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Against the Dying of the Light: Medicine's Quiet Resistance

Victor Grech

The world groans under the weight of war. From the ruins of Gaza to the shelled hospitals of Ukraine, from the famine-stricken clinics of Yemen to the tense standoff over the South China Sea, the twenty-first century, far from fulfilling its promise of peace and progress, has revealed a darker truth. This is the century wherein precision-guided missiles fly faster than ambulances, where cities crumble while laboratories strive to build miracles of healing, and where the medical oath to preserve life is tested by the organised machinery of death. The juxtaposition is grotesque: as one hand reaches for the scalpel, the other reaches for the trigger. And in the middle of this violence we, the medical profession, must not take sides, but remain steadfast, and stubbornly humane.

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COVER PICTURE

The front cover depicts the logo for the forthcoming 11th Malta Medical School Conference. This will be held between 4-6 December at the Mediterranean Conference Centre in Valletta.

Medicine, by its very nature, is an act of resistance. It resists entropy and decay, it resists despair, and above all it resists the cold arithmetic of conflict where lives become collateral, and suffering is strategically ignored. In an era when borders are drawn in blood, and truth itself is fractured along ideological lines, twisted beyond recognition and presented as alternative facts, the physician unwaveringly approaches the broken body with one universal imperative: to heal. To do no harm. To preserve the light, however faint.

Ours is a quiet resistance. It does not march with banners nor chant slogans. It does not command armies or make headlines. But its strength lies in its refusal to surrender to the illogic of destruction. In a hospital ward where a child lies wounded by a drone strike, or a mother clutches her baby in the rubble of a maternity clinic, medicine answers with dignified hard work and does not question who is right, but questions what is needed. A tourniquet. Oxygen. Blood. To keep a heartbeat going.

What a strange paradox we inhabit! The same science that gives us organ transplants, gene therapy, and vaccines that tame pandemics also gives us nerve agents, drone swarms, and hypersonic missiles. Artificial intelligence, hailed as the next frontier in diagnostics and personalised care, is equally being harnessed to guide autonomous weapons to their targets. Biomedicine and bioterror evolve side by side. It is not knowledge we lack, but wisdom.

Furthermore, the violation of medical neutrality in wartime is no longer the rare outrage but the standard backdrop. Hospitals are bombed and ambulances are targeted. Physicians are detained, disappeared, or executed. The Geneva Conventions, once thought to define a sacred zone around the sick and wounded and those who care for them, are daily elided by political convenience and military expedience. Yet in cities under siege, field hospitals continue to function. In refugee camps, under rain and snow, doctors continue to work by torchlight. Indeed, their resistance is not just in what they do, it is in what they refuse to become.

There is power in choosing empathy when fear demands silence. There is power in stitching wounds when the world unravels. Every act of healing is a

refusal of despair or nihilism. Every surgical intervention in a war zone, every vaccination in a refugee settlement, every psychiatric session with a trauma survivor is a candle against the overwhelming dark. Physicians are not do not carry weapons of war – we are not soldiers. But we are, in our own way, warriors of another kind, albeit quiet, relentless, unarmed.

Let us not pretend that medicine is untouched by politics. Access to care is political. Distribution of vaccines is political. Research funding is political. The silence of medical institutions in the face of atrocities is political. But our profession's core remains profoundly ethical: to see in the patient not a passport, not a religion, not an allegiance, but a human like us, a person. That is what makes medicine more than a career. It is a vow to do our best to heal. And in times like these, vows matter more than ever.

The world will not be saved by idealism alone. But neither will it be saved by cynicism. Somewhere in between lies duty, our duty. And medicine, with all its limits and all its miracles, embodies that duty more purely than most callings. We cannot stop wars, but we can refuse to be shaped by them. We cannot stop the bombs, but we can tend to those they leave behind. We cannot reverse death, but we can walk alongside the dying with tender compassion, and ensure that the light does not go out unnoticed.

This editorial is only another small candle in the dark. It is not a call to retreat from the world, but to engage with it more fiercely and even more humanely. To speak out when medical neutrality is breached. To support colleagues working in impossible conditions. To educate ourselves on the ethics of war, peace, and global health. And to remember, always, that medicine is not just about curing illness but also about affirming the value of life, this precious short life of ours, especially when life is being devalued.

In the gathering dusk of a world that sometimes forgets its own humanity, medicine does not shout. It does not rage. It resists, not with fire, but with light. Not with conquest, but with compassion. In every clinic, in every ward, in every battlefield tent, the quiet resistance continues. It is not loud, but it is luminous. *Primum non nocere* – long may medicine endure.

Insulin - The Modern Era

Maria Mizzi, Simon Mifsud

Insulin – a naturally occurring hormone produced by beta cells in the pancreas, has been successfully isolated and purified in the year 1921 by the scientists Banting and Best in Toronto. Since then, more than 100 years later, different formulations and delivery methods have been developed. Type 1 diabetes depends on insulin for survival and reduced morbidity. Therefore, it came naturally with time to research newer technologies that mimic as much as possible the job of the pancreatic beta cells to provide insulin. This led to the development of the first model of continuous subcutaneous insulin infusion in the 1970s. Several advantages have been linked to the insulin pump as opposed to multiple daily insulin injections. Literature mentions better glycaemic outcomes with increased time in range and reduced hypoglycaemic episodes with insulin pumps. Other benefits vary from practical and psychological benefits with regards to the changing mentality towards living with type 1 diabetes, to long-term benefits involving the reduction of micro- and macrovascular complications. Studies are still being conducted to determine whether type 2 diabetic patients could also benefit from such insulin pumps.

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The years 1921 and 1922 saw one of the biggest discoveries in medical history – the discovery of insulin by Banting and Best in Toronto.¹ Prior to the isolation and administration of exogenous insulin, a diagnosis of type 1 diabetes meant a shorter life span, seeing a lot of childhood deaths within 1-2 years from disease onset. Mortality data from a clinic in Boston, Massachusetts concluded that death in young type 1 diabetic patients in their first decade of life has decreased by six times following the availability of insulin in clinical practice.² Following the 23rd January 1922 when insulin was first successfully administered to a 14 year old boy – Leonard Thompson in Toronto General Hospital, clinical improvement was immediate and every child with diabetic ketoacidosis (DKA) started showing immediate improvement with Leonard Thompson himself managing to survive a further 13 years after this day. It was only after May 1922, that by the agreement with the pharmaceutical company Eli Lilly, insulin started to be produced on a larger scale to target more patients.¹

Despite being a drug that literally saved dying children, insulin in its very first days saw a lot of challenges when it came to administration, dose titration and monitoring of its effect. These challenges nowadays are almost unheard of thanks to the evolution of both the drug itself, with the introduction of recombinant human insulin with various modes of action such as short or long acting; and also other technologies surrounding administration and monitoring.¹ Technology has improved in such a way that insulin administration has moved from syringes, to pens and continuous subcutaneous insulin pumps. The concept of insulin pumps goes back to 1963 when Dr. Arnold Kadish designed the first prototype that was less portable than what we are used to nowadays. It was then only in the 1980s that the subcutaneous insulin pump with adequate programmability and portability became available on the market. And since then, technology kept improving to the point that nowadays, there are insulin pumps available that contain a system of continuous blood glucose monitoring whereby blood glucose readings are channelled to the pump itself which calculates and administers prandial insulin boluses – the so called Advanced Hybrid Closed Loop (AHCL) systems.^{3,4}

DISCUSSION

The way a continuous subcutaneous insulin infusion works is by mimicking the pancreas by providing a

continuous release of short acting insulin (the basal rate), and then gives the possibility to administer larger boluses close to meals.^{3,5} The crucial difference compared to the pancreas comes from the fact that the exogenous insulin administered in the fat tissue gets transported to muscle, bypassing the liver. Endogenous insulin on the other hand finds its way to the liver via the portal circulation. This way, there is homeostatic regulation of insulin levels to be able to exert the full desired action peripherally and eventually insulin clearance.⁶

Basal insulin has the aim to control blood glucose during fasting hence replacing the use of long-acting insulin formulations. The basal insulin rate is influenced by many variables including physiology, developmental life stage, activity level, and time of day.⁵ In fact, this is usually set in the pump after discussing with ones Diabetologist. Certain pumps have the facility to programme multiple basal insulin rates which can be chosen then by the patient depending on the specific daily activities.⁷ This is especially helpful during periods of acute illness or strenuous exercise. As a rule, 30-50% of the total insulin dose administered in one day should be in the form of basal insulin, with the rest being boluses administered with meals. The prandial boluses can be administered either as an immediate insulin dose over a short time, or over a longer period of time (extended bolus) depending on how the pump is programmed. The extended bolus is particularly beneficial in association with the consumption of high fat and/or protein meals. Such prandial bolus doses can be calculated according to oral intake and using the facility of bolus calculators which are incorporated in most insulin pumps available on the market.⁵

Although there are various insulin pumps on the market, these essentially consist of a reservoir of insulin which is either connected directly to the subcutaneous tissue via a cannula – the so-called “patch pump”; or else, insulin would be delivered via a tubing system to the cannula in the subcutaneous tissue.^{8,9} All systems available are battery-operated and there are both non-automated as well as automated systems available.^{5,8} The Food and Drug Administration (FDA) of the United States has approved Lispro and Aspart for usage in insulin pumps which can stay in the reservoir for a maximum of 144 hours. Other short-acting formulations of insulin would have different shelf lives depending on the risk of crystallisation, etc. The insulin pump can deliver a basal insulin rate at various rates with the lowest rate being that of 0.01 unit/hour.⁹

The initial cost for an insulin pump varies between around €2300 and €3500, depending on the brand one buys and the features available.¹⁰ Apart from this initial cost for a pump that is set to last at least five years, there is an additional cost of around €1100-€2300 yearly in tubing, cannulas, and other pump exchangeable parts (excluding other equipment such as adhesives, pump pouches, etc.). This yearly cost also excludes the supply of insulin itself, which in countries where treatment is not available on the formulary can amount to thousands per year.^{7,10} Considering the price, this could be a limiting factor to the transition from multiple daily insulin injections (MDI) to the insulin pump, especially in cases where patients fail to have medical insurance cover. Also, the need for trained healthcare professionals to safely run such a service limits the setting up with a large number of patients.⁵

Such systems have the advantage that patients tend to accept it better with improved compliance.³ Also, with regards to food, it allows for better precision of insulin administration as the pump is able to administer smaller doses of 0.05-0.1 units as compared to the 0.5-1 units administered using a syringe or pen. Therefore, improving blood glucose readings as well as eliminating the need for snacking to prevent hypoglycaemic events.⁵ Disadvantages associated with this system include local skin reactions and the need for good training and motivation from the patient's side before introducing such system.³ Also, one needs to take into consideration, the patient's willingness to 'wear' an external medical device 24 hours, before introducing such system.⁹ Taking into consideration all these advantages and disadvantages, a decision to transition from MDI to the insulin pump is taken on an individual basis after a multi-disciplinary team discussion consisting of: Consultant Diabetologist with special interest and training in pump therapy, diabetes specialist nurse and dietician with special interest in diabetes.⁵ In the event of system failures, dislodgement, or damage, there is risk of DKA due to the interruption of insulin supply.⁸

According to the National Institute for Health and Care Excellence (NICE) guidelines on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus, published in July 2008; the pump is only funded in type 1 diabetic patients above the age of 12 years who are unable to reach their target HbA1c level despite optimal care or where increase in doses is difficult in view of multiple hypoglycaemic events. In younger children the pump would only be recommended when insulin administration via multiple daily insulin injections

(MDI) is deemed inappropriate or inconvenient, and with the expectation that at some point after the age of 12 years and before adulthood they are given a trial of MDI.¹¹

In the Standards of Medical Care in Diabetes published by the American Diabetes Association (ADA) in 2022, the recommendation was that automated insulin pumps should be offered to youths, ideally above the age of 15 years, and adults with type 1 diabetes. Where deemed safe to use, such devices were also recommended in other types of diabetes where insulin deficiency is the aetiology.⁸

In a Danish cross-sectional survey consisting of 770 type 1 diabetic patients above the age of 18 years using the insulin pump, it was found that better HbA1c outcomes were obtained in patients who had achieved higher levels of education. A decrease of 0.4% in HbA1c was noted in those progressing to higher education as opposed to those leaving school after primary education.¹² In the case of system failures, dislodgement or damage, there is risk of DKA as insulin supply gets interrupted.⁸

Patient satisfaction and a positive attitude towards the insulin pump was noted as well in the Italian cross-sectional study conducted between February and August 2021 where out of the 182 type 1 diabetic patients interviewed, 83 were using the continuous subcutaneous insulin pump. This was linked to the fact that such patients had an overall positive attitude when it came to the technology itself, as technology-related stress has been shown to be associated with poorer treatment outcomes and compliance.¹³

In a Swedish study published in 2016 on the Journal of Diabetes Science and Technology, data from the Swedish National Diabetes Register between 1st June 2014 and 16th November 2015 revealed that 8799 out of 35725 type 1 diabetic patients included in the study were using a continuous subcutaneous insulin infusion. The majority of these were females with an average age of 41.5 year old. This study then looked at HbA1c difference and albuminuria in patients on continuous subcutaneous insulin infusion when compared to those with MDI – taking also into consideration the reason why the former cohort were started on the pump. The vast majority of patients using the insulin pump had lower HbA1c when compared to patients on MDI. This however wasn't true in those patients where the insulin pump was initially indicated for poor glycaemic control with a high HbA1c. With regards to albuminuria, although it was found that patients using the insulin pump had a higher incidence of albuminuria, this was again linked

with the fact that such patients might have switched to the pump from the MDI regime in view of previously poor glycaemic control, hence already leading to end organ damage and albuminuria.¹⁴

In the multicentre randomised control trial – SCIP RCT published in 2018 on Health Technology Assessment, data from children and young people (aged 7 months to 15 years) started on either a continuous subcutaneous insulin infusion or MDI at diagnosis of type 1 diabetes were compared to each other. This study concluded that overall there was no noted advantage of the insulin pump compared to the MDI in the first year from diagnosis of type 1 diabetes. Also, the insulin pump was not a cost-effective treatment in this particular group of patients. These conclusions were based on the fact that HbA1c levels between the two groups were not significantly different when checked 1 year after start of treatment. Despite these findings, it did show however a better quality of life described especially by parents of such patients.¹⁴ These findings correlate to the recommendations of both the National Institute for Health and Care Excellence (NICE) and the American Diabetes Association (ADA) guidelines with regards to age when insulin pumps should be ideally used.^{8,11}

In the review by Bassi et al published in March 2023, different Automated Insulin Delivery (AID) systems available for clinical use were researched to look at their individual features and overall clinical benefit for type 1 diabetic patients. Such systems studied included the Minimed 780G, which was the first hybrid closed loop system launched by the pharmaceutical industry in 2016, and Tandem Control-IQ amongst others. Overall, all the systems have shown an improved glycaemic control manifested by increased time in range, decreased time below range (hypoglycaemic events), as well as a decrease in HbA1c levels.⁴

Having better glycaemic control reflects on long-term morbidity and mortality. A Swedish study by Steineck, et al published on the BMJ in 2015 compared the incidence of cardiovascular disease and mortality in type 1 diabetic patients on MDI versus those on insulin pumps. Out of the 18168 people studied, 2441 were on the insulin pump, while the rest were on MDI. Such patients were then followed-up for a mean of 6.8 years. With regards to all outcomes studied (including both non-fatal and fatal coronary heart and cardiovascular diseases), patients on the insulin pump had a lower hazard ratio when compared to those on MDI. It was however difficult to conclude whether these findings were

related to any possible clinical or educational factors linked to the insulin pump or the physiology how the insulin pump works.¹⁶

Other studied diabetes-related morbidities included retinopathy and peripheral neuropathy. In a prospective study from the years 2000 to 2014, 989 adolescent patients between the ages of 12 and 20 years that had at least received 12 months of treatment with either the insulin pump or MDI, were studied. Although no statistically significant difference was noted among the two groups when it came to HbA1c levels, patients on the insulin pump showed a lesser incidence of retinopathy and peripheral neuropathy when compared to the MDI.¹⁷

Not only has the insulin pump been shown superior to the MDI system with regards to reducing long-term micro- and macrovascular complications related to type 1 diabetes, but also when it comes to risk of hypoglycaemia. Without any doubt, hypoglycaemia is one of the most feared complications of diabetes that limits reach of adequate treatment targets. From the 21 studies analysed during the meta-analysis by Pickup and Sutton, they concluded that severe hypoglycaemic events were related more to MDI use and this was more prevalent in adults who had been diagnosed with diabetes for a longer time.¹⁸ In the evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycaemia, published on Diabetes Care in 2015, it was recommended that the sensor-augmented insulin pump is a good option apart from patient education, continuous glucose monitoring and pancreatic islet cell transplantation, to prevent severe hypoglycaemia events. In fact the insulin pump was recommended at stage 2 in the proposed treatment algorithm for type 1 diabetes when faced with challenges of hypoglycaemia.¹⁹

Apart from a decrease in severe hypoglycaemic events, in the PR-IAH study (protective and risk factors of impaired awareness of hypoglycaemia in patients with type 1 diabetes), published in 2023, the insulin pump was found to be related to less impaired awareness of hypoglycaemia.²⁰ Also, in the pilot study by Giménez et al, it was shown that after 2 years from starting the insulin pump, there was a noted improvement in patient hypoglycaemia unawareness when compared to patients with MDI.²¹

The use of the insulin pump is also being studied for use in type 2 diabetes especially in around 30% of these patients who are not able to reach their glycaemic targets even with insulin in the form of MDI.^{22,23} HbA1c amelioration was even observed in

type 2 diabetic patients on the pump when compared to those on MDI. In the OpT2mise randomised open-label controlled trial, 331 type 2 diabetic patients were randomised in such a way that 168 patients were started on the insulin pump, while the rest were given MDI. At the end of the 6 months of this study, patients on the insulin pump required less insulin in a day with a mean of 97 units when compared to a mean of 122 units in those patients treated with MDI.²⁴

When it came to quality of life, similarly to patterns seen in type 1 diabetic patients on the pump, patients with type 2 diabetes were also shown to have an improved quality of life. With regards to expense, although initial costs to start and maintain an insulin pump are higher when compared to MDI, in the long term, costs are less when compared to those involved in morbidity management related to poor glycaemic control.^{23,24}

The technology of the insulin pumps has greatly evolved over the years since the first model of the continuous subcutaneous insulin infusion in 1976. The year 2005 saw the introduction of sensor augmented pumps, with a later on added feature of low glucose suspend to stop the pump whenever low blood sugar was detected. In 2009, the patch pump which excluded the need for tubing was introduced. Then, the current most modern technology available since 2019 was that of the AHCL. The way this works is by combining prandial boluses of insulin which are administered, in conjunction to the continuous basal insulin infusion – the latter rate being controlled by continuous blood glucose monitoring incorporated to the system. Such systems promote a more flexible lifestyle and therefore are better accepted especially when it comes to adolescents and young adults.^{4,25}

The bihormonal artificial pancreas (BIHAP), or bionic pancreas, consists of a wearable device which unlike the insulin pump, consists of both insulin as well as glucagon as the hormones that can be potentially delivered to the patient. The concept of closed-loop systems making use of both insulin and glucagon has been around at least since the 1960s where a researcher – Kadish had mentioned the use of both hormones in his work. The advantage of having glucagon alongside insulin incorporated in the pump is that of a lesser incidence of hypoglycaemic events when compared to pumps delivering insulin alone.²⁶ An added advantage of the BIHAP is that, in combination with continuous glucose monitoring, it is able to regulate glucose control via the release of insulin and/or glucagon without the need for the patient to input data such as mealtimes and time of

physical activity. Therefore, it increases the independence of type 1 diabetic patients as the system automatically delivers hormones in response to glucose-sensing mechanisms without the need for carbohydrate counting, etc.²⁷

In the multicentre, prospective, single-arm trial in the Netherlands by Van Bon et al, adults with type 1 diabetes from eight hospitals in the Netherlands were enrolled for this one year trial. 90 type 1 diabetic patients between the ages of 18 and 75 years who had already been using the continuous blood glucose monitor (CGM) for at least three months were assessed for eligibility to participate in trial. Of these 82 were eventually enrolled and finally 71 completed the trial up to the end of the one-year period. Blood glucose data was collected from the patients continuous blood glucose monitors (CGMs) starting 4 weeks before the participants were started on bihormonal pumps, and then patients were monitored three-monthly. Data collected included: time in range (TIR), daily insulin and glucagon use amongst others. Mean TIR achieved at the end of the trial was that of 80.3%, which is better when compared to the 67.0-73.6% of the hybrid closed loop systems (consisting of insulin only). What was also noted is that total daily insulin administered increased by at least three units, while when it came to glucagon administration, this amounted to less than 1mg daily.²⁷ In the 13-week multicentre randomised trial by the Bionic Pancreas Research Group published in The New England Journal of Medicine September 2022 edition, the positive results of a better HbA1c levels were again reiterated when compared to the standard care of MDI.²⁵

At present, the only bionic pancreas approved by the FDA in the United States is the iLET bionic pancreas developed by Beta Bionics. This technology has been available for patient use since 2023.²⁸

Treatment advances alone are only a part in the success story of the management of diabetes – particularly type 1 diabetes. The introduction CGM in 1999 has brought with it greater independence in the life of such patients (irrespective of whether this is paired with an insulin pump or not). The continuous glucose monitor consists of a device with a subcutaneous needle that is worn by the patient and it monitors the blood glucose continuously and then transmitting the collected data either to an app on the patient's smartphone or to a handheld reading device purchased with the monitor. There are currently two systems by which this data can be transferred. Either real-time continuous glucose monitoring (rtCGM) or flash CGM, whereby in the

latter case, the sensor attached to the patient needs to be manually scanned with the reader. Such systems have the ability to issue alarms so that the patient is made aware when the blood glucose is either too low or too high. Finally, the CGM technology in certain cases can also allow the patient's Diabetologist to remotely access blood glucose readings, allowing for the possibility of telemedicine and modernising the approach towards patient care ²⁹

CONCLUSION

The management of diabetes has greatly evolved over the years, especially when it comes to type 1 diabetes, where such a diagnosis meant premature death before the early 1920s. Despite being a 100-year old drug, insulin kept evolving to meet its clinical needs for better patient outcome. Not only different forms of insulin have been developed but also the

way insulin is administered has changed. Compared to early days, less volumes are required and these can be administered in a safer and less uncomfortable way for the patient. The two main forms of insulin administration available at present are the MDI and the insulin pump. The latter became available in the 1970s and is still developing coming up with newer systems in combination with CGM to mimic the function of the pancreas.

Several studies done have proved that insulin pump users showed better Hba1c outcomes, resulting in less long-term micro- and macrovascular complications. Also, less hypoglycaemic events were reported, leading to a better quality of life and patient satisfaction. These patterns were also observed in studies done in type 2 diabetic patients with the insulin pump – hence showing promising results for future use of such technology in this cohort of patients.

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Basic Respiratory physiology in the use of ECMO in Critically-ill COVID-19 patients

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The use of ECMO may help sustain extracorporeal life support in cases where regular less-invasive modalities failed to adequately assist the body in maintaining basic life mechanisms. The authors synthesized information from articles found in trusted search engines using predetermined keywords. Typically, VV-ECMO is used in life-threatening respiratory failure. However, experts must consider relative contraindications, answering the question: 'Will the patient really benefit from this treatment, or will it only add emotional and economic burden, also exposing the patient to various risks of complications?'. The physiology of oxygenation within the lungs, tissues, and ECMO machine, is a modification of the basic principles of respiratory physiology. In typical VV-ECMO cannula insertion, drainage cannula is inserted via the right femoral vein percutaneously and is guided upwards through inferior vena cava with its tip 10 cm below cavoatrial junction while the reinjection cannula will be inserted through the intrajugular vein. This places the artificial lungs in series with the normal lungs rather than in a parallel form. The artificially-oxygenated blood was then returned and mixed with the native venous blood. It is important to measure maximum drainage flow to prevent shunting of the veins by setting the ECMO to the highest flow. Frequent complications during ECMO initiation due to critical COVID-19 manifestations include co-infection up to sepsis and coagulopathy up to complications following it. Therefore, it is always beneficial to acquire multidisciplinary judgement, particularly with hematologists, intensivists, and infectious disease specialists prior, during, and post-ECMO use.

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In accordance to how COVID-19 pandemic had swept across the world at an unprecedented rate, resiliency within the healthcare system in all parts of the world, with no exception to critical care, is being tested. During the early days of the pandemic, no prior extensive knowledge about how the virus operates poses as a major obstacle for critical care physicians to practice appropriate actions during critical care. And even on phases of continuation, the fact that SARS-CoV-2 mutates in order to survive, which suggests a possible outbreak such as those found in the alpha, beta, and delta variant, is unsettling. Aggravated by inequity of worldwide vaccine distribution, it is expected that more variants are coming, especially infecting those who are unvaccinated within the community. In the end, the herd immunity we all longed for does not mean total immunity. There will always be people within the community unvaccinated, both may be due to medical restrictions or due to unwillingness to be vaccinated. In both of these 'acute' and 'continuation' phase, our resiliency in knowledge and resourcefulness to continue providing critical care support through all means possible are being put to a test.

In various variants prior to omicron, SARS-CoV-2 was discovered to mainly affect the lower respiratory system, entering the body via hACE-2 (Human Angiotensin Converting Enzyme 2) receptors with prior cleaving by TMPRSS2 (Transmembrane Serine Protease 2), Cathepsin L, or furin.¹ However, new studies reported the possibility that latest SARS-CoV-2 variants predominantly affects the upper respiratory system via endocytosis, thus explaining an increase in incidence of upper over lower respiratory tract symptoms in COVID-19 patients.^{2,3} Inoculation was then followed by host immune response, possibly started by the phagocytosis of apoptotic-infected-pneumocytes by antigen presenting cells (APCs) such as macrophages and dendritic cells.¹ As researched in prior coronaviruses, viral particles were then drained into the lymphatic system, sensitising B and T cells and activating adaptive immune response specific towards the pathogen.⁴ By purpose, this response isn't fully pathological, unless there are presence of aberrates in multiple inflammatory and thrombotic proteins within the body. Studies had shown that severe COVID-19 infection induces an increase in pathogenic GM-CSF⁺ Th1 cells, inflammatory CD14⁺ and CD16⁺ monocytes, and neutrophil-to-lymphocyte ratio, suggesting that dysregulation of immune response may be the culprit behind critical symptoms shown.⁵

With current knowledge about how different complications emerge according to respective phases within the clinical course, specific care must be directed to control the corresponding underlying cause, in hopes of halting progression of severity.⁶ In cases where severe hyperinflammation reaches vital areas such as the heart, lungs, or the circulatory system as a whole, patients may manifest what was considered as 'severe complications', such as sepsis, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and multi-organ failure. Whilst not directly related to treating the underlying cause, the use of extracorporeal membrane oxygenation (ECMO) serves as a provider of temporary cardiopulmonary support for patients experiencing circulatory failure, with or without concomitant respiratory failure.⁷ The use of ECMO may help sustain extracorporeal life support in cases where regular less-invasive modalities failed to adequately assist the body in maintaining basic life mechanisms, buying time and expanding the time window for a more extensive administration of treatment from critical care physicians. However, it must be noted that ECMO is a resource and labor-intensive therapy requiring interdisciplinary collaboration between trained healthcare professionals.⁸

MATERIALS AND METHODS

The authors reviewed articles using the keyword "Extracorporeal Membrane Oxygenation", "COVID-19", "Critical Care", "Complications", and "Respiratory Physiology" on reputable trusted search engines such as Google Scholar, PubMed, Cochrane, and Embase. Authors also cited information from ELSO (Extracorporeal Life Support Organisation).

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Evolving progressively fast in the last decade, ECMO has been an invaluable state-of-the-art tool increasingly used by critical care physicians. There are two types of ECMO, all based on sites of insertion and are indicated in different cases; best results are obtained if usage is based on the right indication, right patient, and the right ECMO configuration.⁹ In 2020 alone, international use of ECMO reached over 154 thousand runs, mostly run on adults (50%), followed by neonates (29%) and children (20%).¹⁰ Survival rate post-ECLS (extracorporeal life support) reached 69% while survival until

discharge or transfer reached 54%.¹⁰ ECMO works by draining blood from the vascular system, circulating it outside of the body – hence its name, ‘extracorporeal’ – towards a mechanical pump, then reinfusing it back into the circulation, forming a sealed closed circuit.⁹ It works in a similar fashion as the haemodialysis machine, only performing a different function. The mechanical pump effectively works to fully saturate the haemoglobin with oxygen and removing CO₂ prior to reinfusion. Oxygenation, flow rate, and CO₂ elimination can be adjusted within the machine to achieve desired levels of perfusion.¹¹ The two types of ECMO well known are VV (veno-venous) and VA (veno-arterial) ECMO, used respectively to achieve a different type of extracorporeal life support. The main difference between the two is that VV-ECMO is used solely for lung support while VA ECMO may help support both the lungs and the heart.¹²

INDICATIONS AND CONTRAINDICATIONS

While ECMO by itself does not have an absolute indication, it is typically used in life-threatening conditions such as cardiac failure objectively shown by refractory low cardiac output (< 2L/min/m²) and hypotension (SBP <90 mmHg), with or without respiratory failure (PaO₂ < 150 mmHg on FiO₂ > 90%).¹³ However, in clinical setting, the definition of ‘life-threatening condition’ is a vague term indescribable by a single marker, which is why initiation of ECMO is best when determined by a group of interdisciplinary physicians whilst considering various biomarkers and clinical conditions case by case.¹³ Here are a few indicators to keep in mind, possible to be used as an initiating mark, especially in COVID-19¹⁴:

- ARDS with or without respiratory acidosis
- COVID-19 induced viral fulminant myocarditis
- Intractable arrhythmias possibly due to respiratory acidosis

Not without risks, ECMO is contraindicated in a few patients, particularly in centres where resource constraints are apparent. With ECMO serving as the last gatekeeper between life and death, there are actually no consensus between experts about absolute contraindications of initiating ECMO except for the do-not-treat

request made by patients. However, experts must consider the presence of cumulative relative contraindications, hence answering the question: ‘Will the patient really benefit from this treatment, or will it only add emotional and economic burden, also exposing the patient to various risks of complications?’.¹⁵ Each contraindications must be weighted accordingly based on its severity and possibility of recovery. Some experts define these contraindications into ‘absolute’ and ‘relative’ according to their implications towards the clinical outcome. For example, young patients with co-infection of endemic bacterial community-acquired pneumonia identified through cultured and tested for sensitivity and well-controlled by antibiotics differs to old patients with end-stage cancer.¹⁵ It is recommended to refrain from ECMO treatment if there is an absolute contraindication or > 3 relative contraindications.¹⁵ ‘Absolute contraindications’ are as follows:¹⁵

- Signed refusal / do-not-treat status
- Advanced stage of diseases with severely-reduced life expectancy
- Fatal brain injury / diseases with risks of brain stem-related deaths
- Irreversible destruction of vital organs without option of transplantation
- Relative contraindications are as follows:¹⁵
 - Advanced age (usually > 70 years old, particularly with frailty)
 - Severely immunocompromised
 - Ventilator-Induced Lung Injury (VILI) for > 7 days
 - Haematological malignancies
 - Right heart failure (especially on VV-ECMO)
 - Scorings: SAPS II > 60, SOFA > 12, PRESERVE ≥ 5, RESP ≤ -2, PRESET ≥ 6

PHYSIOLOGY OF EXTRACORPOREAL LIFE SUPPORT

The physiology of oxygenation within the lungs, tissues, and ECMO machine, is a modification of the basic principles of respiratory physiology. Due to severe ARDS being the most prevalent indication to initiate ECMO in COVID-19 patients, we will discuss further about VV-ECMO, a type of configuration specific to support the lungs but not the heart. It is

$$(1.1) \quad CaO_2 = (Hb \times SO_2 \times 1.39) + (PaO_2 \times 0.003)$$

$$(1.2) \quad CI = CO \times BSA$$

$$(1.3) \quad DO_2 = CI \times CaO_2 \times 10$$

$$(2.1) \quad CaO_2 = C_3 = \frac{C_{venous} \times Q_{venous}}{T_f} + \frac{C_{ECMO} \times Q_{ECMO}}{T_f}$$

$$(2.2) \quad Q_B = Q_{ECMO} \left(\frac{C_{ECMO} - C_{venous}}{C_3 - C_{venous}} \right) = Q_{ECMO} + Q_{venous}$$

$$(2.3) \quad DO_2 = (Q_B \times BSA) \times \frac{C_{ECMO} \times Q_{ECMO}}{Q_B} + \frac{C_{venous} \times Q_{venous}}{Q_B} \times 10$$

CaO_2 Content of Oxygen in Blood

Hb Haemoglobin

SO_2 Saturation of Haemoglobin

PaO_2 Partial pressure of Oxygen in blood

CI Cardiac Index

BSA Body Surface area

DO_2 Delivery of Oxygen

Q_B Total Blood flow

C_{ECMO}, Q_{ECMO} Content of Oxygen, Flow in ECMO circuit

C_{venous}, Q_{venous} Content of Oxygen, Flow in venous part of native lung

Figure 1 Calculating the oxygen delivery using ECMO in a VV-ECMO circuit

useful to review a little bit about how oxygen is transported throughout the blood. Assuming that oxygen binding capacity is physiologic, we may calculate oxygen content through the following formula 1.1 (**Figure 1**)

Oxygen content (labeled as C) is a measure of volume of oxygen per a certain volume of blood, usually measured as $mL(1)dL^{-1}$. It is a product of haemoglobin g/dL by SO_2 (%) and maximum oxygen carrying capacity per gram of haemoglobin in adults, usually defined as $1.39 mL^1g^{-1}$ in physiologic adults. In cases where oxygen carrying capacity is altered due to various factors (gas intoxication, age, etc.), this coefficient may be modified. The second bracket describes volume of oxygen carried by plasma. Due to its very small carrying capacity, this part of the formula is usually omitted during bedside calculations.

