

MRI of Rotator
Cuff Tendon Tears

Door-to-Imaging Time for Acute
Stroke Patients at the Emergency
Department in MDH

Basic Perceptions
of Anaesthetists Among
the General Public in Malta

Genome-Wide
Association Studies



UNITED FOR LONG-LASTING[†] LDL-C CONTROL¹

LEQVIO is administered every 6 months* and provides effective LDL-C control, supported by 6+ years of data^{1,2}

*Two doses a year after the two initial doses. Single subcutaneous injection at the start of treatment, again at 3 months, and thereafter every 6 months.¹
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inclisiran

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PRESENTATION: Leqvio 284 mg solution for injection in pre-filled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. • **Missed doses:** If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. • **Treatment transition from monoclonal antibody PCSK9 inhibitors:** Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. • **Elderly, hepatic impairment, renal impairment:** no dose adjustment is necessary. Inclisiran should be used with caution in patients

with hepatic and renal impairment. • **Paediatric population:** The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. • **Method of administration:** Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: • **Haemodialysis:** The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. • **Sodium content:** This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

PREGNANCY, LACTATION AND FERTILITY: • There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. • It is unknown whether

inclisiran is excreted in human milk. A risk to newborns/ infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. • No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: Common: Adverse reactions at the injection site.

LEGAL CATEGORY: POM

PACK SIZES: Pre-filled syringe: x1 pre-filled syringe. Pre-filled syringe with needle guard: x1 pre-filled syringe with needle guard.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merriem Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001-2

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

2022-MT-LEQ-24-MAR-2022

References: 1. Leqvio Summary of product characteristics. Novartis. August 2022. 2. RS Wright, FJ Raal, W Koenig, U Landmesser, LA Leiter, GG Schwartz, A Lesogor, P Maheux, Z Tallozy, S Vikarunnessa, X Zang, KK Ray. ORION-8: Long-term efficacy and safety of twice-yearly inclisiran in high cardiovascular risk patients. Data presented at the ESC Congress on August 28, 2023.



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PRODUCT NAME: Cosentyx[®] 150 mg solution for injection in pre-filled pen. **PRESENTATION:** Solution for injection in pre-filled pen. Each pre-filled pen contains 150 mg secukinumab in 1 ml. **INDICATION:** • **Adult plaque psoriasis:** Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. • **Paediatric plaque psoriasis:** Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy. • **Hidradenitis suppurativa (HS):** Cosentyx is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Psoriatic arthritis:** Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease modifying anti rheumatic drug (DMARD) therapy has been inadequate. • **Axial spondyloarthritis (axSpA):** Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. • **Non-radiographic axial spondyloarthritis (nr-axSpA):** Cosentyx is indicated for the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs). • **Juvenile idiopathic arthritis (JIA):** **Enthesitis-related arthritis (ERA):** Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active enthesitis-related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. **Juvenile psoriatic arthritis (JPsA):** Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active juvenile psoriatic arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. **DOSAGE:** • **Adult plaque psoriasis:** The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, a maintenance dose of 300mg every 2 weeks may provide additional benefit for patients with a body weight of 90kg or higher. Each 300 mg dose is given as two subcutaneous injections of 150 mg. • **Paediatric plaque psoriasis:** The recommended dose is based on body weight (refer to SmPC) and administered by subcutaneous injection. Each 75mg dose is given as one subcutaneous injection of 75mg. Each 150 mg dose is given as one subcutaneous injection of 150 mg. Each 300 mg dose is given as two subcutaneous injections of 150 mg. • The 150 mg solution for injection in pre-filled pen is not indicated for administration to paediatric patients with a weight <50 kg. The 150 mg powder for solution for injection presentation is appropriate for administration to this population. • **Hidradenitis suppurativa (HS):** The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg. • **Psoriatic arthritis:** For patients with concomitant moderate to severe plaque psoriasis, please refer to adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection. For other patients, the recommended dose is 150 mg by subcutaneous injection. Based on clinical response, the dose can be increased to 300mg. Each 300 mg dose is given as two subcutaneous injections of 150 mg. • **Axial spondyloarthritis: Ankylosing spondylitis:** The recommended dose is 150 mg by subcutaneous injection. • For all of the above, initial dosing at weeks 0, 1, 2, 3 and 4, is followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300mg. Each 300mg dose is given as two subcutaneous injections of 150mg. • **Non-radiographic axial spondyloarthritis:** the recommended dose is 150mg by subcutaneous injection with initial dosing at weeks 0,1,2,3 and 4, followed by monthly maintenance dosing. • **Juvenile idiopathic arthritis (JIA):** **Enthesitis-related arthritis (ERA)** and **juvenile psoriatic arthritis (JPsA):** The recommended dose is based on body weight (refer to SmPC) and administered by subcutaneous injection at weeks 0,1,2,3 and 4, followed by monthly maintenance dosing. • **Elderly patients:** no dose adjustment required. • **Renal/hepatic impairment:** no dose recommendation. • **Paediatric population:** the safety and efficacy of Cosentyx in children with plaque psoriasis and in the juvenile idiopathic arthritis categories of ERA and JPsA below the age of 6 years have not yet been established. The safety and efficacy of Cosentyx in children below the age of 18 years in other indications have not yet been established. No data are available. • The solution/the syringe/the pen must not be shaken. **CONTRAINDICATIONS:** • Hypersensitivity to the active substance or to any of the excipients.

• Clinically important, active infection. **WARNINGS/ PRECAUTIONS:** • **Traceability:** In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded. • **Infections:** Secukinumab has the potential to increase the risk of infections. Caution should be exercised when considering the use of secukinumab in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggest of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and secukinumab should not be administered until the infection resolves. • **Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):** Cases of new or exacerbations of inflammatory bowel disease have been reported with secukinumab (refer to SmPC). Secukinumab is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. • **Hypersensitivity:** Rare cases of anaphylactic reactions and angioedema have been observed in patients receiving secukinumab. If an anaphylactic reaction, angioedema or other serious allergic reactions occur, administration of secukinumab should be discontinued immediately and appropriate therapy initiated. • **Latex-sensitive individuals:** The removable needle cap of the Cosentyx pre-filled syringe contains a derivative of natural rubber latex. The use of Cosentyx pre-filled syringes in latex-sensitive individuals has not been studied and there is therefore a potential risk of hypersensitivity reactions which cannot be completely ruled out. • **Vaccinations:** Live vaccines should not be given concurrently with secukinumab. Prior to initiating therapy with Cosentyx, it is recommended that paediatric patients receive all age-appropriate immunisations as per current immunisation guidelines. • **Concomitant immunosuppressive therapy:** In psoriasis studies, the safety and efficacy of secukinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. Secukinumab was administered concomitantly with methotrexate (MTX), sulfasalazine and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis). Caution should be exercised when considering concomitant use of other immunosuppressants and secukinumab. • **Hepatitis B reactivation:** Hepatitis B virus reactivation can occur in patients treated with secukinumab. In accordance with clinical guidelines for immunosuppressants, testing patients for HBV infection is to be considered before initiating treatment with secukinumab. • **Women of childbearing potential:** should use an effective method of contraception during treatment and for at least 20 weeks after treatment. **Pregnancy:** As a precautionary measure, it is preferable to avoid the use of Cosentyx during pregnancy. • **Breast-feeding:** Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast feeding to the child and the benefit of therapy to the woman. • **Fertility:** The effect of secukinumab on human fertility has not been evaluated. **INTERACTIONS:** • Live vaccines should not be given concurrently with secukinumab. • In a study in subjects with plaque psoriasis, no interaction was observed between secukinumab and midazolam. No interaction was seen when secukinumab was administered concomitantly with MTX and/or corticosteroids in arthritis studies. **ADVERSE REACTIONS:** • **Very common:** Upper respiratory tract infections (17.7%) (most frequently nasopharyngitis, rhinitis) • **Common:** Oral herpes, Rhinorrhea, Diarrhoea, Headache, Nausea, Eczema, Fatigue. • For a full list of adverse reactions, please refer to the Summary of Product Characteristics. **LEGAL CATEGORY:** POM. **PACK SIZE:** Pack: 1 pre-filled pen. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Ireland. **MARKETING AUTHORISATION NUMBER:** EU/11/14/980/004. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

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To report adverse events electronically please use the following link: www.novartis.com/report or by e-mail at drug_safety.malta@novartis.com.



