prognosis and evidence-based treatment strategies is imperative to improve outcomes in this high-risk population. This review provides a framework for clinicians managing patients with symptomatic ICAS in daily practice.

EPIDEMIOLOGY AND RISK FACTORS

The global prevalence of ICAS varies widely based on geographic region, age, and comorbidities. In the United States, ICAS accounts for approximately 8-10% of ischemic strokes.^{1,2} However, in Asian countries, ICAS may cause up to 30-50% of strokes.³⁻⁵ The REasons for Geographic and Racial Differences in Stroke (REGARDS) study found that black race/ethnicity, living in the Southeastern stroke belt region of the United States, and older age were all associated with increased prevalence of ICAS.⁶

Several modifiable vascular risk factors have consistently been linked with ICAS. These include hypertension, diabetes mellitus, cigarette smoking, and dyslipidaemia.⁷⁻⁹ The severity of luminal stenosis is one of the strongest predictors of recurrent stroke risk. Multiple studies have shown that patients with severe stenosis $\geq 70\%$ are at 2-3

times higher risk compared to those with moderate stenosis $< 70\%$.^{4,10,11}

In addition to traditional risk factors and stenosis severity, certain clinical and imaging characteristics can help further stratify stroke risk in patients with symptomatic ICAS. These include:

- Recent TIA or ischemic stroke within 3 months⁴
- Presence of borderzone or watershed pattern infarcts¹²
- Impaired collateral flow noted on angiographic imaging¹²
- Posterior circulation location¹³
- Clinical features suggesting hemodynamic compromise such as symptoms related to positional change or blood pressure fluctuation¹⁴
- Female sex¹

However, our ability to accurately predict individual risk remains limited. Ongoing studies are investigating novel imaging techniques and biomarkers to better guide prognosis in ICAS.

MEDICAL TREATMENT

All patients with symptomatic ICAS should receive intensive medical therapy focused on secondary stroke prevention. The key components include antiplatelet agents, blood pressure control, lipid management, and lifestyle modifications.

Antiplatelet Therapy

Antiplatelet agents reduce the risk of recurrent ischemic events in patients with non-cardioembolic stroke, including strokes attributed to ICAS. The optimal antiplatelet regimen for symptomatic ICAS has been evaluated in several trials and observational studies.

For patients with a recent TIA or ischemic stroke due to severe (70-99%) ICAS, short-term treatment with dual antiplatelet therapy (DAPT) generally refers to a duration of up to 3 months, as studied in the SAMMPRIS trial.¹⁵ This is not yet an established standard but is commonly referenced in current practice. The recommended doses for long-term prevention are 75-100 mg daily for aspirin and 75 mg daily for clopidogrel. The most studied regimen is combination aspirin plus clopidogrel. The Clopidogrel

plus Aspirin for Infarction Reduction in Acute Ischemic Stroke Study (CLAIR) enrolled patients with TIA or minor stroke due to symptomatic intracranial stenosis.¹⁶ Patients treated with DAPT had significantly fewer microembolic signals detected compared to aspirin alone, suggesting greater platelet inhibition.

Post-hoc analysis of the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial showed that patients with criteria similar to those enrolled in the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial (severe stenosis treated with DAPT for 3 months) had substantially lower rates of the primary endpoint compared to WASID patients treated with aspirin alone (12.2% versus 23%).^{4,16} Although limited by between-study comparisons, these findings further support the benefit of short-term DAPT in patients with severe, symptomatic ICAS.

For long-term prevention, we generally recommend monotherapy with either aspirin or clopidogrel based on evidence from large, randomized trials showing efficacy of these agents for secondary stroke prevention.¹⁵ The combination drug aspirin-dipyridamole and cilostazol are potential alternatives specifically studied in Asian populations with ICAS.^{17,18}

Ongoing trials are investigating the optimal duration of DAPT in symptomatic ICAS. Prolonged DAPT up to 1 year may provide additional benefit but must be balanced with increased bleeding risk. The Combination of Ticagrelor Plus Aspirin for Prevention of Stroke in Intracranial Atherosclerosis (CAPTIVA) trial will compare 1 year of aspirin plus clopidogrel, aspirin plus ticagrelor, or aspirin plus low-dose rivaroxaban for stroke prevention in patients with severe ICAS (NCT05047172).

Blood Pressure Control

Hypertension is highly prevalent among patients with ICAS, and observational data has consistently shown an association between poor blood pressure control and increased risk of recurrent stroke.^{7,19,20} The American Heart Association/American Stroke Association guidelines recommend a target blood pressure <140/90 mmHg for all patients with ICAS.^{17,21,22}

However, recent evidence indicates that over-aggressive lowering may be harmful in certain hemodynamically unstable subsets. The VERITAS study used quantitative magnetic resonance angiography (QMRA) to identify patients with low flow distal to vertebrobasilar stenosis.²³ While QMRA can provide important insights into collateral flow status, it is not yet a standard tool for all TIAs and CVEs due to limited availability and the need for further validation. Among these patients, SBP <140 mmHg was associated with paradoxically higher stroke risk compared to SBP 140-150 mmHg. The mechanism is hypothesized to be further reduction in distal perfusion pressure in the setting of exhausted cerebrovascular reserve. Conversely, studies of patients with carotid occlusion did not show increased risk with lower blood pressure targets.^{14,23}

These data illustrate that blood pressure targets in ICAS should be individualized based on collateral flow status and the anterior versus posterior circulation. More research is needed to clarify the optimal range and identify hemodynamic biomarkers to guide treatment.

Lipid Management

Statins substantially reduce the risk of recurrent cardiovascular events in patients with atherosclerotic disease by decreasing LDL cholesterol. High intensity statin therapy, defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg, lowers LDL by $\geq 50\%$.²⁴

Among patients with ICAS, intensive statin treatment has been associated with improved outcomes and plaque stabilization in several studies.^{21,24-26} The Treat Stroke to Target (TST) trial enrolled patients with a recent ischemic stroke or TIA and ipsilateral large artery atherosclerosis, either extracranial or intracranial.²⁴ Patients randomized to an LDL target <70 mg/dL versus a target of 90-110 mg/dL had significantly lower rates of cerebrovascular events. Based on available evidence, the American Heart Association (AHA) advises treating individuals with ischemic stroke by aiming for a low-density lipoprotein (LDL) cholesterol level below 70 mg/dL using high-intensity statin therapy.²² Similarly, the joint guidelines from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) advocate for lower LDL cholesterol targets compared to prior recommendations. For

very-high-risk patients undergoing secondary prevention, the ESC/EAS guidelines propose reducing LDL cholesterol by 50% from baseline with a target level below 55 mg/dL (1.4 mmol/L). High-risk individuals are advised a similar reduction from baseline with a target below 70 mg/dL (1.8 mmol/L), while those at moderate risk are suggested to aim for LDL cholesterol levels below 100 mg/dL (2.6 mmol/L).²⁷

Lifestyle Modification

Secondary stroke prevention guidelines emphasize lifestyle changes that may reduce vascular risk, including tobacco cessation, weight management, physical activity, and a Mediterranean style diet.^{20,22} In the SAMMPRIS trial, patients who exercised were significantly less likely to have recurrent vascular events, including stroke, myocardial infarction, and vascular death.² The mechanisms are likely multifactorial, mediated through direct effects on endothelial function, inflammation, diabetes control, obesity, and blood pressure.^{17,21} Patients with ICAS should be strongly counselled on the importance of a healthy lifestyle in combination with medications.

IMAGING MODALITIES

To diagnose ICAS, various techniques are used, including conventional cerebral angiography, magnetic resonance angiography (MRA), either computed tomography angiography (CTA), transcranial Doppler ultrasound (TCD), and high-resolution MRI, with non-invasive methods preferred for their lower risk and cost.²⁸ TCD and time-of-flight MRA are effective in ruling out 50-99% stenosis, but CTA, with higher sensitivity and specificity, is favoured in the USA.^{29,30} MRI-based high-resolution imaging provides detailed visualization of the arterial wall, aiding in the identification of atherosclerosis indicators like an eccentric wall and lipid-rich necrotic core.^{31,32} For acute ischemic stroke or TIA, brain and neurovascular imaging using CT or MRI, and large vessel imaging via CTA or MRA, are essential, supplemented by duplex ultrasound (DUS) and TCD. Non-invasive methods are generally preferred, reserving catheter angiography for inconclusive cases due to its associated stroke risk. Despite their limitations in accuracy and sensitivity, non-invasive imaging methods are crucial for excluding moderate

to severe stenosis and guiding initial intensive medical therapy, with catheter angiography providing additional detailed assessment when necessary.

Differences Between Intracranial and Extracranial Carotid Artery Stenosis

Intracranial and extracranial carotid artery stenosis differ significantly in their pathophysiology, clinical presentation, and management. Intracranial stenosis occurs within the arteries inside the skull, such as the middle cerebral artery, while extracranial stenosis involves the carotid arteries in the neck. The smaller vessel diameters and more complex arterial branching of intracranial vessels contribute to a higher risk of ischemic events and present unique therapeutic challenges. Consequently, intracranial stenosis often requires more aggressive medical management, including strict control of risk factors and dual antiplatelet therapy.²⁸ In contrast, extracranial carotid artery stenosis is more frequently managed with surgical interventions, such as carotid endarterectomy or stenting, due to the accessibility and larger size of the affected vessels.³³ Clinically, patients with intracranial stenosis are at a higher risk for recurrent strokes, particularly in the presence of poor collateral circulation, whereas those with extracranial stenosis may present with transient ischemic attacks or strokes primarily due to embolic phenomena.²⁸ These differences necessitate tailored approaches to diagnosis, monitoring, and treatment to optimize outcomes for patients with carotid artery disease.

ENDOVASCULAR TREATMENT

Endovascular treatment for symptomatic ICAS aims to improve cerebral perfusion and reduce stroke recurrence through techniques such as percutaneous transluminal angioplasty with or without stenting (PTAS). However, several randomized controlled trials have failed to show benefit of endovascular treatment over medical therapy alone for initial management.

The SAMMPRIS trial, which enrolled patients with TIA or stroke within 30 days attributed to 70-99% intracranial stenosis, was halted early due to the significantly higher rate of stroke and death at 30 days in the PTAS arm versus the medical arm (14.7%

vs 5.8%, $P=0.002$).³⁴ This difference was driven largely by the periprocedural complications. At the end of follow-up (median 32 months), rates of the primary endpoint (stroke or death within 30 days or ipsilateral stroke thereafter) remained higher in the PTAS arm compared to medical therapy (23.9% vs 14.9%).

Similarly, the Vitesse Stent Ischemic Therapy Study (VISSIT) trial randomized 112 patients to PTAS or medical therapy and was stopped early after an interim analysis showed higher event rates at 30 days with stenting.³⁵ The primary endpoint (composite of any stroke, death, or intracranial haemorrhage within 30 days or ipsilateral stroke between 31 days and 1 year) occurred in 20.0% of the PTAS group versus 6.8% of the medical group.

A trial conducted in China randomized patients with symptomatic middle cerebral artery or basilar artery stenosis to stenting with the Wingspan system versus medical therapy.³⁶ This study enrolled patients at lower risk of complications by excluding those with perforator stroke as the qualifying event. Nonetheless, stenting remained non-superior to medical therapy alone.

Collectively, these data indicate that intracranial stenting provides no benefit over medical therapy as initial treatment for symptomatic ICAS and is associated with increased periprocedural risk. Endovascular stenting may be considered for carefully selected patients who experience recurrent TIAs or strokes despite adherence to optimal medical therapy. These patients should be evaluated on a case-by-case basis, considering factors such as lesion location, patient comorbidities, and potential benefits versus risks. Consequently, major society guidelines currently recommend against stenting for first-line treatment.^{22,37} However, some patients may develop recurrent TIAs or strokes despite adherence to optimal medical therapy. Small case series indicate that for carefully selected individuals who fail medical management, stenting may be performed with lower complication rates approaching those seen with extracranial carotid stenting.³⁶ But controlled data for this subset are lacking.

Ongoing trials are investigating the use of intracranial stenting for secondary prevention after failure of medical therapy. The Chinese Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis

(CASSISS) study aims to enrol 380 patients with symptomatic severe ICAS who experience recurrence on medical therapy to compare Wingspan stenting versus continued medical treatment.³⁸ Future studies should focus on identifying patients at highest risk for recurrence who may derive the greatest benefit from endovascular intervention.

Alternate endovascular techniques that may carry lower procedural risk, such as angioplasty alone or submaximal angioplasty, have also been proposed as rescue options but require more data before routine implementation.^{38–40} Indirect extracranial-intracranial bypass has similarly not shown definitive benefit over medical therapy but continues to be investigated in carefully selected patients.^{41,42}

HIGH RISK GROUPS

High-risk patients typically include those with recent TIA or ischemic stroke within 3 months, severe stenosis ($\geq 70\%$), borderzone or watershed infarcts, impaired collateral flow, posterior circulation involvement, and clinical features suggesting hemodynamic compromise. These patients may benefit from more aggressive treatment and closer monitoring. Given the generally unfavourable risk-benefit profile, endovascular treatment should be reserved for severely symptomatic patients with recurrent events despite optimized medical treatment. However, our methods for identifying the highest risk subset remain imperfect.

Several ongoing studies are using advanced neuroimaging techniques to evaluate novel markers that may better predict individual risk in ICAS. High-resolution MRI can identify characteristics of plaque vulnerability that could increase stroke risk independently of the degree of stenosis.³⁰ Studies using computational fluid dynamics have found that the hemodynamic significance of a stenosis depends on multiple factors including the length, morphology, and downstream vasculature.³¹

Alternate modalities such as measurement of microembolic signals on transcranial doppler may also predict increased risk.⁴³ If validated as an independent prognostic marker, detection of microemboli could help select patients for more aggressive medical therapy or endovascular intervention.

FUTURE DIRECTIONS

While our knowledge surrounding symptomatic ICAS has expanded greatly over the past decade, critical unanswered questions remain:

- What is the optimal blood pressure parameter and target in patients with impaired collateral flow?
- Should management differ for anterior versus posterior circulation ICAS?
- Does intensive medical therapy, including statins and newer antiplatelets, reduce progression of intracranial atherosclerosis and lower dementia risk?
- Can advanced neuroimaging identify plaque features or hemodynamic factors that improve prognostication?
- What subsets of patients with recurrent events despite medical therapy are most likely to benefit from endovascular therapy?
- Would early identification of ICAS and initiation of medical treatment in asymptomatic patients improve outcomes?

Promising areas of research include advanced neuroimaging techniques to better predict stroke risk, studies on novel antiplatelet and lipid-lowering therapies, and trials investigating optimal blood pressure targets based on individual hemodynamic profiles. Additionally, research on early identification and treatment of asymptomatic ICAS to prevent progression and stroke is crucial.

Further research on risk stratification and novel therapies is also greatly needed to address these issues and thereby reduce the burden of stroke and dementia attributed to intracranial atherosclerosis. Both optimized medical treatment and endovascular advances may contribute to improved outcomes in the future.

CONCLUSIONS

In summary, symptomatic ICAS is an important cause of ischemic stroke associated with high rates of recurrence despite standard medical therapy. All patients with symptomatic ICAS should receive intensive control of vascular risk factors, antiplatelet therapy, and lifestyle modification. Dual antiplatelet therapy provides additional benefit for reducing stroke risk in the short-term following ischemic events. Endovascular stenting has not demonstrated benefit over medical therapy alone in clinical trials and is not recommended as first-line treatment. However, carefully selected patients who experience recurrent events despite optimal medical management may be considered for stenting or alternate endovascular techniques on a case-by-case basis. Further research focused on risk stratification and novel therapies is critically needed to improve the historically poor prognosis associated with this disease.

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Utilisation of Cardiac Holter monitoring and Echocardiography following Acute Ischemic Stroke or Transient Ischemic Attack

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Background: The audit was conducted at Mater Dei Hospital in Malta, assessing the adherence to guidelines and the effectiveness of current practices. The audit aimed to evaluate the time interval between stroke events and outpatient cardiac holter monitoring and transthoracic echocardiography (TTE), as well as scrutinize the detection of subclinical atrial fibrillation (AF) in secondary stroke prevention, as per European Stroke Organisation (ESO) recommendations.

Methodology: Retrospective data was obtained from patient records, documenting the number of patients with an ordered outpatient cardiac holter and/or outpatient TTE following an ischaemic stroke or TIA.

Results: The findings reveal that a significant number of patients are experiencing prolonged waiting times. Of the 63 scheduled holters, 71% of patients waited for over 200 days. This delay is concerning, especially considering the high contribution of AF to stroke-related morbidity and mortality. Of the 71 scheduled TTEs, 53.5% of patients waited over 100 days. The audit discovered that, from the 54 performed outpatient cardiac holters, no patients were identified with previously undiagnosed AF during monitoring and from the 71 performed outpatient TTEs 1 identified new onset AF. This emphasizes the potential benefits of extended monitoring durations.

Conclusion: This audit highlights the necessity for enhanced strategies in outpatient cardiac monitoring and echocardiography following ischemic stroke or TIA. Implementing the provided recommendations can significantly enhance AF detection, mitigate the risk of recurrent strokes, and ultimately lead to improved patient outcomes.

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Acute ischemic stroke stands as one of the foremost contributors to global morbidity and mortality, imposing a substantial burden on healthcare systems.¹ It is estimated that stroke affects approximately 1.1 million individuals in Europe annually² and ranks as the second leading cause of death across the continent.³ The ramifications of stroke are not only profound for patients but also strain healthcare systems, a pressure that is anticipated to intensify over time due to the ageing population.⁴

According to the 2020 report "The Burden of Stroke in Europe" conducted by King's College London, the healthcare cost attributed to stroke in Malta approximates 8.8 million euros. This is coupled with an estimated annual incidence of 325 diagnosed stroke cases and a mortality rate of 272 stroke-related deaths. Projections also indicate a foreseen 66% surge in incidence by the year 2035⁵

Given this landscape, it becomes imperative for the healthcare system to proactively engage in stroke prevention and execute robust measures for secondary prevention. Ischemic stroke can arise from various factors, including thrombosis, hypoperfusion, and embolic phenomena⁶. Among these, embolic stroke can be categorised into artery-to-artery embolism and non-artery-to-artery sources. The evaluation of non-artery-to-artery sources necessitates a comprehensive investigation into potential embolic sources, typically encompassing cardiac monitoring and a transthoracic echocardiogram (TTE). TTE is the first line imaging used in Malta in view of its high sensitivity (95%) and specificity (85-90%) for detection of left ventricle (LV) thrombi.

A substantial proportion of ischemic strokes can be attributed to embolic phenomena associated with atrial fibrillation (AF)^{7,8}, underscoring its significant contribution to stroke-related morbidity and mortality.^{9,10} European population estimates suggest a prevalence of atrial fibrillation in the range of 1% to 2%.¹¹ This risk of stroke, secondary to AF, rises dramatically to 23.5% in patients aged 80 to 89.⁸ Remarkably, around 25% of ischemic strokes are linked to AF, yet this figure is likely an underestimate due to the substantial undiagnosed cases of AF.¹²

Given the intermittent nature of AF, a considerable number of affected patients exhibit normal sinus

rhythm on electrocardiogram (ECG) readings during their hospital stay, leading to undetected cases. The optimal secondary prevention strategy for embolic stroke arising from AF involves anticoagulation. However, initiating anticoagulation necessitates the prior detection and documentation of AF on an ECG.^{13,14} Thus, timely identification of AF becomes a pivotal element in secondary stroke prevention, facilitating the timely initiation of anticoagulation treatment and ultimately reducing the risk of recurrent ischemic strokes^{15,16}. Anticoagulation is superior to aspirin or clopidogrel and decreases the risk of embolisation by 70%⁶

Owing to the paroxysmal nature of AF, ESO guidelines recommend that inpatient cardiac monitoring is performed followed by outpatient cardiac monitoring after discharge. Holter monitoring is the most widely used diagnostic tool for non-invasive continuous cardiac monitoring in stroke patients.

This study aims to audit the time interval between stroke event and outpatient cardiac holter monitoring and TTE, while also scrutinising adherence to recommendations by the latest ESO guidelines regarding the detection of subclinical AF in the secondary prevention of stroke/TIA.

MATERIALS AND METHODS

The clinical audit was conducted at Mater Dei Hospital in Malta. Inclusion criteria encompassed patients admitted to the NeuroMedical ward with a diagnosis of ischemic cerebrovascular accident (CVA) or TIA between January 1, 2022, and June 30, 2022, who had either an outpatient TTE or a cardiac holter booked. Retrospective data was obtained from patient records including iCM, CVIS, electronic case summaries. Demographic data and the number of days between the booking and performance of the TTE and/or cardiac Holter were documented using a Microsoft Excel spreadsheet.

The audit encompassed 63 patients with a scheduled outpatient cardiac holter and 71 patients with a scheduled outpatient TTE, aiming to assess potential embolic sources post-stroke. Patients admitted for CVA/TIA within the study's six-month duration who did not meet the inclusion criteria were excluded.

By thoroughly reviewing electronic patient records, the resultant report of the local utilization of outpatient cardiac monitoring and TTE after ischaemic stroke/TIA was compared to evidence based recommendations by the European Stroke Organisation (ESO).

In compliance with data protection regulations, necessary clearance was obtained from Mater Dei Hospital to access patient data. All accessed patient data adhered to the relevant data protection and privacy regulations. Furthermore, all data was analysed in an anonymized format to ensure confidentiality and privacy.

RESULTS

Holter Monitoring

A total of 63 outpatient cardiac Holter monitors were scheduled following ischemic stroke or TIA during the audit period. Five patients did not attend their appointments and were not offered alternative dates, while four patients had Holter monitoring requested but were not assigned a specific appointment date. As shown in [Figure 1](#), 71% of patients experienced waiting times exceeding 200 days before monitoring was performed. Notably, two patients who were awaiting their outpatient Holter appointment were admitted with new-onset atrial fibrillation prior to their scheduled investigation.

Of the 63 scheduled holter monitors, 54 were ultimately performed. None of these investigations detected previously undiagnosed atrial fibrillation ([Figure 2](#)). It is pertinent to mention that all of these holter monitors were configured as 24-hour monitors. Of note, three patients with previously diagnosed atrial fibrillation were also scheduled for outpatient Holter monitoring.

Echocardiography

[Figure 3](#) demonstrates that 8.45% of patients underwent TTE as inpatients, whereas the majority (33.8%) waited between 100 and 149 days for an outpatient TTE appointment.

A total of 71 echocardiograms were performed ([Figure 4](#)), of which 15 demonstrated high-risk findings according to the National Clinical Guidelines for Stroke for the UK and Ireland. These included

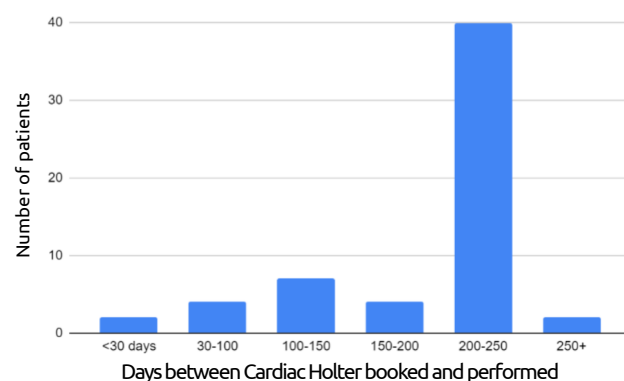


Figure 1 Days between Cardiac Holter booked and performed

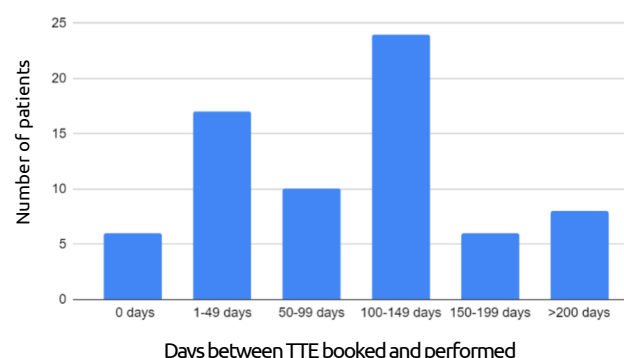


Figure 2 Days between TTE booked and performed

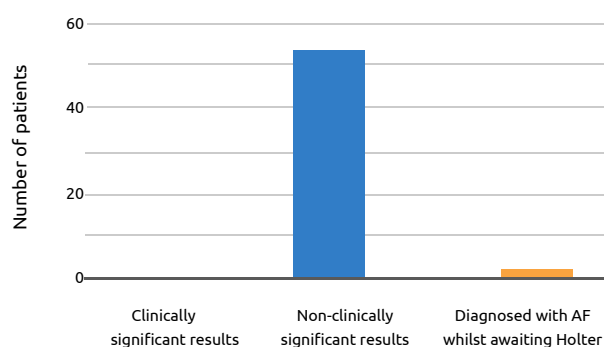


Figure 3 Outcome of performed Cardiac Holter Monitoring

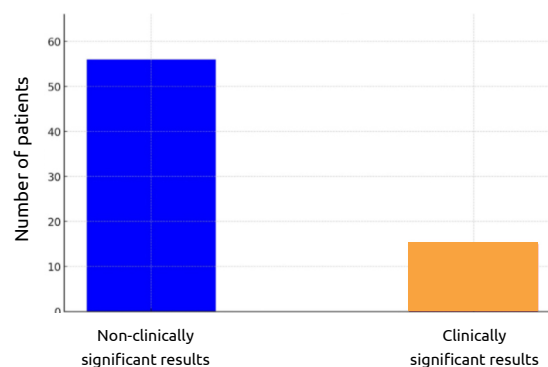


Figure 4 Outcome of performed TTE's

atrial fibrillation, valvular pathology, left ventricular outflow tract obstruction, frequent ventricular ectopy, and impaired global left ventricular systolic function. Overall, 21.12% of investigations yielded clinically relevant findings.

Among the 38 patients with a waiting time exceeding 100 days for TTE, 31.6% demonstrated significant findings.

Nineteen patients in the cohort were under the age of 55 years. Of these, only five underwent a bubble study, with one study demonstrating a patent foramen ovale (PFO). One patient did not undergo a bubble study as a previously documented PFO had been identified during prior admissions.

DISCUSSION

This audit evaluated the utilisation and timing of cardiac Holter monitoring and TTE following ischemic stroke or TIA, highlighting significant delays in access to these investigations and potential implications for secondary stroke prevention.

A key finding was the prolonged waiting time for outpatient cardiac Holter monitoring, with the majority of patients waiting more than 200 days before monitoring was performed. Such delays may hinder the timely detection of AF, a major cause of cardioembolic stroke. Early identification of AF is essential to allow prompt initiation of anticoagulation therapy and reduce the risk of recurrent stroke. The observation that two patients were admitted with new onset AF while awaiting Holter monitoring further emphasises the clinical significance of these delays.

