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EDITORIAL

The changing face of Medicine

Simon Paul Attard Montalto

Many years ago, we had written an article, published in the MMJ, that highlighted the advances that had occurred in Paediatrics during the preceding ten years or so.[1] Now that we are in the twilight of our careers and on the cusp of retirement, we can re-visit this topic with a retro-telephoto lens in combination with a generous dollop of nostalgia.

Prof Simon Paul Attard Montalto
Editor, MMJ

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COVER PICTURE

'House Facade, Allerheiligen, Black Forest, Germany'
Acrylic on canvas, 2.5m by 70cm

Mario Borg first read Pharmacy at Bachelor level (1982-86) and later read History of Art at both Bachelor & Master levels (1994-2001).

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

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As a fresh houseman (now a foundation doctor 1), I would have admitted several adults with ischaemic heart disease on a daily basis. These patients would be given intravenous hydration, adequate analgesia and bed rest. All the guidelines based on STEMI, non-STEMI, etc.[2], simply did not exist, let alone emergency percutaneous coronary intervention (PCI) or thrombolysis,[2] followed by alleviation of symptoms and rapid discharge from hospital. Our typical 'MIs' went home after a few weeks in hospital for slow rehab in the community.

Ultrasound and CT scanning had been around for a few years[3,4], but I witnessed the advent of MRI scanning, later PET and 'clever' labelled isotope scans of various forms and modalities. Many of these imaging techniques, such as MRI, were initially 'niche' or restricted to certain narrow domains, yet are now used in all corners of medicine and surgery. Whereas a simple X-ray sufficed for most orthopaedic complaints, it is now not uncommon to MRI-scan everything that moves! Advances in oncology, endocrinology, diabetes . . . the list goes on and on . . . have been astounding. Refinements in care have been supported by new investigations, assays, gizmos (e.g. smart-readers for glucose monitoring[5]), delivery devices and an entire field of Interventional Radiology.[6] 'Clever' targeted medications have been developed in all pharmacological fields including chemotherapy, radioisotopes, biologicals, . . . etc, etc. The MAB family of drugs alone, i.e. those ending in 'mab' (monoclonal antibodies), have increased astronomically since their introduction during the early part of the millennium![7]

In Neonatology, surfactant[8] to name just one drug, revolutionised the morbidity of premature babies: in the pre-surfactant era (my time!) neonatal senior house-officers (BST1 or 2 equivalents) were up all night intubating and re-intubating tiny tracheae, followed by repeatedly inserting chest drains to relieve air leaks as a consequence of the severity of RDS without surfactant, coupled with the barotrauma that was commonplace with early, crude pressure-driven ventilation techniques. The morning hand-over listed the number of chest drains inserted (usually several!), whereas nowadays most Resident Specialists in Neonatology are required to carry out this procedure very infrequently, such that many are not confident to do so!

Surgical techniques for both children and adults across the board have also changed drastically and, increasingly, supported (or taken over?) by artificial intelligence-driven methodology. Advances and additions in vaccinology (not just for children but expanded to include the elderly, pregnant women, etc.), Public Health and, dare I add, the management of a pandemic have all materialised during my working lifetime.

The jack of all trades – 'Generalists' – have become a rare species, replaced by superspecialists that in some cases are restricted to single-disease consultants. A healthy mix of doctors with different skill sets that can work symbiotically with one another is probably the ideal. Genetics is the buzz-word in nailing a diagnosis for so many diseases and, in many cases, a particular gene mutation will determine treatment options and outcome. Indeed, the influence of genetics in patient management cannot be underestimated and will only continue to increase.

Ultimately, all of the above – by no means comprehensive review – of changes in medicine over 40 years or so have dramatically improved the options for patient care. Thankfully, this has not always been at the expense of the humane side of the caring profession, although it has increased the cost of healthcare tremendously. Inevitably, there is a price to pay for ever-improving Healthcare and this needs to be accepted and budgeted for by the powers-that-be. I look forward to the new changes over the next 40 years...!

REFERENCES

1. Attard Montalto SP, Gatt M, Changing clinical activity in Paediatrics in Malta, 1996-MMJ. 2014; 26:(1) 3-7.
2. Rao SV, O'Donoghue ML, Ruel M, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2025: 151:(13)e771-862.
3. Friedland F Present status of ultrasound in medicine. J Am Med Assoc. 1957; 163:(10) 799-803.
4. Raju TN. The Nobel Chronicles. 1979: Allan MacLeod Cormack (b1924); and Sir Godfrey Newbold Hounsfield (b1919). Lancet. 1999; 354(9190): 1653.
5. Bailey TS, Wallace JF, Pardo S, Warchal-Windham ME, Harrison B, Morin R, Christiansen M. Accuracy and User Performance Evaluation of a New, Wireless-enabled Blood Glucose Monitoring System that Links to a Smart Mobile Device. J Diabetes Sci Technol. 2017; 11:(4) 736-743.
6. Brock KK, Chen SR, Sheth RA, Siewerdsen JH. Imaging in Interventional Radiology: 2043 and Beyond. Radiology. 2023; 308(1):e230146.
7. von Mehren M, Weiner LM. Monoclonal antibody-based therapy. Curr Opin Oncol. 1996: 8:(6) 493-8.
8. Possmayer F, Zuo YY, Veldhuizen RAW, Petersen NO. Pulmonary surfactant: A mighty thin film. Chem Rev. 203; 123:(23) 13209-90.

Corinthia Group Prize in Paediatrics for 2025

The Corinthia Group Prize in Paediatrics for 2025 was awarded to Dr Nathaniel Mercieca, who obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Whilst offering our congratulations to Dr Mercieca, we would also like to congratulate all those who performed admirably during the undergraduate course in Paediatrics. In the accompanying photograph, Dr Mercieca is seen receiving her prize from Professor Simon Attard Montalto, Head of Paediatrics. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.



MMJ

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ORIGINAL ARTICLE

Maltese doctors and their views on End of Life issues

Jurgen Abela

Background

End-of-life (EoL) decisions are challenging for doctors. They involve legal and ethical dilemmas, coupled with personal values. In 2016, a local study was carried out on the views of doctors on some EoL decisions. This study is a follow-up study, with a greater focus on advance care planning and related issues, which were not sufficiently addressed in the first study.

Methods

A mixed methods approach was used. An online questionnaire was distributed electronically to doctors and collected: demographic details of participants; the philosophy of life of the individual; training needs in palliative care; personal views and experiences on particular EoL issues. The necessary ethics approval and organizational approvals were obtained.

Results

195 doctors replied giving a response rate of 15.1%. Hence, caution needs to be applied in interpreting the data, despite a positive non-responder analysis. 142 doctors [72.8% (95%CI 66-78.9)] felt the need of further training in EoL care. For withdrawal/withholding of treatment, 129 doctors (66.1% (95%CI 59-72.8)) did not feel safeguarded. In the case of the doctrine of double effect for treatment intensification, 129 doctors [66.1% (95%CI 59-72.8)] did not feel safeguarded, whilst for advance care planning 122 doctors [62.5% (95%CI 55.4-69.4)] did not feel safeguarded. Issuing a DNR order was the least concerning since 103 doctors [52.8% (95%CI 45.1-59.5)] did not feel safeguarded in this regard.

Conclusion

Despite agreeing with various EoL practices, most doctors felt they were not medico-legally safeguarded and welcomed further training in EoL care.

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Doctors, in various specialties of work, have to care for patients at the end of life (EoL). In these situations, taking difficult decisions is often an arduous task. This has long been recognized.[1] The views of doctors on various aspects, especially EoL care, are crucial to shape and mould the future care of patients within our health system. A study carried out in Malta in 2016 had reported that 90.2% of doctors were opposed to euthanasia but did not delve into end of life care issues and the comfort or discomfort with which doctors approach these issues.[2]

The objectives of this study were to:

- To document and update the views of doctors on various issues on EoL care.
- To assess whether there is a need for training in EoL care.
- To analyze whether doctors feel safeguarded with practices they agree on.
- To put forward ways to address any issues which might arise from this study.

EoL care encompasses a multitude of issues including, for example: withdrawing and withholding of treatment (WDWH); do not resuscitate orders (DNR) and palliative sedation (PS). Each topic very well deserves an in-depth study and review on its own merits. This study was primarily concerned with highlighting the views of doctors on various issues relating to Eol, and whether doctors felt safeguarded when dealing with this subject.

MATERIALS AND METHODS

A questionnaire was constructed based on a previous study carried out locally by the author in 2016.[2] Certain important aspects of care, not covered by the previous study, were included. The questionnaire was then reviewed by colleagues for validity and reliability.

The questionnaire was primarily quantitative in nature and allowed for comments in various sections. Thus, a mixed methods approach was used. The questionnaire was divided into four sections: demographic details and working experience; philosophy of life and its importance in EoL care; experience with EoL care and lastly, EoL issues. Each time participants were asked about a particular EOL issue, they were asked whether they ever practised it themselves; whether they agreed with it and whether they felt safeguarded. Their responses were classified along a 4-point Likert scale.

The questionnaire was distributed electronically to all doctors within the following organisations, after due approval was obtained: Mater Dei Hospital (MDH); Gozo General Hospital (GGH); Mount Carmel Hospital (MCH); Primary HealthCare (PHC); St Vincent De Paule Hospital (SVPR); Karin Grech Hospital (KGH); Sir Anthony Mamo Oncology hospital (SAMOC); The Association of Private Family Doctors (APFD) and the Malta Association of Public Health Medicine (MAPHM). Before contacting the doctors, Faculty Research Ethics Committee (FREC) approval (MED-2022-00063) was sought and granted.

The questionnaire contained an introductory letter, explaining the aims of the study and an electronic link using Microsoft Forms® link to participate in the study. It was accepted that by clicking on the link, the doctor was consenting to participate in the study

The collection period was arbitrarily set for three weeks from when the email shot was sent. The period was deemed suitable so that anyone wanting to participate could participate. No reminders were sent since these were deemed to be intrusive by the author.

The data was collected on Excel® V 16.67 and elaborated using SPSS® V 28.2. Statistical analysis was carried out using a non-parametric approach. In the event of a low response rate (<20%), a non-responder analysis was planned accordingly.

RESULTS

The results are presented in two main sections:

- Quantitative section
- Thematic analysis of responses

Quantitative Analysis

Basic Demographic details

In total, 195 doctors replied to the questionnaire. This gave an overall response rate of 15.1%. This low response rate implied that the findings needed to be interpreted with caution. Due to the low response rate, a non-responder analysis was carried out (**Table 1**). The only possible comparable participant characteristic for such analysis was the specialty of practice. However, when compared to the general medical population as listed on the specialty register of March 2023, there was no significant difference noted [X(2)((9, n=192) =16.029, p=0.0988)]. The age and gender distribution of the respondents is summarized in **Figure 1**, whilst **Figure 2** shows current stage of the respondents in their career. In

Table 1 *Non-responder Analysis*

	Observed	Expected	Expected (%)
Anaesthesia	13	21	11
Emergency Medicine	16	9	5
Family Medicine	73	73	38
Geriatrics	8	6	3
General Medicine	25	25	13
General Surgery	15	11	6
Haem&Onc&PallMed	9	6	3
Obs&Gynae	8	14	7
Paediatrics	8	10	5
Public Health	7	9	5
Psychiatry	10	8	4
	192	**192**	**100**

Total analysed was 192, since 3 responders were classified in Other specialties

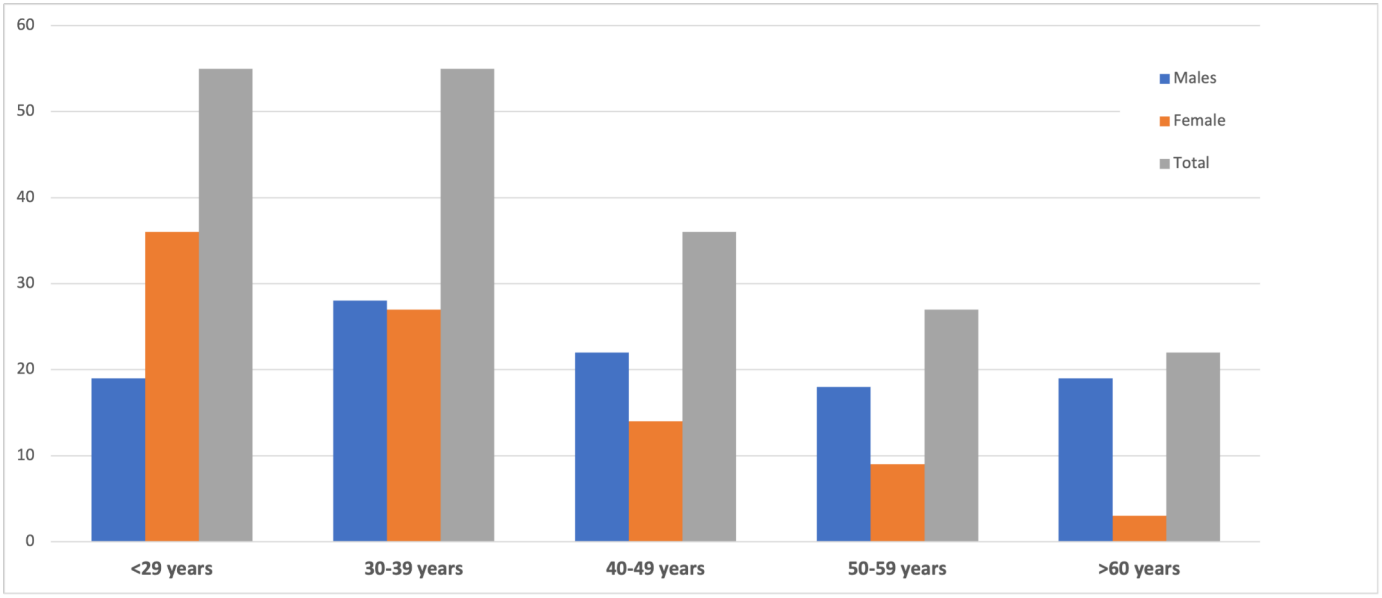


Figure 1 *Age and Gender distribution of respondents*

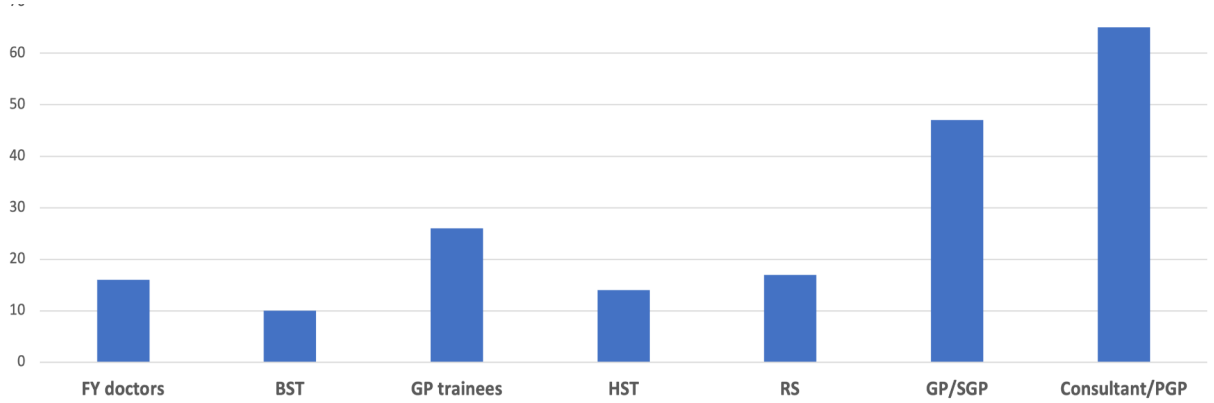


Figure 2 *Stage of Career of Participants. BST - Basic Specialist Trainee; FY - Foundation Year doctors; GP - General practitioner; HST - higher specialist Trainee; PGP - Principal General Preactitioner; SGP - Senior General Practitioner*

line with FREC recommendations, data aggregation and analysis was carried out in a manner to avoid identification of individuals.

Philosophy of Life (POL) & EoL experience

160 doctors [82% (95%CI 75.9-87.2)] identified their philosophy of life as Roman Catholic and 148 doctors [75.9% (95%CI 69.3-81.7)] doctors regarded their philosophy of life as important or very important in taking EoL decisions.

143 doctors [72.8% (95%CI 66-78.9)] admitted that they would benefit from further training in this area. The three most common areas that doctors felt they needed more training in were communication with patients and relatives; pain (and symptom) management and dealing with ethical issues.

EoL Issues and views

Doctors were asked for their views on a variety of EoL practices, including:

- Do Not Resuscitate orders (DNRs)
- Withdrawing and withholding of treatment (WDWH treatment)
- Intensifying analgesia with the aim of reducing pain - doctrine of double effect (DD)
- and Advance Care Planning (ACP)

Participants were asked if they ever conducted such practices and whether they agreed with them in principle. Their responses are summarized in **Table 2**. They were also asked if they felt medico-legally safeguarded with respect to such practices. Their response is summarized in **Table 3**. Palliative sedation (PS) is a practice that was agreed to by 181 doctors (93.3%, 95%CI 88.9-96.4).

Thematic Analysis

For each of the four EoL issues studied, the participants were asked for their comments and personal criteria used on the specific issues. Their responses are summarized below, structured according to the issue, and applying thematic analysis to the various comments received.

DNR

For DNRs, the over-riding issues were the frailty of the patient and the low functional status at the time of such decision/discussion. The presence of comorbidities and multi-organ involvement was also mentioned. One of the more important aspects however was the irreversibility (or not) of the situation. Lastly the responsibility, felt by doctors, in undertaking a DNR order was clearly shown by a particularly striking comment – coming from the surgical field – where it was pointed out that in case of a patient with a DNR order who is undergoing a surgical procedure, such DNR needs to be lifted for 24 hours post-operatively.

Intensification of analgesia (doctrine of double effect)

The overall concept here was the quality of life and comfort of the patient, which for most doctors always came first and foremost. Although a large majority of doctors agreed with the concept of intensification of analgesia to address the quality of life of the patient, most respondents felt more comfortable with such practice at the EoL. Finally, the presence of a serious irreversible medical condition and the symptom burden of the patient were other considerations put forward by doctors.

Withdrawal and Withholding (WDWH) of treatment

In this issue, discussion with family and patient was frequently mentioned and deemed to be crucial. There was an interesting comment from a doctor working in Emergency, who actually pointed out that some EoL practices are linked together, for example, if someone is on a DNR order, he/she would 'automatically' be candidate for WDWH treatment. Finally, the issue of balancing useful treatment with useless invasion of the patient was mentioned by various doctors.

Advance care planning (ACP)

This could be initiated once there is a clear, serious, and irreversible condition. Communication skills are very important in this situation. A change of heart by patients was also put forward as an issue/challenge in this area. Many doctors mentioned the fact that although they are always aware of the need of ACP, the individual patient in front of them affects whether they feel comfortable to put forward this issue or not.

A common theme was present pervasively throughout all the study was the need of doctors, to highlight the legal implications of these issues and have a (safe) framework within which they can work. Quoting just two of the many responses:

"A clear, well defined legal framework for advanced care planning will assist patients and physicians when considering end of life care" (Consultant, Medicine)

"… There needs to be a drive to entrench palliative care into law to safeguard the practitioner and encourage compassionate care" (Consultant, Paediatrics)

Table 2 *Experience and Views on medical issues*

Question	Yes % [95%CI], (n)	No % [95%CI], (n)
DNR		
Did you ever discuss?	84.1% [78.2-88.9] (164)	15.9% [11.1-21.8] (31)
Do you agree?	98.5% [95.6-99.7] (192)	1.5% [0.3-4] (3)
WDWH treatment		
Did you ever WD/WH treatment	81% [74.8-86.3] (158)	19% [13.7-25.2] (37)
Do you agree?	94.9% [90.8-97.5] (195)	5.1% [2.5-9.2] (10)
Intensification of analgesia (doctrine of double effect)		
Did you ever intensify analgesia?	66.2% [59-72.8] (129)	33.8% [27.2-41] (66)
Do you agree?	88.7% [83.4-92.8] (173)	11.3 % [7.2-16.6] (22)
Advance Care Planning (ACP)		
Did you ever discuss ACP?	51.8% [44.5-59] (101)	48.2% [41-55.5] (94)
Do you agree with ACP?	93.8% [89.5-96.8] (183)	6.2% [3.2-10.5] (12)

Table 3 *Investigation frequency and outcome by group*

Question	Medicolegally safeguarded		Medicolegally not safeguarded		Total Safeguarded	Total Not Safeguarded
	Very much safeguarded	Appropriately safeguarded	Not safeguarded	Absolutely not safeguarded		
DNR	2.6% (5)	45.1% (88)	47.7% (93)	4.6% (9)	47.70% (95%CI 40.5-54.9)	52.30% (95%CI 45.1-59.5)
WD/WH treatment	0.5% (1)	33.3% (65)	60.5% (118)	5.6% (11)	33.80% (95%CI 27.2-41)	66.10% (95%CI 59-72.8)
Intensification of analgesia (DD)	1% (2)	32.8% (64)	52.8% (103)	13.3% (26)	33.80% (95%CI 27.2-41)	66.10% (95%CI 59-72.8)
Implementing ACP	2.1% (4)	35.4% (69)	49.7% (97)	12.8% (25)	37.5% (95%CI 30.6-44.6)	62.50% (95%CI 55.4-69.4)
Abiding to ACP	2.6%(5)	34.9%(68)	51.3&(100)	11.3%(22)	37.5% (95%CI 30.6-44.6)	62.5% (95%CI 55.4-69.4)

Another important theme which came out was the need for further training in palliative care, as highlighted by 72.8% of respondents. Quoting one Resident Specialist in Surgery response:

"… It is much needed. I feel that it should be introduced as part of training as regards how to deal with end-of-life patients and how to manage them humanely"

DISCUSSION

EoL decisions are difficult and at times leave doctors in uncomfortable positions. Unfortunately, the low response rate of this study should always be kept in mind when interpreting the findings of this study.

Palliative Sedation (PS) is defined as the "the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and healthcare providers".[3] The strong response agreeing with this practice (93.3%) shows that there is a willingness from doctors to use every possible tool to alleviate distress in patients

An area frequently overlooked in EoL care is the need for doctors to be trained in dealing with these situations, irrespective of their specialty of practice. Consequently, it is high time that all specialist training programmes have an obligatory component which addresses these areas. Locally, as far as is known, only the specialist training programme in family medicine has an obligatory rotation in palliative medicine.[4] The lack of training in this area has also been documented in other countries.[5]

The main objective of this study was to explore the more common ethically challenging practices and the medico-legal comfort with which doctors deal with them. All four ethical dilemmas reviewed ie DNR, ACP, WDWH and DD, are accepted medical practices and were agreed upon and supported by most doctors locally (see **Table 2**).

However, the study has shown that a large majority of doctors do not feel safeguarded abiding by these practices, despite agreeing to them (see **Table 3**). The reasons for such situations are myriad. It can be argued that one of the major factors affecting this conundrum is the confusing definitions which pervade the literature.

The position paper issued by the European Association of Palliative Care (EAPC) in 2016 is thus welcome. It properly defined practices and shed some light on the literature.[6] In this position paper, Non-Treatment decisions are defined as "withholding or withdrawing medical treatment from a person either because of medical futility or at that person's voluntary and competent request." NTDs in fact do not hasten death but "rather accept death as a natural phenomenon through omission of ineffective, futile, very burdensome or unwanted life prolonging procedures".[6,8]

In the light of such definition, the term passive euthanasia frequently (and erroneously) associated with such concepts is indeed inappropriate since euthanasia involves a process which leads to ending the patient's life. This is being clarified since unfortunately, there are instances, even in certain texts, where the term passive euthanasia is mistakenly used to describe Non-treatment decisions.[7] This concept of NTDs falls perfectly in line with the ideas put forward by Pope Francis and the need to restrain what he calls "therapeutic obstinance" in EoL care.[9]

Another possible reason for such quandary – i.e. agreeing to a medical practice but feeling medico-legally unsafe - might lie in a slow-to-adapt local legal system. However, it can be argued that a legal response to alleviate this quandary might not be the best response. This is because the legal process is usually cumbersome and not adept to the possibility of changes in line with the dynamic process related to an illness or changing wishes of the patients. Such need of flexibility came out clearly in the thematic analysis. In addition, the legal process might remove the individual doctor-patient approach which is fundamental to dealing with such situations. This conundrum might also reflect the difficulty which doctors experience in starting conversations needed to discuss such decisions.[7]

Trying to find a way forward to address this situation is important. The Recommended Summary Plan for Emergency Care and Treatment (ReSPECT) adopted by the Resuscitation Council of UK,[10] is a plan to facilitate discussion on DNR. This can be used as an example for the process to be used as a way forward, even for other areas. Whatever process is chosen to facilitate any type of ACP, it must be based on communication with the patient and adopting an individual approach, as opposed to a purely legal approach commonly associated with a living will. Policy makers should also be cognizant of the fact that such individual approach must take into consideration the fact that patients do not exist only in secondary care, but in a variety of contexts including the community, private hospitals, old peoples' home and geriatric hospitals, and that the

data needs to be shared by all professionals involved in the care of patients. We must also not allow paperwork and form-filling to substitute effective and timely communication. Otherwise, we will run the risk of ending in a situation as happened with the Liverpool Care Pathway, where care of patients became secondary to meeting targets and filling of forms.[11] Further to this, there needs to be a greater awareness, openness and readiness to discuss these issues in public fora to raise awareness and de-mystify misconceptions. As stated by one of the participants:

"End of life care is something we do not think about while we are still young and healthy. However, accidents can happen and people can suddenly find themselves in a position where they cannot take decisions. It would be ideal if everyone can be helped to think and plan ahead. There needs to be a mentality as well as a culture change as well amongst Maltese people in order for this to happen! …" (Consultant, Geriatrics)

In the local context, there is a need of a discussion on how to formulate easy-to-use and readily available frameworks, to allow the adoption of these four pivotal medical practices (i.e. DNR, NTDs, DD, and ACP). This should be high on the national agenda. The role of the Malta Medical Council as a guarantor of such frameworks could be useful to allow serenity of practice to our doctors.

Strengths and Limitations

This study was meant to take a detailed snapshot of the ideas of doctors on various EoL issues and whether they felt safeguarded adopting accepted practices at EoL. Certainly, to carry out an in-depth analysis of each individual EoL issue covered, a different methodology would have been more appropriate. This study was not meant to present all the ramifications possible for each EoL issue.

The study tried to include as many doctors as possible. This was achieved by tapping on all government run health entities and beyond. The low response rate detracts from the robustness of the findings, but it is a well-known fact that electronic surveys tend to have the lowest response rate.[12] However, the response rate was similar to other local electronic surveys.[13] The fact that no reminder was sent might have also affected the response rate. On a positive note, the non-responder analysis showed that the population sampled was representative of the general medical population. The fact that the study was devised using a mixed methods approach allowed for a better understanding of the issues involved.

CONCLUSION

The low response impacted the robustness of findings, but the majority of respondents were in favour of practices such as DNR, NTDs, DD, and ACP. Unfortunately, most participants did not feel medico-legally safeguarded when implementing these practices. This could detract from optimal palliative care in various settings at the EoL. There is a need of further training in this area. A concerted and rational effort is needed to address this situation. Frameworks which are flexible and adaptable for a variety of contexts, including secondary care, primary care, old people's home and geriatric care, need to be drafted to address the lacunae in these four medical practices namely DNRs, NTDs, DD and ACP. Finally, there needs to be more local awareness about these four practices and the issues which prevent them from being properly implemented. They are pivotal to deliver proper dignified medical care for patients and should be given priority on the national agenda.

REFERENCES

1. General Medical Council (UK). Treatment and care towards the end of life: good practice in decision making [Internet]. 2010 [cited 2022 Jan 26]. Available from: https://gmc-uk.org/guidance
2. Abela J, Mallia P. Maltese Doctors: views and experiences on end-of-life decisions and care. Malta Med J. 2016;28:(2)16–26.
3. Cherny NI, Radbruch L. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med. 2009;23:581–93.
4. Psaila N, editor. The Specialist Training Programme in Family Medicine Curriculum. 2nd ed. Malta College of Family Doctors [Internet]. 2021 [cited 2023 Jan 26]. Available from: https://

deputyprimeminister.gov.mt/en/phc/stpfm/Pages/Specialist-Training-Programme-Family-Medicine/stpfm.aspx

5. Schmit JM, Meyer LE, Duff JM, et al Perspectives on death and dying: a study of resident comfort with EoL care. BMC Med Educ. 2016;16:297–305.
6. Radbruch L, Leget C, Bahr P, et al Euthanasia and physician-assisted suicide. A white paper from the European Association of Palliative Care. Palliat Med. 2016;30:(2)104–16.
7. Pace J. Staqsini 20 – Mistoqsijiet u tweġibiet etici dwar il-ħajja umana. B'Kara: CAK; p.162.
8. Brassington I. What is passive euthanasia? BMC Med Ethics. 2020;21:(41)1–13
9. O'Connell G. Pope Francis: No to euthanasia, but we should not obstinately resist death. America – The Jesuit Review [Internet]. 2017 [cited 2023 Jan 26]. Available from: https://www.americamagazine.org/
10. Resuscitation Council UK. Recommended Summary Plan for Emergency Care and Treatment (ReSPECT) [Internet]. 2023 [cited 2023 Jan 26]. Available from: https://www.resus.org.uk/respect
11. Knights D, Wood D, Barclay S. The Liverpool Care Pathway for the dying: what went wrong? Br J Gen Pract. 2013;63(615):509–10.
12. Meyer VM, Benjamens S, Moummi M, et al Global overview of response rates in patient and health care professional surveys in surgery. Ann Surg. 2022;275:(1)75–81
13. Harney M, Abela J. A study on the health and well-being of doctors in Malta. Malta Med J. 2022;34:(3)50–71.

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ORIGINAL ARTICLE

The Development of Pressure Injuries in Patients Referred to Mater Dei Hospital from St Vincent de Paul Long Term Care Residence

A retrospective observational study

Marco Grech, Antoine Vella, Josianna Sammut, Naomi Piscopo, Jessica Falzon, Gabriella Muscat, Stefania Grech

Background

Pressure injuries are potentially preventable. They are caused by unrelieved pressure causing damage to underlying tissue via pressure, friction or shearing movements. Pressure injuries are a cause of morbidity and mortality in the elderly population. Elderly patients transferred to acute hospitals are at an increased risk for pressure injury development.

Methods

A retrospective observational study design was adopted. Data was collected from iSOFT and the patients' medical file. The population studied were patients who returned to SVP from MDH between the 1st November 2022 and the 14th February 2023. Data was analysed using SPSS 27.0.

Results

Over 106 days of the study period, 56 patients were referred for acute care. Of these, 19.64% (n=11) developed new pressure injures. The mean length of stay was 9.892 days. The incidence of pressure injuries varied between different departments (Medicine – 18.5%, Surgery – 8.3%, Orthopaedics – 66.7%, Urology 25%, Vascular, Neurology, Ophthalmology and Gynae - 0%). Patients admitted under Orthogeriatrics for a fracture femur had an 80.0% incidence of developing new pressure injuries. The sacral area was the most common site. Most pressure injuries were of Grade 1 (n=7). There was a weak but statistically significant correlation between duration of stay and the development of ulcers (r_s= .36, n = 56, p = .006). Documentation of pressure injuries was absent from the medical notes and inconsistent in the nursing notes.

Conclusion

Prevention is cost effective, results in shorter hospital stays and improves the patients' morbidity, mortality and quality of life. Greater efforts at preventing pressure injuries in this specific population are warranted.

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Pressure injuries are caused by pressure that goes on unrelieved for long enough to cause damage to any underlying tissues. Most of the time this happens in areas of bony prominences. There are also episodes in which the pressure is caused by a medical device-related pressure. Their degree will range from non-blanchable erythema to deep ulcers with extension into a bone. Three mechanisms of injury have been described: pressure, friction and shearing movements.

Pressure injuries are a leading cause of morbidity and mortality in the elderly.[1] Preventing pressure injuries from developing has been shown to be both cost effective and to improve the patients' quality of life.[2-4] Patients who are transferred to an acute general hospital carry an increased risk of developing pressure injuries unless preventive measures are implemented early on during their admission.[5] It has been anecdotally noted that a number of patients residing at St Vincent de Paul Long Term Care Facility (SVP) who were referred to Mater Dei Hospital (MDH) for acute care, returned to SVP with a number of sores. Patients referred from SVP to MDH are generally frail and may have a number of predisposing factors that facilitate the development of pressure injuries.

This study aims at quantitatively analyse the development of pressure injuries in SVP residents who are transferred to MDH for acute care.

METHODOLOGY

Data was collected retrospectively using iSoft and the patients' medical records. All patients re-admitted to SVP from MDH during the period 1st November 2022 to 14th February 2023 had their file analysed by the researchers for the development of new pressure injuries during their admission at MDH.

The data collected included the patient's age, gender, reason for referral, MDH department, duration of stay, development of pressure injuries, degree and sites. We also looked at the medical and nursing notes to identify any documentation available.

The data was then analysed using Microsoft Excel for descriptive statistics and SPSS24.0 for analytical statistics. Significance was achieved when p=0.05 with a confidence interval of 95%

Ethical clearance for this study was obtained from the SVP Medical Director. All data was stored in a password protected online Excel sheet. Password was available only to the researchers. No patient identifying data was collected.

RESULTS

Over the study period (106 days) a total of 56 patients returned to SVP from MDH. Two of these patients were referred twice and one patient was referred three times. This results in a total number of 52 individual patients who were referred to MDH for acute care.

The age of the patients ranged between 57 years and 93 years with a mean of 79.29 years, median of 82 years and a mode of 80 years.

Table 1 shows the total number of days in MDH and the average stay for the whole population of our study and for male and female patients respectively. The range of stay was between 1 and 51 days with a mean of 7.89 days and a mode of 2.0 days.

Our study showed an overall incidence of 19.64% for the new development of pressure injuries in patients admitted for a period of acute care from long term care. Systematic reviews have shown a prevalence of 0.3%-46% for pressure injuries in the aged with an incidence of 0.8-43%.[8] These wide-ranging values are the result of the heterogeneity of the studies included in the systematic review.[9]

48.2% (n=27) of the patients were admitted under Medicine. The reasons for referral varied and included status epilepticus, acute severe asthma, profound hyponatremia, hypomagnesemia, confusion, bilateral pulmonary embolism, stroke, renal biopsy, pneumonia and chest pain. Five of these patients (18.5%) developed pressure injuries.

Surgical admissions (21.4%)(n=12) consisted of a mix of emergencies and elective surgeries. Cases included lower GI bleeds, RIH repair, descending colon perforation, cholecystolithiasis, nephrectomy, transurethral resection of a bladder tumour and elective colonoscopy. Only one (8.3%) of these patients developed a pressure injury.

Table 1 *Days spent in MDH*

	Total population	Males	Females
Number of patients	56	28	28
Total number of days	442	274	168
Average number of days	9.892	9.785	6.0

Vascular admissions (7.1%) (n=4)were all for elective procedures – trans-positioning of a brachio-cephalic fistula, angioplasty of the right AV fistula, fem-pop graft and a left hallux amputation. None of these patients developed a pressure injury despite their already compromised vascular status.

Six patients (10.7%) were admitted for orthopaedic procedures – 5 with hip fractures and 1 for a total knee replacement. 4 (80%) of the 5 patients admitted following a hip fracture developed pressure injuries during their acute stay. 3 out of these four developed multiple pressure injuries (sacrum and heel). The patient admitted for a total knee replacement developed no sores. All 5 patients with a hip fracture were also under the care of orthogeriatricians.

One of the four (25.0%) of the patients admitted under Urology developed a sacral pressure injury.

None of the patients under Ophthalmology (n=1), Gynae (n=1) or Neuro (n=1) developed any pressure injuries during their stay at MDH.

The above findings are summarised in Table 2, whereas Table 3 shows the average length of stay per department.

In all of the cases, no notes relating to pressure injuries could be identified in the medical notes. Nursing notes, on the other hand, were not consistent. For example, a patient may be documented to be suffering from a sacral sore on one day, only for the sore not to be documented on the following day and then be again documented after another day. In some cases, the sore was not documented in the nursing notes but note was made of the type of dressing being used.

Analytical statistics showed a significant correlation between duration of stay and the development of sores. Nonparametric correlation analysis using Spearman's rho was weak (r_s= 0.36, n = 56, p = 0.006).

DISCUSSION

pressure injuries in the elderly are common but potentially preventable. Preventing pressure injuries from developing is cost effective and will have a positive impact on the patient's morbidity, mortality and quality of life.

The deleterious effects of pressure injuries have been well documented in the literature. They are known to cause pain and interfere with the patient's mobility and social activities.[6] pressure injuries have also been associated with negative emotional and social impacts.[7]

Our study showed an incidence of 19.64% for the new development of pressure injuries in patients admitted for a period of acute care from long term care. None of these patients had pressure injuries prior to their admission for acute care. Systematic reviews have shown a prevalence of 0.3%-46% for pressure injuries in the aged with an incidence of 0.8-43%.[8] These wide-ranging values are the result of the heterogeneity of the studies.[9]

The population of this study is at a much higher risk of developing pressure injuries that the average older person. Most will be extremely frail, have limited mobility (which may become worse after they sustain a fracture), may have significant loss in their sensory abilities and may be unable to reposition themselves with ease. A number will also suffer from cognitive impairment and may be unable to communicate discomfort or pain in a verbal way. All these factors increase the risk for these patients

Table 2 *Development of pressure injuries per department*

	Patients admitted	Patients developing pressure injuries
Medical	27	5 (18.5)
Surgical	12	1 (8.3)
Ortho	6	4 (66.7)
Vascular	4	0
Urology	4	1 (25)
Ophth	1	0
Gynae	1	0
Neuro	1	0

Table 2 *Average length of stay per department*

	Average length of stay in days
Medical	5.24
Surgical	11.67
Ortho	10.17
Vascular	11.0
Urology	5.0
Ophth	1.0
Gynae	10.0
Neuro	4.0

to develop a pressure injury unless preventive measures are in place from the very start of their acute hospital stay.[10]

Our study demonstrates an extraordinarily high incidence of pressure injuries in patients referred after suffering a hip fracture. These patients are the ones who will have become immobilised because of their injury. Moreover, many times their operation is repeatedly postponed for one reason or another. This results in prolonged fasting periods which will have a negative impact on the patient's nutritional status. Frequently turning these patients may be difficult because of the pain they experience with each movement. Appropriate mattress provision may not always be timely. Patients referred from SVP to MDH following a hip fracture are automatically seen by Orthogeriatricians from the medical point of view.