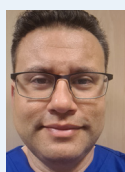
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Issue Guide

- | | |
|--|--|
| <p>06 MRI of Rotator Cuff Tendon Tears</p> <p>13 Door-to-Imaging Time for Acute Stroke Patients at the Emergency Department in MDH</p> | <p>16 Basic Perceptions of Anaesthetists Among the General Public in Malta</p> <p>21 Genome-Wide Association Studies</p> |
|--|--|

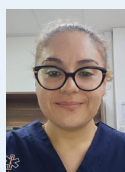
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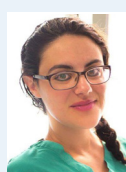
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Cover: Anaesthesia and Intensive Care requires anaesthesiologists to be both highly knowledgeable and technically skilled while utilising increasingly sophisticated equipment. This allows the provision of optimal care to patients of all ages, including the critically ill.

PUBLISHED SINCE OCTOBER 1996

A Letter to my Children

A yellow brick road to adulthood and parenthood. This is what I wish for both of you. Naturally, I wish the same to all your friends. Will this happen? No. However, can we seriously plan such a path for your children? I am optimistic about this.

In their earliest years, your children will start tracing their formamensis on those persons they spend the most time with, which I hope will be you. As they grow older this is replaced to varying degrees by friends, school, and exposure to society's fabric. So, my advice is to carefully gauge your opportunity costs and spend quality time with your children. From experience, I would rather see you take a step back from opportunities that, because there is little or no genuine support, entail having the Sword of Damocles permanently hanging over your head.

You will also soon discover that life can present checkpoints which add sobriety to your soul like salt to a wound. The recent Health Behaviour in School-aged Children (HBSC) study¹ clearly shows that from a surveyed cohort of countries, Maltese 11-year-old girls have the 2nd highest problematic social media use alongside Romania (18%, average for girls 9%) whilst Maltese 13-year-old girls top the chart alongside Romania (28%, average for girls 16%). In keeping with this, the greatest proportion of adolescents, classified at risk of problematic online gaming, is found in Malta for 11-year-old girls (16%, average for girls 10%) 13-year-old girls (14%, average for girls 8%), 13-year-old boys (26%, average for boys 18%), and 15-year-old boys (27%, average for boys 16%).

I know that you feel me since I struggle with both of you about screen time. Knowing that this is a common problem for other parents does not offer me any solace. Given this alarming trend - since this report builds on a previous one - the government should act on this today before tomorrow.

At this stage, one must acknowledge the role that politics plays in your cognitive development. Children are directly affected by seminal decisions - which relate to the social determinants of health - made by policymakers. So, experiencing free childcare schemes, walking past a newly opened Cannabis Harm Reduction Association 251 metres from your school, as well as having your friend become your town's mayor at age 16, can all seriously affect your life's trajectory.

I am explaining all this so that you understand the importance of the policymaker's role in mitigating your risk, as well as that of your peers, of problematic social media use and online gaming. The negative impact of social media on mental health is well-known and ranges from addictions to cyberbullying. Of note is that Australia has recently introduced legislation requiring technology companies to restrict individuals under 16 years of age from accessing their social media platforms.

Malta needs to establish a task force, possibly through the Responsible Gaming Foundation, with members of the quadruple helix to investigate further the effect of social media use on Maltese adolescents and to develop healthy and safe social media and digital gaming habits. In keeping with this, our EU representatives need to lobby for a European action plan in this regard.

My dearest possessions, I will conclude this editorial with the following advice. We are in Christmas time where many people wear smiling faces. In life, you will meet many pernicious characters who, with their yearlong Duchenne smiles, will try to compromise your righteous nature. This primarily stems from the fact that your benevolent actions, done in good faith, are the antithesis of their *raison d'être*. Of course, along the way, you will also find genuine persons who will acknowledge your efforts and support you. That is why you need to be optimistic and realise that you are your greatest strength. To do so you need to seek the company of each other. As siblings, you can help each other to champion those ubuntu values, including social justice, which I observe in you.

Stand up and be counted. Be accountable. Never compromise your honesty, even if this means facing a Semmelweis reflex.

Be resilient and keep moving, forward. Focus on life's tapestry and not on dropped stitches. The future is bright.



1. World Health Organization. A focus on adolescent social media use and gaming in Europe, central Asia and Canada Health Behaviour in School-aged Children international report from the 2021/2022 survey. Volume 6. 2024. Available from: <https://iris.who.int/bitstream/handle/10665/378982/9789289061322-eng.pdf?sequence=2&isAllowed=y>

DA VINCI
HEALTH

MRI of Rotator Cuff Tendon Tears – An Introduction

Part 1: Imaging Protocols and Relevant Anatomy

ABSTRACT

Rotator cuff tendon tears are a common reason to refer a patient for shoulder MR imaging.

The role of the radiologist, in addition to diagnosing the presence or otherwise of an actual tear and assessing the surrounding soft tissue and skeletal structures, is to convey diagnostically and prognostically useful information that helps referring clinicians devise optimal management plans for their patients.

Part 1 discusses how MR imaging of the shoulder is performed, in addition to relevant MR rotator cuff tendon anatomy, whereas part 2 (to be published in the next issue) will describe rotator cuff tendon tears in detail.

KEYWORDS

Shoulder, Magnetic resonance imaging (MRI), Radiology, Rotator cuff, Tendon

INTRODUCTION¹

Shoulder pain and discomfort is a musculoskeletal complaint that doctors and other allied health professionals encounter on a regular basis, only lagging behind lower back and neck pain.

Rotator cuff tears (RCTs) are amongst the commonest causes of shoulder pain in patients over 40 years of age.

A significant proportion (20-50%) of individuals aged 50 years or older have a known RCT, getting more frequent with increasing age, with at least 50% of individuals older than 70 years having an underlying, asymptomatic RCT.²

An intact rotator cuff is an important dynamic stabilizer of the glenohumeral joint, compressing the humeral head against the glenoid cavity, thereby increasing joint stability, as well as providing a stable fulcrum for the deltoid to elevate the arm.

Magnetic resonance imaging (MRI) is very useful in diagnosing shoulder pathology, furthermore, it has played an increasingly important role as a noninvasive test for determining which patients may benefit from surgery.³⁻⁶

Whilst MRI and ultrasound (US) have demonstrated similar sensitivity and specificity for evaluation of the native rotator cuff musculotendinous complex, MRI offers the advantage of allowing optimal structural evaluation of the bone marrow, tendons, muscles, ligaments, capsules, bursae, and labrum, and in any plane desirable.

Most indications for shoulder MRI, including rotator cuff integrity, do not require the administration of intravenous or intra-articular contrast medium.

MRI TECHNIQUE AND PROTOCOLS^{7,8}

The patient is placed in the supine position, with their affected arm by the side, with the shoulder slightly externally rotated. Internal rotation should be avoided as much as possible, in order to optimally evaluate the supraspinatus and subscapularis tendons, as well as the middle glenohumeral ligament.

Excessive external rotation is also undesirable given that this may give rise to false positive diagnoses of small supraspinatus insertional tendon tears anteriorly.

Multiplanar imaging is then acquired in the axial, coronal oblique and sagittal oblique planes.

Coronal oblique imaging is planned parallel to the scapular body or to the supraspinatus tendon, and is to include the entire humeral head.

Sagittal oblique sequences should extend from the lateral aspect of the deltoid muscle, all the way medially to the scapular body.

Axial sequences should extend from above the acromioclavicular joint to below the level of the axillary pouch.

Angled oblique sagittal sequences have also been described in the radiology literature to provide additional diagnostic value, especially in relation to small supraspinatus insertional tendon tears.⁹

Slice thickness should not be more than 3 mm. The sequences utilized usually include a combination of intermediate-weighted (fat-suppressed, fluid-sensitive), T1-weighted and T2-weighted sequences.