Therefore, oxygen delivery per minute (DO_2) measured in $mL^1min^{-1}m^{-2}$ is a product of cardiac index (CI) measured in $L^1min^{-1}m^{-2}$, arterial oxygen content (CaO_2) measured in mL^1dL^{-1} multiplied by 10 to synchronise the units measured. In regards to oxygen delivery and consumption (VO_2), homeostatic

mechanisms played a huge role in keeping $DO_2:VO_2$ (measured in $mL^1min^{-1}m^{-2}$) to a physiologic ratio of 5:1. This condition is sustained as much as possible in extreme conditions such as ARDS, where a decrease in DO_2 occurred due to lung injury combined with an increase in VO_2 occurred due to stress experienced in the body. If this ratio is skewed to a value lower than 2:1, it can be stated that oxygen delivery is inadequate to supply oxygen consumption. Anaerobic metabolism and glycolysis will then be initiated, causing exhaustion and lactic acidosis. In cases where respiratory failure refractory to other forms of invasive ventilator therapies, the patient might be put under extracorporeal life support (ECLS).

Assuming that there is no lung function and no recirculation, total oxygen content (C_t) measured in mL^1dL^{-1} is the mean of both oxygen content times flow post-ECMO machine and native venous blood. Native venous blood is blood that didn't enter the ECMO, flowing through the veins as blood normally would. Total blood flow (Q_B) is a cumulative of ECMO (Q_{ECMO}) and native venous flow (Q_{venous}), also considered as the cardiac output (CO) in VV-ECMO

configuration. Combined, oxygen delivery could be calculated using formula 2.3 (Figure 1). However, the use of complex formulas as these aren't practical in bedside practice, therefore observation of difference between pre- and post-ECMO oxygenator CaO_2 may give a picture to how much DO_2 is given by the machine.

However, it must be noted that recirculation might occur when cardiac output is lower than ECMO flow. In cases where the COVID-19 patient also suffers from any decompensating heart disease, these equations must be altered to include the reduced heart flow.

CLINICAL SETTING: OPERATING VV-ECMO

To operate ECMO in a VV configuration, the operator must first evaluate presence of indications and contraindications within the patient. It is imperative that patients with heart failure be put into VA-ECMO and not VV-ECMO to prevent recirculation, thus partially or completely nullifying therapeutic effects of the machine. The patient must be put under sedation, is paralysed, and his/her definitive airway must be established. Central venous and arterial line must be inserted, allowing haemodynamic monitoring. The operator must plan the circuit based on an estimation of the patients' metabolic rate ($3\text{-}4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

The operator will then insert two types of cannulas into the patients' vessels; one for draining deoxygenated blood and the other for reinjecting oxygenated blood. In double cannulation, drainage cannula is traditionally inserted via the right femoral vein percutaneously and is guided upwards through inferior vena cava (IVC) with its tip 10 cm below cavoatrial junction while the reinjection cannula will be inserted through the internal jugular vein. This places the artificial lungs in series with the normal lungs rather than in a parallel form. The artificially-oxygenated blood was then returned and mixed with the native venous blood. It is important to measure maximum drainage flow to prevent shunting of the veins by setting the ECMO to the highest flow.

Wean the ventilators and adjust sweep gas to keep PaCO_2 at 40 mmHg. After the patient stabilises (around 6-12 hours), perform follow-up analysis to calculate $\text{DO}_2:\text{VO}_2$ ratio via formula written above. If $\text{DO}_2:\text{VO}_2$ is above 3:1, then no changes are needed. If oxygen supply is inadequate and the patient is anaemic, perform transfusion to increase haemoglobin levels. However, if oxygen supply is

inadequate and the patient isn't anaemic, change the drainage cannula to a larger size and increase flow. Alternatives include performing targeted temperature management (TTM) and adding another membrane lung.

In moments where SaO_2 began to increase spontaneously without modification in sweep oxygen nor blood flow, operators must be sensitive to lung recovery. An $\text{SaO}_2 > 95\%$ might indicate the return of native lung function, therefore attempt to wean and decannulate the patient is possible.

COMPLICATIONS

Not risk-free, physicians must also consider complications when initiating the use of ECMO. Meta-analyses recorded frequent complications during ECMO treatment in adults were sepsis (26%), acute renal failure (25%), and multiorgan failure (25%), followed by cannulation-related complications (7%), and central nervous system (CNS) complications (7%).¹⁶

In real-life clinical setting, co-infection is often considered an unavoidable risk though application of all means of aseptic procedures were tightly monitored. This is due to the location, which is the hospital, and due to the fact that blood is an aseptic matter. Even a single bacteria found during staining may indicate a positive bacteraemia. The hospital is usually a tight-packed building where people with different infections were jammed together into rooms (with no exception, the ICU). Reports showed that co-infections were mostly attributed to *Staphylococcus aureus* (46%).¹⁷ Other reports stated that the most common co-infecting pathogens specific during ECMO usage due to COVID-19 are *Stenotrophomonas maltophilia* (28%), *Pseudomonas aeruginosa* (28%), and *Burkholderia cepacia* (19%).¹⁸ Significant correlation was found between BMI, initial disease severity, and antibiotic treatment prior to admission. If undetected and not treated as early as possible, these co-infections may develop into sepsis and septic shock, therefore increasing ICU mortality.¹⁷

Coagulation abnormalities were often found due to the superimposed constant injection of heparin or other anticoagulants to prevent clotting over the existing COVID-19-associated coagulopathy.¹⁹ As in haemodialysis, flowing blood through an external tube induces a prothrombic state, creating clots and therefore requiring infusion of anticoagulants. However, the body itself is naturally prone to bleeding due to excessive consumption of

coagulation factors especially in patients with long duration of hospitalisation prior to ECMO initiation.¹⁹ Other complications include thrombosis on cannula, oxygenator, and acute pulmonary embolism.²⁰ Extracorporeal life support organisation (ELSO) in its COVID-19 interim guidelines recommended operators to follow existing anticoagulation guidelines.²¹ It may also be helpful to rinse the cannulas with heparin prior to insertion.²⁰ Poor management of thrombosis may result in complications such as acute renal failure and other organ dysfunctions.

GLOSSARY

COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
ELSO	Extracorporeal Life Support Organisation
VV	Veno-Venous
VA	Veno-Arterial
SAPS	Simplified Acute Physiology Score
SOFA	Sequential (Sepsis-Related) Organ Failure Assessment
PRESERVE	Predicting Death for Severe ARDS on VV-ECMO
RESP	Respiratory ECMO Survival Prediction
PRESET	Prediction of Survival on ECMO
SO₂	Oxygen Saturation
PaO₂	Partial Pressure of Oxygen
DO₂	Oxygen Delivery
CaO₂	Arterial Oxygen Content
VO₂	Oxygen Consumption

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A Systematic Review of the Effects of Nerve Sparing during Radical Prostatectomy

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This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (2009). MEDLINE, EMBASE, The Cochrane Library, Health Technology Assessment Database, and Web of Science were searched from 1966 to December 2015, yielding 60 records.

RCTs and other controlled or comparative studies were eligible for inclusion. Studies reporting on at least one of the following outcomes, positive surgical margins, continence and potency with data available for nerve sparing and non-nerve sparing groups were included. 16 studies were available for final analysis and included 16269 participants.

Primary outcomes analysed where positive surgical margins and functional outcomes (continence and potency).

Comparing nerve sparing with non-nerve sparing prostatectomy, the proportion of cases resulting in incontinence is lower for nerve sparing prostatectomy.

The proportions of cases resulting in impotence were 0.92 (CI: 0.88 – 0.96) for non-nerve sparing operations, 0.43 (CI: 0.40 – 0.46) for all nerve sparing operations, 0.59 (CI: 0.51 – 0.67) for unilateral and 0.39 (CI: 0.35 – 0.42) for bilateral nerve sparing.

With regards to positive margin rates, these are higher for T3 cancers than for T2 cancers, both for operations that used nerve sparing and for those that did not. For T2 cancers there is little or no difference in the proportion of cases resulting in positive margins for operations with and without nerve sparing. For T3 cancers the proportions of cases with positive margins were practically the same for operations with and without nerve sparing.

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Excluding non-melanoma skin cancer, prostate cancer is the leading cancer diagnosis in men worldwide and the most common cause of cancer related death. The U.S. Cancer Statistics Working Group published prostate cancer incidence and mortality statistics for 2013, 176,450 men were diagnosed with prostate cancer in the United States, with 27,681 patients dying from prostate cancer.¹

For newly diagnosed men, radical prostatectomy offers an excellent prospect of cancer cure.² To standardise the assessment of oncological and functional outcomes after radical prostatectomy the trifecta system was proposed with optimal outcomes being defined as a PSA level of less than 0.2ng/ml, potency sufficient for intercourse with or without pharmacological agent and zero pad use.³ The trifecta outcome can be achieved in 62-70% of patients in centres of excellence.⁴

The description of the course of the cavernous nerve by Walsh and Donker in 1982⁵ proved to be the basis for the development of nerve sparing technique which has resulted in improved post operative potency rates. The association between nerve sparing and continence outcomes is not so clear and is still a matter of debate. Traditional teaching does not support an anatomical relation between nerve sparing and preservation of urinary continence, as the urinary rhabdosphincter is innervated somatically by the extra-pelvic pudendal nerve, and this should not be influenced by nerve sparing. Some authors have attributed an enhanced post-prostatectomy continence rate to a possible intra-pelvic innervation to the rhabdosphincter⁶ and meticulous apical dissection in nerve sparing technique, rather than the preservation of the neurovascular bundles themselves.⁷

The proximity of the posterolateral prostate to the neurovascular bundles inevitably results in a conflict between the desire to preserve functional outcomes and the risk of positive surgical margins (PSM) and biochemical recurrence. The association between nerve sparing and PSM is difficult to ascertain, with patient selection based on biopsy and imaging characteristics confounding a true association between the two. Because pre-operative assessment suffers from limitations in predicting early extra-capsular extension, some authors recommended intra-operative frozen section with excision of the bundle in the event of a positive froze section analysis, and have shown a reduction of PSM with this approach.⁸

The primary aim of this study was to conduct a review of the association between nerve sparing in radical prostatectomy and its association with outcomes of continence, potency and PSM.

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.(2009) MEDLINE, EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register), Health Technology Assessment Database, and Web of Science (science and social science citation index) were searched up to December 2015.

The following terms were searched: ["prostate cancer AND prostatic neoplasms"] AND ["prostatectomy AND radical prostatectomy"] AND ["continence AND urinary incontinence"] AND ["potency AND erectile function AND sexual function"] AND ["margins AND PSM"].

The search strategy did not include or exclude papers based on the surgical approach utilised (open, laparoscopic or robotic) or whether the prostatectomy was combined with a pelvic lymph node dissection or not. No attempt was made to distinguish between different types of nerve sparing, such intra or interfascial dissection. None of the studies included in the analysis made use of sural nerve grating as a method of nerve preservation.

RCTs and other controlled or comparative studies were eligible for inclusion. Studies reporting on at least one of the following outcomes, PSM, continence and potency with data available for nerve sparing and non-nerve sparing groups were included. Only studies where the full original paper was available where included in the final analysis. Studies in languages other than English were excluded. Manual searching of reference lists of relevant publications was performed to identify additional potentially relevant studies. When multiple publications were identified from the same institution and overlapping data sets were used, the publication with the most recent data was included. Any disagreements on study selection or eligibility were resolved with consultation and discussion with a third author.

Two independent authors screened the titles and abstracts obtained. The full text of relevant publications was retrieved for review and included in the analysis if they satisfied the criteria outlined previously. The total number of participants and events were extracted for pooled analysis. Where data was presented as a percentage the raw numbers were calculated. Where more than outcome for continence and

potency was reported at different points of the post-operative follow up, the results at most frequently reported outcome were included, most commonly outcomes at one year after surgery.

All statistical analyses and Forest plots were programmed by RG using R software, version 3.2.5.

RESULTS

Initial search yielded 132 records. After exclusion of duplicates, papers not relevant to this review and papers published in languages other than English, 16 studies were included in the final analysis. A total of 16,023 prostatectomy operations were included in this systematic review. The characteristics of these studies are presented in [Table 1](#).

In all of these studies, nerve sparing treatments were not randomised between patients, but were chosen by specific protocols of the different surgeons. Margin status was assessed after each operation, while continence and potency were assessed in post-operative follow up. No randomised controlled trials were identified which addressed the questions of this review.

Study samples range from 44 (study 9) to 6120 (study 10). The studies were published between 1989 and 2015. In most studies patients underwent open retropubic prostatectomy, although laparoscopic and robot assisted-laparoscopic prostatectomy was also used in some studies. In most the studies the authors present data stratified in non-nerve sparing, unilateral nerve sparing and bilateral nerve sparing groups, in some case this data are presented in two groups, non-nerve sparing and nerve sparing cohorts without distinction being made between unilateral and bilateral nerve sparing cases.

The technique, extent and quality of nerve sparing is not formally accounted for in most of the studies. In one study the definition of nerve sparing was more precisely defined as at least 70% of the neurovascular bundle preserved but this does not take into account damage to microscopic nerves which would not be visible to the surgeon.¹¹

Baseline patient and tumour characteristics were not available in all studies, making assessment of selection bias difficult. In those studies, where such data are available, a selection bias is evident with patients undergoing a nerve sparing procedure having a more favourable clinical stage.

Outcome evaluation was variable in between studies with definitions of potency and continence and

timing of reported outcomes differing significantly. The most common definition of continence was a patient reported no pad use or use of one pad at one year, whilst potency was most commonly defined as the patient reported erections sufficient for vaginal penetration with or without pharmacological aids. The timing of potency recovery differed between studies ranging from 12 to 24 months. In the case of studies reporting on PSM, the definition was uniformly reported as tumour at the inked surface of the prostatectomy specimen.

For each study (subject to the availability of data noted above) we present sample sizes along with the numbers and proportions of cases resulting in each outcome, separately for operations with and without nerve-sparing. For the outcome 'PSM' the numbers and proportions are further classified by cancer type (T2 or T3). Comparisons between the proportions of operations with and without nerve sparing are calculated as risk ratios (RRs) with 95% confidence intervals (CIs). The estimated risk ratios are presented in the form of forest plots on a logarithmic scale, where the size of the symbol (square) is proportional to the precision of the estimate, horizontal lines represent 95% confidence intervals, and a vertical line indicates $RR = 1$ (i.e., no difference in risk between operations with and without nerve sparing).

Some of studies included separate data for unilateral and bilateral nerve sparing operations. These were pooled into one group when comparing outcomes with and without nerve sparing. In addition, for those studies, a secondary analysis comparing outcomes between unilateral and bilateral nerve sparing operations were performed.

The definitions of incontinence and impotence used in outcome evaluation are not standardised across studies. A few studies used validated questionnaires with patient-reported outcomes being the most common method. Also, the baseline pre-operative functional status is not reported in most studies. Formal assessment of quality of life after surgery is not performed in conjunction with continence or potency outcomes in most of the studies included.

Technical factors known to have an impact on continence outcomes, such as bladder neck sparing technique, membranous urethral length and different methods of anastomosing the bladder to the urethra and reconstruction, are not described or reported and therefore not the subject of the study.

Table 1 *Characteristics of included studies*

	Authors	Date of publication	Sample Size	Surgical Approach	Age, years	Comparison Groups
1	Finan et al	1989	68	Retropubic	Mean $\pm$ SD 64.3 $\pm$ 4.9	NNS, BNS
2	Catalona et al	1993	784	Retropubic	Mean $\pm$ SD 64.2 $\pm$ 7.02	UNS, BNS
3	Dalkin et al	2000	170	RRP	NA	NNS, UNS
4	Lu et al	2003	44	RRP	Mean $\pm$ SD 68.7 $\pm$ 4.5	NNS, UNS, BNS
5	Tsujimura et al	2004	135	RRP	Mean $\pm$ SD NNS: 68.1 $\pm$ 0.7 UNS: 67.2 $\pm$ 1.3 NNS: 66.4 $\pm$ 1.5	NNS, UNS, BNS
6	Huland et al	2005	723	RRP	Mean $\pm$ SD NNS: 63.37 $\pm$ 5.93 NS: 61.43 $\pm$ 5.78	NNS, UNS, BNS
7	Studer et al	2006	536	RRP	Mean (IQR) 64 (58 - 68)	NNS, UNS, BNS
8	Zippe et al	2008	156	RRP	Mean $\pm$ SD 64.1 $\pm$ 6.7	NNS, UNS, BNS
9	Lepor et al	2008	1110	RRP	Mean 58.4	NNS, UNS, BNS
10	Hu et al	2010	602	RALP	Mean NNS: 60.5 UNS: 59.0 BNS: 57.8	NNS, UNS, BNS
11	Patel et al	2010	876	RARP	Median (IQR) 61 (56 - 66)	NNS, UNS, BNS
12	Trachtenberg et al	2010	856	RRP, LRP	Mean NNS: 63.4 NS 60.2	NNS, NS
13	Striker et al	2011	945	RRP	Mean NNS: 64.2 UNS 62.3:BNS 59.6	NNS, UNS, BNS
14	Briganti et al	2012	1249	RRP	Mean (Range) 63.8 (39-85)	NNS, UNS, BNS
15	Iversen et al	2014	1649	RRP	Mean (Range) 63 (59 - 66)	NNS, UNS, BNS
16	Cagiannos et al	2014	6120	RRP, LRP, RALP	Mean $\pm$ SD 59.2 $\pm$ 7.1	NNS, UNS, BNS

Urinary continence outcomes

Figure 1 summarises the data for urinary incontinence. Five studies (1, 7, 8, 13 and 14) were included in the comparison between nerve sparing and non-nerve sparing groups. The total number of patients was 2616, with 578 having non-nerve sparing operations and 2038 having nerve sparing operations. One study (study 9) did not report on a non-nerve sparing group but was included in a separate analysis comparing unilateral nerve sparing with bilateral nerve sparing outcomes. In this analysis five studies (7, 8, 9, 13 and 14) were included, with a total of 567 patients having had a unilateral nerve sparing procedure and 2048 patients undergoing a bilateral nerve sparing prostatectomy. Study 1 was excluded from this analysis as it did not report separate outcomes for unilateral and bilateral nerve sparing procedures.

Comparing nerve sparing with non-nerve sparing prostatectomy, for each of the five studies, the proportion of cases resulting in incontinence is lower for nerve sparing prostatectomy. The proportions range from 0.14 and 0.55 for non-nerve sparing operations, and from 0.04 to 0.21 for nerve sparing operations. Except for Study 13, the 95% confidence intervals for the risk ratios do not include $RR = 1$, and the five risk ratios are consistent with a common value. The weighted average RR is 0.40 (CI: 0.35-0.46) with nerve sparing having the lower risk.

Comparing bilateral with unilateral nerve sparing, for the three smallest studies (6, 8 and 9) the proportions of incontinent patients are small and are consistent with $RR = 1$. For the two larger studies (13 and 14) the proportions are clearly lower for bilateral nerve sparing. All five risk ratios are consistent with a common value: the weighted average RR is 0.59 (CI: 0.45 – 0.77) with bilateral nerve sparing having the lower risk.

Potency outcomes

Five studies (2, 3, 4, 5, and 9) were included in the analysis comparing potency outcomes, which is summarised in **Figure 2**. Studies 2 and 9 were excluded in the analysis comparing nerve sparing with non-nerve sparing technique as no non-nerve sparing data were reported. Similarly, study 3 was not included in the comparison between unilateral and bilateral nerve sparing as it did not report outcomes for these separately.

For non-nerve sparing operations, the proportions of cases resulting in impotence are very similar and are consistent with a common proportion for all five studies. Similar consistency is seen for nerve sparing operations, and likewise when considering unilateral and bilateral nerve sparing operations separately. The risks of impotence are therefore well summarised by pooling the counts across all studies

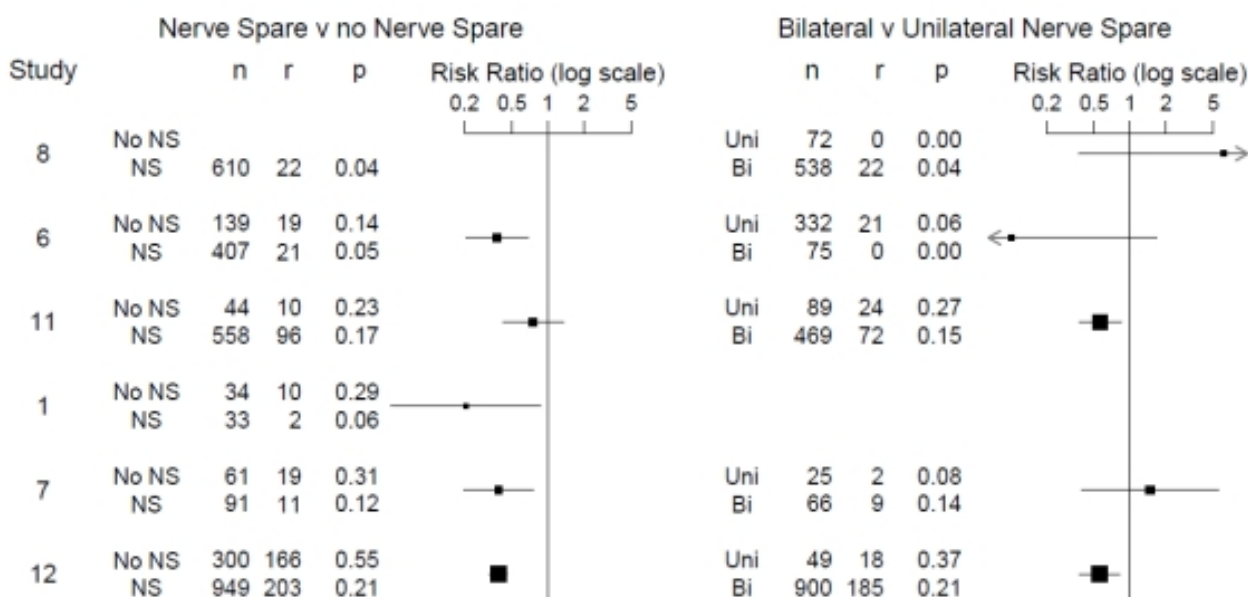


Figure 1 Summary data and forest plots of the relative risk of incontinence (with 95% confidence intervals) for operations with and without nerve sparing, and with bilateral compared with unilateral nerve sparing, for six studies (Table 1): n denotes the number of operations, r is the number with outcome "incontinent" and $p = r/n$ is the proportion incontinent. Studies are listed by increasing order of p for non-nerve sparing operations. Study 9 did not include non-nerve sparing operations and study 1 did not report separate data for unilateral and bilateral nerve sparing.

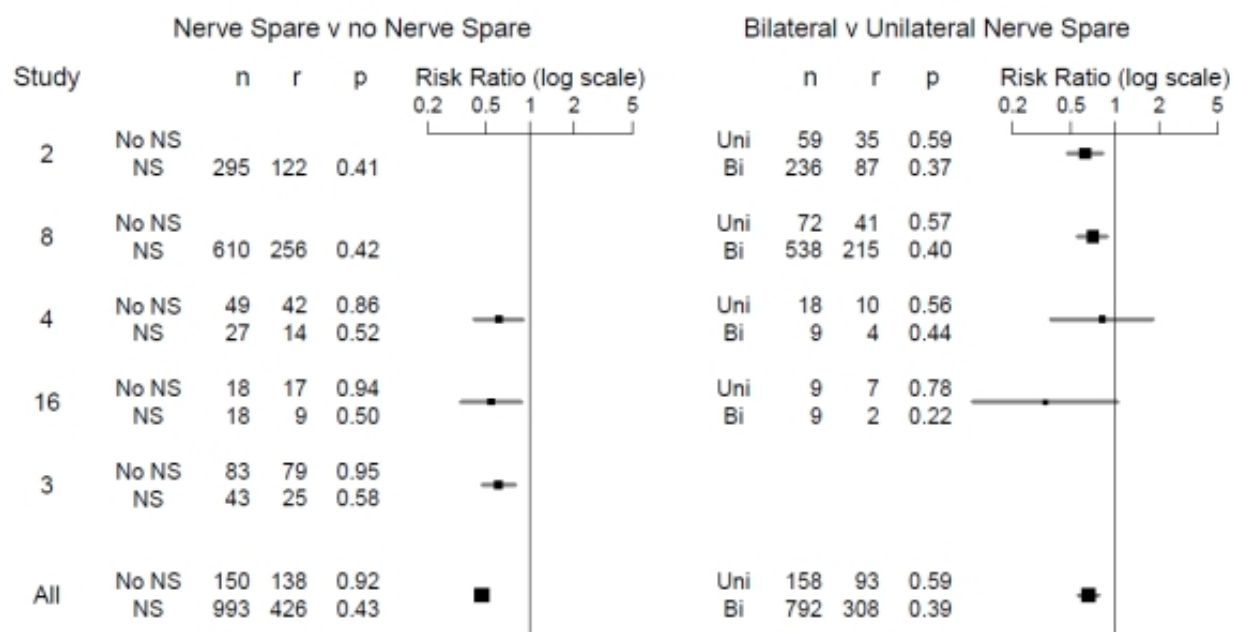


Figure 2 Summary data and forest plots of the relative risk of impotence (with 95% confidence intervals) for operations with and without nerve sparing, and with bilateral compared with unilateral nerve sparing, for five studies (Table 1): *n* denotes the number of operations, *r* is the number with the outcome “impotent” and *p* = *r*/*n* is the proportion of impotent subjects. Studies are listed in increasing order of *p* for non-nerve sparing operations. Studies 2 and 9 did not include non-nerve sparing operations, and study 3 did not report separate data for unilateral and bilateral nerve sparing procedures. For each category of operation, the data are consistent with the same risk of impotence in each study, and the last two rows give pooled data across all five studies.

for each type of operation (see last two rows in Figure 2).

Overall, the proportions of cases resulting in impotence were 0.92 (CI: 0.88 – 0.96) for non-nerve sparing operations, 0.43 (CI: 0.40 – 0.46) for all nerve sparing operations, 0.59 (CI: 0.51 – 0.67) for unilateral and 0.39 (CI: 0.35 – 0.42) for bilateral nerve sparing. These substantial improvements in sexual potency and the direct correlation between post-prostatectomy sexual function and degree of nerve sparing suggests neurovascular preservation as a primary determinant of potency.

PSM outcomes

Seven studies (6, 10, 11, 12, 13, 15, and 16) were included in our analyses comparing positive margin rates after nerve sparing and non-nerve sparing prostatectomy. In these studies, 2593 patients underwent non-nerve sparing resection and 9867 patients underwent a nerve sparing procedure. Because margin outcomes are likely to depend on the type of cancer, we consider these separately for T2 and T3 cancers. The results are presented in Figure 3. The main features are:

- For every study, the proportion of operations resulting in PSM is higher (generally substantially higher) for T3 cancers than for T2 cancers, both for operations that used nerve sparing and for those that did not.
- For T2 cancers there is little or no difference in the proportion of cases resulting in PSM for operations with and without nerve sparing. The risk ratios are plotted as open squares with 95% confidence intervals, which are also given numerically. They are individually consistent with RR = 1, as well as being consistent with a common RR for all studies.
- For T3 cancers: for the bottom five studies (10, 11, 12, 13, and 15) the proportions of cases with PSM were practically the same for operations with and without nerve sparing and consistent with a common risk ratio of 1. But for studies 6 and 16, the proportion with PSM was clearly lower when nerve sparing was used.

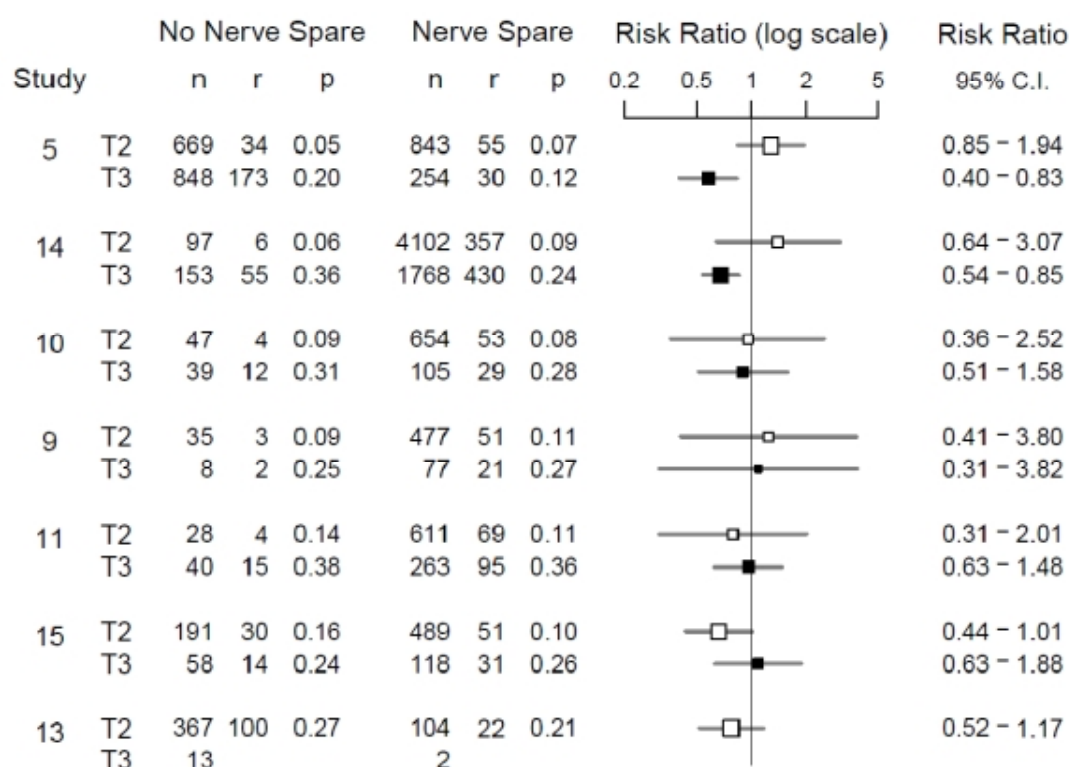


Figure 3 Summary data and forest plots of the relative risk of PSM (with 95% confidence intervals) for operations with and without nerve sparing, for each of the two cancer types (T2 and T3) for seven studies (see table 1): n denotes the number of operations, r is the number with outcome “positive surgical margin” (PSM) and $p = r/n$ is the proportion resulting in PSM. Studies are listed in increasing order of p for non-nerve sparing operations on T2 cancers. Study 15 did not report PSM outcomes for 15 operations on T3 cancers.

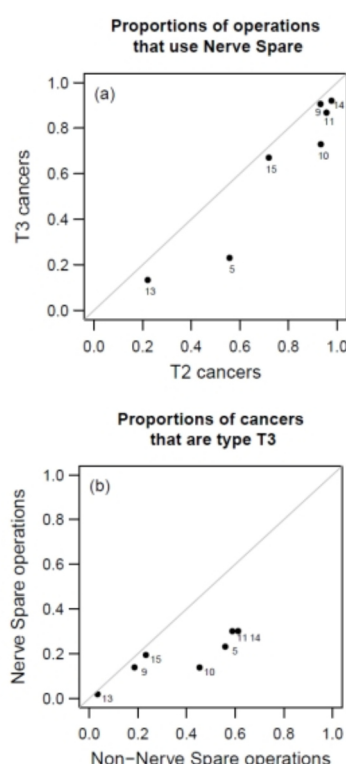


Figure 4 (A) The proportion of nerve sparing operations for T3 cancers plotted against corresponding proportion for T2 cancers, for the seven studies in Figure 1. (B) The proportion of T3 cancers among nerve sparing operations plotted against corresponding proportion among non-nerve sparing operations for the same seven studies.

It is to be expected that the proportion with PSM is higher for T3 than for T2 cancers, and interesting that even for T3 cancers, PSM do not seem to be more frequent following nerve sparing surgery (and indeed are less frequent for studies 6 and 16). For T3 cancers, positive margin risks are not expected to be affected by nerve sparing for anterior and apical tumours, but because the location of the tumour is not reported in any of the studies it is difficult to assess whether tumour location influenced these results.

Figure 4 shows an association between the use of nerve sparing and the type of cancer (T2/T3). In Panel A, the proportion of operations that used nerve sparing ranges from 0.13 to 0.98 for different studies, but nevertheless is always lower for T3 than for T2 cancers. Likewise, in Panel B, the proportion of cancers that are type T3 ranges from 0.02 to 0.61 but is always lower when nerve sparing was used. This possibly reflects good operative selection of patients for nerve sparing, although in studies 10, 12 and 15 the proportions of T3 cancers were similar for operations with and without nerve sparing. In study 10, for example, a high proportion of operations used nerve sparing, but low proportion of cancers were T3 cancers (panel B).