Despite 54 outpatient Holter monitors being performed, no cases of previously undiagnosed AF were detected. This low detection rate may partly reflect the exclusive use of 24-hour monitoring in this cohort. Increasing evidence demonstrates that prolonged cardiac monitoring improves AF detection rates in patients with cryptogenic stroke. A recent randomised study focused on stroke survivors without known AF demonstrated that employing a 10-day Holter after a stroke increased the AF detection rate to 13.5%. In comparison, a group of patients subjected to 24-hour ECG holter monitoring exhibited a detection rate of 4.5%.¹⁷ However, determining the optimal monitoring duration

remains challenging, as excessively prolonged monitoring may not always be feasible or cost-effective.

Additionally, the audit highlighted the need for adherence to ESO guidelines, particularly for patients above 55 years of age. ESO guidelines recommend that patients older than 55 years undergo early inpatient ECG monitoring, followed by outpatient cardiac monitoring exceeding 48 hours. Interestingly, our study encompassed 41 patients aged 55 and above, yet none of them received outpatient cardiac monitoring exceeding 48 hours, raising concerns about the efficacy of the current monitoring practices in this population. The guidelines further advocate for the use of implantable monitoring devices, particularly for patients above 55 with cryptogenic stroke, as opposed to non-implantable devices, to enhance the detection of paroxysmal AF. However, this study did not gather data on the utilisation of implantable cardiac monitoring. Although implantable devices exhibit an elevated AF detection rate when compared to external loop recorders, this discrepancy appears to be attributed to the longer monitoring duration rather than an increased capacity of the device to detect AF.

Potential inefficiencies in resource utilisation were also identified, as three patients with an established diagnosis of AF were scheduled for outpatient Holter monitoring.

The implications of over 70% of patients enduring waiting times exceeding 200 days for outpatient cardiac holter monitoring subsequent to an ischemic CVA/TIA are twofold. Primarily, this delay hinders the timely initiation of appropriate AF treatment, namely anticoagulant therapy. During this interim period, patients are susceptible to developing recurrent strokes or other complications associated with AF. Secondly, for those individuals whose AF is detected more than 200 days following the cerebrovascular event, the substantial passage of time raises questions about whether AF was indeed the cause of the initial stroke or a subsequent discovery.

Delays were similarly observed in the utilisation of TTE following stroke or TIA, with many patients experiencing waiting times exceeding 100 days. Echocardiography is important in identifying structural cardiac abnormalities and potential

cardioembolic sources that may influence management. Among the 38 participants subjected to a TTE waiting time of >100 days, 31.6% exhibited significant findings. Hence, in these 31.6% there was a delay in initiation of anticoagulation as observed when applying the '1-3-6-12 days rule'²⁰, introduced by the European Heart Rhythm Association of the European Society of Cardiology in 2013.²¹ This rule recommends the commencement of anticoagulants one day after TIA, three days after minor stroke (NIHSS score <8), six days after mild stroke (NIHSS score 8-15), and twelve days after moderate-to-severe stroke (NIHSS >15).

The most clinically significant management step following TTE findings is the initiation of oral anticoagulants upon detecting atrial or ventricular thrombi.²² Patients with known AF and/or who are already on anticoagulation, do not gain additional benefit from post CVA TTE.²³ In Malta, this practice is reflected as outpatient TTE are not scheduled for patients previously anticoagulated. Conversely, an article by the 'Journal of the American Heart Association' emphasizes the significance of also performing a TTE in patients already on direct oral anticoagulant therapy to assess comorbid cardiovascular conditions and to understand the primary event.²²

TTE has limited sensitivity for detecting left atrial thrombi, a common cardioembolic source associated with AF.¹⁹ TOE offers greater sensitivity and specificity and may be considered when TTE images are suboptimal or clinical suspicion remains high despite a negative TTE. However, clear guidance on when TOE should be preferred over TTE in post-stroke evaluation remains lacking.

PFO is recognized as a predisposing factor for TIA or stroke, serving as a conduit for paradoxical emboli or thrombi of fat or air from venous to arterial circulation.¹⁸ The audit encompassed 19 patients who were less than 55 years, however only 5 of these patients had a bubble study performed. In Malta, bubble studies are performed in patients less than 55 years. A limitation of our study is the lack of active tracking of the number of bubble studies scheduled and the associated clinical indications. However, only bubble studies which were incidentally found when looking up software data collection on echocardiograms were documented. Moreover, this

data emphasises the importance of enforcing the use of bubble studies in patients less than 55 years who sustained an ischemic stroke or TIA.

Limitations of the audit

Retrospective Design: The audit relied on retrospective data from patient records, which may be subject to incomplete or inconsistent documentation. This could introduce bias or inaccuracies in the analysis, impacting the reliability of the results.

Small Sample Size: The audit included a limited number of patients within a specific timeframe. A larger sample size might provide more robust conclusions and better representation of the target population.

Resource Limitations: The audit did not explore resource constraints within the healthcare system that could contribute to delays in outpatient monitoring. Factors such as staffing shortages, equipment availability, or administrative processes might influence the timeliness of appointments and affect the feasibility of implementing certain recommendations.

Limited Understanding of Patient Non-Attendance: The audit did not explore the reasons why some patients did not attend their scheduled outpatient holter or TTE appointments. Similarly, the audit did not investigate why alternative dates were not offered to patients who missed their appointments

Recommendations

The findings of this audit underscore the critical need for refinement in the utilisation and timing of outpatient cardiac monitoring and echocardiography following ischemic stroke or TIA. Based on the evidence gathered, several key recommendations emerge:

- Appointment scheduling should be optimised to ensure timely cardiac monitoring following stroke or TIA. A vetting system could prioritise outpatient Holter monitoring and TTE for these patients while ensuring appropriate utilisation by excluding those already anticoagulated or with contraindications to anticoagulation.

- Extended monitoring duration: Cardiac monitoring should be extended beyond 24 hours, aligning with ESO recommendations of ≥ 48 -hour outpatient monitoring in patients > 55 years.
- Implantable Monitoring Devices: Given the increased detection rates observed with implantable monitoring devices in patients above 55 years, healthcare facilities should explore the integration of these devices into their monitoring protocols.
- Consider TOE in selected cases where TTE is inconclusive or when clinical suspicion remains high despite a negative TTE.

CONCLUSION

This audit highlights significant delays in the utilisation of outpatient cardiac holter monitoring and transthoracic echocardiography following ischemic stroke or transient ischemic attack, with

waiting times exceeding 200 days and 100 days respectively in a substantial proportion of patients. These delays may limit timely identification of cardioembolic sources and opportunities for secondary stroke prevention.

Improving appointment scheduling and introducing a structured vetting system could prioritise post-stroke/TIA patients while ensuring investigations are appropriately allocated. In addition, local practice should consider extending cardiac monitoring beyond the conventional 24-hour period, in line with the recent ESO recommendations supporting at least 48 hours of monitoring in patients over 55 years, and exploring the role of implantable monitoring devices to improve atrial fibrillation detection.

Overall, optimising access to and selection of cardiac investigations has the potential to improve secondary stroke prevention and patient outcomes.

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Stone-free rate Post Extracorporeal Shock Wave Lithotripsy (ESWL) in the management of Adult Renal Stones

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Background: Extracorporeal Shock Wave Lithotripsy (ESWL) has been, and still is, one of the main kidney stone treatments available at Mater Dei Hospital in Malta and worldwide. This audit is aimed at identifying stone free rates (SFR) and stone factors that influence treatment outcomes.

Methods: Retrospective data collection was conducted by collating stone density, size and type, skin to stone distance and stone free rates for all ESWL treatment sessions performed over a 14-year period between 2008 and 2022. Statistical analysis was performed to identify stone free rates after treatment and stone factors which were shown to be significant in influencing outcome.

Results: The overall SFR was calculated as 30.1% from the 719 ESWL sessions included in this audit. Stone density in Hounsfield Unit (HU) was significantly associated with stone free status after treatment ($p=0.0001$). Stone size was also associated with SFR ($p=0.001$). Skin to stone distance, presenting and stone position were not significantly related to SFR.

Conclusion: The overall SFR was found to be lower than that quoted in most studies, even when accounting for the strict definition of complete clearance of the treated stone used. This audit should hopefully lead to development of treatment protocols in terms of multiple sessions and power ramping, as well as stricter follow-up and continuous re-audit to improve future outcomes.

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The incidence and prevalence of nephrolithiasis is increasing steadily, especially in affluent countries.¹ This is probably attributed to the 'Western way of living' and the rising rates of metabolic syndrome, diabetes and obesity. Kidney stone disease (KSD) poses a significant burden on healthcare system resources – in 2000, it is estimated to have cost around \$2 billion in the US and is increasing by \$1.24 billion per year till 2030.

Treatment of nephrolithiasis involves both the medical and the surgical aspects, though more importance is probably attributed to surgery rather than medical management.² To this time, surgery for KSD involves three main options – extracorporeal shockwave lithotripsy (ESWL), ureteroscopy (URS) and laser lithotripsy or percutaneous nephrolithotripsy (PCNL). ESWL is the earliest and least invasive mode of treatment³ and is still recommended as first or second line treatment for diverse stones in international guidelines.⁴

The primary aim of this audit is to assess stone free rates (SFR) after ESWL treatment offered by the Urology Unit at Mater Dei Hospital in Malta. Stone free was defined as complete clearance of the treated stone as determined by either ultrasound (USS) or Computed Tomography (CT) scan performed a few weeks after the procedure.

Secondary outcomes measured were the SFRs related to stone density, position, size (in longest diameter only), skin to stone distance and in patients with stented ureters.

METHOD

Data was collected retrospectively in November 2023 after the relevant Data Protection clearances were obtained as per GDPR criteria.

All ESWL treatment sessions performed between September 2008 and February 2022 were identified and data pertaining to the stone and patient treated obtained from the hospital online systems – iSOFT Clinical Manager (ICM) and PACS. Data was anonymized throughout. ESWL treatment was performed using a Dornier lithotripter S II with ultrasound localization and a standard protocol throughout.

Stones treated were classified by size, position and density (where CT was available) according to

imaging investigations done prior to the procedure. Stone size was measured in mm and grouped into 0-5mm, 6-10mm, 11-15mm, 16-20mm, 21-25mm and 26-30mm in the longest measured diameter. Stone density was measured in Hounsfield Units (HU) where CT scan was available and grouped as <500, 500-1000 and >1000. Stone position was classified into upper, middle or lower calyx, renal pelvis or pelvi-ureteric junction (PUJ). Skin to stone distance was measured in mm where CT was available. Those patients who had an indwelling stent during their ESWL procedure were also identified.

Stone free status was defined as complete clearance of the treated stone, as determined by USS or CT done within 3 months of the ESWL procedure. Patients who did not have follow-up investigations or an incomplete operation note, were excluded from this audit. Where available, stone composition was also recorded. SFRs in relation to the secondary outcomes were analysed using the Chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables; a p-value of <0.05 was considered as statistically significant.

RESULTS

A total of 778 patients underwent ESWL at MDH during the audit period; 59 were excluded as per pre-defined criteria, leaving 719 patients in the final sample analyzed. Of those not eligible for inclusion in this audit, 48 were lost to follow up or had no follow-up imaging investigations, while the rest did not have a complete operation note. 70% of the treated cohort were male patients.

The most common diagnostic imaging modality used to book patients for ESWL treatment was a non-contrast CT KUB (55%), followed by USS (26.8%) (Figure 1).

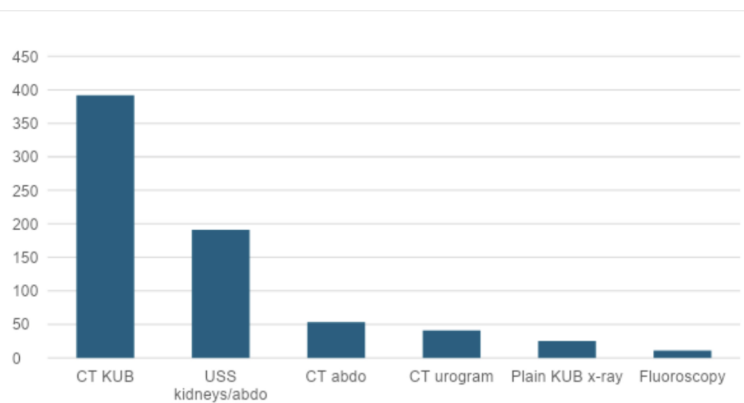


Figure 1 Diagnostic Imaging Modalities used

Diagnostic Imaging Modalities used

The overall SFR as defined for the scope of this audit was 30.1% on first follow-up. The majority of these patients were given only one treatment session per stone.

Subgroup analysis according to secondary objectives was performed. Information regarding indwelling stenting was only available for 497 patients (69.1%) from the audited cohort; of these, only 24 (4.82%) had an indwelling stent during their ESWL session. SFRs for pre-stented patients were worse at 20.8% but this was not found to be statistically significant ($p=0.279$).

The majority (37.9%) of treated stones were located in the lower calyces of the kidneys. SFRs for different locations of stones were not deemed to be statistically significant ($p=0.259$) (Figure 2).

The majority (57.7%) of stones treated were between 6 and 10mm in their longest diameter. On univariate analysis, stone size was found to be statistically significant, $p=0.001$. Stone density could be calculated in 70.2% of cases; 46.1% of these were very dense stones with HUs >1000 (Figure 3). Stone density was strongly significant with regards to SFR ($p=0.0001$), with harder stones having significantly less SFRs than those which were less dense. The average skin-to-stone distance (SSD) measured was 94.4mm. The variation in SSD was not found to be statistically significant for SFRs ($p=0.245$).

Stone analysis was performed where stone fragments were available. A total of 181 stones were sent for analysis, with the commonest stone type detected being calcium oxalate (60%) (Figure 4). SFRs with respect to stone type were not calculated in view of the small numbers available for most stones.

DISCUSSION

Since its introduction in the 1980s, ESWL remains in widespread use by Urology Departments worldwide.⁵ Its use is recommended as first line treatment for certain kidney and ureteric stones by several international guidelines.⁶ ESWL is often considered to be the safest stone treatment available, with complication rates being lower than those observed after ureteroscopic (URS/RIRS), percutaneous (PCNL), laparoscopic or open

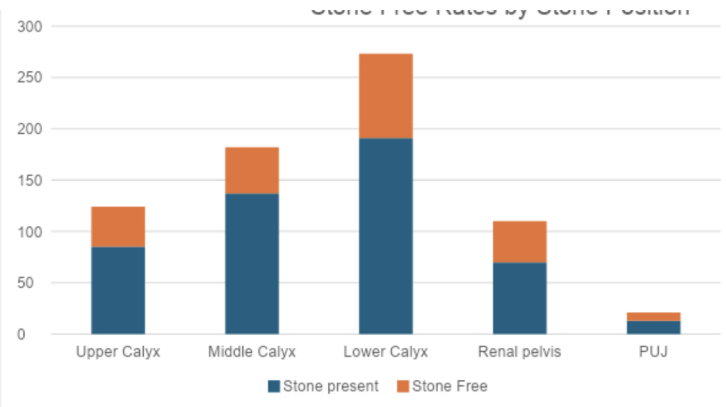


Figure 2 SFRs according to treated stone position

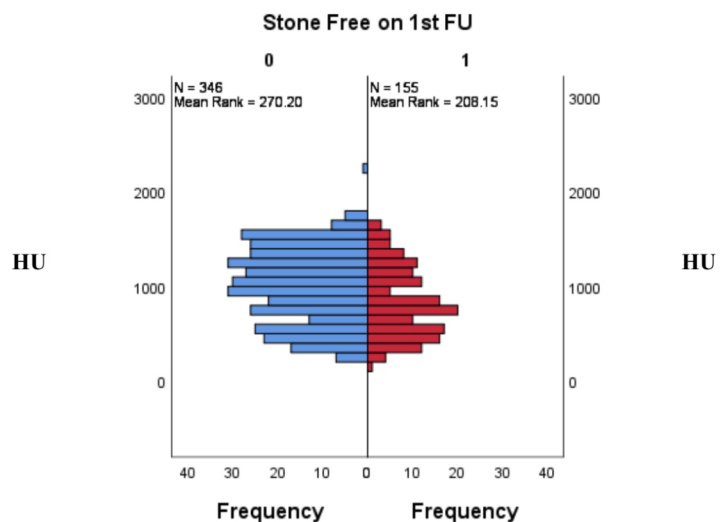


Figure 3 Stone-Free Rate in relation to calculated Hounsfield Unit

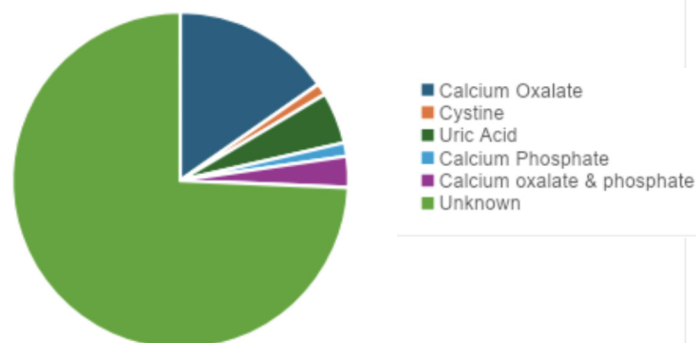


Figure 4 Stone types identified following stone analysis. Stones that were not examined were labeled as "unknown"

surgery.⁷ The downside to ESWL is that SFRs are often lower when compared to those obtained after PCNL or RIRS.

SFRs quoted in the literature vary significantly, often depending on the criteria used by the specific centre when referring patients for ESWL treatment (stone and patient characteristics), operator experience and number of treatment sessions given per stone. Quoted

SFRs are as variable as 86.7% (with over 53% having repeat sessions)⁸ to 46% after one session only.⁹

Several factors have been shown to have a significant effect on ESWL outcome in terms of SFRs. Lower pole stones are notorious for having significantly poorer outcomes compared to other positions in the kidney (47% vs 68-70.5% SFRs).¹⁰ Stone size has also been shown to influence outcomes; smaller stones have a significantly higher chance of being cleared completely, even when they have a high density of >1000HUs.¹¹ High stone density and longer skin to stone distance have also been shown to decrease SFRs after ESWL though results were not consistent across all studies performed.^{12,13}

Several nomograms have been developed to try and predict success of ESWL depending on stone characteristics. One of the most commonly used nomograms is the Triple-D score, which uses stone density (>600HU), skin to stone distance (>12cm) and stone volume (>150mm³) to predict chances of complete stone clearance after one session of ESWL. This was recently updated to a Quadruple-D score with the addition of stone position (lower pole).¹⁴

Besides patient and stone characteristics, centre experience with ESWL and operator skill with targeting have been shown to significantly affect outcomes after treatment.¹⁵ Centres who have dedicated personnel performing a high number of ESWL sessions are expected to have higher SFRs, mainly because of better targeting of shockwaves onto stones.

Another factor which affects quoted SFRs depends on the definition of "stone-free" status used by the respective studies. Studies quoting complete "stone-free" rates will likely show a poorer outcome compared to those quoting "clinically insignificant" stone fragments (smaller than 5mm).¹⁶ Clinically insignificant stone fragments are usually considered as being residual stones smaller than 5mm in their

longest diameter after treatment. Whether this is sufficient to consider the treatment as being successful is controversial – even small stone fragments have been shown to be a nidus for potential future stone formation, needing more treatment eventually. Nowadays, a stricter definition of stone free status is often used and defined as no stones seen on cross-sectional imaging.¹⁷

CONCLUSION

Our audit serves as an assessment of our ESWL outcomes compared to internationally quoted SFRs. In fact our SFR is lower than those quoted in many studies (30.1%), though this could be attributed in part to the fact that a very strict definition of SFR was taken.

Looking at our secondary objectives, only stone density and stone size were significantly associated with a stone free status after treatment. Unfortunately a significant proportion of patients did not have cross-sectional imaging with CT scan prior to their ESWL treatment as recommended by EAU guidelines.¹⁸ This means that we could not measure stone size accurately in a reproducible manner or calculate stone volume. Stone density and skin to stone distance also could not be measured in those patients having no CT scan.

Another limitation of our audit is inconsistent follow-up with imaging being done at variable time frames and using different types (USS vs CT vs KUB).

We recommend that this audit leads to better patient investigation and selection prior to ESWL treatment. Due consideration should be given to having multiple treatment sessions to the same stone over a few weeks to maximise stone fragmentation. Stricter follow-up and regular re-audit could highlight areas where the ESWL service can be improved to obtain better SFRs.

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Improving discharge summary documentation of older adults in a rehabilitation hospital with an electronic discharge template

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Background: During past quality improvement projects at our rehabilitation hospital, inconsistencies were observed in the inclusion of essential information in discharge notes. This had the potential to compromise the continuity of care to other healthcare providers upon discharge. The introduction of an electronic discharge summary template (EDST) aimed to address this issue by providing guidance to clinicians for comprehensive documentation and handover.

Methods: The EDST was developed through a structured process involving feedback from healthcare professionals obtained via structured interviews and questionnaires. One hundred discharge letters were chosen through sample randomization and audited against the EDST criteria. Subsequently, formal training sessions were conducted for foundation year doctors on the utilisation of the template. Post-implementation, another one hundred discharge letters were analysed to evaluate the impact of the EDST.

Results: Initial analysis revealed areas requiring improvement, particularly the Barthel score on admission and discharge, patient weight, and cognitive assessment. Following implementation of the EDST, significant improvements were observed in these areas. Feedback from foundation doctors utilising the EDST guided further refinements to the template.

Conclusion: The introduction of the EDST resulted in improved documentation and overall discharge summary completeness. The sustained utilisation of the EDST within our hospital's electronic discharge system is recommended to support ongoing improvements in discharge communication and patient care continuity.

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Older adults often experience complex medical problems that require a multi-disciplinary approach. Our rehabilitation hospital has a bed capacity of approximately 250 patients, and despite it not being an exclusive geriatric rehabilitation hospital, around 75% of the patients admitted are older than 65 years of age. In most cases, it receives patients discharged from the only acute care hospital on the island. A few patients from the community who require rehabilitation are also admitted, with the aim of returning back to the community at their previous level of function. A comprehensive geriatric assessment (CGA) is needed to achieve maximum rehabilitation potential and not to miss important aspects of care.¹ It is important to ensure the communication of patient information for good follow-up care in the community setting and between different hospitals. The CGA is conducted by a multi-disciplinary team including geriatricians, nurses, pharmacists, and allied health professionals.

It was noted that our conventional electronic discharge summaries did not adequately incorporate all the elements of the CGA, which is specific to the older population. Although some electronic discharge summaries include most of the relevant information, there is a lack of uniformity and documentation. The aim of this quality improvement project (QIP) was to implement interventions to improve the documentation of discharge summaries by designing an electronic discharge summary template (EDST) that will guide doctors on what to write in the discharge letter (DL) and hold interval education sessions on the importance and use of this EDST.

MATERIALS AND METHODS

First Phase

Following consultations with Maltese consultant geriatricians, it was determined that discharge summaries serve as vital communication tools between healthcare providers and should encapsulate CGA findings. It was agreed that an EDST might help doctors include all necessary information. Subsequently, an expert multi-disciplinary board was formed including 3 consultant geriatricians, 2 general practitioners, 2 higher specialist trainee geriatricians, 1 ward nurse, 1 community liaison nurse, 1 pharmacist,

1 physiotherapist, 1 occupational therapist, 1 speech and language pathologist and 1 social worker. This was accomplished using the Delphi method.

Second Phase

A retrospective analysis of 100 randomly selected discharge letters from the previous 5 months was conducted. Each letter was anonymised and assigned a numerical identifier. Data pertaining to the absence of specified headings of the CGA were recorded in a Microsoft Excel Sheet.

Third Phase

The newly devised EDST was piloted within the electronic case summary application used by FY doctors to generate discharge letters. Training sessions were conducted to familiarise these doctors with the template and emphasise its utility in facilitating comprehensive handover to health professionals. This process was iteratively executed over three consecutive quarters involving 24 FY doctors.

Fourth Phase

Feedback was collected from FY doctors, and after consultation with the expert team, the EDST was changed accordingly.

Fifth Phase

After six months of using the pilot template, a further one hundred discharge letters were audited using sample randomization. Statistical package for the Social Sciences (SPSS) was utilised for data collection, and this was analysed using descriptive statistics and the difference of two proportions Z-test to determine if there was a statistical difference between the two sets of data.

RESULTS

In the 1st phase 100% consensus on the ideal format of the EDST was reached after two cycles using the Delphi method.

Pre and post implementation of the EDST

In the 2nd phase, the results showed that 99% of the DLs included an admission note and 95% included past medical history/past surgical history (PMH/PSH).

The majority of the DLs included medical management (88%), and relevant treatment changes (88%). Improvement was needed in other areas, such as the Barthel score on admission (55%) and discharge (47%), weight (2%), and cognitive assessment (53%). After the implementation of the EDST, there was a significant improvement in all of the above sections (see [Figure 1](#) and [Table 1](#)).

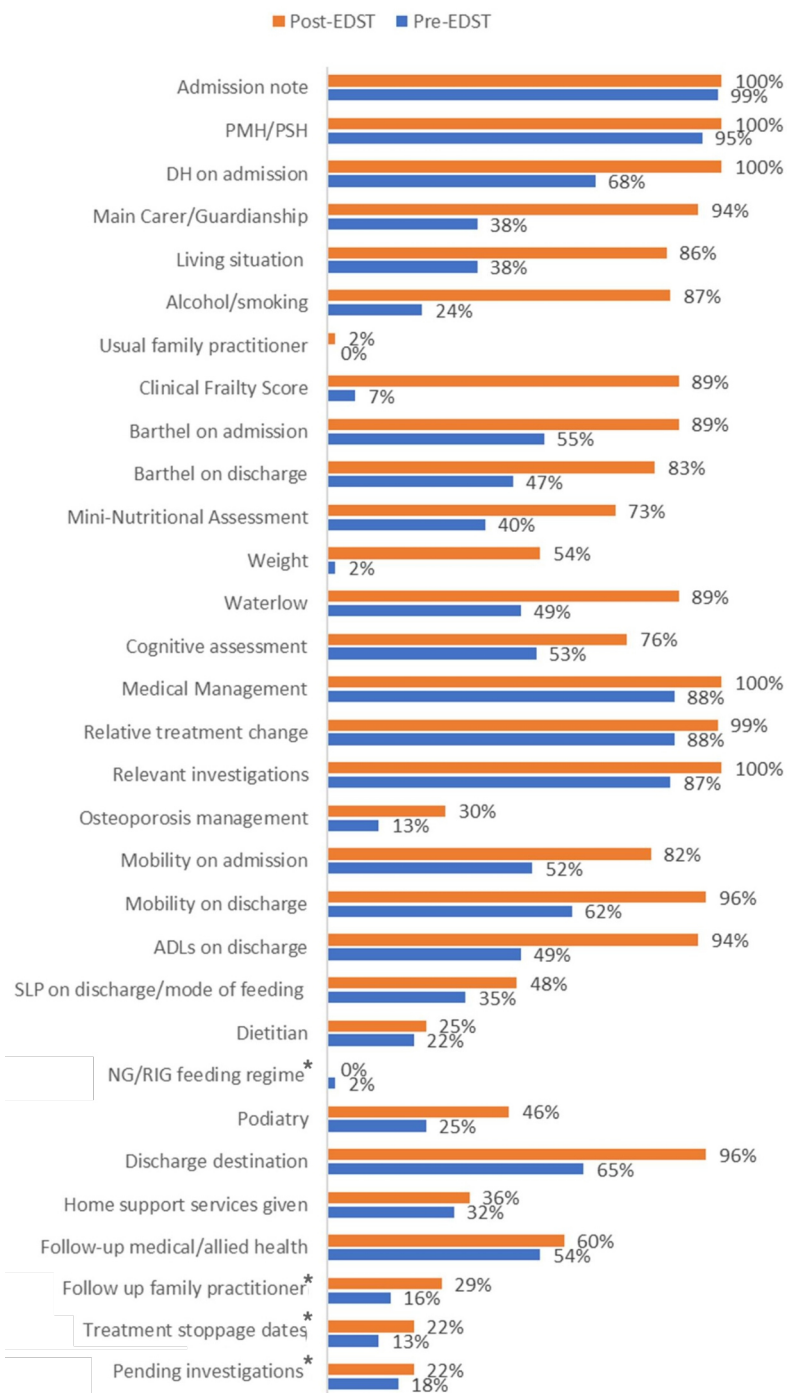


Figure 1 Showing the pre-and-post implementation percentages of main headings on the EDST

Feedback from the users of the EDST

A total of 14 FY doctors answered our feedback questionnaire. Two individuals were foundation year one, and 12 were foundation year two. 13 FY doctors used the EDST. Of these 14 individuals, 13 felt that the newly formulated EDST was useful in writing a discharge summary, while one individual felt that the EDST was time consuming. One individual stated that unfortunately, the family general practitioner is never documented in the clinical notes, and so it was never documented in the summary. One FY also suggested, if applicable, to include another section regarding psychiatric management. 10 FY doctors felt that no improvement was necessary with the EDST. Most of the above concerns were addressed in the subsequent FY doctors' intake.