IMPORTANT ANATOMY^{7,10}

The rotator cuff is a composite of a capsule, ligaments and tendons, histologically consisting of five different layers that fuse together (Fig. 1, a-d), the latter feature contributing to the lamellated appearance appreciated on MR imaging.

The most important of these layers are II and III; layer II is formed by tightly packed tendon fibers arranged in large bundles, whereas layer III consists of thinner, smaller, more disorganized collagen bundles. Layer II fibers are elastic, more resistant to rupture and are well vascularized, whereas layer III fibers are more prone to injury, being inelastic and poorly vascularized.

The histological differences between layers 2 and 3 can potentially explain the origin of partial and delaminating tear patterns.

The histology of the rotator cuff contributes to one of the difficulties of rotator cuff MRI interpretation - the magic-angle effect, or angular anisotropy.^{11,12}

This MRI artifact occurs when normally low-signal structures that are made of organized collagen fibers appear with higher signal intensity on images obtained

with a short echo time (TE). This occurs when the long axes of collagen fibers are oriented at 55° to the main magnetic field, and this tends to affect the rotator cuff tendons at the commonest sites of tears and tendinopathy. It is for this reason that radiologists opt to assess the rotator cuff tendons on long TE sequences (intermediate/T2-weighted).

The *rotator cable*^{13,14} (fig. 2) is a deeper, capsular reinforcement noted along the inferior aspect of the supraspinatus and infraspinatus tendons, coursing perpendicular to the long axis of the corresponding tendons. Histologically, it forms the fourth layer of the rotator cuff complex. The area lateral to it is known as the *rotator crescent*, and is the area at greatest risk of injury.

The rotator cable functionally behaves as a suspension bridge, offloading the rotator crescent fibers, also limiting retraction of any torn supraspinatus or infraspinatus fibers.

It is best appreciated on high-resolution MRI, with some researchers concluding that this yields a better visualization in MR arthrography.

The tendons of subscapularis, supraspinatus, infraspinatus and teres minor are the main components of the rotator cuff complex, along with reinforcing superficial and deep-seated capsular ligaments.¹⁵⁻¹⁷

The *supraspinatus* (fig. 3) is supplied by the suprascapular nerve, inserting predominantly onto the greater tuberosity, with a small proportion of fibers inserting into the lesser tuberosity.

Figure 1. Normal supraspinatus and infraspinatus ultrastructure.¹⁰

a - Drawing shows the different layers of the rotator cuff.

b - Rotator cuff histology.

c,d (medial to lateral) - Oblique-sagittal T1-weighted MR arthrography images.

- Layer 1 - superficial fibers of the coracohumeral ligament;
- Layer 2 - dense parallel collagen fibers from supraspinatus and infraspinatus tendons;
- Layer 3 - smaller collagen fibers of less uniform orientation;
- Layer 4 - rotator cable;
- Layer 5 - superior capsule.

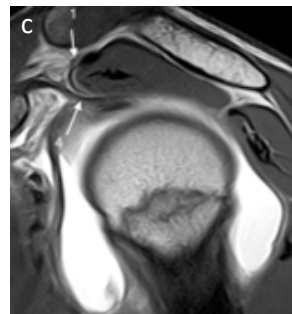
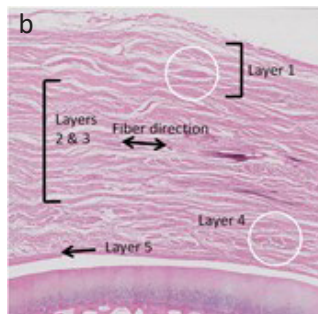
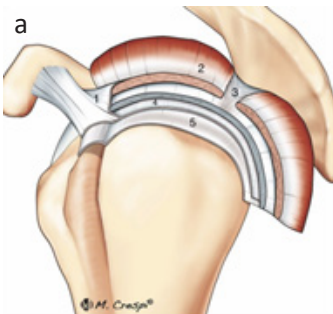


Figure 2. Rotator cable (arrows) demonstrated in the axial (a), coronal (b) and sagittal (c) planes.

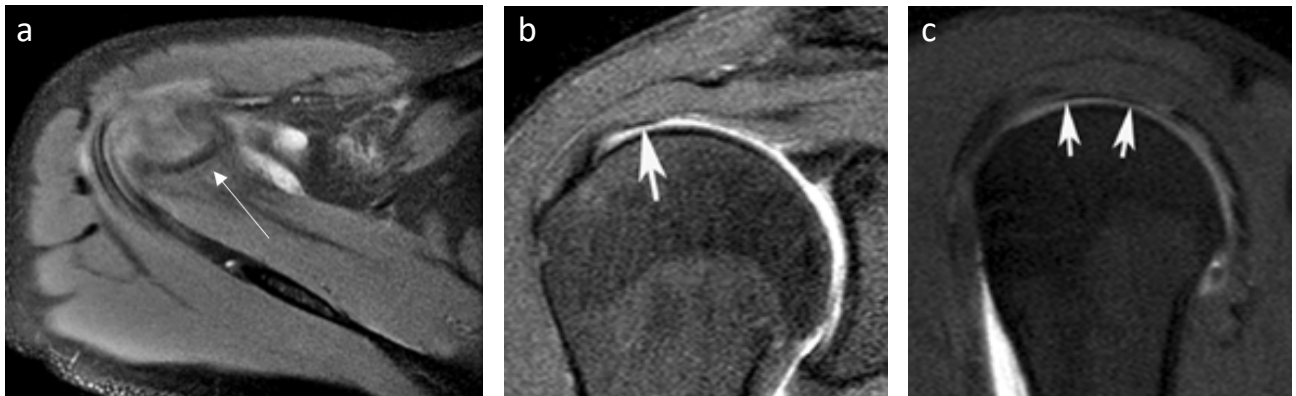
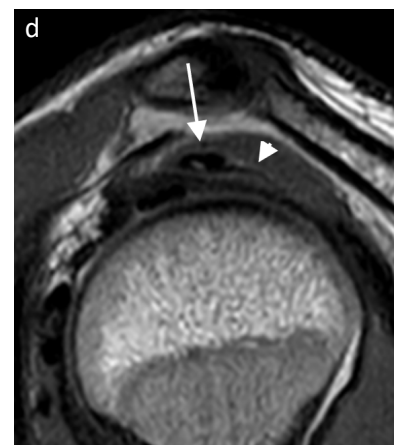
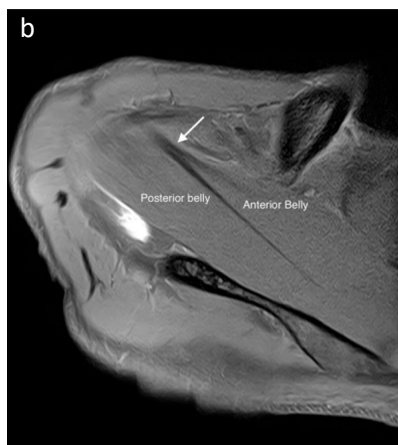
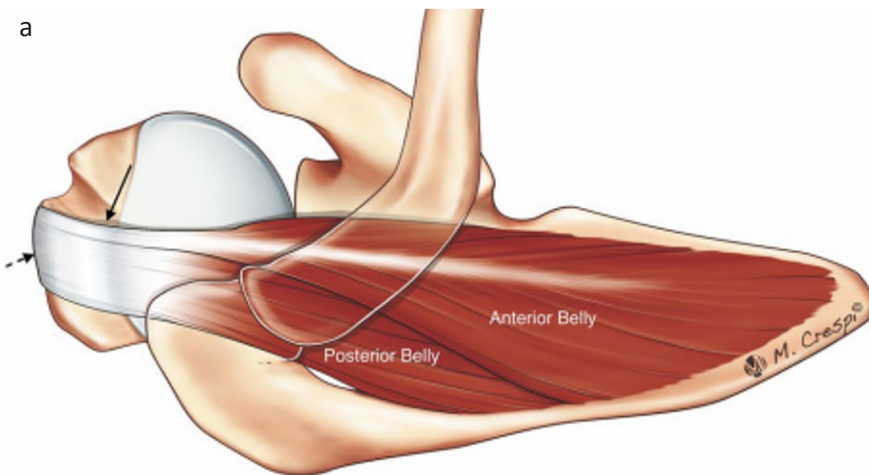


Figure 3. The supraspinatus components.^{10,11}

a - Drawing showing the bellies and tendons of supraspinatus.

b,c - Axial fat-suppressed proton density-weighted MRI showing the anterior belly with its long tendon and insertion (arrows) and the posterior belly with a broader tendon (dashed arrows).

d - Sagittal oblique proton density-weighted MRI showing the narrow anterior tendon (white arrow) and thinner but broader posterior tendon (arrowhead).