On the other hand, it is remarkable that none of the Vascular patients, despite their inherently compromised peripheral circulation, have developed any pressure injuries. Studies may need to be conducted to identify differing practices between the Vascular and Orthopaedic departments.

The lack of notes in all the medical notes is of concern as is the inconsistent documentation in the nursing notes. This could result in pressure injuries being overlooked. It could also be that the acute setting is not geared towards the prevention of pressure injuries and, therefore, their importance may not be acknowledged serious enough to merit a review and a note in the medical file.

A risk assessment that aims to identify at risk patients at A&E level is important. This should include a thorough history and examination and should identify potentially correctable factors.[11] This risk assessment needs to be followed by regular follow-up to monitor the patient's clinical condition with particular attention to factors that may increase the risk of developing pressure injuries. The skin needs to be inspected daily so that any pressure-induced changes are identified as early as possible. Validated risk prediction scales such as the Waterlow scale or the Norton and Braden Scale may also be used to help identify those at risk.[12] It is essential that such a risk assessment is performed as early as possible during the patient's trajectory in acute care. This is because pressure injuries are known to develop withing hours and, therefore, waiting for the patient to be admitted to the ward to perform the risk assessment might be already too late for some of these frail patients.[13]

Attention needs to be given to areas of skin that more likely to be the site of development of pressure injuries. These are usually sites were thin skin overlies a bony prominence. **Figure 1**, taken from Best Practice Statement (Wounds UK, 2012) graphically described the areas that are common sites for pressure injuries.[14]

The three major mechanisms that contribute to the formation of pressure injuries are pressure, shearing

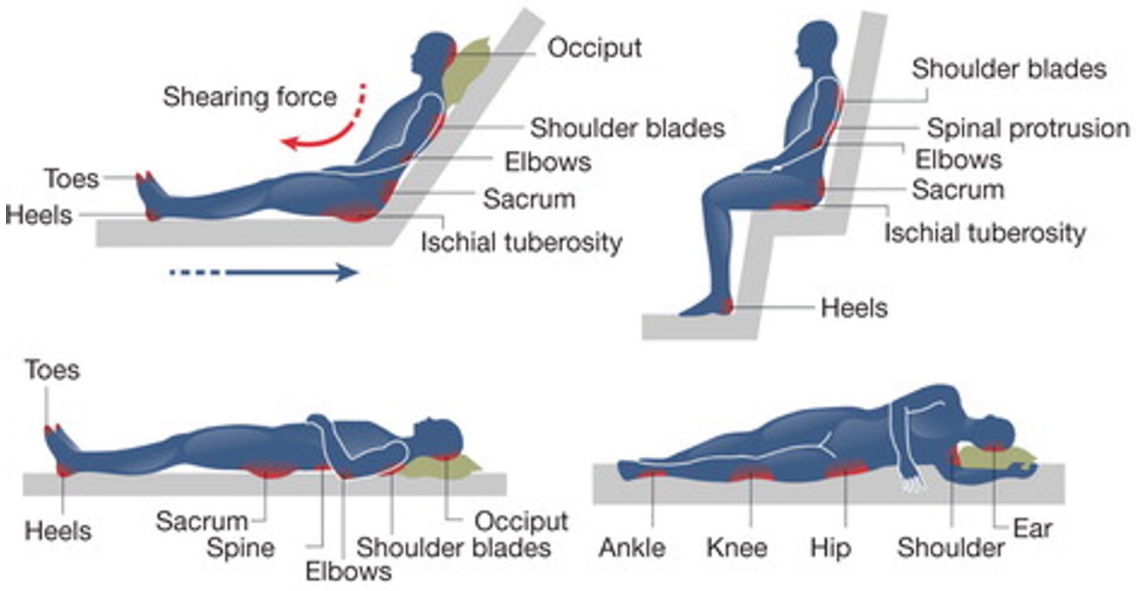


Figure 1 *Common sites for pressure ulcers (taken from Best Practice Statement, 2012)*

forces and friction. As shown in figure 1, the area most likely to develop a pressure injury will depend on the positioning of the patient. Continuous pressure will compromise the blood supply to the underlying tissue leading to hypoxia and possibly necrosis. This process will be much faster in those with an already impaired blood supply, for example, patients with peripheral vascular disease.[15]

Other mechanisms of skin injury include skin rubbing against clothing or bedding. Shearing forces also come into play such as when the end of the bed is elevated. A patient may because of this position, slide on a bed sheet with resultant shearing forces. This in turn causes rupture of blood vessels because of inter-tissue plane movements. This rupture may lead to impaired blood supply and possibly necrosis.[13]

It has been estimated that the treatment of pressure injuries costs the UK NHS 3.8million GBP per day.[16] and may prolong a patient's hospital stay with about 10 days.[17] Prevention of pressure injury is, therefore, cost effective and can result in shorter hospital stays.

LIMITATIONS

This study only investigated a period of 106 days. Larger studies may give a clearer picture of the situation. Only patients from one site (SVP) were included in the study. Further studies to analyse the development of pressure injuries in elderly people living in nursing homes or in the community and admitted to MDH would give a clearer picture. The patients included in our population are the frailest of patients. This may have had a strong bearing on the results. Our data collection did not include frailty levels.

RECOMMENDATIONS

- Setup of a working group between SVP and MDH to identify practices that can be improved to help reduce the number of pressure injuries in SVP patients referred to MDH for acute care
- Provision of more in-house services at SVP to decrease the number of patients needing transfer to MDH
- The introduction of risk stratification and preventive measures at A&E level.
- Avoidance of postponement of orthopedic operations.
- Review of the work practices in the Orthogeriatric department.
- Larger studies to decrease the bias introduced by small numbers.
- Regular reviews by nutritionists to ensure proper nutrition in at-risk individuals

CONCLUSION

Patients residing at SVP are among the frailest in the country. For a variety of reasons, their risk of developing pressure injuries is inherently higher than average. This is further compounded when they are referred to MDH for acute care. Pressure injury prevention has been shown to be possible with proper care. Prevention is cost effective, results in shorter hospital stays and improves the patients' morbidity, mortality and quality of life. Greater efforts at preventing pressure injuries in this specific population are warranted.

REFERENCES

1. Duncan KD. Preventing pressure ulcers: the goal is zero. Jt Comm J Qual Patient Saf. 2007;33:605.
2. Inman KJ, Sibbald WJ, Rutledge FS, et al. Clinical utility and cost-effectiveness of an air suspension bed in the prevention of pressure ulcers. JAMA. 1993;269:1139.
3. Padula WV, Mishra MK, Makic MB, et al. Improving the quality of pressure ulcer care with prevention: a cost-effectiveness analysis. Med Care. 2011;49:385.
4. Pham B, Teague L, Mahoney J, et al. Early prevention of pressure ulcers among elderly patients admitted through emergency departments: a cost-effectiveness analysis. Ann Emerg Med. 2011;58:468.

5. Cortés OL, Herrera-Galindo M, Villar JC, et al. Frequency of repositioning for preventing pressure ulcers in patients hospitalized in ICU: protocol of a cluster randomized controlled trial. BMC Nurs. 2021;20:121.
6. Gorecki C, Brown JM, Nelson EA, et al. Impact of pressure ulcers on quality of life in older patients: a systematic review. J Am Geriatr Soc. 2009;57(7):1175-1183.
7. Kottner J, Hahnel E, Trojahn C, et al. A multi-center prevalence study and randomized controlled parallel-group pragmatic trial to compare the effectiveness of standardized skin care regimens on skin health in nursing home residents: a study protocol. Int J Nurs Stud. 2015;52(2):598-604.
8. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17(6):763-771.
9. Hahnel E, Lichterfeld A, Blume-Peytavi U, Kottner J. The epidemiology of skin conditions in the aged: A systematic review. J Tissue Viability. 2017;26(1):20-28.
10. National Institute for Health and Care Excellence. Pressure ulcers: prevention and management. Clinical Guideline CG179. 2014.
11. Stechmiller JK, Cowan L, Whitney JD, et al. Guidelines for the prevention of pressure ulcers. Wound Repair Regen. 2008;16(2):151-68.
12. European Pressure Ulcer Advisory Panel (EPUAP). Guidelines on treatment of pressure ulcers. EPUAP Rev. 1999;1:31.
13. Headlam J, Illsley A. Pressure ulcers: an overview. Br J Hosp Med. 2020;81(12).
14. Wounds UK. Best Practice Statement: Care of the older person's skin. 2nd ed. London: Wounds UK; 2012.
15. Mervis JS, Phillips TJ. Pressure ulcers: pathophysiology, epidemiology, risk factors, and presentation. J Am Acad Dermatol. 2019;81(4):881-890.
16. NHS Improvement. NHS Improvement: annual report and accounts 2018/19. 2019.
17. Theisen S, Drabik A, Stock S. Pressure ulcers in older hospitalised patients and its impact on length of stay: a retrospective observational study. J Clin Nurs. 2012;21(3–4):380–387.

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ORIGINAL ARTICLE

Intimate Partner Violence and Perinatal Mental Health Disorders

Edith Agius, Andee Agius, Claire Zerafa, Ethel Felice, Neville Calleja

Purpose of study

This study aimed to assess the prevalence of intimate partner abuse amongst pregnant women attending the Perinatal Mental Health Clinic in Malta and were diagnosed with an antenatal or postnatal depression and/or anxiety disorder. Moreover, the socio-demographic variables associated with intimate partner abuse were also investigated.

Methodology

In this study, a survey research design using self-reported questionnaires was used after getting the necessary approvals. The questionnaire used, was an adapted version of the World Health Organisation (WHO) "Violence Against Women Structured Interview", which was modified and translated into Maltese by Debono in 2015, using the WHO translation protocol.

Results

In total, 100 mothers were eligible to participate. A total of 40 out of the 85 participating women (47.05%) reported one or more acts of psychological, verbal, physical or sexual abuse by their intimate partner during pregnancy. Out of the 40 abused women, 13 women (22.50%) reported one type of abuse, while 33 women (77.50%) reported more than one type of abuse. Verbal abuse (42.00%) and psychological abuse (39.00%) were the most common types of reported abuse during pregnancy, followed by physical (13.00%) and sexual abuse (12.00%). Using cross tabulations, the Pearson's Chi-square test examined the association between intimate partner abuse and several socio-demographic variables.

Conclusion

Intimate partner abuse during pregnancy is a worldwide problem. This study confirms that mothers suffering from an antenatal or postpartum depression and/or anxiety disorder are at a higher risk of experiencing intimate partner abuse during pregnancy.

Significance

Little is known about the prevalence of partner violence in pregnant women suffering from a mental health disorder. This study will aim to find out the prevalence of partner violence in such population. Moreover the socio demographic variable will give us more knowledge about risk factors related for experiencing partner abuse during pregnancy.

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Intimate partner violence refers to any behaviour within an intimate relationship that causes physical, psychological or sexual harm to those in the relationship.[1] Intimate partner abuse against women is a serious global problem due to its negative consequences on the woman's physical and mental health.[2] In a study done by the World Health Organisation (WHO) in 2005, revealed that the incidence of physically abused pregnant women was more than 5 in 11 of the 15 countries studied.[3] The lowest figure was 1% in Japan, and the highest was 28% in Peru. Moreover, it was found that in over 90% of women, the reported abuse was carried out by the biological father of the child. The majority of those who reported being beaten during pregnancy had experienced physical abuse by the same partner before being pregnant.[3] A Maltese study conducted in 2015 at the general obstetric wards amongst women after giving birth found that 22% of all mothers were exposed to one or more acts of domestic abuse.[4] This implied that 1 to 2 out of every 5 women had experienced partner abuse during pregnancy.

A meta-analysis conducted by Taillieu & Brownridge in 2010, found that intimate partner abuse during pregnancy is more common than many of the medical conditions pregnant women were routinely screened for. Moreover, this study concluded that although pregnancy was found to be a protective period for some women, it was clearly a period of increased risk of abuse for a significant proportion of pregnant women.[5]

The antenatal period provides a good opportunity for identifying women suffering from intimate partner abuse, because in this period, pregnant women may be more open to discuss partner abuse and may be more ready to make changes in order to protect their unborn baby.[6] For many women, their pregnancy period, may be their only point of contact and follow up with healthcare professionals.[7]

The mental health consequences of intimate partner abuse are extensive. Several studies, conducted across multiple countries, suggested there is a high prevalence rate of intimate partner abuse amongst women suffering from a mental disorder.[8,9] Moreover, Golding in 1999, found out that the severity and duration of physical partner abuse was related to the frequency and severity of depression.[8] A review which examined post-traumatic stress disorder (PTSD) among victims of domestic abuse, similarly, reported that the intensity of symptoms was associated with the extent, severity and type of abuse.[10] Limitations highlighted in these studies included; focusing only on perinatal depressive disorder and not on the full range of perinatal mental health disorders; not specifying the time period partner abuse was experienced and for including studies that did not use validated mental health screening tools.

MATERIALS AND METHODS

The research aim of this study was to assess the prevalence of intimate partner abuse amongst pregnant women attending the Perinatal Mental Health Clinic and diagnosed with an antenatal or postnatal depression and/or anxiety disorder. Moreover, the socio-demographic variables associated with intimate partner abuse were also to be investigated. Another objective of this study was to compare the data generated with the data documented as per a previous study done in Malta by Debono.[4]

Study design and participants

In this study, a survey research design using self-reported questionnaires was used after getting the necessary approvals. The questionnaire used in this study, was an adapted version of the WHO "Violence Against Women Structured Interview", which was modified and translated to Maltese by Debono.[4] using the WHO translation protocol.[11] Although, the WHO tool was already tested for reliability and validity in local[12] and international studies[13], the questionnaire used in the study by Debono[4], was re-tested using Test-Retest Reliability and Face and Content Validity methods.

The survey was divided into two sections. Section 1 consisted of seven questions which cover the emotional, physical and intimate health in a relationship. The purpose of this section was to identify those mothers who are experiencing intimate partner abuse during the pregnancy. Participants were considered to be victims of intimate partner abuse if they responded "Yes" to one (or more) of the questions listed in this section. Section 2 contained nine demographic questions about the participant and her partner.

Eligible criteria for participants included women aged 18 years of over, have the mental capacity to consent for participation and who can read and write in English and/or Maltese.

Data collection

All women attending for their visit with the Perinatal Psychiatrist at the Perinatal Mental Health Clinic, between February 2021 and May 2021, were invited to participate if they met the inclusion criteria. Eligibility was determined by the Perinatal

Psychiatrist leading the clinic as mental capacity to participate in the study was performed for every mother attending for a consultation at the clinic. Once consent was obtained the women completed the self-administered questionnaire.

Ethical considerations

Permission was obtained from the Director of the Department of Psychiatry, Consultant Perinatal Psychiatrist. Maltese Health Ethics Committee (HEC) and from Sheffield Hallam University Research Ethics Committee. The ethical considerations in this study were based on the Nuremberg Code [14], the Helsinki Declaration[15] and the WHO ethical guidelines on researching violence against women.[15]

To ensure autonomy, all participants were given detailed and comprehensive verbal and written information required to make an informed decision regarding their involvement in the research. A written consent form was not required as filling out the questionnaire signified consent. Moreover, all participants were informed that their contribution was on a voluntary basis and that they were free to accept, refuse or withdraw from the study at any time during the research process. To ensure confidentiality, participants were assured that no one except for the investigator would have access to the data gathered from each survey. Anonymity was also ensured since all forms were coded numerically, so that only the investigator could trace the patients' details, in case the participant disclosed that she or someone else was at risk of injury. Furthermore, privacy was safeguarded by providing participants, a private room to fill out the survey. Due to COVID-19 pandemic restrictions, partners were not allowed to accompany the mothers for the appointments, hence this was an added precaution. Due to sensitive nature of the questionnaire, all the participants were asked by the midwife if they felt the need to discuss any personal issues, after filling out the survey. In addition, they were encouraged to take with them a leaflet produced by the local Commission on Domestic Violence, with local helplines should they feel the need to seek help later. To ensure safety for the participants, COVID-19 hospital protocols were followed at all times. In cases, were the questionnaire indicated a risk to the mother and/or children, the researcher discussed with the Consultant Psychiatrist and appropriate mitigation was taken.

DATA ANALYSIS

The data gathered from the surveys was inputted manually and analysed using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 22 and Microsoft Office Excel (2019). The Pearson's chi-square test was used to assess the association between two categorical variables.

RESULTS

In total, 100 mothers were eligible to participate in the study. Out of these, 85 mothers completed and handed in the questionnaire. Therefore, this yielded a response rate of 85%.

Demographic characteristics of women and their partner

Digital Supplementary File 1 and **2** present the sociodemographic details of female and male participants, respectively. Most of the participants were between 31 and 35 years old. Most of the participants and their intimate partners were both Maltese. However, when comparing non-Maltese cohorts, the female to male ratio was 1:3. More than half of the participants (51%) were found to be married to their intimate partner, 26% claimed to be cohabitating with their intimate partner and 23% were single. 60% of all the women had obtained post-secondary and tertiary education when compared to their partners (48%). With regards to employment status, 61% of the women and 87% of their partners were in a fixed employment. When assessing smoking habits, the majority of the women were non-smokers (52%) and only 15% smoked on a daily basis. On the other hand, 40% of their partners were non-smokers and 38% smoked daily. With regards to alcohol use, 41% of the women reported that they did not drink any alcohol during pregnancy, 36% drank only occasionally and 2% reported to drink alcohol daily. When asked about their partner drinking habits, 40% reported that their partner does not drink any alcohol, 38% reported that their partner drinks alcohol daily and 13% reported that their partner only drinks occasionally. Regarding drug use, 92% of the women did not use any illicit drugs and only 2% of participants reported to use drugs occasionally. When asked about their partners' habits, 85% reported that their partner never used any drugs, 2% reported the usage of drugs daily and 5% reported the usage of drugs occasionally.

Frequency and severity of intimate partner abuse during pregnancy

Frequency of intimate partner abuse during pregnancy defined by types of abuse

40 out of 85 women (47%) reported one or more acts of psychological, verbal, physical or sexual abuse by

their intimate partner during pregnancy. This implies that amongst the mothers attending the Perinatal Mental Health clinic, almost half of the mothers will experience some form of intimate partner abuse during their pregnancy. Out of the 40 abused women, 13 women (23%) reported one type of abuse, while 33 women (78%) reported more than one type of abuse. Amongst the 85 participants, verbal abuse (n=36, 42%) and psychological (n=33, 39%) were the most common reported types of abuse during pregnancy. Both physical (n=11, 13%) and sexual (n=10, 12%) abuse were experienced at lower frequencies.

Frequency of psychological intimate partner abuse during pregnancy

The most common reported act of psychological abuse was that partners insisted on knowing where the women were at all times (n=19, 22%), that their partner got angry if they spoke to other men (n=20, 24%) and the restriction of finances (n=17, 20%). In contrast, a fewer number of women claimed that their partner restricted their contact with family (n=11, 13%), restricted their contact with friends (n=11, 13%) and that their partner expected their permission before seeking health care (n=10, 12%).

Frequency and severity of verbal intimate partner abuse during pregnancy

The most common type of verbal abuse reported was that of partners making women feel bad about themselves during pregnancy (n=30, 35%). Additionally, women reported they were humiliated by their partner in front of other people (n=20, 24%) and that their partner did things to intimidate or scare them on purpose (n=21, 25%). Moreover, 9 of the participants, reported that their partner had threatened to hurt either them or someone they care about (11%). 6 out of these 9 women, reported that this abuse occurred on many occasions.

Frequency and severity of physical intimate partner abuse during pregnancy

The most reported physical abuse included being pushed, shoved, or having their hair pulled (n=8, 12%) and that of being slapped or having things thrown at (n=10, 9%). Five mothers reported that they were kicked, dragged or beaten; 4 mothers reported that they were punched during pregnancy, 2 mothers reported being choked or burnt; 2 mothers reported being punched specifically in the abdomen and 1 mother was even threatened with a weapon. Most of the physical abuse reported was experienced on many occasions.

Frequency and severity of sexual intimate partner violence during pregnancy

The most common sexual abuse reported by participants was that women participated in sexual intercourse because they were afraid of their partner's actions in case of refusal (n=9, 11%). Moreover, 5 women reported they were forced to have sexual intercourse and 6 women reported they were forced to degrading activities against their will. The majority of the sexual abuse reported was experienced on many occasions.

Reported fear of partner

Sixty-two participants (73%) were never afraid of their intimate partner, while 15 mothers (18%) reported that sometimes they fear their partner. Four mothers (5%) reported feeling almost constantly scared and 4 mothers (5%) reported they did not want to answer.

Cross tabulations

Association between demographic variables and intimate partner abuse during pregnancy

Thirty-three out of 85 women (39%) experienced some form of psychological abuse by their intimate partners. There was a larger percentage of females aged 25 years or less who were abused (30%) compared to not abused (10%); and a smaller percentage of females aged 31 years or more who were abused (42%) compared to not abused (64%). These percentage differences were significant (p=0.017). Moreover, 11 out of 85 women (13%) experienced physical abuse by their intimate partner during pregnancy. A large percentage of females who were abused were within the 20-25 years age group (45%). These percentage differences were significant as well (p=0.030). Hence, it can be summarized that psychological and physical abuse by intimate partners was more prevalent in the younger females than in the older ones. Mothers who experienced psychological (67%, p=0.023) and sexual abuse (60%, p=0.021) were found to be associated with a partner of age between 26 and 35 years whilst mothers who experienced physical abuse (73%, p=0.001) were more likely to have a partner of age between 20 and 30 years old.

Women's level of education was found to be significantly associated with psychological abuse. Women who had a primary, secondary or postsecondary level of education (85%) were found to be significantly more at risk of physiological abuse then compared to women with tertiary education (p=0.014). Women without a fixed job were found to be more associated with psychological partner abuse (55%, p=0.032). No fixed partner employment was

Table 1 *Association between the prevalence of intimate partner abuse in the general pregnant population when compared to pregnant women diagnosed with a perinatal mental health disorder*

	Population	Abused	Not Abused	Total	p-value
Psychological Abuse	General	45 (15.30%)	252 (84.84%)	297	*< 0.00001*
	Perinatal	33 (38.32%)	52 (61.17%)	85	
Verbal Abuse	General	36 (12.12%)	261 (87.88%)	297	*< 0.00001*
	Perinatal	36 (42.35%)	49 (57.65%)	85	
Physical Abuse	General	8 (2.69%)	289 (97.30%)	297	*0.04871*
	Perinatal	11 (12.94%)	74 (87.05%)	85	
Sexual Abuse	General	5 (1.69%)	291 (98.31%)	296	*0.000026*
	Perinatal	10 (11.76%)	75 (88.23%)	85	
Any form of Abuse	General	66 (22.23%)	230 (77.70%)	296	*< 0.00001*

found to be related to a higher risk of psychological (18%, p=0.001), verbal (11%, p=0.035) and physical abuse (27%, p=<0.0001).

Women who reported physical abuse were more at risk of daily alcohol misuse during pregnancy (9%, p=0.027). Daily smoking habits in men were found to be significantly related to higher rates of psychological abuse (60%, p=0.006) and sexual abuse (80%, p=0.018). Partner's daily use of drugs was found to increase the risk of psychological abuse (6%, p=0.008), verbal abuse (6%, p=0.001), physical abuse (18%, p=<0.0001) and sexual abuse (20%, p=<0.0001).

With regards to marital status, being single and living with partner out of wedlock were found to increase the risk of psychological abuse (p=0.006) and physical abuse (45%, p=0.036). Fear of their partner was found to be more prominent in women who suffered physical abuse (73%, p=<0.0001) and sexual abuse (90%, p=<0.0001) when compared to women who suffered from psychological (42%, p=<0.0001) and verbal abuse (50%, p=<0.0001).

Association between the prevalence of intimate partner abuse in the general pregnant population when compared to pregnant women diagnosed with a perinatal mental health disorder.

Pregnant women suffering from an antenatal or postpartum depression and/or anxiety disorder were found to be at a significant higher risk for all types of intimate partner abuse when compared to the general population of pregnant women (Table 1).

CONCLUSIONS

Intimate partner abuse during pregnancy is a worldwide problem. This study confirms that mothers suffering from an antenatal or postpartum depression and/or anxiety disorder are at a higher risk of experiencing intimate partner abuse during pregnancy. Moreover, young women with lower educational levels who are economically dependent on their partner and who are not married are at the highest risk of suffering from verbal, physical, psychological or sexual abuse. More needs to be done to identify pregnant mothers at risk of abuse at an early stage and offer the necessary interventions.

Knowing the prevalence and socio-demographic variables of intimate partner abuse are only the first step in developing and implementing new interventions to identify and respond early to such abuse. In fact, guidelines published by the WHO in 2013[17] and the National Institute for Health and Care Excellence (NICE) in 2014[18], recommend that mental health professionals should screen for partner abuse as part of a comprehensive psychiatric clinical assessments and that they should be able to provide support and ensure safety when partner abuse is disclosed.

Due to the COVID-19 pandemic, the prevalence of intimate abuse reported in this study might have been more than predicted. Worldwide records from helplines, police forces and other service providers indicate an increase in reported cases of domestic abuse, mostly child maltreatment and partner abuse against women during the COVID-19 pandemic. [19]

REFERENCES

1. World Health Organization. Understanding and addressing violence against women: Intimate partner violence [Internet]. Geneva: WHO; 2021 [cited 2023 Apr 5]. Available from: https://www.who.int/publications-detail-redirect/WHO-RHR-12.36
2. González CJ, Polo UC, González AF, et al. Prevalence and characteristics of intimate partner violence against women with severe mental illness: a prevalence study in Spain. Community Ment Health J. 2014;50:841–7.
3. World Health Organization. Summary report: WHO multi-country study on women's health and domestic violence against women [Internet]. Geneva: WHO; 2005 [cited 2021 Jan 14]. Available from: https://www.who.int/reproductivehealth/publications/violence/24159358X/en/
4. Debono C, Borg Xuereb R, Scerri J, Camilleri L. Intimate partner violence: psychological and verbal abuse during pregnancy. J Clin Nurs. 2017;26:2426–38.
5. Taillieu T, Brownridge D. Violence against pregnant women: prevalence, patterns, risk factors, theories, and directions for future research. Aggress Violent Behav. 2010;15:14–35.
6. O'Reilly R, Beale B, Gillies D. Screening and intervention for domestic violence during pregnancy care: a systematic review. Trauma Violence Abuse. 2010;11:190–201.
7. Devries K, Kishor S, Johnson H, et al. Intimate partner violence during pregnancy: analysis of prevalence data from 19 countries. Reprod Health Matters. 2010;18:158–70.
8. Golding JM. Intimate partner violence as a risk factor for mental disorders: a meta-analysis. J Fam Violence. 1999;14:99–132.
9. Trevillion K, Hughes B, Feder G, et al. Disclosure of domestic violence in mental health settings: a qualitative metasynthesis. Int Rev Psychiatry. 2014;26:430–44.
10. Jones L, Hughes M, Unterstaller U. Post-traumatic stress disorder (PTSD) in victims of domestic violence: a review of the research. Trauma Violence Abuse. 2001;2:99–119.
11. World Health Organization. Process of translation and adaptation of instruments [Internet]. Geneva: WHO; 2014 [cited 2023 Apr 5]. Available from: http://www.who.int/substance_abuse/research_tools/translation/en/
12. Fsadni M, Borg A, Bugeja S, et al A nationwide research study on the prevalence of domestic violence against women in Malta and its impact on their employment prospects [Internet]. 2011 [cited 2023 Apr 5]. Available from: http://www.eurofound.europa.eu/ewco/2010/12/MT1012019I.htm
13. Garcia-Moreno C, Jansen H, Ellsberg M, et al. Prevalence of intimate partner violence: findings from the WHO multi-country study on women's health and domestic violence. Lancet. 2006;368:1260–9.
14. Office for Human Research Protections. The Nuremberg Code [Internet]. 2005 [cited 2023 Apr 5]. Available from: http://www.hhs.gov/ohrp/archive/nurember.html
15. World Medical Organization. WMA declaration of Helsinki – ethical principles for medical research involving human subjects [Internet]. 1996 [cited 2023 Apr 5]. Available from: http://www.wma.net/en/30publications/10policies/b3/
16. World Health Organization. Putting women first: ethical and safety recommendations for research on domestic violence against women [Internet]. Geneva: WHO; 2001 [cited 2023 Apr 5]. Available from: https://www.who.int/publications-detail-redirect/WHO-FCH-GWH-01.1

17. World Health Organization. Global and regional estimates of violence against women [Internet]. Geneva: WHO; 2013 [cited 2023 Apr 5]. Available from: https://www.who.int/publications-detail-redirect/9789241564625
18. National Institute for Health and Care Excellence. Domestic violence and abuse: multi-agency working [Internet]. 2014 [cited 2021 Apr 30]. Available from: https://www.nice.org.uk/guidance/ph50/resources/domestic-violence-and-abuse-multiagencyworking-pdf-1996411687621
19. UN Women Data Hub. Measuring the shadow pandemic: violence against women during COVID-19 [Internet]. 2021 [cited 2023 Apr 5]. Available from: https://data.unwomen.org/publications/vaw-rga

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ORIGINAL ARTICLE

Impulse control disorders following subthalamic nucleus deep brain stimulation in Parkinson's disease: A retrospective analysis

Theresa Mallia, Norma McKean, Josanne Aquilina

Background

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is considered in patients with Parkinson's disease (PD) when there is suboptimal control of motor symptoms. While effective at improving some of these symptoms, its effect on impulsive behaviour can be variable. This retrospective analysis examines the incidence of post-operative impulse control disorders (ICDs) in PD patients who underwent bilateral STN-DBS surgery between January 2011 and December 2018.

Materials and Methods

A questionnaire based on the DSM-5 criteria was used for data collection.

Results

The patient cohort involved a total of 38 patients. Questionnaires were returned by 36 patients (95%). Seven patients (19%) fulfilled diagnostic criteria for ICDs, while six patients (17%) showed features of ICDs that did not fulfill diagnostic criteria.

Conclusion

A significant proportion of our patient cohort reported impulsive behaviour following STN- DBS surgery. This finding therefore warrants evaluation during the follow-up visits of such patients.

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a recognised treatment modality in the management of Parkinson's disease (PD). The mechanism of action, although not yet fully understood, involves selective modulation of disrupted basal ganglia thalamocortical circuits and basal ganglia–brainstem projections, allowing closer to normal motor and non-motor network function.[1]

The primary indication for STN-DBS surgery in PD is disabling motor fluctuations and/or dyskinesias despite optimal medical therapy. Long-term results have confirmed substantial clinical improvement in medically refractory tremor, dopaminergic-responsive motor and non-motor features, as well as in the quality of life of these patients.[2-4]

The effect of STN-DBS on impulsive behaviour and behavioural addictions can be variable. In patients with PD, this behaviour has been linked to dopaminergic treatment, especially dopaminergic agonists with selective affinity for D2-D3 dopamine receptors. Several prospective studies have shown either no increase or alleviation of impulsive behaviour following this procedure. However, worsening of pre-existing behavioural disorders and onset of new impulse control disorders (ICDs) have also been recorded.[5] The four main types of ICDs encountered are pathological gambling, compulsive buying, hypersexuality and compulsive eating.[6]

Risk factors for the development of ICDs include male gender, young age or younger age at PD onset, a past history of smoking, substance misuse, depression and a personality profile characterised by impulsiveness.[6,7] Cultural factors may also contribute to both the prevalence and type of ICD depicted by the patient.[8,9]

This retrospective analysis examines the number of patients who developed impulsive behaviour following STN-DBS surgery. It was performed as part of a service evaluation and continued patient follow-up.

MATERIALS AND METHODS

All PD patients who underwent bilateral STN-DBS surgery between January 2011 and December 2018 in Mater Dei Hospital, Malta, were recruited in this analysis. All patients were above 18 years of age and consented to participation. These patients had shown significant improvement with levodopa therapy, but despite optimal treatment, symptoms were uncontrolled as the disease progressed. None of the patients had a significant history of psychiatric disorders or dementia.

A questionnaire based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) was created in both English and Maltese and answered by the patient cohort. The drug history and date of DBS surgery were also registered. All participants were taking at least one anti-parkinsonian drug, and the use of carbidopa, levodopa, entacapone, rasagiline, benserazide and ropinirole, either alone or in combination, was recorded.

To compare clinical features between groups, continuous data was expressed as mean ± standard deviation (SD), whilst differences in continuous variables were examined using the paired t-tests.

RESULTS

The analysis was carried out on 36 eligible participants, 24 male and 12 female. The mean age at surgery was 58.7 years (SD ± 9.6), with the mean follow up after surgery being 51.2 months (SD ± 28.2).

Of the 35 patients who answered the questionnaire in its entirety, seven patients (19%) fulfilled diagnostic criteria for ICDs, with two of these having two concomitant ICDs. Features of ICDs not reaching diagnostic criteria was documented in 10 patients (29%), with four of these patients having another ICD. Therefore, 13 patients (36%) had either a confirmed diagnosis, or features of, ICDs. One male participant declined to answer questions related to hypersexuality, however he denied other post-operative impulsive behaviour.

Of the seven patients who were found to be suffering from ICDs, five (71%) were male. The two participants who developed two concomitant ICDs were both male. Three males and three female patients developed features of ICDs but did not fulfil diagnostic criteria. Of the remaining 23 patients with no features of ICDs, 19 (83%) were male and 8 (17%) were female.

Seven (54%) of the 13 patients with impulsive behaviour were on dopamine agonists (ropinirole), while ten (43%) of the 23 patients without features of ICDs were on ropinirole treatment. Furthermore, eight (35%) of the 23 patients without ICDs were on a single anti-parkinsonian medication, while three (43%) of the seven patients with ICDs and one (17%) of the six patients with ICD features were on a single drug. When calculating the dopamine equivalent doses between the patients who developed impulsive behaviour and those who did not, no significant difference was established (p=0.21).

When analysing the difference between the patients with features of impulsivity and those without, there was no statistically significant difference in age at time of study (p=0.4), age at DBS insertion (p=0.2), and time from DBS surgery to analysis (p=0.9).

Interestingly, one patient with a history of non-pathological gambling prior to PD diagnosis developed hypersexuality and compulsive eating post-operatively; but did not develop pathological gambling.

A graphical breakdown of separate ICDs can be found below in **Figure 1**, **Figure 2** and **Figure 3** and a more detailed account of the results in **Table 1**.

DISCUSSION

This analysis confirms that ICDs (19%) and features of ICDs (17%) are evident after chronic STN-DBS (with a mean follow-up of 51.2 months).

Several studies have been performed to assess the development of impulsive behaviour following STN-DBS insertion. A retrospective analysis by Merola et al including 150 participants with a post-operative follow up period of 51.6 months (SD ± 25.2), showed that 7.3% of post-operative STN-DBS patients developed new-onset ICDs, with these being more common in females. Furthermore, 45% of the patients suffering from the impulsive behaviour were noted to have developed multiple ICDs, namely pathological gambling, hypersexuality and/or compulsive shopping.[11]

Two other retrospective studies also showed the occurrence of de-novo impulsive behaviour following bilateral STN-DBS surgery. Kim et al showed that nine of 89 patients (8%) developed such behaviours, with these being more common in males.[12] 19% of the population studied by Halbig et al developed ICDs after an average of 34 months following the surgery, with the most common being compulsive shopping.[13]

A prospective analysis by Amami et al reported that 6 out of 43 patients (14%) developed de-novo impulse control behaviours after 36 months of continuous STN- DBS. However, these symptoms were transient and lasted for an average of 15 months. Compulsive eating was the most ICD reported, whilst pathological gambling was the least.[14]

Similar to our results, a male predominance[12-14] and absence of a relationship between impulsivity and post-operative dopaminergic doses is reported in the above studies.[12,14] The analysis by Amami et al[14,] highlights the importance of prospective studies, as such symptoms may be transient and resolve spontaneously.