DISCUSSION

Poor communication between the secondary and primary care settings is a high-risk healthcare event.²This is particularly well evidenced in relation to medication errors following discharge. A well-documented discharge summary of the care received in hospital with primary care is essential for patient safety. International evidence suggests that discharge letters are unsatisfactory for several reasons including; incomplete and inadequate information, unclear follow-up plans, letter inaccuracies, delayed letter delivery, unclear medication information, lack of patient-centeredness (e.g., letter dense with jargon), and miscommunication leading to adverse events such as patient readmissions in the older population.³

Our quality improvement project demonstrated that the new EDST improved documentation in most of the sections studied in the discharge summary. Our study is supported by results obtained from other similar quality improvement projects. Maurice et al^{sup>4} have formulated a similar approach in their project in which they introduced an electronic prompting system in their discharge summary program. The results were also encouraging as the proportion of adequate diagnosis, comorbidities, inpatient care summary and treatment all improved with their interventions. This further confirms our results and supports our finding that an electronic

Table 1 Showing the sampling distribution of two population portions and the p-value. In most of the main headings of the EDST there was significant improvement after the implementation of the EDST

Discharge Letter	Pre-Percentage	Post-Percentage	Z-Score	P-value
Admission Notes	99%	100%	-1.0025	0.16
PMH/PSH	95%	100%	-2.2646	0.012
DH	68%	100%	-6.1721	<0.00001
Main carer/guardianship	38%	94%	-8.3591	<0.00001
Living situation	38%	86%	-6.9926	<0.00001
Alcohol/smoking	24%	87%	-8.9639	<0.00001
Usual family practitioner	0%	2%	-1.4213	0.078
CFS	7%	89%	-11.6058	<0.00001
Barthel admission	55%	89%	-5.3545	<0.00001
Barthel discharge	47%	83%	-5.337	<0.00001
MNA	40%	73%	-4.7068	<0.00001
Weight	2%	54%	-8.1892	<0.00001
Waterlow	49%	89%	-6.1156	<0.00001
Cognitive assessment	53%	76%	-3.3987	0.00034
Medical management	88%	100%	-3.5729	0.00018
Relative tx change	88%	99%	-3.1551	0.00079
Relevant investigations	87%	100%	-3.7288	0.0001
Osteoporosis management	13%	30%	-2.926	0.0017
Mobility on admission	52%	82%	-4.5114	<0.00001
Mobility on discharge	62%	96%	-5.9026	<0.00001
ADLs on discharge	49%	94%	-7.0489	<0.00001
SLP on discharge	35%	48%	-1.8656	0.031
Dietitian	22%	25%	-0.5003	0.31
NG/RIG	0%	2%	-1.4213	0.078
Podiatry	25%	46%	-3.1032	0.00097
Discharge destination	65%	96%	-5.5326	<0.00001
Home support services	32%	36%	-0.5971	0.27
FU Medical + Allied health	54%	60%	-0.857	0.19
FU Family practitioner	16%	29%	-2.2013	0.014
Treatment stoppage dates	13%	22%	-1.6749	0.047
Pending investigations	18%	22%	-0.7071	0.24

prompting system improves the documentation of discharge summaries.

Our results can be attributed to the implementation of the EDST. However, we must also take into consideration that an education session on how to write a discharge summary and how to use the EDST was given to the FY doctors in our quality improvement. Dedicated formal training to FY doctors or medical students on discharge summaries is uncommon.⁵ The quality of discharge letters from medical officers improves throughout the year with experience. Phatal et al⁶ have demonstrated that educational intervention alone improves the overall quality of discharge summaries by introducing a two-hour structured workshop for medicine residents. Earnshaw et al⁷ have shown that education and feedback on discharge summaries have also improved the quality of documentation. We also need to consider that most of the doctors involved were foundation two doctors. These doctors already had 1-year of experience in completing discharge summaries, which may have influenced our results.

Our quality improvement project also involved gathering feedback from FY doctors. Most doctors found the EDST useful and did not suggest any changes to the template. However, two individuals highlighted that the EDST is too time consuming, whilst two others expressed that the EDST has saved them time in writing a discharge summary. Time needs to be considered when writing a discharge summary, as FY doctors are busy and heavily involved with ward responsibilities. Time is a measure that needs to be assessed in future quality improvements using the newly formulated EDST.

Furthermore, our project highlights the importance of stakeholder engagement and iterative refinement in quality improvement initiatives⁸. The involvement of a MDT, comprising healthcare professionals in different specialties and also medical/pharmacist working in the community, ensured that the EDST reflected the diverse needs of clinicians/allied health professionals involved in discharge communication.

Limitations in this quality improvement project were that the format, qualitative content, (i.e., information accuracy), summary length, and overall readability of the discharge summary were not specifically

SUMMARY BOX

What is known about the subject:

- Discharge summaries are essential pieces of medical documentation that are used by both healthcare professionals and patients to understand the events of a hospital admission, and ensure safe handover of care.
- Discharge letter summaries are often of poor quality and contain incorrect or incomplete documentation of patient diagnosis, comorbidities, complications, and procedures.
- Improvement in discharge letter documentation is necessary for a better handover to primary care and to ensure patient safety in the discharge process.

What are the new findings:

- FY doctors did not have a guide on how to write a discharge summary before the implementation of the EDST, and this template helps FY doctors formulate a well-documented discharge summary.
- Most of the FY doctors found the EDST useful in helping them formulate a well-documented discharge summary.
- This quality improvement has shown a significant positive change in documentation and has become the new standard in our rehabilitation hospital.

assessed. Moreover, not all FY doctors engaged in feedback. In the 1st phase of our project, we did not include patients to provide feedback on what they believed should be included in the discharge summary. Additionally, the restrictions in functionality of the electronic case summary program potentially impacts user experience and documentation efficiency.

By standardising documentation practices and promoting MDT collaboration, initiatives like the EDST have the potential to improve care coordination, reduce medical errors, and ultimately enhance patient outcomes in geriatric rehabilitation settings.

Acknowledgements

We would like to thank all the medical and allied health care professionals involved in forming the electronic discharge letter template which was used to carry out this quality improvement project.

Abbreviations

CGA	Comprehensive Geriatric Assessment
EDST	Electronic discharge summary template
DL	Discharge Letter
FY	Foundation year
QIP	Quality improvement project

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Seasonality of pregnancies, births and marriages in Malta

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Objectives: Seasonality of births is almost universal, including in Malta, wherein for 1950-1996 there was a significant peak in marriages paralleled by a peak in births. This study was carried out to ascertain whether this has persisted and to identify potential deviations due to the COVID-19 pandemic.

Study Design and Methods: Anonymous monthly data for 1999-2020 was obtained. This included First birth, First pregnancy (including miscarriages) and total marriages. Analyses were performed with unprocessed monthly time series and seasonally adjusted time series.

Results: All series exhibited minor seasonal variation. Marriages peaked in June and September. First birth and First pregnancy series peaked in October and September, respectively. There was a positive correlation at lag - 11 months for First births with Marriages, and First pregnancies with Marriages and this was higher for Pregnancies than Births. There was a constant negative gap between the actual data and forecasted values for the three series from August 2020.

Conclusion: A higher average number of marriages leads to higher-than-average births 11 months after. The Maltese peaks are associated with month preference for marriage. Marriages, First births and First pregnancies in Malta dropped 72% 17% and 11% respectively during March-August 2020 (Marriages) and December 2020 (First births and First pregnancies) compared to the expected forecasted values, implying a negative impact that is temporally associated with the brunt of the COVID-19 pandemic.

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Seasonality of births has been noted in various countries, including in Malta.¹⁻³ Indeed, an earlier study in Malta had shown that for the period 1950-1996 there was a significant peak in marriages paralleled by a peak in births which lagged after the peak in marriages by 13-14 months. The peak in births was caused by first pregnancies only.³

This study was carried out to ascertain whether seasonality at birth has persisted in relation to first pregnancies, i.e., first time mother has been pregnant and delivered at 22+ weeks of pregnancy, never having suffered a previous miscarriage). Furthermore, potential deviations from expected norms due to the COVID-19 pandemic were also sought.^{4,5}

METHODS

Data

Anonymous aggregated data for births by month and birth order for 1999-2020 was obtained from the National Obstetric Information System, Directorate for Health Information and Research. Monthly marriages were obtained from Malta's National Statistics Office. Since this is an anonymous and aggregated dataset, ethical approval was not needed, and neither was informed consent, for the same reason.

Analysis

The following time series were studied: First pregnancies (as defined above) and Total marriages. Analyses were performed with unprocessed monthly time series and seasonally adjusted time series.

Seasonal adjustment refers to a technique wherein independent trends in time series data are preserved after removing seasonal variations. It employs a series of mathematical and statistical operations, such outlier detection, model identification, decomposition etc., which can be specified in the software.

Seasonality in this study was analysed using JDemetra+ software (version 2.2.2) with Tramo-Seats and RSA5 specifications. JDemetra+ provides seven predefined specifications for both TRAMO/SEATS and X-13 and uses some default specifications for each method.

The data's seasonality was analysed by the TRAMO/SEAT and RSA5 method. It is a model-based seasonal

adjustment method that, in the first step, detects deterministic calendar variation and outliers, and corrects for missing values whilst applying a regression model to the data. Trading day effect and the leap year effect are pre-tested and taken in account. A Malta-specific calendar was used, with pre-specified national holidays.

The regression ARIMA (linear, autoregressive integrated moving average) model chosen was multiplicative with parameters of (3,1,1) (0,1,1) for Marriages and (0,0,0) (0,1,1) for First pregnancies.

In further steps, the following seasonality tests were carried out: the Friedman test for stable seasonality, the Kruskal-Wallis test, for seasonality presence assuming stability, and evaluative seasonal test for detecting the presence of identifiable seasonality. These tests were merged within the final combined seasonality test, which determines whether seasonality is present within the series.

A direct seasonal adjustment approach was carried out with the monthly series First pregnancies, from January 1999 to December 2020. The data series Total marriages was seasonally adjusted for January 1999 to February 2020, due to end-of-series outliers between March-December 2020 caused by COVID-19 effects.

A p value ≤ 0.05 was taken to represent a statistically significant result.

RESULTS

Seasonally adjusted and unadjusted data for the variables in studied are shown in [Table 1](#). Both series exhibited minor seasonal variation, as per [Figure 1](#) and [Figure 2](#). The time series for Marriages exhibits a peak of seasonal variation in June and in September ([Table 2](#)). The First pregnancies ([Table 3](#)) series exhibits peaks of seasonal variation in September and March.

The actual, non-seasonally adjusted data for Marriages and First pregnancies were compared, with forecasted values for March-December 2020, as can be seen in [Figure 3](#) and [Figure 4](#). The time series 1999-February 2020 served as a base for the forecast. From August 2020, there was a constant, negative gap between the actual data and forecasted values for the three series. [Figure 3](#) illustrates the difference.

Table 1 *Marriages / First pregnancies (non- adjusted, seasonally adjusted)*

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1999	156	129	153	144	140	138	178	162	190	160	143	145
2000	153	147	141	160	138	167	162	152	153	157	142	169
2001	128	133	159	134	136	158	159	137	156	156	146	117
2002	164	141	139	145	152	144	151	163	157	152	150	142
2003	139	153	131	132	136	147	178	173	162	176	166	174
2004	155	143	152	118	144	141	137	152	165	149	145	175
2005	145	131	159	128	157	136	143	125	143	164	127	151
2006	156	136	156	159	139	166	124	159	158	173	150	148
2007	137	123	160	140	138	146	135	148	168	162	146	151
2008	167	141	150	141	141	154	158	204	182	177	157	174
2009	159	141	162	143	137	158	184	154	160	171	183	176
2010	174	126	153	139	137	125	162	149	171	140	174	156
2011	168	130	172	150	151	143	180	190	199	167	161	158
2012	168	148	149	127	151	142	171	176	181	188	155	166
2013	151	136	155	130	150	134	152	156	168	169	152	172
2014	157	134	159	143	156	129	176	172	181	167	181	158
2015	184	135	180	163	139	148	167	149	157	174	166	174
2016	195	141	149	165	152	150	141	183	205	193	179	162
2017	150	143	178	143	170	141	172	171	169	183	175	161
2018	153	134	173	135	142	157	156	192	167	158	193	163
2019	154	132	159	147	153	144	178	188	182	182	173	171
2020	184	175	157	159	141	145	175	189	153	166	163	147

Table 2 *Marriages Total monthly data – non-adjusted data*

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1999	74	81	130	186	313	326	279	173	299	246	117	210
2000	83	74	128	194	323	357	256	175	277	232	99	198
2001	46	74	127	166	272	341	204	177	278	231	104	191
2002	51	61	112	205	277	360	248	208	260	242	105	177
2003	51	75	148	171	334	331	256	232	277	253	105	181
2004	78	63	121	195	343	353	274	176	295	251	100	165
2005	60	52	125	216	301	347	290	182	307	249	94	151
2006	50	61	123	231	309	389	275	232	321	242	108	195
2007	37	60	117	187	293	426	302	253	322	222	107	153
2008	51	52	104	161	342	347	298	313	310	252	91	161
2009	36	57	90	159	359	381	295	240	287	224	75	150
2010	58	56	86	175	369	412	360	222	312	299	90	157
2011	45	57	92	162	308	462	372	244	303	253	125	139
2012	59	56	133	186	329	575	345	297	339	218	95	191
2013	52	54	111	179	344	479	304	268	313	223	91	160
2014	55	62	127	189	438	492	340	306	315	266	123	158
2015	69	76	149	203	436	491	387	299	326	281	96	189
2016	65	86	95	249	382	540	429	272	332	282	124	178
2017	84	74	140	222	387	478	410	262	339	236	117	185
2018	73	83	130	221	349	533	311	254	319	247	130	181
2019	73	79	154	186	360	482	305	212	273	213	155	182
2020	68	88	66	45	51	56	61	125	193	164	88	152

Table 3 *First Pregnancy Total monthly data – seasonally adjusted data*

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1999	155	143	153	156	149	143	171	155	175	149	142	143
2000	152	163	141	173	147	173	156	146	141	147	141	166
2001	127	147	159	145	145	164	153	131	144	146	145	115
2002	162	156	139	157	162	150	146	156	145	142	149	139
2003	138	170	131	144	145	154	173	165	149	164	164	170
2004	153	159	152	129	153	148	133	145	152	139	143	171
2005	143	146	158	139	167	143	139	119	132	152	125	147
2006	154	152	155	173	148	175	121	151	145	161	148	144
2007	135	138	159	153	148	154	132	141	154	151	143	147
2008	164	159	149	154	151	163	154	193	167	165	153	169
2009	156	159	161	156	147	169	179	146	147	159	178	171
2010	170	142	152	152	147	134	157	141	157	130	169	152
2011	164	147	171	164	162	154	175	179	182	155	156	154
2012	164	167	148	139	162	153	166	166	166	175	150	162
2013	147	154	154	143	161	145	148	147	154	157	147	168
2014	153	152	158	157	167	140	171	161	167	155	174	154
2015	179	153	178	178	149	161	162	140	145	162	159	170
2016	190	160	148	180	163	163	137	171	189	179	172	159
2017	146	162	176	156	182	154	167	159	156	170	167	158
2018	150	152	171	148	153	171	152	178	155	147	184	160
2019	150	149	158	161	165	157	173	174	169	169	165	168
2020	180	198	156	174	152	158	170	175	142	155	156	145

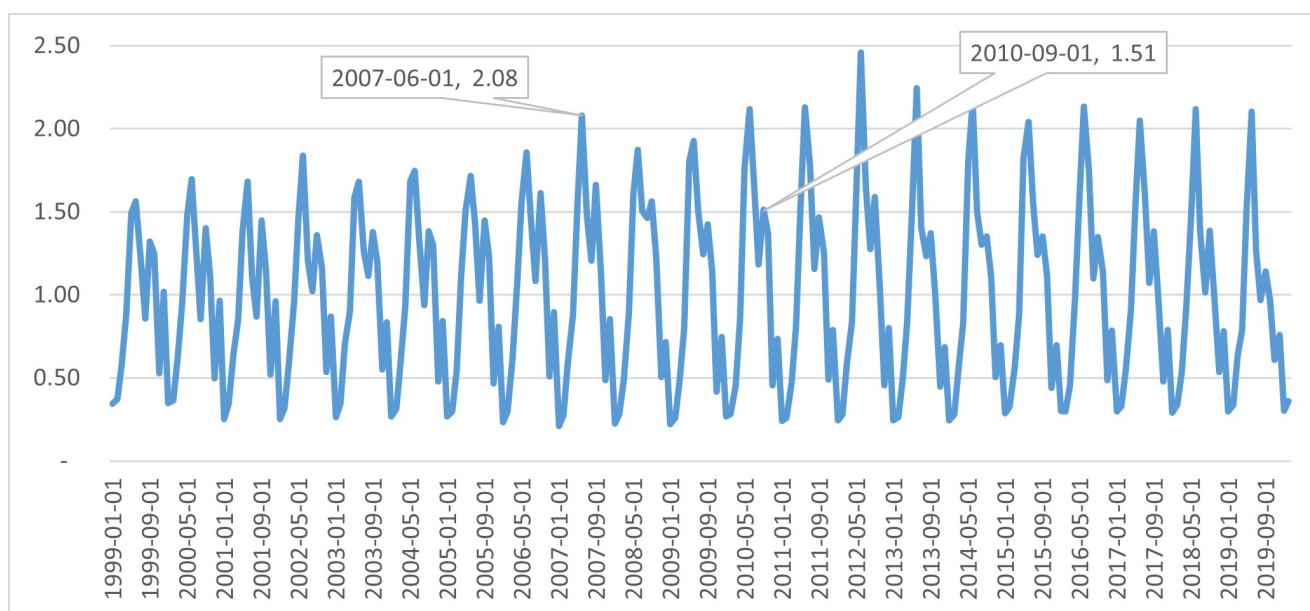


Figure 1 Seasonal patterns for Malta 1999-2020: Marriages.

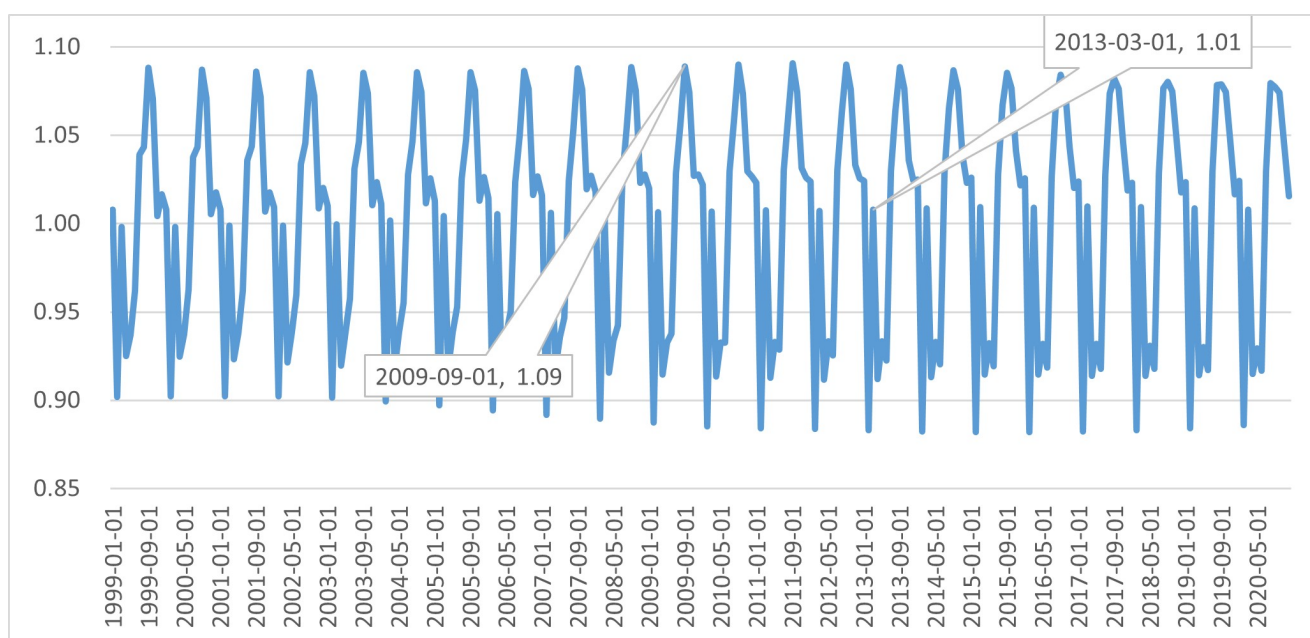


Figure 2 Seasonal patterns for Malta 1999-2020: First Pregnancies

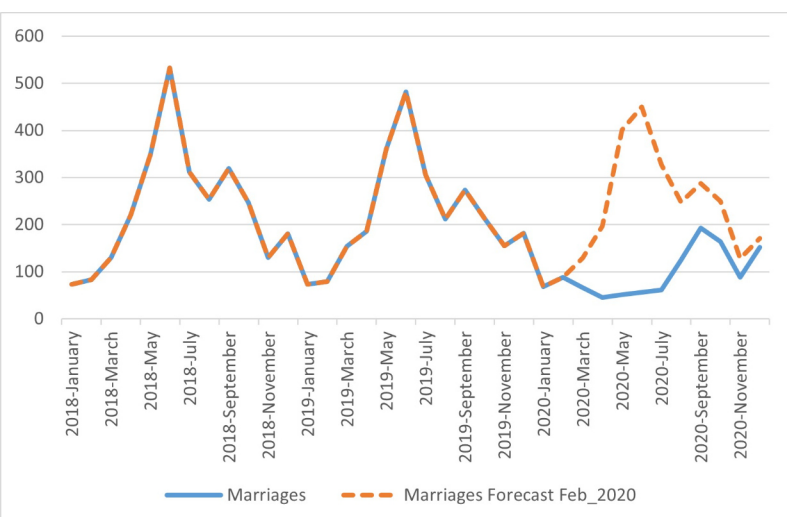


Figure 3 Observed data for Marriages 1999-2020 and forecasted values for March-December 2020

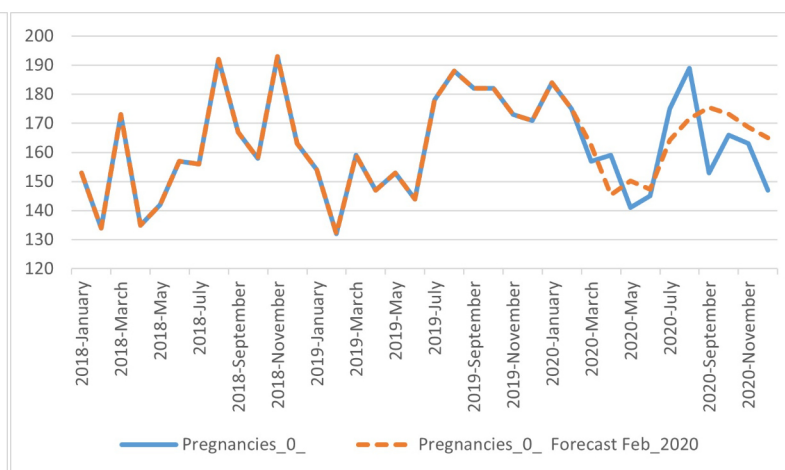


Figure 4 Observed data for First Pregnancies 1999-2020 and forecasted values for March-December 2020

Marriages in Malta dropped 72% during March-August 2020, compared to the expected forecasted values. Similarly, First pregnancies dropped by 8% during September-December 2020. In December, the decrease reached 11% for First pregnancies.

DISCUSSION

The drop in marriages and first pregnancies was temporally associated with the brunt of the COVID-19 pandemic, implying a negative impact on both.^{4,5}

Seasonal patterns in births occur almost universally due to cultural and/or biometeorological factors.

Examples of cultural factors have included festivals, such as a September birth spike probably due to an increase in coital activity in the Christmas period.⁶ Biometeorological factors include agricultural cycles which have been implicated due to potential swings in maternal nutritional status.⁷ Fluctuations may also be due to changes in hours of sunlight and/or temperature.⁸ The best known seasonal patterns occur in the southern United States, with a birth decline in April and May, and in northern Europe with a birth peak in March/April.^{1,9}

A previous paper based on Maltese data had shown a late summer peak in first births only, lagging behind marriages by approximately 10 months,³ an effect

that was similarly noted in Japan.¹⁰ Indeed, seasonal birth patterns have been noted in many countries including birth peaks in Portugal in May and September,¹¹ and July-September peaks in Croatia,¹² The absence of such seasonality is rare and notable.¹³ The Maltese peak had been linked with marriages,³ a link that was also described in other countries.¹⁴⁻¹⁶

The Maltese peak may potentially be attributed to conscious family planning with abstinence or contraception prior to marriage, and this may be due to a residual Roman-Catholic ethos.¹⁷ Alternatively, this may be due to simple economics with couples preferring to start families once they have formally settled down contractually in wedlock.¹⁷ Furthermore, marriages in Malta are often large-scale, and are considered important family and social occasions. Naturally, an outdoor venue is generally preferred in clement Mediterranean weather.¹⁸ Thus, a socio-cultural bias to Spring weddings influences first pregnancies and births in Malta.

Marriages in Malta correlate with first pregnancies, resulting in seasonal patterns for both. The COVID-19 pandemic has reduced marriages and first pregnancies, implying that the global events which appeared in March 2020 also affected the decisions of having first pregnancies.