A SIGNIFICANT PROPORTION (20-50%) OF INDIVIDUALS AGED 50 YEARS OR OLDER HAVE A KNOWN RCT, GETTING MORE FREQUENT WITH INCREASING AGE, WITH AT LEAST 50% OF INDIVIDUALS OLDER THAN 70 YEARS HAVING AN UNDERLYING, ASYMPTOMATIC RCT

Figure 4. Coronal oblique (a) and axial (b) Fat-suppressed proton density fast spin-echo weighted MR images showing the broad insertion of the infraspinatus tendon (arrows) onto the superior and middle facets of the greater tuberosity.



Figure 5. Subscapularis anatomy.

a - Four distinct facets of the subscapularis insertion, displayed on an anatomical specimen;¹⁷

b - Multipennate nature of subscapularis (arrow) as shown on a sagittal oblique T1 weighted image;¹¹

c - Axial fat-suppressed, proton density, fast spin weighted image showing the subscapularis (SSC) attaching onto the lesser tuberosity (arrow), with contributory fibres overlying the proximal humeral intertubercular groove and to the greater tuberosity.¹¹

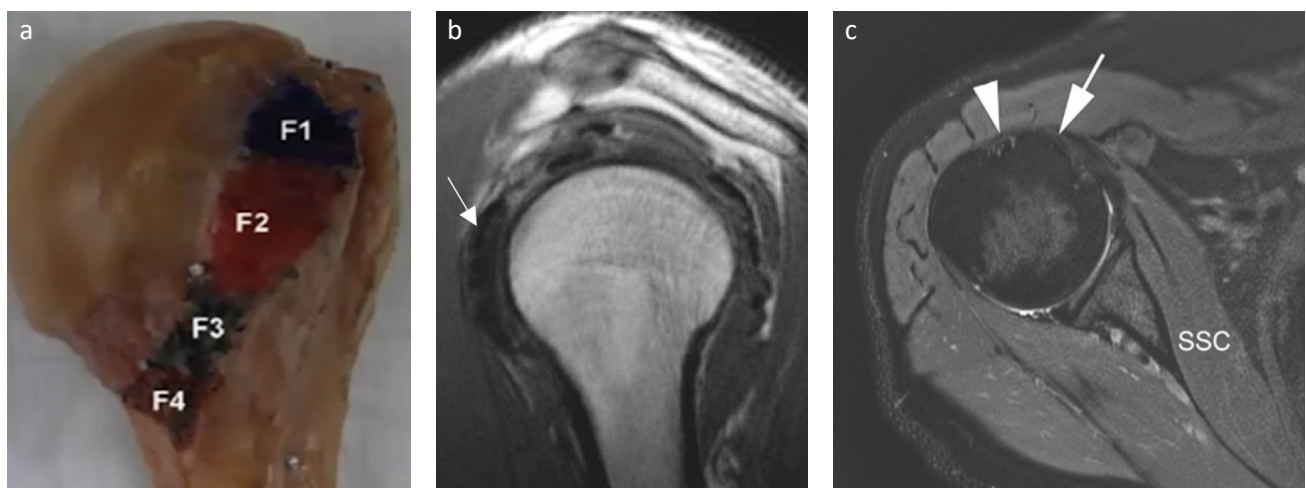
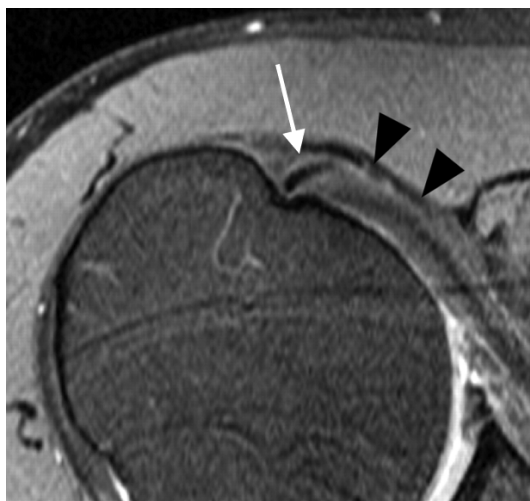


Figure 6. LHBT anatomy.

Axial proton density, fast spin image showing the uniformly hypointense proximal extra-articular LHBT (white arrow) as it lies within the upper proximal intertubercular groove. Note the close association with the subscapularis tendon (black arrowheads).



It consists of two muscle bellies (anterior and posterior), with the larger anterior belly continuing laterally into a thinner central tendon, and the strap-like posterior belly showing an associated broader terminal tendon.

This anatomical arrangement may well explain the predominance of anterior tendon failure, in view of the greater contractile forces being generated by the anterior belly.

The *infraspinatus* (fig. 4) is the primary external rotator, also innervated by the suprascapular nerve. It mainly inserts onto the middle facet of the greater tuberosity, with a smaller portion attaching onto the superior facet.

It consists of two muscle bellies (transverse and oblique), and demonstrates a larger footprint with respect to supraspinatus.

The *subscapularis* (fig. 5) is the largest and strongest rotator cuff component, consisting of multiple (between four and nine) muscle-tendon units that converge laterally. It is innervated by the upper and lower subscapular nerves, and demonstrates a very long, four-faceted insertion onto the humerus, extending downwards from the lesser tuberosity.

Its upper humeral insertion is tendinous in nature, with its lower third being muscular.

The upper fibres of the subscapularis interdigitate with the anterior fibers of the supraspinatus tendon and the rotator interval. This may explain why the subscapularis tendon tears are frequently associated with massive RCTs or rotator interval injuries.

The *teres minor* is the smallest and least injured of the rotator cuff components, classically involved in cases of posterior glenohumeral dislocation. It is innervated by a branch of the axillary nerve, and inserts onto the lowermost facet of the greater tuberosity.

The *long head of biceps tendon* (LHBT - Fig.6) is technically not part of the rotator cuff complex - nevertheless, given its close association by virtue of its origin and course, it is not uncommonly affected whenever there is an underlying RCT.¹⁸

Characteristic LHBT abnormalities associated with RCTs include intra-articular disruption as well as medialisation, which may be intra- or extra-articular.

CONCLUSION

MRI nowadays is a crucial tool in the assessment of RCT tears, helping surgeons and patients make important decisions regarding management. It is therefore imperative that the clinician reviewing the study is familiar with study planning and potential pitfalls, as well as with the underlying multiplanar anatomy.

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Door-to-Imaging Time for Acute Stroke Patients at the Emergency Department in Mater Dei Hospital

ABSTRACT

Acute stroke requires timely intervention, with guidelines recommending CT imaging within 20 minutes of Emergency Department (ED) arrival. This audit assessed the door-to-CT times for acute stroke patients from January to June 2022. Data from hospital systems showed a mean time of 1 hour and 5 minutes, with only 4.4% meeting the 20-minute target. Delays were attributed to factors like incorrect triage and ED overcrowding. This audit concludes that our ED practice does not meet international standards, necessitating further audits to identify and address these delays to improve stroke patient care.

KEYWORDS

Stroke, Door-to-imaging time, Emergency

INTRODUCTION

Stroke is a leading cause of death and long-term morbidity worldwide. Timely intervention in acute ischemic stroke is critical, with local guidelines calling for intravenous administration of recombinant tissue-type plasminogen activator (rtPA) within 4.5 hours of symptom onset.