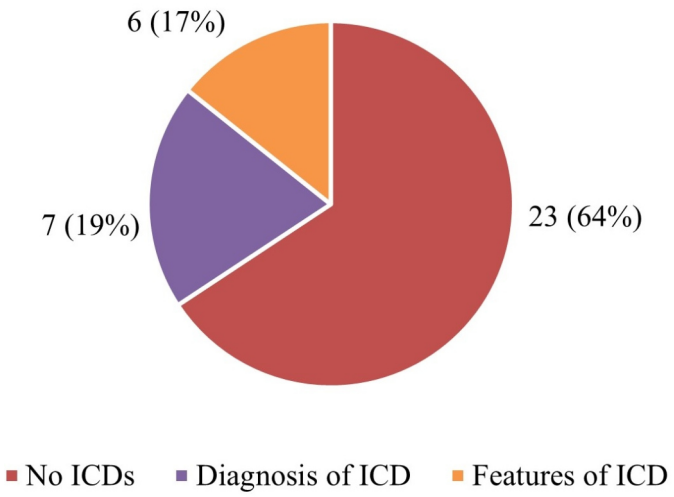


Figure 1 *Post-operative STN-DBS patients*

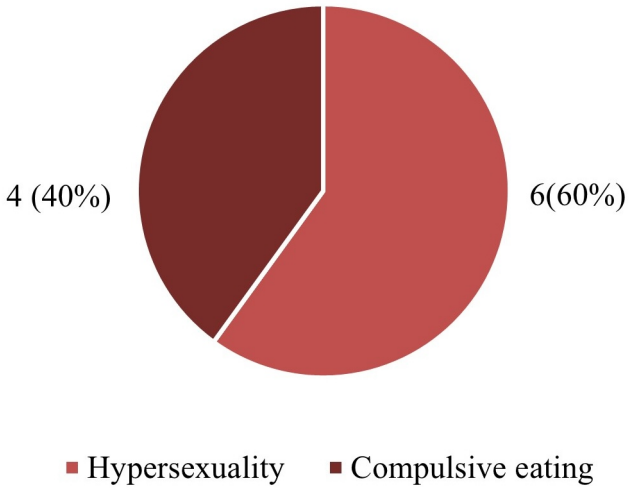


Figure 2 *Features of ICDs not fulfilling diagnostic criteria*

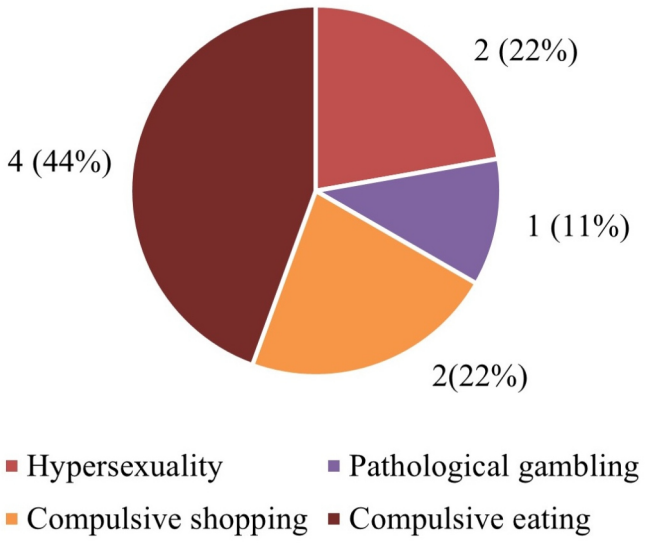


Figure 3 *ICDs reaching diagnostic criteria*

Table 1 *Patients with post-operative impulsive behaviour*

Patient	Age* , Gender	Year of DBS surgery	Post-op ICDs/ features of ICDs	Anti-parkinsonian medication	Dopa equivalent dose of ropinirole[10]
1	57, male	2011	**Compulsive shopping** Features of hypersexuality	Ropinirole 2mg TDS	120mg
2	57, female	2012	Features of compulsive eating	Stalevo® (entacapone-levodopa- carbidopa) Ropinirole 8mg TDS	480mg
3	70, male	2013	**Pathological gambling** Hypersexuality Features of compulsive eating	Stalevo® Ropinirole 2mg TDS	120mg
4	77, female	2013	Features of compulsive eating	Stalevo® Ropinirole 3mg TDS Amantadine	180mg
5	70, female	2014	Features of hypersexuality	Stalevo® Ropinirole 1mg TDS	60mg
6	74, female	2015	**Compulsive eating** Features of hypersexuality	Sinemet® (carbidopa-levodopa) Ropinirole 3.5mg TDS	210mg
7	57, male	2015	Features of hypersexuality	Stalevo® Sinemet®	/
8	70, male	2016	**Compulsive shopping Hypersexuality**	Madopar® (levodopa-benserazide) Carbidopa	/
9	67, male	2016	Features of compulsive eating	Ropinirole 2mg TDS Rasagiline	120mg
10	62, male	2017	**Compulsive eating**	Stalevo®	/
11	52, female	2017	**Compulsive eating**	Co-careldopa® (carbidopa-levodopa)	/
12	47, male	2017	Features of hypersexuality	Stalevo®	/
13	47, male	2018	**Compulsive eating** Features of hypersexuality	Stalevo®	/

**Age (years) at time of study*

Several different hypotheses have been suggested to explain the aetiopathogenesis of ICDs. One hypothesis suggests that impulsivity can occur through the stimulation of the STN and neighbouring tracts, through changes in the processing of associative and limbic information towards cortical and subcortical regions.[15,16] Furthermore, minimal changes in stimulation site and parameters can also lead to different effects. For example, stimulation of the most superior contact within the STN nucleus produces greater effects on decision-making tasks than stimulation of the deepest contact.[17]

Another explanation for the development of impulsivity following DBS insertion is microtrauma during the surgical procedure that may result in damage to the STN or its neighbouring structures associated with motivational behaviours.[14]

In medically treated patients, higher levodopa dosages are associated with the development of ICDs. Therefore, another postulated hypothesis is that patients who undergo DBS insertion have a total higher cumulative exposure to dopaminergic medication due to longer disease duration and

greater disease severity, contributing to the development of such behaviour.[14]

Postoperative dopaminergic therapy reduction, or lack thereof, is also likely to play an important role. Polyvios et al showed that patients who remained on dopaminergic medication postoperatively were more likely to exhibit ICDs.[18] Similarly, in a cross-sectional study by Weintraub et al, patients who remained on dopaminergic medication postoperatively had a poorer outcome in terms of ICDs, when compared to patients in whom dopaminergic treatment was reduced. This is possibly because DBS can sensitize the brain to the behavioural effects of dopamine replacement therapy, especially on an existing background of high impulsivity.[19] Djamshidian et al showed that patients treated with dopamine agonists made significantly more irrational choices than patients who were not on such drugs, with this study also concluding that STN-DBS has no effect in this task.[20]

It has also been suggested that improvement of motor function following DBS surgery facilitates the full expression of behavioural abnormalities that have developed secondary to pre-operative dopamine replacement therapy.[21]

Several limitations were identified in this analysis. Firstly, the cohort of patients was relatively small, with the total number of eligible patients being 38, of which 36 participated. The high questionnaire return rate is a clear strength in this analysis, as 95% of the patients identified participated. This is significant in that the analysis is free of recruitment bias and so gives a clear snapshot of our patient population.

Furthermore, patients may have been subject to response bias as the study was carried out by having patients answer a questionnaire. Also, there was no standardised assessment of pre-operative ICDs in our cohort of patients, making the exclusion of pre-operative ICDs subject to recall bias.

This analysis is a snapshot of DBS patients in our centre, highlighting the reality of ICDs in this patient population. Future work focusing on prospective groups of PD patients who are planned to undergo surgery compared with a control group of non-surgical patients may be more revealing of the true relationship between ICDs and STN-DBS.

CONCLUSION

This analysis confirms that a substantial number of patients suffer from ICDs following chronic STN- DBS. This highlights the importance of screening for ICDs, both prior to DBS surgery and post-operatively during regular follow-up visits, as this would allow a more holistic, effective, and appropriate management of the impulsive behaviours.

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REFERENCES

1. DeLong MR, Wichmann T. Basal Ganglia Circuits as Targets for Neuromodulation in Parkinson Disease. JAMA Neurol. 2015;72:(1)1354-60.
2. Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord. 2006;21 Suppl 14:290-304.
3. Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. Neurology. 2012;79:(1)55-65.
4. Castrioto A, Lozano AM, Poon YY, et al. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. Arch Neurol. 2011;68:(12)1550-6.
5. Abbes M, Lhommée E, Thobois S, et al. Subthalamic stimulation and neuropsychiatric symptoms in Parkinson's disease: results from a long-term follow-up cohort study. J Neurol Neurosurg Psychiatry. 2018;89:(8)836-43.
6. Gatto EM, Aldinio V. Impulse Control Disorders in Parkinson's Disease. A Brief and Comprehensive Review. Front Neurol. 2019;10:351.

7. Maloney EM, Djamshidian A, O'Sullivan SS. Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinson's disease, atypical Parkinsonian disorders and non-Parkinsonian populations. J Neurol Sci. 2017;374:47-52.
8. Cossu G, Rinaldi R, Colosimo C. The rise and fall of impulse control behavior disorders. Parkinsonism Relat Disord. 2018;46:S24-9.
9. Vela L, Martínez Castrillo JC, García Ruiz P, et al. The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: A cross-sectional multicenter study. J Neurol Sci. 2016;368:150-4.
10. Turner J. Parkinson's Measurement [Internet]. [cited 2022 Jan 5]. Available from: https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm
11. Merola A, Romagnolo A, Rizzi L, et al. Impulse control behaviors and subthalamic deep brain stimulation in Parkinson disease. J Neurol. 2017;264:(1)40-8.
12. Kim YE, Kim HJ, Kim HJ, et al. Impulse control and related behaviors after bilateral subthalamic stimulation in patients with Parkinson's disease. J Clin Neurosci. 2013;20:(7)964-9.
13. Hälbig TD, Tse W, Frisina PG, et al. Subthalamic deep brain stimulation and impulse control in Parkinson's disease. Eur J Neurol. 2009;16:(4)493-7.
14. Amami P, Dekker I, Piacentini S, et al. Impulse control behaviours in patients with Parkinson's disease after subthalamic deep brain stimulation: de novo cases and 3-year follow-up. J Neurol Neurosurg Psychiatry. 2015;86:(5)562-4.
15. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev. 1995;20:(1)128-54.
16. Temel Y, Kessels A, Tan S, et al. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. Parkinsonism Relat Disord. 2006;12:(5)265-72.
17. Smeding HM, Goudriaan AE, Foncke EM, et al. Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. J Neurol Neurosurg Psychiatry. 2007;78:(5)517-9.
18. Polyvios D, Rickards H, Cavanna AE. Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. Parkinson's Dis. 2011;2011:1-6.
19. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67:(5)589-95.
20. Djamshidian A, O'Sullivan S, Foltynie T, et al. Dopamine agonists rather than deep brain stimulation cause reflection impulsivity in Parkinson's disease. J Parkinsons Dis. 2013;3:(2)139-44.
21. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry. 2002;72:(6)701-7.

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ORIGINAL ARTICLE

Characteristics & outcomes of children presenting to an Emergency Department with chest pain

Janine Borg, Yana Dimech, Francesca Cassar Galea, Victor Grech, Ruth Farrugia

Background

Chest pain is a frequent presenting complaint to the paediatric emergency department. Although most cases are benign in aetiology, children are still extensively investigated. This study aims to assess whether cardiac risk factors in children with nontraumatic chest pain presenting to paediatric emergency department are appropriately identified and investigated, to review use of cardiac biomarkers and to audit documentation of cardiac risk factors.

Methods

Risk factors in history and examination were identified from international guidelines. Chi tests were used to compare rates of investigations in patients with red flags versus those without. Yield of investigations and documentation for risk factors were also assessed.

Results

A total of 130 children were included, median age 12 years. There were no significant differences in investigation rates between patients with cardiac risk factors (n = 92) and those without (n = 38). Yield from all investigations was minimal. Documentation was poor, with less than two thirds documentation rate for any cardiac risk factor.

Conclusion

Our study confirms that chest pain in children is usually due to benign causes. The yield of blanket laboratory investigations is limited. We suggest a clinical pathway to improve documentation and rationalise use of investigations in children presenting with chest pain to the emergency department.

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Chest pain is a frequent presenting complaint to the paediatric emergency department (PED), with attendances increasing over time.[1] Children mostly have a benign underlying cause, with underlying cardiac pathology present in less than 1%.[2-4] Even though most patients with cardiac aetiology can be identified by a detailed clinical history and examination, an extensive work up is often done. Children with chest pain are also usually triaged as urgent and may take the place of more unwell patients who are triaged at lower urgency.

The primary aim of this study is to assess whether all children with cardiac risk factors are appropriately identified and investigated and to review the use of cardiac biomarkers in children presenting with chest pain to the paediatric emergency department. The secondary aim is to audit the documentation of cardiac risk factors in both history and examination. The ultimate outcome will be a management pathway for children with chest pain in the local setting.

MATERIALS AND METHODS

This is a retrospective observational study involving consecutive patients under the age of 16 years presenting with nontraumatic chest pain to the PED at Mater Dei Hospital in Malta over a period of 5 months between October 2019 to February 2020. The original aim had been to include patient attendance over the whole year, but this was halted because of the COVID pandemic and resultant marked drop in PED patient attendance.[5,6]

Relevant data was obtained from the emergency sheet for discharged patients or the medical file for patients who were admitted to hospital, and this coded data was input into an Excel spreadsheet. The following was included: demographic data including age and gender, time of attendance, clinical presentation, duration of symptoms, associated symptoms, risk factors for underlying cardiac cause, past medical history, investigations, final diagnosis and disposition. Documentation of 'no chronic health problems' was regarded as a negative history for any underlying cardiac or systemic conditions related to chest pain. Investigations included routine blood tests, cardiac biomarkers, electrocardiograms (ECG) and imaging performed at PED. All ECGs were reviewed by a paediatric cardiology trainee. Permission to access data was obtained from the data protection office at Mater Dei Hospital.

Red flags (essential points for identifying cardiac pathology) in the history and examination were identified from international guidelines on the management of children presenting with chest pain at the paediatric emergency department[7-9], as listed in **Table 1**.

Rate and yield of investigations were compared between the group of patients with red flags identified in history or examination to those without any red flags. Chi tests were used assess for significance. Documentation was also assessed for these relevant red flags in history and examination.

RESULTS

All patients presenting with nontraumatic chest pain (n = 130) were included; these accounted for 1.2% of total attendances to PED (n = 10,438) during the study period. There was slight male preponderance with 53% males (n = 69). Median age was 12 years (Interquartile range 9 –14).

Table 1 *Red flags in the history and examination*

Red flags in history taking
Crushing/compressive pain
Exertional symptoms
Radiation to back or arm
Associated symptoms; dizziness, syncope, palpitations, haemoptysis
PMH of cardiac disease, CTD, clotting abnormalities, Kawasaki disease, ICD
Previous cardiac arrest
FH of cardiac disease, sudden death at a young age, inherited arrhythmias
Hypercoagulable state
Recent surgery
Cocaine or amphetamine use
Red flags for examination findings
Murmur
Signs of heart failure: limb oedema or hepatomegaly or pulmonary oedema
Pericardial rub
Decreased/muffled heart sounds
Fever >38.5°C with no obvious source
Haemodynamic instability: hypotension
ECG changes suggestive of acute cardiac pathology

Abbreviations: PMH - *Past Medical History;* CTD - *Connective Tissue Disorder;* ICD - *Implantable Cardiac Defibrillator;* FH - *Family History*

This was the first episode of chest pain for nearly half of the patients (n = 60) with the majority (n = 100) having pain duration of less than 6 hours and 17 patients being symptomatic for over 24 hours. The pain was localised to the left or mid chest in nearly all patients (n = 120). Twelve patients had underlying medical conditions relevant for cardiac aetiology, namely cardiac disease, congenital heart disease, CTD or previous history of Kawasaki disease. None had Marfan's syndrome or an ICD.

Eighty seven patients (67%) had red flags identified on history taking, with the most common being crushing chest pain, followed by fainting (n = 34), as documented in Table 2. Of these, nearly half (n = 40) had 1 red flag, with a maximum of 4 red flags identified in 2 patients. The majority of patients (92%; n = 120) had no relevant findings on clinical examination.

Overall, two thirds of patients had blood tests, with the most common being full blood count, renal profile (n= 86) and troponin (n = 85). Patients having cardiac risk factors (n = 92) had a similar rate of investigations as patients without risk factors (n = 38), as detailed in Table 3.

The yield from all investigations was minimal. Cardiac markers were requested in 85 patients; there was 1 deranged troponin result (Troponin T >14 ng/L) and 2 deranged CK results (CK >192 U/L), in separate patients. All 3 were referred for cardiology follow up and none of them had evidence of cardiac pathology. Full blood count was only significant for 1 patient who was diagnosed with microcytic anaemia and one patient had raised creatinine on renal profile. Of note, for the 45 patients without cardiac biomarkers, 36 (80%) had red flags in history or examination.

ECG was performed for 121 patients; of these 86 (71%) had red flag findings in history or examination.

Table 2 *Frequency of red flag findings in history and examination (total of 92 patients)*

Red Flags History	Positive findings n (%)	
Crushing/Compressive pain	37	(40)
Exertional symptoms	22	(24)
Radiation to back or arm	17	(18)
Associated symptoms: dizziness, syncope, palpitations, haemoptysis	44	(48)
PMH of cardiac disease, CTD, clotting anomalies, Kawasaki, ICD	12	(13)
Previous cardiac arrest	0	
FH of cardiac disease or sudden death	7	(8)
Hypercoagulable state	0	
Recent Surgery	0	
Drug abuse	1	(1)
Red Flags Examination findings	**Positive findings n (%)**	
Murmur	3	(3)
Signs of cardiac failure: hepatomegaly or limb or pulmonary oedema	0	
Pericardial rub	0	
Decreased/muffled heart sounds	0	
Fever >38.5°C (with no obvious source)	8	(9)
Haemodynamic instability: hypotension	0	
ECG changes suggestive of acute cardiac pathology	0	

Table 3 *Investigation frequency and outcome by group*

	Patients with Red Flags n (%)		Patient without Red Flags n (%)		Chi	*p* value
Investigations						
ECG	85	(91)	36	(95)	3.84	0.45
CXR	51	(55)	19	(50)	0.32	0.57
Echo	4	(4)	1	(3)	0.21	0.64
Holter	0		0		-	-
Cardiac MRI	0		0		-	-
Troponin	56	(61)	29	(76)	2.83	0.09
CK	45	(49)	25	(66)	3.08	0.08
Full blood count	57	(62)	29	(76)	2.47	0.11
Renal profile	56	(61)	29	(76)	2.83	0.09
CRP	51	(55)	27	(71)	2.73	0.10
VBG	2	(2)	1	(3)	0.02	0.87
Amylase	9	(10)	4	(11)	0.01	0.89
Outcome						
Admission	12	(13)	3	(8)	0.70	0.40
Repeat presentation	1	(1)	1	(3)	0.42	0.51

Of the 9 patients not having an ECG, 6 (67%) also had red flags in the history or examination. There were no acute ECG changes suggestive of ischaemia, arrhythmias or new cardiac pathology, but 6 ECGs were abnormal (4.9%). All abnormalities were minor or previously known and consisted of one case each of ectopics, junctional rhythm, sinus arrhythmia, sinus bradycardia and known changes in one patient with hypertrophic obstructive cardiomyopathy and another with pre-excitation.

Chest X rays were performed in 54% of patients (n = 70). There was 1 diagnostic finding of pleural effusion - this patient had suggestive findings on clinical examination.

Underlying diagnosis for chest pain was documented for 124 patients (95%), with musculoskeletal origin being the most common (40%). Table 4 shows the range of diagnosis for all patients presenting with chest pain. Children under 12 years of age were more frequently diagnosed with gastrointestinal origin for chest pain (12/60 vs 4/64).

Fifteen patients (11%) were admitted for further investigation and management and another 35 patients (27%) were referred for general or cardiology follow up. No new cardiac pathology was diagnosed in any patients.

Our secondary aim, was assessment of documentation of red flags in history taking and on examination. Table 5 shows these results. There was rather poor documentation overall, with less than two thirds documentation rate for any cardiac risk factor.

Table 4 *Underlying diagnosis for patients presenting with chest pain*

Underlying diagnosis	Number (%)	
Musculoskeletal	50	(40)
Nonspecific	36	(29)
Gastrointestinal	17	(14)
Respiratory	11	(9)
Psychogenic	10	(8)

Table 5 *Documentation of risk factors for underlying cardiac disease*

	Documentation n (%)	
Red Flags – History		
Crushing or Compressive pain	66	(51)
Radiation	67	(52)
Palpitations	81	(63)
Dizziness	66	(51)
Syncope	83	(64)
Drug abuse	5	(4)
Recent surgery	6	(5)
Young onset ischaemic heart disease	1	(1)
Implantable cardiac defibrillator	50	(39)
Connective tissue disorder	4	(3)
FH sudden unexplained death <35 years old	50	(39)
FH cardiomyopathy	22	(17)
Hypercoagulable state	50	(39)
Red Flags – Examination		
Fever without source	50	(39)
Liver edge	50	(39)
Peripheral oedema	66	(51)

DISCUSSION

Parents and carers associate chest pain with serious underlying cardiovascular pathology.[4] However, chest pain of cardiac origin is rare in children.[10,11] In fact, the majority of our patients were diagnosed with musculoskeletal chest pain (35%), in keeping with other international studies.[2] In general, younger children are more likely to have organic cardiorespiratory pathology with older children having more psychogenic chest pain.[11] This was not evident in our population, possibly due to the high rate of diagnosis for non-specific chest pain, of whom a proportion may have underlying psychiatric conditions, most commonly panic disorders.[12]

Despite cardiac chest pain being a rare occasion, it is of utmost importance that these patients are identified and managed appropriately. A retrospective analysis of 484 children with cardiac conditions[13] showed that 76% had originally presented to PED with chest pain; the most common diagnoses for these patients were pericarditis (45%), myocarditis (35%) and pulmonary embolism (10%).

The use of appropriate red flag criteria has been shown to have high sensitivity approaching 100% (but low specificity) for ruling out cardiac origin of chest pain.[14] In fact, a positive or suspicious family history is present for most patients with cardiac conditions predisposing to sudden cardiac arrest but may not always be identified during their first

presentation.[15] Good history taking and examination are imperative in identifying red flags for patients at increased risk of having chest pain of cardiac or life threatening origin. These patients should then have further investigations, with the first line investigation being an ECG.[16] Judicious use of ECG in these patients is still associated with a low yield, with up to 3% contributing to the acute presentation[11,17], mainly myocarditis, pericarditis, Wolff-Parkinson-White and other arrhythmias. In our study, the majority of patients had an ECG, even though they did not have a history and examination suggestive of cardiac disease, with no contributory ECG findings identified. Of note, 6/9 patients without ECG had red flags identified on history taking or examination.

Certain studies suggest that cardiac biomarkers could be beneficial in identifying cardiac conditions such as myocarditis and heart failure and may also be a helpful prognostic indicator.[18] In fact, elevated troponin was the strongest predictor of cardiac diagnosis in a retrospective study analysing value of troponin as a marker for heart disease in previously healthy children.[19] However, the approach of 'screening' patients without underlying risk factors by taking cardiac biomarkers provides limited benefits whilst increasing cost and resource utilisation.[20] More than half of the patients included in our study had cardiac biomarkers, with no significant difference in investigation rate for children with no red flags when compared to those with red flags. Only one patient had an abnormal troponin level; this patient had hypertrophic obstructive cardiomyopathy, was admitted for further observation, and remained well.

It is evident that a thorough history and physical examination will exclude most underlying serious causes for children presenting with chest pain[21] and these should be documented appropriately. Medical notes which are unclear, lack completeness and specificity may result in poor patient outcome[10] and unnecessary investigations.[22] Medical professionals may have taken a comprehensive history and carried out a complete examination, but then fail to communicate this clearly and specifically in the notes. Unfortunately, only one of our patients had full documentation for all the red flags in history and examination, and our results could have been affected by lack of adequate documentation. Further investigations are then not needed in patients for whom a clear etiology, other than cardiac disease, can be established.[23-25]

CONCLUSION

Our study provides an overview of children presenting with chest pain to the PED, and confirms that this is usually due to benign causes. The yield of blanket laboratory investigations is limited. We suggest a clinical pathway to improve documentation and rationalise the use of investigations in children presenting with chest pain to the PED.

This paper is dedicated to the memory of Dr Victor Calvagna

REFERENCES

1. Chen L, Duan H, Li X, Yang Z, Jiao M, Sun K, Jin M. The causes of chest pain in children and the criteria for targeted myocardial enzyme testing in identifying the causes of chest pain in children. Front Cardiovasc Med. 2021;8:582129.
2. Drossner DM, Hirsh DA, Sturm JJ, Mahle WT, Goo DJ, Massey R, Simon HK. Cardiac disease in pediatric patients presenting to a pediatric ED with chest pain. Am J Emerg Med. 2011;29:(6)632–8.
3. Saleeb SF, Li WYB, Warren SZ, Lock JE. Effectiveness of screening for life-threatening chest pain in children. Pediatrics. 2011;128:e1062.
4. Aygun E, Aghun ST, Uysal T, Aygun F, Dursun H, Irdem A. Aetiological evaluation of chest pain in childhood and adolescence. Cardiol Young. 2020;30:(5)617–23.

5. Nijman RG, Honeyford K, Farrugia R, Rose K, Bognar Z, Buonsenso D, et al. Presentations of children to emergency departments across Europe and the COVID-19 pandemic: a multinational observational study. PLoS Med. 2022;19:(8)e1003974.
6. Degiorgio S, Grech N, Dimech YD, Xuereb J, Grech V. Significant reduction in pediatric, population-based hospital admissions due to COVID-19 in Malta. Turk Arch Pediatr. 2022;57:(1)87–92.
7. Paediatric Clinical Practice Guideline – Chest Pain. The Alex Emergency Department, NHS Brighton and Sussex University Hospitals. 2017 [cited 2023 Feb 5]. Available from: https://www.bsuh.nhs.uk/library/wp-content/uploads/sites/8/2020/06/Paediatric-Guidelines-chest-pain.pdf
8. Chest Pain. The Royal Children's Hospital Melbourne. Updated Jan 2023 [cited 2023 Feb 5]. Available from: https://www.rch.org.au/clinicalguide/guideline_index/Chest_pain/
9. Guideline – Differentials of paediatric chest pain. Children's Health Queensland Hospital and Health Service. 2022 [cited 2023 Feb 5]. Available from: https://www.childrens.health.qld.gov.au/wp-content/uploads/PDF/guidelines/gdl-pdf
10. Chun JH, Kim TH, Han MY, Kim NY, Yoon KL. Analysis of clinical characteristics and causes of chest pain in children and adolescents. Korean J Pediatr. 2015;58:(11)440–5.
11. Selbst SM, Ruddy RM, Clark BJ, Henretig FM, Santulli T. Pediatric chest pain: a prospective study. Pediatrics. 1988;82:(3)319–23.
12. Lipsitz JD, Hus D, Apfel HD, Marans ZS, Cooper RS, Albano AM, Gur M. Psychiatric disorders in youth with medically unexplained chest pain versus innocent heart murmur. J Pediatr. 2012;160:320–4.
13. Kane DA, Fulton DR, Saleeb S, Zhou J, Lock JE, Geggel RL. Needles in hay: Chest pain as the presenting symptom in children with serious underlying cardiac pathology. Congenit Heart Dis. 2010;5:366–73.
14. Harahsheh AS, O'Bryne ML, Pastor B, Graham DA, Fulton DR. A multi-institutional analysis from standardized clinical assessment and management plans (SCAMPs®), the Pediatric Health Information Systems Database, and the National Ambulatory Medical Care Survey. Clin Pediatr (Phila). 2017;56:(13)1201–8.
15. Dalal A, Czosek R, Kovach J, von Alvensleben J, Valdes S, Etheridge SP, et al. Clinical presentation of pediatric patients at risk for sudden cardiac arrest. J Pediatr. 2016;171:191–6.
16. Barbut G, Needleman JP. Pediatric chest pain. Pediatr Rev. 2020;41:(9)469–80.
17. Rowe BH, Dulberg CS, Peterson RG, Vlad P, Li MM. Characteristics of children presenting with chest pain to a pediatric emergency department. CMAJ. 1990;143:(5)388–94.
18. Bohn MK, Steele S, Hall A, Poonia J, Jung B, Adeli K. Cardiac biomarkers in pediatrics: An undervalued resource. Clin Chem. 2021;67:(7)947–58.
19. Dionne A, Kheir JN, Sleeper LA, Esch JJ, Breitbart RE. Value of troponin testing for detection of heart disease in previously healthy children. J Am Heart Assoc. 2020;9:e012897.
20. Clerico A, Aimo A, Cantinotti M. High-sensitivity cardiac troponins in pediatric population. Clin Chem Lab Med. 2022;60:(1)18–32.
21. Massin MM, Bourguignont A, Coremans C, Comte L, Lepage P, Gerard P. Chest pain in pediatric patients presenting to an emergency department or to a cardiac clinic. Clin Pediatr (Phila). 2004;43:(3)231–8.
22. Boon AW, Forton J. How to evaluate a child with chest pain. Curr Paediatr. 2004;14:64–70.
23. Selbst SM. Approach to the child with chest pain. Pediatr Clin North Am. 2010;57:1221.
24. Friedman KG, Alexander ME. Chest pain and syncope in children: a practical approach to the diagnosis of cardiac disease. J Pediatr. 2013;163:896.
25. Collins SA, Griksaitis MJ, Legg JP. 15-minute consultation: a structured approach to the assessment of chest pain in a child. Arch Dis Child Educ Pract Ed. 2014;99:122.

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ORIGINAL ARTICLE

An Audit study of Weight and Height monitoring in young people on Methylphenidate attending a National Child and Adolescent Mental Health Community Clinic (CYPS)

Martina Falzon Lia, Gertrude Micallef, Daniel Vella Fondacaro

Background

Attention deficit hyperactivity disorder is one of the neurodevelopmental disorders often seen in young people. The core symptoms include inattention, hyperactivity and impulsivity. .NICE guidelines recommend different treatments for ADHD and the first line pharmacological treatment advised is Methylphenidate. Regular monitoring of weight and height is advised by NICE guidelines for young people on Methylphenidate, as it may cause weight loss and growth retardation. The aim of this audit was to assess compliance with NICE guidelines regarding height and weight monitoring in young individuals attending a National Child and Adolescent Mental Health Community Clinic and receiving methylphenidate treatment.

Method

Retrospective case note analysis was carried out on a sample of 287 young people actively attending the National Child and Adolescent Mental Health Community Clinic. Analysis was focused on determining whether weight and height were being monitored according to guidelines. Factors contributing to inadequate monitoring were identified and the presence of comorbid mental disorders were also noted. Additional data, such as demographics and type of methylphenidate treatments, were also recorded.

Results

Results revealed that weight was monitored according to guidelines in 31.36% whilst weight was monitored in 25.09% of cases. Height and weight were both adequately monitored in 25.09% of the sample. Reasons for under reporting of weight and height and the frequency of other comorbid disorders were also identified.

Conclusion

This audit highlights the need for improved weight and height monitoring of young people on methylphenidate. Different strategies can be implemented to facilitate adherence to monitoring guidelines and ensure the availability of accurate data for healthcare professionals involved in patient follow-up.

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Attention-deficit hyperactivity disorder (ADHD) is a relatively common neurodevelopmental disorder often diagnosed in young people (YP). The prevalence of ADHD among YP has been increasing, with a worldwide-pooled prevalence of 5.29%.[1] The three symptom groups in ADHD are inattention, hyperactivity and impulsivity. For a diagnosis of ADHD to be made, these symptoms must be persistently present in more than one situation/environment and for over a period of 6 months, and must have an impact on the individual's academic, occupational, or social functioning.[2] It has been estimated that 60-100% of children possess another comorbid disorder that often continues into adulthood, such as learning disorders, autism spectrum disorder (ASD), tic disorders, oppositional defiant disorder (ODD), conduct disorder and mood disorders.[3]

Treatment for YP with ADHD involves behavioural therapies (such as parent training programs) and medications for children who are over the age of 5 years.[4] The first line medical treatment for ADHD in children is methylphenidate, which is a stimulant of the central nervous system (CNS) and acts on dopamine transporters (DAT) and norepinephrine transporters (NET), inhibiting synaptic reuptake of dopamine and norepinephrine.[5] The increased availability of dopamine and norepinephrine in the dorsolateral prefrontal cortex helps improve attention and concentration, whilst an increase in these neurotransmitters in the basal ganglia and medial prefrontal cortex will improve hyperactivity and fatigue respectively.[6] Methylphenidate can be associated with adverse effects, such as growth suppression due to a decrease in appetite [7] and insomnia.[8]

Previous research has reported conflicting results on the effects of methylphenidate on the weight and height in children. Methylphenidate was found to have long term effects on growth in YP but slight growth differences were found to attenuate over time.[8] However, other studies have reported clinically significant decreases in weight and height in YP on methylphenidate, especially if prescribed before the age of 12 years, in females [9] and if higher doses were prescribed.[10,11] Conversely, other studies have shown that CNS stimulants are not associated with significant losses in adult weight or height. [12,13]

This audit study aimed to assess the current service offered to YP with ADHD within the Malta national child and adolescent mental health (CAMH) community service by comparing the height and weight monitoring of YP with ADHD with standardised monitoring recommendations.[4]

MATERIALS AND METHODS

Participants

The full list (n = 487) of active cases currently attending the Child and Young People Services (CYPS), a national child and adolescent mental health community clinic, was acquired. Through retrospective case note analysis, complete data was only available for a sample of 287 YP. The inclusion criteria included: 1) YP having a formal diagnosis of ADHD with or without other comorbidities, 2) YP taking methylphenidate (immediate-release or extended-release preparation), 3) YP from 4 to 17 years of age, 4) YP actively attending at CYPS. The diagnosis was made by a psychiatrist/psychologist within the national health service or the private sector.

Data Collection

Retrospective case note analysis between March 2021 and March 2022 was carried out to check whether height and weight monitoring was done according to NICE guidelines. For patients with missing data, a reason for those missing data was obtained from the case notes. Demographic data were recorded. The data obtained were inputted into a password-protected database within an encrypted computer.

Guideline

The guideline used for comparison was the NICE guideline NG87, (1.8.5): Attention deficit hyperactivity disorder: diagnosis and management (Maintenance and monitoring). This guideline recommends that all YP on methylphenidate who are 10 years or younger should have their height monitored every 6 months, and weight monitored every 3 months (every 6 months for YP older than 10 years of age). The data obtained should be plotted on a growth chart for comparison.[4]

ETHICAL INFORMATION

Research governance approval was obtained from the Data Protection Officer of the Malta Mental Health Services (Government of Malta) on the 14th of December 2020. Approval from the Chairman of the Department of Psychiatry (Malta Mental Health Services, Government of Malta) was obtained on the 17th November 2020.

RESULTS

From the total sample (n = 287), 211 (73.52%) were older than 10 years of age whilst 76 (26.48%) were 10 years or younger. Furthermore, 230 individuals (80.14%) were male and 57 individuals (19.86%) were female.

The sample also included 141 patients who were on immediate-release preparation, 105 patients on the extended-release preparation and 41 patients who were taking both preparations of methylphenidate.

31.36% (n = 90) of the patients within the sample had their height monitored according to guidelines, whilst 25.09% (n = 72) had their weight monitored within the specified timeframes of the guideline (NG87). All individuals who had their weight monitored also had their height correctly recorded, thus 25.09% (n=72) had both their weight and height monitored according to guideline. This meant that height and weight monitoring was not carried out as per the NICE guideline in 68.64% (n =197) and 74.91% (n = 215) of patients respectively.

Reasons for underreporting of weight and height according to NICE guidelines included : 1) No-show appointment/appointment cancelled by patient or parents (39.53%, n = 85), 2) appointment postponed due to COVID pandemic administrative issues (13.95%, n = 30), 3) appointments scheduled for after the specified height/weight monitoring timeframe (12.56%, n = 27), 4) appointment by teleconsultation (10.70%, n = 23), 5) failure of weight/height monitoring during the appointment (9.77%, n = 21), and 6) patient attended the appointment and parameters were taken not concordant with guideline (7.91%, n = 17) (Table 1).

Comorbid conditions included ODD and conduct disorder (10.45%, n=30), ASD (8.36% , n=24), learning disabilities (2.79%, n=8), epilepsy (1.05%, n=3) and mood disorders (0.70%, n=2). 76.7% (n = 220) of the sample had no other co-existing mental disorder (Table 2).

DISCUSSION

Overall, this study highlights the need for improved height and weight monitoring in YP with ADHD taking methylphenidate and attending a Malta national CAMH community clinic. This is suggested to meet the recommended standard.[4] Height monitoring was recorded in 31.36% of the sample whilst weight monitoring was recorded in 25.09% of the sample. The better monitoring noted for height when compared to weight monitoring may be explained by the greater likelihood of being given an appointment within a 6-month timeframe (rather than a 3-month timeframe), as suggested by NICE. Previous research has been equivocal; some reported low levels of monitoring.[14], while others reported adequate levels of monitoring of physical parameters.[15] Inadequate monitoring happened mostly due to appointments being cancelled by the patient (39.53%) or the clinic due to the COVID-19 pandemic period (13.95%). Mirroring previous research [16], it was difficult to arrange adequate physical monitoring in YP with ADHD during the peak of the pandemic due to a reduction in face-to-face appointments.

17.68% of patients (n = 38) who attended the clinic within the 3-month/6-month timeframe still did not have the recommended physical monitoring carried out. While acknowledging the need for service improvement, staff burnout and shortage of staff might be a cause. This would be in line with previous research on burnout in mental health services.[17]

Our sample of YP with ADHD consisted of a larger proportion of males (80.14%) than females (19.86%) which complemented gender prevalence ratios reported in previous research.[18] Our study sample also included a larger proportion of YP over the age of 10 years (73.524%) who were on methylphenidate, indicating that older children were more likely to require pharmacological treatment (for schoolwork, exams and overall functioning) than younger patients.

The most common co-morbid mental disorder with ADHD present in this sample of YP were ODD or conduct disorder (10.45%) followed by ASD (8.36%).