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Assessing adherence to pre-operative spirometry testing guidelines among medical doctors in Malta

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Background: Pulmonary complications arising from surgical procedures are frequently encountered in the clinical setting, resulting in high levels of patient morbidity and mortality. It is important to assess the risk of developing these complications during the pre-operative assessment. Spirometry is a simple and non-invasive means of evaluating pulmonary function, yet it should not be utilised unnecessarily.

Aims: To assess whether pre-operative spirometry requests at Mater Dei Hospital, Malta are indicated.

Methods: A retrospective analysis of all pre-operative spirometry requests and tests during September 2022 at the Pulmonary Function Lab at Mater Dei Hospital was performed. Patient characteristics were noted from the pre-operative assessment note. The local guideline entitled 'pre-operative generic investigations for adult elective surgery' was used as the gold standard to determine whether the spirometry request was indicated.

Results: A total of 156 patients had pre-operative spirometry performed in September 2022. Pre-operative spirometry testing was not indicated in 63.5% (n= 99). Patients in whom spirometry was indicated, 54.3% (n=31) had an American Society of Anaesthesiologists (ASA) classification of 3 or above, 29.8% (n=17) were unable to climb two flights of stairs, and 15.8% (n=9) had both indications.

Conclusion: Routine ordering of spirometry is discouraged in the pre-operative period. Instead, pre-operative spirometry should be requested if the patient is classified as an ASA of 3 or above, or if they cannot manage to climb two flights of stairs. Taking a careful approach to choosing which patients undergo pre-operative spirometry could result in reduced costs and shorter waiting times.

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Every year, around 230 million patients worldwide undergo surgical procedures. Current literature shows that hospital mortality rates for such surgical procedures range from 1% to 4%.¹ It is important to recognise that post-operative complications can significantly impact patient outcomes, leading to increased mortality, morbidity and longer hospitalisation stays.

Pulmonary complications can be stratified based on their potential for mortality. They fall into two main categories: major complications like respiratory failure, prolonged mechanical ventilation, or intubation exceeding 48 hours and minor complications like tracheobronchitis, atelectasis, and bronchospasm. It is encouraged to assess pulmonary risks before surgery as it enables the medical professional to implement preventive measures. By doing so, they can effectively reduce the incidence of these complications, ultimately improving patient outcomes and minimising both morbidity and hospitalisation stays.

Spirometry is a non-invasive tool for assessing pulmonary function.³ It measures the forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC), and identifies normal, obstructive, or restrictive ventilatory patterns. These ventilatory impairments (obstructive or restrictive) are associated with underlying medical conditions such as chronic obstructive pulmonary disease (COPD), asthma, or interstitial lung disease.⁴ Consequently, pre-operative spirometry findings are leveraged to forecast the likelihood of postoperative pulmonary complications, particularly among individuals undergoing thoracic surgery.⁵ Nevertheless, its predictive value for patients undergoing non-thoracic surgeries is not clear.

The American College of Physicians published its first clinical guidelines in 2006 for assessing risks to prevent post-operative pulmonary complications in patients undergoing non-cardiothoracic surgeries.⁶ These guidelines prioritise a clinical evaluation to identify risk factors associated with the patients' health and the specific surgical procedure. One important aspect of these guidelines is their recommendation against the routine use of pre-operative spirometry. This recommendation was based on the observation that the available evidence did not conclusively demonstrate the superiority of

pulmonary function testing over a comprehensive assessment of the patient's medical history and a physical examination in predicting which patients were at risk of experiencing post-operative pulmonary complications. These guidelines were developed based on a thorough review of the existing literature. However, they failed to establish a strong relationship between pre-operative pulmonary function test results and the probability of experiencing post-operative pulmonary complications.^{7,8}

In contrast, subsequent studies have suggested a relationship between pre-operative pulmonary function test results and the likelihood of post-operative pulmonary complications in individuals having abdominal surgery.⁹⁻¹⁴

AIMS

The aim of the audit was to determine whether pre-operative spirometry requests at Mater Dei Hospital are indicated.

METHODS

Participants and Study Procedures

The audit consisted of a retrospective analysis of data obtained from 156 patients who had undergone spirometry testing in the period from September 1st to September 30th 2022, at Mater Dei Hospital's Pulmonary Function Lab. The data collection process involved gathering all the spirometry test referrals made by junior doctors at the Pre-operative Assessment Clinic (POAC) for patients scheduled to undergo elective surgical procedures. During a pre-operative visit, the junior doctor needs to conduct history taking and physical examination for each patient before answering several questions that tackle the cardiovascular, respiratory, gastrointestinal, renal, and endocrine systems.

To access patient records, iSOFT Clinical Manager® and Patient Dashboard ® were used. The latter provides access to both POAC clinical notes and spirometry results. Eligible participants were scheduled to undergo a range of elective surgical procedures under general anaesthesia. The following surgical procedures were included: thoracic, upper

and lower abdominal, orthopaedic, gynaecological and Ear, Nose, and Throat (ENT) surgeries. If a patient underwent more than one surgery during this time period, only their initial surgery was included.

The gold standard used was the 'pre-operative, generic investigations for adult elective surgery' guideline established by the Department of Anaesthesia at Mater Dei Hospital. According to this guideline, patients should be referred for spirometry only if they report an inability to climb two flights of stairs, in which case this warrants further discussion with the Perioperative Assessment Clinic (POAC) consultant anaesthetist. Additionally, if any indications of severe systemic disease (ASA 3 or above) are detected during clinical evaluation, lung function testing should be requested.

Within the pre-operative spirometry assessments, Forced Expiratory Volume in 1 second (FEV₁), Forced Vital Capacity (FVC) and the ratio of FEV₁ to FVC (FEV₁/FVC) were measured. Spirometry assessments were conducted by a specialist nurse at the Pulmonary Function Lab. These tests were carried out within 3 months leading to the surgical procedure. The pulmonary function parameters were carefully recorded and patients were categorised through spirometry into a 'normal', 'obstructive', or 'restrictive' group.

Patient demographics were also collected. These included: age, gender, smoking, underlying medical conditions, and type of surgery to be performed. Grades of the complexity of surgery (including major, intermediate, and minor) were collected according to the NICE surgical categorisation guidelines. The American Society of Anaesthesiologists (ASA) physical status classification system was used. Smoking history was classified into three categories: current smoker, ex-smoker, and non-smoker.

Clinical Outcomes

The focus of the audit was to determine whether junior doctors adhere to the 'pre-operative, generic investigations for adult elective surgery' guideline by appropriately referring patients scheduled for elective surgery to undergo pre-operative spirometry testing.

RESULTS

A total of 162 patients underwent spirometry after POYC referral during the 30-day study period. Out of these patients, 6 patients did not have any data on pre-operative spirometry result and hence were excluded. The final analysis included 156 patients. The mean age was 58 years (Table 1). The cohort was made up of 81 males (51.9%) and 75 females (48.1%). Eligible participants were scheduled to undergo a range of elective surgical procedures which were categorised into major (n=52, 33.3%), intermediate (n=50, 32.1%) and minor (n=54, 34.6%) according to the NICE classification (Figure 1).

As per the 'pre-operative generic investigations for adult elective surgery' guideline, spirometry testing was deemed unnecessary in 63.5% (n= 99) of patients

Table 1 Baseline Characteristics of patients

Demographics	Number (%)
Age, years	
Average Age	58
<20	4 (3%)
20-40	20 (13%)
40-60	48 (31%)
60-80	82 (53%)
>80	2 (1%)
Sex	
Male	81 (51.9%)
Female	75 (48.1%)
Smoking History	
Smoker	65 (41.7%)
Non Smoker	77 (49.4%)
Ex-Smoker	14 (9.0%)
Type of Surgery	
Major	52 (33.33%)
Intermediate	50 (32.1%)
Minor	54 (34.6%)

(Figure 2). The main reasons why spirometry was indicated in the remaining 36.5% of the study cohort were: ASA 3 or above (n=31, 54.3%), unable to climb two flights of stairs (n=17, 29.8%) or both (n=9, 15.8%) (Figure 3).

In the cohort of patients for whom spirometry testing was indicated, the results show a range of spirometry patterns. Specifically, we observed that 18 patients exhibited a normal spirometry pattern, while three had an obstructive pattern and 36 had a restrictive pattern. These findings suggest a diverse spectrum of pulmonary conditions within this subgroup of patients. Among the patients who had spirometry indicated, nine patients had asthma, 10 patients had chronic obstructive pulmonary disease (COPD), and three had obstructive sleep apnea (OSA).

In contrast, among the patients for whom spirometry was not indicated, a different set of spirometry patterns were identified. A total of 60 patients in this group showed a normal spirometry pattern. However, in this cohort, 37 patients had a restrictive spirometry pattern, and two had an obstructive pattern. While the patient cohort exhibited comorbidity, the focus was primarily on respiratory conditions. Furthermore, within the cohort where spirometry was not indicated, 37 patients had asthma and two patients had OSA. There were no COPD patients in this cohort.

Throughout the combined restrictive spirometry pattern cohort (n=75), two people were known to suffer from Interstitial Lung Disease (ILD) beforehand. The cohort's forced expiratory time (FET) was subsequently assessed. The results show that 15% (n=11) of the patients with a restrictive spirometry had an FET greater than 6 seconds (Table 2).

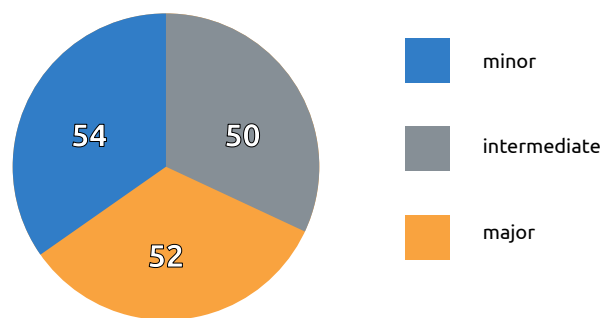


Figure 1 Distribution of surgical procedures according to NICE Surgical Categorisation

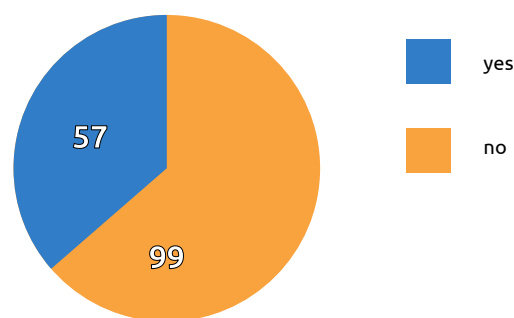


Figure 2 Indication of spirometry testing in our patient cohort

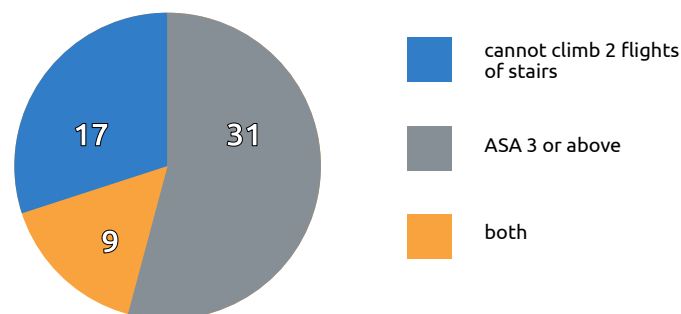


Figure 3 Pie chart depicting the indication for spirometry

Table 2 Combined Summary of Spirometry Results, Respiratory Conditions, and FET

Category	Subcategory	Spirometry Indicated	Spirometry NOT Indicated	Total
Spirometry Results	Normal	18	60	78
	Obstructive	3	2	5
	Restrictive	36	37	73
Restrictive (FET Analysis)	FET >6sec	-	-	11(15%)
	FET <6sec	-	-	62(86%)
Respiratory Conditions	Asthma	9	37	46
	COPD	10	0	10
	OSA	3	2	5

DISCUSSION

The audit on adherence to the 'pre-operative, generic investigations for adult elective surgery' guideline showed that a significant portion of the cohort studied did not undergo spirometry testing as per current local guidelines. Among the cohort for whom spirometry was indicated, the primary reasons included patients with an ASA classification of 3 or above, emphasizing a more comprehensive assessment for higher-risk individuals. Additionally, a significant portion of patients were indicated for spirometry due to their functional limitations, precisely an inability to climb two flights of stairs. However, it is important to note that junior doctors also referred patients for spirometry testing if they smoked or had an ASA of 1 or 2, which was not according to guidelines.

The potential overuse of pre-operative spirometry testing may be attributed to an absence of awareness among junior doctors about the existence and access to local guidelines. If physicians are not aware that these guidelines exist, there could be a tendency to default to a technique of examining all individuals preoperatively. One possible contributing element could be the absence of educational initiatives or lectures specifically aimed at addressing these guidelines.

A multifaceted approach is necessary to resolve these inappropriate investigation referrals. Executing curricula, for instance, by providing lectures, can enhance the understanding of pre-operative testing among junior physicians. Stressing the importance of critical thinking in applying such guidelines, encouraging continuous education, and promoting a culture of continuous learning can contribute to a more judicious use of guidelines and promote evidence-based decision-making.

The analysis of spirometry patterns among patients for whom testing was not initially indicated revealed a distinct set of results. It is important to note that 37 patients had a restrictive spirometry pattern despite spirometry not being deemed necessary according to guidelines.

The observation of a significant number of patients with restrictive patterns raises concerns about the accuracy of our spirometry test results. Assessment of these patients' FET showed that a large majority (85%) had an FET less than the recommended 6

SUMMARY BOX

- The audit on adherence to the 'pre-operative investigations for elective surgery' guideline found out that a significant portion of the cohort studied did not undergo spirometry testing as per local guidelines.
- Before elective surgery, adults should have pre-operative spirometry testing only if they cannot climb two flights of stairs, have an ASA of 3 or above, or if there are suspicions of significant cardiopulmonary comorbidity. It is crucial to consult with the POAC consultant prior to requesting the test.
- The possible excessive use of pre-operative spirometry testing could result from junior physicians lacking awareness of the current local guidelines and their accessibility.
- Implementing targeted educational programs for junior physicians can enhance awareness and understanding of such guidelines.

seconds. This could be explained by potentially incorrect patient technique and compliance, leading to a large amount of false positive restrictive results. None of the patients in the cohort had their results confirmed via referral for plethysmography. The discrepancy between the number of patients with an obstructive pattern and COPD patients can be further explained by, either patients having emphysema without an obstructive pattern on spirometry or, patients having been diagnosed as COPD and started on treatment prior to spirometry being performed.

Overusing pre-operative spirometry testing will affect health care services, overall effectiveness, and patient experience. First, this method can negatively influence healthcare services by contributing to longer waiting times. Unnecessary spirometry testing for people not satisfying guideline criteria can also result in ineffective resource appropriation. Additionally, the excess costs associated with conducting and interpreting unwarranted tests divert resources that could be utilized elsewhere within the health care system. Moreover, patients subjected to

unnecessary testing might experience increased stress, anxiety and longer waiting times.

The limitations of this audit are the following. The short duration of the audit may have influenced the ability to capture longitudinal variations over a prolonged period. The lack of information on patients who were not referred for spirometry testing restricts the understanding of the entire population. Future audits should consider longer timelines and include data on the whole population for more accurate findings.

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Treating severe Ig-E mediated Allergic Adult Asthmatics with Omalizumab outside the dosing table

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Introduction: According to the summary of product characteristics of omalizumab, patients whose weight and/or total IgE falls outside the dosing table are not eligible to receive omalizumab. In view of the absence of alternative biological agents for asthma in Malta at time of data collection, it was decided that such patients would receive the maximum recommended dose of 600mg every 2 weeks.

Methods: The aim of this study was to assess the safety, efficacy and tolerability of adult patients receiving omalizumab for asthma who did not fall within the dosing table and compare these factors to patients within the dosing table. All adult patients receiving omalizumab for more than one year were recruited. Data collection included demographic data, baseline weight, IgE levels, side-effects reported, number of exacerbations, hospitalizations and corticosteroids needed.

Results: Our cohort included 71 patients (mean age 48.8 ± 13.3 , 45% males). When comparing patients who received omalizumab according to the recommended dosing chart ($n=56$) versus those who did not ($n=15$), there was no statistical significance for treatment discontinuation ($p=0.79$). Mean baseline IgE was higher in the outside of dosing category ($p=0.001$). Mean total number of exacerbations since treatment initiation was significantly less for the outside of dosing category ($p=0.01$) as was the mean total number of systemic corticosteroid courses ($p=0.02$). There was no statistical significance in hospitalization rate ($p=0.09$).

Conclusions: Our results reaffirm our decision to treat severe IgE-mediated asthmatic patients with an IgE level and/or weight outside the dosing chart with the maximum recommended dose with good clinical outcomes and good safety and tolerability profiles.

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Omalizumab is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to free and membrane-bound immunoglobulin E (IgE) antibodies. It is the first biologic to have been approved internationally and is currently used globally for severe allergic asthma. It is indicated as an add-on therapy in patients with severe persistent allergic asthma who have positive reactivity to a perennial aero-allergen, elevated IgE level, reduced lung function and symptoms consistent with poor asthma control despite maximal treatment.^{1,2}

Dosing of omalizumab is calculated according to dose determination charts and is administered every 2 or 4 weeks depending on a patient's baseline IgE level and the patient's weight. According to the Summary of Products Characteristics (SPC) for omalizumab, the maximum recommended dose is 600mg every two weeks. If a patient's IgE level or body weight is outside the limits of the dosing table, omalizumab should not be prescribed.³

In view of the absence of availability of alternative biological agents for severe allergic asthma at our local hospital, it was decided that our patients in whom omalizumab was clinically indicated but fell outside the dosing table in view of the patient's elevated body weight and/or IgE level, and hence not eligible to receive the medication, they would still receive the maximal dose of 600mg every 2 weeks.

The aim of this study was to assess the safety, efficacy and tolerability of adult patients receiving omalizumab for severe allergic asthma who did not fall within the recommended dosing regime. The aim was to compare these factors to patients receiving omalizumab within the dosing table.

Our intention was not to compare participants asthma status pre- omalizumab treatment to their current status post- treatment, since patients that need biological therapy such as omalizumab already indicates that they have poor asthma control with recurrent exacerbations needing systemic corticosteroids and/or hospital admissions, on full maximal inhaler treatment with high dose inhaled corticosteroids and long-acting beta-2-agonists, +/- leukotriene receptor antagonists, and long-acting muscarinic antagonists as per the Global Initiative for Asthma (GINA) guidelines.⁴

MATERIAL AND METHODS

Omalizumab was approved and made available in Malta in 2012. Dosing of omalizumab is calculated according to dose determination chart as per the SPC depending on a patient's baseline IgE level and the patient's weight.

All adult patients over the age of 16 receiving omalizumab therapy for more than one year at our local hospital, Mater Dei Hospital (MDH), the only tertiary center in Malta, were recruited for this retrospective study. These patients had been consented for any future studies related to omalizumab that may be conducted on initiation of treatment. The study was approved by University of Malta Research Ethics Committee.

Data collection was carried out between January and December 2022. This was carried out during outpatient visits, using admission and discharge notes from iSOFT Clinical Manager and Electronic Case Summary (ECS), as well as the patients' files. Data collected included demographic data, omalizumab doses received, baseline weight and IgE levels, number of exacerbations treated at home, health center or needing hospital admission, and the number of times rescue medication was needed, as well as the number of oral corticosteroids (OCS), nebulizers, and/or antibiotics required. The term exacerbation was defined as worsening of patient's symptoms from the patient's usual baseline, necessitating an increase in the usual treatment.⁴

For the purpose of this study, once data collection was concluded, our patient cohort was divided into two groups; the group that fell outside the dosing table as per the SPC due to elevated body weight and/or IgE level (who were receiving the maximum recommended dose of 600mg every 2 weeks), and the other cohort that fell within the dosing table as per the SPC (these patients were being treated and dosed according to the dosing table).

Data analysis was carried out using SPSS Statistics Version 29. Student t-test was used to compare numerical variables while a Chi-squared test was used to compare categorical variables. A p value ≤ 0.05 was taken to be statistically significant.

RESULTS

Our cohort included 71 patients (mean age at the start of treatment 48.8 ± 13.3) who had been receiving omalizumab for more than 1 year. The age range was between 16 to 74 years old, with 32 patients (45%) being male. The mean baseline IgE level was 613.2 ± 609.2 IU/ml, and the mean weight was 79.4 ± 16.7 kg. Of these, 17 patients (23.9%) had omalizumab stopped throughout the course of the treatment: 12 patients (16.9%) due to treatment inefficacy, 2 patients (2.8%) due to intolerable side-effects and 3 patients (4.2%) due to non-asthma related mortality (Table 1). Intolerable side-effects included severe myalgias and arthralgias.

Table 2 compares the demographic data and treatment discontinuation of patients receiving omalizumab treatment outside ($n = 15$) versus those within ($n = 56$) the dosing table. 4 (26.7%) patients had their treatment stopped in the outside of dosing category: 2 (13.3%) patients due to treatment inefficacy, 1 (6.7%) due to intolerable side-effects and 1 (6.7%) due to unrelated death. In the other category 13 (23.2%) patients had their treatment stopped: 10 (17.9%) patients due to treatment inefficacy, 1 (7.7%) patient due to side-effects and 2 (3.6%) patients due to mortality. There was no statistical significance between both groups with respect to treatment discontinuation ($p = 0.79$).

Following elimination of patients in whom treatment was stopped, 11 patients fell outside the dosing range (mean age 46.9 ± 12.3) versus 43 patients (mean age 48.1 ± 13) within the dosing table. Statistically, males predominated in the outside of dosing category ($p = 0.026$). The mean baseline IgE was higher in the outside of dosing category (1653.3 ± 769.8 IU/ml) compared to the other category (394 ± 261.2 IU/ml). This comparison was statistically significant ($p = 0.001$) (Table 3).

When comparing patients receiving omalizumab within the dosing table to those outside, the mean total number of exacerbations since initiation of treatment (1.1 ± 1.58) was significantly less for the outside of dosing category ($p = 0.01$). Similarly, the mean total number of OCS courses was less (0.63 ± 1.21 ; $p = 0.02$). No statistical significance was noted in the total number of hospitalizations since initiation

Table 1 Demographic data and treatment discontinuation of total cohort of participants

Demographic data - total cohort (n=71)	
Mean age at start of treatment ($\pm$ SD), years	48.8 (13.3)
Age range, years	16 -74
Gender - males (%)	32 (45)
Mean baseline IgE ($\pm$ SD), IU/ml	613.2 (609.2)
Mean weight ($\pm$ SD), kg	79.4 (16.7)
Treatment discontinuation	
Treatment stopped, n (%)	17 (23.9)
Treatment inefficacy, n (%)	12 (16.9)
Intolerable side-effects, n (%)	2 (2.8)
Unrelated death, n (%)	3 (4.2)

Table 2 Comparison of demographic data and treatment discontinuation of all patients receiving omalizumab treatment outside versus those within dosing table

	Outside dosing range (n=15)	Within dosing range (n=56)	p-value
Demographic data			
Mean age at start of treatment ($\pm$ SD) years	49.9 (12.5)	48.5 (13.6)	0.56
Age range, years	28 - 67	16 - 74	/
Gender - males (%)	12 (80)	22 (39.2)	0.005
Mean baseline IgE ($\pm$ SD), IU/ml	1533.7 (684.7)	366.7 (245)	<0.001
Mean weight ($\pm$ SD), kg	82 (20.4)	78.7 (15.7)	0.56
Treatment discontinuation			
Treatment stopped, n (%)	4 (26.7)	13 (23.2)	0.79
Treatment inefficacy, n (%)	2 (13.3)	10 (17.9)	0.3
Intolerable side-effects, n (%)	1 (6.7)	1 (7.7)	0.82
Unrelated death, n (%)	1 (6.7)	2 (3.6)	0.66

of treatment ($p = 0.09$) though this was less in the outside of dosing category (Table 4).

DISCUSSION

Allergic asthma accounts for approximately 70% of asthma, and IgE is essential in its inflammatory process. Omalizumab blocks the binding of IgE to its high affinity receptor on the surface of mast cells and basophils. Consequently, the release of inflammatory mediators is inhibited.^{5,6}

Clinical studies have demonstrated that omalizumab reduces exacerbations during peak viral seasons with favourable outcomes in several randomized control trials (RCTs). In 2014, a review evaluating 25 RCTs in patients with moderate to severe allergic asthma found that omalizumab compared with placebo reduced asthma exacerbations by approximately 25%, reduced hospitalization rates, and allowed reduction of ICS doses^{5,6}. In addition, a meta-analysis

evaluating 86 observational studies and publications on real-world data on omalizumab, from January 2005 to October 2018, on treatment response, lung function, exacerbations, oral corticosteroid use, patient reported outcomes, health care utilisation, and school/work absence at 4, 6, and 12 months after treatment, found improvement across the board, confirming and complementing the efficacy data of such RCTs.⁷

Our retrospective study is the first of its kind to be carried out in our main local hospital and to date there is minimal literature on omalizumab treatment in asthmatic patients whose weight and/or IgE levels fall outside the dosing table. Patients who have a higher weight or IgE than that specified on the omalizumab dosing table are not usually eligible to receive such treatment in other countries.

The mean weight of our cohort who did not fall within the dosing table was still within range, suggesting that most patients would not have been eligible for omalizumab in view of the very raised IgE level, rather than the increased weight. Once removing those patients in whom treatment was stopped, results showed that males were more likely to fall outside of the dosing chart. We speculate that males are more likely to have a higher BMI, which would be in keeping with the WHO Regional Obesity Report 2022, which reports Malta as being one of the highest countries with an obese population including adults (predominantly males) and children.⁸

The original omalizumab dosing table when it was first approved had upper bodyweight and IgE limits of 150 kg and 700 IU/mL respectively. A study carried out by Kornmann et al⁹ assessed the safety of omalizumab in patients with IgE/bodyweight combinations above those in the original dosing

Table 3 Demographic data of patients in whom omalizumab was continued (removing those whose treatment was stopped)

	Outside dosing range (n=11)	Within dosing range (n=43)	p-value
Mean age at start of treatment (±SD), years	46.9 (12.3)	48.1 (13)	0.78
Age range, years	28 - 62	16 - 68	/
Gender - males (%)	9 (81.8)	19 (44.2)	0.026
Mean baseline IgE (±SD), IU/ml	1653.3 (769.8)	394 (261.2)	0.001
Mean weight (±SD), kg	81.2 (19.3)	79.8 (16.3)	0.82

Table 4 Comparison of asthma outcomes in patients receiving omalizumab outside versus those within the dosing table.