In this systematic analysis, we analysed the effect of sparing the neurovascular bundle on post-operative continence, potency and positive margin rates.

Post prostatectomy continence outcomes are significantly better in patients undergoing nerve sparing procedures. The pathophysiological basis for this remains a matter of debate. In one of the papers, nerve sparing procedures were associated with a longer urodynamic functional urethral length post-prostatectomy, this probably independently contributing to better continence outcomes.¹² In a large German series, where the authors use frozen section neuroSAFE technique, they conclude that it is meticulous apical dissection and preservation of anatomical structures in the vicinity which contribute to continence rather preservation of the NVB that results in better continence outcomes.⁸ This correlates with the results of this review, where a significant difference in continence rates was detected between nerve sparing and non-nerve sparing operations, however there is only very little additional benefit with bilateral nerve sparing compared to unilateral nerve sparing, indicating that this benefit is not directly related to the degree of cavernosal nerve preservation. It may be that limited use of diathermy around the urethra and seminal vesicles as is standard during nerve sparing prevents damage to somatic nerves associated with the maintenance of continence.

The results for potency rates are also in favour of nerve sparing, with similar and consistent patterns across all the studies. There exists a significant benefit in post-operative sexual function comparing non-nerve sparing, unilateral nerve sparing and bilateral nerve sparing procedures, indicating that the degree of preservation of the NVBs is the main determinant of post prostatectomy erectile function. Although it is the preservation of the neural component that is the general thought to be responsible for erectile function, tumescence is also a vascular phenomenon and preservation of the vascular component might also contribute to improved potency rates after surgery for prostate cancer.

The results for positive margin rates are perhaps less subject to potential reporting biases compared to those for the functional outcomes. The definition of positive margin is uniform across studies and more robust being less subjective and not subject to influence by the timing of reporting. However, although margin status does correlate with

oncological results after surgery, standardised reporting using the Trifecta system uses post-operative PSA reading rather than margin status as a surrogate for the quality of oncological resection.

We analysed margin rates comparing nerve sparing and non-nerve sparing cases and performed a separate analysis of T2 and T3 cancer procedures. As expected, procedures on T3 cancers result in a higher proportion of PSM compared to T2 cancers. However even T3 cancers the use of nerve sparing did not result in a higher rate compared to non-nerve sparing procedures. This is possibly related to accurate pre-operative mapping of prostate cancer and surgical planning with nerve sparing being undertaken in cases contralateral to the presumed extracapsular extension of the tumour. If so, this would suggest that a proportion of cancers staged as T3 can still safely undergo nerve sparing prostatectomy depending on the location of the tumour in relation to the NVBs. In practice, a lower proportion of T3 cancers were selected to have a nerve sparing procedure as shown in [Figure 2A](#).

Our review has several limitations. It includes only published results in the English language, all of which are from non-randomised studies (i.e., patients were not randomly allocated to treatments). An absence of RCTs in this area is stark and makes the systematic review timely. The results of the individual studies are subject to various difficulties in interpretation related to their non-randomised nature. These may include selection bias in baseline characteristics, such as age, PSA level and tumour stage, in favour of nerve sparing cases. Surgeon experience, differences in outcome definition and timing of outcome reporting, surgical technique variation, and loss to follow up introduce additional risk of bias.

The absence of RCTs and risk of bias limit the recommendations for clinical practice which can be extrapolated from this review. Performing nerve sparing with same aim of improving continence rates should be considered in impotent patients (particularly as we do not see an increased risk of PSM, even in T3 cancers). The argument for NVB preservation in patients who strongly wish to maintain sexual function after prostate cancer surgery is a stronger one, and nerve sparing can also be performed in T3 cancer patients who have had their cancer accurately staged with adequate imaging and biopsy and tumour location and extent permits a clear margin of resection.

CONCLUSION

This systematic review demonstrates a positive association between nerve sparing and better functional outcomes after prostate cancer surgery. The association with potency is more robust than that for continence outcomes. None of the studies showed evidence that nerve sparing might increase the risk of PSM either for T2 or for T3 cancers. In two studies, the observed proportion of PSM for operations on T3 was in fact lower with nerve sparing. The reason for this is unclear.

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An Audit on the Consumption of Inhalational Anaesthetic Agents at Mater Dei Hospital

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Background

Inhalational anaesthetic agents carry a considerable cost, both economic and environmental. Consumption of such medications is related to the fresh gas flow, which is controlled by the attending anaesthetic team.

Method

Data was collected over a period of twelve weeks with intermittent, random observations of fresh gas flow rate and anaesthetic agent concentration performed by an investigator not being actively involved in the anaesthesia delivery. The type of procedure performed, time from induction, age of the patient and the type of airway device used were also collected.

Results

A total of three hundred and thirty-eight visits were made. The median FGF observed was 2L/min. Sevoflurane was the commonest anaesthetic gas used at a median MAC of 1.25.

Conclusion

A more economical use of anaesthetic agents is possible, with a potential reduction of FGF from 2L/min to 1L/min or less.

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Since the first successful demonstration of an anaesthetic agent in 1846,¹ anaesthesia is one of the few fields in medical care that utilizes therapeutic agents in a gaseous form. Indeed, the anaesthetic workstation has been developed with the aim of safely delivering anaesthetic gases together with oxygen to a patient during surgical procedures.

A carrier gas, known as fresh gas flow, is passed through dedicated vaporizers (**Figure 1**). The resulting gas mixture is then delivered to the patient during ventilation. The concentration of the anaesthetic gas is adjusted by the vaporizer setting, as a percentage volume of the total fresh gas flow.

The current anaesthetic practice uses isoflurane, sevoflurane and desflurane. These have different properties that influence anaesthetic choice (**Table 1**, **Table 2**). Isoflurane is cheaper but has a slower recovery. Desflurane is expensive but offers the fastest recovery. Sevoflurane is sweet-smelling and is the best choice for a gaseous induction, such as in paediatric anaesthesia. Minimum alveolar concentration (MAC) is the minimum concentration of an inhalational anaesthetic agent, that is the end-tidal concentration, required to prevent muscle movement in response to a surgical stimulus in 50% of patients, at room temperature and pressure. MAC is expressed as a percentage of the inspired gas mixture and is a measure of the potency of the inhaled agent. An agent with a higher MAC value will have a lower potency as it means that a higher concentration of the agent is required to achieve the desired effect²

The cost of an inhalational agent is dependent on the choice of agent and on the fresh gas flow. Since the vaporizer will deliver an amount of anaesthetic agent as a percentage volume of the fresh gas flow, the consumption of anaesthetic agent is directly proportional to the fresh gas flow. Modern anaesthetic systems with a circle breathing system allow reusing of exhaled gas, but any excess is vented to atmospheric air. Indeed, anaesthesia accounts for 0.1% of the total daily output of greenhouse gases.³ This may seem negligible, but such reasoning does not consider the longevity of some anaesthetic gases compared to CO₂.⁴ Furthermore, it is possible to reduce this amount by changing anaesthetic practices.

The aim of low-flow anaesthesia is to replenish the consumed gases with as little fresh gas as possible whilst ensuring carbon dioxide is removed from the circuit to avoid rebreathing. This will reduce the amount of volatile agents escaping into the environment, therefore saving costs.⁵ For this to be

Table 1 *Physical properties of common currently used volatile anaesthetic agents*

	Sevoflurane	Isoflurane	Desflurane
MAC (%)	1.8	1.18	6
Oil/Gas Solubility	53	97	19
Blood/Gas Solubility	0.6	1.4	0.42
Boiling point (°C)	58	48	23.5
% Metabolism	3	0.2	0.02
Vapour Pressure at 20°C (mmHg)	157	238	669

Table 2 *Advantages and disadvantages of each inhalational anaesthetic agent*

	Sevoflurane	Isoflurane	Desflurane
Stability in light	+++	+++	+
Pleasant smell	+++	-	-
Flammable	-	-	+
Stability with soda lime	+	+++	+++
Cost	++	+	+++
Metabolism	+++	++	+
Potency	++	+++	+
Recovery	++	+	+++
Ease of administration	++	++	-
Bronchodilation	+++	+	+
Cardiovascular stability	+++	+	+

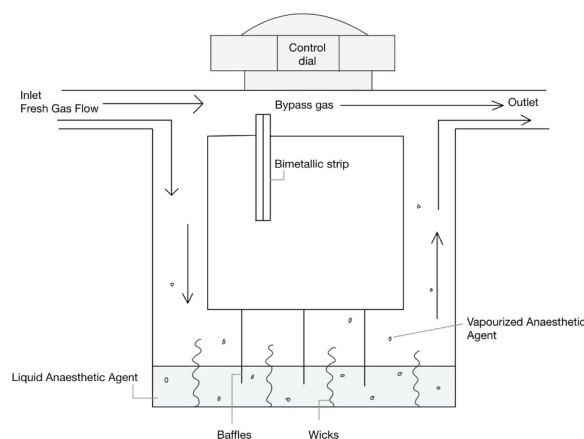


Figure 1 *Diagram of a simplified variable bypass vaporizer used for Sevoflurane and Isoflurane*

effective, at least 50% of the exhaled gas volume must be returned to the patient after removing carbon dioxide. With modern anaesthetic machines, this could be achieved using flows between 1-2 L/min.⁶ Low flow anaesthesia is described to be less than 1 L/min by Foldes in 1954 and minimal flow anaesthesia to be 0.5 L/min by Virtue in 1974.⁷

This observational study aims to highlight the consumption of inhalational anaesthetic agents in daily use at Mater Dei Hospital. This is done by investigating the fresh gas flow and corresponding agent concentration during anaesthesia after ten minutes have elapsed from the start of anaesthesia.

METHOD

The study was an observational study carried out prospectively in one centre. Permission to carry out the study was granted by the relevant authorities, including Data Protection. Ethical approval was not sought since this study did not involve any subjects.

The primary outcome was the use of fresh gas flow during maintenance, and the use of volatile anaesthetic agent. Secondary outcomes included oxygen concentration used in anaesthesia, the relationship between airway device and anaesthesia concentrations, and the cost of anaesthetic agents, as discussed below.

Data was collected over twelve weeks. Intermittent, random observations of fresh gas flow rate and anaesthetic agent concentration were performed by an investigator not involved in the anaesthetic care. This was done by randomly dividing time slots between investigators when to visit theatres. The individuals responsible for setting the fresh gas flows were higher specialist trainees and above including resident specialists and consultants. However, the level of seniority was not noted, and thus ad-hoc observations were made. Data on the type of procedure performed, time from induction and the type of airway device used was also collected.

Procedures performed under general anaesthesia with a volatile anaesthetic were included in this study. This included emergency, urgent, and elective cases. No data was collected if no volatile anaesthetic agent was used, such as if surgery was performed under local or regional anaesthesia, or if total intravenous anaesthesia was used. The data was collected at least ten minutes after induction of anaesthesia. Any visits made before ten minutes were excluded.

Table 3 Cost of Inhalational Anaesthetic Agents

	Sevoflurane	Isoflurane	Desflurane
Volume in Bottle (mL)	250	250	240
Cost per Bottle (€)	74.85	24.21	85.15
Cost per mL (€)	0.299	0.097	0.341

All data was gathered into an Excel® sheet (version 2202, Microsoft, California, US). Statistical analysis was performed with R (version 4.2.2), using R Studio (version 2023.03.0+386). Univariate analysis was performed with non-parametric tests where appropriate. Data was first checked for normality and skewness using visual methods. Testing for normality was done using the Shapiro-Wilk test. When appropriate, t-tests, Mann-Whitney U tests, Kruskal-Wallis test and chi-squared tests were used for univariate analysis. Most results reported showed skewness, so median values are reported, rather than means. With a p-value of 0.05 or less, the result was taken to be significant.

Finally, an estimate of the cost of volatile agent use in Mater Dei Hospital was calculated. The cost of each anaesthetic agent was obtained from hospital sources (Table 3). The median gas flow and median concentration for each gas were multiplied to obtain the median consumption of each gas. This was translated into the consumption of liquid agent as described by Biro et al⁸ and the cost per hour was then calculated.

RESULTS

In total, there were 383 visits spread over 35 days, of which 244 visits were done during maintenance of anaesthesia with a volatile agent (Figure 2). The median time of visit from the start of induction was 49 min (IQR: 20 – 90 min).

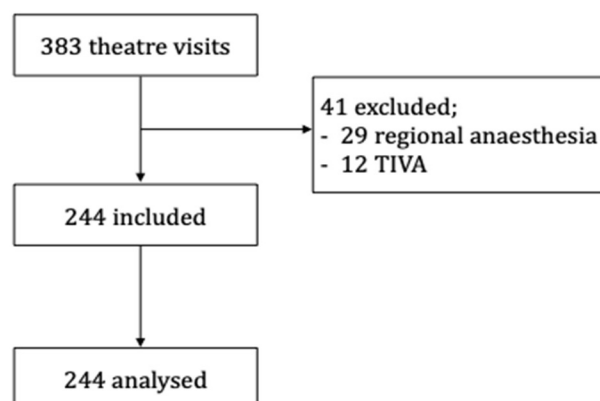


Figure 2 Consort flow of results

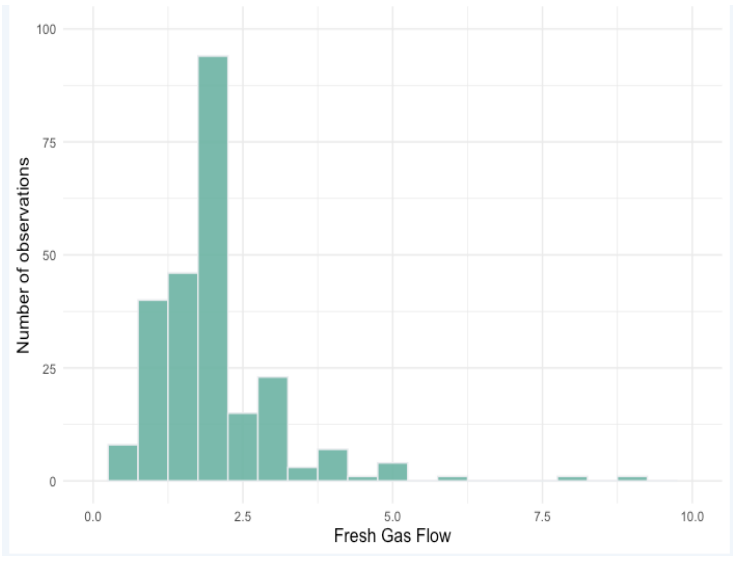


Figure 3 Distribution of Fresh Gas Flow in L/min

The median Fresh Gas Flow (FGF) used at the time of the observation was 2L/min (IQR 1.5 – 2 L/min), with a maximum of 9 L/min in one case. This is shown in [Figure 3](#).

The most used inhalational anaesthetic agent was Sevoflurane, used in 205 cases (84%), followed by Isoflurane in 32 cases (13%) and Desflurane in 7 cases (3%). The median FGF used for each gas was not statistically different (Sevoflurane: 2L/min, Isoflurane: 2L/min and Desflurane 1.2L/min, $p=0.061$).

The median consumption of each agent was calculated and used to calculate an estimated cost per hour using each anaesthetic agent, shown in [Table 4](#).

In the case of Sevoflurane, there was no relationship between the FGF and the vaporizer setting as shown in [Figure 4](#). The mean concentration of Sevoflurane used on the vaporizer was not statistically different at different levels of FGF.

We observed that the majority (71%) of cases involved endotracheal intubation (ETT: 173 cases vs LMA: 70). There was no statistical difference

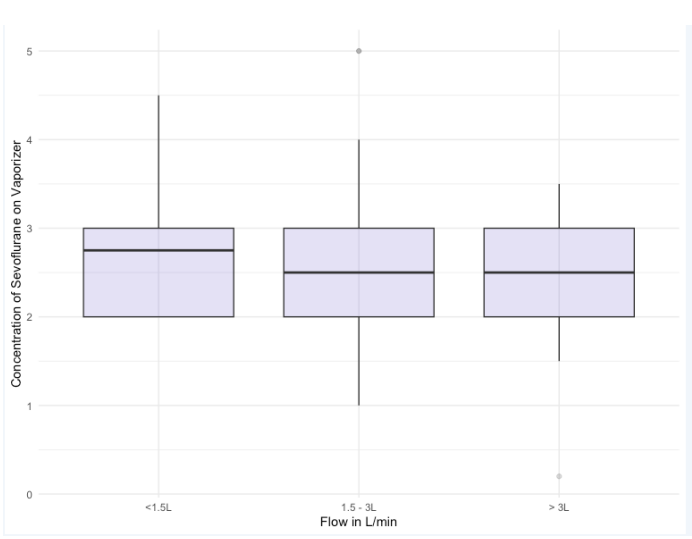


Figure 4 Relationship between concentration of sevoflurane on vaporizer and flow in L/min

between the choice of airway and FGF (both 2L/min, $p=0.099$).

There was no relationship between the FGF employed and the time from induction when sevoflurane was used. Due to the low number of cases involving either isoflurane or desflurane, we did not perform a similar analysis for these anaesthetic gases.

The mean oxygen concentration observed in this observational study was 0.6 (SD: 0.085). There was no difference when the type of volatile agent was compared. There was also no relationship between FGF and oxygen concentration.

DISCUSSION

We have shown that in a single-centre operating theatre suite, the median fresh gas flow was 2L/min. This is consistent with data from other centres. Dexter et al found an average fresh gas flow of approximately 2L/min in a single centre in 2001, with a reduction to 1.27L/min⁹ when re-assessed in 2006.

Table 4 Consumption of each agent and cost per hour

Anaesthetic Agent	Median FGF (L/min)	Concentration %	Consumption, Vapour (mL/min)	Conversion 1ml liquid agent to volatile (ml)	Consumption, Liquid (mL/min)	Cost per Hour (€)
Sevoflurane	2	2.5 [IQR: 2-3]	50	184	0.27	€4.88
Isoflurane	2	1.5 [IQR: 1.2-2]	30	195	0.15	€0.87
Desflurane	1.2	6 [IQR: 5.5-7]	72	210	1.34	€6.96

In another observational study carried out using information gathered from the anaesthetic machines databases over 2008 covering 11,700 cases, the mean FGF for Sevoflurane was 2.49L/min, for Isoflurane 1.89L/min and for Desflurane 1.87L/min.¹⁰ More recently, in 2018, an audit at Memorial Sloan Kettering Cancer Centre, USA found a mean FGF of 2.55L/min when using sevoflurane.¹¹ During the audit, potential bias could have arisen because participants might have been more cautious when setting their fresh gas flows if they were aware of the ongoing audit, even though the investigators were discrete.

Currently, no best practice guidelines exist on the use of fresh gas flows or the practice of low-flow anaesthesia. The Royal College of Anaesthetists, in their 2020 quality improvement compendium, recommend the use of low-flow anaesthesia by reducing initial rates during induction to 6L/min and then moving to 0.5L/min or less after intubation as an intervention to reduce carbon emissions.¹²

The manufacturer of sevoflurane recommends a flow rate of 1-2L/min to limit potential exposure to compound A. It is licensed for use of an exposure limited to 2 MAC hours at flow rates of 1-2L/min.¹³ There are no recommendations for isoflurane and desflurane. According to R. Ross Kennedy et al, Sevoflurane has demonstrated safe usage at fresh gas flow rates below 1L/min, Furthermore, it has been established that Compound A, at concentrations encountered in anaesthesia, does not exhibit harmful effects on humans.¹⁴

In the current economic and environmental constraints, knowing the consumption of anaesthetic agents and optimising such use might be beneficial. Volatile anaesthetic agents, nitrous oxide and fluorinated agents such as sevoflurane, isoflurane and desflurane are greenhouse gases and ozone-depleting,¹⁵ therefore exerting a negative environmental impact. The main concern is the contribution to climate change¹⁶ The global warming potential (GWP) is used to compare the global warming impacts of different gases by comparing them to carbon dioxide. The GWP of halogenated volatile anaesthetics is up to 2000 times greater than carbon dioxide.¹⁷ Through the anaesthetic gas scavenging system, the minimally metabolised volatile agents are vented to the atmosphere limiting exposure to personnel in theatre. However, waste gases may cause adverse effects with chronic exposure making it crucial to limit waste.¹⁵ The use of low-flow anaesthesia is one way to achieve this, where a fresh gas flow rate of less than the minute

volume is used. The European Union is proposing to ban Desflurane starting January 2026.¹⁶ Isoflurane has the least environmental impact due to its relatively short atmospheric lifetime and its decreasing use. The 100-year horizon GWP for Desflurane is 20 times higher than Sevoflurane. In addition, it has a three times lower potency than sevoflurane (MAC is three times higher), making its environmental impact more pronounced.¹⁷ explaining the proposal to restrict its use. This should not, however, be viewed as the solution for environmental sustainability in anaesthesia and other measures should still be taken such as using low-flow anaesthesia. In this audit, only 2.8% of the total cases used desflurane, whilst the majority, 84%, used sevoflurane and the remaining 13.2% isoflurane.

The consumption of volatile anaesthetic agents is a significant cost in hospitals. The carrier gases, oxygen and air should also be given importance to limit waste.¹⁸ The cost of these agents depends on their potencies and the fresh gas flow rate (besides market price). By reducing FGF accordingly, the amount of drug delivered to the circuit is reduced without changing the amount entering the patient. Using isoflurane, the most economical volatile agent, could offer advantages for maintaining anaesthesia lasting less than three hours. It may be reasonable to use Sevoflurane or Desflurane for longer procedures as their poor solubility allows for better use of low-flow anaesthesia and leads to a more rapid recovery.¹⁹ The mean Sevoflurane use was 51ml/min meaning that approximately 4.88 euro every hour was spent when using sevoflurane at the recorded fresh gas flow rates.

In this audit, we looked at the FGFs during the maintenance of anaesthesia and ignored the first ten minutes from induction which would be considered as the wash-in period. The wash-in time refers to the time it takes to saturate the circle system with the desired concentration of the volatile agent. Factors which influence the wash-in-period include the concentration of the anaesthetic agent (as set on the vaporizer), patient factors and fresh gas flow. From a clinical perspective, it is preferable to have an initial high-flow to thoroughly saturate the circle system during the wash-in period quickly. Leijonhufvud F, et al have shown that using a FGF of more than 6L/min will not increase speed for the wash-in period. The longest time it took to reach the desired concentration using low flows was 431.3 seconds using low flows.²⁰ Thus, we deemed it appropriate to assume that after ten minutes after induction of anaesthesia, the fresh gas flows should have been set for what would be used during maintenance. Arslan et al showed that low-flow anaesthesia can be

performed safely and efficiently without the initial high fresh gas flow phase. When compared to 4L/min, a FGF of 1L/min after intubation required more time to achieve a target MAC value of 0.7 (2.7 minutes vs 4.8 minutes), but lower consumption of anaesthetic agent.²¹ This practice would further help to reduce waste and pollution.

In our practice, the median oxygen concentration used in the FGF was 0.61. Patients are at a higher risk of absorption atelectasis with a higher oxygen concentration during induction and maintenance of anaesthesia.²² During induction, due to potential emergencies, the risk-benefit of a high inspired fraction of oxygen justifies the use of preoxygenation. However, in most cases during maintenance of anaesthesia, lower oxygen concentrations of 0.3-0.4 may be used which would be beneficial for the patient in addition to other economic and environmental advantages. There is conflicting data on whether higher oxygen concentrations prevent surgical site infection or postoperative nausea and vomiting.²³

We propose that a concerted effort should be made to reduce wastage and costs. An educational campaign targeting anaesthetists may be prepared, together with visual cues to remind anaesthetists to lower the fresh gas flows.

Reducing a fresh gas flow from 2L/min to 1L/min in our study would have meant reducing the consumption of Sevoflurane from a median of

50mL/min to just 27.5mL/min. This would mean reducing Sevoflurane costs by €1.30 per hour, a savings of 45%. One centre had carried out monthly stop audits to assess fresh gas flow rates and shared the information relating to cost of the volatile agents via a 'low-flow board'. By doing so each month they had seen a trend towards the use of low-flow anaesthesia.²⁴

However, education alone may not be enough, and ultimately, more centres are opting for automated systems that adjust the fresh gas flow during a procedure.

Pioneered in the 1980s, such systems became commercially available in 2003. They are now widely available and used. There is a capital expenditure since such systems require the use of dedicated electronic vaporizers, but Kalmar et al have shown that the consumption of Sevoflurane decreased by an average of 40% after the introduction of anaesthetic machines capable of such automated gas flows²⁵⁻²⁶

CONCLUSION

The recorded fresh gas flows from Mater Dei Hospital show responsible use of anaesthetic agents and are comparable to other centres. However, improvement can be made by employing minimal-flow methods. It would be worthwhile to conduct a follow-up audit in the future to assess the effect of these findings on fresh gas flow usage.

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Patients' Satisfaction with Healthcare Provision in an Out-patient Setting in Malta

Gabriel Gauci, Kathleen England

Background

Patients' experience and satisfaction are key aspects of the delivery of patient-centered health care and are influenced by multiple factors. The private out-patient health services in Malta have a high utilisation rate, especially in the context of primary care. Previous data suggested a difference in terms of patient satisfaction and experience between the public and private sectors.

Method

The study involved a secondary analysis of data collected on patient satisfaction with primary and secondary out-patient healthcare services from the European Health Interview Survey (EHIS) carried out in 2019/2020. The EHIS sample was a representative sample of 4413 participants resident in the Maltese Islands stratified by age, gender and locality of residence.

Results

The demand for healthcare services is high with 77.2% having visited a GP in the previous 12 months. The primary care services are still heavily reliant on the private sector. There is an overall high rate of satisfaction throughout. There was a statistical difference between the public and private sectors, with higher satisfaction reported for private consultations. Overall, doctors obtained lower satisfaction scores in terms of involvement in decisions about care.

Conclusions

Maltese patients are generally satisfied with the level of care provided during medical consultations. The lower score in terms of involvement in the care provided may indicate a need to focus on a better patient-centered approach. A need to address the gaps between the public and private health care services is evident in the need to target further interventions that aid better primary care public service utilisation.

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Malta's National Healthcare Service (NHS) is primarily funded through general taxation and seeks to provide free healthcare coverage to all residents.¹ Most healthcare services are hospital-based, with in-patient and out-patient services primarily delivered through public hospitals. Primary care services are offered through health centres or community care clinics, which seek to provide various multidisciplinary primary care services at a community level.²

The private sector supplements public health services through private hospitals, clinics, and General Practitioner (GP) services. Although the public and private sectors function independently, the government has several public-private partnership agreements to support public services. Such agreements generally involve using private facilities to shorten waiting lists for specific procedures and investigations.

Primary care services are the first level of care and an entry point to the health care system. GPs have a gatekeeping role by recognising what can be treated within primary care and what requires referral to higher levels of care.^{3,4} In Malta, GPs may refer patients for specialist review within the public services by filling in an online referral form. Specialist appointments are then issued on an out-patient basis according to the case's urgency. Patients, however, also have the option to see a medical or surgical specialist in the private sector. Private specialist appointments can often be set up with or without a GP referral; thus, patients can set up an appointment directly with a chosen specialist.

Public healthcare services in Malta are free at the point of use, but notwithstanding this, the use of private healthcare services remains high. This is particularly evident in primary care, where the private sector is estimated to cater to over two-thirds of the demand for services.^{3,5,6} Most private primary care services are offered through solo/independent practices; only a few group practices exist.^{3,7} Regarding secondary care, a few private hospitals and clinics provide in-patient services, medical imaging services and theatre procedures within the private sector. Patients using private healthcare services can pay out-of-pocket or through voluntary health insurance policies.

Patient Satisfaction in Healthcare

Patient satisfaction can be defined as the state of happiness that the patient experiences when using a

healthcare service.⁹ This became an important measure of efficiency and effectiveness and is a standard for evaluating healthcare services.⁹ Most complaints in healthcare settings relate to interpersonal aspects of care and communication rather than clinical or technical errors.¹⁰ The patient's experience and satisfaction within the healthcare system are multifactorial. They can be linked to both provider-related factors (such as facilities, interpersonal skills, etc.) and patient-related factors (such as age, personality, educational level, etc.).¹¹ As a result, collecting data relating to the patient's care experience remains pertinent to identifying and addressing such issues.

A difference in patient experience and satisfaction between Malta's private and public healthcare services has been reported.^{12,13} This difference may explain the reported higher rate of utilisation of private services.

This study used secondary data analysis from the European Health Interview Survey (EHIS)¹⁴ to identify patterns in health service use and possible differences in patient satisfaction and experience between the public and private sectors.

METHODOLOGY

The EHIS is held every five to six years in all EU countries. It aims to obtain valuable data on health behaviour, healthcare use, and morbidity across all EU member states.¹⁵

The EHIS was last conducted in Malta in 2019/2020. At the time of data collection, the target population was all individuals aged 15 and over who resided in private residences in Malta and Gozo. The National Statistics Office extracted the sample, which consisted of a random sample stratified by age, gender, and residence locality. The effective sample size reached was 4413 out of an eligible 6430 (response rate of 68.6%), with the target sample size being 4000 respondents.

A descriptive secondary analysis of data collected through the EHIS is presented to provide an updated insight into the use of public and private healthcare services regarding visits to GPs and medical/surgical specialist consultations. Data on the patient experience and overall consultation rating were analysed to determine differences between the private and public sectors. This is then discussed in the context of existing research and assessed for any significant differences between the two sectors.

Digital Supplementary File 1 highlights the EHIS questions which were used for the analysis.

Two questions in the EHIS (HC.9 and HC.18) asked participants when they had last visited a GP and medical or surgical specialist, respectively. Participants answering these questions could choose from the following answers: 'in the last 12 months', 'more than 12 months ago', or 'never'. The other questions included in the analysis (HC.13-HC.17 and HC.22-HC.26) were based on a Likert-type response where patients could rate their experience of care for the domains explored, eg 'Yes'; 'Yes to some extent'; 'No'; 'No, definitely not'; and 'Do not know'.

For the analysis, primary care (GP) consultations are considered within a clinical setting (in-office) since the questionnaire did not directly enquire about patient satisfaction in the context of home GP visits.

Statistical Analysis

Data were analysed using IBM® SPSS® v.28. First, a descriptive analysis was conducted to identify trends and patterns in the data. Then, statistical testing was conducted to determine whether there were significant differences between the public and private healthcare sectors for each domain.

Chi-squared testing used a *p*-value of 0.05 and a 95% confidence interval to determine significance. Fisher's exact test was used for small numbers (values less than 5). Significance testing was carried out for the public and private sectors in primary care services and specialist services, respectively. Primary care and medical/specialist services were not compared directly since they consist of separate specialities and represent two different levels of care.

RESULTS

Table 1 summarises the responses given for the overall rating of the last medical consultation (questions HC.17 and HC.26).

The level of satisfaction in terms of consultation times, explanation of treatment, opportunity to ask questions, and involvement in care was high throughout. The percentage ratings (aggregate responses) of each of these domains (questions HC.13-HC.16 and HC.22-HC.25) are illustrated in Figure 1 & Figure 2.

Primary Care (General Practitioner) Services

77.2% of participants had visited a GP in the previous 12 months. 69.4% visited a private GP, and 30.5% visited a health centre doctor in the same period.

In terms of length of consultation (HC.13), 96.4% of those visiting a private GP felt that consultation time was enough as opposed to 91.5% of those who had visited a health centre doctor (*p*< 0.001). 96.9% of those visiting a private GP felt that things were explained understandably (HC.14). This was slightly less for health centre visits, with 90.1% giving a positive response (*p*<0.001). 96.9% of those visiting a private GP agreed they were allowed to ask questions (HC15). This dropped to 79.1% for health centre GP visits (*p*<0.001).

A lower satisfaction score was noted in terms of involvement in care decisions (HC.16), to which only 87.7% (private GP) and 79.9% (health centre GP) answered 'yes' or 'yes, to some extent' to this question (*p*<0.001).