Table 1 *Reasons for underreporting of weight and height in case notes*

No-show/Cancelled by patient	39.53% (n= 85)
Postponed due to COVID pandemic period	13.95% (n=30)
Appointments scheduled after specified timeframe	12.56% (n=27)
Appointments by teleconsultation	10.70% (n=23)
Attended but weight/height monitoring not done	9.77% (n=21)
Attended but weight/height monitoring not done as per guidelines	7.91% (n=17)
Other	5.58% (n=12)

Table 2 *Comorbid mental disorders noted in case notes*

Coexisting Mental Disorder	Frequency	Percentage
None	220	76.65 %
Autism Spectrum Disorder	24	8.36 %
ODD/CD	30	10.45 %
Mood disorders	2	0.70 %
Learning disability	8	2.79 %
Epilepsy	3	1.05%

These findings mirror previous research, where ODD and ASD were reported to be common comorbidities with ADHD.[19–21] Furthermore, ADHD was the most common comorbidity present in ASD with rates of 40-70%.[21–23] This study has audited the national child and adolescent mental health service offered to YP with ADHD, excluding patients who are being seen in private clinics. Therefore, this might have introduced an element of selection bias, possibly affecting the generalisability of the results. However, this limitation might have been mitigated since a big proportion of YP with ADHD are seen at CYPS, which is the only national community CAMH service.

The COVID-19 pandemic might have also negatively skewed the results obtained due to the disruption in appointments. This was listed in the results as a main reason for underreporting of height and weight monitoring.

CONCLUSION

This audit highlights the need for improved physical monitoring (height and weight) for YP with ADHD who attend CYPS and are on methylphenidate. The authors recommend sessions with CAMH service professionals to encourage standardised physical monitoring as suggested by NICE guideline NG87. When appointments are given beyond the recommended timeframe, the parents should be instructed to monitor any changes in height and weight themselves or by visiting the health centre; the information can then be sent to CYPS for documentation. Electronic databases for growth charts are also recommended to centralise patient data, ensure data storage reliability, and for better access of data. The authors also recommend a second audit cycle once the above changes are implemented to ensure an improvement in physical monitoring of ADHD patients attending the Malta national community CAMH service.

SUMMARY BOX

- Attention deficit disorder is a neurodevelopmental disorder commonly diagnosed in young people attending CYPS.
- Methylphenidate is the first line pharmacological treatment for this condition recommended by NICE guidelines.
- Young people on methylphenidate require regular monitoring as recommended by NICE guidelines.
- This study was carried out on a sample of 287 young people who were actively attending CYPS during the specified time frame and were on Methylphenidate.
- It was noted that weight was monitored in 25% whilst height was monitored in 31% of the sample.
- Reasons for underreporting of these parameters and comorbid conditions were also explored.

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity disorder
YP	Young People
ASD	Autism Spectrum disorder
ODD	Oppositional Defiant disorder
CNS	Central Nervous System
DAT	Dopamine transporter
NET	Norepinephrine transporter

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164:(6)942–8.
2. World Health Organization. ICD-11 for Mortality and Morbidity Statistics. Geneva: WHO; 2023 [cited 2023 May 2]. Available from: https://icd.who.int/browse11/l-m/en#/http%3A%2F%2Fid.who.int%2Ficd%2Fentity%2F821852937
3. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: a review of literature. World J Clin Cases. 2019;7:(17)2420–6.

4. National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: diagnosis and management. NICE guideline NG87. 2018 Mar 14 [cited 2023 May 2]. Available from: https://www.nice.org.uk/guidance/ng87
5. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th ed. Cambridge: Cambridge University Press.
6. Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology. 6th ed. Cambridge: Cambridge University Press.
7. Halford JC, Blundell JE. Pharmacology of appetite suppression. Prog Drug Res. 2000;54:25–58.
8. Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants on height and weight: a review of the literature. J Am Acad Child Adolesc Psychiatry. 2008;47:(9)994–1009.
9. Díez-Suárez A, Vallejo-Valdivielso M, Marín-Méndez JJ, de Castro-Manglano P, Soutullo CA. Weight, height, and body mass index in patients with attention-deficit/hyperactivity disorder treated with methylphenidate. J Child Adolesc Psychopharmacol. 2017;27:(8)723–30.
10. Powell SG, Frydenberg M, Thomsen PH. The effects of long-term medication on growth in children and adolescents with ADHD: an observational study of a large cohort of real-life patients. Child Adolesc Psychiatry Ment Health. 2015;9:50.
11. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. Arch Gen Psychiatry. 1983;40:(3)317–21.
12. Biederman J, Spencer TJ, Monuteaux MC, Faraone SV. A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. J Pediatr. 2010;157:(4)635–e1.
13. Harstad EB, Weaver AL, Katusic SK, et al. ADHD, stimulant treatment, and growth: a longitudinal study. Pediatrics. 2014;134:(4)e935–44.
14. Davies E, Khan M, Jones C. Do you mind if I take your blood pressure? Physical health monitoring of children and young people on ADHD medication amidst a pandemic. BJPsych Open. 2021;7(Suppl 1):S183–4.
15. Bansal N, Hayat M. Audit of ADHD medication prescription and monitoring in intellectual disability services, Greater Glasgow & Clyde. BJPsych Open. 2021;7(Suppl 1):S66.
16. McGrath J. ADHD and Covid-19: current roadblocks and future opportunities. Ir J Psychol Med. 2020;1–8.
17. Morse G, Salyers MP, Rollins AL, Monroe-DeVita M, Pfahler C. Burnout in mental health services: a review of the problem and its remediation. Adm Policy Ment Health. 2012;39:(5)341–52.
18. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics. 2012;9:(3)490–9.
19. Connor DF, Steeber J, McBurnett K. A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. J Dev Behav Pediatr. 2010;31:(5)427–40.
20. Kotte A, Joshi G, Fried R, et al. Autistic traits in children with and without ADHD. Pediatrics. 2013;132:(3)e612–22.
21. Antshel KM, Zhang-James Y, Wagner KE, Ledesma A, Faraone SV. An update on the comorbidity of ADHD and ASD: a focus on clinical management. Expert Rev Neurother. 2016;16:(3)279–93.
22. Kaat AJ, Gadow KD, Lecavalier L. Psychiatric symptom impairment in children with autism spectrum disorders. J Abnorm Child Psychol. 2013;41:(6)959–69.
23. Joshi G, Faraone SV, Wozniak J, et al. Symptom profile of ADHD in youth with high-functioning autism spectrum disorder: a comparative study in psychiatrically referred populations. J Atten Disord. 2017;21:(10)846–55.

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ORIGINAL ARTICLE

An Audit on Admission Outcome Measures in a National Child and Adolescent Mental Health Inpatient Unit

Luana Vassallo, Daniel Vella Fondacaro

Background

Young people with severe or complex mental health symptoms may require observation and treatment in a mental health inpatient setting. The National Institute for Health and Care Excellence (NICE) guidance recommends that "all healthcare and Child and Adolescent Mental Health Services (CAMHS) professionals should routinely use, and record in the notes, appropriate outcome measures". These may take the form of self-/clinician-reported questionnaires and screening items.

Aims

To analyse the use of pre- and post-admission outcome measures for admissions to a national child and adolescent mental health inpatient unit (Young People's Unit – YPU, Mount Carmel Hospital, Malta) and to suggest recommendations for implementation to improve the completion rate of pre- and post-admission outcome measures.

Methodology

A retrospective case note analysis was carried out on all YPU admissions, between the 1st of January 2022 and the 31st of December 2022, to analyse the completion of pre- and post-admission outcome measures. Outcome measures included the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA), the 6-item Kutcher Adolescent Depression Scale (KADS-6), the Moods and Feelings Questionnaire (MFQ), the Tool for Assessment of Suicide Risk - Adolescent (TASR-A), and the Children's Global Assessment Scale (CGAS). Demographic data were also recorded. These outcome measures (usually filled in by on-call doctors) were selected as they were the ones assigned in the ward for completion during patient admissions.

Results

Out of all admissions (n = 83), the MFQ was the lowest completed with a 0% completion rate, both for the pre- and post-admission phases. During the pre-admission phase the KADS-6 was completed the most (n = 22, 26.5%), followed by the TASR-A (n = 18, 21.7%), the HoNOSCA (n = 12, 14.5%), and the CGAS (n = 7, 8.4%). During the post-admission phase, the KADS-6 (n = 13, 15.66%) and the HoNOSCA (n = 13, 15.66%) were completed the most, followed by the TASR-A (n = 12, 14.50%) and the CGAS (n = 10, 12.04%).

Conclusion

This audit study showed that more awareness is required about the importance of outcome measures. The authors recommend educational sessions with professional staff members to emphasize the importance of outcome measures, and a re-audit study. They also recommend a qualitative study with staff members to elicit possible causes related to the low rate of completion of outcome measures.

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Mental disorders in young people are ideally treated in a community setting (rather than in a hospital) within child and adolescent mental health services (CAMHS), thus avoiding risks towards the young person's psychosocial development, educational achievements etc.[1] However, those with complex or severe mental health symptoms may require care and treatment in an inpatient mental health setting.[1] The National Institute for Health and Care Excellence (NICE) guidance [2] recommends that "all healthcare and CAMHS professionals should routinely use, and record in the notes, appropriate outcome measures". Such outcome measures may take the form of self-/clinician-reported questionnaires and screening items.

Outcome measures help provide an understanding of the effectiveness of the service being provided while monitoring young people's mental health status within an inpatient setting.[3] Completing outcome measures is an important aspect for one's admission as it would highlight any changes in the individual's mental health from admission to discharge. They also help to contextualise the significant changes in the patient's mental health variables.

The aims of this research were to analyse the use of pre- and post-admission outcome measures for admissions to the Young People's Unit (YPU), Mount Carmel Hospital, Malta, in 2022; and to suggest recommendations for implementation to improve the completion rate of pre-post-admission outcome measures.

MATERIALS AND METHODS

Study Sample and Procedure

The study sample included all YPU admissions between the 1st of January 2022 and the 31st of December 2022. A retrospective case note analysis was carried out to analyse the completion of pre- and post-admission outcome measures; the data were recorded and tabled accordingly.

Outcome Measures

The outcome measures below were selected because they were the assigned measures for admissions within the inpatient unit. The first outcome measure was the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA), which is a 15-item practitioner-rated scale for young people aged 5 to 17 years which assesses multiple mental health components, such as overactivity, self-harm, hallucinations/delusions, peer relationships etc. It has shown good apparent face validity and interrater reliability (intraclass correlation coefficient of more than 0.8 in eight of the subscales).[4] The second outcome measure was the practitioner-rated 6-item Kutcher Adolescent Depression Scale (KADS-6), which assesses depressive symptoms, and has reported sensitivity and specificity rates of 92% and 71% respectively.[5] It also showed good reliability (α = 0.74) and convergent validity with the Beck's Depression Inventory-II (r = 0.44).[6] The third outcome measure was the Moods and Feelings Questionnaire (MFQ) [7] with reported excellent internal reliability (α = 0.91 to 0.93) and concurrent validity of more than 0.40 in most of its items.[8] The fourth outcome measure was the Tool for Assessment of Suicide Risk - Adolescent (TASR-A).[9] No information is available on the tool's validity and reliability since this was not designed as a predictive or diagnostic tool, but as a means of summarising one's suicidal assessment.[10] The fifth outcome measure was the Children's Global Assessment Scale (CGAS), which reported evidence of discriminant validity and excellent interrater reliability (intraclass correlation coefficient = 0.84).[11] At YPU, these outcome measures are usually completed by the on-call doctors or doctors carrying out the pre-/post-admission reviews. The relevant demographic data were also recorded for the purpose of this audit study.

Guideline

The NICE guidance [2] used for comparison in this audit was NG134, 1.1.2.5: "All healthcare and CAMHS professionals should routinely use, and record in the notes, appropriate outcome measures (such as those self-report measures used in screening for depression or generic outcome measures used by particular services) …".

Ethics

Research governance was granted by the Data Protection Officer of the Malta Mental Health Services, Government of Malta. Approval to present and publish was also obtained by the Chairman of the Department of Psychiatry (Malta Mental Health Services, Government of Malta). All data were stored in a password-protected spreadsheet within an encrypted computer.

RESULTS

A total of 83 YPU admissions were recorded during the year 2022. Of these, 63.9% (n = 53) were females whilst 36.1% (n = 30) were males (Figure 1). Out of

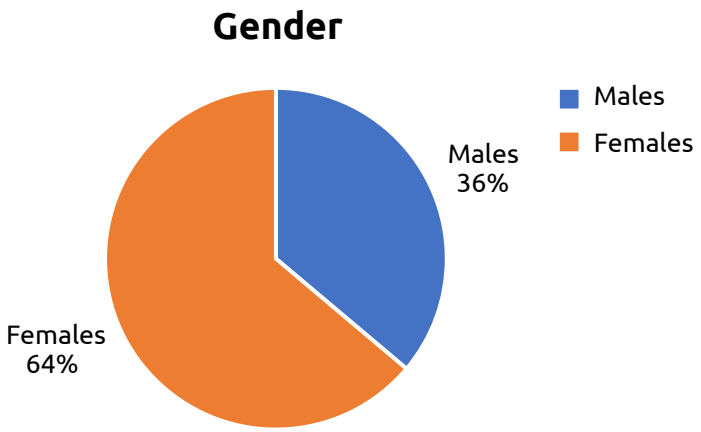


Figure 1 *Baseline characteristics of subjects between groups*

the 83 YPU admissions, 24% of which were re-admissions (n = 20). Pre-admission outcome measures were completed on the day of admission or within 24 hours of the admission. Post-admission outcome measures were completed on the day of discharge (post-admission review).

Results (Figure 2, Figure 3) revealed that the Moods and Feelings Questionnaire was the least completed measure with a 0% completion rate for both the pre-admission and the post-admission phases. During the pre-admission phase, the KADS-6 was completed most (n = 22, 26.5%), followed by the TASR-A (n = 18, 21.7%), the HoNOSCA (n = 12, 14.5%), and the CGAS (n = 7, 8.4%). During the post-admission phase, the KADS-6 (n = 13, 15.66%) and the HoNOSCA (n = 13, 15.66%) were completed the most, followed by the TASR-A (n = 12, 14.50%) and the CGAS (n = 10, 12.04%).

In females, the most completed outcome measure was KADS-6 (n = 27, 35.1%), followed by TASR-A, HoNOSCA, and CGAS. In males, the most completed outcome measure also was the KADS-6 (n = 12, 35.3%), followed by TASR-A whilst HoNOSCA and CGAS were completed equally.

Only 27.7% (n = 23) and 20.5% (n = 17) of admissions had outcome measures completed during the pre-admission and post-admission phase respectively. This meant that 72.3% (n = 60) of admissions did not have any outcome measures completed upon admission, while 79.5% (n = 66) of admissions did not have any outcome measures completed upon discharge. It was also noted that the date was not always appropriately documented on the outcome measure sheets.

DISCUSSION

This audit study looked at the completion rate of outcome measures in a national inpatient unit within CAMHS. This first audit cycle showed a generally low completion rate of outcome measures. This was even lower than previous similar research in CAMHS [12], which also reported low outcome measure completion rates with subsequent improvement in completion rates by introducing a Commissioning for Quality and Innovation target (e.g., CGAS completion rates improved from 41% to 75%).

One may postulate different reasons for the low completion rates of outcome measures. One possible reason might be staff burnout. The high workload and pressures placed on mental health staff might account for overwhelming levels of burnout, decreasing efficiency.[13] Another possible reason for the low completion rates is understaffing within the inpatient unit, which has been heavily documented in mental health settings.[14,15] Furthermore, since in YPU

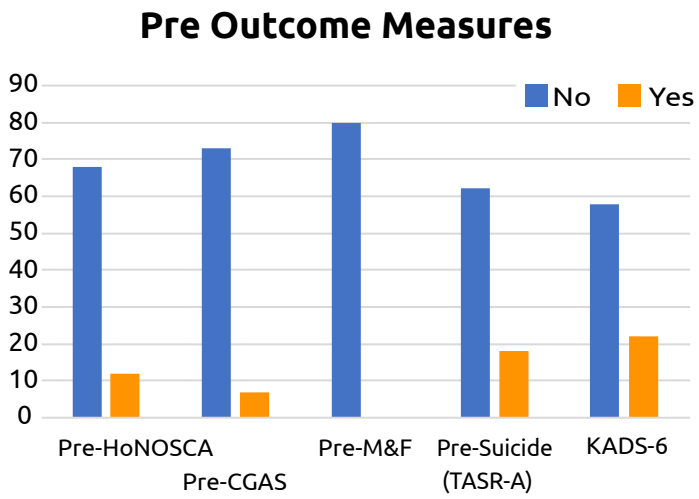


Figure 2 *Results Showing Completed Pre-Admission Outcome Measures*

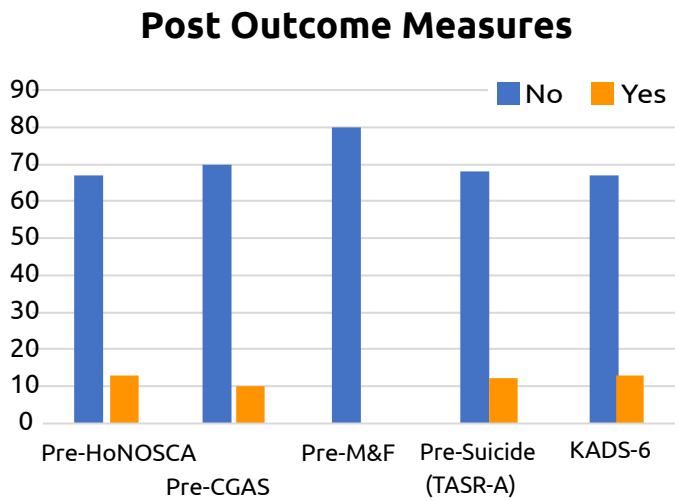


Figure 3 *Results Showing Completed Post-Admission Outcome Measures*

only doctors generally complete these outcome measures, this adds more work to the already overstretched working schedule. Therefore, all members of the multidisciplinary team should be able to complete such questionnaires with patients.

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CONCLUSION AND RECOMMENDATIONS

This first audit cycle highlights the low completion rates of outcome measures within a national inpatient child and adolescent mental health inpatient unit. Therefore, the authors are putting forward the following recommendations:

1. Recommendations for Practice: i) Psychoeducation material and sessions for mental health professional staff members about the importance of outcome measures in practice; ii) to include outcome measures with patient admission and discharge papers; iii) to encourage all members of the multidisciplinary team (including non-medical staff) to complete outcome measures; iv) to include the date and time on the outcome measure forms, v) to work on an official inpatient package of outcome measures.
2. Recommendations for Research: i) To carry out the second loop of the audit after three months of psychoeducation, thus completing the audit cycle; ii) To carry out a qualitative study to explore reasons for the low completion rates of outcome measures; iii) To carry out a prospective service evaluation using outcome measure analysis to assess the effectiveness of inpatient admissions.

SUMMARY BOX

What is already known

- The use of outcome measures is recommended by NICE guidelines and may take the form of questionnaires
- These will help contextualise the patient's feelings and monitor their progress
- These outcome measure should be applied to all admission to an inpatient young people's unit by mental health professionals

New findings

- Further emphasis on the importance of outcome measures is required, as evidenced by low completion rates

ABBREVIATIONS

CAMH	Child and Adolescent Mental Health Services
CGAS	Children's Global Assessment Scale
HoNOSCA	Health of the Nation Outcome Scales for Children and Adolescents
KADS-6	6-item Kutcher Adolescent Depression Scale
MFQ	Moods and Feelings Questionnaire
NICE	National Institute for Health and Care Excellence
TASR-A	Tool for Assessment of Suicide Risk – Adolescent
YPU	Young People's Unit

REFERENCES

1. Edwards D, Evans N, Gillen E, et al. What do we know about the risks for young people moving into, through and out of inpatient mental health care? Findings from an evidence synthesis. Child Adolesc Psychiatry Ment Health. 2015;9:55.
2. National Institute for Health and Care Excellence (NICE). Depression in children and young people: identification and management. NICE guideline NGLondon: NICE; 2019 [cited 2023 May 8]. Available from: https://www.nice.org.uk/guidance/ng134
3. Kilbourne AM, Keyser D, Pincus HA. Challenges and opportunities in measuring the quality of mental health care. Can J Psychiatry. 2010;55(9):549–57.
4. Gowers SG, Harrington RC, Whitton A, et al. Brief scale for measuring the outcomes of emotional and behavioural disorders in children. Health of the Nation Outcome Scales for children and adolescents (HoNOSCA). Br J Psychiatry. 1999;174:413–6.
5. LeBlanc JC, Almudevar A, Brooks SJ, Kutcher S. Screening for adolescent depression: comparison of the Kutcher Adolescent Depression Scale with the Beck depression inventory. J Child Adolesc Psychopharmacol. 2002;12(2):113–26.
6. Quintão S, David S, Gusmão R, Kutcher S. Contribution to the validation of the Kutcher Adolescent Depression Scale (KADS-6) in a Portuguese population. Psicol Reflex Crit. 2015;28:313–21.
7. Angold A, Costello EJ, Messer SC, Pickles A. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. Int J Methods Psychiatr Res. 1995;5(4):237–49.
8. Thabrew H, Stasiak K, Bavin LM, Frampton C, Merry S. Validation of the Mood and Feelings Questionnaire (MFQ) and Short Mood and Feelings Questionnaire (SMFQ) in New Zealand help-seeking adolescents. Int J Methods Psychiatr Res. 2018;27(3):e1610.
9. Chehil S, Kutcher P. Suicide risk management: a manual for health professionals. 2nd ed. Hoboken (NJ): Wiley-Blackwell; 2012.

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ORIGINAL ARTICLE

Introduction of an ITU Outreach and Follow-up Service at Mater Dei Hospital

Verena Köhl, Stephen Sciberras , Michael Buttigieg

Background

Background: Recently, critical illness is seen more as a continuum of care across the whole hospital stay rather than focussed solely on the ITU admission. Hospital services such as Outreach Teams, Transition Programs and Follow-up Clinics have been introduced worldwide. They focus on specific aspects of patient care such as early recognition of critical illness and rehabilitation goals. The latter is dealing mostly with the Post Intensive Care syndrome (PICS), a hereditary and complex state related specifically to ITU survivors. Mater Dei Hospital has recently launched an ITU Outreach and Follow-up Service. We analysed their data collected over one year.

Methods

A mobile phone application "ITU Flow" was designed on a Microsoft@ Power Platform. We collected data related to the referral and discharge process. The application works as an essential auditing and communication tool of the service.

Results

Patients followed-up were mostly surgical or those suffering from respiratory failure and required only one review by the ITU team. Most issues dealt with were related to the chest, weakness or drug prescription and stayed long term. The Emergency Department made most referrals concerning patients with respiratory and/or cardiovascular failure. Almost 40% of patients were immediately admitted to ITU and in one fifth of cases significant changes to patient care had to be made. Only 12% were deemed unsuitable for ITU, a very small number was admitted at a later stage.

Conclusion

ITU survivors appear to suffer from PICS at least in the short term, and possibly in the long term as well, as demonstrated by repeated visits after ITU discharge. This warrants individualised and interdisciplinary care. An ITU follow-up clinic in an Outpatient setting should be considered. Pre-selection of patients is essential to run the service cost efficient. Most ITU referrals lead to an admission or to major changes to the treatment plan. The Outreach Team thus contributes significantly to patient care outside ITU or assists in immediate transfer if necessary.

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In recent years, critical illness is seen more and more as a continuum of care expanding far beyond the actual stay at the Intensive Care Unit with several distinct stages. The journey starts with transfer of the critically ill patient to the Intensive Care Unit, followed by a timely discharge to an HDU/monitored bed or a ward setting, later to a rehabilitation centre and then finally home.[1,2]

At any time along the process towards discharge from hospital, the patient is at risk of deterioration and possible subsequent readmission to ITU, with mostly unfavourable outcomes.[3] Mortality and morbidity in patients readmitted to ITU is high [4,5] and several studies have shown that critical illness affects a patient's health and well-being long-term, and far beyond the acute event itself.[6,7] Some survivors' quality of life, in fact, remaining below average for up to five years.[8]

The complex health issues affecting ITU survivors, which comprise cognitive, psychiatric and/or physical disability, have been summarized under the term PICS (Post Intensive Care Syndrome).[9-11] Furthermore, the early recognition of the deteriorating patient and the smooth transition from a high dependency setting to the ward are crucial moments for a favourable patient outcome.

Internationally, several models exist detailing how to ease the communication between the different entities of patient care including Rapid Response Teams[12], ITU Outreach Teams[13] and liaison nurses.[14] Such teams may be led by physicians, nurses or a combination of the two.

Mater Dei Hospital has recently introduced an ITU Outreach and Follow-up Service led by senior members of the ITU team with the following tasks:

1. identifying the deteriorating patient early;
2. starting adequate emergency care in the ward;
3. facilitating transfer to a clinical area offering higher level of care;
4. facilitating the transition of care from ITU by performing reviews in the wards within 24 to 48hrs after the patient has been discharged; and
5. identifying early those patients who show signs of PICS related issues, with the intention to prevent disease progression and to highlight specific needs for future rehabilitation.

To support this service, members of the ITU team developed an in-house mobile app called ITU Flow. This was designed to ease communication between team members as well as to audit the service.

This paper demonstrates the results and observations made over one year after the introduction of the service and gives an outlook on future improvements and initiatives.

METHODS

The mobile phone application "ITU Flow" used by the Outreach Team was designed on a Microsoft® Power Platform (Microsoft® Corporation, US), using Power Apps as the interface and Sharepoint Lists as a database. This platform is hosted on MITA servers, which ensures GDPR-compliancy and also improves security.

The application consists of two separate components, one dedicated to new referrals to ITU and the other dedicated to patients discharged from ITU.

Once a patient is referred to ITU, a member of the ITU team will use the ITU Flow application to collect the following data: patient demographics, the ward the patient is currently in, date and time of referral, the referring specialty, acute organ failures detected on initial assessment, whether a previous review had been performed, and the decisions taken by the team. The data is then stored in a secure Sharepoint list and available for future reference.

When a patient is discharged from ITU, an ITU discharge letter is prepared using the same app and uploaded on iSoft. This also collects the following data: patient demographics, discharge date, future ward, diagnosis on discharge and whether any specific concerns exist that the team should be focusing on during their ward reviews.

In a meeting of all ITU consultants a list of frequently encountered issues related to an ITU stay was agreed upon and included in the app as a drop-down menu. The items are all related to PICS, either directly or indirectly. We specifically assess the patients on the following: weakness, renal function, nutrition, analgesia, microbiology/antibiotics, swallowing, medication, chest/breathing, vascular access, delirium/PTSD, tracheostomy care and deranged blood tests. A textbox allows further notes to be added as needed. After the patient review, a decision is made on whether the patient requires further visits or if they can be discharged from the follow-up program. The ITU Outreach doctor also alerts non-

medical and AHP staff such as physiotherapists, speech language therapists or dieticians if needed.

The application is used by the Outreach Team to track the referrals who have not been admitted to ITU and the patients discharged from ITU who still require some follow-up.

In this way, it serves as a communication tool between members of the Outreach Team, allowing an easy form of documentation.

Ethics approval was granted by the University Research Ethics Committee of the University of Malta.

Statistics

Data was exported from Sharepoint Lists to Excel® (Microsoft, California, US). This was analysed using RStudio (RStudio: Integrated Development Environment for R, Version 2023.06.1+524, Boston, Massachusetts, USA), with R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). All data was first tested for normality using visual methods and with Shapiro-Wilk's normality test. Where appropriate, parametric tests were used, but most data showed high levels of skewness. In such cases, median and IQR are reported, and non-parametric tests were used for analysis.

RESULTS

Referrals

From March 2022 to March 2023 a total of 778 patients were directly referred to the ITU Outreach Team. The mean age of all referrals was 61 years (IQR: 49-76), with the age distribution being shown in **Digital Supplemental Figure 1**. Most referrals were made by the Emergency Department (29%), followed by the Medical Wards (16%) and admissions from Emergency Theatres (9%), as shown in **Digital Supplemental Figure 2**. The majority of patients suffered from respiratory or cardiovascular failure followed by renal failure and haematological disturbances (**Digital Supplemental Figure 3**).

While 38% of patients were admitted straight to ITU after the first review, 6.4% were seen twice or more before a decision to admit was taken (**Figure 1**). In 21% of cases no changes to the current treatment plan had to be made. Almost 12% of all referred patients were not ITU candidates while 20% needed advanced organ support, notably respiratory support in other enhanced care areas (CCU, SHDU and MAUs).

Between March 2022 and March 2023, a total of 731 patients were followed up on after discharge from

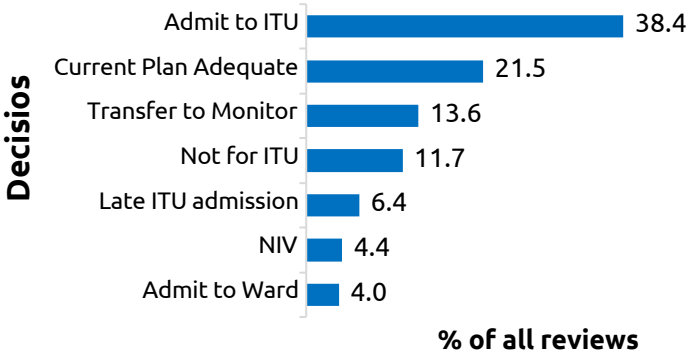


Figure 1 *Decisions taken by the Outreach Team after patient review*

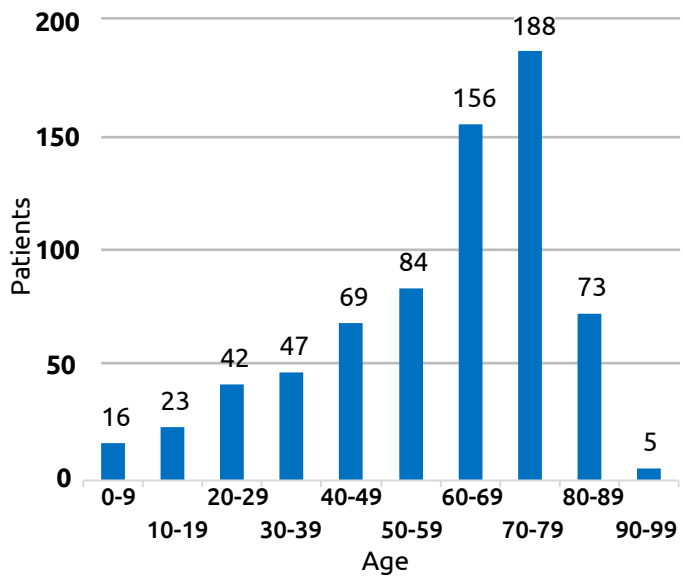


Figure 2 *Age Distribution Discharged Patients*

the Intensive Care Unit. The median age was 64.0 years (IQR: 47.0 – 74.0), with the youngest patient being three years old and the oldest 94 years old (**Figure 2**). Most patients were admitted after emergency or elective general surgery (134 patients, 18.3%), with Type 1 Respiratory failure (71 patients, 9.7%) being the second most common reason for ITU admission (**Figure 3**). Neuropsychiatric emergency such as overdoses and delirious states are the third most common diagnosis (53 patients, 7.2%). Urosepsis is listed separately from other bloodstream infections as it was the most common cause of sepsis (23 patients, 52%). COVID related admissions accounted for only 2.3% of all admissions (17 patients).

The wards receiving the majority of patients after discharge were the surgical wards (Surgical, HDU, NSW, Orthopaedics, ENT, Urology, Plastics, CSW) with 49% of all transfers, followed closely by the medical

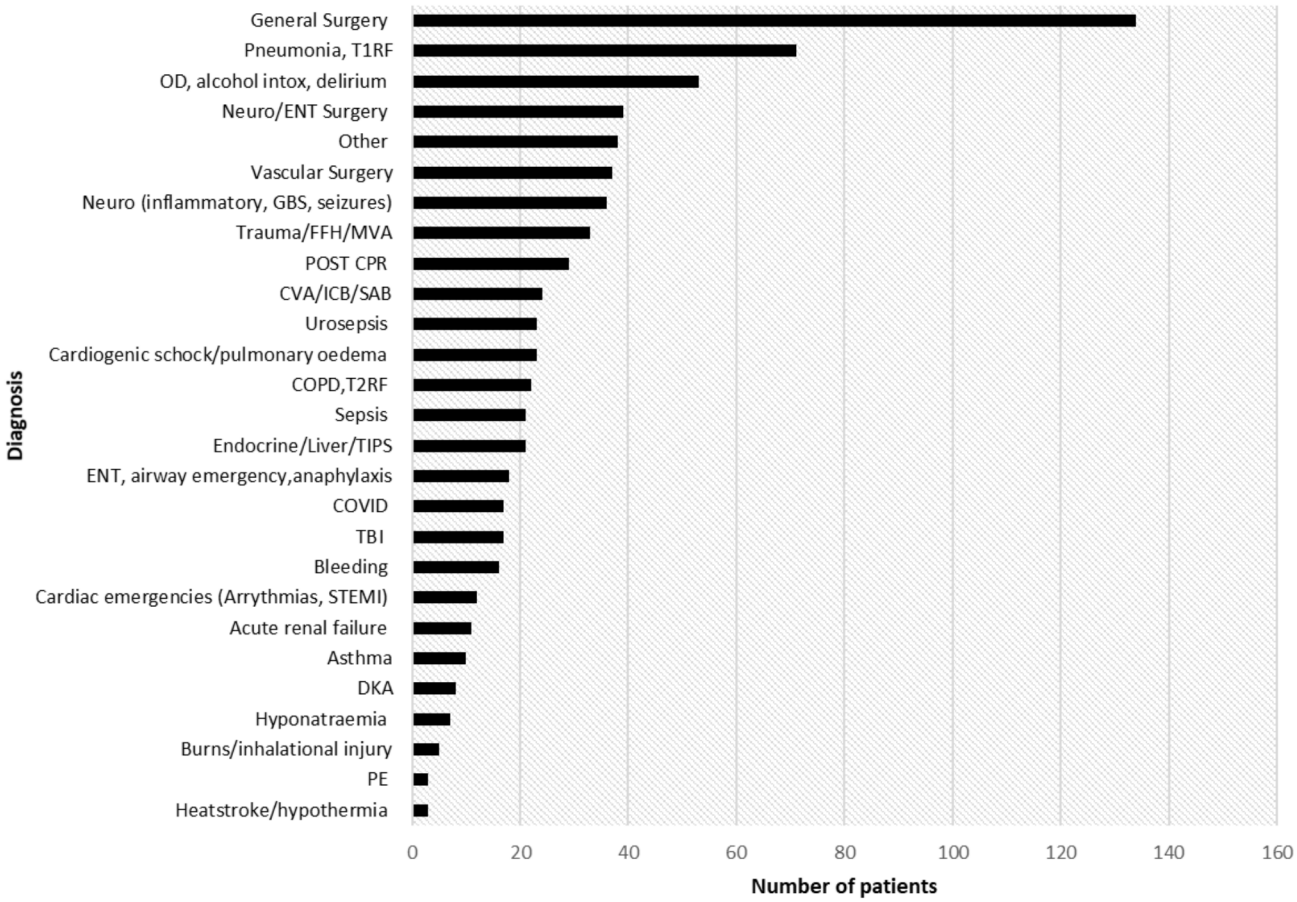


Figure 3 *Distribution of medical diagnosis across the sample population*

wards (Medical, MAU, NMW, CMW) with 31%. 9.6 % of all patients were transferred to a surgical higher dependency unit, as shown in Figure 4.

The ITU Outreach Team performed a total of 1,057 post-discharge reviews, with most patients required only one review. However, 10.6 % of patients required a minimum of 3 and 3.5% needed 4 or more visits (Figure 5).

The majority of patients demonstrated none or only one ITU related issue during the follow-up visits. A total of 14% had 3 or more areas of concern being brought to attention by the team (Digital Supplemental Figure 4).

The most common concern to the follow-up team were issues related to the chest (42.3 %) and overall muscle weakness (12.6 %). Issues related to the prescription of medication (antibiotics, analgesia, sedatives and psychotropic medication) were also common (Digital Supplemental Figure 5).