	Outside dosing range (n=11)	Within dosing range (n=43)	p-value
Mean duration of treatment (±SD), years	5.45 (3.14)	6.4 (3.03)	0.4
Asthma outcomes			
Mean total number of exacerbations since start of treatment, n (±SD)	1.1 (1.58)	3.3 (4.7)	0.01
Mean total number of hospitalizations since start of treatment, n (±SD)	0.36 (0.67)	1.1 (2.6)	0.09
Mean total number of OCS courses since start of treatment, n (±SD)	0.63 (1.21)	2.51 (4.47)	0.02

table. Results overall showed 69 adverse events, none of them serious, reported by 26 patients. Analysis of laboratory measurements, vital signs and ECG data revealed no adverse findings of clinical relevance. The safety and pharmacokinetic/dynamic findings from this were consistent and supported the extension of the omalizumab dosing table to include those patients with higher IgE/ bodyweight combinations.⁹ The dosing table was in fact extended to the current one being used nowadays to accommodate a higher IgE level.

The second reason for patients falling outside the dosing table is due to an elevated IgE level of more than 1500 IU/ml, as was the case in most of our patients. This implies that patients who are more likely to benefit from omalizumab improves asthma sufficiently to warrant a decrease in corticosteroid requirements, despite the patients falling outside the dosing table. These findings emphasize the clinical effectiveness of omalizumab in this cohort of patients.¹²

One may speculate that patients outside the dosing table might actually be underdosed, but our findings show that they still did comparably well in terms of exacerbation rates and number of steroid courses, as suggested by the statistically significant p values. It is known that some patients respond better than others when given omalizumab treatment. Given that only 11 patients were within the outside of dosing category, one could speculate that this could be by coincidence that this group responded better than the other cohort.

Limitations of the study included a small sample size from a single center, although representative of the whole Maltese population. There was no selection bias as all patients receiving omalizumab for more than 1 year were included in the study. However, recall bias was a limitation to this study as data was collected retrospectively. Patients could have omitted, under- or

SUMMARY BOX

- Mean total number of exacerbations was less for the outside of dosing category as was the mean total number of systemic corticosteroid courses.
- Omalizumab may be used safely outside the dosing table based on our results.
- Our results call for the need for further larger multicenter studies to confirm our findings, with the aim of potentially further expanding the dosing table.

overestimated their exacerbations and symptoms, as well as steroid courses, for which they may not have been recorded in the medical notes including health center/GP visits and self-medication. Another limitation was that parameters including lung function, eosinophils, FENO, duration of asthma diagnosis, co-morbidities such as ENT pathologies, urticaria as well as asthma control questionnaires/ tests were not measured, since it is a retrospective study, therefore we could not compare both groups before treatment initiation.

Despite our cohort in the outside of dosing category is a small one, these results reaffirm the decision to treat severe IgE-mediated asthmatic adult patients with an IgE level and/or weight outside the dosing chart with the maximum recommended dose. Our study calls for the need for further larger multicenter studies to confirm that severe IgE-mediated allergic asthmatics may still receive omalizumab at the maximum recommended dose with good clinical outcomes and tolerability despite falling outside the recommended dosing table especially when alternative biologics other than omalizumab are not available, not clinically indicated or are contra-indicated. In addition, further research into the subject should include more diverse patient populations whilst investigating other biologics for severe allergic asthma.

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Recurrence rate and prognostic factors in laparoscopically resected colorectal malignancies

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Background: There are limited data on the 2-year recurrence rate and prognostic factors for recurrence in laparoscopically resected colorectal malignancies. The aim of this study was to determine the 2-year recurrence rate and prognostic factors for recurrence of colorectal carcinoma in patients who underwent elective laparoscopic colectomy.

Methods: Data from patients with colorectal carcinoma who had undergone elective laparoscopic colectomy in HPUSM were retrospectively reviewed. All patients who had a follow-up of at least 24 months and traceable records were included in the study, whereas patients with concurrent pathologies were excluded. Patients' clinicopathologic data and follow-up data for 2 years after surgery were examined. Cox proportional hazard regression was used to determine the possible prognostic factors for colorectal cancer recurrence.

Results: Of 40 patients, five patients had recurrence within 2 years after surgery, representing a recurrence rate of 12.5%. The average time to recurrence was 21.2 months, with the earliest recurrence occurring on the 15th day after surgery. Postoperative serum level of carcinoembryonic antigen (CEA) was the prognostic factor for colorectal cancer recurrence [hazard ratio (HR): 1.05, 95% CI: 1.00, 1.10, $p = 0.04$].

Conclusion: The results of our study showed that the 2-year recurrence rate in this study setting was 12.5%. The significant prognostic factor for recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy was postoperative CEA levels.

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Colorectal carcinoma is any malignant growth that develops in any part of the colon (from the appendix to the anorectal junction). It is one of the most common cancers worldwide and the second most common in Malaysia with an incidence rate of 21.3 per 100,000 population.¹ Locally, the majority of colorectal cancers are diagnosed at stage III or IV and account for 63.5% of newly diagnosed cases.²

Surgical resection is considered the primary treatment modality in most cases, and curative outcomes can be achieved with appropriate adjuvant therapy. With regard to oncologically meaningful resection, the surgeon aims for complete removal of the primary tumour, its main vascular pedicle, and the lymphatic drainage basin of the affected colonic segment.³ Resection can be performed through either the "modern" laparoscopic or the "conventional" open approach.

After primary curative resection, the incidence of colorectal cancer recurrence ranges from 10% to 30%, with the highest recurrence rate reported for stage III.⁴⁻⁷ In the majority of cases, approximately 80%, recurrence occurs within the first two years after resection, underscoring the need for more frequent follow-up during this period.^{7,8}

Based on the latest data from the Malaysian National Cancer Registry, 70.8% of colorectal cancer cases were treated by surgical resection between 2008 and 2013, while 88.4% of patients diagnosed with stage III colorectal cancer were treated surgically.¹ Of these patients who underwent surgical resection, approximately 16% underwent laparoscopic colectomy.¹ Laparoscopic procedures have yielded better outcomes, such as less postoperative pain, faster return of bowel function, and subsequently shorter hospital stays and faster return to work. These advantages make the laparoscopic approach more favourable compared to open surgery.⁹ Here at Hospital Pakar Universiti Sains Malaysia (HPUSM), one of Malaysia's largest teaching hospitals, laparoscopic surgery has been performed since the mid-1990s, but laparoscopic colectomy for colorectal cancer has only recently become the method of choice. Because laparoscopic resection of colorectal malignancies is a technically challenging procedure, the learning curve for the inexperienced surgical team is steep.¹⁰ Consequently, short- and long-term

outcomes can be greatly affected in this process of acquiring new skills.

Currently, there are no data on our progress regarding the oncologic outcome of laparoscopically resected colorectal cancer. It is possible that more available information may help enforce the laparoscopic approach to resection of colorectal carcinomas. Perhaps they can help us identify any shortcomings in our perioperative management and postoperative follow-up. We felt it necessary to report our findings on the recurrence rate and prognostic factors in laparoscopically resected colorectal malignancies. This study examined the data of patients with colorectal carcinoma who underwent laparoscopic colectomy at HPUSM in Malaysia from January 2007 to December 2014. This study also investigated the 2-year recurrence rate and possible prognostic factors for colorectal cancer recurrence in patients who underwent elective laparoscopic colectomy.

METHODS

Participants

This is a retrospective observational cohort study of patients diagnosed with colorectal cancer who underwent elective laparoscopic colectomy at Hospital Pakar Universiti Sains Malaysia (HPUSM), Malaysia from January 2007 to December 2014. During the study period, 53 patients with colorectal carcinoma underwent elective laparoscopic colectomy sampled from the HPUSM hospital surgical records. Forty patients met the eligibility criteria. Inclusion criteria for this study included patients diagnosed with colorectal cancer who underwent elective laparoscopic colectomy during the study period and had a postoperative follow-up of at least 2 years. Patients who missed follow-up or had concurrent pathology were excluded. Ethical approval was granted by the Ethics Committee of Universiti Sains Malaysia (USM) in Kelantan, Malaysia (reference number: USM/JEPeM/17010059).

Data collection

Secondary data were collected as part of this study. The list of patients who underwent elective laparoscopic colectomy for colorectal cancer at HPUSM Hospital during the eight years from

January 1, 2007 to December 31, 2014 was obtained from the operating room census books. Patient case notes and the hospital's patient information database were reviewed in detail to obtain clinical data and other information needed for the study. All required information was entered into the data collection form to avoid bias. Variables required for the study included patient demographics, serum carcinoembryonic antigen (CEA) level before and after surgery, preoperative and postoperative diagnosis and cancer staging, histopathology report of the resected specimen, time interval between surgery and initiation of adjuvant therapy, and presence of evidence of recurrence and mortality.

Data analysis

Descriptive statistics (frequency and percentage for categorical variables; mean and standard deviation for numerical variables; median and IQR for skewed variables), Kaplan-Meier analysis, and proportional Cox hazard regression were used as methods of analysis. Kaplan-Meier analysis was used to determine the median survival of patients diagnosed with colorectal cancer who underwent elective laparoscopic colectomy. Cox proportional hazards regression was used to identify potential prognostic factors for colorectal cancer recurrence. Statistical analysis was performed using SPSS/Win software (version 22, SPSS, Inc., Chicago, IL, USA). The significance threshold was set at 0.05.

RESULTS

Patient demographic and clinical characteristics

Of the 53 patients who underwent elective laparoscopic colectomy for colorectal cancer, 40 patients met the inclusion and exclusion criteria and were enrolled in the study. Thirteen patients were excluded because follow-up was not possible after 1 year ($n = 9$) and data were incomplete or missing ($n = 4$). **Table 1** shows the characteristics of patients with colorectal carcinoma who underwent elective laparoscopic colectomy. The mean age of patients was 61.3 years. Approximately 55% of patients had co-morbidities, including combinations of diabetes, hypertension, and ischaemic heart disease, while 45% had no co-morbidities. The pre-operative stage was predominantly Stage II and III.

Table 1 Characteristics of patients with colorectal cancer who underwent elective laparoscopic colectomy ($n = 40$)

Variables		
Age (years), mean (SD)	at diagnosis	61.3 (10.90)
	at surgery	61.5 (10.89)
Gender, n (%)	Male	22 (55.0)
	Female	18 (45.0)
Race, n (%)	Malay	36 (90.0%)
	Chinese	4 (10.0%)
Co-morbidities, n (%)	Diabetes	4 (10.0%)
	Hypertension	7 (17.5%)
	Ischaemic heart disease	2 (5.0%)
	Diabetes and hypertension	8 (20.0%)
	Diabetes and ischaemic heart disease	1 (2.5)
	None	18 (45.0)
Preoperative clinical staging, n (%)	Stage I	5 (12.5)
	Stage II	12 (30.0)
	Stage III	13 (32.5)
	Stage IV	9 (22.5)
	Unstaged	1 (2.5)
Postoperative clinical staging, n (%)	Stage I	4 (10.0)
	Stage II	14 (35.0)
	Stage III	12 (30.0)
	Stage IV	10 (25.0)
Site of tumour, n (%)	Caecum	1 (2.5)
	Ascending colon	0 (0.0)
	Transverse colon	1 (2.5)
	Descending colon	1 (2.5)
	Sigmoid colon	6 (15.0)
	Rectosigmoid colon	13 (32.5)
	Rectum	16 (40.0)
	Anorectum	2 (5.0)
Presence of synchronous tumour, n (%)	2 (5.0)	
Pre-operative serum CEA, median (IQR)*	9.0 (34.1)	
Post-operative serum CEA, median (IQR)**	2.9 (3.2)	

SD, standard deviation; IQR, interquartile range; CEA, carcinoembryonic antigen

*Serum carcinoembryonic antigen (CEA) levels were taken for 39 patients.

**Serum CEA levels were taken for 37 patients. Two of these patients succumbed 1 month post-operatively; one due to complication of ventilator-acquired pneumonia as a sequela of anastomotic leak and another due to respiratory failure secondary to lung metastases. The remaining patient had progressive disease and succumbed to disease progression of liver and lung metastases, at 6 months post-surgery.

A total of 10 cases underwent laparoscopic surgery from 2007 to 2011, and a total of 30 cases underwent laparoscopic surgery from 2012 to 2014 (**Supplementary Table 1**). The histopathologic characteristics of patients with colorectal carcinoma who underwent elective laparoscopic colectomy are described in **Supplementary Table 2**. Adjuvant treatment of patients with colorectal carcinoma who underwent elective laparoscopic colectomy is described in **Supplementary Table 3**.

Five patients experienced disease recurrence within 2 years after surgery, and the 2-year recurrence rate was 12.5%. The median time to disease recurrence was 21.2 months (SD 3.70) (**Supplementary Table 4**). When plotted on the Kaplan-Meier diagram (**Figure 1**), no median recurrence time could be determined. The earliest case of recurrence occurred 15 months after surgery. This patient was at stage III.

Prognostic factors for recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy

Table 2 shows simple Cox regression analyses on the potential prognostic factors for colorectal cancer recurrence in patients who underwent elective laparoscopic colectomy. Postoperative CEA level was a significant prognostic factor for colorectal cancer recurrence. Patients with a higher postoperative CEA score were at higher risk for recurrence of

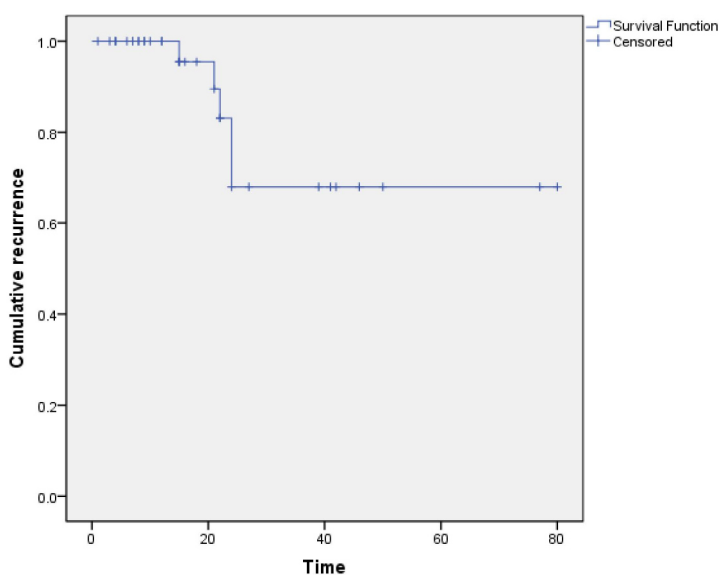


Figure 1 Kaplan Meier Curve for cumulative recurrence of laparoscopic resected colorectal carcinomas

Table 2 Prognostic factors for recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy from simple Cox regression analyses (n = 40). ^aCrude Hazard ratio (95% confidence interval)

Variables	Regression coefficient (b)	Crude HR (95% CI) ^a	Wald stats (df)	p value
Gender				
Male	0.00	1.00		
Female	0.77	2.17 (0.36–3.06)	0.72 (1)	0.398
Age at diagnosis	0.04	0.96 (0.84–1.10)	0.32 (1)	0.570
Co-morbidities				
None	0.00	1.00		
1	0.41	1.51 (0.21–10.78)	0.17 (1)	0.681
2	0.19	1.21 (0.11–13.39)	0.03 (1)	0.875
CEA				
Pre-operative	0.01	1.00 (0.99–1.02)	0.16 (1)	0.692
Post-operative	0.05	1.05 (1.00–1.10)	4.24 (1)	0.040
Final T stage				
T1	0.00	1.00		
T2	-0.71	0.49 (0.03–8.01)	0.25 (1)	0.618
T3	-0.63	0.53 (0.05–5.97)	0.26 (1)	0.611
T4	-0.79	0.45 (0.03–7.30)	0.31 (1)	0.576
Final N stage				
N0	0.00	1.00		
N1	2.30	9.94 (0.89–111.32)	3.47 (1)	0.062
N2	1.54	4.68 (0.42–51.65)	1.59 (1)	0.208
Final M stage				
M0	0.00	1.00		
M1	0.59	1.80 (0.30–10.76)	0.41 (1)	0.521
Lymph node harvested	-0.07	0.93 (0.80–1.09)	0.76 (1)	0.383
Lymphovascular invasion				
No	0.00	1.00		
Yes	1.14	3.14 (0.44–22.48)	1.30 (1)	0.255
Not mentioned	1.59	4.88 (0.44–54.40)	1.66 (1)	0.197
Perineural invasion				
No	0.00	1.00		
Yes	0.93	2.52 (0.35–18.08)	0.85 (1)	0.357
Not mentioned	0.10	1.10 (0.10–12.18)	0.01 (1)	0.938
Adjuvant therapy				
None	0.00	1.00		
Chemotherapy	10.37	0.69 (0.08–6.72)	0.04 (1)	0.947
Chemo-radiotherapy	11.29	0.46 (0.03–8.12)	0.05 (1)	0.942

laparoscopically resected colorectal cancer [hazard ratio (HR): 1.05, 95% CI: 1.00, 1.10, $p = 0.04$]. Gender, age at diagnosis, presence of one or more concomitant diseases, preoperative CEA level, final T, N, or M stage, number of lymph nodes harvested, presence of lymphovascular or perineural invasion, and presence of adjuvant therapy were not significant prognostic factors for colorectal cancer recurrence.

DISCUSSION

The present study investigated the 2-year recurrence rate and the possible prognostic factors for recurrence of colorectal carcinoma in patients who underwent elective laparoscopic colectomy. In our study, the local 2-year recurrence rate was 6.0%. The results were not significantly different from those of the Norfolk Surgical Group study in Virginia, which examined the oncologic treatment outcomes of laparoscopic colectomy.¹¹ Between June 1992 and September 1993, 39 laparoscopic-assisted colectomies were performed in patients with colorectal carcinoma. In this study, the 2-year recurrence rate was 9%.¹¹ In the review of long-term outcomes of laparoscopic-assisted colectomy for colorectal carcinoma performed in Japan between January 1993 and September 1999, the recurrence rate after a median follow-up of 58 months was 12.1% in patients with stage II or III.¹²

We examined several possible prognostic factors that might influence the recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy, including sex, age at diagnosis, presence of one or more concomitant diseases, CEA level, end-stage T, N, or M, number of lymph nodes harvested, presence of lymphatic or perineural invasion, and presence of adjuvant therapy.

Our study showed that postoperative CEA level is a significant prognostic factor for colorectal cancer recurrence. Patients with a higher serum CEA level 3 months after surgery have a higher risk of recurrence. In this study, preoperative CEA level was not a significant prognostic factor for colorectal cancer recurrence. Serum CEA is a useful marker and tool for preoperative prognosis and postoperative follow-up. Because of its relatively low sensitivity and specificity, it is less useful for diagnosis in

asymptomatic patients.¹³ In the past, a higher preoperative serum CEA level has been shown to be significantly associated with disease recurrence and to have a negative impact on survival as an independent prognostic factor when the level is ≥ 5 ng/mL.^{14,15} In our study, univariate analysis identified postoperative CEA as a significant prognostic factor for colorectal cancer recurrence and survival. While further multivariate studies may be needed to confirm its independent role, these findings suggest that postoperative CEA remains a critical reference for monitoring. In the era of precision and personalized medicine, this serum biomarker may guide decisions regarding adjuvant chemotherapy or targeted therapy, depending on patient response.

Other factors studied, such as sex, age at diagnosis, presence of one or more comorbidities, end-stage T, N, or M, number of lymph nodes harvested, presence of lymphatic or perineural invasion, and presence of adjuvant therapy, were not significant prognostic factors for colorectal cancer recurrence.

Diabetes mellitus has been reported to be not only a factor that may increase the risk of colorectal cancer occurrence, but also poorer disease-free survival and higher all-cause mortality.¹⁶ However, those who underwent laparoscopic colorectal resection had better and earlier recovery of the immune level such as lower C-reactive protein, lymphocyte, neutrophil and natural killer cell that enhance the recovery peri-operatively.²⁸ Interestingly, the elderly patients who underwent this approach shown better physical and quality of life changes hence improved recovery peri-operatively.³⁰ In our study, we found that two of the five patients with recurrence were diabetic, while only four of the 12 patients had a poor postoperative outcome either in terms of morbidity or recurrence. This leaves seven diabetic patients who did not experience recurrence or mortality within the 24-month follow-up period of this study.

Patients at an advanced stage have a higher risk of recurrence, ranging from 11 to 61% in stage II patients and from 32 to 88% in stage III patients.⁷ Locoregional recurrence was also more likely in rectal cancer than in colon cancer, possibly because it is more difficult to achieve a wide margin near the pelvis while preserving important structures.¹⁷ In addition, recurrence occurred ranging in 14.8% at 2 years follow up and 2-year survival rate

was noted to be 87.7% among the study.²⁹ In our study, we found that most cases of recurrence occurred preoperatively at either stage III or IV, and four of the five patients had rectal cancer. In local context, by knowing these factors, we can learn, improve and identify modifiable prognostic factors such as comorbidities, lifestyles and stage at diagnosis that can be improve and give better peri-operatively hence give better prognosis and survival of this cohort colorectal malignancies. Awareness, early screening and educational initiatives will be much driven by these findings especially improvement in advanced minimally invasive approach and current peri-operatively approach.

Under the microscope, there are several factors that may indicate a worse prognosis or a higher risk of recurrence. This seemingly exhaustive list includes a lower nodal take ¹⁸, the histologic type of tumor, and patterns of lymphatic, vascular, or perineural invasion. The factors of particular interest to us were nodal sampling because, according to some authors, it reflects the oncologic quality of surgery and has an impact on oncologic outcome.¹⁸⁻²² In our study, among patients with recurrent disease, only two patients had at least 12 lymph nodes sampled.

The increased risk of an unfavorable outcome in the presence of perineural invasion and lymphatic invasion is well known but still underappreciated, as pointed out by Schneider and Langner ²³ in a review of prognostic stratification of colorectal cancer patients. In our study, the presence or absence of perineural invasion was not reported in 11 patients, whereas the status of lymphatic invasion was not reported in two patients. Of our patients who had recurrence, only two had both lymphovascular and perineural invasion, whereas one patient had neither.

Postoperative adjuvant therapy for colorectal cancer has been shown to improve outcomes, although opinions differ on the optimal time to start adjuvant therapy in different studies ^{15,24-27}. A meta-analysis found that adjuvant therapy started after 8 weeks was associated with worse overall outcome but not with lower recurrence-free survival.²⁴ Unfortunately, up to 70% of our patients, including all who developed recurrence, received adjuvant therapy, with a median time to initiation of therapy of 16.5 weeks (SD 14.88). Of the patients with recurrent

SUMMARY BOX

What is known about the subject

- One of the commonly studied endpoints of oncologic treatment outcome is the recurrence rate which, in colorectal cancer occurs most commonly within the first 2 years post resection.
- It is possible that more available information may help enforce the laparoscopic approach to resection of colorectal carcinomas. Perhaps they can help us identify any shortcomings in our perioperative management and postoperative follow-up.

New findings

- The recurrence rate of 12.5% for laparoscopically resected colorectal cancers done in Hospital Pakar Universiti Sains Malaysia (HPUSM) is comparable to recurrence rates reported in studies done internationally.
- A higher CEA level taken during the first follow-up clinic visit suggests a higher risk for recurrence and thus, may be used as an early indicator for recurrence.

disease, those with stage II and III underwent chemoradiotherapy, whereas those with stage IV received chemotherapy only. The duration of initiation of adjuvant therapy varied widely among these patients, ranging from 4 to 20 weeks. Possible reasons for such a delay in the start of adjuvant therapy include a gap in available oncology services and patient utilization, as well as reluctance or apprehension of patients and/or their family members to undergo adjuvant therapy.

Recent technology of minimally invasive approach for these colorectal malignancies such as robotic assisted surgery, usage of indocyanine green, synchronous resection of metastasis, usage of artificial intelligence and others had improved the surgical and oncological outcomes for patients.³¹⁻³⁵

Some limitations were noted in this study. This study has the usual limitations of a retrospective study. Four patients were no longer in follow-up after one year, and records for nine patients were either lost or could

not be located. The oncologic treatment outcome of colectomy for colorectal cancer is often measured by recurrence rates and 5-year disease-free survival. However, because laparoscopic colectomy is still in its infancy in our setting, we chose to study it for a minimum of 2 years. We advocate a prospective study with a larger number of patients to examine the results of long-term follow-up. This will provide us with an evidence-based outcome and help us in the management of colorectal carcinoma in patients who have undergone elective laparoscopic colectomy. In addition, future research directions that can be recommend such as improve quality of life, optimize of comorbidities, develop awareness and screening of this colorectal malignancies. In addition, study on tumor biology profiling besides depend on CEA that neither specific nor sensitive testing.

CONCLUSION

In conclusion, we found the recurrence rate of 12.5% for laparoscopically resected colorectal cancers done in HPUSM is comparable to recurrence rates reported in studies done internationally. This suggests that laparoscopic colectomy for colorectal cancers can be safe in the early stages of implementation under guidance of surgeons trained in the colorectal subspecialty. A higher CEA level taken during the first follow-up clinic visit suggests a higher risk for recurrence and thus, may be used as an early indicator for recurrence. As we catch on with the rising trend of minimally invasive surgery, continued effort towards self-audit and research is warranted to improve our surgical outcomes.

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Identification of Fetal Intrauterine Growth Restriction in Pregnancy-Induced Hypertension Women in Saudi Arabia

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Introduction: There is evidence that intrauterine growth restriction (IUGR) has negative effects on pregnancy. Placental dysfunction, which limits foetal growth, is intimately related to pregnancy-induced hypertension. This study aims to identify the IUGR in women with pregnancy-induced hypertension.

Methods: This cross-sectional study, which was done at the Obstetric Department of the Maternity and Children Hospital (MCH) Sakaka, Aljouf, Saudi Arabia, between January 2021 and January 2022, included 162 women with pregnancy-induced hypertension (PIH). Whether nulliparous or multiparous, all of the PIH women were between the ages of 16 and 45. We observed IUGR and outcomes in accordance with the criteria listed in the operational definition. Clinical examinations, patient data files, and ultrasound reports were used to collect the data.

Results: Of these, 105 (64.8%) had foetal detected intrauterine growth restriction, which included low Apgar scores of 19.3%, abortions at 11.4%, low birth weights at 19.3%, preterm births at 20%, and stillbirths at 13.3%. According to our findings, the mean SD values for the population as a whole were 38.95 ± 8.92 , 33.73 ± 6.92 , 3.00 ± 2.0 , 4.91 ± 1.52 , $1,811 \pm 3.32$ and 4.21 ± 1.21 for the maternal age, gestational age, duration of disease (weeks), baby weight (grams), and Apgar score, respectively. The relationship of stillbirth in PIH women to maternal age, gestational age, and parity is 89%, 88.8%, 86.6%, 72.7% and 84.2%, 88% and 87.6%, 85% at considered ($p = 0.00$), ($p = 0.05$) and ($p=0.00$), respectively.

Conclusion: The frequency of intrauterine growth restriction (IUGR) in patients with PIH was found to be 64.8%. IUGR is frequently a complication of hypertensive disorders during pregnancy.