Table 1 Overall Rating of Last Medical Consultation (Excluding 'Do Not Know' answers)

Overall Rating of Last Medical Consultation					
Rating	Very Good	Good	Fair	Bad	Very Bad
Health Centre Doctor	51.9%	37.9%	7.6%	1.1%	0.6%
Private Family Doctor	69.0%	28.0%	2.4%	0.3%	0.1%
Government Medical/ Surgical Specialist	58.0%	32.4%	6.6%	2.0%	0.5%
Private Medical/Surgical Specialist	67.0%	27.2%	3.9%	0.6%	0.6%

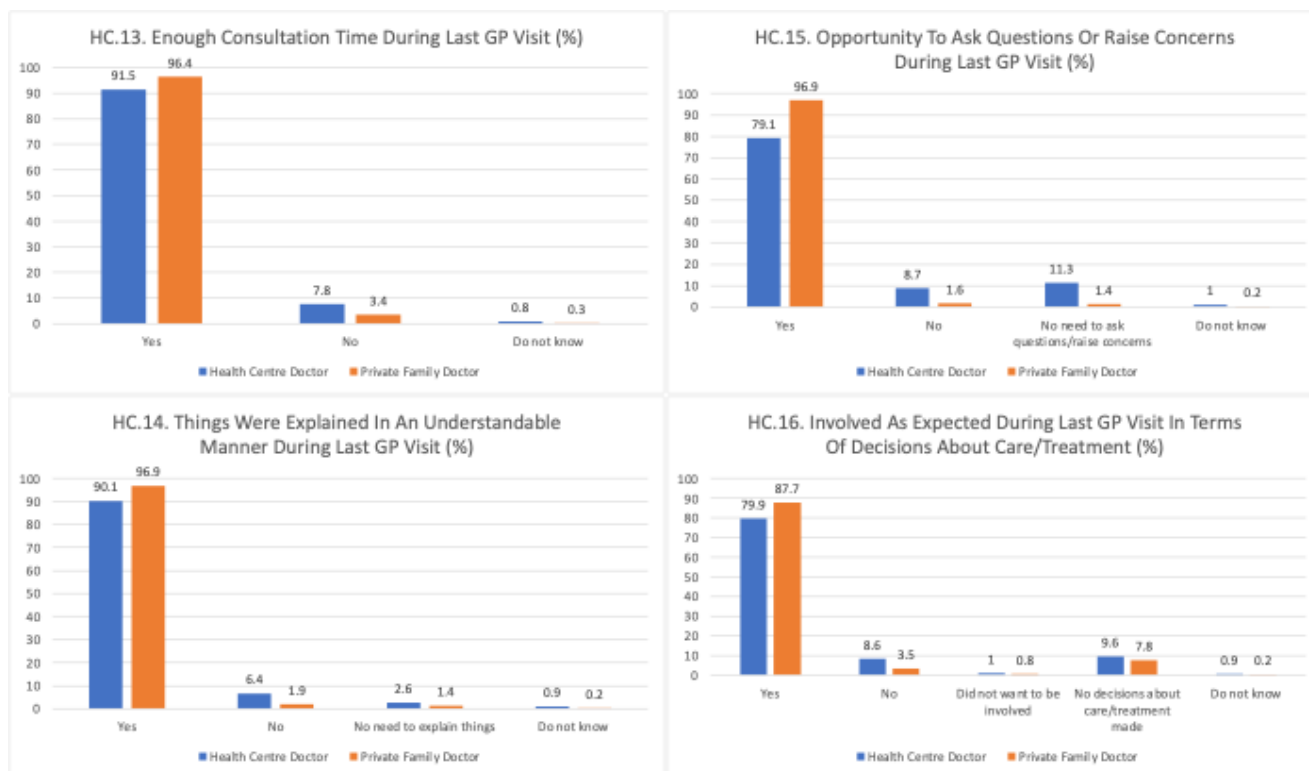


Figure 1 Responses for Questions HC.13 - HC. 16: GP Consultations

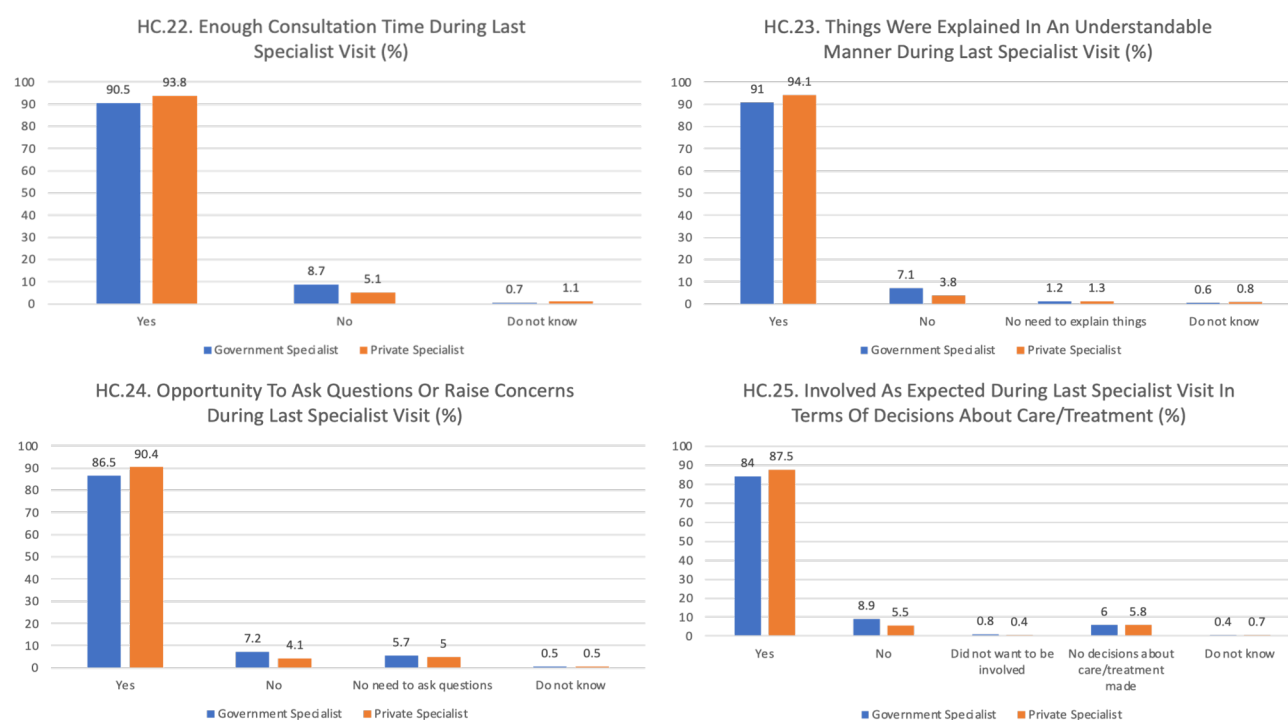


Figure 2 Responses for Questions HC.22 to HC.26: Medical/Surgical Specialist Consultations

Secondary Care Specialist Services

The satisfaction scores for primary care services are congruent with those obtained for secondary care specialist visits.

Visits to medical or surgical specialists (secondary care) were less than GP visits, with 34.3% of respondents having visited a medical or surgical specialist in the previous 12 months. 25.6% had visited a secondary care specialist doctor within the private sector, and 18.4% visited a specialist within the government health services.

Responses for question HC.22 on the length of consultation times for secondary care visits were similar to those obtained for GP visits, with 93.8% (private specialist) and 90.5% (government specialist) agreeing that consultation time was enough ($p < 0.001$). 94.1% of respondents felt things were explained understandably (HC.23) during private secondary care specialist visits compared to 91% in the public sector ($p = 0.016$).

For secondary care specialist visits, there was a lower satisfaction for opportunities to ask questions (HC.24) compared to the other questions posed, with 90.4% (private practice) and 86.5% (government specialist) agreeing that they could ask questions during the consultation ($p = 0.019$). Similarly, scores were lower for involvement in care decisions (HC.25) during secondary care specialist visits, with 87.5% and 84% answering 'yes' or 'yes, to some extent' for private secondary care specialist and government secondary care specialist visits, respectively ($p = 0.033$).

Despite the high overall satisfaction rates, there was a statistically significant difference between the public and private sectors. The private sector scored more positively on the questions posed in the EHIS.

DISCUSSION

EUROSTAT¹⁶ data shows that an average of 81.4% of the population across the 27 EU member states consulted a medical doctor in the previous 12 months.¹⁶ In Malta, an estimated 79.9% of the population had consulted a medical doctor in the last 12 months, making it slightly less but close to the European average.

Data from the EHIS demonstrates that the demand for healthcare services is high, with 77.2% of respondents having visited a GP the previous year. 34.3% had visited a medical or surgical specialist in the same period. Although these rates are similar to

the EU average, there was a slightly higher rate of GP consultations in the previous 12 months (EU average of 75.6%) and a lower rate of specialist consultations (EU average of 51.9%).¹⁶ This may indicate higher accessibility to primary care services in Malta.

The dependence on private primary care services is still evident. Indeed, 69.4% of respondents had visited a private GP in the previous 12 months compared to 30.5% who had visited a government GP in the same period. This is consistent with earlier data suggesting that the private sector caters for 70% of the primary care services in Malta.^{1,3,12,13} Similarly, there was a higher rate of specialist consultation in the private sector (25.6%) than in the public sector (18.4%), but this difference is much less pronounced.

Although the demand and rate of utilisation of services do not directly reflect clinical outcomes or care, this data shows that overall, Maltese patients tend to consult more private doctors, especially for primary care issues. Differences between the two sectors may explain the reliance on private primary healthcare services. Continuity of care is considered one of the core values of general practice. The public health centre system does not have a well-established follow-up or GP registration system, and most public GP services are offered on a walk-in basis. In the private sector, patients can choose their own doctor and have a higher level of continuity of care, allowing them to establish a patient-doctor relationship with their GP.⁷ Patients using health centre (public) services cannot form a long-standing patient-doctor relationship as they cannot get regular care from the same doctor. The importance of continuity of care in primary care is also emphasised by the World Organisation of Family Doctors (WONCA), which emphasises that patients should ideally have a named family doctor to improve the quality and effectiveness of care and provide consistent and personalised healthcare.⁸

Recently, several initiatives were launched to improve public primary health services, such as introducing electronic patient records and new collective agreements for doctors. Nevertheless, the resources available within the public sector, especially regarding staff, still need to be improved compared to the workload and demand for services. On the other hand, it is also noted that private practitioners work with much fewer resources (e.g. access to investigations, results, etc.) and often for longer hours compared to those working in the public sector. It may be argued that these factors are also reflected in patients' experience and satisfaction, as discussed below.

Patient Satisfaction

Patient-centred care has become an essential aspect of healthcare services across EU countries. It has been widely implemented to identify patients' expectations and needs and improve the quality of care.¹⁷ As previously highlighted, identifying factors affecting patients' satisfaction and experience is critical to developing patient-centred policies to improve patient care.

In Malta, the evaluation of patient-centred care has been previously explored. The National Health Interview Survey (NHIS) (2002) had already reported a high rate of utilisation of private services and higher satisfaction in the private sector.¹³ A study by Agius later confirmed the difference in patient satisfaction between public and private primary care services, which was highly significant.

In our analysis, data from the EHIS shows that patients are satisfied with the services they receive across all sectors, as reflected in the high overall rating of their last consultation. However, A significant difference exists between the public and private sectors for both GP and specialist visits, with higher satisfaction rates in the private sector. The questions in the EHIS explore several interpersonal domains which may influence patient satisfaction. Indeed, although there was an overall positive rating across all questions, the difference between the private and public sectors persists throughout the analysis.

Regarding GP visits, it is noted that GPs scored very well for consultation time and explanation in an understandable manner. Scores for health centres were, however, lower with statistical significance. The lowest score was in terms of involvement in decision-making, rated as 'yes' for 87.7% of private GP visits and 79.9% for health centre GP visits. Only 79.1% of respondents agreed they were given enough opportunity to ask questions during their last health centre visits compared to 96.9% during their previous private GP visit.

While the statistical difference was achieved for all questions, health centre doctors scored notably lower regarding the opportunity to ask questions and involvement in care. Such results are congruent with a study by Pullicino et al, in which private primary care services scored higher in terms of 'continuity of care', 'comprehensiveness of care', and the application of a biopsychosocial approach and poorer in terms of access to care – accessibility and out-of-hours services.¹⁸ A more in-depth and explorative qualitative analysis of the factors contributing to these issues might be warranted to address these interpersonal aspects.

SUMMARY BOX

What is already known about the subject

- Patients' experiences and satisfaction have become necessary to assess the quality of care.
- There is a high utilisation of private health services, especially in primary care.
- The two health services reported a difference in patient experience and satisfaction.
- The EHIS provides data on patient experiences regarding GP and secondary care medical or surgical specialist visits.

What are the new findings?

- Data from the EHIS was analysed, and the high demand for healthcare services was confirmed.
- Reliance on private primary care services is still high.
- Overall, the domains explored throughout both sectors had high satisfaction rates for GP and secondary care specialist visits.
- A difference in patient experience and satisfaction between the public and private sectors is confirmed again.
- GPs and secondary care specialists scored worst regarding patients' involvement in decisions about care and treatment.

The lower rating score noted in question HC.16 on involvement in decision-making was similarly noted for visits to secondary care medical/surgical specialities. Indeed, 87.5% (private specialist) and 84% (government specialist) of respondents agreed that they were involved in decisions about care during their last specialist visit. Such results may indicate that patients wish to be more involved in decision-making and may signify the need to raise awareness among Maltese practitioners on patient-centred care and involvement in care.

Interpersonal aspects of consultation, including the time allocated, involvement in care, and attention given to the patient, all correlate positively with the quality of the consultation.¹⁷ Data from the Organisation for Economic Co-operation and Development (OECD) is congruent with the data obtained in Malta. Indeed, the OECD reports that most patients report positive interactions with doctors. Similar to Malta, the OECD data shows that the majority of patients felt that the doctor spent enough consultation time with them (EU average

84% for 2020), provided easy-to-understand information (EU average 90.5% for 2020) and involved them in care decisions (EU average 82.1% for 2020). The Netherlands scores exceptionally high in these three aspects.¹⁷ While it is difficult to compare due to possible variations in culture, survey coverage and response rates¹⁷, differences in the healthcare systems might also explain the higher satisfaction rates in the Netherlands. The Netherlands has a higher expenditure per capita on health and lower out-of-pocket spending than the EU average, with healthcare services funded through a regulated framework of mandatory insurance policies.¹⁹ The country has a robust primary care system, with a reported low hospital admission rate and among the lowest mortality rates from preventable and treatable causes in the EU.¹⁹

Our analysis confirms that patients' experience differs between the public and private health sectors, and patients tend to report higher satisfaction in the private sector. The data is congruent with previous studies evaluating patient satisfaction in primary care, as discussed above.

Despite the high overall satisfaction rates, the analysis supports the need for an in-depth explorative evaluation of healthcare services to ensure that all stakeholders' perceptions, needs, and demands (care providers and patients) are addressed. Further research should focus on identifying possible solutions to shift resource utilisation and maximise the use of primary care, with an emphasis on patients' experience and satisfaction.

LIMITATIONS

The study involves a secondary analysis of quantitative data and does not provide qualitative insight into the reasons for any discrepancies between public and private healthcare services. The original interview was aimed at obtaining general

data on several health indicators and was not solely focused on access to and experience of the healthcare services.

CONCLUSION

The analysis confirms the high demand for healthcare services in Malta, mainly primary care services. It once again highlights the heavy reliance on private primary care services and the discrepancy in experience and satisfaction between public and private services. Nevertheless, the data indicates high satisfaction with the attributes explored across both sectors.

While the data obtained in the EHIS is quantitative, it can be postulated that patients appreciate a patient-centred approach whereby they are listened to and allowed to understand, ask and make informed choices. The significant difference between the public and private sectors supports this. The main prima facie differences between the public and private sectors are related to how the private sector services can be accessed and how they are provided. This analysis supports further exploratory evaluation to identify ways the gap in patient satisfaction between the public and private sectors can be reduced.

ABBREVIATIONS

EHIS	European Health Interview Survey
EU	European Union
GPs	General Practitioners
HCS	Health Centres
NHS	National Health Service
OECD	Organisation for Economic Co-operation and Development

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The efficacy of SARS-CoV-2 booster dose on SARS-CoV-2 inpatient epidemiology

an overview on disease severity and mortality

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Background

The world is moving into the 3rd year of the SARS-CoV-2 pandemic. There is no doubt that vaccination has been crucial in significantly reducing the impact of the pandemic. Given the novelty of the SARS-CoV-2 vaccines and the waning immunity over time, data is required to determine the efficacy of SARS-CoV-2 booster doses.

Methods

The comparative observational study included 451 eligible inpatients at Mater Dei Hospital, Malta. Hospital software and bed management databases were used to extract cases of confirmed infection in patients aged 17 years and older. Patients were stratified into two study arms: boosted and non-boosted cohorts. Disease severity was calculated based on clinical criteria and the Modified Chest X-Ray Score. A Pearson-Chi square test of independence was then used to analyse the data to acquire and compare rates of disease severity and mortality between the two groups.

Results

5.6% of non-boosted patients required intensive care unit admission compared to 0% of the boosted population. 8.8% of non-boosted patients developed severe illness compared to 5.5% of the boosted group. The study also found higher rates of ARDS and mortality in non-boosted inpatients, with a higher male predominance.

Conclusion

This study underpins the superior protection offered by a booster dose of SARS-CoV-2. It also points to a time-dependent waning in immunity, highlighting the importance of robust vaccination programmes.

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Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection has caused havoc in healthcare systems and international socioeconomics.¹ Vaccination against SARS-CoV-2 has been observed to significantly reduce both the morbidity and mortality in various countries.²⁻⁴ In Malta, the national vaccination programme was initiated in December 2020, with a booster dose programme starting in September 2021. The population was vaccinated using one of the EMA-approved vaccines i.e Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine), Janssen (Ad26.COV2.S), the Moderna COVID-19 (mRNA-1273) vaccine and the Pfizer BioNTech (BNT162b2) COVID-19 vaccine. Janssen (Ad26.COV2.S) vaccine consisted of one dose whereas the others required two doses for completion. In the booster programme, only Moderna (mRNA-1273) and the Pfizer BioNTech (BNT162b2) COVID-19 vaccines were utilised.

In both programmes, the elderly and immunocompromised populations were given priority. By the start of September 2021, approximately 94.5% of the total eligible population of 438,321 people had received two doses of the vaccine.^{5,6} with 67% of people aged over 18 having received their first booster shot by January 2022.⁷

Unfortunately, new spikes in case numbers were observed in autumn and winter of 2021 with the emergence of viral variants such as the Delta variant and Omicron variant. With growing evidence of waning vaccine immunity overtime, as well as the heightened infectivity of the variants,⁸ a national booster programme was introduced. It was postulated that the booster provided protection from infection and even reduction in disease severity in cases of infection.^{9,10} The aim of this study was to analyse the efficacy of SARS-CoV-2 first booster vaccine dose in reducing disease severity and mortality rate in Malta.

METHOD

Study Design

A comparative observational study was performed, looking at the vaccination status of all in-patients with symptomatic SARS-CoV-2-related illness hospitalised at Mater Dei Hospital, Malta between October 2021 and mid-January 2022. This included patients who tested positive for SARS-CoV-2 in the community, patients who swabbed positive for SARS-CoV-2 through routine hospital admission swabbing and eventually developed symptomatic SARS-CoV-2-

related illness and patients who tested SARS-CoV-2 positive and developed SARS-CoV-2-related symptoms during their hospital stay. A nasopharyngeal PCR swab was utilized throughout the study. The study population was limited to patients aged 17 years and over. The eligible cohort was split into two arms: Non-boosted arm i.e fully-vaccinated patients without a booster dose and Boosted arm i.e fully-vaccinated patients with an addition of a booster dose. Exclusion criteria for this study were unvaccinated patients, immunocompromised patients, patients who were ineligible for booster dose (that is patients who had swabbed positive for SARS-CoV-2 less than 3 months after SARS-CoV-2 vaccine completion) and patients on whom we had incomplete data.

Data protection and legal approval were obtained from the Data Protection Manager and legal office respectively at MDH. Ethical approval was obtained from the Health Ethics Committee within the Directorate for Health Information and Research of Malta.

All patient data was anonymised. SARS-CoV-2 patients were flagged through the hospital's Bed Management notifications and hospital software, iSoft Clinical Manager (iCM) and Patient Dashboard (PD), with data being gathered retrospectively and in real time by the authors of the study. Demographic data including age, gender, date, duration of admission and mortality was collected from iCM. The reasons for hospital admission, admissions to Intensive Therapy Unit (ITU), as well as respiratory status (hypoxia, low oxygen saturations, shortness of breath) and immune status (immunocompetent vs immunocompromise) of patients were obtained from patients' electronic discharge summaries, patient administration system (CPAS), iCM, medical notes and visit histories.

Immunocompromise was defined as all those patients on immunosuppressive or immunomodulatory biological treatments, chemotherapy, radical radiotherapy, steroids for at least a month, solid organ transplant recipients, human immunodeficiency virus infection, haematological malignancy or history of such malignancy, and genetic disorders affecting the immune system.¹¹

Patients in the two arms of the study group were stratified according to disease severity based on a combination of clinical and radiological criteria as per **Table 1** below.

Mild disease was defined as the presence of SARS-CoV-2 symptoms with/without mild SARS-CoV-2 radiological changes without the presence of hypoxia. Moderate disease was defined as presence of COVID-19 symptoms with mild SARS-CoV-2 radiological changes and hypoxia (oxygen saturations of less than 94% on room air on arterial blood gas testing or bedside pulse oximetry) or moderate SARS-CoV-2 radiological changes without hypoxia. Severe disease was defined as the presence of SARS-CoV-2 symptoms with moderate/severe SARS-CoV-2 radiological changes and hypoxia. Critical disease was defined as patients requiring high flow nasal oxygen (HFNO) or endotracheal intubation secondary to SARS-CoV-2.

Chest imaging was reviewed through Picture Archiving and Communication System (PACS) imaging software with the degree of radiological changes being stratified according to the Modified Chest X-Ray scoring system.¹² The scoring was calculated by drawing two horizontal lines, dividing the lungs into 6 regions, with each region scoring between 0-2 (0 being normal, 1 infiltrates/consolidations less than 50% of the regions and 2 infiltrates/consolidations of more than 50%) giving a final score from 0-12, mild being score of 1-4, moderate being score of 5-8, severe being score of 9-12, as depicted in [Table 1](#) above.

Details regarding vaccination status were obtained from the PD and discharge summaries. This included the number of doses, dates of vaccination and vaccination brands received by patients against SARS-CoV-2. Vaccination status was considered to be valid if the last dose of the vaccine (either second

dose or booster or first dose of Janssen (Ad26.COV2.S) was taken not less than 2 weeks prior to the patient testing positive for SARS-CoV-2.

Comparison was drawn between the rate of severe and critical illness in patients who received a booster vaccine dose at least 14 days prior to testing positive for SARS-CoV-2 and those who were not boosted. Comparison was also made between SARS-CoV-2 acute respiratory distress syndrome (ARDS)-related in hospital mortality rate in patients who received a booster vaccine dose at least 14 days prior to testing positive for SARS-CoV-2 and those who were not boosted.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software (version 23) was used for statistical analysis. A p value of less than 0.05 was considered to indicate statistical significance.

A one-sample Kolmogorov-Smirnov test was performed to analyse test distribution. Test-distribution was found to be normal ([Digital Supplement File 1](#)).

A Pearson Chi-square test of independence was used to analyse the relation between not receiving a SARS-CoV-2 booster and hospitalisation with severe or critical SARS-CoV-2 illness. The null hypothesis was that there is no relationship between not receiving a SARS-CoV-2 booster and severe or critical SARS-CoV-2 illness. The alternative hypothesis was that there is a statistically significant association between these two variables.

Table 1 Stratification of SARS-CoV-2 Disease using Clinical and Radiological Criteria

Severity of SARS-CoV-2 Disease	Clinical Criteria	Radiological criteria - Modified Chest X-Ray Scoring System
Mild	SARS-CoV-2 symptoms without hypoxia	Normal (score 0) or Mild i.e (score 1-4)
Moderate	SARS-CoV-2 symptoms without hypoxia	Moderate (score 5-8)
	SARS-CoV-2 symptoms with hypoxia	Mild (score 1-4)
Severe	SARS-CoV-2 symptoms with hypoxia	Moderate (score 5-8) or Severe (score 9-12)
Critical	SARS-CoV-2 symptoms with hypoxia requiring HFNO or intubation	Moderate (score 5-8) or Severe (score 9-12)

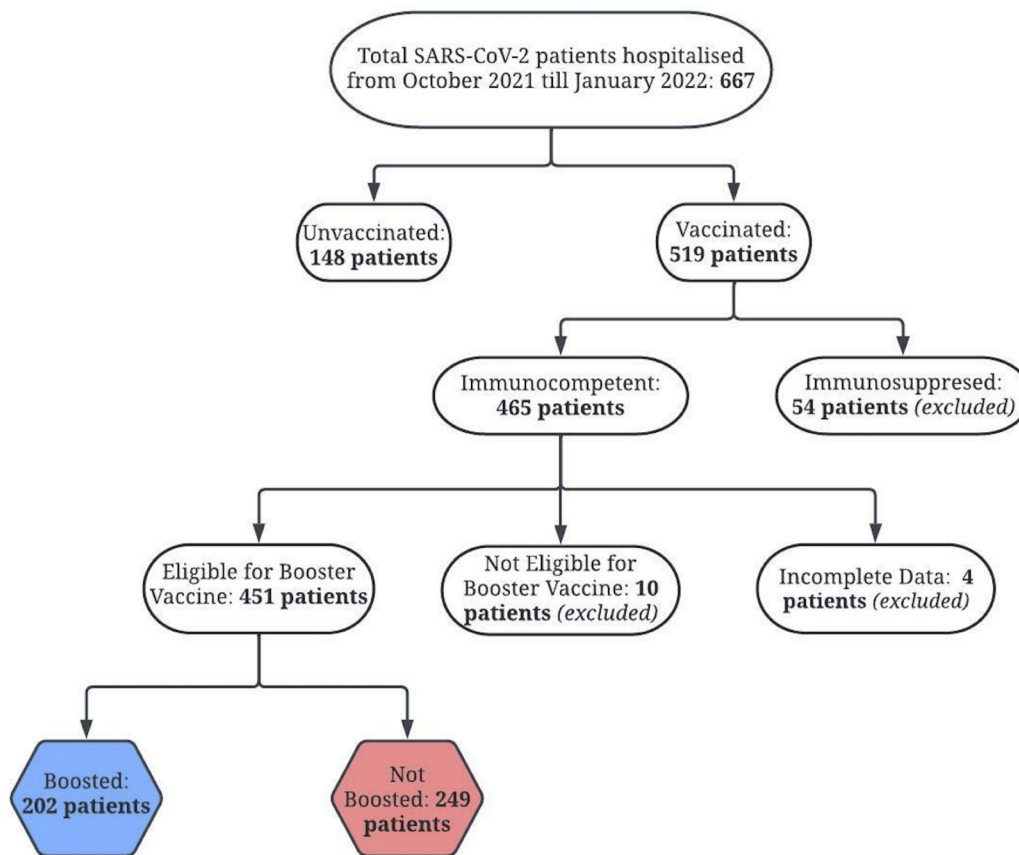


Figure 1 Study population

A Pearson Chi-square test of independence was used to analyse the relation between not receiving a SARS-CoV-2 booster and SARS-CoV-2 ARDS-related deaths. The null hypothesis was that there is no relationship between not receiving a SARS-CoV-2 booster with SARS-CoV-2 ARDS-related deaths. The alternative hypothesis was that there is a statistically significant association between these two variables.

A simple linear regression model analysis was performed to analyse potential variables that effected significantly SARS-CoV-2-related admissions to ITU (as the dependent variable).

RESULTS

Out of a total of 667 patients testing positive for SARS-CoV-2 during the study period, 451 patients satisfied the inclusion criteria, of which 202 patients were included in the boosted group and 249 patients in the non-boosted group (Figure 1).

When comparing gender and age, the boosted group was noted to have a higher proportion of female patients compared to the non-boosted group (52% vs 47%) as well as significantly more patients over the age of 70 years (73% vs 29% respectively) (Table 2).

The study population was vaccinated with the following SARS-CoV-2 vaccines: 72.7% received Pfizer BioNTech (BNT162b2), 20.9% received Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine, 3.1% received Janssen (Ad26.COV2.S) and 2.9% received Moderna COVID-19 (mRNA-1273). 77.7% of the boosted arm received Pfizer BioNTech (BNT162b2) as a booster vaccine whilst 21.8% received Moderna COVID-19 (mRNA-1273) (Table 3).

Importantly, there were zero patients classified as critical in the boosted group as compared to 6.4% in the non-boosted group (predominantly between the age of 41 and 80 years), (Table 2, Table 4). The latter correlates with admission to ITU, 0% vs 5.6% in the boosted group and non-boosted group, respectively. 12 patients (86%) of the non-boosted group that required ITU admission secondary to SARS-CoV-2 pneumonia were males.

The study found significantly more non-boosted patients with severe/critical SARS-CoV-2 related illness compared to the boosted population (boosted group: 5.4% vs non-boosted group: 18.0%, $p = 0.001$). Furthermore, a simple linear regression model demonstrated that the booster/vaccination status was a statistically significant independent variable to SARS-CoV-2 related admissions to ITU ($p < 0.001$) (Digital Supplement File 2).

Table 2 Demographics and clinical characteristics of the Study Population

	Unvaccinated n %	Boosted-Group n %	Non-Boosted Group n %
Sex			
Male	69 46.6%	97 48.0%	132 53%
Female	79 53.4%	105 52.0%	117 47%
Age-distribution			
17 – 30 years	27 18.2%	2 1%	32 12.9%
31 – 40 years	27 18.2%	2 1%	38 15.2%
41 – 50 years	16 10.8%	10 5.0%	42 16.9%
51 – 60 years	22 14.9%	16 8.0%	24 9.6%
61 – 70 years	25 16.9%	24 11.9%	42 16.9%
71 – 80 years	15 10.2%	63 31.1%	40 16.1%
>80 years	16 10.8%	85 42%	31 12.4%
Severity of SARS-CoV-2 illness			
Asymptomatic	41 27.7%	61 30.2%	63 25.3%
Mild	47 31.8%	98 48.5%	114 45.8%
Moderate	17 11.5%	32 15.8%	34 13.7%
Severe	28 18.9%	11 5.5%	22 8.8%
Critical	15 10.1%	0 0%	16 6.4%
SARS-CoV-2 related ITU admissions			
ITU admissions	11 7.4%	0 0%	14 5.6%
Non-ITU admissions	137 92.6%	202 100%	235 94.4%
Mortality			
ARDS-related deaths	7 4.7%	2 1%	11 4.4%
Males	4 57.1%	2 100%	7 63.6%
Females	3 42.9%	0 0%	4 36.4%
17 – 30 years	0	0	0
31 – 40 years	1	0	0
41 – 50 years	0	0	1
51 – 60 years	0	0	2
61 – 70 years	2	0	0
71 – 80 years	2	0	3
>80 years	2	2	5
Non-ARDS related deaths	6	17	6

Table 3 Vaccine/booster brands administered to the study group

		No of patients	%
Vaccine Brand	Pfizer BioNTech (BNT162b2)	328	72.7%
	Moderna COVID-19 (mRNA-1273)	13	2.9%
	Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine)	94	20.9%
	Janssen (Ad26.COV2.S)	14	3.1%
	Missing data	2	0.4%
Booster Brand	Pfizer BioNTech (BNT162b2)	157	77.7%
	Moderna COVID-19 (mRNA-1273)	44	21.8%
	Missing data	1	0.05%

Table 4 Stratification of SARS-CoV-2 Disease according to age groups in Boosted vs non-Boosted groups

Age years	Asymptomatic count (%)	Mild count (%)	Moderate count (%)	Severe count (%)	Critical count (%)
Boosted Group					
17 - 30	0 (0%)	1 (1%)	1 (3.1%)	0 (0%)	0 (0%)
31 - 40	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
41 - 50	2 (3.3%)	8 (8.2%)	0 (0%)	0 (0%)	0 (0%)
51 - 60	9 (14.8%)	7 (7.1%)	0 (0%)	0 (0%)	0 (0%)
61 - 70	8 (13.1%)	13 (13.3%)	2 (6.2%)	1 (9.1%)	0 (0%)
71 - 80	24 (39.3%)	26 (26.5%)	10 (31.3%)	3 (27.3%)	0 (0%)
>80	16 (26.2%)	43 (43.9%)	19 (59.4%)	7 (63.6%)	0 (0%)
Non-Boosted Group					
17 - 30	11 (17.5%)	20 (17.5%)	1 (2.9%)	0 (0%)	0 (0%)
31 - 40	19 (30.2%)	15 (13.2%)	2 (5.9%)	1 (4.5%)	1 (6.2%)
41 - 50	7 (11.1%)	22 (19.3%)	9 (26.5%)	1 (4.5%)	3 (18.8%)
51 - 60	4 (6.3%)	10 (8.7%)	1 (2.9%)	5 (22.7%)	4 (25.0%)
61 - 70	8 (12.7%)	19 (16.7%)	6 (17.6%)	6 (27.3%)	3 (18.8%)
71 - 80	5 (7.9%)	15 (13.2%)	12 (35.3%)	5 (22.7%)	3 (18.8%)
>80	9 (14.3%)	13 (11.4%)	3 (8.8%)	4 (18.2%)	2 (12.5%)

5.5% of the boosted group (all over the age of 60 years) had severe SARS-CoV-2 related illness as compared to 8.8% of the non-boosted group (predominantly within the age range of 51-80 years), however, this difference did not reach statistical significance ($p=0.116$).

Gender was shown to be an independent variable to SARS-CoV-2-related admissions to ITU, irrelevant of their booster status as per simple linear regression model equation ([Digital Supplement File 2](#)).