When comparing the trajectory of the concerns upon discharge, the data shows that most problem areas persisted (Figure 6). This is particularly true for the

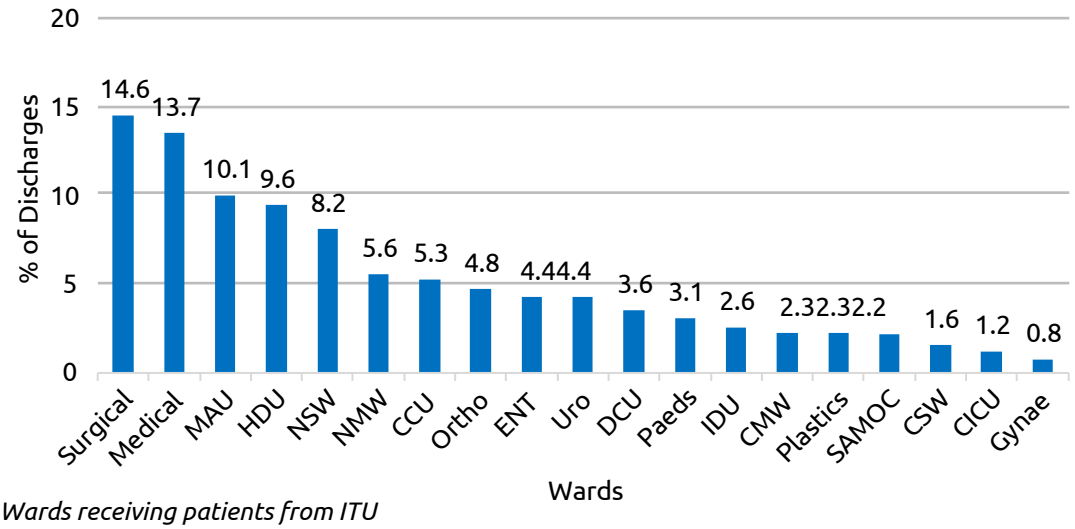


Figure 4 *Wards receiving patients from ITU*

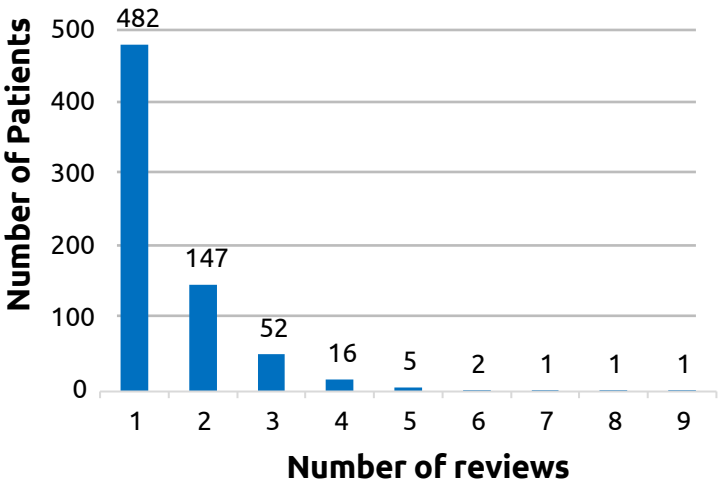


Figure 5 *Number of ward reviews per patient after discharge from ITU*

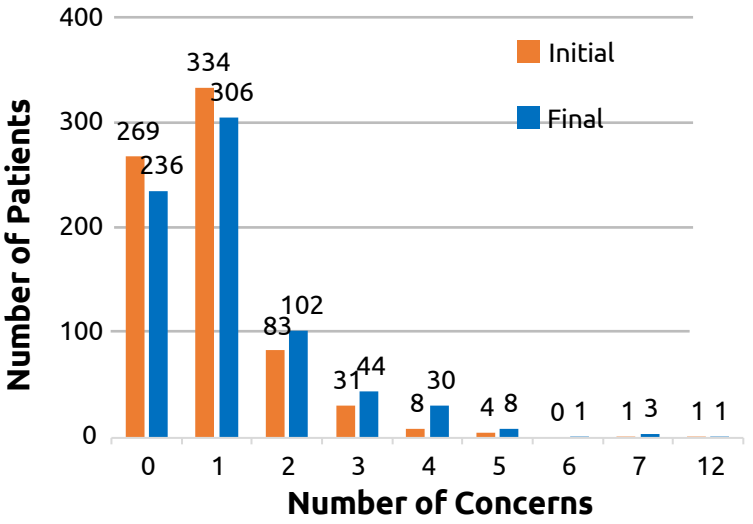


Figure 6 *Comparison number of concerns between first and last visit*

most frequently encountered issues: chest, kidney injuries and muscle weakness (Figure 7). Indeed, follow-up identified new concerns during subsequent visits.

DISCUSSION

Over the last few years, the Intensive Care Community started to broaden their clinical interest from the patient's stay inside the Intensive Care Unit to the period before and after, shaping the concept of ITU without borders or Critical Care Transition Programs. [15-17] During the time before admission, the focus is mostly on the early recognition of the deteriorating patient and the quick initiation of appropriate care resulting in the worldwide introduction of Medical Emergency Teams (MET) or Rapid Response Teams (RRT). Their overall effect on patients' outcomes are mixed, however there is evidence that they can improve the survival rates of in-hospital CPRs, assist with end of life decisions and help to decrease the number of unplanned ITU admissions [18,19,20]. Care after ITU focuses on the various rehabilitation needs of this particular patient group summarised under the term "Post Intensive Care Syndrome" (PICS) (21). The Post Intensive Care Syndrome is a complex state comprising several sequelae such as: weakness, PTSD, malnourishment and chronic pain lasting often for many months sometimes up to years after critical illness.[22,23] The intense rehabilitation needs of ITU survivors have been addressed as early as 2009 by the National Institute for Health and Care Excellence (NICE).[24] It is

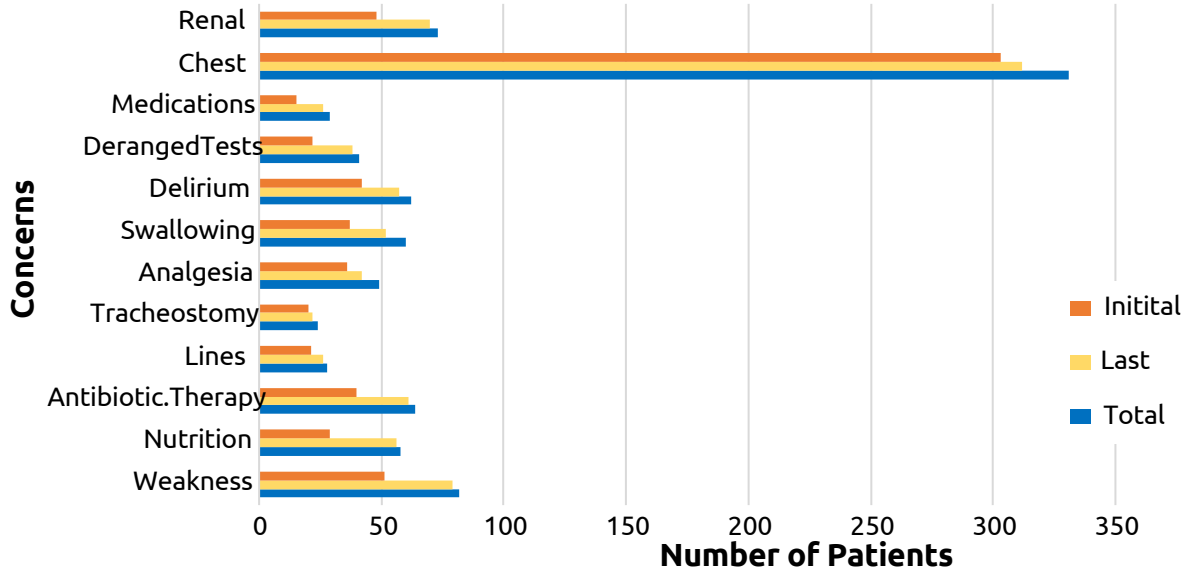


Figure 7 *Detailed list of specific concerns on the first and last visit of followup*

recommended to identify patients suffering from PICS early and to plan a rehabilitation pathway before discharge from hospital. ITU Follow up services have since then been introduced in several countries [25-27] despite mixed results on their effects on patient outcome. The lack of evidence has been attributed to their heterogeneous nature [28,29] and lack of randomised controlled trials.

We recently introduced an Outreach and Follow-up Service at Mater Dei Hospital, and we wished to assess the impact of this service on the clinical course of ITU patients out of ITU.

ITU Outreach

Over one year 778 patients were directly referred to the Outreach Team. This data does not include elective post-op referrals or CPRs and underestimates the true number, as input of the data is dependent on the individual performing the review. The team received most referrals from the Emergency Department concerning respiratory and circulatory failure. The team admitted the majority of patients after the first review (38%) but also referred nearly 15% to enhanced care wards – wards offering NIV and monitored beds.[34] The escalation of care was thus in most cases warranted. In 20% of the cases, the role of the Outreach Team was an advisory one and no major changes to the current treatment plan or patient location had to be made. Notably, in only 6% of cases the patients needed ITU admission at a later stage. It is difficult to interpret this number without further details but it could mean that in the majority of cases the solutions offered by the Outreach Team were sufficient. 11% of cases were not suitable ITU candidates. Even this number is hard to interpret without further details on the specific case but it could mean that the Outreach Team did contribute to ceilings of care and end of life decisions.

Follow-up Program

Over one year, the ITU team followed up on 761 patients after discharge from the Intensive Care Unit resulting in 1,867 reviews. Our data shows that most patients were admitted to ITU post operatively. Accordingly, most of our reviews were done in surgical wards. On average, surgical patients do not stay long in our ITU and it is not surprising that most of the patients only required one post discharge visit. The second most frequent diagnosis was Type-2 Respiratory failure, which explains how one of the main concerns during the ward visits were related to the chest. This entailed a high secretion load, a new chest infection or concerns raised by the physiotherapists regarding cough strength. Interestingly, a total of 14% of patients worried the team enough to expand their follow-up care to more than 3 visits. Preselection of the patients is thus crucial to remain cost effective, to address staff shortage and focus efforts on those in need; an important observation made by other Follow-up Teams in the past.[30] The amount of concerns per patient dealt with by the intensivists supports this conclusion. Most patients had none or only one area of concern to address taking into consideration that the team primarily assessed issues related to the previous ITU stay to avoid interference with general ward management. Our results with regards to frequency of PICS related sequelae is reflected in current literature. Motor deficits, decreased lung function and delirium are common in ICU survivors.[31] Most of these deficits remained even after the team made a decision to stop regular ward visits. PICS is a long-term condition and can persist even for months after discharge. We did not review the patients after discharge from hospital but seeing that a high percentage still had respiratory issues and muscle weakness on our last visit raises the question for the need of an ITU Follow up clinic at Mater Dei Hospital. Furthermore, one of the functions of the team could be to raise awareness and help to further strengthen the relationship between doctors and allied health professionals such as physiotherapists, nutritionists and occupational therapists. Literature shows that transitional services can help ease anxiety of patients and families during the transition period from higher levels of care to peripheral wards and can also help prevent miscommunication during handover.[32,33]

Since the service was introduced, the ITU started using an electronic discharge summary that is accessible on the same application (ITU Flow) and also uploaded on iSoft. The document provides the ITU Outreach doctor with enough information to make decisions during the visit without reading through the ITU stay notes and assists in a smoother flow of information on discharge.

Limitations

This was a single centre study and the results might therefore not all be transferrable to another institution. Furthermore, we did not assess PICS related symptoms with established questionnaires. A future project would involve a similar study design with added questionnaires for the more common PICS related sequelae such as the HADS and DSM-5 for quantifiable data on anxiety, depression or PTSD related symptoms. As some of these disorders of mental health can develop at a later stage or in the case of PTSD per definition begin months after the

traumatic event, some tests would have to be run at a Follow-Up Clinic after patient discharge from hospital.

CONCLUSIONS

Mater Dei Hospital has been successfully running an ITU Outreach and Follow up service since 2021. This is the first data analysis collected over one year (March 2022- March 2023). The data shows, that our ITU survivors suffer from long term sequelae, which warrant individualised plans for rehabilitation and interdisciplinary care. A future long-term follow-up in form of an Outpatient Clinic should be considered. Preselection of patients in need of further ITU input is essential to run the service in a time and cost-effective manner. A post ITU visit can raise awareness to the specific needs this particular group of patient has and promote interdisciplinary communication. In the future data collection will focus more on quantifiable data to assess symptoms like weakness or PTSD with questionnaires or activity measures like grip strength and 6-minute walk tests. The Outreach Team helped to facilitate the transfer of critically ill patients to the Intensive Care Unit and also assisted in making significant changes to the treatment plan outside ITU. Over the past year the mobile application has undergone several updates and in the future the Outreach Team will collect data on the severity scores of ITU referrals with the aim to assist hospital plans to expand enhanced care wards and to improve communication between the wards, the Emergency Department and the Intensive Care Unit.

REFERENCES

1. Meyer J, Brett SJ, Waldmann C. Should ICU clinicians follow patients after ICU discharge? Yes. Intensive Care Med. 2018 Sep;44:(9)1539–41.
2. Ostermann M, Vincent JL. ICU without borders. Crit Care. 2023 May 13;27:(1)186.
3. Rosenberg AL, Hofer TP, Hayward RA, Strachan C, Watts CM. Who bounces back? Physiologic and other predictors of intensive care unit readmission. Crit Care Med. 2001 Mar;29:(3)511–8.
4. Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med. 2010 Aug 3;153:(3)167–75.
5. Lone NI, Gillies MA, Haddow C, et al. Five-year mortality and hospital costs associated with surviving intensive care. Am J Respir Crit Care Med. 2016 Jul 15;194:(2)198–208.
6. Modrykamien AM. The ICU follow-up clinic: a new paradigm for intensivists. Respir Care. 2012 May;57:(5)764–72.
7. Ohtake PJ, Lee AC, Scott JC, et al. Physical impairments associated with post-intensive care syndrome: systematic review based on the World Health Organization's International Classification of Functioning, Disability and Health framework. Phys Ther. 2018 Aug 1;98:(8)631–45.
8. Herridge MS, Tansey CM, Matté A, et al. Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011 Apr 7;364: (14)1293–304.
9. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012 Feb;40:(2)502–9.
10. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. J Transl Int Med. 2017 Jun 30;5:(2)90–2.
11. Jones C. What's new on the post-ICU burden for patients and relatives? Intensive Care Med. 2013 Oct;39:(10)1832–5.
12. Lyons PG, Edelson DP, Churpek MM. Rapid response systems. Resuscitation. 2018 Jul;128:191–7.
13. Ostermann M, Vincent JL. ICU without borders. Crit Care. 2023 May 13;27:(1)186.

14. Tabanejad Z, Pazokian M, Ebadi A. A systematic review of the liaison nurse role on patient's outcomes after intensive care unit discharge. Int J Community Based Nurs Midwifery. 2014 Oct;2:(4)202–10.
15. Rosa RG, Maccari JG, Cremonese RV, Tonietto TF, Cremonese RV, Teixeira C. The impact of critical care transition programs on outcomes after intensive care unit (ICU) discharge: can we get there from here? J Thorac Dis. 2016 Jul;8:(7)1374–6.
16. Haruna J, Masuda Y, Tatsumi H. Transitional care programs for patients with high nursing activity scores reduce unplanned readmissions to intensive care units. Medicina (Kaunas). 2022 Oct 27;58:(11)1532.
17. Neto R, Carvalho M, Paixão AI, Fernandes P, Castelões P. The impact of an intensivist-led critical care transition program. Cureus. 2022 Jan 17;14:(1)e21313.
18. Lyons PG, Edelson DP, Churpek MM. Rapid response systems. Resuscitation. 2018 Jul;128:191–7.
19. Maharaj R, Raffaele I, Wendon J. Rapid response systems: a systematic review and meta-analysis. Crit Care. 2015 Jun 12;19:(1)254.
20. Rozen T, Butt W. Rapid response teams: how are they best used? Crit Care. 2016 Aug 19;19:253.
21. Preiser JC, Herridge M, Azoulay E. Post-Intensive Care Syndrome. 1st ed. Springer; eBook ISBN 978-3-030-24250-3.
22. Van Der Schaaf M, Bakhshi-Raiez F, Van Der Steen M, Dongelmans DA, De Keizer NF. Recommendations for intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. Minerva Anestesiol. 2015 Feb;81:(2)135–44.
23. Sevin CM, Bloom SL, Jackson JC, Wang L, Ely EW, Stollings JL. Comprehensive care of ICU survivors: development and implementation of an ICU recovery center. J Crit Care. 2018 Aug;46:141–8.
24. National Institute for Health and Clinical Excellence (NICE). Rehabilitation after Critical Illness [Internet]. London: NICE; 2009 Mar.
25. van Mol M, Ista E, van Dijk M. Implementation and evaluation of a follow-up programme after intensive care treatment: a practice development project. Intensive Crit Care Nurs. 2018 Dec;49:6–13.
26. Busico M, das Neves A, Carini F, et al. Follow-up program after intensive care unit discharge. Med Intensiva (Engl Ed). 2019 May;43:(4)243–54.
27. Schofield-Robinson OJ, Lewis SR, Smith AF, McPeake J, Alderson P. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. Cochrane Database Syst Rev. 2018 Nov 2;11:(11)CD012701.
28. Rosa RG, Ferreira GE, Viola TW, et al. Effects of post-ICU follow-up on subject outcomes: a systematic review and meta-analysis. J Crit Care. 2019 Aug;52:115–25.
29. Garcea G, Thomasset S, McClelland L, Leslie A, Berry DP. Impact of a critical care outreach team on critical care readmissions and mortality. Acta Anaesthesiol Scand. 2004 Oct;48:(9)1096–100.
30. Garcea G, Thomasset S, McClelland L, Leslie A, Berry DP. Impact of a critical care outreach team on critical care readmissions and mortality. Acta Anaesthesiol Scand. 2004 Oct;48:(9)1096–100.
31. Inoue S, Hatakeyama J, Kondo Y, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. Acute Med Surg. 2019 Apr 25;6:(3)233–46.
32. Sjöstedt V, Bladh A, Chaboyer W, Johansson L. Patient experiences of an intensive care liaison nurse support service. Intensive Crit Care Nurs. 2022 Aug;71:103250.
33. Li B, Yang Q. The effect of an ICU liaison nurse-led family-centred transition intervention program in an adult ICU. Nurs Crit Care. 2023 May;28:(3)435–45.
34. Faculty of Intensive Care Medicine. Enhanced Care: Guidance on Service Development in the Hospital Setting. London: FICMN; 2020..

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ORIGINAL ARTICLE

Boys Under 6 Months Presenting with their First Febrile Urinary Tract Infection

Francesca Gauci, Marie Claire Grech, Daniela Grima, Valerie Said Conti

Background and Introduction

Urinary tract infections are common in children and can cause morbidity. International and local guidelines differ in their recommendations for the investigation of infants following a first febrile UTI, especially for those under 6 months of age. In particular, most medical guidelines do not offer any recommendation for early surgical referral. We looked at a cohort of boys less than 6 months of age presenting with their first UTI and sought to determine whether any features in the investigation paradigm should alert a paediatrician to consider early referral to paediatric surgery.

Method

We performed a retrospective analysis of all boys less than 6 months of age presenting with their first febrile UTI to the emergency department of Mater Dei Hospital in the period between January 2020 to December 2021.

Results

38 boys were included. All underwent a renal US: 13 (34%) had an abnormal US. An MCUG was abnormal in 72.7% of boys with an abnormal US vs 32% of those with a normal US, but this was not statistically significant. DMSA was more likely to be abnormal in those with an abnormal US and abnormal MCUG; all boys with a normal US and normal MCUG had a normal DMSA scan. Twelve boys underwent cystoscopy: 11 had abnormal findings. Only 1 boy had previous normal US and MCUG; all the rest had an abnormal MCUG with/without an abnormal US. 9 boys with positive findings on cystoscopy were aged 2 months or less with a median age of 7 weeks at presentation.

Conclusion

For this cohort we determined that one should proceed to an MCUG even if the US findings are normal; a DMSA scan is not helpful in deciding whether to proceed to cystoscopy; the 'top-down' approach for investigation should not be advocated for boys less than 2 months of age; boys with first febrile UTI aged 2 months or less should be referred for consideration of cystoscopy.

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Urinary tract infection (UTI) in children is a common and potentially serious condition that may be difficult to recognise, particularly in infants in whom obtaining and interpreting samples may be challenging. Signs of UTI in infants are non-specific and include fever, vomiting, lethargy, irritability, poor feeding, failure to thrive, haematuria and foul-smelling urine. Urine dipstick demonstrates raised leucocytes and positive nitrites (although the latter may be falsely negative since neonates and infants void frequently), urine microscopy of uncontaminated urine shows pyuria and bacteriuria, and urine culture shows a growth of a single organism with >10(5) colony forming units/ml.

UTI in the neonatal period has a male predominance and infections are more frequently caused by non-Escherichia coli organisms with a higher risk of urosepsis.[1] Incidence of UTI in boys is highest during the first 6 months (5.3%), while the converse occurs in girls with an incidence of 2% in the first 6 months.[1] Escherichia coli remains the commonest causative organism, however atypical organisms have been associated with congenital renal tract abnormalities. A UTI can be the first presentation of a congenital structural abnormality of the urinary tract,[2] which risks long term consequences including renal scarring. In fact, each febrile UTI increases the risk of renal scarring by 2.8%.[1] The investigations and follow up of UTI in children have been widely debated. Such investigations need to be evidence based, minimally invasive and judicious as they place a heavy burden on health care resources. Investigations can also be an unpleasant experience for both parents and infants. Internationally and locally, published guidelines endeavour to minimise unnecessary investigations in infants and are based on age group and gender, on whether an infection is typical or atypical and on whether an infection is recurrent. Most guidelines do not include any recommendations for surgical referral, and we set out to investigate which cohort of boys with first presentation of urinary tract infection benefits from a surgical review.

MATERIALS AND METHOD

We performed a retrospective analysis of all admissions to Mater Dei Hospital with a first UTI in the period from January 2020 to December 2021. Data was obtained from handover documents of ward admissions, from iSOFT clinical manager, discharge letters and notes and included age of presentation, gender, urinalysis results, micro-organism grown from urine culture and imaging results including renal ultrasound (US), micturating cystogram (MCUG) and dimercaptosuccinic acid scan (DMSA). Findings at cystoscopy were documented. Use of antibiotic prophylaxis was studied. Patients already under investigation for congenital anomalies of the kidney and urinary tract were excluded.

RESULTS

There were 62 admissions with first time UTIs in infants less than 6 months old between January 2020 and December 2021. 38 cases were male (61.3%) as shown in Table 1. Of these, 12 (31.6%) were <2 months old, 13 (34.2%) were 2-3 months old and 13 (34.2%) were 3-6 months old at the time of admission.

Urinalysis

24 boys (63.2%) had a positive urinalysis result (elevated leucocytes, nitrite positive), whilst 5 boys (13.1%) had an equivocal urinalysis result (mildly elevated leucocytes, nitrite negative). 9 cases (23.7%) had a negative urinalysis result but had a growth on urine culture. 36 out of the 38 boys had a positive culture. In 2 boys (5.2%) the urine sample was contaminated but the urinalysis was strongly suggestive of a UTI.

Cultures

Escherichia coli was the commonest growth (61.5%) followed by *Klebsiella pneumoniae* (15.4%), ESBL positive *Escherichia coli* (7.7%), *Klebsiella oxytoca* (2.6%), *Streptococcus agalactiae* (2.6%), *Morganella morganii* (2.6%) and *Proteus mirabilis* (2.6%), as shown in Figure 1.

38 male cases	
Age cohort	**Number of cases**
< 2 months	12
2-3 months	13
3-6 months	13

Table 1 *Age cohorts of male cases presenting with first UTI <6 months of age*

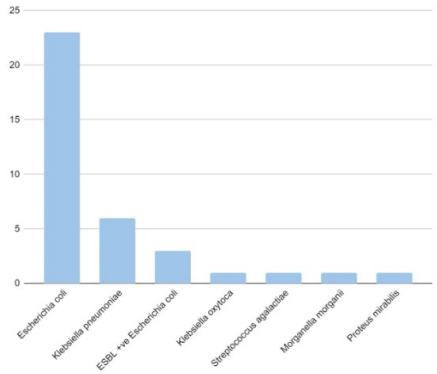


Figure 1 *Bacterial culture growths of males presenting with first UTI <6 months*

Four boys presented with urosepsis with Escherichia coli (50%) and Klebsiella pneumoniae (50%) cultured from both blood and urine.

Ultrasound Scan

All 38 boys underwent a renal ultrasound. 13 cases (34.2%) had an abnormal ultrasound: kidney size discrepancy in 3 (7.9%), hydronephrosis +/- distal dilated ureter/s in 6 (15.8%), pelvi-calyceal splitting in 2 (5.3%), evidence of pyelonephritis in 1 (2.6%) and incidental urachal remnant in direct connection with bladder in 1 (2.6%). 25 cases (65.8%) had normal ultrasound findings.

MCUG

An MCUG was performed in 36 cases (94.7%). Of the 13 boys with an abnormal ultrasound, 11 had an MCUG and this was abnormal in 8 cases (72.7%; 95% CI: 39-92%) (Table 2). Two boys did not undergo an MCUG (one had kidney size discrepancy and the other had a urachal remnant). All 25 boys with a normal US underwent an MCUG and this was abnormal in 8 (32%; 95% CI: 16-35%). This did not reach statistical significance, p= 0.034 (Fisher's exact test).

DMSA scan

A DMSA scan was performed in 26 cases (68.4%), with the findings shown in Table 3. In 7 cases (18.4%), the procedure was either refused, or the patient did not turn up.

Considering the 8 boys with an abnormal US and abnormal MCUG, DMSA was performed in 7 and was abnormal in 4.Considering the 8 boys with a normal US and abnormal MCUG, DMSA was performed in 7 and was abnormal only in 1.

Diethylenetriamine/Mercaptoacetyltriglycine (DTPA/MAG3 scan)

A DTPA or MAG3 scan was not performed in any of the cases identified.

Cystoscopy

12 of the 38 boys (31.6%) eventually proceeded to a cystoscopy - 11 had abnormal findings (Table 4). Six of the 8 boys with an abnormal US and abnormal MCUG underwent cystoscopy which was abnormal in 5 (83%). Five of the eight boys with a normal US and abnormal MCUG underwent cystoscopy which was abnormal in all (100%).

One boy with normal US, normal MCUG and normal DMSA scan underwent cystoscopy because of a complex presentation (presented with recurrence of symptoms while still recovering from the first

Table 2 *MCUG findings*

MCUG in cases with abnormal US findings	MCUG in cases with normal US findings
4 Dilated posterior urethra	1 Dilated posterior urethra
1 Bilateral VUR (grade 4)	3 Bilateral VUR (grade 3 in 1, grade 4 in 2)
2 Unilateral VUR (grade 4 in 1, grade 5 in 1)	4 Unilateral VUR (grade 1 in 1, grade 2 in 1, grade 3 in 2)
1 Urinary diverticulum	17 normal
3 Normal	
2 Not performed	

Table 3 *DMSA findings*

DMSA findings			
Abnormal US + Abnormal MCUG n = 7	**Abnormal US + Normal MCUG** n = 2	**Normal US + Abnormal MCUG** n = 7	**Normal US + Normal MCUG** n = 10
2 Smaller left kidney with reduced function (38%)	1 Smaller right kidney with normal function	1 Horseshoe kidney with no cortical scarring	10 Normal
1 Duplex left kidney with smaller lower moiety and global reduction in uptake (34%)	1 Normal	6 Normal	
1 Smaller left kidney with normal function			
3 Normal			

Table 4 *Cystoscopy findings according to age at presentation*

Cystoscopy findings	
</= 2 months of age	**> 2 months of age**
5 PUV	1 PUV
3 Bilateral VUR	1 Bilateral VUR
1 Unilateral wide ureteric orifice	1 Normal

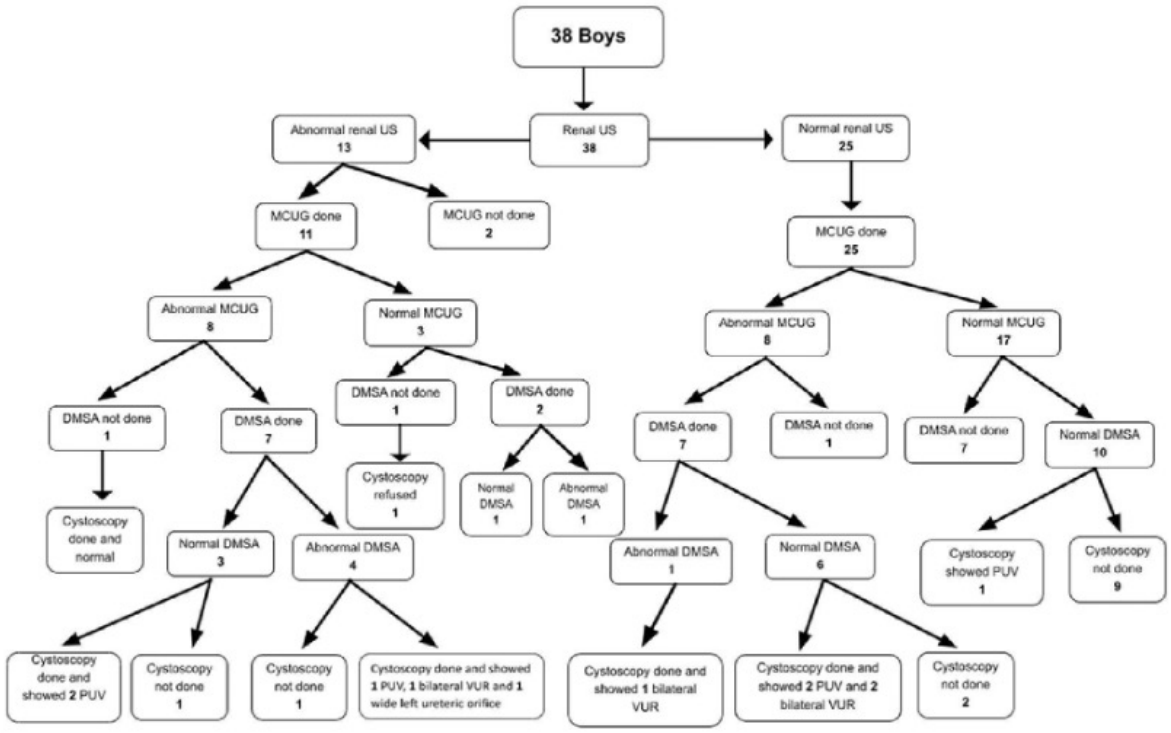


Figure 2 *Flow chart demonstrating imaging performed and findings*

presentation) and posterior urethral valves were diagnosed at cystoscopy. 9 boys with positive findings on cystoscopy were aged 2 months or less with a median age of 7 weeks at presentation.

Figure 2 demonstrates the imaging performed and their findings.

Prophylaxis

25 boys (65.8%) presenting with first UTI at <6 months of age were started on prophylaxis at presentation: trimethoprim/sulfamethoxazole (55.3%), nitrofurantoin (7.9%) or ciprofloxacin (2.6%). Diagnoses included: posterior urethral valves[6], high grade vesico-ureteric reflux[6], low grade vesico-ureteric reflux[2], bladder diverticulum[1], dilatation of the posterior urethra on MCUG[1], pelvicalyceal splitting on US[1], renal size discrepancy on US and DMSA[1], mild hydronephrosis and bilateral ureteric dilatation on US[1] and 6 cases with normal investigations.

5 cases with confirmed PUV had a urinalysis which was clearly suggestive of a UTI (1 only had mildly elevated leucocytes and nitrites negative) but all cases had Escherichia coli on urine culture.

For the 9 cases with a negative urinalysis but a positive urine culture, 2 cases had low grade vesico-ureteric reflux on MCUG, 1 case had an incidental urachal remnant on renal US scan and 1 case had mild pelvicalyceal splitting of one kidney on renal US. The rest had normal findings on imaging.

DISCUSSION

Urinary tract infection is one of the commonest bacterial infections in childhood with congenital anomalies of the kidney and urinary tract being a major risk factor. International and local guidelines have been published to describe the presentation, diagnosis and management of such infections. An attempt is made to determine which children will benefit from further investigation and avoid painful procedures, parental worries and costly investigations when these are not necessary. The guidelines include recommendations for imaging depending on the clinical presentation, age and gender and the micro-organism grown. Infection is defined as typical or atypical, and recurrent. Most guidelines define an infection as being atypical if there is no response to treatment within 48 hours, if the child is septic/very unwell, if there are abdominal masses, if there is renal impairment, if there are signs of upper tract involvement or infection with a non-Escherichia coli micro-organism.

The guidelines differ in their recommendations for medical imaging: we therefore referred to 5 medical guidelines [3-7] and 1 surgical guideline.[1] Of note, both the American and Italian guidelines exclude infants

<2 months of age citing that this cohort requires special considerations. Only one medical guideline gave recommendations on referral to paediatric urology. The South Australian Paediatric Clinical Practice Guidelines on UTI in Children recommends that referral should be considered urgently if there is suspicion of renal tract obstruction, high grade vesico-ureteric reflux, recurrent and atypical UTI, structural neurological abnormality or suspected neurogenic bladder.[7] The Swedish guideline gives detailed recommendations for the management of VUR.[8-9] The National Institute for Health and Care Excellence (NICE) does not recommend routine surgical management of VUR.[3] We therefore studied a cohort of boys less than 6 months of age presenting with their first UTI to establish recommendations for referral for cystoscopy.

A cohort of 38 boys less than 6 months of age presenting to Mater Dei Hospital with their first febrile urinary tract infection was reviewed. We analysed the urinalysis and culture results as well as any ultrasound, MCUG and DMSA scan results. We documented cystoscopy findings of the boys who underwent the procedure.

For infants with a first UTI presenting before 6 months of age all the guidelines recommend a renal ultrasound (US). All boys in this cohort had a renal ultrasound and this was abnormal in 13 of 38 (34.2%). 72.7% of boys with an abnormal US had an abnormal MCUG; 32% of boys with a normal US had an abnormal MCUG. The yield of having an abnormal MCUG was thus higher when the US was also abnormal, however, this did not reach statistical significance ($p<0.34$, Fisher's exact test). The fact that the numbers were small needs to be taken into consideration. The guidelines differ in their recommendation for performing an MCUG and the practice patterns have shifted considerably towards a less invasive approach in recent years[10]; the consensus in the medical guidelines is to perform an MCUG under the age of 6 months if the US is abnormal, if the presentation is atypical or if it is recurrent. The European Association of Urology and European Society for Paediatric Radiology guidelines go further and recommend an MCUG even with a normal renal US in infants <1 year to exclude VUR.[11] Our findings at MCUG in boys with an abnormal US included dilated posterior urethra and high grades of reflux of 4 – 5; with a normal US, MCUG findings included dilated posterior urethra and lower grades of reflux of 1 – 4, but which still constitute major findings. Hence, we conclude that an MCUG is indicated even if the ultrasound findings are normal.

Six of the 8 boys with an abnormal US and abnormal MCUG proceeded to cystoscopy and only one had a normal cystoscopy. The others all had major findings. Only 3 of these boys had an abnormal DMSA scan. Thus, findings at DMSA scan were not a good marker to identify boys with serious underlying abnormalities found on cystoscopy. Similarly, 4 of the 6 boys who had a normal DMSA scan with a normal US and abnormal MCUG and who proceeded to cystoscopy had posterior urethral valves or high grade bilateral VUR at cystoscopy. Hence, DMSA scan was not found to be helpful in deciding whether to proceed to cystoscopy or not. This is not to say that a DMSA scan is not useful in the management paradigm because the results do influence certain surgical decisions, for example, in the management of VUR, but this study has shown that an abnormal MCUG is more useful in deciding whether to proceed to cystoscopy or not. Two approaches in the imaging following a UTI have been put forward.[12] The 'top-down' approach (US followed by DMSA scan) looks for any scars which can correlate with high grade VUR and an MCUG is performed only if renal involvement is present. The 'bottom-up' approach (US followed by an MCUG) looks for bladder involvement to detect VUR. In our experience, the findings on DMSA scan did not correlate with the findings on cystoscopy and we would advocate the 'bottom-up' approach using US and MCUG in boys <6 months presenting with their first UTI in whom posterior urethral valves, besides VUR, need to be excluded.

One child with a normal renal US and MCUG and DMSA scan underwent cystoscopy and was found to have posterior urethral valves. He had presented with recurrent symptoms of UTI while still recovering from his first presentation, making it difficult to define whether this was an unresolved first febrile infection or a recurrent infection. Nonetheless, this was a complex presentation in a boy less than 3 months of age and highlights the recommendations by most guidelines to use clinical judgement and decide on a case-by-case basis when making decisions at this young age.

11 out of 12 cystoscopies performed were abnormal. Of note, 6 boys (50%) started out with a normal renal US. Of these, 5 had an abnormal MCUG and 4 had an abnormal DMSA scan. Six boys (50%) started out with an abnormal US. All had an abnormal MCUG and 3 had an abnormal DMSA scan. 9 boys with positive findings on cystoscopy were aged 2 months or less with a median age of 7 weeks at presentation. Thus, the top-down approach in boys less than 2 months of age is likely to miss those with significant findings on cystoscopy.

SUMMARY BOX

What is known:

- Perform a urine culture only when urinalysis is suggestive
- Renal US should be performed in all boys <6 months of age

What are the new findings:

- Perform an MCUG in all boys <6 months presenting with their first UTI even if the US is normal
- The sensitivity of DMSA scan after a first UTI is poor. Do not rely on a DMSA scan to decide whether to proceed to cystoscopy, therefore the top-down approach is not reliable in this age-group
- Boys <2 months of age should be recommended for cystoscopy
- New local guidelines must include detailed recommendations for antibiotic prophylaxis

Escherichia coli is a common pathogen in urinary tract infections since the bacteria have evolved a mechanism using fimbriae which allow them to attach to the urothelium and withstand the stresses of urine flow.[13] Reports in the literature suggest that the presence of atypical micro-organisims such as *Klebsiella* and *Proteus* are more likely to be associated with underlying structural anomalies[14,2] Nonetheless, in this study, 5 of the 6 boys who had posterior urethral valves at cystoscopy presented with a urinalysis which was suggestive of a UTI and *Escherichia coli* was grown in all. This cohort had a higher percentage of *Escherichia coli* cultured in cases of PUV when compared to other studies with rates of 26.7%.[15] Hence, the presence of *Escherichia coli* does not preclude a serious underlying anomaly.

The boys with a normal urinalysis and a growth on culture all had minor findings on imaging. The guideline recommends that a urinalysis is first performed, and a culture is sent only if the urinalysis suggests a UTI. This has been shown to be a valid recommendation from this study.

CONCLUSION

This study has highlighted the importance of recommending boys less than 2 months of age for cystoscopy. It has also confirmed that a normal US does not exclude serious underlying abnormalities. The 'top-down' approach is not recommended in boys less than 6 months of age: a clear understanding of any bladder pathology is essential and an MCUG is best recommended. Local guidelines need to be updated with recommendations for cystoscopy and MCUG in our younger cohorts and with advice on antibiotic prophylaxis. Ultimately, we aim to establish consistent clinical practice by following evidence-based guidelines in order to reduce the number of unnecessary investigations which place a burden on the health services. We also aim to limit radiation exposure in neonates and infants, avoid unnecessary anxiety and stress to both the infant and the parents both when procedures are performed and while results are awaited.