Imaging plays a critical role in evaluating patients presenting with symptoms of an acute stroke, prior to treatment initiation. Owing to its speed, accurate depiction of acute intracranial disease, and availability, CT stroke protocol is the first-line imaging modality used in the emergency setting to rapidly diagnose and quantify patients presenting with probable ischemic strokes and to enable appropriate urgent management.^{1,2}

Local guidelines dictate that an immediate CT Stroke protocol ('immediate' is interpreted to mean that this should be done immediately upon patient presentation), consisting of a CT Brain and CT Angiography (CTA), for patients presenting within 6 hours of symptom onset is required.

The current NICE Pathway for acute stroke states that immediate brain imaging should be performed for patients presenting with acute strokes fulfilling any one

of the following criteria: (i) candidates for thrombolysis or early anticoagulation treatment; (ii) on anticoagulant treatment; (iii) a known bleeding tendency; (iv) a depressed level of consciousness (Glasgow Coma Score (GCS) <13); (v) unexplained progressive or fluctuating symptoms; (vi) papilloedema, neck stiffness or fever; (vii) severe headache at onset of stroke symptoms. The term immediate, with regards to brain imaging, is defined as ideally the next slot but definitely within 1 hour, whichever is sooner. For all patients presenting with acute stroke not fulfilling the above criteria, scanning should be performed as soon as possible and within a maximum of 24 hours from the onset of symptoms.³

Of note is the UK's NHS National Stroke Service Model guidance which further narrows down the recommendation i.e. an optimal stroke imaging pathway should have stroke imaging, interpretation and transfer decisions within 20 minutes of the patient's arrival to the ED.⁴

The revised American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend that all patients admitted to hospital with suspected acute stroke should receive brain imaging evaluation on arrival to hospital. Patients who may be candidates for thrombolysis or thrombectomy should also have a brain imaging performed within 20 minutes of arrival in the ED.⁵

AIM

The aims are twofold:

- To calculate the time elapsed between patient registration at the ED and performance of brain CT (door-to-CT time).
- To evaluate whether the 20-minute target was met, as recommended by both the AHA/ASA and the UK's NHS Improvement National Stroke Service Model.

METHOD

This is a retrospective analysis of patients presenting to the ED with symptoms of acute stroke, who fulfilled the criteria for a CT Stroke, between the period of January to June 2022.



The inclusion criteria were that patients had to be above the age of 16 years and presented with acute stroke symptoms, with any one of the following conditions:

- i. indications for thrombolysis or early anticoagulation treatment
- ii. currently on anticoagulant treatment
- iii. known bleeding tendency
- iv. depressed level of consciousness (GCS <13)
- v. unexplained progressive or fluctuating symptoms
- iv. presence of papilloedema, neck stiffness, or fever
- vii. severe headache at onset of stroke symptoms.

Data collection involved filtering through the Picture Archiving and Communication System (PACS) and reviewing CT Strokes ordered from the ED to gather patient information. Subsequently, this information was utilized to collect the registration time and Emergency Severity Index (ESI) from Clinical Patient Administration System (CPAS), as well as the time of CT Stroke performance from the iSoft Clinical Manager (iCM) programs at Mater Dei Hospital. Following the data collection, the door-to-CT time (from ED arrival to performance of CT Stroke) was calculated.

RESULTS

Overall, 137 patients had a CT Stroke performed over 6 months at the ED. 65 (47.4%) were female while 72

(52.6%) were male. 21 (15.3%) were registered as ESI 1 (most urgent), 113 (82.5%) as ESI 2, 2 (1.5%) as ESI 3 and 1 (0.7%) patient was registered as ESI 4.

The mean door-to-CT time over the 6 months was 65 minutes whilst the median door-to-CT time was 56 minutes. The shortest door-to-CT time was 7 minutes whilst the longest was 6 hours and 59 minutes. Figure 1 illustrates the door-to-CT time for all patients.

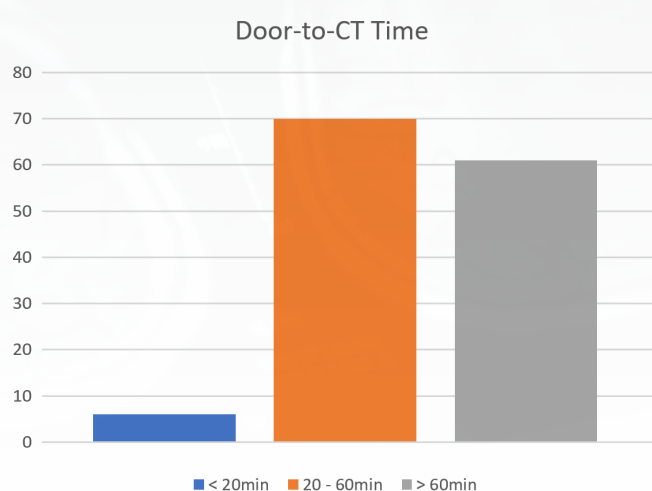
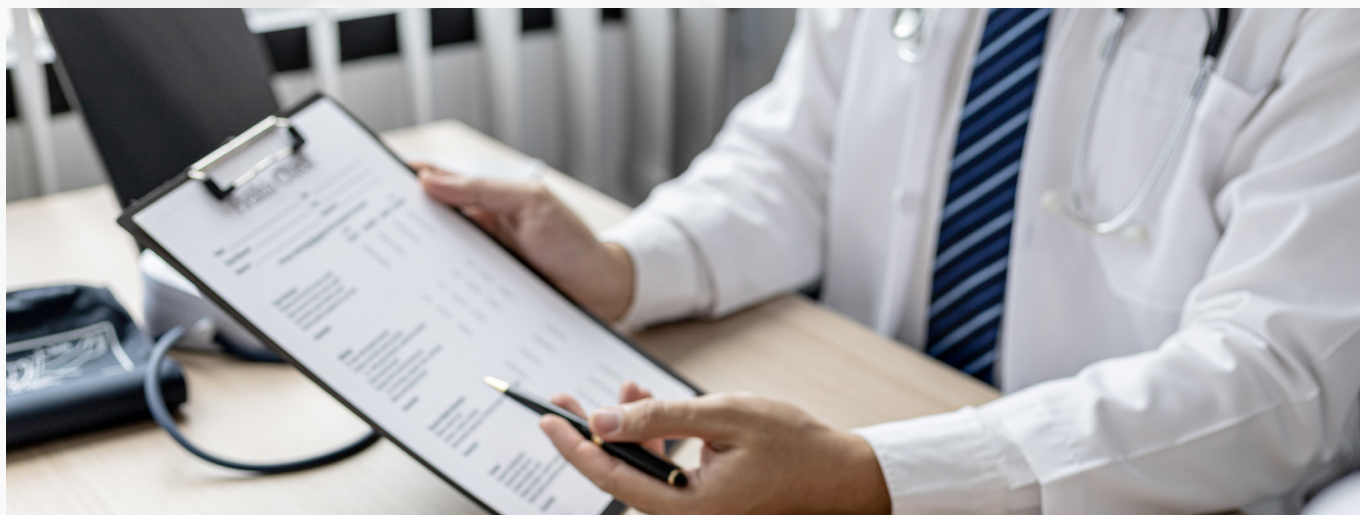


Figure 1. Only 6 patients (4.4%) had a CT performed within 20 mins, whilst 70 patients (51.1%) within 1 hour, and 61 patients (44.5%) over 1 hour.



DISCUSSION

The benefit of both thrombolysis and thrombectomy is highly time-dependent. Providing treatment within the therapeutic window improves the functional outcomes post-stroke.^{6,7}

The results obtained show that the ED at Mater Dei Hospital is currently not in-line with international guidelines. Various factors might explain such a delayed CT imaging namely: incorrect triage, ED overcrowding, uncontrolled blood pressure and fluctuating neurological deficit.^{8,9} Arriving by own transport can cause delays in the triage process. Patients must first register at the door upon arrival, after which they must wait to be triaged and identified as stroke patients before doctors are notified. Additionally, any uncertainty regarding the onset time of symptoms may lead to uncertainty of the patient's eligibility for intervention, potentially delaying the urgent CT scan.