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The second most frequent medical condition found during pregnancy is hypertension, which, combined with bleeding and infection, significantly increases maternal complications and death.¹ Pregnancy-induced hypertension (PIH), a significant cause of maternal and neonatal morbidity and mortality, has virtually disappeared from the clinical landscape in developed countries thanks to better prenatal care and rapid medication.² However, it remains a significant obstetric issue in developing nations like ours and among the rural populace, and its consequences are to blame for the majority of PIH mortality.³ Pregnancy-related hypertension has an impact on the outcome of the foetus and is linked to intrauterine death, low birth weight, and a higher risk of admission to the neonatal intensive care unit. It was discovered to be the main reason for stillbirth in a hospital-based study from MCH Sakaka, Aljouf, Saudi Arabia. While the cause of hypertensive disorders of pregnancy is yet unknown, the rate of virulence from hypertension during pregnancy is significantly more in underdeveloped countries than in the developed world.⁴ It is frequently believed that PIH and unexplained intrauterine growth restriction are connected to placental insufficiency and intimately linked to placental malfunction, which causes foetal growth restriction. Foetuses with birth weights below the 10th percentile for gestational age are said to have intrauterine growth restriction (IUGR).⁵ Intrauterine growth restriction is thought to affect 5% of pregnant women in general, and it affects 28% of pregnant women in PIH. Low Apgar scores (19%), abortion (11%), low birth weight (31%), preterm birth (2%), stillbirth (10%), neonatal morbidities and deaths, and even long-term effects on children are all caused by IUGR.⁶ Reducing prenatal and neonatal problems, mortality, and morbidity is facilitated by early identification of intrauterine growth limitations.⁵ Hence, the aim of our study is to the assessment of the IUGR in pregnancy-induced hypertension women.

MATERIAL AND METHODS

The Maternity and Children Hospital (MCH) Sakaka, Aljouf, Saudi Arabia, received 162 pregnant women between January 2021 and January 2022 for this cross-sectional study. all pregnant women between the ages of 16 and 45, whether nulliparous or multiparous and were recruited for the study after

receiving verbal consent. All of the PIH patients underwent IUGR and outcome evaluations in accordance with the operational definition's criteria (PIH= after 20 weeks of pregnancy, blood pressure greater than 140/90 measured twice, more than six hours apart, without any evidence of protein in the urine, IUGR is defined as a weight below the 10th percentile for gestational age as seen on ultrasonography. and Apgar score was below 6 at 5 minutes, Babies who were born with low birth weights typically weighed less than 2,500 grams, preterm birth: the delivery of a child before 37 weeks of pregnancy, and Stillbirth: the delivery of a dead child after 24 weeks of pregnancy). By means of clinical examinations and ultrasound, we evaluated each individual. The data was gathered using a pre-made proforma. Considering that there are 162 individuals with pregnancy-induced hypertension, the lowest prevalence of IUGR in PIH is 28%12 d=7%. Women who were expecting were not included, as were those who had ischemic heart disease, connective tissue/autoimmune illnesses, or known chronic renal disease. SPSS version 22.00 was used to analyze the data. The frequency and percentage were calculated taking into account the following factors: IUGR, PIH findings, parity, length of illness, mode of delivery, and maternal and gestational age. Maternal and gestational age, as well as the length of the disease, were determined using the mean and standard deviation (SD). The following characteristics were stratified: maternal and gestational age, mode of birth (cesarean section or vaginal delivery), parity, and length of the disease in order to see their effects on the outcome and manage effect modifiers. Categorical variables were subjected to the post-stratification chi-square test at a 95% confidence level, and a p-value of 0.05 was deemed statistically significant. The University of Jouf's ethical review board gave the study its approval.

RESULTS

Over the course of the 1-year trial period, 162 cases of PIH were assessed for intrauterine growth restriction. [Table 1](#) and [Figure 1](#) show the demographics and clinical characteristics of the study. A total of 105 (64.8%) IUGRs were detected in PIH women.

The mean SD values for the total participant group were.84±7.86, 43.61±5.76, 4.83±1.44, 3.00±3.0,

Table 1 Demographic characteristics of study participants

Factors	Frequency (%)
Maternal age (yrs)	
20	32 (19.7)
21-30	53 (32.7)
31-40	59 (36.4)
Over40	18(11.1)
Gestational weeks (age)	
28	51 (31.4)
28-34	59 (36.4)
35-37	31 (19.1)
Over 37	21 (12.9)
Parity	
0-1	73 (45
2-5	47 (29
Over 5	42 (25.9)
Delivery approach	
CS	86 (53)
Vaginal delivery	64 (39.5)
Spontaneous abortion	12 (7.4)
IUGR	
Yes	105 (64.8)
No	57 (35.1)

Table 2 The participants of this study variables with mean ±SD

Measurable variables	Mean ±SD
Age of mother	37.84±7.86
Age of Gestational weeks	43.61±5.76
Disease period	4.83±1.44
Parity	3.00±3.0
Infant weight	1812±3.33
Apgar score	4.34±1.30

Table 3 Outcomes of IUGR

Factors	Number (n= 105) %
low Apgar score	29 (19.3)
Abortion	12 (11.4)
Low birth weight	29(19.3)
Preterm birth	21(20)
Stillbirth	14(13.3)

1812±3.33and 4.34±1.30, for the mother's age (years), gestational age (weeks), disease duration (weeks), baby weight (grams), and APGAR score respectively (Table 2).

The outcome was a low Apgar score of 29 (19.3%), abortion of 12 (11.4%), low birth weight of 29 (19.3%), preterm birth of 21 (20%), and stillbirth of 14 (13.3%) in 105 (64.8%) foetal IUGR, as shown in Table 3, Figure 2 and Figure 3.^{7,8}

However, our findings and stratification for the factors under research are as follows: Regarding the IUGR in connection to maternal age, the percentages were 37.5% (16–19 years), 25.7% (20–29 years), 28.5% (30–39 years), and 10.4% (40–45 years) [p = 0,00]. The IUGR was 36.1% (21-34 years) and 63.8% (35–42 years) in relation to gestational age [p = 0.05]. The IUGR was 61.9% for nulliparous parity and 38% for multiparous (p=0.00), whereas the IUGR was 53% for cesarean section deliveries and 39.5% for vaginal deliveries (p=0.21). Table 4 shows the relationship between maternal age, gestational age, and parity with stillbirth.

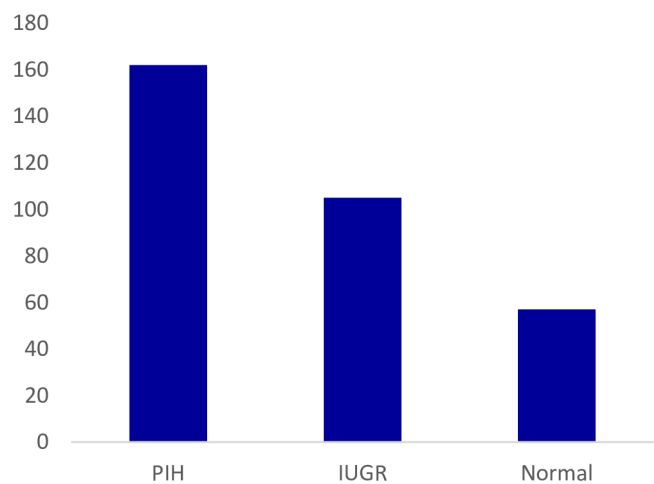


Figure 1 Normal foetal and IUGR in PIH women

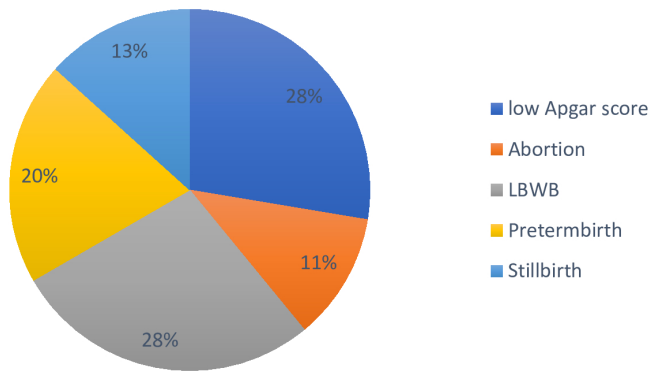


Figure 2 Status of IUGR in PIH women

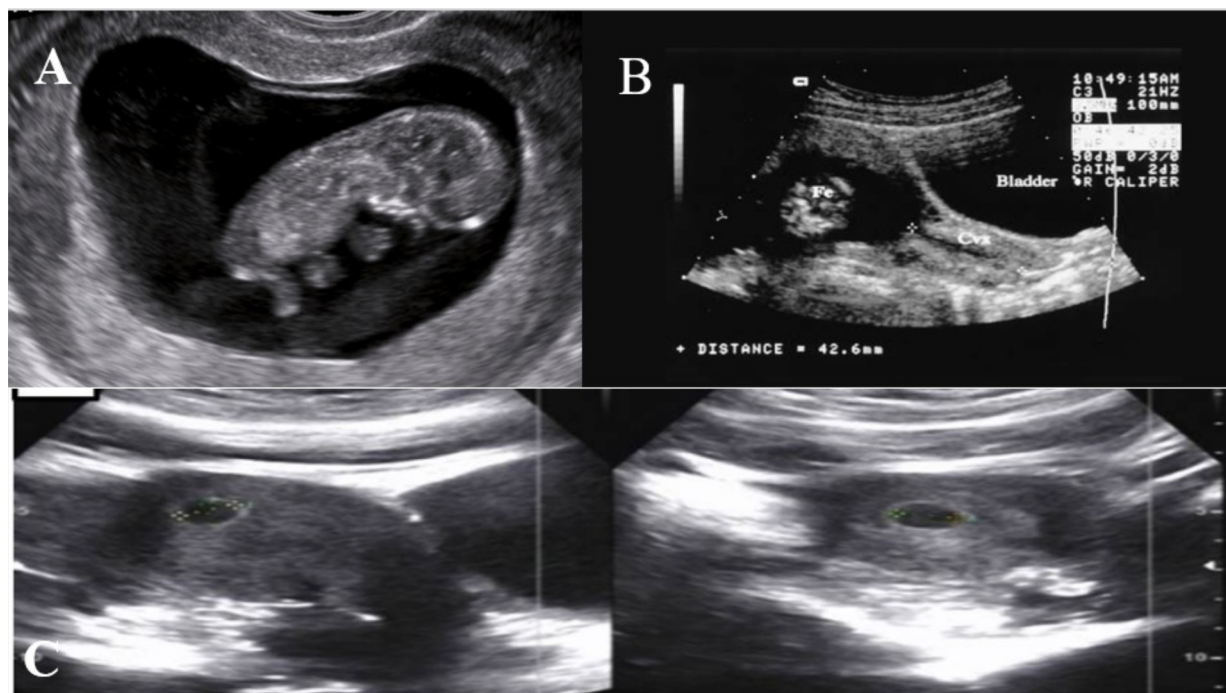


Figure 3 (A) 2D ultrasound imaging of a 9 weeks gestation fetus in utero(normal). (B) the cervix (Cvx) can be seen clearly and measured. A cervical length of less than 25–30 mm is associated with an increased risk of preterm delivery. (C) The yolk sac was not clearly shown under ultrasonography at 6 weeks of gestation indicating embryo damage (Threatened abortion)^{7,8}.

Table 4 Relationship of stillbirth in PIH women associated with the age of maternal, gestational, and parity

Factors	Stillbirth			
	Yes (%)	No (%)	Total (%)	P value
Maternal age (years)				
16-19 (years)	4 (10.8)	33(89.1)	37 (35.2)	
20-29(years)	3 (11.1)	24 (88.8)	27 (25.7)	
30-39(years)	4(13.3)	26 (86.6)	30 (28.5)	0.00
40-45(years)	3(27.2)	8(72.7)	11 (10.4)	
Total	14	91	105	
Gestational weeks (age)				
21-34	6 (15.7)	32(84.2)	38(36.1)	
35-42	8 (11.9)	59 (88)	67 (63.8)	0.05
Total	14	91	105	
Parity				
Nulliparous	8 (12.3)	57(87.6)	65(61.9)	
Multiparous	6(15)	34(85)	40(38)	0.00
Total	14	91	105	

DISCUSSION

When compared to gestations without hypertension problems, hypertensive pregnancies have higher rates of perinatal morbidity and mortality, and the major foetal consequence of these pregnancies is IUGR.⁹ Early morbidity is adversely affected by the degree of intrauterine growth restriction.¹⁰ Through placental microcirculation, the foetus receives nutrients and oxygen from the mother during embryogenesis and development. Pre-eclampsia and pregnancy-induced hypertension are intimately linked to placental malfunction.⁹ The lack of blood that is well-oxygenated and rich in all nutritional components reaching the fetomaternal unit during pregnancy is the direct cause of pregnancy-induced hypertension and intrauterine growth limitation.¹¹ There was a correlation between the mother's parity and pregnancy-induced hypertension. PIH is prevalent in primigravida and is likely the primary cause of IUGR and low placental weight.¹² In our study, 64.8% of patients with IUGR the primigravida (61.9%), and the remaining were multiparous (38%), this is comparable with a study conducted formerly where primigravida was 57.5%, and similar results were reported in a different study.¹³ Our findings are analogous to those of research on IUGR conducted in Japan, where 57% of cases had early-onset PIH and 43% had late-onset PIH.¹⁴ It was discovered such early-onset moderate to severe PIH could raise the danger of foetal death, whereas delivery by cesarean section could lower hazards in PIH-affected women. In line with the earlier study, the current study found that 13.3% and 19.3% of pregnant women with pregnancy-induced hypertension, respectively, had stillbirths.¹⁵ The current study's findings highlighted low birth weight and prematurity as the perinatal repercussions and

revealed a low stillbirth rate. Early detection of hypertension and the implementation of the appropriate treatment increased the likelihood of a healthy pregnancy for both the mother and the foetus.¹⁶ The previous study found that pregnancy-induced hypertension was present in 5% of the women who experienced stillbirth, a low birth weight of 16%, and Apgar score of 20%, in addition to preterm birth.¹⁷ The current study's findings revealed a link between PIH and having a child with a w birth weight. The increased risks associated with PIH are concerning because low birth weight is a key predictor of adult health outcomes and also has a long-term impact. Therefore, one of the methods to lower the risk of low birth weight and its effects is to prevent and/or manage PIH.¹⁸ An increased risk of poor perinatal outcomes was linked to hypertensive problems during pregnancy. However, Preterm delivery, low birth weight babies, neonatal death, and low Apgar scores were all more likely to occur in pregnant women with hypertensive diseases. The observation that effective quality improvement programs can contribute to high-quality care in a situation with limited resources highlights the need to maintain the focus on improving care quality.

CONCLUSION

In the current study, intrauterine growth restriction, which is usually a complication of hypertensive disorders of pregnancy, was recorded at 64.8%, with low Apgar scores of 29 (19.3%), abortion at 12, low birth weight at 29, preterm birth at 21, and stillbirth at 14.3% as outcomes. Therefore, in contemporary obstetrics, assessing this growth abnormality is a simple process that may be quickly detected and tracked using clinical and ultrasonographic screening.

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Prevalence and Associated Factors to Acceptance of Tuberculosis Preventive Treatment for Latent Tuberculosis at Health Clinics in Putrajaya, Malaysia

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Introduction: Latent tuberculosis infection (LTBI) is defined as the presence of Mycobacterium tuberculosis antigen without the evidence of tuberculosis infection. Approximately 5-10% of untreated LTBI would progress to clinically active tuberculosis during their lifetime or usually within 5 years. This study aimed to determine the facilitators, barriers, and associated factors to acceptance of Tuberculosis Preventive Treatment (TPT) among patients attending health clinics in Putrajaya.

Methods: A cross-sectional study utilizing a questionnaire that included sections on demographic data along with facilitators and barriers to TPT were distributed to newly diagnosed and active LTBI patients who were attending health clinics in Putrajaya between December 2021 to June 2022. Data analysis was done with SPSS v26.0.

Results: 63.8% of 177 patients who were involved in this study accepted TPT. The identified facilitators were, perceived ability to comply with the treatment, able to come for follow up and received comprehensive information about Latent Tuberculosis and its treatment. The most reported barriers to acceptance for TPT were concern about the side effects from treatment, long-waiting time and stigma. Older aged participants (median 37 years old, IQR=11), male gender (71%), other ethnic groups (80%), self-employed (100%), lower education level (100%) and good knowledge (68%) had higher acceptance for TPT. Female patients had 0.43 lower odds of accepting TPT than male patients (95% CI=0.21-0.86, p=0.02).

Conclusion: The prevalence of acceptance of TPT was 63.8%. The identified facilitators, barriers and determinants can be used in planning strategies to better educate patients on the benefits of TPT.

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Tuberculosis (TB) is an infectious disease primarily impacting the pulmonary system, caused by *Mycobacterium tuberculosis* bacteria. Transmission occurs through airborne droplets released when infected individuals cough, sneeze, or expectorate. Malaysia faces a substantial public health challenge due to TB. According to the Global Tuberculosis Report 2020, approximately 10.0 million individuals contracted TB, resulting in 1.4 million deaths in 2019¹ In 2020, Malaysia reported 23,644 TB cases, of which 91.7% were newly diagnosed cases and 58.0% were smear positive pulmonary TB cases.² The TB mortality rate in 2019 was 7.1 per 100,000, exceeding the WHO's End TB Strategy target. Malaysia aims to decrease TB-related deaths to less than 85 per year by 2035.¹ One of the key strategies to achieve this goal is the active detection of Latent Tuberculosis Infection (LTBI) and prompt initiation of treatment.

Latent tuberculosis infection (LTBI) refers to a condition where the immune system maintains a persistent response to *Mycobacterium tuberculosis* antigens without any clinically evident active TB manifestation.³ Globally, approximately a quarter of the population, around 1.7 billion people, have LTBI.⁴ Diagnosis of LTBI is based on positive Tuberculin Test or Interferon Gamma Release Assay (IGRA) results, along with the absence of symptoms suggestive of active TB and normal or unchanged chest X-ray findings. [Table 1](#) presents the different cut-off values applicable to various patient groups.

In Asia, the prevalence of Latent Tuberculosis Infection (LTBI) is highest in Southeast Asia, approximately 31%, followed by 28% in the Western Pacific region. In contrast, other regions worldwide have LTBI prevalence rates ranging from 11% to 22%.⁴ Individuals with LTBI face a lifetime risk of developing active TB estimated to be between 5% to 10%. This risk is particularly elevated in children under five years of age and individuals with compromised immune systems.

Treating LTBI can effectively prevent the progression of 60% to 90% of cases into active TB.⁵ The management of latent TB infection is of paramount importance in the context of the country's high burden of TB and overall disease burden. For adults with LTBI, there are four treatment options available, as outlined in [Table 2](#) below.

The primary objective of this study is to investigate the facilitators, barriers, prevalence, and related factors influencing the acceptance of Tuberculosis Preventive Treatment (TPT) among patients visiting health clinics in Putrajaya, Malaysia. The lack of previous research on the determinants of TPT acceptance in Malaysia, along with the prevalence of Latent Tuberculosis Infection (LTBI) in the country, serves as the driving force behind conducting this study. By identifying the factors that promote or hinder TPT acceptance, the research aims to provide valuable insights that can contribute to enhancing TB prevention and control strategies in the region.

Table 1 TST Cut-off values for different groups

Positive (TST) reactions	At-risk groups
>=5mm	• PLHIV • Organ transplant recipients • Persons who are immunosuppressed for other reasons (e.g. those taking the equivalent of >15 mg/day prednisolone for 2:1 month or taking anti-TNF treatment)
	All other high risk individuals including healthcare workers and children (except newborns and infants <3 months)
	Individuals from countries with low incidence of TB
>=10mm	
>=15mm	

Table 2 Treatment option for latent tuberculosis infection

Drug	Duration	Interval	Dosage
Isoniazid	Six months/ nine months	Daily	5 mg/kg, max 300 mg
Isoniazid+ rifampicin	Three months	Daily	INH: 5 mg/kg, max 300 mg RIF: 10 mg/kg, max 600 mg
Rifapentine+ isoniazid	Three months	Weekly	INH: 15 mg/kg, max 900 mg RPT: <50 kg; 750 mg >50 kg: 900 mg
Rifampicin	Four months	Daily	10 mg/kg, max 600 mg

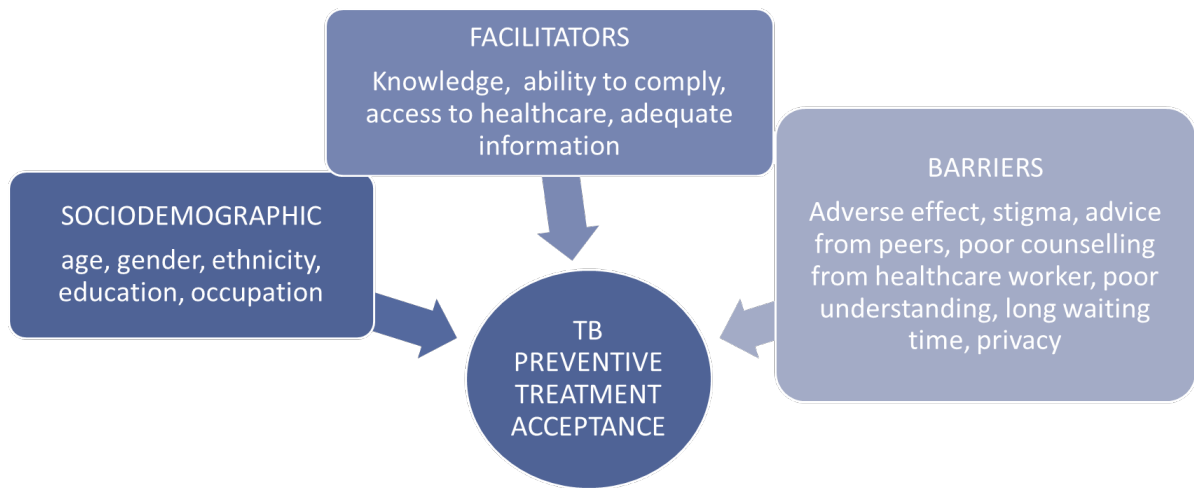


Figure 1 *The conceptual framework of this study*

Figure 1 shows the conceptual framework of this study.

METHODS

Study design and population

From December 2021 to June 2022, a cross-sectional study was done at two health clinics in Putrajaya Presint 9 and 18, Wilayah Persekutuan Putrajaya. These clinics cater to patients with various infectious diseases, including LTBI, active Tuberculosis (TB), and other outpatient conditions. The study enrolled patients diagnosed with LTBI who had scheduled follow-up appointments with healthcare providers. These participants were screened for active TB and adverse effects related to TPT at three different time points: 3 months, 9 months, and 12 months after their initial visit. These follow-up intervals are following the recommendation of the Malaysian Clinical Practice Guideline of Tuberculosis.¹

The study's inclusion criteria encompassed patients aged 18 years and above, who had been diagnosed with LTBI (Criteria used to diagnose latent tuberculosis infection among adults in this study are tuberculin test of more than 10mm or a positive Interferon-Gamma Release Assay [IGRA] test, a normal chest X ray and must be asymptomatic of tuberculosis symptoms) and received routine follow-up care at the designated health clinics. Inclusion into this study also required participants to provide informed consent, test negative for active TB, and demonstrate proficiency in either the English or

Malay language. On the other hand, the exclusion criteria comprised pregnant individuals, those below 18 years of age, those with active TB, patients with current acute critical conditions, and individuals with severe psychiatric illnesses affecting their ability to adhere to medication or respond to the questionnaires.

Educational level was categorized into four groups: no formal education, primary education, secondary education, and tertiary education. "No formal education" pertained to individuals who had not received any schooling through formal systems. "Primary education" denoted those who had completed formal schooling between the ages of 7 and 12 years. "Secondary education" encompassed those who had completed formal schooling between the ages of 13 and 17 years. Finally, "tertiary education" referred to individuals who had pursued any formal education beyond high school within formal institutions, such as undergraduate or postgraduate degrees.

Occupation was classified into five groups: unemployed, retired, self-employed, government servant, and private sector workforce. "Unemployed" individuals were those available for work but had not secured employment. "Retired" participants are those who had ended or completed their professional activities. "Self-employed" refers to individuals working on their own. "Government servant" included those working with the Malaysian government, while "private sector workforce" indicated individuals employed by private companies.

Sample size determination

The Raosoft method was used to determine the required sample size for this study. With a 95% confidence level and a 5% margin of error, considering a population size of 91,900 (based on local data from the Dept. of Statistics Malaysia in the 4th quarter of 2018), the estimated sample size was 383. However, to account for a 10% non-response rate, we increased the sample size to 421.

To optimize the number of participants with LTBI within the constraints of the study site, we adopted convenience sampling. Out of the 181 LTBI individuals approached, 4 declined to participate, resulting in 177 LTBI respondents who completed the study. This yielded a high response rate of 97.8%.

Study procedure

The data collection for this research was conducted using self-administered questionnaires. The study population was invited to participate in the research during their initial or subsequent visits to the health clinics. Once they expressed their willingness to take part, the investigators provided them with detailed information about the study, including its purpose and methodology. This information was conveyed both in written form and verbally.

The participants were assured of the confidentiality of their responses, and they were informed about the voluntary nature of their involvement. They were explicitly informed of their right to withdraw from the study at any point without any impact on their follow-up care in the clinic. To formalize their participation, each participant received and signed a patient information sheet and a consent form.

The questionnaire was made available to the participants in both online and hardcopy paper formats, allowing them to choose their preferred mode of answering the questionnaire.

Study instrument

The research team developed a questionnaire by drawing upon existing published literature and subjected it to face validation by 16 individuals from diverse backgrounds.⁶⁻⁷ Additionally, feedback was obtained from 4 expert panels, consisting of 2 family

medicine specialists, a respiratory physician, and a public health specialist.

Following the validation process, a pilot study was carried out involving 20 patients. The sections of the questionnaire that assessed facilitators and barriers demonstrated good internal reliability, as evidenced by Cronbach's α coefficients of 0.796 and 0.906, respectively. These coefficients indicate the consistency and homogeneity of responses within each section of the questionnaire.

Data analysis

The data analysis was conducted using SPSS version 26.0 for Windows. Categorical data were presented as frequencies and percentages, providing a clear representation of the distribution of each category within the dataset. Numerical data were reported as means and standard deviations, offering a summary of the central tendency and dispersion of the quantitative variables.

To investigate the factors associated with the acceptance of TPT, a simple logistic regression analysis was performed. This analysis was done to assess the individual relationships between each variable and the likelihood of TPT acceptance.

Subsequently, variables with a p-value less than 0.25 in the simple logistic regression analysis were selected as candidates for the multiple logistic regression model. This step aimed to identify the determinants of TPT acceptance while considering the potential influence of multiple confounding factors simultaneously.

The final results of the multiple logistic regression model were presented as adjusted odds ratios, indicating the strength of association between each independent variable and the likelihood of TPT acceptance after adjusting for other factors in the model. Statistical significance was determined using a significance level of $p < 0.05$.

Ethical approval

The study received ethical approval from the Medical Research and Ethics Committee of the National Institute of Health Malaysia (NMRR-22-00209-4EV (IIR)).

RESULTS

Socio-demographics of the participants

The researchers approached a total of 181 potential participants for the study. Among them, 4 individuals declined to participate, resulting in a response rate of 97.8%. The remaining participants were enrolled in the study after ensuring that they met all the inclusion criteria and did not have any of the exclusion criteria (Figure 2).