Abbreviations

UTI	Urinary tract infection
PUV	Posterior urethral valves
VUR	Vesico-ureteral reflux
MCUG	Micturating cystogram
US	Ultrasound scan
DMSA	dimercaptosuccinic acid scan
DTPA/MAG3	Diethylenetriamine/ Mercaptoacetyltriglycine
NICE	National Institute of Health and Care Excellence

REFERENCES

1. Hoen LA 't, Bogaert G, Radmayr C, Doogan HS et al Update of the EAU/ESPU guidelines on urinary tract infections in children. J Pediatr Urol 2021;17:201.
2. Vella C, Said Conti V, Torpiano J, Grech V. The relationship between infecting organisms and underlying structural anomalies in children with urinary tract infections. Malta Medical Journal 2008;20:22.
3. Verrier Jones K, Banerjee J, Boddy S et al/em>. Overview | Urinary tract infection in under 16s: diagnosis and management | Guidance | NICE. [online] Nice.org.uk. 2007 [cited 2022 Jan 05]. Available from: https://www.nice.org.uk/Guidance/CG54
4. Roberts K, Urinary tract infection: Clinical Practice Guidelines for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months. Pediatrics 2011;128(3):595-610.
5. Brandström P, Lindén M. How Swedish guidelines on urinary tract infections in children compare to Canadian, American and European guidelines. Acta Paediatr 2021;110(6):1759-1771.
6. Ammenti A, ALberici I, Brugnara M et al/em>. Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. Acta Paediatr 2019;109(2):236-247.
7. Soliman N, Khurana S, Kellett S, La Vanda C, Crafter S, Cooksey R. South Australian Paediatric Clinical Practice guidelines: Urinary tract infection in children [online] 2021 [cited Jan 05]. Available from: https://extappssahealth.sa.gov.au/PracticeGuidelines/Home/DownloadPDF?Filename=Urinary%20Tract%20Infection%20in%20Children_Paed_v1_pdf
8. Hewitt IK, Montini G. Childhood urinary tract infections: A Swedish perspective and comparison with other published guidelines. Acta Paediatr 2021;110(6):1708-1710.
9. Brandström P, Lindén M. How Swedish guidelines on urinary tract infections in children compare to Canadian, American and European guidelines. Acta Paediatr 2021;110(6):1759-1771.
10. Mattoo TK. Contemporary Management of Urinary Tract Infection in Children. Pediatrics 2021;147:6.
11. Hoen LA 't, Bogaert G, Radmayr C, Doogan HS et al Update of the EAU/ESPU guidelines on urinary tract infections in children. J Pediatr Urol 2021;17:204.
12. Uwaezuoke S, Ayuk A, Muoneke U. Urinary Tract Infection in Children: A Review of the Established Practice Guidelines. EMJ Microbiol & Infect Dis 2020;1:61.
13. Wullt B. The role of P fimbriae for Escherichia coli establishment and mucosal inflammation in the human urinary tract. Int J Antimicrob Agents 2003;6:605.
14. Friedman S, Reif S, Assia A, Mishaal R, Levy I. Clinical and laboratory characteristics of non-E. coli urinary tract infections. Arch Dis Child 2006;91(10):845-6.
15. Tambo FFM, Tolefac PN, Ngowe MN et al/em>. Posterior urethral valves: 10 years audit of epidemiologic, diagnostic and therapeutic aspects in Taounde gynaeco-obstetric and paediatric hospital. BMC Urology 2018;18(1):46.

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ORIGINAL ARTICLE

Predictors of poor outcome severe pneumonia children in the paediatric intensive care unit

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Introduction

Severe pneumonia children frequently have poor outcome during hospitalization in PICU. However, the predicting of mortality is hampered by lacking evidence about the risk factors in Indonesia. This study aimed to determine risk factors that associated with mortality in children with severe pneumonia admitted to the pediatric intensive care unit (PICU).

Methods

This was a single-center case-control study in the PICU at Prof. Dr. I.G.N.G Ngoerah Hospital, Indonesia between January 2019 and December 2020. Children and adolescents who aged 28 days to 18 years old with severe pneumonia were included and divided into death and survivor groups. Patients with incomplete medical record data, history of perinatal lung disease, major congenital anomaly, or cyanotic congenital heart disease were excluded. Demographic, clinical, and laboratory data were obtained from medical records. Statistical analysis was conducted using χ^2-test for bivariate and binary logistic regression for multivariate analysis.

Results

160 subjects were included with median age was 7 and 9 months in the death and survivor group respectively. Multivariate analysis showed SpO_2 < 90% at arrival, PELOD-2 score ≥ 7, hemoglobin < 8 g/dL, lymphopenia, and procalcitonin ≥ 0.5 ng/mL were associated with mortality (adjusted odds ratio [aOR] 17.29, 95%CI 4.82-61.43; aOR 18.37, 95%CI 4.14-81.43; aOR 4.05, 95%CI 1.16-14.13; aOR 3.59, 95%CI 1.09–11.75; aOR 7.64, 95%CI 2.61-22.40, respectively). Invasive mechanical ventilation and malnutrition were not associated with mortality.

Conclusion

SpO_2 < 90% at arrival, PELOD-2 score ≥ 7, hemoglobin < 8 g/dL, lymphopenia, and procalcitonin ≥ 0.5 ng/mL are risk factors for mortality in children with severe pneumonia.

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Pneumonia is a common infectious disease worldwide that can occur at any age, though can cause critical illness in children that requires intensive care.[1] The annual incidence of pediatric pneumonia varies geographically, ranging from 6.4 to 231 episodes per 1,000 children.[2–4] Despite the decreasing mortality rate of pneumonia in developed countries, pneumonia continues to cause morbidity and hospitalization in developing countries[4] and form substantial disease burden in healthcare settings.[5,6] The disease is also the leading cause of death in children, with age-standardized mortality rates of 38.9 per 100,000 children and 80% of deaths occurring between the ages of 1 and 59 months.[2,7]

It was estimated that 10.3% to 37.2% of children suffering from pneumonia would require admission to the pediatric intensive care unit (PICU)[1,4] with the mortality rate of severe pneumonia in PICU ranged from 5.9% to 13.5%.[7–10] This high rate of mortality in PICU warrants early and specific treatment through identification and classification of risk factors for mortality in patients admitted to PICU. Several studies have described some risk factors, ranging from clinical to laboratory characteristics, that associated with morbidity and mortality in patients with pneumonia in the PICU.[9,11–14] The data about these risk factors for mortality of patients with severe pneumonia is important to clinician for recognizing high risk populations, establish appropriate early intervention, and reduce in-hospital complications and mortality[7,15] especially in the area with scarce facilities.[9]

It is important to perceive the simple objective clinical signs and laboratory values as risk factors for mortality, as diagnosis and management of severe pneumonia in low-income settings rely on these parameters. Although many studies have identified risk factors for poor outcomes in patients with severe pneumonia in the PICU, data on these risk factors in Indonesia, particularly in Bali, are still limited. To our knowledge, there were only few studies in Indonesia that have described predictors of mortality in children and with only small sample size.[16-18] Furthermore, the other limitations of evidence from previous studies also came from the population of samples were predominantly in less than five age group.[8–10]

Therefore, we sought to evaluate other demographic, clinical, and laboratory characteristics, including age, nutritional status, SpO_2 at arrival, invasive mechanical ventilation, Pediatric Logistic Organ Dysfunction (PELOD)-2 score, haemoglobin, lymphocyte count, and procalcitonin level, and identify the association of these parameters with mortality in severe pneumonia children admitted into the PICU.

MATERIAL AND METHODS

Study design and population

This was a single-center unmatched case-control study conducted between January 2019 to December 2020 in the multidisciplinary care PICU of Prof Dr IGNG Ngoerah Hospital, Bali, Indonesia with maximum capacity of 9 beds and 9 mechanical ventilators. The inclusion criteria in this study were 1) pediatric patients between 28 days and 18 years of age when admitted to the PICU, 2) established diagnosis of severe pneumonia, and 3) were documented in the PICU's medical register. We excluded patients with history of perinatal lung disease, major congenital anomaly, presence of cyanotic congenital heart disease, and incomplete data in medical records.

The sample size was determined based on formula for study design to compare proportions of two populations. The degree of significance was 5%, the power was 80%, and proportion of risk factors based on previous studies.[7,9] Therefore, total minimum sample in both case and control groups was determined to be 108 subjects (54 subjects each).

Data collections

The paper based PICU medical registry of all pediatric patients admitted during study period were screened retrospectively. The eligible patients who met the inclusion and exclusion criteria were included by consecutive sampling method. The subjects were assigned into two groups, the survivor and death groups, based on condition at the time discharge from PICU. Medical information data each subject was collected using a standard case report form and included demographic characteristics (age and gender), weight, height, nutritional status, comorbidities, mechanical ventilation type (invasive or noninvasive), duration of mechanical ventilation, ventilator-free days, PICU and hospital length of stay, and laboratory values (haemoglobin, lymphocyte, procalcitonin, and blood gas analysis) from electronic hospital data information system. We chose these variables based on the previous literature and were uncomplicated to be measured. Therefore, could be applied to our center and other limited-facilities healthcare.

Severe pneumonia was diagnosed by attending physicians as the presence of clinical signs (febrile respiratory illness and lower respiratory tract infection signs), supported by radiological evidence, and accompanied by danger signs, such as chest in-drawing, cyanosis, difficulties breastfeeding, or unconsciousness.[3,19] This study included all pneumonia cases and did not differentiate by specific type (i.e., community- or hospital-acquired) during analysis.

Patient nutritional status was assessed on first day admitted in PICU based on actual subject weight compared to ideal body weight based on the World Health Organization (WHO) growth chart by Waterlow and further classified into well-nourished (above 80%) and moderate-severe malnourished (below 80%).

The lowest measured SpO_2 at arrival by portable pulse oximetry was recorded when the subjects were transferred to the PICU. The SpO_2 less than 90% at arrival was considered the hypoxemia state.

PELOD-2 score is continuous scale and indicates organ dysfunction, which consists of ten variables for five vital organs, namely the neurologic, cardiovascular, renal, respiratory, and hematologic organ systems. The higher score indicates poorer prognosis. The PELOD-2 score was measured in the first 24 hours of admission to the PICU. Organ dysfunction was determined when PELOD-2 score was equal or more than 7 without lactate examination.

Lymphocyte absolute count and haemoglobin level were obtained through routine complete blood count. Lymphocyte count was categorized into two categories: 1) below normal value (lymphopenia) and 2) normal, based on age-specific normal ranges from previous literature.[20] haemoglobin values were divided into two categories with a cutoff of 8 g/dL (< 8 g/dL and ≥ 8 g/dL).[9] Procalcitonin levels were obtained through blood chemistry and divided into two categories, < 0.5 ng/mL and ≥ 0.5 ng/mL. The worst laboratory values were documented when more than one laboratory examinations were available.

Data Analysis

The collected data were analyzed using SPSS for windows version 25.0. Descriptive analysis described the baseline characteristics of subjects in each group. Continuous data were presented as mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if not normally distributed. Categorical data were presented as absolute numbers and percentages. Bivariate analysis was conducted to evaluate the association of mortality with each risk factor using x^2-test. Binary logistic regression was used for multivariate analysis and included variables with p value less than 0.20 in bivariate analysis. P-value less than 0.05 was considered statistically ohsignificant.

Ethical Approval

This study was approved by Research Ethics Committee at Faculty of Medicine Udayana University Prof Dr IGNG Ngoerah Hospital, Denpasar (No. 295/ UN14.2.2.VII.14/LT/ 2021).

RESULTS

Between January 2019 and December 2020, 1019 patients were admitted to PICU, and 192 patients met the inclusion criteria. Thirty-two subjects were excluded due to the presence of perinatal lung disease or cyanotic congenital heart disease or incomplete medical record data or multiple congenital anomalies. Therefore, 160 subjects with severe pneumonia were enrolled in this study. Figure 1 illustrates the process of subject recruitment.

The median age of participants was 7 (IQR 2–47) months for the death group and 9 (IQR 3–48) months for the survivor group. The patients of both groups were predominantly male (58.9% and 57.5% in the

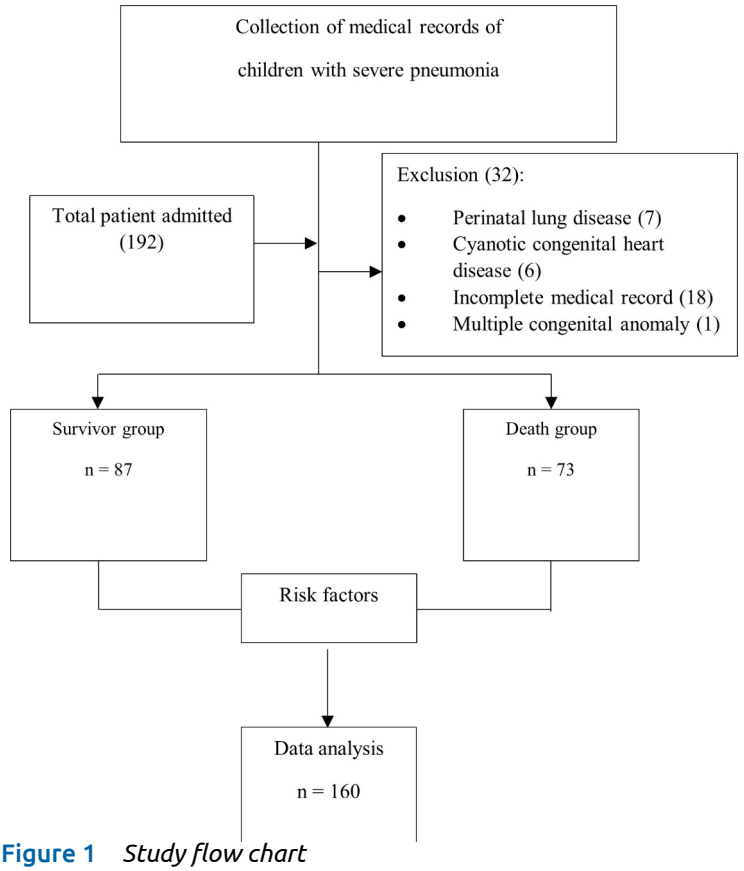


Figure 1 *Study flow chart*

Table 1 *Baseline characteristics of subjects between groups*

Characteristic	Outcome	
	Death (n=73)	Survivor (n=87)
Male n (%)	43 (58.9)	50 (57.5)
Age, months median (IQR)	7 (2-47)	9 (3-48)
Comorbidities n (%)	53 (72.6)	55 (63.2)
Cardiovascular n (%)	23 (31.5)	24 (27.6)
Neurology n (%)	12 (16.4)	15 (17.2)
Haematology-Oncology n (%)	6 (8.2)	5 (5.7)
Immunology n (%)	9 (12.3)	1 (1.1)
PICU LoS, days median (IQR)	4 (2-9)	9 (5-15)
Hospital LoS days median (IQR)	6 (3-15)	20 (12-30)
Ventilator-free days days median (IQR)	0 (0)	22 (15-25)
Length of MV days median (IQR)	4 (2-9)	6 (3-12)
PELOD-2 score median (IQR)	7 (5-8)	3 (1-4)
P/F ratio median (IQR)	171 (113-248.5)	305 (241-352)

Table 2 *Bivariate analysis of some risk factors that associated with mortality*

Risk Factors	Outcome		OR (95% CI)	p value
	Death	Survive		
Age < 60 months n, (%)	56 (76.7)	66 (75.9)	1.0 (0.50-2.17)	0.90
Invasive mechanical ventilation n, (%)	64 (87.7)	60 (69.0)	3.2 (1.39-7.35)	*≤0.001**
SpO_2 < 90% at arrival n, (%)	41 (56.2)	7 (8.0)	14.6 (5.95-36.02)	*≤0.001**
PELOD-2 score ≥ 7 n, (%)	40 (54.8)	4 (4.6)	25.1 (8.33-75.87)	*≤0.001**
Moderate-severe malnutrition n (%)	29 (39.7)	20 (23.0)	2.2 (1.11-4.38)	*0.02**
Haemoglobin < 8 g/dL n, (%)	26 (35.6)	9 (10.3)	4.7 (2.07-11.10)	*≤0.001**
Lymphopenia n, (%)	26 (35.6)	20 (23.0)	1.8 (0.92-3.70)	0.07
Procalcitonin ≥ 0.2 ng/mL n, (%)	58 (79.5)	27 (31.0)	8.5 (4.15-17.77)	*≤0.001**

**Significant p < 0.05 by x2-test*

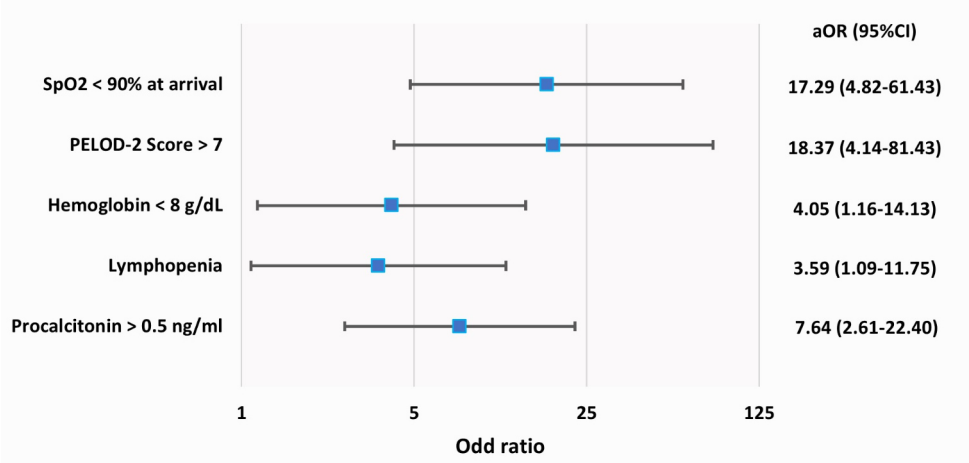


Figure 2 *Multivariate analysis of risk factors of associated with mortality by logistic regression. The plot and error bars represent the odd ratio and confidence interval for each risk factors.*

death group and survivor group, respectively). Cardiovascular disease was the most common comorbidity found in both the survivor group (27.6%) and death group (31.5%), followed by neurological disorders, which had a prevalence of 17.2% and 16.4% for the survivor group and death group, hematology-oncology, and immunology disorders. Median PELOD-2 score was 7 (IQR 5–8) for the death group and 3 (IQR 1–4) for the survivor group, as detailed in **Table 1**.

Bivariate analysis indicated that six risk factors were significantly associated with mortality. These factors were invasive mechanical ventilation, SpO_2 < 90% at arrival, PELOD-2 score ≥ 7, haemoglobin < 8 g/dL, moderate-severe malnutrition, and procalcitonin ≥ 0.5 ng/mL (**Table 2**). However, only five risk factors (SpO_2 < 90% at arrival, PELOD-2 score ≥ 7, haemoglobin < 8 g/dL, lymphopenia, and procalcitonin ≥ 0.5 ng/mL) were independently associated with severe pneumonia mortality in multivariate analysis, as detailed in **Figure 2**.

DISCUSSION

Respiratory infections and illnesses, such as pneumonia, are significant causes of morbidity and mortality, particularly in developing countries. Early detection of severe clinical manifestations and well-timed admission to intensive care is crucial for lowering mortality[5], and identification of risk factors for mortality at admission or during the clinical course is helpful to anticipate and observe treatment during hospitalization.[21]

The risk factors for severe pneumonia mortality vary between countries, regions, and communities. In Indonesia, only three studies have evaluated risk factors of mortality. Kisworini et alsup>17 found tachycardia and anemia and Meliyanti et alsup>16 found bacteremia and low weight as significant risk factors for mortality. Valentania et al[18] described modified PIRO score (malnutrition, complicated chest radiograph, hypoxemia, hypotension, CRP, procalcitonin, and organ dysfunction) could predict mortality of pneumonia. In this study, we found that SpO_2 < 90% at arrival, haemoglobin < 8 g/dL, PELOD-2 score ≥ 7, lymphopenia, and procalcitonin ≥ 0.5 ng/mL were associated independently with mortality.

This study was conducted in Prof Dr IGNG Ngoerah Hospital, as tertiary health center in Bali province, Indonesia. The diagnosis of patients admitted in PICU highly varied, consists of multidisciplinary care, and included pediatric patients who aged 28 days-18 years old. Therefore, the patients could represent all pediatric pneumonia patients that generally treated in PICU. This study was conducted at referral hospital for COVID-19 patients. However, because of small number (only 4) of pediatric patients required intensive care during study period, we decided to not include those patients into study.

Evaluation of SpO_2 is a simple, fast, and noninvasive method to measure arterial oxygenation. The WHO has recommended its clinical use to determine the requirement for oxygen administration for patients with hypoxemia, particularly in low-middle income countries,[22] and states a threshold of < 90% as indicative of hypoxemia requiring immediate referral to the hospital.[23] An abnormal SpO_2 measured by pulse oximetry alone or ratio between SpO_2 / FiO_2 commonly indicates a ventilation–perfusion mismatch caused by a pulmonary illness in pediatric acute respiratory distress syndrome (ARDS).[23] In our PICU, pneumonia were found to be main cause of pulmonary ARDS with the median SpO_2/FiO_2 ratio

were 165.[24] This study found that SpO_2 < 90% at arrival was associated with mortality, with an adjusted OR (odds ratio) of 17.29 (95%CI 4.82-61.43). This result is consistent with previous studies by Shi et alsup>9 and Zhang et alsup>11 that found significant associations between SpO_2 < 90% and mortality, with an adjusted OR of 8.77 (95% CI 2.14–45.02). Colbourn et alalso found that SpO_2 < 90% predicted death independently compared with SpO_2 ≥ 90% (risk ratio 9.37; 95% CI 2.17–40.4; p=0.003).[23] In a study including 5,054 children in four hospitals in the Philippines, hypoxemia (SpO_2 < 90%) was associated with death in children hospitalized with severe pneumonia in both < 2 months and 2–59 months age groups (aOR 4.69; 95%CI 2.23–9.56 and aOR 5.06; 95%CI 3.67–6.94, respectively).[25]

The PELOD score is a frequently used scoring system that describes multiple organ dysfunction in pediatric patients. Different cutoff points have been reported in the literature and may be due to differences in patient characteristics, facilities, and staff capability at each center.[26] This study found a PELOD-2 score ≥ 7 without lactate measurement to be associated significantly with mortality in patients with severe pneumonia with an adjusted OR of 18.38 (95%CI 4.14-81.43). A similar result was found by Shi et alsup>9, who showed that the proportion of multiple organ failure in the non-survivor group was significantly higher than that of the survivor group (21.5% versus 3.5%; p = 0.040). A higher PELOD-2 score indicates multiple organ dysfunction and poorer prognosis, and the most common organ dysfunction seen in sepsis patients is related to the respiratory system.[27] A previous study by Wati et alsup>28 found that most patients admitted to the PICU had three organ dysfunction (42.9%), with a median PELOD-2 score of 6 (IQR 8), and 58.3% of those who had three organ dysfunction died.

Of the complete blood count indices, mortality was associated with low lymphocyte count (aOR 3.59; 95%CI 1.09-11.75). These results are supported by the study by Wang et alsup>14 that found that lymphopenia increased mortality risk 7.68 times (95% CI 2.57–22.9) compared to normal lymphocyte values. Similarly, Chen et alsup>29 reported that abnormal lymphocyte count was significantly associated with more severe pneumonia and predicted further intensive care admission (OR 3.87; 95% CI 3.45–4.35). Significant lymphopenia has been recognized as a sign of blood lymphocyte dysfunction during infections.[30] Lymphopenia reflects impaired immune responses, especially among patients with severe infection and sepsis and may be the key factor in the inability to survive sepsis.[30] Therefore, this blood parameter could be used as a predictor of mortality in pneumonia patients as well. haemoglobin level < 8 g/dL was associated with mortality (aOR 4.05; 95%CI 1.16–14.13). Anemia as a predictor of mortality in patients with pneumonia has been consistently reported in previous studies[9,11,17,21,25] and could be due to impaired oxygen transport in patients who have low haemoglobin levels. In addition, the presence of pneumonia concurrent with anemia could worsen hypoxic conditions and lead to a higher risk of death.[17] Moschovis et alsup>31 stated that anemia was a predictor of worse prognosis and unresponsiveness to treatment among children with pneumonia, particularly when accompanied by anemia at high altitudes. Anemia and lymphopenia in this study was considered not only caused by severe infection but also the comorbidities, as the hematology and immunology disorders were prevalent in our settings.

Procalcitonin is an inflammatory biomarker that found to increase by several folds during inflammation, such as during a bacterial infection.[32] Prior studies found as high as 16.1% of total patients and 21% of severe pneumonia patients had positive blood cultures.[33,34] The bacterial etiology, represented by high procalcitonin level, could lead to more severe manifestations of pneumonia. This study found that procalcitonin levels ≥ 0.5 ng/mL increased risk of mortality (adjusted OR 7.64; 95%CI 2.61-22.4). This result is supported by Yadav et alsup>32, who reported that procalcitonin level greater than 2 ng/mL was a predictor of more severe pneumonia manifestation and indicated a higher risk for complications including empyema, pneumothorax, septic shock, ARDS, and prolonged hospitalization. However, a contrary result was reported in the studies by Shi et aland Zhang et al which found no association between procalcitonin and mortality in patients with severe pneumonia.[9,11] These conflicting results are expected due to variability in cutoffs for procalcitonin, analysis methods, populations, study settings, and outcomes. This suggests further study is necessary to evaluate optimum cutoff value to predict mortality in children with severe pneumonia.

Patient age has been considered as a risk factor for mortality among patients with pneumonia in previous studies. However, this study found that age was not associated with risk of mortality. This result is supported by Shi et alsup>9, who reported no difference in fatal outcomes for patients aged 1–14 years old and those aged less than 1 years old. In contrast, Williams et alsup>13 found that age less than 2 months old and 10 years old significantly

increased the risk of mortality compared to children aged 2 months old (OR 1.22 and 1.87, respectively), though children aged 5 years old had a lower risk of mortality (OR 0.84). These contradictory results may be due to the large variations in age groups and cutoffs used in prior studies.[9,11,13,21]

Invasive mechanical ventilation was associated significantly with mortality in bivariate analysis, though not in multivariate analysis. Similarly, a previous study by Shi et alsup>9 showed that the requirement for mechanical ventilation was not associated significantly in multivariate analysis, despite it being associated significantly in bivariate analysis. In contrast, Sudarmadji et alsup>35 reported that intubated patients with severe pneumonia had a higher risk of death (OR 6.00; 95% CI 2.77–12.97), and Ramachandran et alsup>8 stated that assisted ventilation was independently associated with fatal pneumonia cases.

Malnutrition is associated with altered metabolism, worsens the prognosis of severely ill children and contributes to higher mortality, longer length of hospital stay, and higher health cost.[36] In this study, moderate-severe malnutrition was not associated significantly with mortality in patients with severe pneumonia in multivariate analysis A similar result was found by Shi et alsup>9, who reported that the prevalence of malnutrition in the death and survivor groups was not significantly different. In contrast, Ramachandran et alsup>8 showed that a weight-for-age Z score less than -3 SD had a 2.25 times higher risk of mortality. This result could be due to differences in anthropometric measurements of malnutrition. Previous studies primarily used weight-for-age as an indicator of malnutrition, while this study used the ratio of actual subject weight to ideal body weight based on the WHO growth chart.

This study had some limitations. First, it used a retrospective unmatched case-control design that is prone to biased patient selection due to incomplete previous data provided in medical records and unmatched in design. However, this study included only complete medical records confirmed with objective supporting examination to minimize selection bias and warranted further study with matching between case and control group. Second, the study sample size was relatively small, with resulting wide confidence intervals in certain outcomes. Third, specific mechanical ventilation parameters were not included in the analysis, which could have provided more information for further analysis, research, and patient treatment. Fourth, this study did not mention socio-demographic factors (parental education, parental occupation, family income, geography, housing, number of family members) as the unavailability of these data in medical records. Finally, this study did not mention specific immunization history, such as history of measles, MMR, Hib, pneumococcal, and influenza vaccines, that may affect the severity of pneumonia in children.

SUMMARY BOX

What is the already known about the subjects

- Prevalence of children with pneumonia who require admission to the pediatric intensive care unit (PICU) was high
- Anticipating of risk factors for mortality is important to establish appropriate early intervention, reduce in-hospital complications and mortality.

What are the new findings?

- Simple objective measurement and laboratory such as SpO_2 < 90% at arrival, haemoglobin < 8 g/dL, and lymphopenia were associated independently with mortality in pediatric patients with severe pneumonia.
- Invasive mechanical ventilation and malnutrition were not associated with mortality and warrants further study to reveal the association.
- These findings suggest that patients with SpO_2 < 90% at arrival should be treated and evaluated rigorously, and blood transfusion should be considered in patients who had haemoglobin < 8 g/dL, particularly in mechanically ventilated patients.

REFERENCES

1. Hsu CL, Lee YS, Chen CJ, et al A population-based analysis of children with pneumonia among intensive care units in Taiwan. J Microbiol Immunol Infect. 2015;48:(2)153–9.
2. McAllister DA, Liu L, Shi T, et al Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. Lancet Glob Health. 2019;7:(1)e47–57.
3. Juvén T, Mertsola J, Waris M, et al Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J. 2000;19:(4)293–8.
4. Cilla G, Oñate E, Pérez-Yarza E, Nogues A, Perez-Trallero E. Incidence of hospitalization due to pneumonia in children aged less than 3 years. Open Infect Dis J. 2009;3:27–30.
5. Divecha C, Tullu MS, Chaudhary S. Burden of respiratory illnesses in pediatric intensive care unit and predictors of mortality: experience from a low resource country. Pediatr Pulmonol. 2019;54:(8)1234–41.
6. Tan KK, Dang DA, Kim KH, et al Burden of hospitalized childhood community-acquired pneumonia: a retrospective cross-sectional study in Vietnam, Malaysia, Indonesia and the Republic of Korea. Hum Vaccin Immunother. 2018;14:(1)95–105.
7. Koh JWJC, Wong JJ-M, Sultana R, et al Risk factors for mortality in children with pneumonia admitted to the pediatric intensive care unit. Pediatr Pulmonol. 2017;52:(8)1076–84.
8. Ramachandran P, Nedunchelian K, Vengatesan A, Suresh S. Risk factors for mortality in community-acquired pneumonia among children aged 1–59 months admitted in a referral hospital. Indian Pediatr. 2012;49:(11)889–95.
9. Shi T, Chen C, Huang L, et al Risk factors for mortality from severe community-acquired pneumonia in hospitalized children transferred to the pediatric intensive care unit. Pediatr Neonatol. 2020;61:(6)577–83.
10. Ao XX. The epidemiology of hospital death following pediatric severe community-acquired pneumonia. Ital J Pediatr. 2021;47:(1)25.
11. Zhang Q, Guo Z, Bai Z, MacDonald NE. A 4 year prospective study to determine risk factors for severe community-acquired pneumonia in children in southern China. Pediatr Pulmonol. 2013;48:(4)390–7.
12. Acuna J, Galeano F, Aguiar C, et al Risk factors for mortality in children with severe community-acquired pneumonia admitted to a pediatric intensive care unit. Pediatr Crit Care Med. 2018;19(6 Suppl).
13. Williams DJ, Zhu Y, Grijalva CG, et al Predicting severe pneumonia outcomes in children. Pediatrics. 2016;138.(4)
14. Wang LJ, Mu SC, Lin CH, Lin MI, Sung TC. Fatal community-acquired pneumonia: 18 years in a medical center. Pediatr Neonatol. 2013;54:(1)22–7.
15. Kasundriya SK, Dhaneria M, Mathur A, Pathak A. Incidence and risk factors for severe pneumonia in children hospitalized with pneumonia in Ujjain, India. Int J Environ Res Public Health. 2020;17:(13)4637.
16. Meliyanti A, Rusmawatiningtyas D, Makrufardi F, Arguni E. Factors associated with mortality in pediatric pneumonia patients supported with mechanical ventilation in developing country. Heliyon. 2021;7:(5)e07063.
17. Kisworini P, Setyati A, Sutaryo S. Mortality predictors of pneumonia in children. Paediatr Indones. 2010;50:(3)149–53.

18. Valentania V, Somasetia DH, Hilmanto D, Setiabudi D, Nataprawira HMN. Modified PIRO severity score as a predictor for mortality of children with pneumonia in Hasan Sadikin Hospital, Bandung, Indonesia. Multidiscip Respir Med. 2021;16:(1)735.
19. Assa NP, Wati DK, Subanada IB, et al Full outline of unresponsiveness score as a predictor of outcomes in critically ill pediatric patients. Paediatr Indones. 2020;60:(2)77–82.
20. Lanzkowsky P. Manual of Pediatric Hematology and Oncology. Elsevier; 2005.
21. Salih K, Bilal J, Karsani A. Risk factors of mortality among children admitted with severe pneumonia at a reference hospital in Khartoum, Sudan. Am J Med Med Sci. 2015;5:130–4.
22. Schult S, Canelo-Aybar C. Oxygen saturation in healthy children aged 5 to 16 years residing in Huayllay, Peru at 4340 m. High Alt Med Biol. 2011;12:(1)89–92.
23. Colbourn T, King C, Beard J, et al Predictive value of pulse oximetry for mortality in infants and children presenting to primary care with clinical pneumonia in rural Malawi: a data linkage study. PLoS Med. 2020;17:(10)e1003300.
24. Noviyani NMR, Suparyatha IBG, Wati DK, Hartawan INB. Outcome comparison between pulmonary and extrapulmonary acute respiratory distress syndrome in pediatric intensive care unit. Am J Pediatr. 2020;6:(4)442–7.
25. Dembele BPP, Kamigaki T, Dapat C, et al Aetiology and risks factors associated with the fatal outcomes of childhood pneumonia among hospitalised children in the Philippines from 2008 to 2016: a case series study. BMJ Open. 2019;9:(3)e026895.
26. Leclerc F, Duhamel A, Deken V, et al Can the pediatric logistic organ dysfunction-2 score on day 1 be used in clinical criteria for sepsis in children? Pediatr Crit Care Med. 2017;18:(8)758–63.
27. Simanjuntak YR, Saputra I, Triratna S, et al Validation of PELOD-2 score as a predictor of life-threatening organ dysfunction in pediatric sepsis. Paediatr Indones. 2020;60:(5)227–32.
28. Wati DK, Hartawan INB, Suparyatha IBG, et al Profil sepsis anak di Pediatric Intensive Care Unit Rumah Sakit Umum Pusat Sanglah Denpasar-Bali. Sari Pediatr. 2019;21:(3)152–8.
29. Chen L, Miao C, Chen Y, et al Age-specific risk factors of severe pneumonia among pediatric patients hospitalized with community-acquired pneumonia. Ital J Pediatr. 2021;47:(1)1–13.
30. de Pablo R, Monserrat J, Prieto A, Alvarez-Mon M. Role of circulating lymphocytes in patients with sepsis. Biomed Res Int. 2014;2014:671087.
31. Moschovis PP, Banajeh S, MacLeod WB, et al Childhood anemia at high altitude: risk factors for poor outcomes in severe pneumonia. Pediatrics. 2013;132:(5)e1156–62.
32. Yadav KK, Awasthi S, Takia L, et al Procalcitonin and C-reactive protein in WHO defined severe and very severe community-acquired pneumonia: a hospital-based cross-sectional study. Clin Epidemiol Glob Health. 2015;3:S3–9.
33. Usman MR, Wati DK, Subanada IB. The outcome of antibiotic therapy among children with severe community-acquired pneumonia. Bali Med J. 2015;4:(2)89–92.
34. Priskila M, Wati DK, Suparyatha IBG, et al Pola kepekaan bakteri yang terisolasi dari kultur darah terhadap antibiotik di Unit Perawatan Intensif Anak RSUP Sanglah Denpasar tahun 2015–Medicina. 2019;50:(3)594–8.
35. Sudarmadji S, Wati DK, Sidiartha L. Faktor risiko pada lama rawat dan luaran pasien perawatan di unit perawatan intensif anak RSUP Sanglah Denpasar. Sari Pediatr. 2016;17:(6)455–62.
36. Suriadji D, Wati DK, Sidiartha I, et al Prevalence and association of cost and hospital malnutrition in Pediatric Intensive Care Unit Sanglah Hospital during Crit Care Shock. 2017;20.(1)

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ORIGINAL ARTICLE

Ubiquinone Supplementation Lessens the Negative Impacts of Occupational Lead Exposure by Reducing Inflammation

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Lead occupational exposure has been increasingly reported by healthcare providers as an important challenge in industrial settings. Ubiquinone is a natural substance that has a role in the electron transport chain and oxidation-reduction pathway. In this study, we evaluated the effects of ubiquinone on inflammatory markers in workers who were exposed to lead in their routine daily work, as determined by measurement of lead levels in their blood at the start of the study, and compared to the control group. This study is a randomized, blind, placebo (control (two-month clinical trial. 61 people who had spent at least a year in an industrial environment were divided into two groups. In the ubiquinone group, 31 participants received 200 mg/day of ubiquinone-containing capsules for two months, and in the placebo group, 30 participants received a placebo capsule of starch daily for two months, At the end of the study, there was a withdrawal of one participant from the ubiquinone group and two participants from the placebo group. The inflammatory biomarker high-sensitivity C-reactive protein was measured using a turbidimetric immunoassay, while TNF-? and IL-6 plasma levels were determined using an ELISA. These measurements were done at the start of the study and after two months to compare the results of these parameters in the ubiquinone and placebo groups. After two months of ubiquinone supplementation, there was a statistically significant improvement in TNF- and IL-6 concentrations, but it did not affect CRP levels in the study participants.