The mortality rate of hospitalised and non-immunocompromised SARS-CoV-2 patients (deaths attributed to acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 pneumonia and not underlying chronic comorbid diseases) was 4.4% in the non-boosted population when compared to 1% in the boosted group. It seems that the non-boosted patients had a higher risk of ARDS-related death than the boosted patients (Boosted group 1% vs non-boosted group: 4.4%, $p = 0.031$). A male predominance was noted amongst the ARDS-related deaths, 2 patients (100%) in the boosted group and 7 patients (64%) in the non-boosted group, as shown in [Table 2](#).

Of interest, 14 (87.5%) of the critical admissions in the non-boosted group tested positive for SARS-CoV-2 and required hospitalisation beyond 5 months after completing their SARS-CoV-2 vaccination regimen.

DISCUSSION

Various studies have shown that SARS-CoV-2 vaccine immunity wanes over time and a booster dose seems to restore this immune decline resulting in a decrease in disease severity and mortality.^{3,13} Our study similarly seems to show a significant decrease in severe and critical SARS-CoV-2 disease in the boosted. In fact, zero patients with critical SARS-CoV-2-related disease were documented in the boosted arm of the study. Our study also demonstrates a statistically significant decrease in in hospital mortality in the boosted arm.

Malta with a population of approximately 516,000⁶ has one major acute hospital, Mater Dei hospital (MDH). Virtually all SARS-CoV-2-related hospitalisations during the study period were admitted to this major 1000 bed hospital. The only exception being a small number of elderly patients who contacted SARS-CoV-2 whilst residing in one long term hospital facility and were deemed not eligible for escalation of treatment and thus were

managed in the said hospital without being transferred to MDH. The fact that virtually all SARS-CoV-2 positive patients were managed at MDH meant that the management of these patients was standardized and data collection was facilitated, possibly giving more power to our study.

Potential sources of bias include; the relatively small numbers in our cohort and the use of different vaccine brands during the vaccination and booster programmes. However, one notes that the majority of eligible patients (approximately 70%) received the Pfizer BioNTech (BNT162b2) vaccine for their primary vaccination and booster dosing.

We would like to highlight that even though we report 0 critical patients in the boosted arm, there were 2 ARDS-related deaths in severely comorbid boosted patients, in whom escalation of treatment/ITU admission was deemed medically futile and thus did not meet the criteria to include in the critical disease cohort.

Of interest was the observation that the proportion of non-boosted patients with critical disease included significantly more males than females. In fact, the male gender was deemed to be an independent risk for SARS-CoV-2-related admission to ITU in our simple linear regression model above.

The study also shows that there was a trend to younger age for the non-boosted arm of the cohort. This reflects one facet of vaccine/booster hesitancy, a phenomenon which seems to be more prevalent amongst the younger population.

One other observation that emerged from the study was that a sound majority of the critical admissions to ITU in the non-boosted arm had received their primary vaccination more than 5 months prior to their illness. This points towards waning immunity which has been observed by other studies¹⁴⁻¹⁶ thus underpinning the importance of timely boosting of the primary vaccination regimens.

The emergence of variants during the pandemic, with their different propensity towards increased infectivity and different disease severity, meant that during our study period the epidemiology changed from a majority prevalence of Delta variant (98% in October-November 2021) on to the emergence of the Omicron variant (85% Omicron BA.1 in December 2021: 82% Omicron BA.1, 12% Omicron BA.1.1 and 5% Omicron BA.2 in January 2022 as per verbal communication with/data collected by the Molecular Diagnostics Department in Mater Dei Hospital). To try to mitigate the bias potentially created by this changing epidemiology, we extended our study

period to try to cover both the Delta high prevalence period and the Omicron high prevalence period in approximately equal periods.

CONCLUSIONS

At the time of submission, it was envisaged that another SARS-CoV-2 booster (4th dose) was going to be required in the near future. This came at a time of increasing vaccine hesitancy and pandemic fatigue. Our study indicates that a booster dose in the general immunocompetent adult population significantly reduces the chances of critical SARS-CoV-2-associated diseases. Although SARS-CoV-2 is

nowadays, no longer considered a public health emergency, our study highlights the importance and role of vaccination strategies in curbing disease-severity in pandemics.

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Prophylactic Antibiotics and Hospitalisations following Transrectal Prostate Biopsy: *a local retrospective cohort study*

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Background

Prostate biopsy is an important tool in prostate cancer diagnosis. However, transrectal prostate biopsy is associated with a number of complications, including infectious complications. This local cohort study aims to assess the incidence of such complications and 30-day readmission rates, and any predisposing factors for said complications including patient co-morbidities, type of prophylactic antibiotics used and biopsy approach.

Methods

A retrospective review was carried out for men over 18 years of age who underwent transrectal prostate biopsy from January 2021 to December 2021.

Results

A total of 373 patients were included. 184 (49.4%) underwent systematic biopsy, 115 (30.8%) underwent combined and 59 (15.8%) underwent targeted biopsy. The commonest antibiotic prophylaxis regime is ciprofloxacin, metronidazole and gentamicin. 30-day readmission count was 19 (5.1%). The commonest complication requiring readmission was lower UTI (n=14 (73%)), 70% of these has *Escherichia coli* cultured in the urine.

Conclusion

This study replicated the findings that infectious complications are the most common cause of readmission after transrectal biopsy and that *E.coli* is the most common causative organism for infectious complications post biopsy. This study does not replicate the findings from similar studies which showed that the number of cores yielded correlates with the risk of infection post biopsy, nor does it confirm that increased age, DM or a high BMI increases the risk of developing post biopsy infection.

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The gold standard of prostate cancer detection is a transrectal ultrasound (TRUS) guided biopsy. Transrectal biopsies of the prostate are easily done as a day case setting without the need for general anaesthesia. Patients undergoing transrectal biopsy of the prostate are given antibiotic prophylaxis due to the risk of infectious complications.¹ MRI guided transrectal prostate biopsies have become more frequent due to the ability to target areas of suspicion which results in improved detection of prostate cancer. In addition, by reducing the amount of cores retrieved complication rates are reduced without the need to compromise prostate cancer diagnosis.²

Bleeding is the most common complication.³ A variety of factors have been documented which affect the frequency of bleeding post prostate biopsy. The use of anticoagulation medication and the number of cores retrieved during the procedure increase the incidence of bleeding.⁴

Antimicrobial prophylaxis significantly reduces post operative infectious complications and in turn the need for hospitalisation.⁵ The most common antibiotics prescribed are fluoroquinolones for a variable duration, but studies have shown that antibiotic prophylaxis for more than 24 hours provides no significant benefit.^{6,7} Infectious complications such as UTI, epididymitis and sepsis still arise despite patients' compliance to antimicrobials and the use of techniques to reduce such risk.⁴

The risk of urinary retention post TRUS prostate biopsy is low and is not correlated to the number of cores taken during the procedure.⁸ This is usually short lasting and rarely requires any form of intervention.⁹

The purpose of this study is to assess whether comorbidities, the type of prophylactic antibiotics used and the approach for prostate biopsy sampling influence post operative complications while also looking at the complication rate and what complications arose within a 30-day time period. This will help to better guide antibiotic prescribing to improve the outcome of transrectal ultrasound guided prostate biopsies.

METHODS

A retrospective review was carried out for men over 18 years of age who underwent transrectal prostate biopsy from January 2021 to December 2021 (12 months). These dates were selected to allow the opportunity to gather information on the different

prophylactic antibiotics used. Data was collected from a Mater Dei Hospital (MDH) database. All the prostate biopsies were performed under the supervision of five consultant urologists and one consultant radiologist.

Data was collected over a period of 3 months from 16th February 2022 until 20th May 2022. Using the local healthcare software system (iSOFT and patient dashboard), discharge summaries and inpatient/outpatient records in MDH and Gozo General Hospital (GGH).

Preoperative variables for patients who underwent transrectal prostate biopsy included patient demographics, type of biopsy, number of cores taken, comorbidities including diabetes and immunosuppression, on anticoagulation or antiplatelets, catheterised 24 hours prior to the biopsy, previous antibiotic use within 30 days before biopsy, prophylactic antibiotics used and the duration of antibiotics. Post operative 30-day readmission was documented, length of stay, reason for readmission, Clavien-Dindo severity and antibiotic treatment given and duration.

Statistical analysis was performed using Fisher's exact test for categorical variables. Independent sample t-test and one-way ANOVA analysis was used for continuous variables. Results were considered significant if $p < 0.05$. IBM SPSS Statistics (Version 26) was used for data analysis. Approval for this study was obtained from the University of Malta Research Ethics Committee FREC number- UREC-DP2112004MED.

RESULTS

A total of 373 patients were included in this retrospective review. Mean age was 70.03 years. The commonest biopsy type was TRUS systematic ($n=184(49.3\%)$) followed by TRUS combined ($n=115(30.8\%)$) and TRUS targeted ($n=59(15.8\%)$). Out of 373 patients, 66 patients (17.7%) suffered from diabetes mellitus, 10 (2.7%) were immunocompromised 7 (1.9%) of which were on immunomodulators. 4 (1.0%) patients had previous antibiotic use within 30 days before the prostate biopsy. This could be due to patients who would have been given antibiotics in the community and therefore not picked up in the study. None of the patients had an indwelling catheter. 103 (27.6%) patients were on antiplatelets or anticoagulation.

The minimum number of cores taken was 3 with a maximum of 28. The least number of cores was taken

in TRUS targeted while the maximum in TRUS systematic. The average number of cores in TRUS targeted was the least amounting to 6.46 cores, TRUS combined had an average of 10.63 cores while TRUS systematic had an average of 14.62 cores. Studies show that more cores increase the risk of sepsis but this was not represented in our study cohort. Age ($p=0.990$), BMI ($p=0.31$) and Diabetes Mellitus ($p=0.25$) were not statistically significant in patients who were readmitted with prostate biopsy complications. **Table 1** summarises the numerical

findings including the p values for correlation with admission rates.

There was no statistical significance between the antibiotics used and the readmission rate. This can be attributed to the fact that the main concern is the transrectal route and that we need to move towards the transperineal approach for prostate biopsy sampling. The commonest antibiotic prophylaxis regime is ciprofloxacin, metronidazole and gentamicin with gentamicin being given as a stat dose at the induction of prostate biopsy.

Table 1 Summary of Results showing the p values for Correlation with admission rates where applicable (Pearson – Chi Square for categorical variables, Pearson correlation for continuous variables)

Demographics	Range	Mean	p -value
Age	47.09 - 88.06	70.03	0.99
BMI	19-40	28.96	0.31
Potential Risk Factor for Post Biopsy Complication	(n=)	%	p -value
Diabetes Mellitus	66	17.69	0.25
Immunosuppressed	10	2.68	0.54
On Immunomodulators	7	1.87	
Indwelling Catheter	0	0.00	
On Antiplatelets or Anticoagulants	103	27.61	
Had previous Antibiotics within <30days	4	1.07	0.64
Type of Biopsy	(n=)	%	p -value
TRUS systematic	184	49.3	
TRUS combined	115	30.8	
TRUS targeted	59	15.8	
Overall	373	100	0.125
No of Cores per Biopsy Type	Range	Average	p -value
TRUS systematic	4-28	14.62	
TRUS combined	5-20	10.63	
TRUS targeted	3-14	6.46	
Overall	3-28	11.99	0.49
No of Prophylactic Antibiotics	Range	Average	p -value
Number of Antibiotics	0-4	1.95	0.844

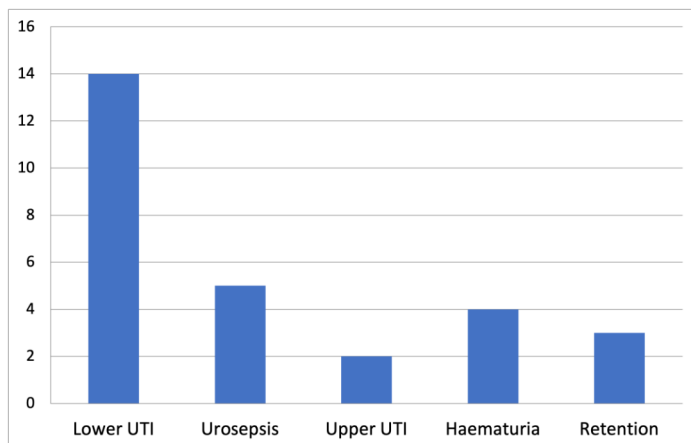


Figure 1 Number of patients requiring hospitalisation after developing a complication post transrectal prostate biopsy

From 373 patients the 30-day readmission count was 19 (5.1%). The commonest complication requiring readmission was lower UTI (n=14 (73%)). The other 27% included upper UTI, retention, haematuria and urosepsis (Figure 1). The average interval from prostate biopsy to readmission was 6 days with an average length of stay of 7.5 days. All readmissions were treated with intravenous antibiotics (Figure 2). From 19 readmissions 7 had positive urine cultures on readmission, 70% of these has *Escherichia coli* cultured in the urine.

DISCUSSION

Prostate cancer is a worldwide major health concern. It is the second most common cancer diagnosis in men with approximately 1.4 million diagnoses globally in 2020.⁹ Diagnosis of prostate cancer is dependent on clinical history, digital rectal examination, prostate specific antigen (PSA) measurement, as well as imaging techniques and prostate biopsy.

The European Association of Urology (EAU) Prostate Cancer guidelines¹⁰ recommend the use of Magnetic Resonance Imaging (MRI) prior to biopsy in both biopsy-naïve and in those with prior negative biopsy in the detection of Prostate Cancer base on the MRI-FIRST study.¹¹ These guidelines go on to recommend a combined targeted and systematic approach when MRI is positive in biopsy-naïve men, whilst targeted biopsy alone is indicated in men with previous negative biopsy but a positive MRI, and systemic biopsy alone is only indicated in those with a prior negative biopsy with a negative MRI but a high clinical suspicion of Prostate cancer.¹⁰ In this study the vast majority (49.3%) of the 373 patients underwent a systemic biopsy alone. Although the study did not stratify patients into biopsy-naïve and prior negative biopsy, or into MRI positive or negative, this finding indicates a lack of adherence to EAU recommendations. This is important when bearing in mind that systematic biopsy alone had an average 14.6 core yield, as oppose to 6.46 in the targeted group of this study. Although this study did not conclude that an increased number of cores is associated with increased risk of sepsis, this has been shown in other studies.² This study also reports no association with Diabetes Mellitus (p=0.25) in terms of readmissions with prostate biopsy complications. However, this is likely to be due to the small number of Diabetes Mellitus sufferers (p=66) included in the study resulting in a statistical analysis which is far from powered.

The 30-day readmission rate in this study was of 5.1%, with 3.75% of patients being readmitted in view of a lower UTI. In a retrospective observational study performed in Ängelholm and Helsingborg, Scania, Sweden, the authors found an overall infection rate of 5.4% post biopsy with 3.9% of the patients

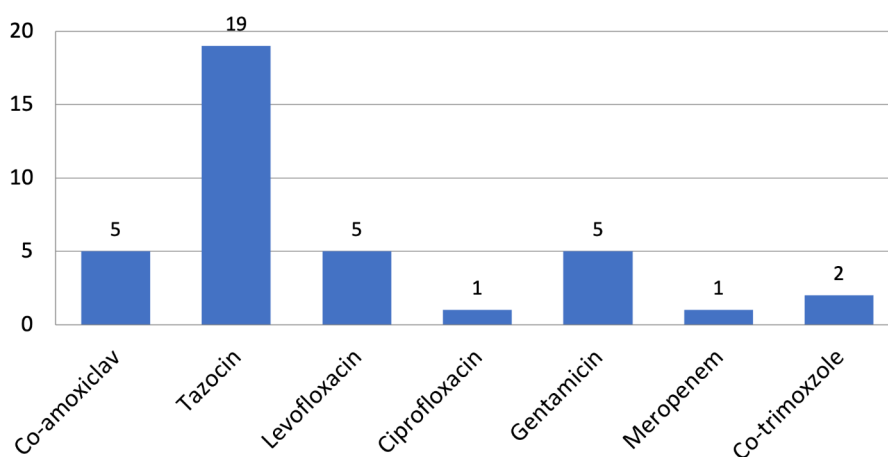


Figure 2 Intravenous Antibiotics used to treat infectious complications in patients requiring hospitalization following transrectal prostate biopsy

requiring hospitalisation for intravenous antibiotics¹², the latter percentage is very similar to that reported here. No attempt was made in our study to detect the number of patients who contracted an infection and were treated in primary care, and therefore an overall infection rate cannot be reported.

Infectious complications are significantly higher following transrectal biopsy when compared to transperineal biopsy¹³, and hence the EAU guidelines now strongly suggest performing prostate biopsy using the transperineal approach.¹⁰ However, in cases where a transrectal approach is used several steps may be taken to reduce the risk of infectious complications including the use of povidone-iodine for rectal cleansing, and the use of prophylactic antibiotics.¹⁰ This study showed that a combination of ciprofloxacin, metronidazole and gentamicin was the most prescribed prophylactic regime locally. Whilst augmented prophylaxis (with the use of two or more antibiotic classes) is suggested by the EAU¹¹, the prophylactic, empirical use of fluoroquinolones (like ciprofloxacin) is now strongly discouraged by the European Medicine Agency (EMA) due to the severe and potentially irreversible adverse reactions which may affect several organ systems.¹⁴ Alternative prophylactic antibiotics have also been suggested, including fosfomycin trometamol.¹⁰ In a metanalysis which included 59 randomized controlled trials, Pilatz et al showed that antibiotic prophylaxis reduces infectious complications from transrectal biopsy, and that fosfomycin trometamol was an alternative to fluoroquinolone with reduced rates of infectious complications.¹⁵ In the local cohort included in this

study fosfomycin trometamol was used alone or as part of an augmented prophylaxis protocol in 126 patients (33.8%), of which 5 (3.9%) required readmission.

This study showed that *E. coli* was the most common organism cultured in the urine and blood in patients with post prostate biopsy infection. This is in keeping with the results from a study performed in Canada by Lange et al in which *E. coli* was the cause of urosepsis after transrectal biopsy in 67% of the patients with positive cultures.¹⁶

CONCLUSION

This study replicated the findings that infectious complications are the most common cause of readmission after transrectal biopsy, and that the rate of readmission due to infectious complications is in the region of 3.9%. Moreover, it replicated the finding that *E. coli* is the most common causative organism for infectious complications post biopsy. The study highlights the urgent requirement for local antibiotic prophylactic guidelines for transrectal prostate biopsy. The infection rate also emphasises the EAU recommendation in favour of transperineal biopsy, and hence implies a need for local expertise in this technique. This study does not replicate the findings from similar studies which showed that the number of cores yielded correlates with the risk of infection post biopsy, nor does it confirm that increased age, DM or a high BMI increases the risk of developing post biopsy infection.

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Level of Serum Melatonin & Sialic Acid in Patients with Beta-thalassemia versus Normal Individuals

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Symptoms of thalassemia minor may begin to manifest as early as infancy or later in life. In addition to mild to severe anemia, patients with this disorder may also present with developmental delays and skeletal abnormalities. The main objective of the subsequent investigation was to assess and compare blood levels of melatonin and sialic acid in patients with Beta-thalassemia and healthy individuals. This case-control study compared the serum levels of healthy individuals with those of Beta-thalassemia patients. The total sample size of the study was 104. Out of these 52 individuals were grouped under the category of control group which had healthy individuals. The other group also consisted of 52 individuals who were diagnosed with Beta-thalassemia. These results indicated that there was a significant decrease in serum melatonin as in the controlled group it was 12.07 pg/ml and in the case group it was found as 7 pg/ml, $p < 0.01$. The value of Ceruloplasmin was also seen significantly different, as the level of Ceruloplasmin increased in the case group (34.13 mg/ml) as compared to the healthy individuals (51.08 mg/ml). Additionally, the other major findings were the fall of Hb in the case group which was 7 g/dL as compared to the control group where the means was 12.56 g/dL. In conclusion melatonin and sialic acid could be added to the list of measured parameters in patient with beta-thalassemia and might be served as a marker for diagnosis and prognosis.

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Beta-thalassemia is a disorder where the production of hemoglobin is reduced.¹ All cells in the body receive oxygen through hemoglobin, a protein found in red blood cells, that helps deliver oxygen throughout human body. But, unfortunately, for those who suffer from -thalassemia, their hemoglobin levels may be dangerously low. This means that their body does not receive enough oxygen, which can lead to a whole host of health problems.^{2,3} In addition, affected individuals have anemia, which can have more serious effects such as pale complexion, weakness, and fatigue. There are three types of beta thalassemia, which are categorized based on the severity of the symptoms they cause. Thalassemia major, also known as Cooley's anemia, is the more severe of the two types, and can lead to life-threatening complications. Meanwhile, thalassemia intermedia and thalassemia minor are less severe, but still require proper management and care.⁴

During the first two years of life, the main signs and symptoms of thalassemia begin to manifest themselves.⁵ Anemia in children can be fatal. They fail to thrive because they cannot gain weight and grow as fast as normal, as well as may develop yellowish discoloration of the sclera and the skin. Affected individuals may have misaligned bones and enlarged spleens, livers, and hearts. Adolescents with thalassemia major may have delayed onset of puberty.^{6,7} Many thalassemia major patients endure severe pain and often require blood transfusions to replenish red blood cells.⁸ Long-term blood transfusions can cause iron to build up in the body, negatively affecting the liver, heart, and hormones.

The last carbohydrate residue of many glycoproteins is Sialic acid. The shape of glycoproteins is maintained by negatively charged polar molecules, which are essential for the function and durability of the protein.^{9,10} Desialylation is like the villain who initiates the catabolism of glycans by removing the terminal sialic acid residues on glycans. This process is a pivotal part of sialic acid metabolism and has a significant impact on the structure and functions of glycans, including glycoprotein.

Desialylation of proteins results in the loss of sub-terminal galactose residues, which leads to the removal of the protein from circulation by galactose receptors in the liver, leading to early termination.¹¹ Compared to thalassemia major,

thalassemia intermedia is less severe. Symptoms of mild thalassemia may first appear in infancy or later in life. Affected individuals may have developmental delays and bone abnormalities in addition to mild to moderate anemia.¹² In a recent investigation, blood samples from 18 patients with thalassemia major and 10 controls were examined to determine the sialic acid content of red blood cell membranes.¹³ Among patients who underwent splenectomy several years ago, only four had a lower-than-average salivary acid to protein weight ratio. In the 14 patients who were still alive but did not have their spleen removed, the salivary acid/protein ratio was 50% higher than usual.^{14,1} The primary purpose of the following study is to evaluate the level of serum sialic acid and melatonin of the patients with Beta-thalassemia and compare it with the levels of normal individuals.

PATIENTS AND METHODS

The study is a case-control research comparing the blood serum levels of Serum Melatonin and Sialic Acid in normal individuals and compared to blood serum levels in the patients with Beta-thalassemia.

In total, 104 subjects were enrolled, with half of these being healthy controls, and the rest being individuals who suffered from Beta-thalassemia.

Laboratory analysis was performed on blood drawn in the morning after a 10-hour fast. Informed consent signed and collected from all participants, blood withdrawn and serum collected, frozen at -20°C until analysis. Serum melatonin levels were quantified by enzyme-linked immunosorbent assay (ELISA) using a kit. Haematological parameters were obtained with an automated hematology analyzer (BC-300 PLUS - Mindray, China). Serum total sialic acids was measured by colorimetric method using commercial kit (Elabsience, USA).

The evaluated parameters included Melatonin(pg/ml), Ceruloplasmin [mg/ml], Copper [μmol/L] and Selenium μg/L. The study further evaluated PCV (%), WBC (x10⁹/L), Monocytes(x10⁹/L), Hb (g/dL), Lymphocytes (x10⁹/L), and Neutrophils (x10⁹/L).

All statistical analyses were performed using SPSS. From the observed parameters, the continuous variables were expressed as mean ± SD and compared by one-way analysis of variance (ANOVA) and post hoc test in Turkey. The significance level was adjusted to P < 0.05 and confidence interval 95%.

Table 1 Serum measured parameters between studied groups

Parameters	Serum		p value
	Group A(Control)	Group B	
Melatonin (pg/ml)	12.07 ± 4.74	7 ± 3.52	0.01
Sialic acid (mmol/L)	1.61±0.13	3.1±0.51	0.001
Ceruloplasmin (mg/ml)	34.13±2.74	51.08±4.97	0.001
Copper (µmol/L)	13±2.98	25±2.24	0.001
Selenium (µg/L)	51. ± 19	39.87±21.2	0.001

RESULTS

The serum levels of the measured parameters are presented in [Table 1](#). There was a significant difference between the controls and the patients with Beta-Thalassaemia.

The haematological parameters are presented in [Table 2](#). Again, these was a significant difference between the two groups.

There was a significant decrease in serum melatonin (controls: 12.07 pg/ml vs case group: 7.0 pg/ml, $p < 0.01$). The levels of sialic acid and ceruloplasmin were significantly different, as the level of total sialic acid and ceruloplasmin increased in the case group (3.1mmol/L, 51.08mg/ml, respectively) as compared to the healthy individuals (1.61mmol/L, 34.13mg/ml, respectively). As expected, there was a drop in haemoglobin levels in the case group as compared to the control group (control: 12.56 g/dL vs case group: 7 g/dL).

DISCUSSION

This study showed that the melatonin levels in the blood serum significantly decreased in the patients with Beta-thalassemia. Such findings

have been discussed in multiple studies previously. It has been found that red blood cells (RBCs) or erythrocytes are particularly susceptible to oxidative stress due to the lack of a nucleus and mitochondria, the presence of iron-containing hemoglobin, and the presence of large amounts of fatty acids in their specially designed lipid bilayer membranes.^{16,17} The main function of RBCs is to deliver oxygen to the tissues.¹⁸ Therefore, red blood cells must flow through the microvasculature, which requires high structural deformability and elasticity of red blood cells. The deformability of erythrocytes depends on the availability of a healthy cytoskeletal framework and fluid membrane.¹⁹ The structural and functional composition of erythrocyte homeostasis may be disturbed by various conditions. One of them is ROS, which causes hemolytic anemia in thalassemia patients and leads to oxidative damage of red blood cells. Melatonin is a potent free radical scavenger and antioxidant that successfully protects red blood cells from oxidative damage.²⁰ Melatonin also enhances the gene expression of antioxidant enzymes in red blood cells and chelates free iron. Erythrocytes produce and store large amounts of

Table 2 Haematological finding between studied groups

Parameters	Serum		p
	Group A(Control)	Group B	
PCV (%)	37.87±3.76	23.1± 4.79	0.001
Hb (g/dL)	12.65 ± 1.3	7± 1.4	0.001
WBC (x 10 ⁹ /L)	5.6±2	13.2± 7.98	0.001
Monocytes (x 10 ⁹ /L)	0.86±0.3	1.77±1.3	0.001
Lymphocytes (x 10 ⁹ /L)	2.84 ± 0.68	5.86 ± 2.01	0.01
Neutrophils (x 10 ⁹ /L)	2.43±0.76	5.97±0.67	0.01

melatonin, which has a local protective effect. All this suggests that melatonin is a significant factor in safeguarding the structural and functional integrity of red blood cells.²¹

The findings also showed that haemoglobin levels was markedly reduced in the patients of Beta-thalassemia. This is not unexpected, since beta-thalassemia is known to have such an effect. Beta-thalassemia patients have low levels of hemoglobin, resulting in oxygen shortages in several body regions.²² In addition to this, low hemoglobin levels prevents sufficient oxygen from reaching tissues. Recent studies indicate that patients with beta-thalassemia are more prone to developing atypical blood clots, which can be detrimental to their overall health.²⁴

Finally, a fascinating discovery was made during research. Scientists found that thalassemic erythrocyte membranes have approximately 25% less glycolic acid compared to normal erythrocyte

membranes. Through the process of density centrifugation, they also observed that glycoconjugate from aged thalassemic erythrocytes had only half the level of sialic acid compared to that of young thalassemic erythrocytes. These findings shed light on the unique characteristics of thalassemic erythrocytes and offer new insights into the nature of glycoconjugate in aging cells.²⁵ Thalassemic erythrocytes' plasma and erythrocyte membranes were examined for potential sialic acid activity. In contrast to plasma from healthy donors, there was no evidence of enhanced sialic acid activity in patient plasma. The enhanced sialic acid hydrolysis in erythrocytes with thallasemia should thus be explained by additional locations of sialic acid activity or other scenarios.²⁶

CONCLUSION

The study has shown that the level of melatonin of the patients with Beta-thalassemia is reduced, whereas the levels of sialic acid is increased.

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The frequency of paroxysmal tonic spasm in multiple sclerosis

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Background

Multiple sclerosis (MS) is one of the most important neurological diseases with autoimmune pathogenesis characterized by demyelination of the central nervous system (CNS) with various spectrum of neurological manifestations. The most common form which is the relapsing-remitting type can be presented with visual, sensory, motor, cerebellar, and sphincteric disturbances lasting for days or even months.

Objectives

To determine the frequency of paroxysmal tonic spasms in a group of Iraqi multiple sclerosis patients and to determine possible disease characteristics associated with increased risk of paroxysmal tonic spasms.

Method

A cross-sectional study included 110 patients that have been diagnosed with MS based on 2017 McDonald criteria and visited regularly the MS clinic at Ibn-Sina specialized hospital (period, 01.09.2022-01.02.2023). These patients were diagnosed with TS clinically and evaluated radiologically and by electroencephalography to exclude conditions other than Tonic spasm.

Results

A total of 16 MS patients (14.5%) had paroxysmal TS. Older age patients and those with long disease courses and high EDSS scores were found to be correlated with the occurrence of tonic spasms. Moreover, pyramidal and sensory system impairments were significant risk factors for paroxysmal Tonic spasms.

Conclusions

Tonic spasm is significantly associated with Multiple sclerosis with a frequency of 14.5%. Motor system impairment and higher EDSS score were the most remarkable predictor risk factors to have a tonic spasm.

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Multiple sclerosis (MS) is recognized as one of the most common disabling neurological disease that can affect young to middle age people with a peak incidence between 20-40 years of age. It is an autoimmune disease of the central nervous system manifested by chronic inflammation with prominent myelin loss and subsequent gliosis and nerve axons loss, while more advanced cases are characterized by less inflammation and more neurodegeneration representing the progressive stage of the disease.^{1,2}

MS can result in loss of the myelin sheath surrounding axons in the brain and spinal cord including the optic nerves and with time this will damage the myelin and the axons to variable severity causing various neurological symptoms and signs that can impair the quality of life of these patients.^{3,4}

Although MS is known primarily to affect the subcortical white matter of the brain including the optic nerves and spinal cord, high-resolution MRI can show evidence of inflammation involving even normally appearing white and grey matter, in the cerebral cortex and basal ganglia.⁵

Paroxysmal tonic spasms (TS) can be recognized by multiple, acute onset, short lasting and stereotyped events which might take short time ranging from a few seconds to a few minutes, with an episodic presentation that may last for days to months after their start.^{6,7} In the episodes that continue for longer than 24 hours, they can be identified as a disease recurrence. These symptoms may manifest either as MS initial symptoms or later on in the course of the condition.⁸

The reported incidence of paroxysmal tonic spasms ranges between 1.6% and 17% in patients with MS during the course of their disease, of which 24% occur as the initial presentation of the disease.^{6,7,9–}

¹¹ Although the relapsing-remitting form of the disease is the most common pattern linked to the occurrence of tonic spasms, it has also been described in the setting of progressive MS.¹¹ Despite paroxysmal tonic spasms are commonly associated with many neurological diseases like multiple sclerosis, they remain underdiagnosed and pose a diagnostic challenge These must be distinguished from MS-related events such localized fits and sleep problems. Additionally, tonic spasms might be misdiagnosed as the temporary worsening of a pre-existing neurological impairment brought on by numerous circumstances such as fever and infections.^{12,13}

Paroxysmal tonic spasms may be categorized on the basis of several characteristics such as painful or

painless, kinetic or non-kinetic, and generalized or localized.^{12–16} An episode of unilateral upper extremity flexion and lower extremity extension with a chance of spreading to the face or neck is known as a generalized tonic spasm.^{16–18}

AIM OF THE STUDY

To establish the frequency of paroxysmal tonic spasms in a group of Iraqi multiple sclerosis patients and to determine possible disease characteristics that can be associated with increased risk of paroxysmal tonic spasms.

METHODOLOGY

One hundred ten patients were included in this cross-sectional study, these patients were chosen sequentially to represent our MS population in Iraq when they visited our specialized MS clinic of Ibn-Sina teaching hospital from September 2022 to February 2023. Demographic parameters (age, sex, and disease duration) were recorded and patients were diagnosed with MS based on 2017 revised criteria established by McDonald.¹⁹

The neurological study was done on all patients with MS and the following factors were determined for MS patients: age, gender, MS disease prognosis, the longevity of disease, and the Expanded Disability Status Score (EDSS scores)²⁰ were used clinically to assess the functional systems involvement and patient disability in this study. The time of occurrence of paroxysmal tonic spasm in relation to disease onset was noted if TS was reported.

Patients were diagnosed with TS if they reported multiple, short-lasting, sudden onset, and stereotyped attacks of dystonic posturing that could last seconds to minutes.^{6,7} All patients were evaluated by MRI and EEG to exclude alternative conditions like seizures or sleep disorders which had been excluded from this study.

The study was done in conformity with the Declaration of Helsinki's principles and informed approval was taken from all the participants. The protocol of the study was approved by the Department of Medicine, College of Medicine, University of Mosul (approval date: November 29, 2022, no: MDSC-4).