Previous studies^{5,7,10} have shown the effect of different interventions on reducing in-hospital delay for patients with acute ischemic stroke. Interventions shown to reduce such delay include increased healthcare education about recognizing possible stroke symptoms, hospital prenotification by Emergency Medical Services, having an organised 'code stroke' protocol and a specialized stroke team, and the use of a severity stroke scale preferably the NIH Stroke Scale/Score.^{4,11,12} Better communication between ED and radiology staff is also recommended in order to prioritise stroke patients and to reduce delays, i.e., if a CT scan for a suspected stroke is anticipated, reserving a time slot in advance can significantly reduce wait times for imaging.¹⁰

LIMITATIONS AND FURTHER STUDIES

In keeping with the above, a limitation of this audit is the fact that delays due to patient stabilisation prior to CT stroke transfer may have affected door-to-imaging

times. Further studies to investigate this, with a view to establish specific protocols, are recommended.

It is also recommended that an analysis of door-to-imaging times in other regions of specific countries is undertaken; this could then be used to track and compare the prognosis of stroke patients.

CONCLUSION

This audit reveals that our current local practice is not in line with international guidelines. Our recommendations are for further audits to be carried out to evaluate the reason for such delays, with a view to reduce precious investigation and treatment time and improve prognosis.

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Basic Perceptions of Anaesthetists Among the General Public in Malta

ABSTRACT

The clinical speciality of anaesthesia has extended its scope well beyond the administration of anaesthesia. Anaesthetists play critical roles in intensive care, obstetrics, the emergency department, and chronic pain management. Basic perceptions of the general public regarding anaesthetists were assessed during two separate outreach events. Of 125 adults, 91.2% recognised that the anaesthetist manages anaesthesia during surgery. Only 68% identified the anaesthetist as a doctor. Additionally, 96% believed anaesthetists work in operating theatres, but were unsure when it came to other departments, showing further efforts are needed to ensure that the public understands the role of anaesthetists in the healthcare system.

INTRODUCTION

The clinical speciality of anaesthesia has evolved over the years and now spreads far beyond the administration of anaesthesia during surgical procedures. Beyond the operating room, anaesthetists lead the intensive care unit, facilitate safe and pain-free childbirth, resuscitate acutely unwell patients around the hospital and run chronic pain services, demonstrating their diverse and far-reaching impact on healthcare. We aimed to assess the perception of the general public on this speciality during two separate outreach events in 2023: the Association of Anaesthesiologists of Malta's stand at Science in the City Festival (SiTC) in Valletta and World Anaesthesia Day (WAD) celebrations at Mater Dei Hospital.



METHODS

The platforms chosen for the questionnaires were two educational events open to the general public, welcoming people of all ages, nationalities, and educational backgrounds. The multiple choice questions were: 'What is your age?', 'Who puts you to sleep when you have an operation?', 'Do you think an anaesthetist is a doctor?' and 'Where do you find an anaesthetist?' Individuals were approached by trainees or specialists from the Department of Anaesthesia, Intensive Care and Pain Management at Mater Dei Hospital using random, convenience sampling. They were invited to participate in a brief questionnaire. The anonymised responses were inputted in a Google Form and the results were analysed.

RESULTS

Age Group

125 responses

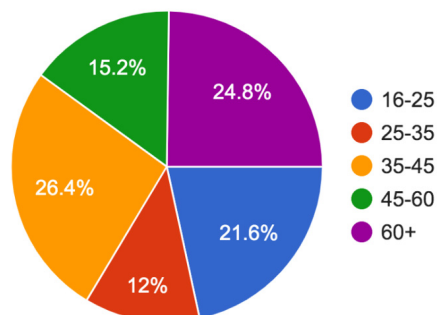


Figure 1. Age Group Distribution of Questionnaire Participants.

People under 16 were excluded. Of 125 adults, the majority of respondents (91.2%) were aware that the anaesthetist is responsible for managing the anaesthetic during surgery, with 4% believing it was a nurse's role and 2.4% thinking it was the surgeon's responsibility.

THE ANAESTHETIST'S ROLE IN THE SCENARIO OF LABOUR AND DELIVERY ALSO SEEMS TO BE INCOMPLETELY UNDERSTOOD IN THE SAMPLE GROUP

Who puts you to sleep when you have an operation?

125 responses

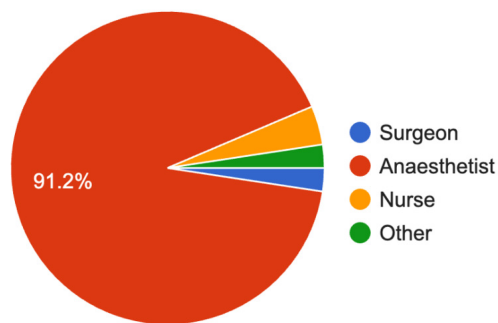


Figure 2. Distribution of responses to the anaesthesia provision question.

Only 68% of interviewees believe that the anaesthetist is a qualified doctor.

Do you think an anaesthetist is a doctor?

125 responses

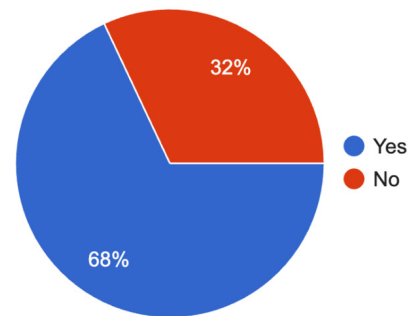


Figure 3. Distribution of responses relating to whether an anaesthetist is a doctor.

With regards to the work the anaesthetist is involved in, 96% believe anaesthetists work in the operating theatres. Around half the participants also mentioned the emergency department, the delivery suite, and the intensive care unit as other areas where anaesthetists work. Only 26.4% of people thought the anaesthetist is involved in any work in the hospital wards.

Where do you find an anaesthetist?

125 responses

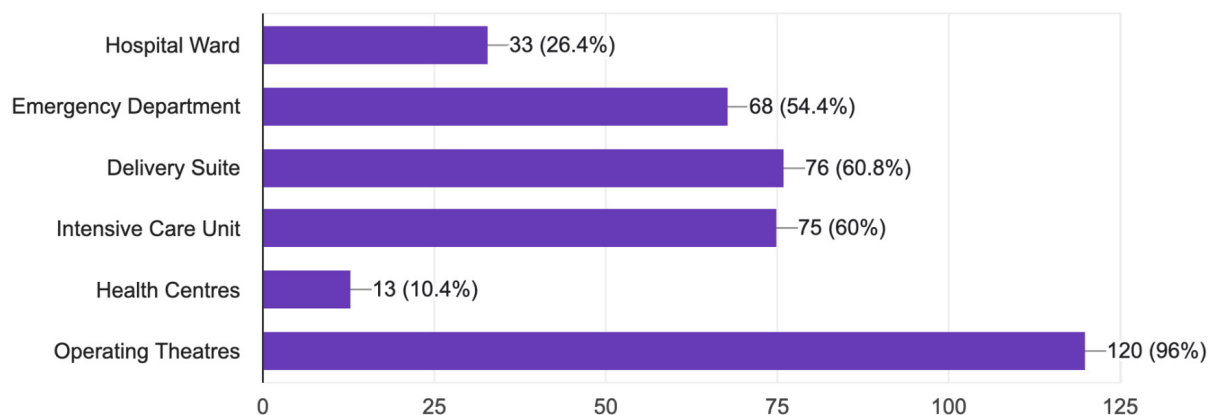


Figure 4. Distribution of responses to where an anaesthetist works.