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The industrial revolution of the 18th century led to major changes in working conditions so exposure to heavy metals became an inevitable risk..[1] The current work environment has emerged as one of the most significant global public health concerns.[2] The interaction between the environment and the biological system is one of the major factors that govern an individual's health. The danger of exposure to heavy metals and their associated negative effects is increased by numerous activities, such as those that deal with petroleum, metal processing, vehicle maintenance, mining, and coal burning.[3] Nowadays, a series of studies have shown that heavy metals are the primary risk factors linked to the emergence of several pathophysiological illnesses. Essentially, the pathways by which they cause harmful consequences to involve inflammation and oxidative stress in the heart, lungs, and blood vessels.[4,5]

Many studies show that exposure to heavy metals that arise from occupation or environmental pollution results in low-grade inflammation. At the cellular level, the alteration of metabolic homeostasis is the main cause of heavy metal toxicity. This happens as a result of the accumulation of an excessive amount of heavy metal within different tissues. The metallic deposits then interfere with enzymatic, metabolic, and mitochondrial processes, which impair biological function.[6] The pharmacokinetics of each metal, as well as the route of exposure, determine how much of this malfunction and subsequent injury occurs.[7]

Lead is a naturally occurring heavy metal that is primarily found in conjunction with sulfur, and is distinguished by its high density, malleability, weak conductivity, and corrosion resistance. Because of its physio-chemical properties, lead is widely used in a variety of industries. The main ways that humans are exposed to lead are through the consumption and inhalation of contaminated foods, drinks, air, and soil.[8]

In the blood, lead has a half-life of about 30 days, after which it transfers into soft tissues like the kidneys, brain, and liver before being dispersed as lead phosphate to bones, teeth, and hair.[9]

Lead poisoning results in the production of ROS (Reactive Oxygen Species) like hydroperoxide, hydrogen peroxide, and singlet oxygen. These free radicals are produced by lead exposure. When ROS and antioxidant defences are out of balance, the body experiences oxidative stress. Oxidative stress causes the release of pro-inflammatory mediators, cellular dysfunction, and injury[10]and in turn, this increases the risk of unfavourable health outcomes like cancer and cardiovascular disease.[11]

Ubiquinone-10, (also known as coenzyme Q10 or CoQ10) is a lipid-soluble benzoquinone with a side chain containing 10 isoprenyl units. Ubiquinone exists in its reduced form (ubiquinol), which functions as an antioxidant. Small amounts of ubiquinone are produced both endogenously and naturally in a variety of foods, including fish and meat.[12] It is a crucial part of the electron transport chain within the adenosine triphosphate (ATP) synthesis machinery.[13] To fully realize ubiquinone's value as a natural treatment for illnesses associated with inflammation, the precise mechanisms involved still need to be elucidated. Ubiquinone controls the gene expression of other molecules involved in the oxidative reduction pathway and provides effective defence against the oxidation of lipid membranes, proteins, and nucleic acids.[14] Additionally, Peroxisome proliferator-activated receptor (PPAR)-mediated anti-inflammatory response is activated by ubiquinone, which can operate as an agonist of PPARs.[15] Ubiquinone's therapeutic effects are linked to its role in scavenging free radicals and suppressing inflammatory signalling pathways by modulating inflammatory expression.[16]

According to a systematic review, the occupationally lead-exposed group had considerably more lead in their blood and inflammatory markers, such as cytokines (IL-4, IL-6, IL-10, and TNF-α), than the control group[17] A correlation between high blood lead levels and a higher than normal level of C-reactive protein (CRP) has been observed by a study performed by Sirivarasai et al.[18] Previous research has shown that taking a ubiquinone supplement can lower levels of circulating CRP, which is produced by the liver and fat cells and is regarded as a biomarker for the severity of systemic inflammation in the body. Ubiquinone also reduces IL-6 and TNF-α mRNA expression in the liver.[19] Ubiquinone is an add-on therapy that has been proven to be useful in the treatment of metabolic illnesses in several randomized controlled trials (RCTs). However, the results of these studies are inconsistent since they used small sample sizes and participants with varying levels of health.[13,20] The current study aims to determine whether there is a link between ubiquinone administration and a reduction in inflammatory markers in populations who work with heavy metals.

MATERIALS AND METHODS

The Research Committee of the College of Pharmacy at the University of Mosul in Iraq has approved the study project. The current investigation was

conducted in Mosul's main industrial areas. The study was conducted from the beginning of May until the end of June 2022.

Study design

This is a randomized, blind, placebo-control, two-month clinical trial. Participants had at least a year of exposure to an industrial environment. Before study initiation, the lead concentrations in the blood of people included in the study were measured and compared with the concentration of lead in the blood of a normal healthy individual.

Subjects

In the current study, 76 people were evaluated for their suitability to participate, but only 61 of them agreed to participate; the others were excluded because they did not meet the inclusion and exclusion criteria. They have held a variety of jobs with a high risk of heavy metal exposure. These included those who worked as painters, gas station and local generator workers, and car repairers. They ranged in age from 18 to 75 years. They were split into two groups randomly. During the follow-up period, three participants withdrew from the study (Figure 1). In addition to the study participants, five normal individuals who work as farmers were considered as a control to confirm the occurrence of bioaccumulation of lead in subjects included in the study.

Data collection and specimen

Name, age, drinking and smoking habits, time spent working in an industrial area, and contact information were acquired directly from the participant. The concentrations of tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) were measured by suitable laboratory tests for participants before and after the study. The concentration of lead was measured for all candidates before confirming their inclusion in the study, in addition to measuring it in the control group.

Each participant in this study gave 3 ml of venous blood, these samples were drawn in the morning. The blood sample was transferred to vacutest (gel) tubes. By leaving the collected blood at room temperature for two hours, it can coagulate. The coagulated blood is then centrifuged for 15 minutes at a speed of 3000 rpm to obtain the serum. This procedure is repeated after two months to get a second sample.

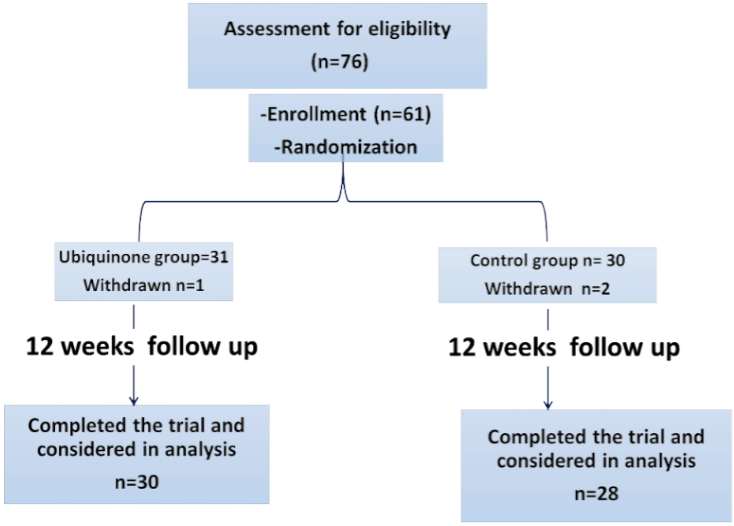


Figure 1 *Patient flow diagram of the study*

Blinding and Compliance

Following the registration of volunteers and receiving their approval to take part in the study, the names of the volunteers were separated at random into two groups, 31 in the ubiquinone group and 30 in the placebo group. The ubiquinone group took the coenzyme CoQ-10®, a product of the NATROL® company in the United States, at a dose of 200 mg per day for two months; while the placebo group took starch-containing pills, administered daily for two months. To ensure blindness, Q10 and starch were placed in the same container. Treatment side effects were evaluated using self-reported questionnaires. In this study, compliance assessment was done by counting tablets.

Inclusion and Exclusion criteria

Men who worked in a variety of industrial professions and were exposed to occupational lead meet the inclusion criteria. These included people working in the industrial area of Mosul city. Their ages were between 18 and 75. Car repair, gas station and local generator workers, and painters were among the jobs included. Those people have lead accumulated in their blood, and the concentrations of lead in their bodies are significantly higher than the average Bioaccumulation of lead in participating individuals was confirmed statistically since the concentrations of lead in the blood of each participant were compared with the average lead concentration of normal control, and subjects with significantly higher lead concentrations in their blood were included in the study.

Where the exclusion criteria include women, males who are under 18 years old, over 75 years old, alcoholics, people who have worked in an industrial field for less than a year, who have a lead concentration in their blood with no significant difference compared to the control group, or other

jobs that do not significantly expose workers to industrial pollutants are excluded from inclusion as professions. All volunteers are working in Mosul's industrial regions. Patients with diabetes, renal failure, neurological illnesses (Parkinson's disease, epilepsy, and essential tremor), stroke, gastrointestinal problems (chronic diarrhoea and inflammatory bowel diseases), and renal failure were also excluded from the trial.

Laboratory Test

Lead concentration was measured by atomic absorption spectrophotometry according to the manufacturer's instructions manual. The inflammatory biomarker high-sensitivity C-reactive protein (hs-CRP) was measured using a turbidimetric immunoassay kit from LDN Co., Germany, and plasma levels of TNF-α and IL-6 were assessed using an ELISA kit from Boster Biological Technology Co., Wuhan, China.

RESULTS

The study included 61 men, all of whom received 200 mg of ubiquinone supplements for two months and were considered the ubiquinone group, while the other 30 received starch-containing tablets and were considered the placebo group. All of these events occurred at random after the participants' acceptance and important information was filled out. After two months of study, one participant from the ubiquinone group and two from the placebo group were dropped, so the total number of participants in the ubiquinone group and placebo group is 30 and 28, respectively.

Demographic characteristics

All participants were males, and they showed an age difference with 55% of them being older than 40 years, as shown in Table 1. Also, there was a difference in the participants' jobs in that about half of them worked in a gas station, and the others were equally distributed between working for local generators, car mechanics, and painters. Another important difference between participants was the duration of time they spent in these jobs, with 43% of them spending less than five years in their current jobs, 35% spending between five and ten years in their jobs, and 25% spending more than ten years in their jobs. Another characteristic of participants was their smoking habit: 40% of them smoke 10-20 cigarettes per day, while 33% smoke more than 20 cigarettes per day.

The pre-study results for participants and the normal control group show that the concentration of lead in the study's included groups was significantly higher than in a normal individual, with a p-value less than 0.05 in all workers exposed to occupational lead

Table 1 *Demographic parameters for the studied groups*

Demographic parameters		Control (n=28)	Ubiquinone (n=30)
Age (years)	<20	2	3
	20-30	4	5
	30-40	5	7
	>40	17	15
Jobs	Car repairing	5	6
	Gas station	12	10
	Local generators	5	7
	Painting	6	7
Duration of work (years)	<5	11	14
	5-10	12	9
	>10	5	7
Number of cigarette per day	No smoking	3	5
	<10	4	4
	10-20	11	12
	>20	10	9

Table 1 *Demographic parameters for the studied groups*

Table 2 *The concentration of lead in the blood of participants compared to that of normal individuals*

Parameters	Control group farmers	Painter	Gas station workers	Local generators workers	Car repairers
Mean(µg/100ml)	2.72	7.06	7.44	7.80	6.83
SD	0.90	2.12	2.23	3.25	1.84
Max	3.76	9.07	9.65	11.63	9.14
Min	1.68	4.17	4.35	4.25	4.36
***p*-value**	-	*0.004*	*0.000*	*0.015*	*0.000*

Table 3 *Percentage of compliance of study participants*

Percentage of compliance	Control (n=28)	Ubiquinone (n=30)
less than 85%	7.14%	3.3%
90% -85%	10.7%	6.7%
90%-95%	39.3%	30.0%
more than 95%	42.9%	60.0%

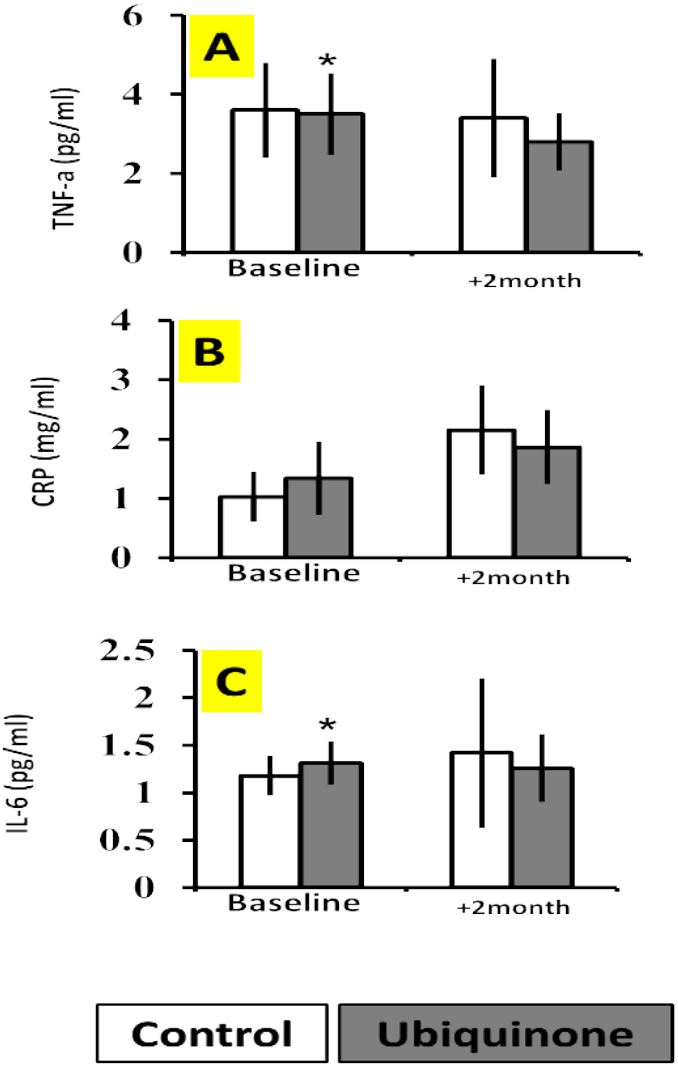


Figure 2 *Ubiquinone slightly reduced pro-inflammatory markers after 2 months of therapy in workplace lead-exposed individuals. Data expressed as mean ± SD, n=58, *P<0.05, * significantly higher as compared to ubiquinone group after 2 months of therapy.*

exposure. The concentration of lead in various participants according to their occupation, along with a p-value comparison to the control group (Table 2). It is worth mentioning that the World Health Organization has set a lead guideline limit of 1µg/100ml.

Participants tolerated ubiquinone supplements well, with no unobserved side effects, and the ubiquinone group's compliance was measured by counting the tablets that remained at the end of the study. Table 3 shows the compliance of the ubiquinone group with their supplement tablet during the study period. Compliance in the ubiquinone group was less than 85% in 3.3% of participants, but the majority of patients have excellent compliance.

There was a significant positive correlation in TNF-α concentration after two months of using ubiquinone supplements, with a decrease of about 0.6 pg/mL (p=0.05), whereas the TNF-α concentration in the placebo group was unchanged (Figure 2A).

The results found a non-significant decrease in CRP in the ubiquinone group after two months of using a ubiquinone supplement that is about 0.3 mg/L (p-value = 0.078). Also in the placebo group, there was a non-significant reduction in CRP concentration (Figure 2B).

The results revealed a significant decrease in IL-6 in the ubiquinone group after two months of using a 0.16 pg/mL ubiquinone supplement (p-value 0.05). While in the placebo group, there was a comparable increase in IL-6 concentration (Figure 2C).

DISCUSSION

Lead was the biomarker utilized to evaluate the degree of heavy metals exposure. The lead concentration in the blood of participants from variable occupations was measured at the start of the study. The study discovered significant increases in lead concentrations in workers in these occupations. Similar results were observed by Singh et al(2022), who found that workers in heavy metals-related occupations have a higher-than-normal level of lead in their blood.[21] Additionally, Muller et al[22] discovered significant increases in lead concentrations in workers in the plating industry.

Ubiquinone is a biologically active substance that regulates gene expression, is a natural antioxidant, and serves as a vital cofactor in the cellular metabolic pathway. The justification for its usage as a dietary supplement and in medical settings is based on these functions.[13,23]Therefore, many studies were conducted for a more comprehensive understanding of the effects of ubiquinone on inflammatory markers. An earlier study discovered that Ubiquinone lowers CRP levels by reducing hepatic mRNA expression of IL-6 and TNF-α. Ubiquinone is effective in several randomized controlled trials for metabolic illnesses.[24]

There was a statistically significant improvement in TNF-α concentration after two months of ubiquinone supplementation in the current study. Although it was higher in the placebo group than in the ubiquinone group at the start of the study, the TNF-α value in the placebo group did not change after two months of ubiquinone supplementation.

This is similar to the results of a meta-analysis study conducted by Zhai et al on nine randomized clinical trials with different dosage forms of ubiquinone supplements and for different durations of ubiquinone supplementation. Three of the clinical trials measured plasma TNF-α levels. Patients with metabolic illnesses who took ubiquinone supplements had significantly lower levels of TNF-α than those who took a placebo, according to the review.[23]

Other meta-analysis studies that support our findings include Farsi et al and Fan et al, who discovered that oral ubiquinone supplementation was significantly effective in lowering serum TNF-α p levels.[25,26]

The effects of inflammatory markers have been studied in patients with different clinical conditions. To begin, Abdollahzad et al observed ubiquinone effects in reducing TNF-α overproduction in an RCT on 44 rheumatoid arthritis patients.[27] Similarly, administration of ubiquinone to patients with multiple sclerosis has resulted in that significant decrease in TNF-α in the intervention group compared to placebo group.[28] These beneficial effects of ubiquinone on TNF-α levels were also observed in patients with multiple sclerosis who received ubiquinone supplementation.[28] In addition to investigating its impact on migraine patients, which yielded comparable results with significant improvement in TNF-α levels.[29]

In contrast to Gokbel et al's study, 100 mg/day ubiquinone administration has shown no effects on TNF-α levels in healthy volunteers. This is most likely due to normal TNF-α levels at the start of the study or an insufficient ubiquinone supplement dosage.[30] Another study published by Raygan et al found that patients with metabolic syndrome who took 100 mg/day of ubiquinone for eight weeks experienced no change in their inflammatory markers. According to the study, the trial design, length, and ubiquinone supplement affect this outcome.[31]

The results of the current study show a statistically non-significant reduction in CRP level of about 0.3 mg/L in the ubiquinone group after using CoQ10 supplementation for two months, while in, the placebo group there is an elevation in CRP level during the study period. Lee et al[32] did not observe an association between the level of high-sensitivity CRP and ubiquinone intake in those suffering from coronary artery disorders.[31] This finding disagrees with a study performed in Iran by Taghizadeh et al, which observed a significant relationship between CRP level and ubiquinone supplementation in 22 polycystic ovarian women who took 200 mg of CoQ10 for eight weeks in an RCT.[33]

Similar findings were observed by Farsi et al, who conducted a study on 20 nonalcoholic fatty liver disease patients by examining IL-6 levels before and after three months of 100 mg CoQ10 supplementation.[25] These studies' substantial CRP reduction may be related to the study subjects' high baseline CRP levels.

This study demonstrates ubiquinone's potent ability to lower IL-6 levels in people exposed to heavy metals. This finding is similar to the results of a meta-analysis conducted by Fan et al.[26] Other RCTs with similar findings, such as Bagheri Nesami et al[34], examined the correlation between CoQ10 supplementation and plasma IL-6 levels in 30 hypertensive patients and compared it to a similar number of patients who received a placebo. Their results indicated that ubiquinone results in a statistically significant improvement of IL-6. On the other hand, studies performed by Gokbel et al[30] and Farsi et al[25] found no correlation between CoQ10

supplementation and plasma IL-6 level, this endogenous response to occupational heavy metal exposure could be explained in the context of cellular response to the surrounding milieu whether being irritant, such as metal or even changes in oxygen levels,[35,36]or due to presence of other underlying diseases.[37,38]

CONCLUSION

This clinical study found that taking 200 mg of ubiquinone daily for two months reduced TNF-α and IL-6 levels in people exposed to heavy metals but had no effect on CRP levels.

REFERENCES

1. Gu J, Shi Y, Zhu Y, et al Ambient air pollution and cause-specific risk of hospital admission in China: A nationwide time-series study. PLoS Med. 2020 Aug 6;17:(8)e1003188.
2. Wold LE, Simkhovich BZ, Kleinman MT, et al In vivo and in vitro models to test the hypothesis of particle-induced effects on cardiac function and arrhythmias. Cardiovasc Toxicol. 2006 Mar;6:69-78.
3. Wang C, Zhu G, Zhang L, Chen K. Particulate matter pollution and hospital outpatient visits for endocrine, digestive, urological, and dermatological diseases in Nanjing, China. Environ Pollut. 2020 Jun 1;261:114205.
4. Li YJ, Takizawa H, Kawada T. Role of oxidative stresses induced by diesel exhaust particles in airway inflammation, allergy and asthma: their potential as a target of chemoprevention. Inflamm Allergy Drug Targets. 2010 Sep 1;9:(4)300-5.
5. Al-Huda N, Yahya A, Althanoon ZA. Assessment of the effects of coenzyme q10 supplementation on oxidative stress markers in the population exposed to environmental pollution. 2022;21:2927-33.
6. Hamed ZS, Al-Alsadoon LH, Shaban KA, Taqa GA. Influence of coenzyme Q10 on hyperlipidemia induced in mice. MMSL. 2021;91:(3)208-15.
7. Jaishankar M, Tseten T, Anbalagan N, et al Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol. 2014 Jun;7:(2)60.
8. Yousef AO, Fahad A, Abdel Moneim AE, et al The neuroprotective role of coenzyme Q10 against lead acetate-induced neurotoxicity is mediated by antioxidant, anti-inflammatory and anti-apoptotic activities. Int J Environ Res Public Health. 2019 Aug;16:(16)2895.
9. Engwa GA, Ferdinand PU, Nwalo FN, Unachukwu MN. Mechanism and health effects of heavy metal toxicity in humans. Poisoning in the modern world-new tricks for an old dog. 2019 Jun 19;10:70-90.
10. Ajarem JS, Hegazy AK, Allam GA, et al Heavy metal accumulation, tissue injury, oxidative stress, and inflammation in dromedary camels living near petroleum industry sites in Saudi Arabia. Animals. 2022 Mar 11;12:(6)707.
11. Flora SJ. Arsenic-induced oxidative stress and its reversibility. Free Radic Biol Med. 2011;51:(2)257-81.
12. Hansen M, Kuhlman AC, Sahl RE, et al Inflammatory biomarkers in patients in Simvastatin treatment: No effect of co-enzyme Q10 supplementation. Cytokine. 2019;113:393-9.
13. Abiri B, Vafa M. Impact of coenzyme Q10 on inflammatory biomarkers and its role in future therapeutic strategies. Clin Nutr ESPEN. 2021;43:25-30.
14. Groneberg DA, Kindermann B, Althammer M, et al Coenzyme Q10 affects the expression of genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. Int J Biochem Cell Biol. 2005;37:(6)1208-18.

15. Alam MA, Rahman MM. Mitochondrial dysfunction in obesity: potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome. J Diabetes Metab Disord. 2014;13:(1)1-11.
16. Alimohammadi M, Rahimi A, Faramarzi F, et al Effects of coenzyme Q10 supplementation on inflammation, angiogenesis, and oxidative stress in breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Inflammopharmacology. 2021;29:(3)579-93.
17. Kalahasthi R, Nagaraju R, Balachandar R, Bagepally BS. Association between occupational lead exposure and immunotoxicity markers: A systematic review and meta-analysis. Toxicology. 2022;465:153047.
18. Sirivarasai J, Wananukul W, Kaojarern S, et al Association between inflammatory marker, environmental lead exposure, and glutathione S-transferase gene. Biomed Res Int. 2013 Jan 1;2013.
19. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111:(12)1805-12.
20. Fallah M, Askari G, Soleimani A, et al Clinical trial of the effects of coenzyme q10 supplementation on biomarkers of inflammation and oxidative stress in diabetic hemodialysis patients. Int J Prev Med. 2019;10.
21. Singh P, Mitra P, Goyal T, et al Levels of lead, aluminium, and zinc in occupationally exposed workers of North-Western India. J Basic Clin Physiol Pharmacol. 2022;33:(2)191-7.
22. Muller CD, Garcia SC, Brucker N, et al Occupational risk assessment of exposure to metals in chrome plating workers. Drug Chem Toxicol. 2022 Mar 4;45:(2)560-7.
23. Zhai J, Bo Y, Lu Y, et al Effects of coenzyme Q10 on markers of inflammation: a systematic review and meta-analysis. PLoS One. 2017;12:(1)e0170172.
24. Kunitomo M, Yamaguchi Y, Kagota S, Otsubo K. Beneficial effect of coenzyme Q10 on increased oxidative and nitrative stress and inflammation and individual metabolic components developing in a rat model of metabolic syndrome. J Pharmacol Sci. 2008 Jan 1;107:(2)128-37.
25. Farsi F, Heshmati J, Keshtkar A, et al Can coenzyme Q10 supplementation effectively reduce human tumour necrosis factor-α and interleukin-6 levels in chronic inflammatory diseases? A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2019 Oct 1;148:104290.
26. Fan L, Feng Y, Chen GC, et al Effects of coenzyme Q10 supplementation on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2017 May 1;119:128-36.
27. Abdollahzad H, Aghdashi MA, Jafarabadi MA, Alipour B. Effects of coenzyme Q10 supplementation on inflammatory cytokines (TNF-α, IL-6) and oxidative stress in rheumatoid arthritis patients: a randomized controlled trial. Arch Med Res. 2015 Oct 1;46:(7)527-33.
28. Sanoobar M, Eghtesadi S, Azimi A, et al Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double-blind, placebo, controlled randomized clinical trial. Nutr Neurosci. 2015 May 1;18:(4)169-76.
29. Dahri M, Tarighat-Esfanjani A, Asghari-Jafarabadi M, Hashemilar M. Oral coenzyme Q10 supplementation in patients with migraine: Effects on clinical features and inflammatory markers. Nutr Neurosci. 2019;22:(9)607-15.
30. Gokbel H, Gergerlioglu HS, Okudan N, et al Effects of coenzyme Q10 supplementation on plasma adiponectin, interleukin-6, and tumour necrosis factor-α levels in men. J Med Food. 2010;13:(1)216-8.
31. Raygan F, Rezavandi Z, Dadkhah Tehrani S, et al The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome. Eur J Nutr. 2016;55:(8)2357-64.

32. Lee BJ, Huang YC, Chen SJ, Lin PT. Effects of coenzyme Q10 supplementation on inflammatory markers (high-sensitivity C-reactive protein, interleukin-6, and homocysteine) in patients with coronary artery disease. Nutrition. 2012 Jul 1;28:(7-8)767-72.
33. Taghizadeh S, Izadi A, Shirazi S, et al The effect of coenzyme Q10 supplementation on inflammatory and endothelial dysfunction markers in overweight/obese polycystic ovary syndrome patients. Gynecol Endocrinol. 2021;37:(1)26-30.
34. Bagheri Nesami N, Mozaffari-Khosravi H, Najarzadeh A, Salehifar E. The effect of coenzyme Q10 supplementation on pro-inflammatory factors and adiponectin in mildly hypertensive patients: a randomized, double-blind, placebo-controlled trial. Int J Vitam Nutr Res. 2015;85(3-4):156-64.
35. Merkhan MM, Shephard MT, Forsyth NR. Physoxia alters human mesenchymal stem cell secretome. J Tissue Eng. 2021 Oct;12:20417314211056132.
36. Forsyth NR, Steeg R, Ahmad M, et al Mimicking Physiological Oxygen in Cell Cultures. Cell Cult Technol. 2018:129-37.
37. Kovalova Y, Sukhonos N, Brek V, Smolianyk K. Irisin, interleukin-33 and interleukin-37 in patients with ischemic heart disease and obesity. Med Čas. 2021;55:(3)87-93.
38. Miljković D, Todorović S. Significance of C-reactive protein determination in patients with metabolic syndrome. Med Čas. 2021;55:(2)51-8.

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ORIGINAL ARTICLE

Epidemiology and Clinical Features of Covid-19 Patients Admitted To Udayana University Hospital, Bali, During The First Two Years of Covid-19

Cokorda Agung Wahyu Purnamasidhi, Ni Made Dewi Dian Sukmawati, Anak Agung Ayu Yuli Gayatri, I Made Susila Utama, I Ketut Agus Somia, Ketut Tuti Parwati Merati, I Dewa Made Sukrama

Background

In only a year, COVID-19 had changed a lot of regular human lifestyle. World Health Organization (WHO) declared COVID-19 as a global pandemic in March 2020. At March 2020, COVID-19 had entered Indonesia. Soon, Bali harbor the first death due to COVID-19 in the nation.

Method

The study collected data from medical records of patients admitted to Udayana University Hospital from April 2020 to March 2022. This report comprises epidemiological, clinical, and laboratory characteristics as well as treatment and outcome of the patients while discharged.

Results

Patients mean age was 45.75 years old, with male constituting 53.8% of patients admitted. 113 (3.7%) patients had a history of international travels prior to admission. Almost all patients had fever (90.8%), and a majority had cough (79.3%) and sore throat (58.3%). Then, it was followed by less common traits such as chest tightness (39.7%), myalgia (31.3%), headache (29.4%), cold (19.0%), anosmia (15.1%), dizziness (12.7%), and diarrhea (4.6%). Laboratory results during admission showed an average leukocyte count of $1.76 \pm 1.07 \times 10^9$ cells/L, neutrophil of $4.69 \pm 2.96 \times 10^9$ cells/L, and lymphocyte of $1.76 \pm 1.07 \times 10^9$ cells/L.

Conclusion

The first two year of COVID-19 pandemic in Indonesia had shown how public health policies shaped the epidemiological characteristics of our patients. However, Udayana University Hospital being a tertiary referral COVID-19 hospital justifies a higher mortality rate of 5.2% compared to other studies.

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At the end of 2019, a mysterious unknown pneumonia-like outbreak was first observed in Wuhan, Hubei. Epidemiologically traced, all cases admitted to the hospital had some sort of contact with Huanan Wet Market. Soon, the government and the world were alerted by the emergence of a novel coronavirus, temporarily named 2019-nCoV and soon definitively named as SARS-CoV-2. The virus soon emerged to be a notoriously infectious pathogen, forcing WHO as the international global health custodian to declare that the world is facing a COVID-19 pandemic.

Due to most cases being asymptomatic or showing really mild and non-specific symptoms, patients infected by SARS-CoV-2 often goes unnoticed. This trait elevates reproductive numbers through undetected communal and international transmission. Currently, no antiviral agent and treatment protocol has been proven to be both efficacious and safe to combat the pathogen, therefore preventing the spread is the best way to control the pandemic.[1] Preventing deaths in high-risk patients with comorbidities through strict outbreak-control protocols and physical distancing may help mitigate the impact of COVID-19 pandemic.

Although COVID-19 is, first and foremost, a global health crisis, it has evolved to become a collateral multisectoral damage due to both deaths and policies instigated by the outbreak.[2] Therefore, policies established mainly driven by social and economic conditions compromises ideal outbreak containment strategies. This becomes even more prominent on developing countries, where strict lockdowns may prompt chaos and looting.[3] These policies came with the expense of new clusters, proven by increasing number of cases post-holiday in January 2021 although special holiday travel restrictions were issued in Bali.[4]

Lukewarm policies contributed to shape the case count curve, once again emphasizing how political and economic interest affects public health. Therefore, we collected medical records regarding epidemiology and initial experiences, clinical features, and management of all confirmed COVID-19 patients admitted to Udayana University Hospital, Bali, Indonesia in one year from April 2020 to March 2022.

MATERIALS & METHODS

This study analyzes observational study reports secondary data of all 3048 confirmed COVID-19 patients admitted to Udayana University Hospital up to the end of March 2022. Patient was deemed diagnosed positive COVID-19 if RT-PCR results showed positive. This report comprises epidemiological, clinical, laboratory, and radiological characteristics as well as treatment – antiviral therapy, antibiotics, anticoagulant, and ventilator support – during admission and the outcome of the patients when discharged. Patients below 18 years old were excluded from analyses.

An analysis using SPSS Statistics 25 was performed to present final results of data gathered during this research. Test of distribution using Shapiro-Wilk test if the number of subjects were below 30 and Kolmogorov-Smirnov test if the number of subjects were above 30. The test was performed to determine the format of reporting, with mean (± standard deviation) for data distributed normally and median (Q_1-Q_3) for data not distributed normally. Ethical approval was released by the ethical committee of Udayana University (No: 1010/UN1422VII14/LT/2020). Information about subjects were kept highly confidential and are only used in accordance with research ethical guidelines.

RESULTS

A total of 3048 subjects admitted to Udayana University Hospital between April 2020 to March 2022 were included in the study (Figure 1). Patients excluded were those with an age lower than 18 years old and those isolated but was negative through RT-PCR result. Patients included had a mean age of 45.75 (SD ± 15.40) years old, ranging from 18 up to 90 years old. Male patients were more prevalent, constituting 53.8% of all patients admitted. Almost all patients

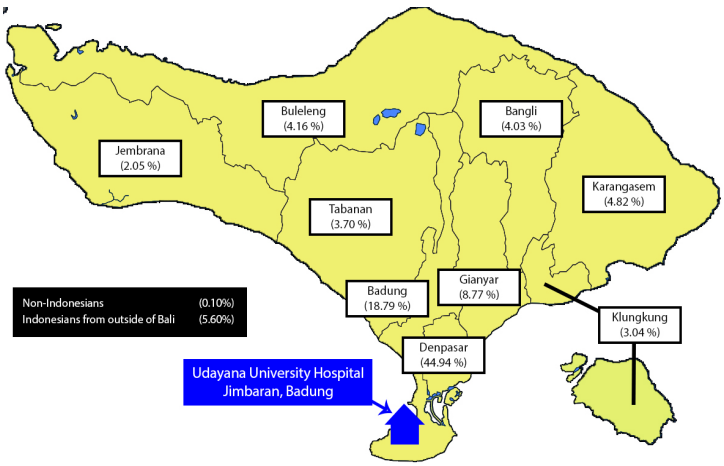


Figure 1 *District Origins of COVID-19 Patients Admitted to Udayana University Hospital Between April 2020 to March 2022 (n=3048)*

Table 1 *Demographic Profile of COVID-19 Patients (n=3048)*

Category	Frequency	Percentage
Age Group		
18–20	67	2.2
21–40	1122	36.8
41–60	1311	43
61–80	521	17.1
≥81	27	0.9
Gender		
Male	1640	53.8
Female	1408	46.2
Occupation		
Private Corporation Employee	960	31.5
Housewife / Household Assistant	329	10.8
Entrepreneur	329	10.8
Public Worker	293	9.6
University Student	250	8.2
Healthcare Worker	168	5.5
Retired / Unemployed	149	4.9
Migrant Worker	122	4
Merchant	85	2.8
Teacher	70	2.3
Laborer	61	2
Farmer	58	1.9
State-Owned Corporation Employee	49	1.6
Others	125	4.1
Recent Travel		
Yes	113	3.7
No	2935	96.3

admitted were Indonesian (99.3%). A complete demographic profile of our patients could be seen in Table 1.

Udayana University Hospital is a tertiary referral hospital dedicated as a major COVID-19 center in Bali. In cases where people came for other emergencies such as trauma, Udayana University Hospital will only stabilize the patient and further refer them to other healthcare centers. In one year since admitting its first COVID-19 patient, Udayana University Hospital had received patients referred from every regency in Bali (94.40%), Indonesians from regions out of Bali (5.60%), and non-Indonesian patients (0.10%). A majority of our patients came from Denpasar (44.94%), Badung (18.79%), and Gianyar (8.77%). Clinical profile of our patients may be seen in Table 2 while the laboratory profile may be seen in Table 3.