Statistical analysis

In case of parametric data, the Anderson Darling test was used to test the continuous data for normal

distribution using. Normally distributed data were represented in tables or graphically plotted as mean±SD. Non-normally distributed variables were plotted in boxplot and whisker as the median and interquartile range (percentile range, 25% to 75%) was used to represent the data. Non-parametric data were represented as the number of cases (and %). Statistics analysis was conducted using the Chi-square test or Fisher exact test (total sample <20 and if 2 or more with expected frequency less than 5), the differences in the median of the two groups were assessed by the Mann-Whitney U test (when data do not follow a normal distribution).

Odds-ratio (with 95% confidence intervals) was assessed by binary logistic regression analysis when the outcome can be categorized into 2 binary levels, and if possible, the probability plot was used to present the relationship. Minitab version 17.0, SPSS version 20 and medcalc version 14.8 software package were used to perform the statistical analysis, with a p-value of <0.05 being regarded as significant.

RESULTS

Paroxysmal tonic spasms were found in 16 patients with MS patients (14.5), while the remaining 94 patients (85.5%) did not have TS as demonstrated in Figure 1.

Demographic characteristics and its association with TS

Out of 110 patients in the study group, 73 (66.3%) were females, 37 (33.7%) were males, and the median age was 28 years.²²⁻³⁹ Age was found to be significant as higher age was reported in patients with TS compared with patients who did not report any episodes of TS (mean age in patients with TS: 40 years vs mean age in patients without TS: 24 years, $p < 0.001$). Regarding gender, we found that among the 16 patients who had TS; 13 patients (81.2%) were females while the remaining 3 patients (18.8%) were males. On the other hand, 60 patients out of 94 (63.8%) who did not have TS were females while 34 patients (36.2%) were males. The difference was not statistically significant (Table 1).

MS course and TS

The association between the MS subtype and RLS is demonstrated in Table 2, where 88 patients (80.0%) had RRMS, 16 patients (14.5%) had SPMS and 6 patients (5.5%) had PPMS. Among the 16 patients with MS/TS+ 13 patients (81.2%) had RRMS, 2 patients (12.5%) had SPMS and 1 patient (6.2%) had

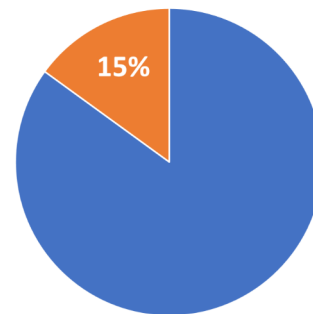


Figure 1 The frequency of paroxysmal tonic spasm in multiple sclerosis

Table 1 Demographic characteristics of MS patients and their association with tonic spasm

	No. TS	TS	Total	p-value
Number	94	16	110	-
Age (years)	Median (IQR) 24 (21 – 34) Range 16 – 56	40 (35 – 45) 28 – 55	28 (22 – 39) 17 – 56	<0.001
Sex	Female 60 (63.8%) Male 34 (36.2%)	13 (81.2%) 3 (18.8%)	73 (66.3%) 37 (33.7%)	0.233

Table 2 Association between MS subtype and TS

	Not	RLS	Total	p value
RRMS	75 (79.7%)	13 (81.2%)	88 (80.0%)	0.857
SPMS	14 (14.8%)	2 (12.5%)	16 (14.5%)	
PPMS	5 (5.3%)	1 (6.2%)	6 (5.5%)	

PPMS. On the other hand among the 94 patients with MS/TS- 75 of them (79.7%) had RRMS, 14 patients (14.8%) had SPMS and 5 patients (5.3%) had PPMS. There is no significant association between MS subtypes and RLS.

Duration of MS and TS

The occurrence of paroxysmal tonic spasms was associated by the duration of MS, with an odds ratio

Table 3 Functional system involvement distribution by tonic spasm

		No TS	TS	Total	p value
Number		94	16	110	-
Sensory	No	24	9	33	0.006
	%	25.5%	56.2%	30.0%	
Pyramidal	No	21	12	33	<0.001
	%	22.3%	73.7%	30.0%	
Cerebellar	No	14	2	16	0.575
	%	14.8%	12.5%	14.5%	
Visual	No	22	3	25	0.428
	%	23.4%	18.8%	22.7%	
Brain stem	No	19	2	21	0.587
	%	20.2%	12.5%	19.1%	

of 1.47 for each year in disease duration (95%CI: 1.254-1.733, $p<0.001$).

EDSS score and TS

Regarding the association between EDSS score and the presence of TS, the median EDSS score for patients with TS was 3.5 (IQR:2.5-5) while for patients without TS, it was 1 (IQR:1-2). There was a significant association between high EDSS with TS risk, with an odds ratio of 12.95 (95%CI: 3.803 – 44.083, $p<0.00$).

Function system status

Only motor and sensory systems involvement were significant in association with TS as illustrated in **Table 3**. Nine patients, out of 33 MS patients with sensory system impairment, had a paroxysmal tonic spasm, this difference was significant with P value of 0.006 and from 33 MS patients who had motor functional system impairment, 12 had paroxysmal tonic spasms, the difference is much significant with p value <0.001 .

Treatment of MS in our locality is mainly based on using the standard international protocols, These 110

patients with multiple sclerosis are on disease-modifying treatment provided by the Iraqi ministry of health for free as shown in **Table 4**.

DISCUSSION

The present study has identified that there is a significant association between MS and TS with a prevalence of TS in MS patients of 14.5%, this rate is in the line with the general frequency of abnormal movement that has been reported in MS including paroxysmal tonic spasm which shows a frequency between 1.6% to 17%.¹² Although the exact cause is still not clearly understood, several pathophysiological mechanisms have been proposed to explain the association between MS and the occurrence of various abnormal movements including paroxysmal TS. The most accepted theory was proposed by Osterman et al whereby paroxysmal events caused by the signal generation and spread of ectopic and spontaneous nerve motifs by the demyelinated axons and these waves transversely transmitted (ephaptic transmission) to other normal axons within the nerve fibre tracts and ultimately appeared as paroxysmal TS.²¹

The strength of this theory is based on the fact that proprioceptive and tactile stimuli are well known to trigger many types of tonic spasms. Moreover, an alternative theory is based on the effect of “inflammatory irritation” that characterizes inflammatory demyelinating diseases like MS also has been suggested based on the remarkable response of these TS to corticosteroids in many documented cases.²² Yet, a third possible theory is that partially demyelinated nerve fibres are known to have ion channel dysfunction.²³ Such configuration in ion channels will make minor physiological stimuli cause a great nerve stimulation, such as in hyperventilation when low ionized calcium is known to trigger TS. This theory can be supported by the remarkable effect of antiepileptic drugs and the carbonic anhydrase inhibitor acetazolamide on the frequency and severity of attacks.

Analysis of the results concerning the demographic characteristics has revealed that the older the age, the more significant chance for developing TS, This reciprocal association could be critically related to the fact that older MS patients have a greater tendency for developing more inflammation, demyelination and plaque formation due to advancement of disease pathogenicity, such demyelination in neuronal axons and their connections with other tracts in the brain and spinal

Table 4 The disease-modifying group used in Iraqi MS patients

Treatment	No.(%)
Interferon Beta-1B (Injections)	88 (80%)
Fingolimod (Oral)	12(11%)
Natalizumab (Infusion)	10 (9%)

cord will cause greater sensory and motor disease burden which is also found to be significant in the current study.

The association between MS subtypes and the risk of developing TS has been negatively confirmed in this study, perhaps because all MS subtypes have the same pathological effect on the CNS with inflammation, demyelination gliosis and neurodegeneration.^{1,2}

The present research has demonstrated that increasing disease duration correlates directly with the prevalence of TS (the risk of developing TS increased by a rate of 1.5 folds per year). This association could be explained perhaps in the context of the fact that the longer MS disease duration, the longer ongoing inflammation and plaque formation and the higher tendency to indulge motor and sensory system deficits which in turn has been greatly linked with the risk of complaining from TS.

The significant reciprocity between the decline in the functional system and developing TS was identified in the study, this was unusually true for sensory and pyramidal system involvement. However, the deficits in the impairment of brainstem, cerebellar and visual functional systems have negatively conjoined with the risk of having TS. This association perhaps could be illustrated in the context of the fact that corticospinal tracts and spinothalamic tracts which

control motor and sensory perception are the main structures involved in MS.²⁴ It's also worthy to mention that the paroxysmal symptoms including TS have been claimed to be linked with the deficits of ascending spinothalamic sensory tracts relative to central somatosensory processing deficits due to abnormal peripheral afferent input, taking into consideration that this aforementioned explanation is only weakly supported by scientific evidence.²⁵⁻²⁷

This study shows a significant correlation between a higher Expanded Disability Status Score and the risk of developing TS. This can also be explained by the fact that the disability measured by EDSS score depends mainly on the pyramidal weakness which in turn is considered a significant risk for developing TS.

CONCLUSION

Paroxysmal tonic spasm is significantly associated with MS. Predictor risk factors include older age patients, longer MS duration, patients with motor and sensory system disability and patients with higher global EDSS scores, results strengthen the idea that the inflammatory damage correlated with MS may induce paroxysmal TS. The prompt identification of TS is important, especially in MS patients as proper treatment can result in dramatic improvement of patient quality of life.

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Effects of *Zingiber Officinale* on shear bond strength of orthodontic bracket adhered into re-bonded tooth surface

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Background

One of the most practical, basic and commonly used tests for evaluating the adhesion resistance of bonded orthodontic brackets is shear bond strength. The ideal shear bond strength of the bracket to enamel is anticipated to resist bracket failure during the orthodontic treatment, while not causing enamel damage during de-bonding and maintaining the enamel integrity after finishing treatment. The aim of this study was to evaluate the shear bond strength of the brackets adhered into bonded and re-bonded teeth surfaces of fluorescent orthodontic adhesive modified by incorporation of *Zingiber officinale* essential oil.

Materials and Methods

Sixty recently extracted human lower first premolars caries-free teeth were used in this study. The teeth were randomly divided into 6 groups. The bonding control, bonding with a fluorescent orthodontic adhesive modified with 1%, 2% *Zingiber officinale* essential oil, control after re-bonding, and re-bonding with a fluorescent orthodontic adhesive modified with 1%, 2% *Zingiber officinale* essential oil. In the re-bonding three groups, they were de-bonded by the bracket removing plier (base method) and the remaining adhesive was removed. Then anew bracket was re-bonded in the same protocol. The shear bond strength was measured in Mega Pascal at cross head speed 1 mm/min. Then, adhesive remnant index was evaluated by a stereomicroscope 10X. Statistical analysis was with p value at $p < 0.05$.

Results

The shear bond strength of the control bonding group was significantly higher than the modified bonding groups with 2% *Zingiber officinale* essential oil. Whereas, the control after re-bonding group was higher than the modified re-bonding groups with no statistical significant difference. The distribution of the adhesive remnants index scores was significantly different among the study groups.

Conclusion

Generally, *Zingiber officinale* essential oil addition into fluorescent orthodontic adhesive reduced the shear bond strength in the bonded and re-bonded groups, particularly in the bonding modified with 2% concentration.

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Although orthodontic therapy has various advantages, the appliance's retaining surfaces make cleaning challenging and contribute necessarily to food accumulation and dental plaque formation¹ Orthodontic patients had a higher rate of enamel demineralization than people who were not receiving orthodontic treatment.² Cariogenic streptococci adhesion was found to be higher for the orthodontic types of cement and adhesives than for the bracket itself.³ Since the invention of bonding brackets, researchers and clinicians have attempted to enhance the characteristics of bonding agents.⁴ Essential oils may be encouraging ingredients for contributing to the antimicrobial property of composite resin materials.^{5,6} Zingiber officinale (ZO) has been regarded as a safe herbal medicine because there have been no observed medication or herb interactions but only minor negative impacts associated with its use.⁷ Carvacrol and thymol both showed antibacterial activity against cariogenic bacteria, periodontitis-causing bacteria and antifungal action.^{8,9}

Bracket failure from the teeth is still a major concern during orthodontic therapy, which can impact tooth enamel, lengthen overall treatment time, due to re-bonding procedures, and increase the overall cost of the orthodontic procedure.¹⁰ The insufficient dryness of the teeth post-etching and saliva contamination are two common reasons for bond detachment.¹¹ The bond detachment was more frequent on posterior teeth than anterior teeth, and it was more frequent on the lower arch than the upper arch.¹⁰ By utilizing a blue light emitting illumination source, the Fluorescence-assisted recognition protocol distinguishes between resin composites and tooth structures¹², resulting in a more precise, efficient, safe, and time-savable protocol for correct adhesive removal.^{13,14}

MATERIALS AND METHODS

Sample Collection and Inclusion Criteria

The Dentistry Faculty at the University of Mosul provided ethical approval (UoM.Dent/H.DM. 51/22). The teeth were sorted into six groups at random sampling, with every group involving ten teeth. The requirements for tooth collection included teeth free of hypo-plastic zones, caries, cracks, gross anomalies, restorations, not exposed to any sort of orthodontic or endodontic treatment, and no history of prior treatment with various chemical agents including alcohol, and hydrogen peroxide.¹⁵ To ensure that the chosen teeth were sound, a magnifier (X5) was used to examine the labial surface of the teeth. Any soft tissue residues were washed and eliminated. Sixty lower premolars were preserved in distilled water after extraction

and at room temperature around (22 C°±3) for a peak period of one month¹⁶ To prevent the growth of microorganisms, the water was changed weekly for the remainder of the research experiments.¹⁶

Preparation of Modified Adhesive

The electrical sensitive balance (Kern, Germany) was used to prepare the ratios of the modified adhesive with ZO essential oil (Sigma-Aldrich, USA). The micropipette (DRAGON lab, China) had been utilized to aspirate ZO essential oil, at 1% and 2% concentrations in the (weight to weight) ratio. The modified adhesive (Maquira, Brazil) had been incorporated by utilizing a plastic spatula and a sterile glass slab.¹⁷ To attain a homogenous consistency, the blend had been manually blended for around one minute in a semi-dull area, the blend was at that point spread out on a surface to diminish porosity.¹⁷⁻¹⁹ The altered adhesive was at that point exchanged to a sterilized expendable syringe, and a bit of tape of a dull colour was utilized to ensure the blend from coordinate light presentation.¹⁷ The concentrations of the ZO oil were chosen as takes after: to begin with group 10 µL of ZO oil in 1gm of the adhesive, and the second group 20 µL of ZO oil, in 1 gm of the adhesive.

Sample Preparation

Plastic rings were utilized, with the measurement of 26 mm stature, 18 mm interior distance across, and 20 mm exterior distance across. The rings were filled to around half their stature by a dental stone. After the stone was set, the teeth were secured within the plastic rings by applying sticky wax to the stone's surface, the teeth positioned opposite to the ring's base and within the centre of the ring.²⁰

The ring was installed on the surveyor's platform so that its long axis was essentially parallel to the surveyor's analytical rod, as shown in **Figure 1**, and the cold cure acrylic resin filled the ring until the



Figure 1 Mounting procedure: surface parallelism after acrylic pouring



Figure 2 Bracket under constant pressure



Figure 3 De-bonding procedure from occlusal view

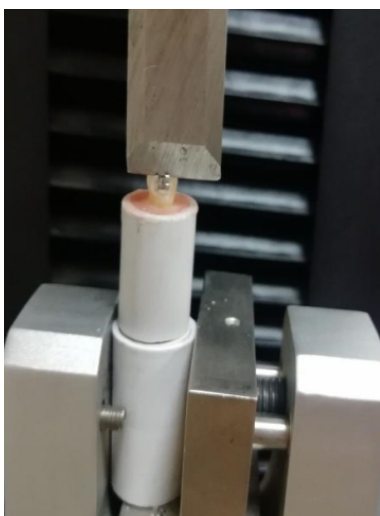


Figure 4 The SBS testing in a universal testing machine with a knife-edged blade

cementoenamel junction.²¹ After the setting of the cold cure resin, the teeth were polished for about 10 seconds with non-fluoridated pumice by utilizing a polishing cup and a slow-speed handpiece. After thoroughly rinsing the tooth surface with water for ten seconds to remove any pumice or debris, the teeth were ready for use.²¹

Bonding Procedure

The buccal surface of the enamel of each tooth was treated with 37% ortho-phosphoric acid (Gel Acid – Maquira) for about 15 seconds and later washed with water for 10 seconds according to the manufacturer's instructions and subsequently, air dried by the triple syringe and a chalky appearance was observed.²² The clamping tweezers held the standard Edgewise bracket 0.022-inch slot without a hook (Dentaurum, Germany), then a layer of the orthodontic adhesive was applied at the base of the bracket, and then the researcher transferred the bracket to the centre of the buccal surface of the crown of premolar tooth at a distance of approximately 4.5 mm from the occlusal surface as shown in.²³ A load of 200 gm was applied at a right angle to the bracket in keeping with pressure standardizing protocols (Figure 2), and then the dental explorer removed the excess of the orthodontic composite before curing.²⁴

The Woodpecker light curing device then started the curing procedure with an intensity of (900-950) mW/cm² measured with a light-intensity tester (Woodpecker, China). The curing light was applied for 20 seconds on the distal, mesial, gingival and occlusal aspects respectively²⁰, so the curing was extended for about 80 seconds. Following the completion of the bonding process, all specimens were retained in the distilled water for twenty-four hours, just before de-bonding and re-bonding procedures had been carried out.²⁵

De-bonding and Re-bonding Procedures

The bracket was detached with the bracket removing plier using the (base method) for de-bonding in which the plier's beaks were positioned at the point of the interlayer between the bracket and the tooth (Figure 3).²⁶ The instrument squeezed the bracket until the separation from the enamel.^{27,28} The tungsten carbide burs eliminated the remaining adhesive from the buccal surface by utilizing a slow-speed handpiece until no visible residue was noticed, polishing was done using a rubber cup with pumice at 5000 rpm for 30 seconds.²⁹ Then, the new bracket was re-bonded in the same previous protocol that was previously mentioned.

Table 1 The descriptive statistics for the SBS after mixing with ZO

Variable	Mean	SD±	Minimum	Maximum
Control	18.31	6.95	9.20	31.70
Modified with 1% ZO	12.58	6.25	6.60	24.60
Modified with 2% ZO	6.51	3.03	3.50	14.30

SBS measurement unit is megapascal.

Shear Bond Strengths Measurement

So after the bonding and re-bonding procedures, all specimens were left in distilled water for twenty-four hours at room temperature before the monitoring by the universal testing machine (GESTER, China).³⁰ At a crosshead velocity of 1 millimeter/minute, the stress necessary for the detachment of the brackets was calculated in Newtons (N).³⁰ The specimens were then secured in the device's bottom jaw such that the bracket base paralleled the shear force orientation, as can be seen in Figure 4.³¹ The test's findings were electronically documented.¹⁶ The applied load at the fracture point was captured in Newton and then changed to (MPa) by dividing the de-bonding force by the surface area of the bracket, which is a round (9 millimetres) based on the manufacturer's catalogue (MPa = N/mm²).²¹

Adhesive Remnant Index (ARI)

ARI quantified the amount of residual adhesive residue on the enamel surface.^{32,33} The ARI scores were utilized to identify the locations of bond failure among the enamel, resin, and bracket base. After de-bonding, the teeth were inspected with a stereomicroscope at 10X magnification. The following are the scores, which range from 0 to 3:

- 0. No adhesive left on the enamel surface.
- 1. Only about half of the adhesive is on the surface of the enamel.
- 2. More than half of the adhesive on the surface of the enamel.
- 3. With a bracket base impression, all of the adhesive on the enamel.

Table 3 One-way analysis of variance for shear bond strength among the bonded and re-bonded groups

	Sum of Squares	DF	Mean Square	F	P-value
Between Groups	1087.22	5	217.44	10.50	0.001
Within Groups	1117.99	54	20.70		
Total	2205.21	59			

Table 2 The descriptive statistics for the SBS re-bonded adhesive

Variable	Mean	SD±	Minimum	Maximum
Control	7.01	3.18	4.10	14.30
Modified with 1% ZO	6.72	3.64	2.30	14.20
Modified with 2% ZO	8.92	2.01	6.20	12.50

SBS measurement unit is megapascal.

RESULTS

Descriptive Analysis of SBS (Bonded Groups)

Table 1 depicts the descriptive data (mean and standard deviation) for SBS. This information included the standard deviation, minimum, maximum and mean. SBS values for every bonded research group. Based on the description of the original bonded groups, the control revealed a higher SBS mean value, followed by the modified adhesive with 1% ZO essential oil, and the 2% group had the lowest mean value.

Descriptive Analysis of SBS of the Re-bonded Groups

The descriptive of the re-bonded groups (mean and standard deviation) revealed that orthodontic adhesive modified with 2% ZO essential oil group had the highest SBS mean value followed by the control after re-bonding group, while the 1% group showed the lowest mean value as depicted in the Table 2.

Analysis of Variance of SBS among the Bonded and Re-bonded Groups

Table 3 shows the outcomes of the (ANOVA) test statistic, which demonstrated a significant difference in the mean values of the SBS for the various bonded and re-bonded groups in this research at p <0.05.

As depicted in Table 4, a more specific multiple comparison (Scheffe's) test, was administered among all the research groups, discovering a significant difference between the control group and the control after re-bonding. Furthermore, except for the 1% modified bonding group, there was a significant difference between the control bonding group and all of the modified groups in this study. Finally, there was no significant difference between the control after re-bonding and all of the study's modified groups at p <0.05.

Adhesive Remnant Index

The chi-squared test showed that there was a statistically significant difference in ARI score among

Table 4 The multiple comparisons among the bonded and re-bonded groups

	Mean Difference	Std Error	p value
Control			
Bonded after modifying with 1% ZO	5.73	2.03	0.180
Bonded after modifying with 2% ZO	11.79	2.03	0.001
Control after re-bonding	11.30	2.03	0.001
Re-bonded after modifying with 1% ZO	11.59	2.03	0.001
Re-bonded after modifying with 2% ZO	9.39	2.03	0.002
Bonded after modifying with 1% ZO			
Bonded after modifying with 2% ZO	6.06	2.03	0.133
Control after re-bonding	5.57	2.03	0.206
Re-bonded after modifying with 1% ZO	5.86	2.03	0.160
Re-bonded after modifying with 2% ZO	3.66	2.03	0.665
Bonded after modifying with 2% ZO			
Control after re-bonding	.049	2.03	1.000
Re-bonded after modifying with 1% ZO	0.20	2.03	1.000
Re-bonded after modifying with 2% ZO	2.40	2.03	0.922
Control after re-bonding			
Re-bonded after modifying with 1% ZO	0.29	2.03	1.000
Re-bonded after modifying with 2% ZO	1.91	2.03	0.970
Re-bonded after modifying with 1% ZO			
Re-bonded after modifying with 2% ZO	2.20	2.03	0.946

the different study groups, $\chi^2(5) = 24.187$, $p = 0.001$, with a mean rank ARI of 21.15 for control group, 23.70 for re-bonded control, 21.15 for 1% bonded group, 50.55 for 2% bonded group, 29.40 for 1% rebounded and 37.05 for the 2% re-bonded group.

DISCUSSION

Compared to the demands for composite restorations in the operative dental branch, in which the restorations are aimed to serve a longer period,

an orthodontic adhesive must be simple to remove at the end of the orthodontic therapy with no risks to teeth surfaces.³⁴ The ZO methanolic as well as crude extract have an incredibly ultrahigh cariostatic ability.³⁵ The reason behind selecting the mandibular first premolar as a sample in the current study is because of the high rate of the bracket, failure occurs on the lower premolars as compared with uppers.¹⁰ Previous research reviewed the adhesive residue's removal, and probable enamel harm, and noticed that the usage of fluorescent adhesives with

ultraviolet light, provides fast, convenient, and more efficient removal of the remnants.^{12,36} The existing research observed a significant decline in SBS after the re-bonding. However, our results are in contrast to the outcomes of previous reports that the SBS was not different significantly^{37,38} or the SBS value elevated after re-bonding of the new brackets^{39,40}, but in a study by Eslamian et al the SBS was lower after re-bonding.⁴¹ The existing research results are consistent with previous research, which discovered that after immersion in eucalyptus oil, the shear forces of the composite resin were diminished to the lowest value. Peppermint oil, like eucalyptus oil, lessened shear forces.^{41,42} Free-radical seekers tend to involve phenolic acids, flavonoids, as well as polyphenols. The chemical nature of polyphenols makes them excellent for free radicals adventuring as well as attracting metal ions⁴³⁻⁴⁵ Free radicals inhibited the polymerization of methyl-methacrylate by phenolic compounds, with eugenol serving as the most potent inhibitor.⁴⁶

Previous literature on *Salvadora persica*'s impact on the health of the oral cavity concluded that the meswak-treated self-etching subgroup had the least bond strength explained due to the presence of certain essential oils in meshwork-extract, which may interfere with the bonding process, while, higher bond strength was noticed in the total-etching subgroup, as the remaining oil gets washed away in the etch-and-rinse process.⁴⁷

A comparison of the present findings and similar research might be complicated. This seems to be due to the numerous bracket loadbearing devices utilized (bovine /human teeth or plastic blocks), the various size of the sample, bracket kinds (different models, recycled or new), bracket base surface area, or shear bonding strength evaluation procedures (shear or tensile) utilized. Furthermore, because of variations in methodological approaches, such as tooth choice, kinds of preventive components, exposure intervals, the concentration of the antimicrobial agent, bonding system, as well as whether or not the thermos-cycling approach is utilized.^{48,49} The morphological characteristics of the enamel might be a significant factor that influences multiple styles of adhesive failure during de-bonding.⁵⁰ Less adhesive

on the tooth after de-bonding in orthodontics means that removing it will take the orthodontist less time and effort, so, a lower ARI score would be preferable.⁵¹ Since the majority of the specimens in each of the four groups fell within the 0–1 range, (control group, re-bonding control, 1% bonding, 1% re-bonding, 2% re-bonding) the bracket and the majority of the adhesive were removed together during the de-bonding process. So that minimal effort is required to remove any remaining adhesive and it can do so without damaging the dental enamel.

Eslamian et al explored the role of numerous de-bonding patterns on the shear strength of stainless steel brackets and concluded that the noticed weakness in the shear strength is most probably due to incomplete disturbance of the etching sequence, and weakening retentive enamel morphological characteristics.⁴¹ The demineralizing dentin as compared to sound dentin, its SBS with resin was much lower.⁵² This may be explained by the mineral loss from the dentin peri-tubular and inter-tubular regions, which impairs the ability of the monomers to bond in demineralized dentin. The remaining unsupported collagen system acts as water-filled channel.⁵² The composite resin's ability to bond in the enamel surface may be decreased because of the hydrophilic substrate.⁵² Although natural products with their various forms have several applications in different medical and dental fields^{53,54}, further studies are indicated to improve their efficacy in dental practice.

CONCLUSION

From this study, it was concluded that, the incorporation of ZO, an essential oil, to the fluorescent adhesive, reduce the shear bond strength in the bonded and re-bonded brackets particularly with 2% concentration. The ARI revealed an evident difference among the study groups.

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Neurological findings and magnetic resonance imaging in patients with low back pain in Ninevah province

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Background and objectives

Low back pain (LBP) has increasingly reported as a common musculoskeletal disorder in clinical settings carrying great impact on individual and health system. The aim of the present study was to identify the findings of the magnetic resonance imaging (MRI) and clinical neurological symptoms together with their correlation with patients overall socioeconomic status.

Methods

A total of 60 LNP patients were enrolled in the present study (25 males; 35 females). MRI were conducted for individual patients and the neurological findings were reported represented by pain, disc bulging, spinal stenosis, degenerative changes, together with demographic and geographic data.

Results

The results confirmed that age, BMI, and educational levels were confounding determinant for development of LBP and male versus female developed LBP in similar ration. Spinal canal stenosis, pain, and Spondylolisthesis were hallmark associated with LBP.

Conclusion

MRI changes associated with LBP has revealed that a high percentage of LBP could potentially carry serious undelying illness and therefore MRI should be done for all patients with LBP.

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Low back pain (LBP) is one of the most common problems that most people experience at some point in their life. In the past decade, back pain has been the main cause of disability and is still one of the most frequent health problems.¹ As in other developed nations, the lifetime prevalence of back pain was found to be more than 80% in a study of the Japanese population.¹ The long-term loss of function caused by low back pain may have a significant economic effect on the nation in terms of lost wages, medical expenses, and disability benefits.²

There are two distinct categories of causes of LBP: specific, after specific spinal causes (radiculopathy or spinal degenerative disease), and nonspecific, which may be determined by a thorough history and clinical examination.³ Chronic LBP considered nonspecific when no obvious cause can be detected clinically or by MRI imaging findings.² Patients who suffer from back pain due to radiculopathy, spinal stenosis, or discomfort from a specific location in the spine benefit the most from an MRI.⁴ Diagnostic imaging is only advised for individuals with suspected disc herniation infection, fracture, or malignancy or when invasive intervention is planned in patients with low back pain.⁵

The human spine is a delicate and complex structure that can experience a variety of disorders. From disc herniation to nerve root impingement and disc degeneration, these issues can all be detected through the high-intensity zone of an MRI scan. However, it is important to note that not all individuals with lower back pain will display these problematic markers. Even when these abnormalities are present, they may not necessarily be the root cause of the pain. But here is where things become interesting: the presence or absence of these abnormal findings on an MRI can significantly impact the prognosis for those suffering from lower back pain. Despite the fact that not all cases of LBP will show these markers, it is still worth considering an MRI as part of the evaluation process. By doing so, medical professionals can gain valuable insights into the underlying issues causing the pain and develop more effective treatment plans.⁶

Lower back pain can be a real pain in the neck. But fear not, nowadays, MRI of the lumbar spine is the investigation of choice for doctors looking to diagnose the problem. And when it comes to evaluating disk morphology, MRI is the method of choice, with a sensitivity of 60-100% and specificity of 43-97% for disk herniation. T1- and T2-weighted sagittal and axial MR images are the way to go. They can visualize the vertebral endplates and

intervertebral disks with stunning clarity. T2-weighted images are especially impressive, as they show excellent contrast between the outer part of the annulus (which is more fibrous tissue and therefore shows low signal) and the inner part of the annulus and nucleus pulposus (which have more water content and therefore show high signal). And here's a fun fact: in younger individuals, an area of low-intensity signal may be visible in the middle of the nucleus pulposus in a non-degenerated disk. This is actually considered a normal observation and probably represents a higher concentration of proteoglycans causing signal loss on T2-weighted images.^{5,6}

This work was conducted to study the clinical presentations and the risk factors in individuals with LBP and the relationships with MRI examinations based on whether or not certain spinal abnormalities were found. Moreover, MRI results may not be sufficient to determine the cause of back pain. MRI may detect soft tissue such as discs, nerves, and muscles, which are all probable origins of LBP. No information was available in Mosul concerning MRI and neurological results in individuals with LBP, according to the city's database.

PATIENTS AND METHODS

In this cross-sectional observational study; no changes have been done to patients' ongoing medication profiles. The study was evaluated and approved by the medical research ethical committee (Ninevah University, No. 10 on 24.08.2021). The study Written consent of agreement was collected from patients to participate in this study. Patients were referred by collaborative outpatient neurologists private clinic throughout the study period, with the majority of the patients being in chronic conditions. The diagnosis was made using MRI at Mosul teaching hospital, referring from different departments in different hospitals mainly from the neurology unit as an outpatient or as admitted patients, all of them complaining of LBP that not responding to conservative treatment, MRI data were collected using MRI 1.5 Tesla Philips Achieva scanner with a standard 16 channel phased array lumbar spine coil machine. The following parameters were used: Sagittal, axial T1 (TR 461.0, TE 8.0), T2 (TR 2620.4, TE 100.0), and Myelogram (TR 8111.0, TE 1000.0) were done for each patient (Figure 1).

Patients with non-specific chronic back pain were considered suitable for participation in this study.

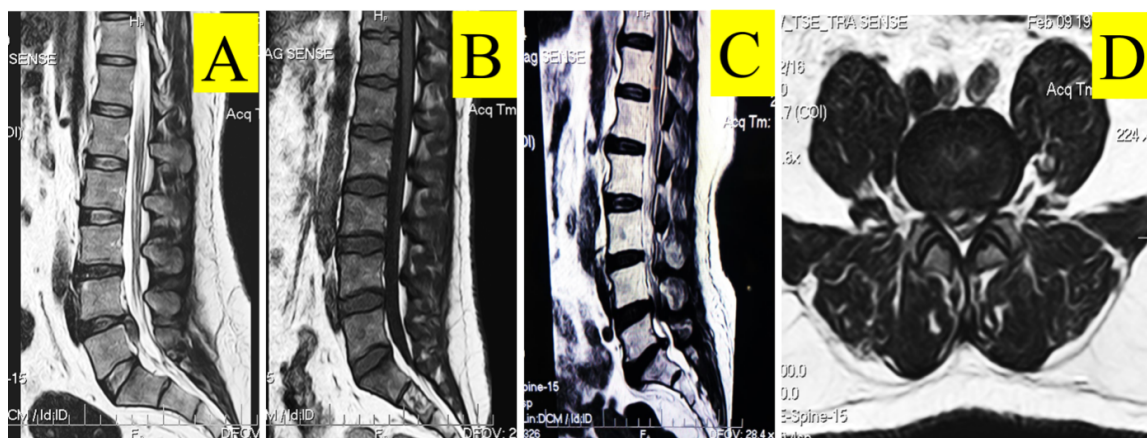


Figure 1 A representative images for four cases presented to the clinic (A) 41 years old male presented with lower back radiating to lower limbs; T2W sagittal image showing posterior central herniation with caudal migration of L4-5 disc causing spinal canal stenosis. (B) 34 years old male patient presented with lower backache; T1W sagittal image showing normal intervertebral discs, no significant bulging, no spinal canal stenosis. (C) 56 years old male presented with lower back radiating to lower limbs; T2W sagittal image showing posterior central herniation of L5-S1 disc causing spinal canal stenosis associated with degenerative endplates changes. (D) 37 years old female patient presented with backache radiating to right lower limb; T2W axial image showing circumferential disc bulging with right paracentral disc herniation indenting right lateral recess.