DISCUSSION

Anaesthesia as a medical speciality has seen significant achievements, especially in recent decades. Whilst previously being considered a “behind the scenes” speciality, the involvement of anaesthetists in so many facets of patient care has proven anaesthesia to be one of the main pillars of the healthcare system. However, worldwide studies show that the anaesthetist's role continues to be incompletely understood.¹⁻⁴ This questionnaire is probably the first of this kind in Malta and was done to analyse this perception amongst the local population.

The majority of interviewees were aware that anaesthetists play a pivotal role in perioperative care and 91% are able to recognise the anaesthetist as the person administering anaesthetic during surgery, compared with 42-94% in various recent studies in other countries.¹⁻⁴ In fact, anaesthetists ensure patient safety and comfort not only before, but also during and after surgery. Anaesthetists decide on a tailored anaesthetic plan to suit individual patients with varying medical conditions and advise on necessary investigations and treatment to optimise any conditions prior to surgery, ensuring patients' safety during surgical interventions. Once in theatre, they also carefully monitor vital signs and adjust anaesthesia doses to maintain optimal surgical conditions, not leaving the patient's side throughout. Furthermore, their expertise in pain management is crucial for postoperative care, helping patients recover smoothly and comfortably.

However, a significantly lower percentage of people were aware of the anaesthetist's role beyond the operating room. 60% of those asked recognise that anaesthetists are involved in the intensive care setting, compared to 25-32% in other studies.^{2,3} In actual fact, anaesthetists assume the primary caregiving responsibility for patients in intensive care, monitoring their day-to-day condition closely, and making critical decisions around their care whilst at their most vulnerable.

The anaesthetist's role in the scenario of labour and delivery also seems to be incompletely understood in the sample group. Anaesthetists are actively engaged in formulating a plan for birth, be that in providing epidural pain relief during labour or providing various types of anaesthesia for caesarean sections, both in the planned and emergency settings. They are also vital in providing care for any emergencies that can arise, such as postpartum haemorrhage. Local data shows that anaesthetists are involved in the care of over half the obstetric population in the peripartum period.⁵

With regards to the emergency department, 54% correctly identified anaesthetists' involvement here. Anaesthetists respond to CPR (cardiopulmonary resuscitation) calls for patients who arrive in cardiac arrest, trauma calls for patients who are involved in accidents leading to severe trauma and calls for any patients in any severe medical condition. Similarly, anaesthetists are also found in any of the hospital wards, being called to review patients with any severe organ failure, ranging from sepsis to severe heart failure, and respond to the CPR call for patients in cardiac arrest. Their role in these situations is to help with the initial phases of stabilisation and to decide on the need for continued treatment in the intensive care unit.

Anaesthetists are also experts in chronic pain medicine, and lead the Chronic Pain Clinic, working to review patients suffering from chronic pain and formulating management plans ranging from medication regimes, to joint and nerve infiltration together with physiotherapy and psychological support.

Interestingly, 68% of the interviewees thought anaesthetists were specialised doctors, fitting within the range observed in international publications i.e. 37-79%.^{1-2,4} Anaesthetists are, in fact, qualified doctors who then choose to specialise for a further 5-8 years in the field of anaesthesia, intensive care and pain management. They often work in a multidisciplinary team consisting of surgeons, medics, nurses, midwives, radiologists, and physiotherapists, amongst others, to provide services throughout the hospital.

There are definite benefits to educating the general public about the role of the anaesthetist. When patients face any type of illness which requires surgery, especially a major one, they always ponder the possibility of postponing or actually forgoing surgery, especially as the prospect of being unconscious and not in control generates fear of the unknown. Being armed with knowledge and, more importantly, trust in the anaesthesia process as well as all other healthcare professionals involved, patients are empowered and may experience an improved hospital experience.

A limitation identified in the questionnaire was the cohort of subjects interviewed. Attendees of SiTC were presumably interested in scientific topics, while the general public present at Mater Dei Hospital attended WAD. In future, to eliminate bias, questions could be added asking about the participants' level of education and previous experience with having surgical procedures. It is also recommended that further research is carried out utilising a validated questionnaire and with a larger sample size.

Furthermore, in the question relating to places of work (options in Figure 4), 'Hospital Ward' may have been an ambiguous term, and the only incorrect option (at the time of the questionnaire) was 'Health Centres'. Notably this section was asked in the form of closed questioning which could have been relatively suggestive. Open questioning may have elicited a more reliable response from the participants. Finally, though unlikely, the same individual may have attended both outreach events and responded to the questionnaire twice.

CONCLUSION

This initial study into the perceptions of members of the general public in Malta in relation to the roles of anaesthetists seems to indicate that awareness of who delivers anaesthesia is comparable to international literature, though knowledge of the anaesthetist's role beyond the operating theatre is more limited. Educational outreach events like Science in the City and World Anaesthesia Day celebrations at Mater Dei Hospital offer valuable opportunities for interactive discussions in a non-threatening environment.

Continuation of such efforts allows for enhanced anaesthetists' professional recognition and trust, which hopefully translates into improved patient experiences.

ACKNOWLEDGEMENTS

We thank the members of the Department of Anaesthesia, Intensive Care and Pain Management at Mater Dei Hospital, who voluntarily helped with data collection during the two events: Science in the City 2023 and World Anaesthesia Day 2023. The stand at the Science in the City as well as the World Anaesthesia Day were organised by the Association of Anaesthesiologists of Malta (www.aam-malta.org).

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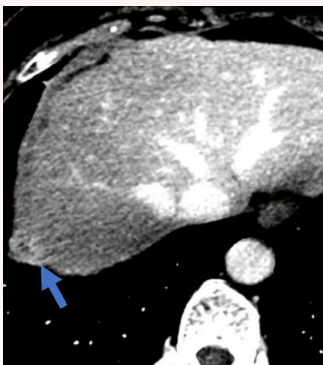


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Genome-Wide Association Studies

ABSTRACT

Genome-Wide Association Studies (GWAS) detect associations between genetic variants and traits in population samples. Single-nucleotide polymorphisms (SNPs) are the most common genetic variants studied. GWAS started as an experimental exercise some 20 years ago, but has since matured and has a range of applications, including helping to understand the biology of disease and predicting genomic risk with the potential to be used as a biomarker and in patients' stratification. GWAS signals are also used to identify drug targets, leading to genomics-driven drug discovery.

INTRODUCTION

GWAS are a powerful platform to identify genetic variations associated with a specific disease or trait. The studies typically compare the genomes of subjects with a particular disease or trait to individuals who do not have the disease or trait, thus identifying particular variations in the DNA that are more common in the affected subjects. Currently, single nucleotide polymorphisms are widely used as 'genetic variants'. A single nucleotide polymorphism (abbreviated SNP, pronounced snip) is defined as a genomic variant at a single base position in the DNA.

THE FIRST GWAS

The first GWAS was published in 2005 and it focused on 'age-related macular degeneration' (ARMD).¹ Specifically it compared 96 patients with ARMD and 50 healthy subjects as a control. This study found two SNPs of significance located in the gene that encodes complement factor H. This was not expected and resulted in further functional research with the aim to base therapy for ARMD on the complement system.

Today there are countless GWAS. Indeed, this tool has generated many impressive and strong associations between a wide range of traits and diseases. Furthermore, it has matured into very useful applications, like helping to understand the biology of disease and predicting genomic risk with the potential to be used as a biomarker and in patients' stratification. GWAS signals are also used to identify drug targets helping to improve drug development efficiency.

SINGLE NUCLEOTIDE VARIANTS

A Single Nucleotide Variant (SNV) occurs when a single nucleotide is substituted for another. An SNV qualifies as an SNP when the variant is present in 1% or more of the population being considered.

When a nucleotide substitution occurs in a protein-coding region of the gene, this leads to one of three changes. In a 'synonymous change', there is no change in the coded amino acid because amino acids are coded through multiple codons. In a 'non-synonymous change', there is a change in the coded amino acid. This in itself may or may not be pathogenic depending on whether the amino acid substitution affects the protein configuration and hence its function. The third change is called a 'stop gain change'. Here the substitution results in a stop codon. As a consequence, the coded protein is prematurely truncated and usually is not functional.