The participants' median age was 36 years old, with a standard deviation of ± 12 years. The majority of the participants were male, of Malay ethnic group, employed in the government sector, and had attained a tertiary level of education (Table 3).

The overall acceptance rate of TPT among the participants was 63.8% (N=177).

Among the participants, the most reported facilitators for TPT uptake included their perceived ability to adhere to the treatment, ensuring attendance at follow-up visits, and receiving sufficient and comprehensive information regarding latent tuberculosis and its treatment (Table 4).

The median knowledge score related to TPT acceptance was 16, with an interquartile range of 4.5. A score of 16 and above was considered indicative of good knowledge, while scores below 16 suggested poor knowledge regarding the importance of TPT acceptance.

The primary barrier to the acceptance of TPT among the participants was the fear of treatment-related adverse effects. The second most prevalent obstacle was the lengthy waiting time experienced by the participants. The third most reported barrier was the social stigma associated with TPT (Table 5). These findings highlight the challenges faced by individuals in accepting TPT, which may impact their willingness to undergo preventive treatment.

Latent TB infection and TB preventive therapy knowledge association with acceptance

In the study, it was observed that majority of the participants (68.1%) with good knowledge about latent tuberculosis and its prevention agreed to undergo preventive therapy for latent TB. However, upon

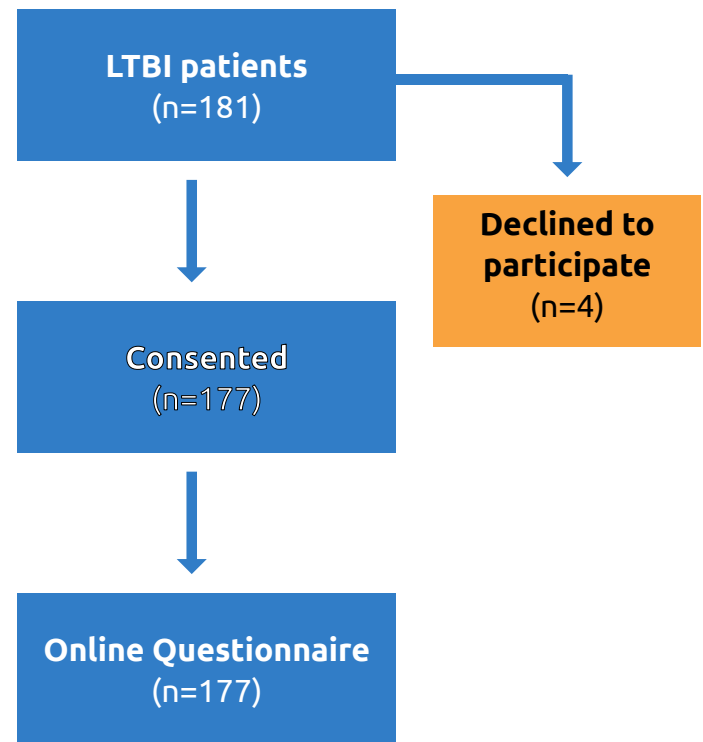


Figure 1 Study enrolment flow

Table 3 Sociodemographic characteristics of the participants (N=177)

Variable	Frequency, N (%)
Age (Years) - Median +/- IQR	36 +/- 12
Gender	
Male	93 (52.3)
Female	84 (47.7)
Ethnicity	
Malay	164 (92.7)
Chinese	5 (2.8)
Indian	3 (1.7)
Others	5 (2.8)
Occupation	
Unemployed	19 (10.7)
Pensioner	2 (1.1)
Self-employed	1 (0.6)
Government sector	132 (74.6)
Private sector	23 (13.0)
Level of education	
None	0 (0.0)
Primary	1 (0.6)
Secondary	39 (22.0)
Tertiary	137 (77.4)

Table 4 Responses towards different facilitating domains for latent TB preventive therapy acceptance (N=177)

Facilitator	Strongly disagree n (%)	Disagree n (%)	Agree n (%)	Strongly agree n (%)
Knowledge				
Q1 Active Tuberculosis is an airborne disease	2 (1.1)	14 (7.9)	84 (47.5)	77 (43.5)
Q2 Active Tuberculosis is fatal if left untreated	1 (0.6)	2 (1.1)	84 (47.5)	90 (50.8)
Q3 5–10% of Latent Tuberculosis patients will progress to Active Tuberculosis in their lifetime if not treated	2 (1.1)	17 (9.6)	97 (54.8)	61 (34.5)
Q4 Latent Tuberculosis is not infectious	8 (4.5)	22 (12.4)	83 (46.9)	64 (36.2)
Q5 People with HIV, organ transplant recipients and intravenous drug user are at high risk of acquiring Latent Tuberculosis	6 (3.4)	26 (14.7)	89 (50.3)	56 (31.6)
Q6 I am NOT at risk of getting Drug Resistant TB if I stop Tuberculosis Preventive Therapy before the due period	16 (9.0)	98 (55.4)	56 (31.6)	7 (4.0)
Q7 will NEVER develop any symptoms after infection with Latent Tuberculosis	9 (5.1)	76 (42.9)	77 (43.5)	15 (8.5)
Q8 I am at LOW risk of getting Active Tuberculosis	14 (7.9)	73 (41.2)	78 (44.1)	12 (6.8)
Able to comply to treatment				
I have no problem taking Isoniazid treatment for 6 months	6 (3.4)	39 (22.0)	95 (53.7)	37 (20.9)
Able to come for follow up				
I have no problem coming to regular appointments at the clinic	4 (2.3)	34 (19.2)	99 (55.9)	40 (22.6)
Adequate information				
I have received in-depth information of LTBI and the treatment	5 (2.8)	53 (29.9)	94 (53.1)	25 (14.1)

Table 5 Response towards different barrier domains for latent TB preventive therapy acceptance (N=177)

Barrier	Strongly disagree n (%)	Disagree n (%)	Agree n (%)	Strongly agree n (%)
Therapy related factors				
I am afraid of getting side effects from the treatment	6 (3.4)	59 (33.3)	100 (56.5)	12 (6.8)
Social related factors				
I fear the stigma from society if I take the treatment	13 (7.3)	41 (23.2)	80 (45.2)	43 (24.3)
I was told by others NOT to take the treatment	96 (54.2)	63 (35.6)	35 (19.8)	5 (2.8)
Clinic related matters				
My concerns were NOT taken into account by the health workers during the consultation	25 (14.1)	108 (61.0)	39 (22.0)	5 (2.8)
I had to wait for a long time to see the doctor	11 (6.2)	67 (37.9)	85 (48.0)	14 (7.9)
There is NO privacy during the consultation	29 (16.4)	88 (49.7)	55 (31.1)	5 (2.8)

statistical analysis using logistic regression, this relationship was found to be not statistically significant (adjusted OR:1.9; 95%CI:0.95-3.82) (Table 6).

Sociodemographic factors association with acceptance

The study found that a higher proportion of male participants (71%) agreed to take TPT compared to female participants (56%) (Table 6).

The uptake of TPT was higher among participants with certain sociodemographic factors, including older age, male sex, ethnicity other than Malay, Chinese or Indian, self-employment, and a lower level of formal education (Table 6).

However, upon conducting multiple logistic regression analysis to examine the factors associated with the acceptance of TPT, it was

Table 1 Response towards different barrier domains for latent TB preventive therapy acceptance (N=177)

Variable	LTBI Agree to take n (%)	LTBI Disagree to take n (%)	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Social demography						
Age (Median, IQR)	37 (IQR 11)	35 (IQR 10)	1.005 (0.974 – 1.039)	0.747	Exclude	
Gender						
Male	66 (71.0)	27 (29.0)	Ref		Ref	
Female	47 (56.0)	37 (44.0)	0.52 (0.279 – 0.967)	0.04	0.43 (0.21 – 0.86)	0.02
Ethnicity						
Malay	105 (64.1)	59 (35.9)	0.445 (0.49 – 4.074)	0.473	0.73 (0.07 – 7.80)	0.79
Chinese	2 (40.0)	3 (60.0)	0.167 (0.01 – 2.821)	0.214	0.09 (0.004 – 1.87)	0.12
Indian	2 (66.7)	1 (33.3)	0.5 (0.19 – 12.9)	0.676	0.58 (0.02 – 17.08)	0.75
Others	4 (80.0)	1 (20.0)	Ref		Ref	
Occupation						
Unemployed	14 (73.7)	5 (26.3)	Ref		Ref	
Pensioner	1 (50.0)	1 (50.0)	0.36 (0.19 – 6.85)	0.50	0.4 (0.02 – 8.16)	0.55
Self employed	1 (100.0)	0 (0.0)	5.8×10^8 (0.00 – 0.00)	1.00	6.5×10^8 (0.00 – 0.00)	1.00
Government	78 (59.1)	54 (40.9)	0.52 (0.18 – 1.52)	0.23	0.54 (0.18 – 1.68)	0.29
Private	19 (82.6)	4 (17.4)	1.70 (0.38 – 7.49)	0.49	2.04 (0.43 – 9.71)	0.37
Level of education						
No formal / Primary	1 (100.0)	0 (0.0)	Ref		Exclude	
Secondary	29 (74.4)	10 (25.6)	0.0 (0.00 – 0.00)	1.00		
Tertiary	83 (60.6)	54 (39.4)	0.0 (0.00 – 0.00)	1.00		
Knowledge						
Good	64 (68.1)	30 (31.9)	1.48 (0.80 – 2.74)	0.21	1.9 (0.95 – 3.82)	0.07
Poor	49 (59.1)	34 (40.9)	Ref		Ref	

determined that gender was the only significant factor. Specifically, female patients had 0.43 lower odds of accepting TPT for latent TB compared to male participants (95% CI: 0.21-0.86, P: 0.02) (Table 6). Other sociodemographic factors examined did not show statistically significant associations with TPT acceptance in this study.

DISCUSSION

This study found that 63.8% of the 177 surveyed patients agreed to undergo TPT. However, other studies have reported different acceptance rates for TPT, indicating that acceptance rates may vary due to different socio-demographic factors and clinic capabilities across the study populations.⁸⁻⁹

The most common barriers to TPT acceptance identified in this study were fear of medication side effects, long waiting time, and stigma, which align with the findings of a systematic search by Liu et al⁸. Similarly, a Swedish study also reported that medication adverse side effects were a significant barrier to treatment acceptance and completion.¹⁰

Among the socio-demographic factors, older patients, males, individuals from other ethnic groups, self-employed individuals, and those with lower education levels showed a higher acceptance rates of TPT, akin similar to findings of a study by Musaaazi which also showed that older aged individuals tend to be more receptive to treatment with TPT.¹¹ Although good knowledge about latent TB did not significantly influence the decision to undergo preventive therapy in this study, it is important to note that health literacy may influence how knowledge affects treatment attitudes across different study populations. A study by Colson et al showed good knowledge as one of the predictors to treatment acceptance.⁹ However, based on our study, good knowledge does not significantly improve the acceptance of treatment. This difference may be due to constraints of our healthcare providers in providing education to the patients with TPT due to human resource and time constraint.

The study's finding that female participants had lower odds of accepting TPT is consistent with the results of a study by Colson et al, which showed that men were more likely to accept TPT than women.⁹ The reasons behind this difference are not

clear, but other studies have suggested that men may have greater belief in tuberculosis treatment, while women may experience more tuberculosis-related stigma compared to men.¹²⁻¹³ Further research may be needed to explore these gender-related differences and consider potential adjustments in clinical approaches for women with latent TB infection who require preventive treatment.

By identifying facilitators and barriers to TPT acceptance, a more robust and targeted public health interventions such as increased mass media campaign to promote the benefits of TPT usage and risk of not using it, and policy initiatives aimed at improving LTBI management in Malaysia can be implemented including the use of reminder systems for those who initially reject the usage of TPT.

It is hoped by completion of this and other similar studies, the adherence of healthcare providers in managing LTBI and prescribing treatment for it will be improved, in line with the recommendation of the Malaysian Clinical Practice Guideline of Tuberculosis.¹

Strengths and limitations of the study

Strengths

This study has several advantages. The prevalence of TPT acceptance and other health characteristics can help to assess disease burden in a specific population and this information can assist healthcare planners and policymakers in allocating resources effectively and devising targeted interventions to combat TB in the region.

As one of the few quantitative studies on LTBI and TPT acceptance, this research enriches the existing body of knowledge in this area. Future researchers can build upon these findings and conduct further investigations to deepen their understanding of latent TB infection and optimize treatment strategies for the affected patients.

Conducting the study in urban settings offers unique perspectives on TPT acceptance among urban populations with latent TB infection. Since urban areas may present distinct challenges and opportunities related to healthcare access and attitudes toward treatment, the findings can help tailor interventions and policies to better serve this specific demographic profile.

Limitations

This study has certain limitations. Cross-sectional studies possess limited capability in establishing causality, thereby precluding determination of causal relationships between independent and dependent variables.

Another limitation lies in selection bias, wherein certain individuals from the latent tuberculosis (TB) population may be more likely to be included in the study sample due to the restricted number of study sites. The study exclusively comprises urban residents, potentially limiting its representation for the entire LTBI population.

Additionally, the relatively small sample size may impede the detection of significant differences in the outcomes. Consequently, the results and conclusions may be subject to bias and lack generalizability to broader populations.

In addition, the sampling method used in this study was convenience sampling. This sampling method was used because of time constraint and limited names in tuberculosis registry. The researchers will try to recruit more centers to ensure the use of a more robust sampling method to ensure representativeness of the population in future studies.

Recommendation for clinical practice

To enhance the management and outcome of LTBI within the population, there is a need to provide patients with increased encouragement and education to accept latent TB treatment. Raising awareness of LTBI among the population can be

effectively achieved through regular health talks, targeted advertisements, and educational campaigns on social media platforms.¹⁴ By engaging in these awareness-raising efforts, healthcare professionals can foster greater acceptance of latent TB treatment through greater knowledge sharing, leading to improved health outcomes, policy support and a reduction in the burden of LTBI.¹⁵

Recommendation for research

The study was limited to only two health clinics in Putrajaya district. To ensure more robust and accurate data, future research should extend its scope to encompass a broader range of urban and rural regions across Malaysia. This broader representation would enhance the generalizability and reliability of the study's findings.

CONCLUSIONS

The acceptance rate of TPT for LTBI was observed to be relatively low, at 63.8%. This suggests that the rate of initiating treatment might be even lower. Acceptance of TPT was found to be influenced by various factors, including the socio-demographic characteristics of the patients, particularly being male. The identification of facilitators, barriers, and associated factors of acceptance of TPT provides valuable insights that can be utilized to enhance patient education regarding the advantages of TPT. By addressing these factors, healthcare providers can better promote the acceptance of TPT among individuals with LTBI.

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The Malta Medical Journal Students' Corner

The following abstracts have been selected and will be published in the Malta Medical Students' Journal. They can be accessed on the following link: <https://mmsjournals.org/links/mmsa>

Sleep and the Brain: Neurological Insights into Rest and Cognition

Andre Mifsud, MD3; John Cefai, MD3

Sleep is a fundamental yet often overlooked biological process essential for maintaining optimal brain function, cognition, and physical recovery. This review synthesizes current evidence on the neurophysiological, cognitive, and restorative dimensions of sleep, with emphasis on its translational relevance for medical students, student athletes, clinicians, and patients. We explore the underlying neurological mechanisms governing sleep regulation, including circadian rhythms, neurotransmitter activity, and neural control systems such as the VLPO and orexin pathways. The cognitive implications of sleep are examined through its role in attention, learning, and memory consolidation, supported by theories like synaptic homeostasis and stage-dependent neuroplasticity. Furthermore, we analyse how sleep deprivation and disorders such as sleep apnoea detrimentally affect physical performance, emotional stability, and overall health. The physiological basis of muscle recovery during sleep and the consequences of inadequate rest on repair and endurance are also discussed. Finally, emerging innovations in sleep science, including wearable technologies, pharmacological aids, and neurotechnological research, are reviewed to highlight future directions and challenges. Collectively, this literature review underscores sleep as an active, restorative process vital for cognitive integrity, physical resilience, and long-term wellbeing.

Nutraceuticals for Cystic Fibrosis

Manuela Grech, MD4

Cystic Fibrosis (CF) is a prevalent genetic disorder characterized by a diverse array of clinical presentations affecting multiple organ systems. The primary objective of this paper is to delve into the aetiology and pathophysiological mechanisms underlying CF, with a particular focus on exploring the potential therapeutic benefits of various nutraceutical interventions in alleviating the clinical manifestations associated with this condition. Notably, certain nutraceutical compounds have emerged as promising candidates for mitigating the adverse effects of CF and improving the overall wellbeing and quality of life among affected individuals. Through a comprehensive examination of these nutraceutical agents, this study aims to shed light on their mechanisms of action and efficacy in managing CF-related symptoms and complications.

Innovations in home-based care for older adults and their impact on quality of life in Malta

Sybilie Mireille Cauchi, MD3

Malta's over-80s population will triple by 2050, straining community care facing 130-day waits and 40.3% isolation. This study evaluates how Smart home technology and Active aging enhance quality of life. Analysis reveals residential care costs the state €47.71/night, while residents contribute 80% of their pension. This is significantly more onerous than community care, where daily costs can be as low as

€0.57. Main gerontology recommendations include establishing a Quality Assurance Unit and mandatory training. These reforms in Malta are vital for achieving a sustainable society by 2030.

Paediatric Oesophageal atresia with tracheoesophageal fistula and duodenal atresia (case study)

Peter Calleja, MD3 ; Luke Camilleri, MD4

A complicated type of paediatric surgery case as reviewed in this paper consists of a neonate with two special types of GI atresias : a duodenal atresia (DA) and oesophageal atresia (OA) with distal tracheo-oesophageal fistula (TEF). Atresia can be defined as the congenital absence or obstruction of a normally patent lumen or orifice. DA is due to a failure of duodenal recanalization around the 4th to 10th week of gestation. OA/TEF arises from a defect in the formation of the tracheo-oesophageal septum.

The patient was prenatally diagnosed with DA via the double bubble sign on ultrasound. Post natally, an attempted nasogastric (NG) tube insertion failed and coiled, confirming OA. The double bubble sign being present simultaneously (such as in DA).

Surgical goals involve fistula ligation , division and restoration of continuous lumen. The standard procedure for OA/TEF (most commonly type C) is primary repair via thoracotomy or thoracoscopy, with end to end anastomosis. DA is primarily repaired via duodeno-duodenostomy, using the Diamond shaped (Kimura) procedure/anastomosis. The management includes utilising a replogle tube for suction and sham feeding.

Addressing the Long-term Effects of Cancer Treatments

Waleed Ahmed , MD1

Cancer survivorship has become a growing area of clinical and public health focus as advancements in early detection and treatment have significantly improved survival rates worldwide. However, the increase in long-term survivors has brought to light a spectrum of chronic physical and psychological sequelae that can persist years after treatment. This literature review examines the enduring physiological sequelae,

including cardiotoxicity, endocrine dysfunction, neurological impairment, and musculoskeletal decline. Psychological challenges such as anxiety, depression, post-traumatic stress symptoms, fear of recurrence, and body image disturbances are also discussed. It explores current and emerging interventions, including multidisciplinary survivorship care models, survivorship care plans (SCPs), rehabilitation programmes, and digital health innovations that aim to enhance post-treatment quality of life. The review also analyses emerging research trends in precision survivorship care, which seek to translate evidence-based interventions into sustainable practice. Policy and healthcare-system implications are discussed with particular emphasis on Malta, where the National Cancer Plan (2017–2021) outlines a framework for integrated survivorship care but faces challenges in implementation, equity, and long-term funding. The review concludes by stating that the long-term effects of cancer treatment demand coordinated multidisciplinary care, robust policy frameworks, and continued research to improve survivor outcomes and quality of life.

CaMKII α Overactivity and Epileptogenesis in TLE: Proposing Novel Inhibitors

Simone Bottai , MD3

Ca²⁺/Calmodulin Dependent Kinase II (CaMKII α), a serine/threonine kinase abundantly expressed in neurons throughout the brain, plays a crucial role in regulating synaptic plasticity. This dodecameric complex presents a regulatory domain (T-site residues 274–314) and a Ca²⁺/calmodulin-binding site (S-site residues 301–314) in each subunit which together form a contiguous groove mediating the enzyme's synergistic activation. CaMKII α is critical for long-term potentiation (LTP) and long-term depression (LTD). The balance between these opposite forms of plasticity and the degree of enzymatic activity depends on the frequency of excitatory synapse activation and the specific site of CaMKII α autophosphorylation.

Temporal Lobe Epilepsy (TLE), the most common yet typically treatment-resistant focal epilepsy, is characterised by recurrent unprovoked seizures and dyscognitive symptoms greatly affecting patients' quality of life. Synaptic plasticity is central to its pathogenesis, with key players being CaMKII isoforms

and glial fibrillary acidic protein, as evidenced by their increased expression in affected tissue. Evidence proposes increased CaMKII signalling as a contributor to maladaptive synaptic remodelling and epileptogenesis, although the causal relationship between this overactivity and TLE remains unclear. Consequently, this data highlights CaMKIIa inhibitors (e.g., AIP, Evans Blue) as promising novel focus for antiepileptic therapy studies.

ADHD in Women's Health: The Influence of Hormonal Transitions During the Menstrual Cycle, Pregnancy, and the Postpartum Period *Abhishek Sah Frendo, MD2; Martha Cassar, MD2*

Attention-deficit/hyperactivity disorder (ADHD) in women is shaped by hormonal transitions across the menstrual cycle, pregnancy, and the postpartum period. Fluctuations in oestradiol and progesterone influence dopaminergic function, executive control, and emotional regulation, producing phase-dependent variation in symptoms and treatment response. Adolescence is marked by heightened neuroendocrine sensitivity, pregnancy by heterogeneous clinical trajectories, and the postpartum period by oestrogen withdrawal, sleep disruption, and increased psychiatric vulnerability. Evidence supports phase-sensitive assessment, individualised pharmacological and behavioural management, and early reproductive planning. Longitudinal research integrating neuroendocrine, clinical, and functional outcomes is required to guide evidence-based care for women with ADHD across the reproductive lifespan.

Keywords: ADHD, women, menstrual cycle, pregnancy, postpartum, hormones

A literature review of the effect of energy drink consumption on academic performance amongst medical students

Shazney Falzon, MD2

Energy drinks are widely consumed among university students, particularly those enrolled in academically demanding programmes such as medicine. Existing literature indicates that students often consume energy drinks to combat fatigue, enhance alertness,

and improve concentration, especially during examination periods. The primary active ingredient, caffeine, has been shown to provide short-term improvements in attention, reaction time, and perceived cognitive performance.

Despite these potential short-term benefits, numerous studies have raised concerns about the adverse effects of frequent or excessive energy drink consumption. High caffeine intake has been associated with sleep disturbances, including reduced sleep duration, poorer sleep quality, and delayed sleep onset. Poor sleep quality has consistently been linked to impaired academic performance, diminished cognitive functioning, and reduced memory consolidation. Additionally, research suggests that energy drink consumption may be associated with increased stress, anxiety symptoms, and other negative health outcomes among university students.

Effect of obesity on natural fertility in women of reproductive age: A literature review

Leanne Cassar, MD2

The global prevalence of obesity has risen substantially in the recent decades, while also raising concerns about its impact on women's reproductive health, particularly among those of reproductive age. Obesity is associated with multiple factors that may impair natural fertility, including hormonal dysregulation, ovulatory dysfunction, and adverse metabolic changes. This literature review aims to examine and synthesize current evidence regarding the relationship between obesity and natural fertility in women of reproductive age. It explores proposed biological mechanisms, including endocrine and metabolic alterations, as well as observed effects on ovulatory function and time to conception. By summarizing existing research, this review highlights the potential influence of obesity on natural fertility and underscores the importance of weight management in supporting reproductive health.

Nitrous Oxide induced neuropathy correlated with MRI imaging

Thomas Saliba, Sanjiva Pather, Henri Maisonnier

The neurotoxic effects of Nitrous Oxide (N_2O), a recreational drug also known as laughing gas, are well known. Despite its declining use in medical settings due to side effects, N_2O abuse is on the rise, particularly among young people. Amongst the most serious side effects is neurotoxicity, caused by a reduction in the bioavailability of vitamin B12.

We report the case of a 27-year-old male who, after heavy recreational use of N_2O , presented to the emergency department, complaining of bilateral paraesthesia in his arms and legs, leading to their hospitalisation. A blood test was performed, finding decreased vitamin B12 levels. An electromyography found a decreased conduction speed of the left sural nerve and an MRI revealed hyperintense zones in the dorsal column of the cervical spinal cord, compatible with N_2O toxicity. The patient's vitamin B12 deficiency was corrected, and they received physical therapy as an inpatient, before continuing to receive outpatient treatment once they were able to use a walking frame.

The neurotoxicity of N_2O is linked to the induction of vitamin B12 deficiency, which can lead to demyelination. This diagnosis can be made despite the presence of normal serum vitamin B12 levels, probably due to a reduction in cellular bioavailability. Homocysteine levels may be elevated in N_2O toxicity, providing a crucial diagnostic clue. Treatment is based on reversing the vitamin B12 deficiency, but no consistent regimen has been established. The prognosis varies but may be improved by prompt treatment with vitamin B12.

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Nitrous oxide (N_2O) gas, commonly known as laughing gas, has long been used as an anaesthetic in medical settings.¹⁻³ However, its use is declining due to its known side effects which include neurotoxicity resulting from reduced vitamin B12 bioavailability in cases of abuse.^{1,2} Recently, there has been a reported rise, particularly amongst young people, in the abuse of this substance with the lifetime prevalence in the UK being around 38.6%, being the thirteenth most used recreational drug according to the Global Drug survey of 2021.⁴⁻⁶ When inhaled, N_2O creates a sense of euphoria, but can also cause dizziness, slurred speech, drowsiness and can even cause loss of consciousness in some cases.^{2,7} Although most use the drug infrequently, with little harm ensuing, there appears to a subset of users that use it significantly more often and may develop dependency.⁵ Symptoms of nitrous oxide abuse have been reported as mainly neurological, with subacute combined spinal cord degeneration, likely linked to the decrease in bioavailable vitamin B12.⁸

CASE REPORT

A twenty-seven-year-old male presented to the emergency department complaining of bilateral paraesthesia in their arms and legs which had been developing over the past two weeks, without any history of recent trauma. The patient's daily treatment was 20mg of methylphenidate and two 500mg pills of diosmin (450mg) and hesperidin

(50mg). The neurological exam showed decreased tactile and pain sensitivity in the legs and feet, with the patient being unable to stand. The patient exhibited dysmetria when asked to perform a finger-to-nose test, attributed to a lack of strength. The rest of the physical exam was normal. The physician requested a cervical spine CT-exam to exclude a disc hernia. The patient was then seen by a neurologist, to whom he admitted having heavy recreational use of N_2O , having consumed multiple balloons, filled with N_2O from small canisters, two weeks prior. A blood test was performed, revealing vitamin B12 < 150ng/L, a slightly increased white blood cell count (11 000/ mm^3), increased fibrinogen (472mg/dl), increased direct bilirubin (0,3 mg/dl) and GPT (44 U/L) and a slightly increased CRP (12.8mg/L). The rest of the blood test was normal. The patient promptly hospitalised and seen by a neurologist, whom, suspecting N_2O toxicity, requested a CSF analysis, an electromyography and an MRI.