Patients were excluded if they met any of the following criteria: they were under the age of 18 years, patients had previous severe trauma, previous surgery in the spine, scoliosis, significant comorbid conditions or extensive, diffuse pain, clinical indications of polyneuropathy or polyneuropathymyofascitis, inflammation, connective tissue disorders, tumour of the spin, and osteotomy operation of the ilium were excluded. There was no local pain in the back during palpation and all patients were negative in the sacroiliac (SI) joint pain-provocation tests, including distraction, compression, sacral thrust, and pelvic torsion.

This study documented the demographic information of the participants from the outset and estimated their BMI. All patients received a thorough clinical neurological examination, which included a thorough assessment of the lower limbs to rule out the presence of radiculopathy or polyneuropathy in the legs.

The pain was assessed using descriptors, distribution, duration, severity, time course, pain-relieving posture, and current consumption of analgesics or other medications known to mitigate pain, among other things. The current pain intensity at rest and during movement, as well as the mean and maximum pain intensity during the preceding four weeks, were all recorded.

During the interview with the neurologist, indicators for that neuropathic pain were evaluated, such as accidental polyneuropathy or radiculopathy, nerve conduction tests and needle electromyography were

done on the lower limbs. Other causes of polyneuropathy as vitamin B12 and folate levels deficiency, thyroid hormone levels, serum protein electrophoresis, complete blood count, serum creatinine, bilirubin and transaminases, blood glucose and glycated haemoglobin (Hb_{A1C}), serum lipid profile were routinely checked. These parameters were evaluated routinely as a part of annual check, the values were up to the normal standard ranges, hence, we didn't mention them in the present study.

RESULTS

The results of this work showed that male patients represent 42% ($n=25$) of the patients (age range 20-62 years, 44.8 ± 17 years; weight 92.68 ± 22 , height 172.9 ± 6.6 and BMI 31.2 ± 8.7), while female patients represent 58% ($n=35$) of the patients (age range 27-65 years, 48.9 ± 11.4 years; weight 84.14 ± 17.4 , height 164.8 ± 4.9 and BMI 30.99 ± 6.4), [Table 1](#).

Table 1 Anthropometric measures of studied sample

Parameter	Male $n=25$	Female $n=35$	p value
Age (Years)	44.8 ± 17	48.9 ± 11.4	0.4
Weight (Kg)	92.7 ± 22	84.1 ± 17.4	0.2
Height (cm)	172.9 ± 6.6	164.8 ± 4.9	0.0002
BMI(kg/m^2)	31.2 ± 8.7	31.0 ± 6.4	0.9
Gender	41.7% (25)	58.3% (35)	0.04

Table 2 Geographic information of the studied sample

Parameter	Male <i>n</i> =25	Female <i>n</i> =35	<i>p</i> value	Chi-square
	Residence			
Rural	48%	54%	0.4	0.72
Urban	52%	46%		
	Education			
No formal education	12%	46%	0.0001	
Primary	36%	34%		
Secondary	40%	20%		
High education	12%	0 %		

The residence distribution in the male group includes 52% (13 patients) of them living in urban areas and 48%(12 patients) living in rural areas, whereas in the female group, 54% (19 patients) of them lived in a rural area and 46 % (16 patients) lived in an urban area. A few male patients graduated; 12% (3 patients), with no formal education, 12% (3 patients), 36% (9 patients) with primary education and 40% (10 patients) with secondary education. All female patients were housewives, with no formal education 46% (16 patients), 34% (12 patients) with primary education and 20%(7 patients) with secondary education. 28% of the male patients were retired 16% were drivers, 8% were teachers and 48% are self-employers (Table 2).

Table 3 Relation between gender and severe pain score

Pain severity	Male n=25	Female n=35	p value	Chi-square
Mild	2(8%)	5(14%)	0.5	0.44
Moderate	12(48%)	16(46%)	0.9	0.01
Sever	11(44%)	14(40%)	0.84	0.04

According to the pain score, 8% of male patients presented with mild pain, 48% with moderate pain and 44% presented with severe pain. In females, 14.3% presented with mild pain, 45.7% with moderate pain and 40% presented with severe pain, non-significant differences existed between the groups (Table 3).

Table 4 Clinical information pertained to pain

Parameter	Male <i>n</i> =25	Female <i>n</i> =35	<i>p</i> value	Chi-square	
Post-operation history	0%	5.7%			
	Site of pain				
	Right	40%	52%	0.2	2.87
	Left	40%	34%		
	Both side	20%	14%		
	Pain radiation				
	No radiation	16%	26%	0.0001	26
	Right	40%	23%		
	Left	40%	26%		
	Both side	4%	25%		

Out of 60 patients, only 5.7% (n=2) of females (no males) were reported to have past-surgical history. According to the site of pain, there were non-significant differences between males and females (p = 0.2). Males represented 40% on either side while 20% represented pain on both sides, while in females 52% (18 cases) had pain on the right side, 34% (12 cases) with left side pain and 14 % (five cases) had pain on both sides. According to the radiation of pain, 26% (9 cases) had no pain radiation. Other 26% of the cases (9 patients) had radiated pain in the left leg. Patients with right leg radiation pain represent 22% (eight cases) and the remaining 26% (9 cases) presented with both sides of radiation. According to the site of pain: 40% (10 cases) had pain on the left side, 40% (10 cases) with left side pain and 20 % (five cases) had pain on both sides (Table 4).

MRI of individual patients revealed that 80% of males and 69% of females were shown positive MRI results, while 20% of males and 31% of females were negatively represented in MRI (Table 5).

Table 5 MRI finding based on gender

Parameter	Male n=25	Female n=35	p value	Chi-square
MRI positive	80%	69%	0.048	3.9
MRI negative	20%	31%		

Patients with severe pain (12 males and 14 females) were found to suffer from other symptoms such as spinal canal stenosis and spondylitis. The presence of Spinal canal stenosis in a patient with severe pain was 10 patients (29%) female and 10 patients (40 %) male patients. The presence of spondylolisthesis in a patient with severe pain was 4 patients (26.6%) in females and 2 patients (15 %) in male patients (Table 6).

Table 6 Correlation between severe pain and spinal canal stenosis & spondylolisthesis

Gender	Severe pain	Spinal canal stenosis	Spondylolisthesis
Male	12	10	2
Female	14	10	4

Degenerative endplates changes, it is found in 33 patients (55%), including 21 female patients and 12 male patients. The percentage of association between degenerative changes and L 4-5 disc bulging was 80% in male patients and 66% in females, while stenosis was 40% in male patients and 49% in female patients (Table 7).

DISCUSSION

In the present study, more female patients were recruited from the studied sample than male patients with quite similar ages and BMI. Similarly, in a study conducted by Thapa et al, most of the patients' age was around 40 years old.⁷ Additionally, Savage et al, have reported that comparing MRI of older to younger patients reportedly showed that age is an important factor in developing LBP-associated degeneration.⁸ In contrast, Al-Saeed et al, conducted a study in Kuwait and they reported that even younger patients (less than 30 years) could develop LBP with associated MRI changes.⁹ The results of this work showed that being overweight is associated with a greater incidence of LBP in both gender in accordance with the study conducted by Chou et al.¹⁰

In a study conducted on hotel workers by Wami et al, most of the patients showing back pain were females.¹¹ The higher rate in females could be explained in the context that females are more prone to musculoskeletal ailments.¹² Similarly in Lebanese study conducted on housewives found that up to three-quarters of the housewives suffered from LBP.¹³

Whether patients live in a rural or urban area does not make a difference in the overall distribution of back pain. These could be in part related to the fact that most rural dwellers moved to the city for work and engaged in office work with only a few farming works done in the villages mostly done by females. There are reports that most of the daily activities which are involved lifting heavy materials ultimately led to LBP.^{14,15}

Table 7 Incidence of degenerative endplates changes findings

Patients defect	Male n=25	Female n=35	p value	Chi-square
Degenerative changes	12(48%)	21(60%)	0.6	0.25
Disc bulging	20(80%)	23(66%)	0.6	0.24
Spinal stenosis	10(40%)	17(49%)	0.6	0.17

Educational levels seem to greatly impact the distribution of back pain in the female group. Most non-educate females have back pain than educated, however, the male group show inverse proportions with increased back pain with educational levels. These variations are perhaps related to the nature of female daily activity pertaining to household work which needs long times of sitting and standing either for cocking, knitting, sewing, and cleaning activity. In contrast, male work usually involved either office work (sitting) or non-office-based work which do involve handling and lifting heavy objects. This variation inevitably shapes the fate of body bone degeneration and subsequently neural deficits associated with LBP.¹⁶⁻¹⁸ The educational levels support the notion that those with less education are more likely to suffer from incapacitating back pain than those with higher education. A higher amount of evidence supports the idea that education has an impact on the duration and/or recurrence of back pain episodes than the evidence to support the idea that education has an impact on back pain incidence.^{19,20}

The severity of pain was similar between males and females and at all levels whether mild, moderate, or severe. Similarly, the site of pain whether left or right has shown no differences between males and females. However, pain is radiating either to the left or right and is more obvious in males than females.¹⁶⁻¹⁸

On MRI examination, most patients diagnosed with MRI as a positive and more positive rate were present in males than females. In addition to back pain, other symptoms coexist, such as degenerative changes, disc bulging, and spinal stenosis. Females tend to present with degenerative changes and spinal stenosis more than males, however, males are represented with disc bulging. These findings agree with the study conducted by Choi et al, who have found that most patients (80%) expressed a certain degree of degenerative changes at MRI levels ranging from disc degeneration, spinal stenosis,

endplate changes, spondylolisthesis, nerve root compression, disc contour, and others.²¹

Concerning findings on MRI imaging, most patients with positive findings were male. These findings agreed with the results obtained by Al-Shami & Hameed.²² The importance of the link between the severity of degenerative changes discovered in imaging studies, and the presence and intensity of LBP were described by this work, especially between L4-5 with a higher incidence in males than females.²² According to the imaging profile 20% of the male patients presented with LBP while 31.5% of females presented with LBP, ranging from normal picture to severe spinal canal stenosis, including different types of disc bulging, spondylolisthesis, and degenerative changes.

We have uncovered an intriguing correlation between the intensity of pain and the presence of spinal canal stenosis on MRI scans. This discovery is consistent with previous findings, as noted in Kasch et al, work, which also identified a clear link between the severity of pain and the occurrence of spinal canal

stenosis. In other words, our results provide further evidence to support this important medical connection.²³ Degenerative endplates changes are considered a significant MRI findings in patients with chronic backache, more common in elderly people, this work results showed degenerative endplates changes seen in more than half of patients, the outcome looks similar to Jensen RK.²⁴ Disc bulging was found to be most common findings in patients with chronic backache, seen in most patients & was most common cause, while in Ibrahim H, disc bulging noted in 60% only.²⁵ Stem cells and platelet rich plasma could potentially play a great role in the treatment of arthritis and could be applied for LBP due to their anti-inflammatory activity.^{26,27}

CONCLUSION

LBP associated with neurological findings presents as positive MRI results and is typically associated with spinal canal stenosis, Spondylolisthesis, and pain. Females has shown higher MRI positive cases than males.

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When it's more than just a sore throat: Lemierre's syndrome

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Lemierre's syndrome is a rare condition typically affecting healthy young adults, however its diagnosis is often delayed, which may be fatal. In this report, we present a typical case of this condition: a 25 year old gentleman presenting with fever, cough and sore throat who was found to have superficial thrombophlebitis of the right external jugular vein with blood cultures positive for *Fusobacterium necrophorum*. Multifocal lung consolidations were identified on CT thorax. He was started on appropriate antibiotic and anticoagulant therapy and made a full recovery. Through this report, we aim to increase awareness of this condition, particularly as a possible cause of sepsis in an otherwise healthy patient.

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CASE REPORT

A previously healthy 25 year old gentleman presented to the Emergency Department with a 1 week history of fever (more than 39°C), sore throat and productive cough which persisted despite a course of antibiotics (azithromycin). He also reported occasional haemoptysis.

On examination he was found to have low oxygen saturations and an ENT review revealed a hard lump on the right side of the larynx and non-specific pharyngeal erythema.

Blood investigations revealed an elevated white cell count with left shifted neutrophils and a high c-reactive protein. Blood cultures and a viral screen were also taken. Routine admission chest X-ray (CXR) showed patchy airspace shadowing in the left middle lung zone. He was thus started on empirical antibiotic therapy (tazobactam-piperacillin and clarithromycin).

In view of the CXR findings, he underwent a CT thorax which revealed multifocal areas of consolidation throughout both lungs and small bilateral pleural effusions (**Figure 1**). No intrathoracic lymphadenopathy was seen and mild splenomegaly was reported in the upper abdomen.

The intrapulmonary findings were believed to be secondary to septic emboli, and he thus underwent a transthoracic echo which was negative for infective endocarditis. In view of the neck mass on examination as well as to look for any other areas of infection, he also underwent an ultrasound of the neck, which revealed superficial thrombophlebitis of the right external jugular vein with extension of



Figure 1 A CT scan of the thorax showing bilateral multifocal consolidations and bilateral pleural effusions

thrombosis into the right internal jugular vein (**Figure 2**). No intracranial abnormalities were demonstrated on a CT scan of the brain.

Viral screen taken on admission for Epstein-barr virus (EBV), cytomegalovirus (CMV), hepatitis and human immunodeficiency virus (HIV), serum mycoplasma antibodies and serum and urinary investigations for Legionella and Strep. pneumoniae were negative. Blood cultures however grew *Fusobacterium necrophorum* (sensitive to penicillin, metronidazole, clindamycin, meropenem and imipenem).

Therefore, a diagnosis of Lemierre's syndrome was suspected and antibiotics were modified according to sensitivities. There was a good clinical response to meropenem and clindamycin. He was also started on anticoagulation – initially on intravenous heparin, which was then switched to a direct oral anti-coagulant (rivaroxaban).

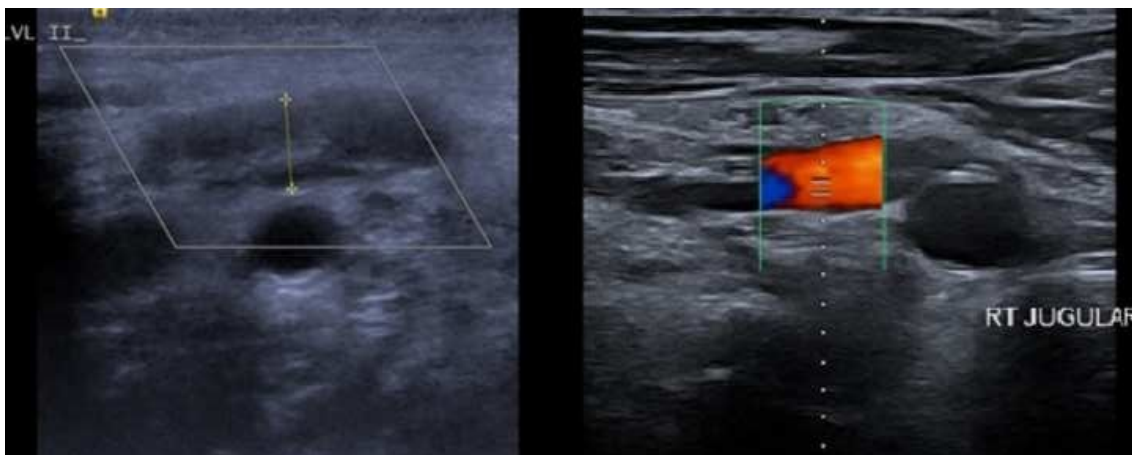


Figure 2 Ultrasound scan of the neck showing thrombosis of the right external jugular vein (EJV), with slight extension into the right internal jugular vein (left image), with the right image showing patency of the right jugular vein 3 months after treatment.



Figure 3 Comparison of Chest X-rays, prior to treatment and two months after treatment

OUTCOME AND FOLLOW-UP

The patient improved remarkably on the upgraded antibiotics and anticoagulation and was thus discharged home on oral antibiotics (clindamycin for a total course of 21 days) and rivaroxaban for a total of 3 months.

He was followed up with repeat ultrasound scans of his neck (Figure 2) and CXRs (Figure 3) over the next few months, which showed complete resolution of both the jugular vein thrombosis and the areas of consolidation within the lungs.

DISCUSSION

Lemierre's syndrome is a rare condition typically affecting healthy young adults. It is characterised by pharyngitis followed by thrombophlebitis of the internal jugular vein (IJV) with possible spread to the lungs, liver or brain.¹ The diagnosis is often delayed, hence it is associated with significant morbidity and mortality if not diagnosed and treated promptly.²

It is a rare condition often referred to as the 'forgotten disease' due to the low reported incidence after the pre-antibiotic era.³ However, it is thought that it is not as rare as previously believed, possibly due to increasing antibiotic resistance or decreased antibiotic prescription for upper respiratory tract infections (URTIs)⁴, which are more commonly due to a viral aetiology.

Early accurate diagnosis requires a high degree of clinical suspicion, particularly since it presents with nonspecific symptoms similar to benign URTIs.² It is however essential, as this condition may be life threatening if untreated, and effective treatment

options are available if a timely diagnosis is carried out.

This case highlights the fact that diagnosis is often delayed; it was only suspected after internal jugular vein (IJV) thrombosis, a recognized typical complication of the condition, was noted on imaging, and further confirmed by identification of the most common causative organism (*Fusobacterium necrophorum*) on blood cultures.

Treatment involves antibiotics; penicillins given for 2 to 6 weeks, together with metronidazole or clindamycin due to macrolide- and increasing penicillin-resistance.⁵ As happened in our case, most patients are treated empirically with antibiotics for a bacterial infection or pneumonia suspected on blood results or chest imaging, prior to diagnosis.

SUMMARY BOX

- The physician should consider Lemierre's syndrome as a possible cause of sepsis particularly in previously healthy patients. Early diagnosis and treatment is paramount as the condition can be life threatening.
- The following should prompt the possibility of Lemierre's syndrome: (i) pharyngitis which persists for more than 5 days, particularly if treated with macrolides (most common causative organism tends to be macrolide-resistant), (ii) pharyngitis associated with lateral neck pain or swelling, (iii) pharyngitis followed by sepsis or multiple pulmonary lesions.

The role of anticoagulation is still controversial. Some authors report use only in patients who fail to improve despite antibiotics, and in those with thrombophilia, cerebral venous sinus thrombosis or arterial thrombosis. Other authors have reported use in all patients with this condition.⁶ Surgery is often reserved for drainage of neck abscesses. IJV ligation or excision may rarely be required in cases of persistent septic embolization despite medical treatment.⁷

CONCLUSION

In this report we present a typical case of Lemierre's syndrome, in which accurate diagnosis was delayed despite the classical presentation. We thus aim to increase awareness of this condition, particularly as a possible cause of sepsis in an otherwise healthy patient.

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An Uncommon case of Cushing's Syndrome: Ectopic ACTH secretion

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Cushing's syndrome (CS) is the end result of long-standing exposure to increased levels of cortisol. This can be divided into two groups: exogenous and endogenous hypercortisolaemia. The former is usually the result of prolonged exposure to synthetic glucocorticoids. On the other hand, endogenous causes result from increased release of cortisol by the adrenal glands and can be ACTH-dependent or ACTH-independent. 80% of endogenous CS is due to ACTH-dependent cortisol excess secondary to a pituitary adenoma [1]. The remaining endogenous causes of CS are due to ACTH-independent adrenal causes (adrenal hyperplasia, adrenal adenomas, and adrenal carcinomas), followed by unknown sources, and ectopic ACTH secretion by neoplasms. The authors present a case of ectopic ACTH-dependent hypercortisolism due to an aggressive metastatic neuroendocrine tumour.

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CASE PRESENTATION

A 61-year-old gentleman presented to the accident and emergency department with mild haemoptysis and dyspnoea. The patient also complained of weight gain, increasing waist circumference, and lower limb swelling. Baseline parameters showed that the patient was hypertensive (BP: 170/60 mmHg). Physical examination noted the presence of cushingoid features. These included centripetal obesity, Cushingoid facies, easy bruising, peripheral oedema, and skin atrophy. Hyper-pigmentation was also noted.

Past medical history included hypertension which was previously controlled by amlodipine 10mg daily. He had no known drug allergies and was a lifelong heavy smoker.

INVESTIGATIONS

Laboratory investigations revealed the presence of hypokalemia of 2.83 mmol/l (normal range: 3.5-5.1 mmol/l) and hypernatremia of 154 mmol/l (normal range: 135-145 mmol/l). He was hyperglycemic with an HbA1c of 7%. The patient's complete blood count showed neutrophilia. On presentation, the patient was also noted to have biochemical jaundice with a bilirubin of 38.6 micromol/L and slight deranged hepatic enzymes with a gamma-glutamyl transferase of 145 U/l (normal range: 8-61 U/l) and an alanine aminotransferase of 105 U/l (normal range: 5-41 U/l).

In light of the above presentation, especially the presence of haemoptysis, the patient underwent a

computed tomography (CT) scan of his thorax, abdomen, and pelvis. This revealed the presence of diffuse pulmonary and liver lesions. The latter lesions were suggestive of metastasis. The CT scan also noted coarse structure of the left femoral head indicative of avascular necrosis.

In view of the patient's presentation and the CT findings, the clinical suspicion for endogenous hypercortisolism was high. Hence, a 9 am cortisol was taken and was found to be elevated at 2512 nmol/l (normal range: 145-619 nmol/l). A 24-hour urinary free cortisol was also high at 3236 nmol/24h (normal range: 57.7- 806.8 nmol/24h). ACTH levels were found to be inappropriately elevated.

Furthermore, there was non-suppressibility to both low-dose and high-dose dexamethasone suppression tests (DST).

Pituitary Magnetic Resonance imaging (MRI) excluded pituitary causes. The CT findings, absence of pituitary pathology on MR, and failure to suppress to high dose DST were more indicative of ectopic ACTH secretion. A Magnetic Resonance Cholangio-Pancreatography (MRCP) was performed for further characterization of the liver pathology. This showed the presence of multiple bilobar hypovascular lesions. These were biopsied and histopathology was consistent with a metastatic high-grade neuroendocrine carcinoma favouring a lung primary (**Figure 1**). In view of this, plasma Chromogranin A was taken and found to be elevated at 250mcg/l. 24-hour urinary 5-hydroxyindoleacetic acid level was within normal limits.

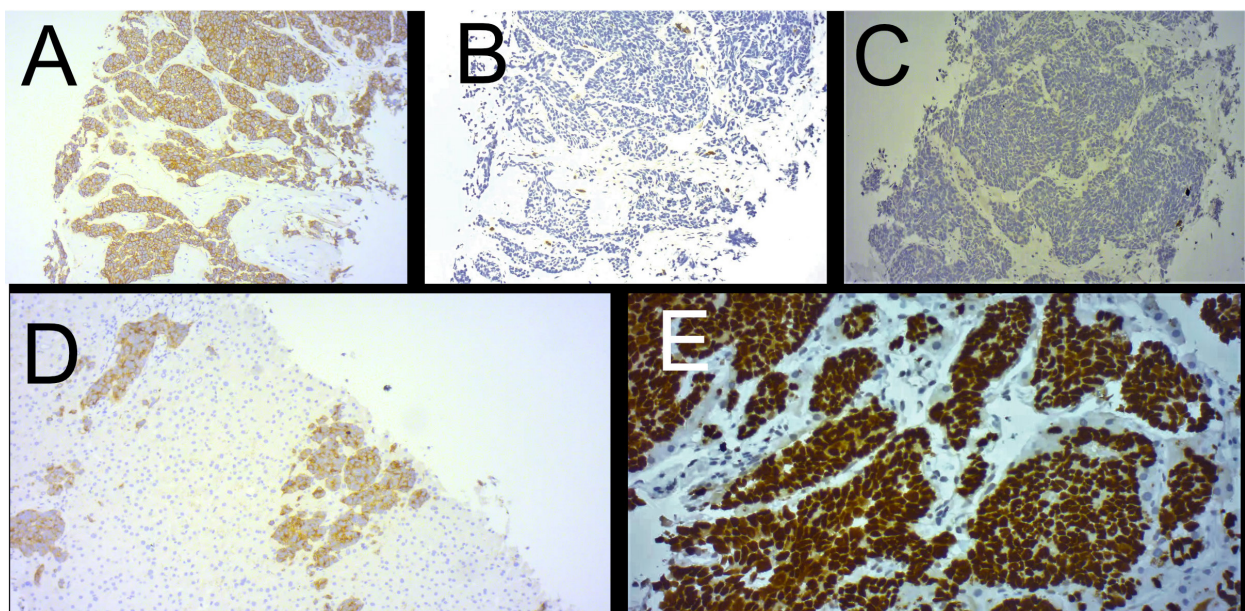


Figure 1 Liver core biopsies show infiltration of liver parenchyma by a tumour composed of solid nests of cells having a high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei with some nuclear moulding, and brisk mitotic activity. On immunohistochemistry, the tumour cells show strong and diffuse positivity for CD56, synaptophysin, and TTF-1 and very focal CK7 positivity. CK20 is negative. These features are in keeping with a metastatic high-grade neuroendocrine carcinoma, likely from a lung primary. A) H&E stain B) CK7 stain C) CD56 stain D) Synaptophysin E) TTF-1 stain

Table 1 *Types of NET, hormone released, and syndrome associated with the tumour²*

Tumour	Hormone released	Syndrome
ACTHoma	ACTH	Cushing's Syndrome
Atypical carcinoid	5-Hydroxytryptophan, histamine	Atypical Carcinoid
Carcinoid	Serotonin, tachykinin, prostaglandins	Carcinoid
Insulinoma	Insulin, pro-insulin	Whipple's trial
Gastrinoma	Gastrin	Zollinger Ellison Syndrome
Glucagonoma	Glucagon	4D Syndrome
Somatostatinoma	Somatostatin	Somatostatinoma syndrome
VIPoma	Vasoactive intestinal peptide (VIP)	Verner-Morrison syndrome

MANAGEMENT

Electrolyte derangement was aggressively treated alongside his hypertension and diabetes mellitus.

Oncology input was sought and in view of advanced disease, the patient was not deemed to be a candidate for surgery. Medical treatment for endogenous ectopic ACTH production involved metyrapone. Ketoconazole was contraindicated in view of deranged liver function tests.

DISCUSSION

Our case represents a patient who suffered from ACTH-dependent CS secondary to ectopic ACTH production from a lung NET.

NET may be functional or non-functional. Functional NET compromises a group of malignancies which are responsible for the secretion of several biopeptides (Table 1).² These tumours are most commonly associated with the thoracic cavity and gastrointestinal tracts. The prevalence of ectopic ACTH secretion in patients with NET is around 3.2%.³

Our patient presented with CS as a result of high circulating levels of cortisol. Cortisol is a catabolic hormone produced by the zona fasciculata in the adrenal cortex. 90% of this cortisol is transported bound to cortisol binding proteins.¹ The causes of CS can be appreciated in Figure 2.^{4,5}

The initial assessment should include one of the following confirmatory tests: urinary free cortisol (two measurements), late-night salivary cortisol (at least two measurements), 1 mg overnight dexamethasone suppression test, or the longer low-dose DST (2mg/day for 48 hours). If any of the above tests are abnormal, the use of another confirmatory

test is recommended.⁶ Low-dose DST followed by corticotropin-releasing hormone (CRH) stimulation test may be of value in differentiating between CS and pseudo-CS. This involves the administration of 100mcgs of CRH following a 48hour low-dose DST. A cortisol level above 38nmol/l, measured 15 minutes after administration of CRH was found to predict CS.⁷

The next step in investigating CS would be to measure ACTH levels. If levels are low, ACTH-independent causes should be suspected. On the other hand, if ACTH levels are high or inappropriately normal, then one should investigate for ACTH-dependent causes. If the pituitary scan is normal, an ectopic etiology should be considered as in our case. Establishing the ectopic cause via directed CT scanning may be helpful.⁷ In patients with ACTH-dependent CS where no clear source is identified, bilateral inferior petrosal sinus sampling is recommended.⁷ In our case, the longstanding history of smoking and the new-onset haemoptysis pointed towards lung pathology which was confirmed on CT and histopathology results.

Treating ectopic ACTH syndrome (EAS) may be challenging. The Endocrine Society Clinical Practice Guideline; Treatment of Cushing's Syndrome recommends localizing and resecting the ectopic ACTH-secreting tumour with node dissection as appropriate as a first-line treatment option.⁸

Furthermore, Miller CA & Ellison EC also suggest that in patients with metastatic neuroendocrine tumours limited to the liver, one can consider resection or cryoablation of the liver metastases, or even liver transplantation following resection of the primary tumour.⁹

In patients with EAS for whom surgery is not possible due to metastatic nonresectable tumours or an occult tumour or in those who are severely ill, medical

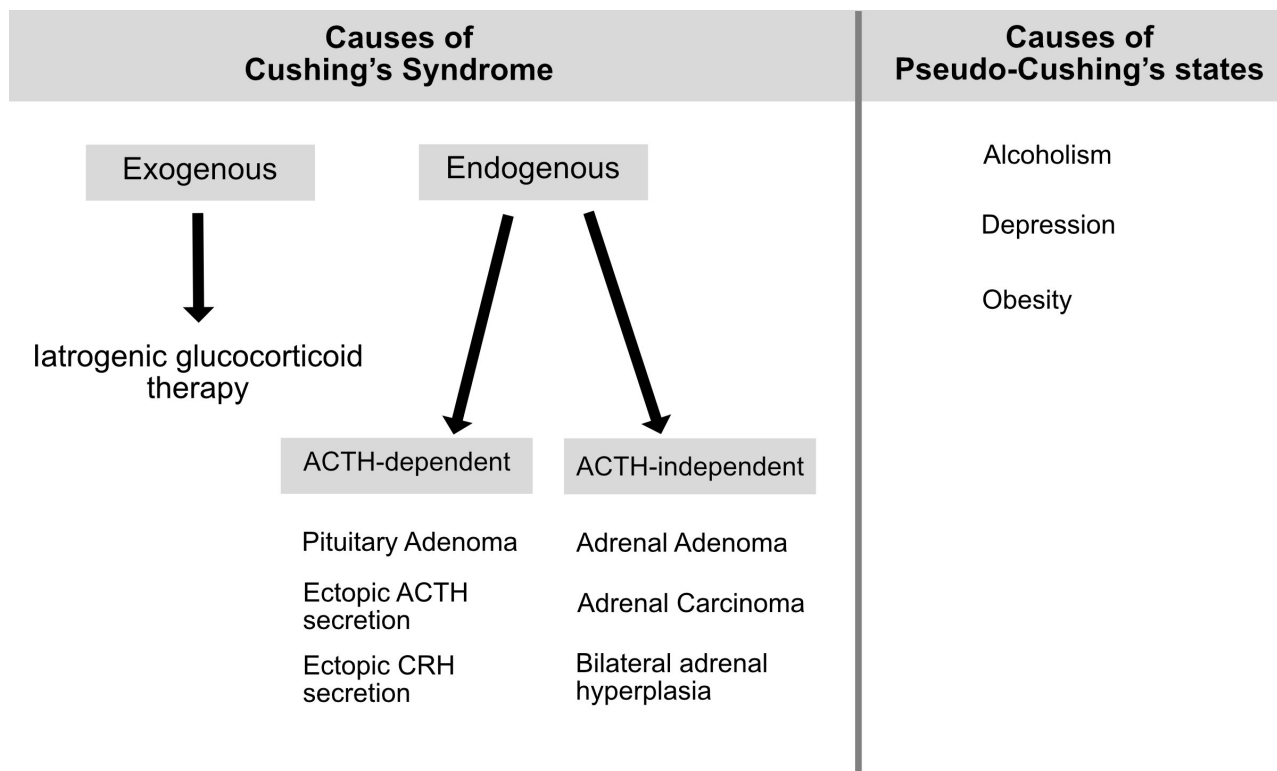


Figure 2 Causes of Cushing's syndrome and pseudoCushing's states

therapy with steroidogenesis inhibitors can serve as primary treatment. These include; ketoconazole, metyrapone and etomidate.⁸

Recent preliminary data suggest that a new 11-hydroxylase inhibitor known as LCI699 may have a promising potential role in patients with EAS. However, the latter requires confirmation in clinical trials with a significant number of patients with EAS.¹⁰

In an expert operational opinion, slow-acting cortisol-lowering drugs such as mitotane and mifepristone may also have a role in patients with EAS.¹⁰ Of note, physicians need to be careful when prescribing mitotane in addition to other medications including anti-neoplastic agents, as mitotane has a potent and long-lasting inducing effect on the enzyme CYP3A4. This can lead to clinically relevant drug-drug interactions.¹¹

Both the Endocrine Society guideline and the expert opinion, mention the use of agents that inhibit ACTH

secretion by the NET. These include somatostatin analogues such as octreotide, the dopamine-2 receptor agonist cabergoline and tyrosine kinase inhibitors such as vandetanib, sorafenib and sunitinib.^{8,10}

In occult or metastatic EAS or in patients with very severe ACTH-dependent CS who cannot be promptly controlled by medical therapy, the Endocrine Society Clinical Practice Guideline also suggests bilateral adrenalectomy.¹⁰ Albeit an effective treatment option, bilateral adrenalectomy is weighed down by significant perioperative mortality and morbidity rates, the risk of developing Nelson's syndrome, and other long-term complications that can result in reduced life expectancy.¹² The possibility of Nelson's syndrome in adults ranges from 8-47%.¹³

In conclusion, this case highlights the need for a high degree of clinical suspicion as well as the diagnostic investigations required for establishing the aetiology of CS.