POLYGENIC RISK SCORES

GWAS has enabled the ideation of a Polygenic Risk Score (PRS). A PRS is a calculation of the risk for a disease based on the disease-associated SNVs across the genome. PRSs are envisioned as very promising tools to predict the basic risks of common and complex diseases, in keeping with the fact that GWAS studies are addressing bigger sample sizes. However, PRSs can be used for more than the prediction of basic risk. Indeed, PRSs have various potential clinical niches. For example, PRSs could be used to predict symptoms and thus offer a clinical tool to decide and tailor better treatment. PRSs also have the potential to be used clinically to distinguish between aggressive and non-aggressive behaviour of a specific disease. More importantly, PRSs can improve strategies for better screening and prevention.

TRANSLATIONAL APPLICATIONS

CARDIOVASCULAR DISEASE

Despite notable advances, risk prediction models for cardiovascular disease have remained relatively imprecise, including for young adults and specific subpopulations. A current approach that has been proposed is genetic profiling which includes GWAS. Such genetic endeavours can clarify contributory mechanisms of cardiovascular diseases. Indeed it is also believed that this would permit earlier tailored prevention and drug discovery.

Disease development is associated with multiple factors. The 'liability threshold model' is based on the notion, that specifically monogenic, polygenic and non-genetic factors are contributory to reaching a threshold of developing a disease.²

GWAS have definitely established that cardio-metabolic diseases have a polygenic basis. Individually, the polygenic variants found are only of small risk, but when taken

together they increase the risk substantially.³ As discussed before, a PRS embodies the total number of genetic variants that a person has, enabling the assessment of his/her heritable risk of developing disease.⁴

Many of the common cardiovascular diseases contribute to the development of atrial fibrillation (AF).⁵ However, GWAS studies have also shown that genetic variation also contributes. For example, individuals who suffer from early-onset AF show a 2.1% prevalence of loss-of-function variants of the Titin (TTN) gene.^{6,7} Other GWAS analyses show 134 loci associated with AF.^{8,9} However, these are common and have a small contributory effect. The discovery of an increasing number of these common genetic variants in turn leads to a more reliable predictive value of AF PRSs.^{10,11}

Table 1 lists other examples of cardiometabolic diseases with a polygenic basis for which data is being collected and predictive PRSs are being developed.

Table 1. Examples of Cardiometabolic Disease PRSs.

Cardiometabolic disease	Reference
Hypertrophic cardiomyopathy	12
Heart failure	13
Channelopathies • QT interval prolongation • Brugada syndrome	14,15 16

DIABETES

Type 1 diabetes mellitus (T1DM) is an autoimmune disease, where insulin-producing β cells in the pancreas are killed by immune cells. GWAS have found over 200 gene variants associated with T1DM.¹⁷ These variants are mostly found in non-coding regions of the genome. Kim et al.¹⁷ reported that such SNPs result in dysregulation in the enhancer-based immunity of T1DM patients.

On the other hand, Hubacek et al.¹⁸ found 21 SNPs that can be used to predict the risk of T2DM and its complications, like neuropathy, nephropathy and leg ischemia. They found these SNPs within the genes that code for FTO (fat mass and obesity-associated protein), TCF7L2 (transcription factor 7-like 2), and ARAP1 (ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1).

Of note is the fact that Shoaib et al.¹⁹ evaluated PRSs for T1DM and T2DM. They propose that such scores can differentiate between the two, and thus help in their correct diagnosis and treatment.

ONCOLOGY

PROSTATE CANCER

PRS is also emerging as a genetic approach to stratify the risks of prostate cancer (PC). This PRS approach integrates other variants in genes (besides the classical

ones). Even though the role of these variants may be unknown they are being found more often in prostate cancer patients. The Nordic Twin Study of Cancer²⁰ shows a 57% heritability of PC, with BRCA1/2 (breast cancer 1/2), HOXB13 (homeobox B13), CHEK2 (checkpoint kinase 2) and MMR (mismatch repair) being high penetrance genes. However, GWAS studies²¹ identified approximately 170 single nucleotide polymorphisms associated with PC risk which could explain 25% of the familial risk. Using PRS for PC has the potential to classify subgroups with the highest risk. Also, as the models for risk prediction improve, they will differentiate between clinically aggressive and non-aggressive disease, possibly reducing the need for invasive procedures.

BREAST CANCER

Single high-risk gene pathogenic variants for breast cancer (BC) include *BRCA1* (BreastCancer 1), *BRCA2* (Breast Cancer 2) and *TP53* (Tumour Protein 53). Such variants often need high-risk screening. But beyond these classical risk genes, PRS in breast cancer based on SNPs in GWAS explains more than 30% of heritability for breast cancer.²² Potentially, PRS for BC can improve strategies for better screening and prevention. Specifically, SNP18, SNP77, SNP143, and SNP313 are some of the SNPs that are candidates for breast cancer risk prediction. Females of non-white European ancestry have their risk for BC over-predicted using these PRSs and further research is ongoing to address this.

DEMENTIA

Alzheimer's disease (AD) is a complex disease that also has a polygenic basis. Thus PRSs have the potential to predict which individuals are more at risk. *APOE* $\epsilon 4$ allele is considered to be the biggest risk factor for developing AD.²³ Relatively recent GWASs also point to immune genes²⁴ and associations of immune diseases like psoriasis and rheumatoid arthritis with increased risk of developing AD.²⁵ Furthermore, PRSs for AD could be used to predict symptoms like cognitive decline^{26,27} and thus offer a platform that could be used to decide on treatment earlier on.

LONGEVITY

Genetics play a significant role in longevity and more research is being done to investigate 'longevity genes'. Longevity is a polygenic trait, depending on the collective small influence of many genes. Genetic studies, like GWAS of families with long-lived individuals indicate a longevity locus on chromosome 3, more specifically the 5q33.3 locus,²⁸ which has been found to be associated with a healthy cardiovascular system and a healthy physical functioning.

Other GWAS studies point to gene variants of APOE (Apolipoprotein E) and FOXO3A (forkhead box O3A) genes.²⁹ APOE gene codes for a major apoprotein in chylomicrons and functions in the normal catabolism of lipoproteins rich in triglycerides. FOXO3a is a transcription factor. One function of FOXO3a is to suppress mutations resulting from DNA double-strand breaking. It is proposed that it binds to genes which are then expressed to bring about apoptosis.

DRUG DISCOVERY

GWAS implicate genomic risk loci for diseases and traits. This knowledge can lead to a better understanding of the biology of disease and hence helps in the identification of new drug targets. For example, various GWAS studies pointed to the IL-12/IL-23 (Interleukin 12/Interleukin 23) pathway for Crohn's disease.³⁰ Subsequently, this led to clinical trials that targeted this pathway to treat Crohn's disease.³¹ IL-12 and IL-23 are important cytokines in mucosal inflammation, especially of the gut.

Another example was the discovery of the loss-of-function variant of the PCSK9 (proprotein convertase subtilisin/kexin type 9) gene. This inspired the research and the discovery of an inhibitor of the PCSK9 protein.³² Pharmacological inhibition of PCSK9 is now an established therapeutic option to treat hypercholesterolemia. Specifically, evolocumab is a monoclonal antibody that inhibits PCSK9³³ and lowers levels of low-density lipoprotein (LDL) cholesterol by 60%.

And research searches on. Indeed, the large amounts of GWAS datasets provide the potential for discovering novel drugs, investigating drug combination treatments, identifying side effects or drug resistance, and also GWAS-based repurposing of drugs.³⁴ In fact, in 2021, 66% of the drugs approved by the FDA were based on human genetic mechanisms underlying the disease.

CONCLUSION

Undoubtedly, GWAS research is in hyperdrive with no signs of slowly down. What started as an experimental exercise some 20 years ago, has come a long way and greatly matured. Indeed, it is generating new information that will definitely continue to help in gene discovery. Increasingly GWAS loci, together with other -omic tools, are being translated and deciphered into biological processes and clinical targets and hence propel the potential for theranostic applications. GWAS together with other platforms will continue to help in bridging sequence to consequence.

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