The electromyography exam revealed a decreased conduction speed of the left sural nerve. The CFS analysis was normal.

The patient was treated with 1mg of vitamin B12 per day via intramuscular injection (IM) on the 3rd day after admission. This regiment continued for one week, followed by 1mg IM per week thereafter.

The MRI revealed hyperintense zones in the dorsal column of the cervical spinal cord from C2 to C6 in T2-weighted sequences (**Figure 1** and **Figure 2**).

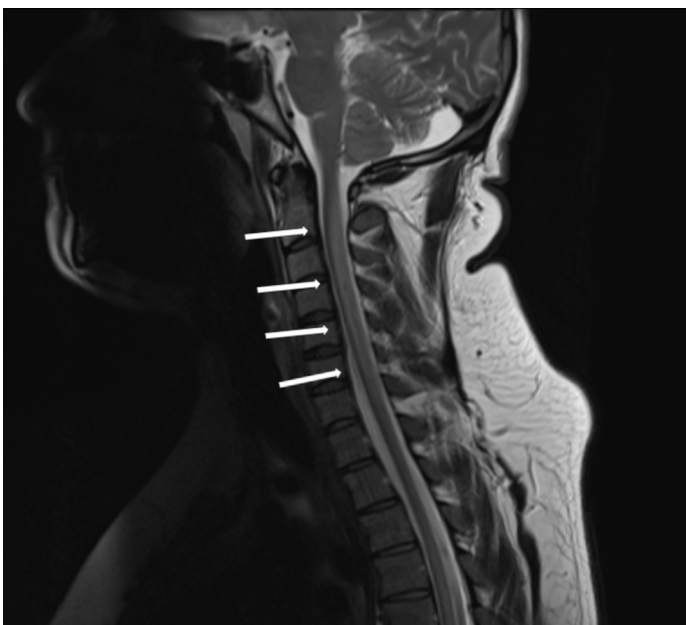


Figure 1 Sagittal T2-weighted image of the cervical spine showing a hyperintense signal from C2 to C6 within the spinal cord (arrows)

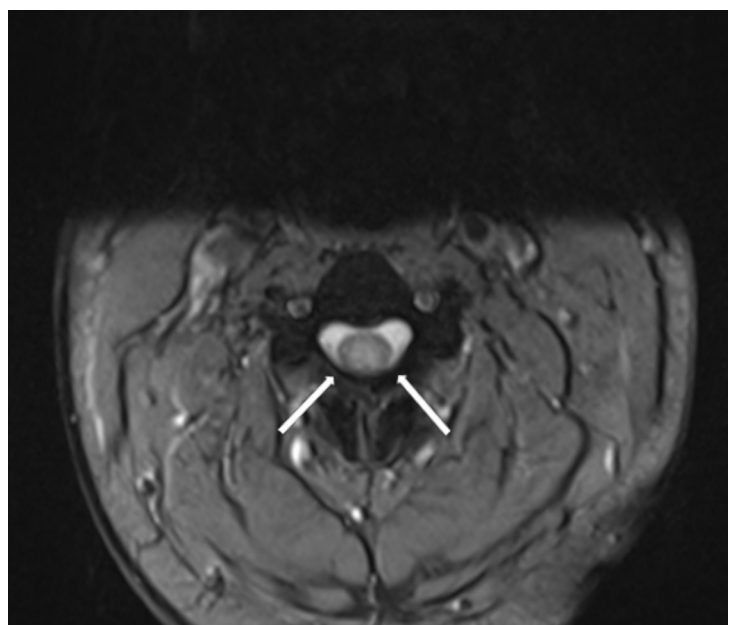


Figure 2 Axial T2-weighted image of the cervical spine showing a hyperintense signal (arrows) within the dorsal column of the spinal cord

Further T1-weighted imaging, with and without gadolinium, did not show any anomalies or enhancement (Figure 3 and Figure 4). This exam was deemed compatible with N₂O toxicity.

The patient's clinical evolution was positive; quickly regaining some of his strength. A follow up blood test performed 8 days later showed vitamin B12 levels above the norm due to the treatment. Following this, the patient underwent 2 months of intensive physical therapy as an inpatient. During this time, he regained much of his strength, being able to walk without support between parallel bars, though requiring a walking frame to move around. However, he continued to exhibit limited ataxia and required help to get up if he fell. He was discharged after 2 months to an outpatient clinic to continue his treatment once he was able to move using a walking frame. After 4 months he regained of the ability to walk at a pace of 5km/h for 20 minutes and use a stationary bicycle for the equivalent distance of 10km. He showed marked strength improvement, however he remained ataxic and had difficulty maintaining balance. At six months the patient continued to have difficulty maintaining balance and had not yet regained the ability to run.

DISCUSSION

Nitrous oxide abuse is a growing problem, with an increased prevalence amongst teenagers and young adults.⁹ The gas is often inhaled from the balloons.⁹ Other methods of administration include direct inhalation from the canister, connecting the

canister to a face mask or releasing it into a bag which is then placed over the head of the user.⁹

Nitrous oxide toxicity can result in subacute combined degeneration of the dorsal and lateral spinal columns as well as the spinocerebellar tract.^{2,10} The symptoms include paraesthesia, which our patient presented with, and sensory ataxia which can be associated with loss of proprioception.^{2,7,10} Symptoms can progress to spasticity, clonus, muscle weakness, paraplegia, and faecal and urinary incontinence.^{7,10} Further features of the disease can be peripheral axonal degeneration as well as central nervous symptoms such as Lhermitte phenomenon.^{7,10}

The MRI features of this condition are T2-signal hyperintensity of the posterior, and sometimes lateral column, of the spinal cord.^{8,10} Cases of mild contrast-enhancement of the lesions have also been described.⁸ However, some cases exist where there are no visible MRI abnormalities.⁸

There are many purported mechanisms for the neurotoxicity of N₂O involving the induction of vitamin B12 deficiency, classically defined as a serum level under 200pg/ml.² One theory is the N₂O affects vitamin-B12 by permanently oxidising cobalt ions and making the vitamin non-functional without decreasing the concentration itself.^{2,8} Vitamin B12 is an essential co-factor in turning homocysteine into methionine, which is necessary for the methylation of myelin, and methylmalonic acid.^{2,8} In this way, N₂O toxicity can result in demyelination.⁸ One should note that due to

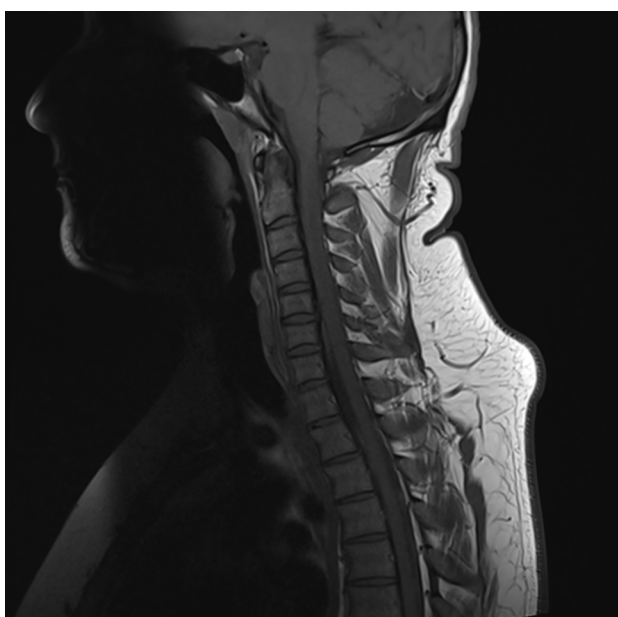


Figure 3 SSagittal T1-weighted image of the cervical spine showing no hyper or hypointense areas within the spinal cord

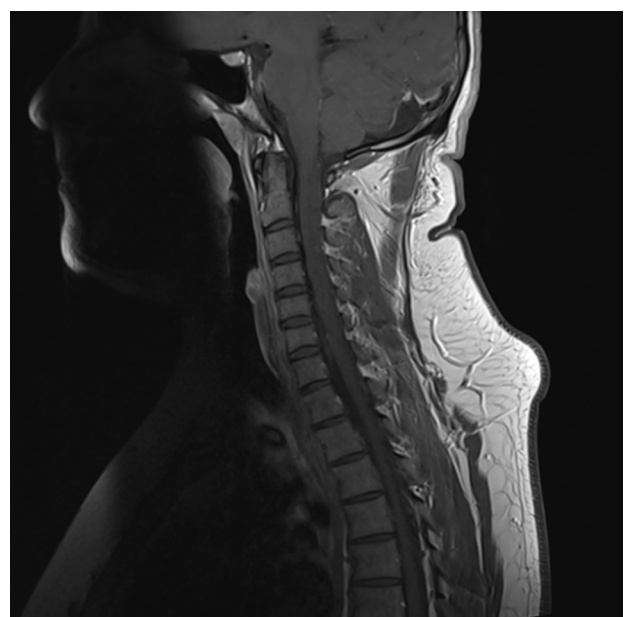


Figure 4 Sagittal T1-weighted contrast-enhanced image of the cervical spine showing no zones of focal enhancement

the method of action of N₂O, vitamin B12 levels may appear normal, which could be due a disruption of vitamin B12 availability at the cellular level.^{2,8} For this reason, one should also test homocysteine levels, as these may be elevated in N₂O toxicity and provide an essential clue for the diagnosis.⁸

The treatment of nitrous oxide toxicity is based on reversing the vitamin B12 deficiency, with no consistent treatment regimen being apparent amongst the various case reports.⁸ The prognosis is variable, but seems to depend upon prompt treatment, with intramuscular vitamin B12 seeming to be associated with better outcomes than oral supplementation.⁸ Importantly, this treatment must be accompanied by folate supplementation to avoid the methyl folate trap¹¹. To our knowledge, no guidelines exist for the required length of the treatment.

CONCLUSION

Nitrous oxide is a commonly used recreational drug which can occasionally present with severe neurological side effects. Patients presenting with bizarre neurological symptoms that are clinically compatible with N₂O toxicity, abuse of the substance should be suspected.

MRI features typically include spinal cord T2 hyperintensities centred on the posterior and lateral columns, though these may be absent in some cases. Patients should undergo a blood test for vitamin B12 levels, which may also be normal, and homocysteine levels, which should be increased in cases of N₂O toxicity.

Once the diagnosis of N₂O toxicity is established, prompt vitamin B12 administration, alongside folate supplementation, is required. However, even with rapid diagnosis and treatment, a positive prognosis for the patient is not guaranteed.

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A case of antiphospholipid syndrome associated with bilateral intermediate uveitis

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A 61 year old male presented with blurred vision after being treated for an unknown source of infection. He was found to have bilateral intermediate uveitis after urgent ophthalmological review. Blood results showed a genuine persistent thrombocytopenia. In view of the history of bilateral intermediate uveitis in association with a genuine thrombocytopenia, further blood investigations were taken. Further investigations revealed positive anticardiolipin antibodies, β_2 glycoprotein antibodies and a strongly positive lupus anticoagulant test. Uveitis is an uncommon presentation of antiphospholipid syndrome. This case report outlines a case of bilateral intermediate uveitis in association with antiphospholipid syndrome.

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A 61 year old gentleman presented to the Accident and Emergency Department at Mater Dei Hospital, Malta with a self-reported history of fever in the previous two weeks, associated with back pain and an antalgic gait and that had persisted despite a course of Amoxicillin followed by a course of Doxycycline. This gentleman had sustained a mechanical fall in a quarry with trauma to the left lower limb one month prior to presentation, for which he had not sought medical advice. On presentation his blood pressure was within normal limits at 132/85, pulse rate was 74 beats per minute and he was afebrile.

Physical examination revealed an antalgic gait and a traumatic left lower limb laceration which appeared to be healing. Lower limb tone, reflexes and sensation were normal. On presentation he denied diplopia or any visual disturbance, with full cranial nerve examination also being normal.

Laboratory investigations on admission showed a genuine thrombocytopenia that was confirmed with a blood film. C-reactive protein was raised at 140 mg/L however erythrocyte sedimentation rate was within normal limits (13mm first hour). Liver function tests showed predominant transaminitis with a normal bilirubin level (12.8 micromoles/L). Alanine aminotransferase level was 95 U/L, alkaline phosphatase level 144 U/L and gamma glutamyl transferase 71 U/L. Blood and urine cultures returned negative.

A computerised tomography scan of the thorax, abdomen and pelvis excluded the presence of any abscesses. The lumbar spine was also imaged with magnetic resonance imaging, with the imaged axial skeleton showing red marrow persistence.

In view of sepsis with an unknown source of infection on admission, he was treated with broad spectrum intravenous antibiotics with combined tazobactam and piperacillin for two weeks. There was good clinical response with concurrent normalisation of inflammatory blood markers, but persistence of thrombocytopenia.

On the thirteenth day of hospitalisation, the patient developed visual disturbance which he described as seeing "black spots". Urgent ophthalmology review was sought, which confirmed bilateral intermediate uveitis with vitreous condensation in both eyes. This was treated with dexamethasone 0.1% eye drops every three hours for eleven days, which was then tailed down by one drop every 5 days. An improvement in vision was reported by the patient after two weeks

of dexamethasone eye drops treatment and his vision was fully restored after 4 weeks.

In view of the history of bilateral intermediate uveitis in association with a genuine thrombocytopenia, further blood investigations were taken. Of particular note, anticardiolipin antibodies and $\beta 2$ glycoprotein antibodies were positive as well as a strongly positive lupus anticoagulant test. Thrombocytopenia persisted despite improvement of the patient's clinical condition. Serum angiotensin converting enzyme was mildly elevated.

A diagnosis of antiphospholipid syndrome was made and low dose aspirin was started. Repeat serum testing after six weeks continued to confirm the persistence of antiphospholipid antibodies, B2-glycoprotein antibodies and lupus anticoagulant. **Table 1** below shows other tests that were taken to exclude secondary causes of bilateral uveitis.

Table 1 Table of results

Serological tests	
Platelets	50 - 94 x10 ⁹ /L
Bilirubin	12.8 micromoles/L
Alanine aminotransferase	95 U/L (5-41)
Alkaline phosphatase level	144 U/L (40-129)
Gamma glutamyl transferase	71 U/L (8-61)
Complement 3 & complement 4	Normal
Serum protein electrophoresis	No monoclonal band detected
Anticardiolipin antibodies	Positive
B2 glycoprotein antibodies	Positive
Anti-nuclear Antibodies	Positive
ANCA	Negative
Lupus anticoagulant	Strongly Positive
Syphilis	Negative
Serum Angiotensin converting enzyme	88U/L (20-70)
HLA B27	Negative
HLA B51	Negative
Cytomegalovirus IgM & IgG	Negative
Toxoplasma IgM & IgG	IgM negative, IgG positive
Bartonella Serology	Negative
Borrelia Serology	Negative
Rickettsia conorii IgM antibodies	Negative
Radiological Imaging	
CT thorax, abdomen and pelvis	no evidence
MR lumbar spine	multilevel degeneration of the spine
MR head	Empty sella syndrome, but otherwise normal
MR orbits	Non-specific retro-orbital fat inflammatory changes.
Positron emission tomography	No signs of large vessel vasculitis

DISCUSSION

Antiphospholipid syndrome is a hypercoagulable disorder which is acquired later in life. The main presenting features leading to investigation and diagnosis are thrombotic conditions and pregnancy-related adverse outcomes. Thrombotic events may affect the venous, arterial and/or microvascular component. Antiphospholipid syndrome can be linked to other autoimmune diseases, such as systemic lupus erythematosus (SLE). In this case, this would be referred to as secondary antiphospholipid syndrome which accounts for half of the cases of antiphospholipid syndrome.¹

Diagnosis depends on the presence of: lupus anticoagulant, anticardiolipin antibody, and anti-beta 2 glycoprotein I antibody. The antibody which is related most to thrombosis and adverse pregnancy outcomes is lupus anticoagulant which is detected in platelet-deplete plasma, particularly the presence of higher IgG titres compared to IgM and their persistence for at least 6 months.¹

It is not uncommon to detect antiphospholipid antibodies in seemingly healthy individuals. This would however be detected at low titres. In fact, the lupus anticoagulant or anticardiolipin antibodies have been detected in 1-5% of young healthy subjects. Also, the anticardiolipin and anti-beta 2 glycoprotein I antibodies have been detected in 12% of the older portion of the population. Antiphospholipid antibodies can be induced through an infectious process, via both viruses and bacteria; such as: human immunodeficiency virus (HIV), hepatitis B and C, leprosy, and syphilis. However, antiphospholipid antibodies which are secondary to the above-named infectious processes are not linked to a pro-thrombotic state of the antiphospholipid syndrome. The detection of antiphospholipid antibodies can also be linked to underlying malignancy.¹

Low platelet count is a feature common to one third of the patients with antiphospholipid syndrome. This

happens via activation and aggregation of platelets secondary to the binding of beta 2 glycoprotein I receptors on platelets. Thrombocytopenia is usually mild. In severe cases, corticosteroids, intravenous immunoglobulins and rituximab can be used.¹

As mentioned earlier, antiphospholipid syndrome is a prothrombotic condition that can lead to thrombosis in the microvascular compartment including in the eye.¹ In a review and metanalysis by Turk et al, ocular complications in antiphospholipid syndrome occur in 35% of the cases, with retinal infarctions and haemorrhages being the more predominant features.²

Intermediate uveitis is linked to both infectious and non-infectious causes; with multiple sclerosis, sarcoidosis and intraocular lymphoma being the most mentioned for the latter category.³ In 2021 a retrospective study that had been done showed that the presence of either of the antiphospholipid antibodies was found in 20.6% of patients with uveitis, that otherwise had no other features of systemic thrombosis suggestive of antiphospholipid syndrome. The majority of these patients, had exclusively anterior uveitis.⁴

Antiphospholipid syndrome is associated with HLA typing as demonstrated by both animal and human models, with: HLA-DR4, HLA-DR7, HLA-DRw53 and HLA-DQB1*0302 being the ones mostly shown to be related in the latter. However, there are inter-racial differences in the HLA associations. Major Histocompatibility complex genes have an effect on both disease manifestation and the production of antibodies.^{5,6}

SUMMARY

Uveitis is an uncommon presentation of antiphospholipid syndrome.

Persistent thrombocytopenia is a feature of antiphospholipid syndrome.

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A case of Dapsone-induced Haemolytic Anaemia without glucose-6-phosphate dehydrogenase deficiency “mind the bite”

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Introduction: Some drugs induce haematotoxicity as a consequence of increased oxidant stress, especially in susceptible patients, namely those with glucose-6-phosphate dehydrogenase deficiency. Less commonly, it occurs in non-deficient individuals, as we report in this case.

Case report: A patient with a dermatological condition (and multiple comorbidities), being treated with dapsone, is hospitalized due to sepsis with multiorgan dysfunction, including anaemia and thrombocytopaenia. After a good initial response, the haematological dysfunction worsens, suggesting more contributing factors other than the initial septic insult.

Conclusion: It is essential to establish a broad evaluation of each patient, considering a careful review of their past medical history, multiple comorbidities and associated medications. A multidisciplinary discussion can assist in better diagnosis and follow-up of patients. In this particular case, the peripheral blood smear and biochemistry findings were crucial clues to establish the diagnosis.

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Haemolytic anaemia (HA) in a patient with multiple comorbidities and polymedicated should always raise suspicion for drug-related adverse effects.¹ The mechanisms by which drugs can induce haemolysis varies: for example, some antibiotics, non-steroidal anti-inflammatory drugs, analgesics and anti-cancer drugs prompt autoimmune HA, some medications cause thrombotic microangiopathy and other induce an exacerbation of oxidative stress or methaemoglobinemia, in which dapsone is included.²

CASE REPORT

We report the case of a 75-year-old female, cognitively intact but with multiple medical comorbidities, namely cardiovascular (essential hypertension with hypertensive heart disease), metabolic (obesity and Type 2 diabetes mellitus, with end-organ damage), renal (nephropathy of diabetic/hypertensive etiology with chronic kidney disease at KDIGO stage 3b) and immunological (euthyroid chronic autoimmune thyroiditis). The patient was originally diagnosed with pemphigus foliaceus in Dermatology consultation. She started lepicortinolone at that time at a dose of 60 mg for 2 weeks, but after initial partial clinical improvement, there was systematic recurrence on weaning. Several months afterwards she developed marked worsening and progression of the lesions to the anterior thorax, abdomen, shoulders, external genital region, face, ears, accompanied by severe itching, marked insomnia, and uncontrollable diabetes secondary to corticosteroid treatment. For these reasons, she came to the emergency department and was hospitalized to complete aetiologic study and have a proper medical approach. On discharge, dapsone was introduced, 100 mg and then 50 mg every other day (after being excluded glucose-6-phosphate dehydrogenase (G6PD) deficit), desloratadine, and prednisolone 40 mg. In baseline analytical terms, she had hemoglobin (Hb) of 12 g/dL (normal (N) 12 – 16), normal liver function tests and serum creatinine of 1.5 mg/dL (N 0.6 – 1.1).

Two weeks after being discharged, she presented to the emergency department with a history of fever and altered mental status in the last two days. After evaluation and study, she was admitted again, with a diagnosis of sepsis starting in acute pyelonephritis,

with associated multiorgan dysfunction: volume-refractory hypotension requiring vasoactive agents, need for non-invasive ventilation, acute kidney injury (with a serum creatinine peak of 2.28 mg/dL). Further evaluation revealed elevated inflammatory parameters (c-reactive protein of 361 mg/L (N < 5) and procalcitonin of 25.5 ng/mL (N < 0.5)), anaemia (11 g/dL on admission) and thrombocytopaenia (115 000/uL; N 150 000 – 400 000). Treatment was empirically initiated with piperacillin/tazobactam. The initial blood cultures showed growth of Gram-negative bacilli, identified to be *E. coli* resistant to amoxicillin/clavulanic-acid, ampicillin and cefuroxime, and sensitive to ceftazidime and piperacillin/tazobactam, so the antibiotherapy was switched to ceftazidime. In the first days, she evolved favorably concerning all the dysfunctions initially presented, except for the haematological one – there was a progressive worsening of the anaemia (up to a minimum Hb value of 7.1 g/dL). In this context, the peripheral blood smear was meticulously reviewed, revealing the presence of keratocytes and “mushroom” cells (Figure 1A and 1B). Given these findings, the analytical study was extended, revealing 5% of reticulocytes (N 0.5 – 2.0), Heinz bodies (Figure 1C and 1D), lactate dehydrogenase of 374 U/L (N 125 – 220), total bilirubin of 2.4 mg/dL (N 0.2 – 1.2) at the expense of nonconjugated fraction and undetectable haptoglobin, findings that favored the hypothesis of haemolytic anaemia. A direct Coombs test was performed, which was negative, excluding autoimmunity as the cause of haemolysis. To perform

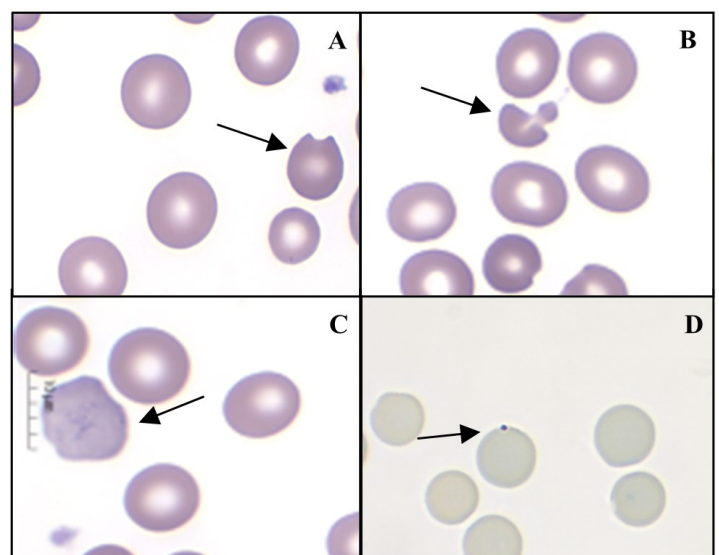


Figure 1 Blood smear of the patient, x1000, May-Grunwald-Giemsa coloration (A–C) and new methylene blue coloration (D): A – keratocyte (bite cell); B – “mushroom” cell (“pincer” cell); C – polychromatophile; D – Heinz body.

a biopathological validation of the laboratory results, the clinical file was reviewed, including all the medications she was taking at the time of admission. The hypothesis of an iatrogenic etiology for these haematological findings due to dapsone was placed and, accordingly, methemoglobin was measured – which would be increased (7.1%; N 0.4 -1.5). It was also verified that, besides not having G6PD deficit, the patient did not have a haemoglobinopathy either. Dapsone was discontinued, resulting in an increase in Hb up to 10 g/dL, which also corroborates dapsone being the cause of these haematological alterations.

DISCUSSION

This clinical case reveals the importance of a holistic assessment of each patient. Even though the initial haematological disorders observed could have been justified by the septic condition, the persistent single dysfunction after significant general improvement, motivated the consideration of other etiological factors.

Dapsone is a synthetic sulfone, belonging to the class of antibiotics, used to prevent and treat some infectious and inflammatory diseases. Currently, its use is more related to the treatment of some dermatological conditions and as a second-line option in the prophylaxis of *Pneumocystis jirovecii*-pneumonia.² After being metabolized in the liver by cytochrome p450, its active metabolites (hydroxylamines) are responsible for inducing not only its therapeutic effects but also adverse effects, the most frequent being nausea, loss of appetite, and haematotoxicity (manifested mainly by methemoglobinemia and haemolytic anaemia). Methemoglobinemia occurs in about 15% of patients and haemolysis in about 20%. These effects are dose-dependent.³

The main mechanism involved in developing haematotoxicity is oxidative stress, exacerbated in patients with G6PD deficit or Hemoglobin H disease, since they have decreased natural antioxidant defenses, and are, therefore, more sensitive to oxidative processes. Thus, it is always recommended to study the G6PD activity before the initiation of treatment with dapsone. However, there are several described cases in the literature of patients who, even in the absence of a deficit related to the G6PD enzyme or haemoglobinopathies, ended up developing serious cases of haematological dysfunction associated with dapsone therapy, in different clinical contexts.⁴⁻⁸

This case also demonstrates how, given certain findings, the clinical process review and a timely extension of the analytical study during the biopathological validation of the laboratory results can be beneficial for a patient diagnosis. Thus, clinical-laboratory communication and joint case discussions can help to a quick and efficient confirmation of an eventual hypothesis.

CONCLUSION

When suspecting the presence of HA, it is mandatory to perform a peripheral blood smear for the evaluation of red cell morphology. The findings should give some clues about the possible mechanism of haemolysis. Also, in polymedicated patients, it is crucial to perform a complete review and suspect if any of the drugs could be the cause of haematotoxicity. Even in patients with a plausible etiology for the presence of anaemia, it is important to consider secondary causes that might contribute to the progressive worsening conditions.

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