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Unilateral Pulmonary Oedema secondary to Anterior Mitral Valve Leaflet Prolapse

Sarah Camilleri, Maria Aquilina, David Sladden

Cardiogenic unilateral pulmonary oedema (UPE) is an uncommon clinical condition which is often mistaken for lower respiratory tract infection (LRTI). It is typically caused by asymmetric systolic flow reversal in the right pulmonary veins due to severe mitral valve regurgitation (MR). We describe the case of a 41-year-old woman with a history of undifferentiated chronic mixed connective tissue disease, Raynaud's disease and pituitary adenoma who presented with acute shortness of breath (SOB), chest tightness, orthopnoea and paroxysmal nocturnal dyspnoea. A computerized tomography pulmonary angiogram (CTPA) showed signs consistent with pulmonary oedema secondary to congestive heart failure. This prompted urgent echocardiography which revealed a flail and prolapsing A2 leaflet of the mitral valve with a posteriorly-directed MR jet, resulting in systolic flow reversal in the pulmonary veins which is consistent with severe MR. The patient underwent an urgent mitral valve (MV) replacement and optimization of medical therapy, resulting in clinical and radiographic improvement.

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Cardiogenic unilateral pulmonary oedema (UPE) is an uncommon clinical condition which is often misdiagnosed for presumed lower respiratory tract infection (LRTI). Diagnostic challenges carry an increased risk of morbidity and mortality. UPE is commonly due to asymmetric systolic flow reversal in the right pulmonary veins caused by severe mitral valve regurgitation.

CASE PRESENTATION

We describe the case of a 41-year-old Caucasian woman who is a known case of undifferentiated chronic mixed connective tissue disease, Raynaud's disease and pituitary adenoma. She presented to the emergency department with acute worsening of shortness of breath (SOB) that had started a few days prior. This was worse at night and on exertion. She also complained of occasional chest tightness, orthopnoea and paroxysmal nocturnal dyspnoea (PND).

Salient clinical findings on examination included pallor, lethargy, restlessness and SOB. The patient had a blood pressure of 109/75 mmHg, regular pulse of 110 bpm, afebrile body temperature and oxygen saturations of 88% on room air. Lung auscultation revealed bibasal coarse crepitations which were more prominent over the right mid zone. Heart sounds were unremarkable. Chest X-ray showed bilateral airspace shadowing, more prominent on the right (**Figure 1**). Laboratory investigations showed a white cell count (WCC) of $10.64 \times 10^9/L$ with neutrophils of $7.71 \times 10^9/L$, haemoglobin of 11.9 g/dL, creatinine of 46 $\mu\text{mol/L}$, C-Reactive Protein (CRP) of 32.4 mg/L, B-natriuretic peptide of 2867 pg/mL and no acute troponin rise from 11 to 7 ng/L. Serum electrolytes were within normal limits.

In the context of these findings, the patient was admitted to hospital and started on intravenous Co-Amoxiclav and Clarithromycin to treat a suspected pneumonia. On day two of admission, the patient complained of worsening SOB and pleuritic chest pain. A D-dimer was taken which was found to be 1373 ng/mL. Subsequently, a computerized tomography pulmonary angiogram (CTPA) was performed. This showed a well-defined area of ground glass opacification in the right lower lung zone, small bilateral pleural effusions and cardiomegaly which all demonstrate signs consistent with pulmonary oedema secondary to congestive heart failure (**Figure 2**). A transthoracic echocardiogram was then performed which revealed acute mitral regurgitation (MR) secondary to anterior mitral valve prolapse. In order to better visualise the anatomy, a transoesophageal echocardiogram (TOE)

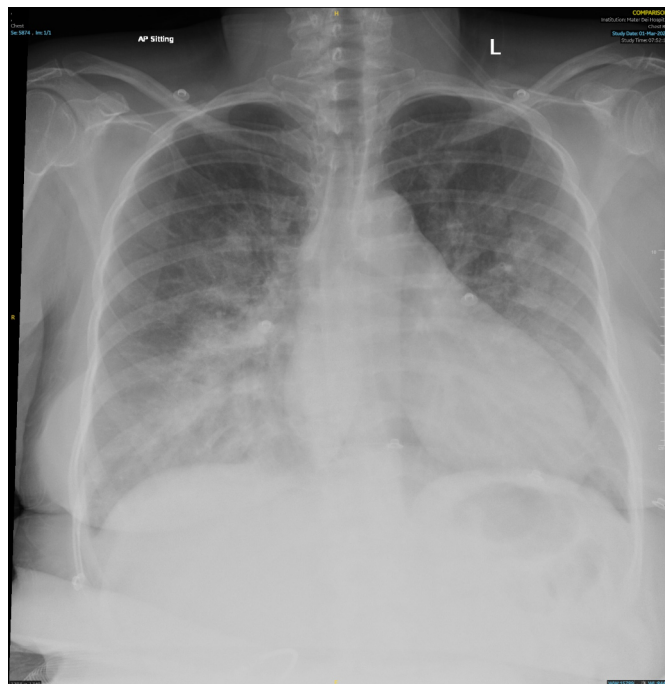


Figure 1 An anteroposterior chest X-ray taken on admission showing bilateral airspace shadowing more prominent on the right

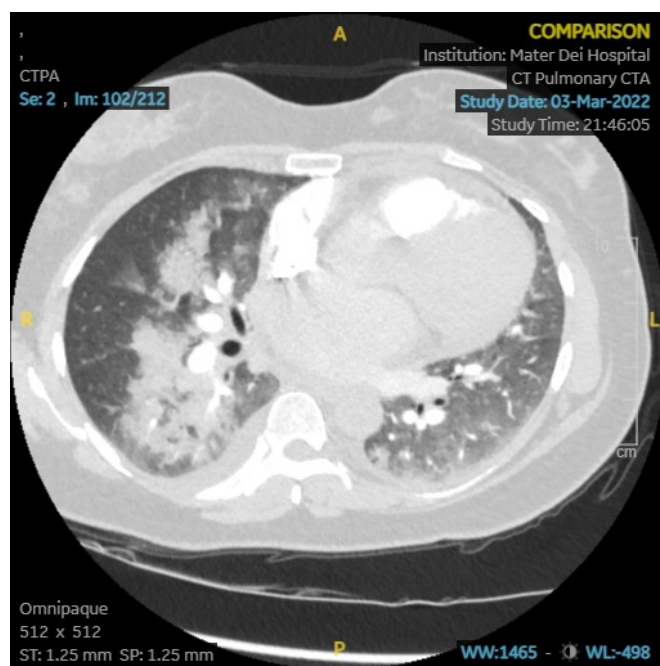


Figure 2 An axial view of a CTPA showing well-defined area of ground glass opacification in the right lower lung, interlobular septal thickening and bronchovascular bundle thickening. All signs are consistent with pulmonary oedema secondary to congestive heart failure.

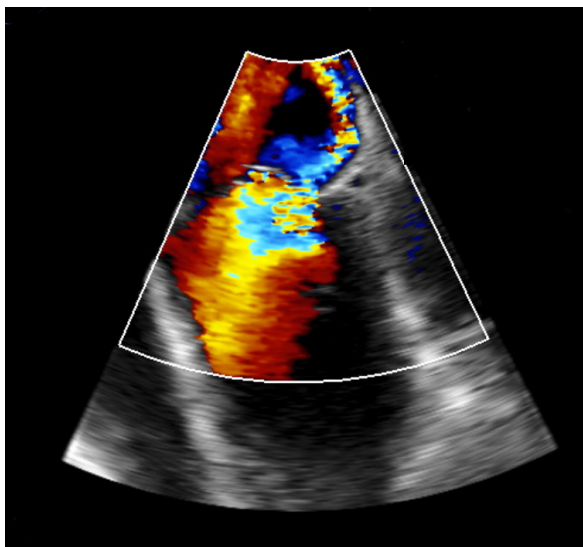


Figure 3 A still image from the TOE showing regurgitant blood flowing into the left atrium secondary to a posteriorly-directed MR jet

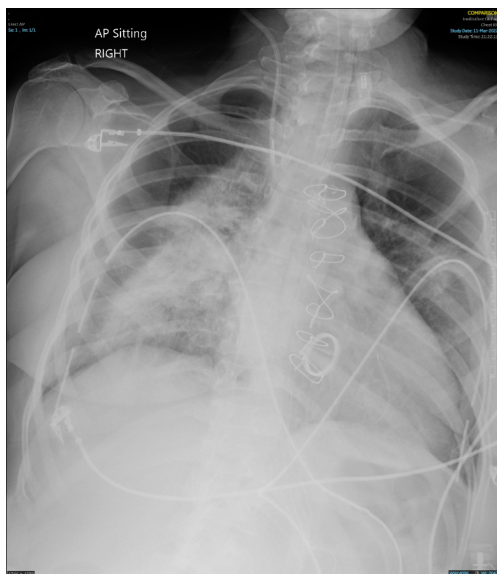


Figure 4 An anteroposterior chest X-ray post mechanical MV replacement showing midline sternotomy wires and clear demarcation of a right sided UPE

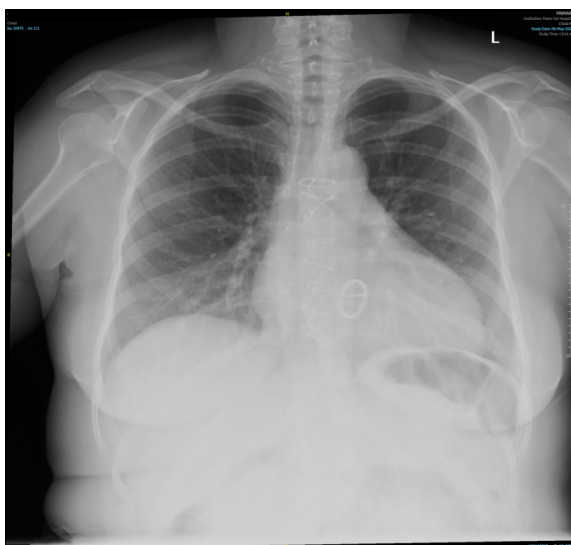


Figure 5 A six-week follow-up anteroposterior chest X-ray showing complete resolution of right sided pulmonary oedema, mechanical MV replacement and midline sternotomy wires

was done. This showed a mildly dilated left ventricle with good systolic function and a normal sized right ventricle with good function. It also confirmed the presence of a flail and prolapsing A2 leaflet of the mitral valve with a posteriorly-directed MR jet (Figure 3). This resulted in systolic flow reversal in the pulmonary veins which is consistent with severe MR (grade of $\geq 3/4$). There were no vegetations visible on the cardiac valves.

In light of these findings, the patient underwent an urgent mitral valve (MV) replacement. Adjustments to the patient's medical treatment were done and repeat chest X-rays post-operatively showed improving right-sided lower lobe pulmonary oedema (Figure 4, Figure 5).

DISCUSSION

Literature to date has shown that UPE is strongly associated with severe organic or functional mitral valve regurgitation. Due to its rarity and atypical clinical presentation, UPE is often misdiagnosed, resulting in an independent increased risk of mortality due to the delay in treatment.

Our patient presented with typical clinical features of heart failure and pulmonary oedema. Initial findings on chest X-ray showed a radiological pattern in keeping with bilateral opacification, which was more prominent in the right middle lung zone. Pneumonia is one of the differentials for these X-ray findings. However, as demonstrated in other articles, the unilateral radiological findings could have been secondary to the regurgitant MV jet or the anatomical drainage and position of the pulmonary veins.¹

Other reports frequently documented leucocytosis as being a common finding in patients with UPE secondary to severe MR.^{1,2} This is echoed in our case as our patient had a leucocytosis in the absence of fever and with negative blood cultures. In fact, there was no significant clinical improvement with antibiotic therapy.

An observational study by Attias et al, highlights the importance of taking into account the clinical course along with the patient's physical condition when making the correct diagnosis.¹ A comprehensive assessment including adequate history taking, clinical examination, appropriate use of laboratory investigations and conventional radiological imaging is key to diagnosing UPE. Storto et al suggest that CT imaging is not necessary to diagnose UPE but is useful to recognise the radiological pattern of increased hydrostatic pulmonary congestion.³

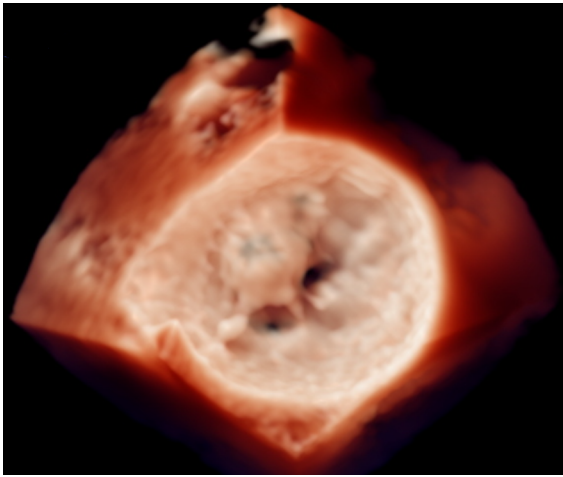


Figure 6 A 3-dimensional reconstruction of the TOE images showing papillary chordal rupture as seen from the left atrium

Given the difficulty in detecting MR on clinical examination, especially in patients presenting with acute SOB, bedside transthoracic echocardiographic examination remains an important tool in the diagnosis of UPE. In this case, an echocardiogram showed thickening of the anterior leaflet at the site of chordal rupture. TOE showed a flail and prolapsing A2 anterior leaflet of the mitral valve with a posteriorly-directed MR jet. The direction of the regurgitating jet is positioned in such a way so as to cause an asymmetric systolic flow reversal, whereby the mean pulmonary capillary pressures are higher in the right middle lung lobe leading to UPE.

As a consequence, the patient was investigated for an organic cause of MR, possibly resulting from rheumatic fever or infective endocarditis. With regards to the latter, no vegetations were visible on the cardiac valves and blood cultures were negative. Ischemic MR was excluded since troponin levels, ECG findings and relatively normal left ventricular dimensions on echocardiography were not consistent with dilated cardiomyopathy or with coronary artery disease. Moreover, a 3-dimensional reconstruction of the TOE images from the left atrium showed a papillary chordal rupture (Figure 6). Having previously been diagnosed with undifferentiated

chronic mixed connective tissue disease and Raynaud’s disease, the cause in our case points towards organic rather than functional MR.

CONCLUSION

UPE is an uncommon condition which typically manifests as an opacity in the right lung caused by severe mitral valve regurgitation. The direction of the regurgitating jet is positioned in such a way so as to cause an asymmetric systolic flow reversal, with a predilection to the right pulmonary veins. An abnormal increase in hydrostatic pressure in the pulmonary circulation causes fluid to accumulate in the extravascular compartment of the lung parenchyma resulting in pulmonary congestion and oedema.

An important take home message from this case is that UPE should be considered to be one of the differentials when radiological imaging is consistent with unilateral opacification. Maintaining a high index of suspicion is crucial in making the correct diagnosis since early detection and treatment of UPE significantly decreases the risk of mortality with good patient outcome.

ABBREVIATIONS

UPE	Unilateral pulmonary oedema
LRTI	Lower respiratory tract infection
SOB	Shortness of breath
PND	Paroxysmal nocturnal dyspnoea
WCC	White cell count
CRP	C-Reactive protein
CTPA	computerized tomography pulmonary angiogram
MR	Mitral regurgitation
TOE	Transoesophageal echocardiogram
MV	Mitral valve

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CASE REPORT

Serial Ultrasound-guided Stellate Ganglion Block using Bupivacaine, Dexamethasone, and Methylcobalamin to Treat Complex Regional Pain Syndrome type II

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Background

Stellate ganglion block (SGB) has been widely used as a therapeutic approach for refractory complex regional pain syndrome (CRPS), but clinical outcome varies, long-term pain-relieving effect is unknown, and most studies employed local anesthesia per se. We would like to address if the combination of bupivacaine (Bupi), dexamethasone (Dex), and methylcobalamin (MeCbl) can provide a clinically meaningful reduction of pain intensity and quality, as well as improving patient's sleep and functional qualities in a sustainable fashion.

Case presentation

We performed a monthly serial SGB to a painful CRPS type II patient using Bupi and Dex in the first 2 months, then added MeCbl into the regimen until the fifth month onward. We measured weekly baseline pain intensity using baseline and evoked NRS, pain quality and affective using McGill Short-Form Questionnaire (SF-MPQ), sleep quality using Pittsburgh Sleep Quality Index (PSQI), and functional activities using Pain Disability Index (PDI) questionnaire during pre-procedure until the end of the fourth week post procedure. All spectra of pain assessments were also compared between pre- and post-addition of MeCbl and tested using independent t test analysis. Repeated SGBs were safely performed in the absence of significant adverse effects. A dramatic reduction of all spectra of pain measurements, comprising baseline (-62.5%), evoked (-60%) NRS, SF-MPQ (-39.4%), PSQI (-53.3%), and PDI (-56.9%) was observed immediately after procedure. The addition of MeCbl was able to further reduce the baseline (mean reduction 1.38 [-12.5%]; 95% CI 0.53 – 2.22; $p=0.003$), evoked (mean reduction 1.17 [-20%]; 95% CI -0.16 – 2.50; $p=0.048$) NRS, SF-MPQ (mean reduction 3.38 [-24.2%]; 95% CI 0.70 – 6.05; $p=0.016$), PSQI (mean reduction 1.29 [-13.4%]; 95% CI -0.22 – 2.8; 0.089), and PDI (mean reduction 9.75 [-26.2%]; 6.96 – 12.54; $p<0.0001$), compared to the first week of first injection. Clinical improvements were stable and sustainable until the end of observation period.

Conclusions

Monthly serial US-guided SGB with Bupi, Dex, and MeCbl were proven to be safe, clinically effective, and sustainable to ameliorate baseline and evoked pain intensity and quality, as well as improving sleep quality and functional activities of a subject with CRPS type II.

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Complex regional pain syndrome (CRPS) is defined as a syndrome of chronic severe pain, motor, sensory, autonomic, and trophic disturbances. International Association for the Study of Pain (IASP) classifies CRPS into two types, type I when there is a trivial or limb injury remote to the affected symptom areas, while type II (also known as causalgia) when there is an overt injury to specific major nerves or branches preceding the symptoms onset.¹ While conservative treatments comprising pharmacological therapy, physical rehabilitation, and occupational therapy remain the first line treatment of CRPS, some patients may not respond well and experience persistent debilitating pain which impairs their sleep and functional quality in general.² Stellate ganglion blockade (SGB) can be offered as an alternative procedure in the treatment of CRPS, particularly in those with refractory cases. The underlying mechanism of action is through inhibition of both pre- and post-ganglionic sympathetic nerves, given that sympathetic nervous system (SNS) overactivity may have a role in CRPS.³ However, SGB outcome varies, and long-term prognosis is unclear, which may be partially explained by the use of local anesthetic injection alone in most studies. We therefore wanted to explore the potential addition of dexamethasone and methylcobalamin as an adjuvant for ultrasound (US)-guided SGB in CRPS type II case. The addition of dexamethasone was to prolong the effect of the local anesthetic agent and we postulated a negative effect on aberrant sympathetic activity.⁴⁻⁷ Whereas methylcobalamin is an active form of vitamin B12 with well-established evidence of its ameliorating capacity toward various types of neuropathic pain under high therapeutic index, according to multiple observational and clinical studies.⁸⁻¹⁰

CASE PRESENTATION

A 37-year-old male patient presented to the pain clinic, complaining of constant pain in his right arm, wrist, and hand in the past 15 years. At the time of onset, he had been involved in a traffic accident in which he had sustained closed fractures (proximal humerus, radius, and ulnar) and a total right-sided brachial plexus palsy. The patient underwent multiple open reduction and internal fixations of the fractured bones before the fixing plates were removed 9 years later, along with gracilis muscle and intercostal nerve transfer to treat the brachial plexus palsy. Following the last surgery, motor strength began to recover by which he was able to abduct, adduct, flex, extend, pronate, and supinate the proximal arm muscles to a greater extent than the

forearm, wrist, and hand muscles. In addition, he also regained partial sensation to coarse touch, pressure, vibration, and proprioception more significantly at the upper than his lower arm.

Pain was felt consistently following the accident. Initially he felt aching and cramping at his arm, but after several weeks post-surgery, severe pain subsided and pain quality was described as lancinating, burning, cramping, and numbness in the affected area. The pain was felt continuously and he experienced allodynia (it got worse by touch or skin exposure to clothing or cold air or water). He also complained that the pain increased with exercise/exertion. Pain intensity was equally reported on the right arm, forearm, wrist, and hand, both anterior and posterior.

On physical examination, motor strength was reduced (MRC grade 3, 3, 4-, 4 on the hand, wrist, forearm, and arm flexion and extension, respectively), accompanied significant muscle atrophy and slightly increased tone. The patient held his limb in a shoulder and arm guarding position with flexion contracture. Sensation was impaired to fine touch, vibration, temperature, and proprioception in the whole right arm. Allodynia, hyperalgesia, and paresthesia were all present in the affected region. Baseline and evoke pain NRS were 8/10 and 10/10, respectively and Short-Form McGill Pain Questionnaire (SF-MPQ) score was 33/45. Pain was identified as affecting sleep and impair daily activities with global Pittsburgh Sleep Quality Index (PSQI) and Pain Disability Index (PDI) scores of 15/21 and 65/70, respectively. We diagnosed patient with CRPS type II according to 1994 IASP CRPS diagnostic criteria.¹

The patient underwent right SGB under US guidance in semi-lateral decubitus positioning. A linear ultrasound probe of 4-13 MHz was used to identify key anatomical landmarks including the C6 cervical nerve root (bounded by the more prominent anterior [Chassaignac] tubercle), longus colli (LC) muscle, longus capitis (Lc) muscle, prevertebral fascia, carotid artery (CA), and internal jugular vein (JV). The area was then scanned caudally to identify the C7 level with its prominent posterior tubercle and vestigial anterior tubercle along with the presence of the vertebral artery in the vicinity. The primary target for SGB was the prevertebral fascia located superior to LC, lateral to CA. A lateral, posterior-to-anterior, transverse approach was used. A 3.5 inch 25-G spinal needle was introduced in-plane to the probe under constant ultrasound monitoring and aseptic procedure.¹¹ Color flow doppler was activated to

avoid any accidental blood vessel punctures. Upon reaching the target, 2 mL of normal saline was injected for hydrolocation. Upon target confirmation and 3 mL of 0.5% bupivacaine HCl, 10 mg (2 mL) of dexamethasone were administered consecutively (Figure 1). The procedure was repeated monthly for 5 consecutive months, and from the third injection onward, 500 µg (1 mL) of methylcobalamin were also administered. During each procedure, a successful SGB was determined objectively by the presence of Horner's syndrome and increased cutaneous arm temperature immediately after the procedure, that the patient reported as lasting for up to 36 hours post injection (Figure 2).

Subjectively, the patient reported marked reduction of hyperalgesia and allodynia intensity from the first injection, lasting about 3-4 weeks, as well as improved quality and duration of sleep, and increased functional and social activities afterward. Measurable reductions of pain intensity and quality, and significant improvements in sleep quality and functional activities were noted by baseline (-62.5%) and evoked (-60%) NRS, SF-MPQ (-39.4%), PSQI (-53.3%), and PDI (-56.9%) (Figure 3). The addition of methylcobalamin from the third injection procedure onward led to further improvements baseline (-12.5%) and evoked (-20%) NRS, SF-MPQ (-24.2%), PSQI (-13.4%), and PDI (-26.2%). We compared all rating scale values weekly between pre- and post-addition of methylcobalamin (i.e. week 0 of first injection to week 8 vs. week 9 post-third injection to week 20) and obtained a modest-but-significant mean reduction of all measurements, except PSQI as displayed in Table 1.

Overall, the reduction in pain was sustained during the four-week intervals between injections. Pain quality and intensity, as well as sleep and functional quality fluctuated but values remained below baseline prior to next SGB.

DISCUSSION

Our patient was diagnosed with CRPS type II according to 1994 IASP criteria. We included this patient in our study due to several reasons. Firstly, he suffered from florid (full-blown) causalgia with severe neuropathic pain, dysesthesia, vasomotor impairments, and motor dysfunction.¹² Secondly, his baseline pain quality and intensity, as well as sleep and functional activity index were considered moderate-to-severe, consequently and thirdly, because he declined all oral or intravenous therapies through personal choice. However, he accepted to

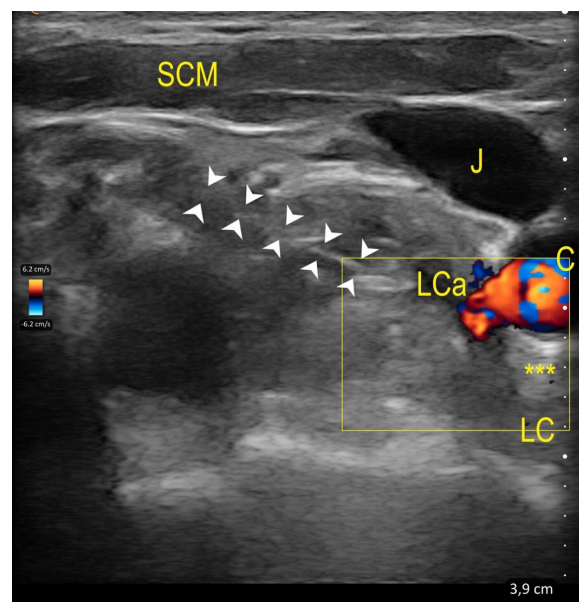


Figure 1 US-guided SGB block. A lateral, posterior-to-anterior, transverse approach was used, with needle inserted in-plane to the probe with color flow Doppler to address vasculatures and aid in hydrolocalization. C: carotid artery; J: jugular vein; SCM: sternocleidomastoid muscle; LCa: longus capitis muscle; LC: longus colli muscle; Arrowheads: penetrating needle; ***: prevertebral fascia and target for SGB.

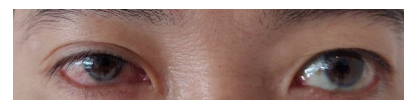


Figure 2 Horner's syndrome comprising ipsilateral ptosis, with slight enophthalmos and pupillary miosis was noted immediately after injection. Horner's syndrome is an objective sign of successful sympathetic block. Of note, conjunctival injection was observed, indicating unopposed activation of parasympathetic nervous system activity

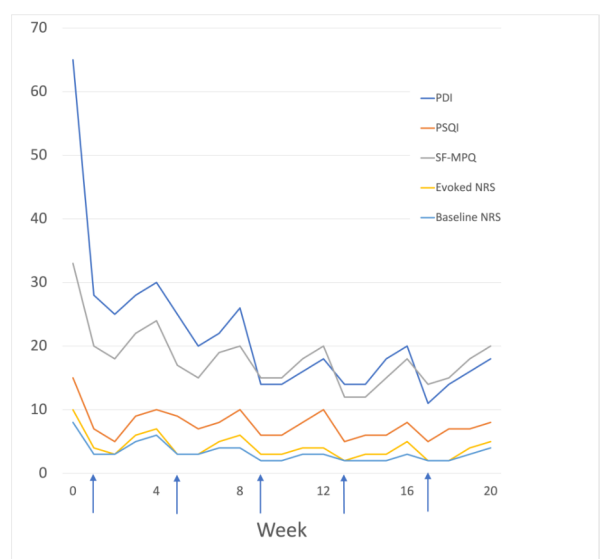


Figure 3 Pain intensity and quality, as well as sleep and functional capacity measured over time from baseline to week 20 post monthly serial injection. NRS: numerical rating scale; PDI: pain disability index; PSQI: Pittsburgh sleep quality index; SF-MPQ: the short-form McGill pain questionnaire. Arrows denote time of injection.

Table 1 Baseline and evoked NRS, SF-MPQ, PSQI, and PDI scores of pre- and post treatment group differences

Parameters		Mean $\pm$ SD	Mean reduction n	95% CI	p value*
Baseline NRS	Pre-MeCbl	3.88 $\pm$ 1.13			
	Post-MeCbl	2.50 $\pm$ 0.67	1.38	0.53 – 2.22	0.003
Evoked NRS	Pre-MeCbl	4.50 $\pm$ 1.77			
	Post-MeCbl	3.33 $\pm$ 1.07	1.17	-0.16 – 2.50	0.048
SF-MPQ	Pre-MeCbl	19.38 $\pm$ 2.83			
	Post-MeCbl	16.00 $\pm$ 2.76	3.38	0.70 – 6.05	0.016
PSQI	Pre-MeCbl	8.13 $\pm$ 1.73			
	Post-MeCbl	6.83 $\pm$ 1.47	1.29	-0.22 – 2.8	0.089
PDI	Pre-MeCbl	25.50 $\pm$ 3.30			
	Post-MeCbl	15.75 $\pm$ 2.63	9.75	6.96 – 12.54	<0.0001

*p value significant at <0.05; mean difference significance was computed with independent t test using SPSS version 23.0.

undergo SGB. We initially consider the sole administration of bupivacaine, but decided to add non-particulate corticosteroid and methylcobalamin. We chose a non-particulate steroid to minimize the risk of arterial embolism. For the same reason, we opted to use ultrasound guidance to better visualize soft tissue structures in the vicinity of prevertebral fascia.

Although the effect of local anesthesia may last for approximately a week, it was postulated that SGB promotes reduced firing of nociceptive fibers of the pathological pain pathways, thus providing analgesia effect that may outlast the local anesthesia's onset of action.¹³ The addition of Dex was shown to prolong the clinical effects of bupivacaine toward suppression of aberrant sympathetic activity. In fact, a double-blind RCT involving the addition of 8 mg of dexamethasone to bupivacaine for TAP block was shown to significantly prolong the effect of anesthesia by approximately 41% compared to bupivacaine alone.¹⁴ In our patient we observed significant reductions of pain intensity and quality, and significant improvements in sleep quality and functional activities since the beginning of first injection. We suspect that the significant response may have been partially due to patient's naïve, medication-free state prior to the procedure, which primed him toward a maximized response to the medications used for SGB. The corresponding

reduction seemed to be stable and sustainable over the course of four weeks until the onset of subsequent injection.

To our best knowledge, we were the first to clinically administer methylcobalamin via SGB for CRPS type II. Its mechanism of action is pleiotropic, including enhancing nerve myelination, promoting axonal regeneration, protecting the nerve against glutamate-induced neurotoxicity, and inhibiting ectopic spontaneous discharge.^{15,16} However, its potential role in SGB is unknown, though it may potentially act as an indirect modulator and enhances nociceptive firing suppression of sympathectomy-simulated environment. Regardless, given the clinically significant favorable effects of MeCbl toward ameliorating CRPS type II's baseline and evoked pain intensity and quality, as well as improving sleep quality and functional activities, its therapeutic use can be prudently justified ad interim, preceding the discovery of its exact mechanism of action.

Even though we achieved clinically observable signs of sympathetic block via Horner's syndrome and increased cutaneous temperature, it was uncertain if total block was achieved by SGB. In addition, there has been a subclassification of CRPS, comprising 1) vasomotor-predominant, 2) neuropathic pain/dysesthesia-predominant, and 3) florid CRPS¹², by which it is still unknown if SGB will benefit to all of

these subgroups equally. However, given the account of consistent clinical improvements across multiple spectra of measurements, we prudently assume to have achieved the necessary therapeutic goal. The long-term therapeutic effects of SGB using a combination of bupivacaine, dexamethasone, and methylcobalamin, as well as dose regimen and administration interval which exert the longest and most optimal pain amelioration intensity, quality, duration, and its impact toward sleep and functional qualities, need to be addressed in a well-designed and sufficient observational period of clinical trial.

CONCLUSION

Monthly serial US-guided SGB with bupivacaine, dexamethasone, and methylcobalamin were proven to be safe, clinically effective, and sustainable to ameliorate baseline and evoked pain intensity and quality, as well as improving sleep quality and functional activities of a subject with CRPS type II.

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