Out of all patients treated up to March 2022, majority of them recovered (94.8%) and were safely discharged. The fatality rate within our hospital (5.2%) is slightly higher compared to those described in literatures per age group due to referred patients admitted in already complicated conditions or that these patients had complex comorbidities.[5]

Figure 2 shows the number of monthly admissions and deaths between April 2020 to March 2022, where there are peaks connected to real-life situations happening within the province and the country.[6]

DISCUSSION

In our study, we found that a majority of our patients (79.8%) were of working age (21-60 years old). Male predominates our patients by a slight 53.8%. This demographic state occurs due to a large number of women within the country operates as housewives, though it didn't exclude the possibility of outbreaks on market which will mainly elevate number of women infected. Men in working age had a higher mobility and frequent contacts with other people. This is consistent with some studies which men of working age predominates total number of cases.[7-12]

In terms of occupation, 31.5% of patients admitted were private corporation employee. This was due to premature installment of new normal policies such as allowing employees under 45-years old to work from office.[13] This was followed by reopening of larger public facilities on June 1.[13] This reopening caused housewives / household assistant (10.8%), entrepreneurs (10.8%), and public workers (9.6%) to place second to fourth. Healthcare workers composed 5.5% of all cases, consistent with some studies.[9] This is

Table 2 *Clinical Profile of COVID-19 Patients*

Category	Frequency	Percentage
Symptom		
Fever	2768	90.8
Cough	2417	79.3
Sore Throat	1777	58.3
Chest tightness	1210	39.7
Myalgia	954	31.3
Headache	896	29.4
Cold	579	19
Anosmia	460	15.1
Dizziness	387	12.7
Diarrhea	140	4.6
Comorbidity		
Hypertension	683	22.4
Diabetes Mellitus	439	14.4
Heart Disease	326	10.7
Chronic Lung Disease	108	3.5
Malignancy	24	0.8
HIV	12	0.4
Kidney Disease	61	2
Autoimmune Disease	3	0.1
Others	87	2.9
Antivirus		
Faviripavir	1735	56.9
Remdesivir	1187	38.9
Oseltamivir	105	3.4
Molnupiravir	30	1
Lopinavir/ritonavir	21	0.7
Antibiotic		
Azithromycin	1612	52.9
Levofloxacin	600	19.7
Chloroquine	259	8.5
Meropenem	55	1.8
Therapy		
Vitamin C	2972	97.5
Anticoagulant	951	31.2
Plasma Convalescence	52	1.7
Tocilizumab	34	1.1
IVIG	9	0.3
Regdanvimab	5	0.2
Hospitalization		
≤14 days	1993	65.4
14–20 days	743	24.4
21–28 days	234	7.7
>28 days	78	2.6
Discharge		
Recovered	2889	94.8
Died	159	5.2

Table 3 *Laboratory Profile of COVID-19 Patients*

Parameter	Mean (± SD)
Hemoglobin (g/dL)	13.63 (± 1.70)
Hematocrit (%)	40.22 (± 4.64)
Leukocyte (×10^9/L)	7.16 (± 2.86)
Lymphocyte (×10^9/L)	1.76 (± 1.07)
Neutrophil (×10^9/L)	4.69 (± 2.96)
Neutrophil Lymphocyte Ratio	3.62 (± 3.89)
Platelet (×10^9/L)	246.13 (± 99.50)
Aspartate Transaminase (U/L)	42.50 (± 36.61)
Alanine Transaminase (U/L)	42.14 (± 36.07)
Blood Urea Nitrogen (mmol/L)	12.76 (± 5.62)
Serum Creatinine (mg/dL)	0.75 (± 0.31)
Random Blood Glucose (mg/dL)	119.84 (± 57.22)

higher in earlier months due to unprepared systems and inadequate personal protective equipment (PPE) availability, also seen in some studies.[12]

International travel history as recent as 14 days were recorded in only 3.7% patients, in which all of them happened during the first 3 months. Most of them were migrant workers, where their work setting does not tightly implement COVID-19 protocols and many have forced them to go home due to economic instability.[11,14]

Almost all of patients admitted had fever (90.8%), followed by cough (79.3%), sore throat (58.3%), and chest tightness (39.7%). Anosmia, which is a relative indicator to a moderate to mild COVID-19, was rarely seen (15.1%). Due to Udayana University Hospital being a tertiary referral COVID-19 hospital, symptoms shown were higher than described in literatures. Almost all findings are consistent with a some studies, except that fever affects almost all patients in our hospital.[9,11,12]

Hypertension (22.4%) is the most common comorbidity in patients admitted, followed by diabetes mellitus (14.4%), heart disease (10.7%), and chronic lung disease (3.5%). Although there were other comorbidities, most do not happen in a significantly large amount. This is consistent with a some studies, where hypertension tops the list,[10] followed by the rest three comorbidities.[9,11,12]

In accordance to therapies published by Indonesian Association of Internal Medicine, we administered azithromycin (52.9%), levofloxacin (19.7%), chloroquine (8.5%), and meropenem (1.8%) combined with faviripavir (54.69%), remdesivir (38.9%), oseltamivir (3.4%), molnupiravir (1.0%), and lopinavir/ritonavir (0.7%) to our patients. Almost all of our patients were given vitamin C (97.5%), and a

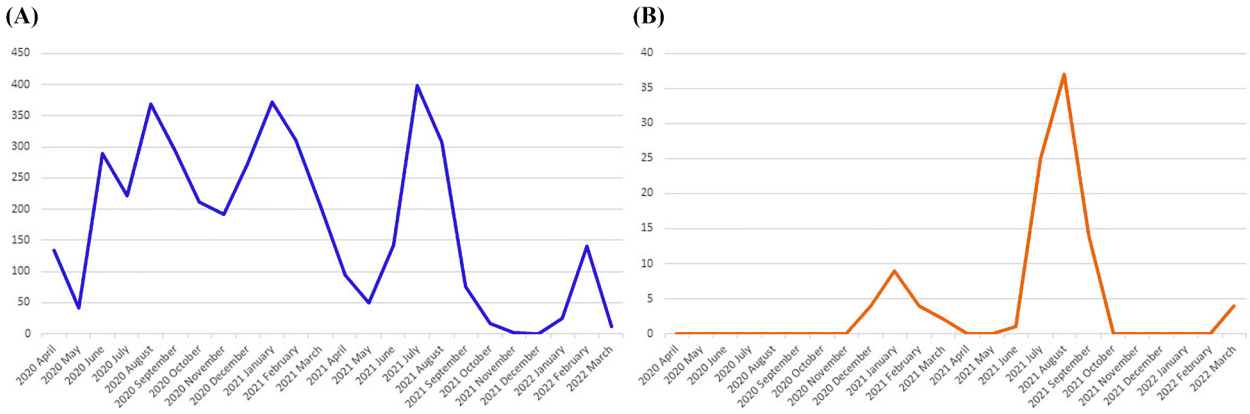


Figure 2 *Monthly Admission (a) and Death (b)*

few were given anticoagulants (31.2%) as a prophylaxis to possible coagulopathies. Plasma convalescence therapy were given only to critical patients in ICU (1.7%). Tocilizumab (1.1%), IVIG (0.3%) and Regdanvimab (0.2%) only given on critical patients.

Most of our patients were hospitalized <14 days (65.4%), followed by 15-20 days (24.4%), 21-28 days (7.7%), and >28 days (2.6%). We do not find any significance between duration of hospitalization and age nor COVID-19 symptom level classification.

Mortality rate in our hospital reached 5.3%, a higher amount than those in literatures possibly due to being a tertiary referral hospital.[11] Udayana University Hospital only admits moderate to severe and critical COVID-19 cases; therefore, it is justifiable that the mortality rate is higher than those in literatures which observes a larger array of population.

Notable Event: Early International Transmission

COVID-19 entered Indonesia via international transmission. During this early period, Indonesian government decided not to close international flights nor establish and quarantine policies to limit possible international transmission.[15] Travels weren't restricted and quarantine policies weren't established soon enough. This mistake subsequently shapes how the pandemic progress. Profile of patients admitted during the first 2 months of the pandemic were dominated by patients that had a history international travel as recent as 14 days prior to hospitalization.

Most were migrant workers, travelling back to Indonesia either via international flight or trade ship. Due to no COVID-19 outbreak containment measures, significant number of patients with a history of international travel were recorded.[16] We also found some patients with travel history from countries experiencing outbreak at that moment such as United States and Italy.[6]

We found that the same trend happened in other countries, where both travel history to high-risk countries accompanied with a delayed travel restriction policy establishment became the start of international spread.[17,18] These people may then further attend superspreading events (SSEVs), exponentially increasing transmission.[17,19] Even in some countries, only a small fraction of first wave patients were of their nationality.[7]

Notable Event: Superspreading Events and Holidays

A spike seen from December 2020 up to February 2021 was not mainly due to long-distance travelers. There were strict travel restrictions were imposed to limit mobility between different cities and provinces, cases still rose up to 2.5 times its original numbers before these holidays.[6,20]

This brings us to another possibility: rising number of cases were due to intracity (potentially SSEVs). Although objectively there was less travelling, – metrically measured by a decrease in gasoline usage during December 2020 compared to November 2020[21] – there is an increase in offline shopping activity on malls. Enclosed and packed indoor shopping centers were full of people in the mood for new year shopping haul.[22,23]

Terminologically, SSEV is an event where a person infected with a certain infectious disease spreads the pathogen into an unusually high amount of people; usually due to being in an ideal condition for the pathogen to spread.[24] Added by the fact that COVID-19 spreads through aerosol, enclosed air-conditioned indoor setting is an ideal place to massively transmit

COVID-19.[25] This trend high number of cases were seen throughout January until February.

Massive SSEVs also happened in India during Kumbh Mela 2021, where 9.1 million pilgrims reportedly took a holy dip in Ganga.[26] Observers and experts said that COVID-19 protocols were breached: mask mandates were not strictly enforced and physical distancing impossible.[26] This event skyrocketed new cases from 15 to 400 thousand per day.[27]

CONCLUSION

Our study concludes that in terms of demographic data, patients admitted into our hospital were comparable to other studies. However, in terms of symptoms, patients admitted into our hospital showed more severe forms of the symptoms. International travel history and migrant workers predominates the first two months due to loose travel restrictions, followed by healthcare workers on the second and third month due to inadequate PPE, then followed by office workers due to premature reopening of offices. Even though maximum capacity measures in office were capped at 50% by the government, many offices broke the rules per police findings. Soon, housewives and entrepreneurs created market and shopping mall clusters, skyrocketing their numbers to each compose 10.8% of our patients. Next, intracity activities during public holidays turned transmission due to long-distance travel into transmission due to SSEVs in shopping centers. Both of this trend is comparable to countries outside Indonesia, where international transmission first occurs due to late COVID-19 travel restriction policy establishment, and as soon as cases went down, government began to loosen restrictions which creates chances for SSEVs to form.

SUMMARY BOX

The first two year of COVID-19 pandemic in Indonesia had shown how public health policies shaped the epidemiological characteristics of our patients.

Common COVID-19 symptoms observed in this study's tertiary center site include fever, cough, and sore throat; followed by less common traits such as chest tightness, myalgia, headache, cold, anosmia, dizziness, and diarrhea.

Tertiary referral centers had a higher mortality rate compared to other sites.

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REFERENCES

1. Lotfi M, Hamblin MR, Rezaei N. COVID-19: Transmission, prevention, and potential therapeutic opportunities. Clin Chim Acta. 2020;508:254–66.
2. McKee M, Stuckler D. If the world fails to protect the economy, COVID-19 will damage health not just now but also in the future. Nat Med. 2020;26:640–2.
3. Allen K. Downtown Chicago under lockdown in wake of looting, violent unrest - ABC News [Internet]. 2020 [cited 2021 Jul 12]. Available from: https://abcnews.go.com/US/downtown-chicago-lockdown-wake-looting-violent-unrest/story?id=72280021
4. Koster W. Surat Edaran Nomor 2021 Tahun 2020 Tentang Pelaksanaan Kegiatan Masyarakat Selama Libur Hari Raya Natal dan Menyambut Tahun Baru 2021 dalam Tatanan Kehidupan Era Baru di Provinsi Bali [Internet]. Gubernur Bali; 2020 Dec 15 [cited 2021 Jul 12]. Available from: https://infocorona.baliprov.go.id/wp-content/uploads/2020/03/SURAT-EDARAN-NOMOR-2021-TAHUN-pdf

5. Levin AT, Hanage WP, Owusu-Boaitey N, et al Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol. 2020;35:(12)1123–38.
6. Our World In Data. Coronavirus (COVID-19) Cases [Internet]. 2021 [cited 2021 Aug 9]. Available from: https://ourworldindata.org/coronavirus
7. Khamis F, Al Rashidi B, Al-Zakwani I, Al Wahaibi AH, Al Awaidy ST. Epidemiology of COVID-19 infection in Oman: Analysis of the first 1304 cases. Oman Med J. 2020;35:(3)1–4.
8. Grasselli G, Zangrillo A, Zanella A, et al Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323:(16)1574–81.
9. Cummings MJ, Baldwin MR, Abrams D, et al Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763–70.
10. Grasselli G, Zangrillo A, Zanella A, et al Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323:(16)1574–81.
11. Guan W, Ni Z, Hu Y, et al Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382:(18)1708–20.
12. Wang D, Hu B, Hu C, et al Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323:(11)1061–9.
13. United Nations Office for the Coordination of Humanitarian Affairs. The Community's Perception of COVID-19 [EN/ID] - Indonesia [Internet]. ReliefWeb. 2020 [cited 2021 Aug 6]. Available from: https://reliefweb.int/report/indonesia/communitys-perception-covid-19-enid
14. Suteja R, Novianti P, Dewi K, et al Migrant Workers of Indonesia: Transmission Channels of SARS-CoV-2 Amidst COVID-19 Pandemic in Indonesia. Int J Med Rev Case Rep. 2020;0:1.
15. Ramli RR, Jatmiko BP. Banyak Pemda Ingin Tutup Bandara, Ini Respon Kemenhub. Kompas [Internet]. 2020 Mar 26 [cited 2021 Jul 14]. Available from: https://money.kompas.com/read/2020/03/26/053109326/banyak-pemda-ingin-tutup-bandara-ini-respon-kemenhub
16. Hoehl S, Karaca O, Kohmer N, et al Assessment of SARS-CoV-2 Transmission on an International Flight and among a Tourist Group. JAMA Netw Open. 2020;3:(8)e2018044.
17. Mat NFC, Edinur HA, Razab MKAA, Safuan S. A single mass gathering resulted in massive transmission of COVID-19 infections in Malaysia with further international spread. J Travel Med. 2020;27:(3)1–4.
18. Luo G, McHenry ML, Letterio JJ. Estimating the prevalence and risk of COVID-19 among international travelers and evacuees of Wuhan through modeling and case reports. PLoS One. 2020;15:(6)e0234955.
19. Wang L, Didelot X, Yang J, et al Inference of person-to-person transmission of COVID-19 reveals hidden super-spreading events during the early outbreak phase. Nat Commun. 2020;11:(1)1–6.
20. Jelita IN. Ini Isi SE Kemenhub tentang Perjalanan Transportasi saat Nataru [Internet]. Media Indonesia. 2020 [cited 2021 Aug 9]. Available from: https://mediaindonesia.com/humaniora/370758/ini-isi-se-kemenhub-tentang-perjalanan-transportasi-saat-nataru
21. Pertamina. Konsumsi Pertamax Turbo dan Pertamax Melonjak Signifikan Saat Libur Natal dan Tahun Baru 2021 [Internet]. Pertamina. 2020 [cited 2021 Aug 9]. Available from: https://www.pertamina.com/id/news-room/news-release/Konsumsi-Pertamax-Turbo-dan-Pertamax-Melonjak-Signifikan-Saat-Libur-Natal-dan-Tahun-Baru-2021
22. Sumirat C. Jelang Natal di Manado, Pusat Perbelanjaan Mulai Ramai Pengunjung [Internet]. iNews.id. 2020 [cited 2021 Aug 9]. Available from: https://sulut.inews.id/berita/jelang-natal-di-manado-pusat-perbelanjaan-mulai-ramai-pengunjung

23. Savitri I. Pusat Perbelanjaan Mulai Ramai Pasca-Natal, Pengunjung Sempat Takut [Internet]. Tribun News. 2020 [cited 2021 Aug 9]. Available from: https://manado.tribunnews.com/2020/12/27/pusat-perbelanjaan-mulai-ramai-pasca-natal-pengunjung-sempat-takut
24. Lewis D. Superspreading drives the COVID pandemic - and could help to tame it. Nature. 2021;590(7847):544–6.
25. Qian H, Miao T, Liu L, et al Indoor transmission of SARS-CoV-Indoor Air. 2021;31:(3)639–45.
26. Rawat S. 9.1 million thronged Mahakumbh despite Covid-19 surge: Govt data - Hindustan Times [Internet]. Hindustan Times. 2021 [cited 2021 Aug 10]. Available from: https://www.hindustantimes.com/cities/dehradun-news/91-million-thronged-mahakumbh-despite-covid-19-surge-govt-data-html
27. Our World In Data. Coronavirus (COVID-19) Testing - Statistics and Research [Internet]. 2020 [cited 2021 Jul 13]. Available from: https://ourworldindata.org/coronavirus

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ORIGINAL ARTICLE

Sequences Analysis and Identification of Motifs in TTMV and TTMDV Viruses: A Systematic Review

Gayathri ArumughanKanu, Raed Abu Odeh, Zamberi Bin Sekawi, Zulkefley Bin Othman

Objective

The goal of this study is to examine and assess the literature on the consensus sequence(s) in TTMV and TTMDV viruses, as well as their heterogeneity and features.

Methods

Published, complete sequences of TTMV and TTMDV were identified and retrieved using BLAST search. Bioinformatics tools such as ClustalW, phylogenetic mapping, and MEME were used to align and identify consensus sequences of these Anelloviruses.

Results

The complete genome and ORF demonstrated general sequence differences at the nucleotide and protein levels. The phylogenetic tree of TTVMV and TTMDV revealed a cluster of strains that diverge significantly. Furthermore, common consensus sequences (motifs) were also identified.

Conclusion

These findings reveal significant structural variations between TTMV and TTMDV strains. They have a similar identity in terms of consensus or MOTIF in the sequences but are not organized in the same region. Instead, they are unique to all sequences that may lead to the expression of analogous proteins, even though their genomic length and genetic identity are vastly different.

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The non-enveloped, circular, single-stranded DNA viruses Torque teno mini virus (TTMV) and Torque teno midi virus (TTMDV) were found in the Anelloviridae family in 2000 and 2007, respectively.[1] These viruses are defined by their extremely high prevalence, relatively uniform worldwide distribution, increased genomic variability, and apparent pan-tropism at the host level. TTMDV has a genome size of 3.24-3.25 kb, while TTMV has a genome size of 2.86-2.91 kb.[2] Both viruses have a similar genome structure, including an untranslated region (UTR), an open reading frame (ORF), and a short G/C rich region (**Digital Supplementary File, Figure 1**).[3,4]

Polymerase chain reaction (PCR) with Torque Teno Virus(TTV)-specific primers that partially matched homologous sequences in TTMV was used to identify TTMV, which is distantly related to TTV.[1] In cultured cells transfected with recombinant TTV DNA as well as in bone marrow cells taken from an infected patient, three different mRNAs of 2.9-3.0 kb, 1.2 kb, and 1.0 kb with common 50 and 30 termini were found, all transcribed from the genomic, minus-strand of TTV DNA.[5,6] These three mRNAs share a brief splicing sequence of about 100 nucleotides (nt). Furthermore, the 1.2-kb and 1.0-kb mRNAs have 1700 nt and 1900 nt of extra splicing, respectively, resulting in the development of two unique open reading frames (ORF3 and ORF4). TTV or TTMV infection is ubiquitous, although the link between TTV and disease is unknown.[7,8] TTMDV was reported by Ninomyia et al[8] as a cross between TTV and TTMV; nonetheless, despite current databases containing numerous entire genomic sequences of the virus, information on TTMDV remains scant. TTV, TTMV, and TTMDV have quite different genomic structures, and all three viruses have four ORF regions and a GC-rich UTR with few highly conserved or consensus sequences. Variation in genome organization caused by modest variations in sequence identity across the genomes has been reported often among isolates of the same type, raising concerns about the functionality of these variant genes. Given that these viruses function similarly in the host, the current work attempts to examine and further analyze their behavior using various bioinformatics tools. TTV received the majority of research and understanding, while little or no research on TTMV and TTMDV has been done thus far, justifying the need for conducting the study on the current two viruses in particular.

METHODS

Sequences used in the present study

The National Center for Biotechnology Information (NCBI) tool was used to perform a random search on the TTMV and TTMDV viruses and to identify and retrieve the full-length genome sequences. Viral ORF and protein sequences were retrieved for the same viruses. **Digital Supplementary File, Tables 1 and 2** (a and b) show the DNA and ORF's sequences used in the study for TTMV and TTMDV, respectively. The NCBI search yielded nine full-length genomes of TTMV variants and two ORF's (ORF 1 and ORF 2) for both DNA and proteins, which were used for this study (**Digital Supplementary File, Table 1**).

Phylogenetic analyses of TTMV and TTMDV

MEGA 10 software[9] was used to align the genomic sequences for both TTMV and TTMDV. With default parameters, the ClustalW method in MEGA10 was used to align DNA sequences. The distance matrix was calculated by using distance and the maximum composite likelihood with Gap/Missing data treatment was conducted by 1000 replicates. Obtained distance matrix and maximum liklihood was used for constructing Molecular phylogenetic analysis. Bootstrap proportions were determined using 1000 replicates to assess the analysis's robustness. A similar procedure was used with the ORF sequences of the other two viruses.

MOTIF Detection and Measurement of Similarities

Multiple EM for Motif Elicitation (MEME), an EM-based technique, was utilized to screen for motif sequences in the TTMV and TTMDV.[10] Genome and ORF sequences of each virus (Digital Supplementary File, Figure 1, Tables 1 and 2) were submitted into MEME (http://meme.nbrc.net/meme/version 5.1.1). Each motif set's information content value (IC - relative entropy of the motif compared to a uniform background frequency model) was measured.

RESULTS

The sequences clustered in distinct clades, according to phylogenetic analyses (Digital Supplementary File, Figure 2 for TTMV and Digital Supplementary File, Figure 3 for TTMDV). In this review, we looked at 9 full TTMV sequences and their associated ORF DNA and protein sequences, as well as 11 complete TTMDV sequences and their respective ORF DNA and protein sequences. The 11 TTMDV isolates found in the current investigation and the 9 previously described TTMV isolates were compiled into a phylogenetic tree, which likewise showed a high level of genetic divergence between the various strains.The DNA and protein sequences of both TTMV and TTMDV were found to be significantly different. However, the difference is more noticeable in protein sequences than in nucleotide sequences. In TTMV and TTMDV, MEME analysis

indicated the presence of three MOTIFS for each set of sequences (Digital Supplementary File, Figure 3a, 4a 5a, Table 3a and 3b). The hypothesized genomic organization and transcription profile of TTMDVs are comparable to TTMVs, as evidenced by the maintenance of the coding capability for ORF1 and ORF2 proteins as well as two joint proteins (ORF3 and ORF4).

DISCUSSION

Studies have revealed up to a 30% heterogeneity in genomic sequences between TTV, TTMV, and TTMDV.[2,11–13] There are several distinct genotypes can infect the same person at the same time, and different viral genotype combinations frequently predominate in different organs. *Anelloviruses* infect healthy humans, and co-infections with numerous distinct lineages are widespread[14–17] and these lineages make up a person's "personal anellome." Within the *Anelloviridae* family, there are three genera of human anelloviruses: *Alphatorquevirus* (torque teno viruses (TTVs), *Betatorquevirus* (torque teno mini viruses (TTMVs), and *Gammatorquevirus* (torque teno midi viruses (TTMDVs), which share just 35% pairwise nucleotide identity. According to the findings, the differences between TTMV and TTMDV are substantially bigger in protein sequences than in nucleotide sequences. To illustrate this further, TTMV revealed 99% similarity in DNA sequences but only 51% similarity in protein sequences, implying that viruses carry 50% heterogeneity within the same species. TTMDV, on the other hand, has a 56% similarity in DNA sequences and a 50% similarity in protein sequences, which is rather interesting and unusual.

The reason for the wide genomic variation in these viruses and the process by which it happens are unknown. One theory is that these viruses mutate quickly. Many studies have looked at the nucleotide sequences of different isolates, indicating either the same sequence's persistence over time or alterations in the host's sequence.[18–20] DNA viruses like human herpesviruses[21–26] JC virus[27] and papillomaviruses[28–30], have some genetic heterogeneity, but *Anelloviruses* have plenty. There are at least two possibilities for why this is the case. If its replication is carried out by a host DNA polymerase complex due to the absence of a polymerase gene in the TTV genome.[31] such significant genetic variability would indicate that it has been there for hundreds of thousands, if not millions, of years.

Second, only a small number of these viruses contain all of the necessary components to properly infect hosts, or co-infections with other isolates may bring the required components together.[32] Concurrent infections with hepatitis viruses (HBV and HCV, for example) have been extensively studied, and high viral loads in chronic hepatitis C patients have been linked to the development of hepatocellular carcinoma.[33] The histological grade in hepatocellular patients with TTV-HCV co-infection appeared to be higher than in those infected with just HCV.[34] Furthermore, it has been proposed that ORF3 of TTV genotype 1a encodes a protein that is comparable to HCV's nonstructural protein 5A (NS5A). This protein is vital in the antiviral response generated by IFN[34]. Furthermore, Matsubara et al[35] discovered TTMV in infant cord blood, implying that, like other intrauterine viruses such as the human immunodeficiency virus 1, rubella virus, cytomegalovirus, and parvoviruses, TTMV could be transferred from mother to child.

In comparison to TTV, little is known regarding the prevalence, infection, recombination, and co-infection of TTMV and TTMDV in healthy and infected individuals. However, these *Anelloviridae* viruses have a similar genome organization, including an untranslated region (UTR), an open reading frame (ORF), and a short G/C rich region, with nucleotide and amino acid levels in the ORF portions that are quite variable. However, while these assertions are theoretically supported, more specific experimental evidence is needed to assess the pathogenicity of these viruses. Because they replicate through the rolling circle method, the preceding statement supports consensus sequences are thought to play a vital role in replication and recombination.

Third, the process by which viruses evolve through recombination is critical to occur on a regular basis[36,37] for these viruses. TTV, for example, shares some characteristics of *Circoviridae* [38] viruses, such as a negative-stranded circular DNA genome, but it is otherwise unique from them. On the other hand, the TTV genome is nearly twice as massive as that of *Circoviridae* members. A recent study suggested that intra-genomic recombination is a cause of TTV genome diversity[39] and that frequent recombination processes mask differences between viral populations[37]

However, Jelcic et al[40] have cast doubt on this, stating that the reported recombination events are merely PCR artifacts.

Furthermore, a recent study suggested that the *Epstein-Barr* virus, a herpesvirus, functions as a helper for TTV in terms of recombination during co-infection.[41,42] DNA viruses lack their own replicative machinery, as they rely on the host's DNA

polymerases, which have a high level of proofreading capacity. However, the ssDNA genomes of parvoviruses have been found to evolve fast, and this enhanced mutation rate could be explained by the single-stranded genome's ability to encode replication proteins.[43] In the current study, the first phylogenetic tree[2] based on TTMV genomic sequences revealed a large cluster of strains with ORF1 nucleotide and amino acid divergences of roughly 42% and 67%, respectively.[1,44] On the other hand, the evolutionary distances between these sequences are within the range. Although the TTMDV data is scarce; nevertheless, new database searches have turned up multiple whole genomic sequences.

For the three anelloviral genera, the International Committee on Taxonomy of Viruses (ICTV) classification is entirely based on ORF1 analysis, with a species demarcation threshold of 35% nucleotide sequence identity (Alphatorquevirus, Betatorquevirus, and Gammatorquevirus). Alphatorquevirus, which includes 29 species (Torque teno virus 1–29), Betatorquevirus, which includes 12 species (Torque teno mini virus 1-12); and Gammatorquevirus, which includes 15 species (Torque teno midi virus 1-15), are other related viruses that may be members of these genera but have not been assigned to separate species. Based on the frequency pattern of evolutionary distances in the phylogenetic analysis, this observation strongly suggests that these TTV and TTMDV represent different strains that may belong to the same genotype. The fact that primate isolates cluster phylogenetically shows that anelloviruses constitute a long-lived family with genetic variety resulting from millions of years of evolution. The clustering of these viruses was discovered to be similar to that of human and primate HPVs.[45]

The phylogenetic groups of TTMV and TTMDV are poorly understood[46], although a comparison of TTMV ORF1 sequences revealed considerable divergence, and whole-genome analysis of TTMDV revealed sequence clustering.[46] Furthermore, despite the three viruses having a similar genome architecture, their ORFs are significantly diverse at both the nucleotide and amino acid levels[7] The central area of ORF regions[47], whose translation product comprises an arginine-rich sequence in the N terminus, has the highest rate of sequence divergence resulting in amino acid conversions, which helped us analyze and comprehend the ORF regions of TTMV and TTMDV. More intriguingly, the ORF1 proteins of the N-terminal region contains arginine repeats.[48] This arginine-rich region is remarkably similar to the ARM motif seen in *circovirus* Cap proteins, which has been shown to bind DNA.[48,49] This trait could indicate that ORF1 protein, like *circovirus* Cap proteins, is important for ssDNA packing.[49] ORF2 protein, on the other hand, is most likely a regulatory protein that aids the virus in disrupting the host's immune response.[50,51] Recently, potential new species have been discovered mostly in the TTMV and TTMDV genera. The latter is presumably more difficult to detect in methods without viral enrichment and, as a result, are less well understood.

Furthermore, based on its N-terminal arginine-rich region, which is shared with the circovirus capsid proteins, Nishizawa et al and Erker et alsup>48,52 postulated that ORF-1 encodes the viral capsid protein, although the functions of the proteins expressed by ORF-2 and ORF-3 are still unknown. An origin of replication in the conserved area is used to identify anelloviruses to learn more about their special characteristics on host-specific reactions.[39,53] These genomes contain conserved motifs similar to those found in *Circoviridae* family rolling-circle replication related proteins (Rep proteins).[54] A conserved mononucleotide necessary for rolling-circle replication has also been identified, which is already present in single-stranded DNA viruses.[55,56] In silico investigations of potential proteins expressed by these sub-viral components, as well as virus transcripts extracted from TTV-infected cultures, have identified signature motifs of proteins involved in autoimmune illnesses.[57]

CONCLUSION

It is important to note that viruses sometimes use many motifs for a single activity. If the primary motif is absent, they might be able to evolve systems to use alternate ones. Within host cells, these motifs mediate connections and molecular functions. As a result, a growing body of evidence points to themes as possible targets for therapeutic drugs. It is crucial to stress that understanding functional motifs will aid in the prediction of protein properties, cellular connections, or the potential function of a protein. Future study should establish the relationship between functional motifs and protein functional analysis and/or prediction. Additionally, these investigations may help in defining virus tropism and researching newly developing viruses and motifs that can infect living organism.

REFERENCES

1. Takahashi K, Hijikata M, Samokhvalov EI, Mishiro S. Full or near full length nucleotide sequences of TT virus variants (types SANBAN and YONBAN) and the TT virus-like mini virus. Intervirology. 2000;43:(2)119–23.
2. Okamoto H, Nishizawa T, Tawara A, et al. TT virus mRNAs detected in the bone marrow cells from an infected individual. Biochem Biophys Res Commun. 2000;279:(2)700–7.
3. Farsani SMJ, Jebbink MF, Deijs M, et al. Identification of a new genotype of Torque Teno Mini virus. Virol J. 2013;10:(1)1–7.
4. Davidson I, Shulman LM. Unraveling the puzzle of human anellovirus infections by comparison with avian infections with the chicken anemia virus. Virus Res. 2008;137:(1)1–15.
5. Kamahora T, Hino S, Miyata H. Three spliced mRNAs of TT virus transcribed from a plasmid containing the entire genome in COS1 cells. J Virol. 2000;74:(21)9980–6.
6. Breathnach R, Benoist C, O'Hare K, Gannon F, Chambon P. Ovalbumin gene: evidence for a leader sequence in mRNA and DNA sequences at the exon-intron boundaries. Proc Natl Acad Sci USA. 1978;75:(10)4853–7.
7. Biagini P, Uch R, Belhouchet M, et al. Circular genomes related to anelloviruses identified in human and animal samples by using a combined rolling-circle amplification/sequence-independent single primer amplification approach. J Gen Virol. 2007;88:(10)2696–701.
8. Ninomiya M, Nishizawa T, Takahashi M, et al. Identification and genomic characterization of a novel human torque teno virus of 3.2 kb. J Gen Virol. 2007;88:(7)1939–44.
9. Kumar S, Stecher G, Peterson D, Tamura K. MEGA-CC: computing core of molecular evolutionary genetics analysis program for automated and iterative data analysis. Bioinformatics. 2012;28:(20)2685–6.
10. Bailey TL, Johnson J, Grant CE, Noble WS. The MEME suite. Nucleic Acids Res. 2015;43(W1):W39–49.
11. Biagini P. Human circoviruses. Vet Microbiol. 2004;98:(2)95–101.
12. Heller F, Zachoval R, Koelzer A, et al. Isolate KAV: a new genotype of the TT-virus family. Biochem Biophys Res Commun. 2001;289:(5)937–41.
13. Hijikata M, Takahashi K, Mishiro S. Complete circular DNA genome of a TT virus variant (isolate name SANBAN) and 44 partial ORF2 sequences implicating a great degree of diversity beyond genotypes. Virology. 1999;260:(1)17–22.
14. Bal A, Sarkozy C, Josset L, et al. Metagenomic next-generation sequencing reveals individual composition and dynamics of anelloviruses during autologous stem cell transplant recipient management. Viruses. 2018;10:(11)633.
15. Moustafa A, Xie C, Kirkness E, et al. The blood DNA virome in 8,000 humans. PLoS Pathog. 2017;13:(3)e1006292.
16. Rani A, Ranjan R, McGee HS, et al. A diverse virome in kidney transplant patients contains multiple viral subtypes with distinct polymorphisms. Sci Rep. 2016;6:(1)1–13.
17. Young JC, Chehoud C, Bittinger K, et al. Viral metagenomics reveal blooms of anelloviruses in the respiratory tract of lung transplant recipients. Am J Transplant. 2015;15:(1)200–9.
18. Ball JK, Curran R, Berridge S, et al. TT virus sequence heterogeneity in vivo: evidence for co-infection with multiple genetic types. J Gen Virol. 1999;80:(7)1759–68.
19. Gallian P, Berland Y, Olmer M, et al. TT virus infection in French hemodialysis patients: study of prevalence and risk factors. J Clin Microbiol. 1999;37:(8)2538–42.
20. Irving WL, Ball JK, Berridge S, et al. TT virus infection in patients with hepatitis C: frequency, persistence, and sequence heterogeneity. J Infect Dis. 1999;180:(1)27–34.

21. Smith DB, Inglis SC. The mutation rate and variability of eukaryotic viruses: an analytical review. J Gen Virol. 1987;68:(11)2729–41.
22. Ablashi DV, Balachandran N, Josephs SF, et al. Genomic polymorphism, growth properties, and immunologic variations in human herpesvirus-6 isolates. Virology. 1991;184:(2)545–52.
23. Aitken C, Sengupta SK, Aedes C, Moss DJ, Sculley TB. Heterogeneity within the Epstein-Barr virus nuclear antigen 2 gene in different strains of Epstein-Barr virus. J Gen Virol. 1994;75:(1)95–100.
24. Busson P, Edwards RH, Tursz T, Raab-Traub N. Sequence polymorphism in the Epstein-Barr virus latent membrane protein (LMP)-2 gene. J Gen Virol. 1995;76:(1)139–45.
25. Meyer-Konig U, Ebert K. Simultaneous infection of healthy people with multiple human cytomegalovirus strains. Lancet. 1998;352(9136):1280–1.
26. Triantos D, Boulter AW, Leao JC, et al. Diversity of naturally occurring Epstein-Barr virus revealed by nucleotide sequence polymorphism in hypervariable domains in the BamHI K and N subgenomic regions. J Gen Virol. 1998;79:(11)2809–17.
27. Agostini HT, Ryschkewitsch CF, Singer EJ, Stoner GL. JC virus regulatory region rearrangements and genotypes in progressive multifocal leukoencephalopathy: two independent aspects of virus variation. J Gen Virol. 1997;78:(3)659–64.
28. Ong CK, Chan SY, Campo MS, et al. Evolution of human papillomavirus type 18: an ancient phylogenetic root in Africa and intratype diversity reflect coevolution with human ethnic groups. J Virol. 1993;67:(11)6424–31.
29. Pushko P, Sasagawa T, Cuzick J, Crawford L. Sequence variation in the capsid protein genes of human papillomavirus type J Gen Virol. 1994;75:(4)911–6.
30. Chan SY, Delius H, Halpern AL, Bernard HU. Analysis of genomic sequences of 95 papillomavirus types: uniting typing, phylogeny, and taxonomy. J Virol. 1995;69:(5)3074–83.
31. Okamoto H, Nishizawa T, Kato N, et al. Molecular cloning and characterization of a novel DNA virus (TTV) associated with posttransfusion hepatitis of unknown etiology. Hepatol Res. 1998;10:(1)1–16.
32. Khudyakov YE, Cong ME, Nichols B, et al. Sequence heterogeneity of TT virus and closely related viruses. J Virol. 2000;74:(7)2990–3000.
33. Tanaka Y, Primi D, Wang RYH, et al. Genomic and molecular evolutionary analysis of a newly identified infectious agent (SEN virus) and its relationship to the TT virus family. J Infect Dis. 2001;183:(3)359–67.
34. Sampietro M, Tavazzi D, Martinez di Montemuros F, et al. TT virus infection in adult beta-thalassemia major patients. Haematologica. 2001;86:(1)39–43.
35. Matsubara H, Michitaka K, Horiike N, et al. Existence of TT virus DNA and TTV-like mini virus DNA in infant cord blood: mother-to-neonatal transmission. Hepatol Res. 2001;21:(3)280–7.
36. Worobey M. Extensive homologous recombination among widely divergent TT viruses. J Virol. 2000;74:(16)7666–70.
37. Manni F, Rotola A, Caselli E, Bertorelle G, Di Luca D. Detecting recombination in TT virus: a phylogenetic approach. J Mol Evol. 2002;55:(5)563–72.
38. Miyata H, Tsunoda H, Kazi A, et al. Identification of a novel GC-rich 113-nucleotide region to complete the circular, single-stranded DNA genome of TT virus, the first human circovirus. J Virol. 1999;73:(5)3582–6.
39. Leppik L, Gunst K, Lehtinen M, Dillner J, Streker K, de Villiers EM. In vivo and in vitro intragenomic rearrangement of TT viruses. J Virol. 2007;81:(17)9346–56.
40. Jelcic I, Hotz-Wagenblatt A, Hunziker A, Zur Hausen H, de Villiers EM. Isolation of multiple TT virus genotypes from spleen biopsy tissue from a Hodgkin's disease patient: genome reorganization and diversity in the hypervariable region. J Virol. 2004;78:(14)7498–507.

41. Luo K, Zhang L. Enteric transmission of transfusion-transmitted virus. Chin Med J (Engl). 2001;114:(11)1201–4.
42. Borkosky SS, Whitley C, Kopp-Schneider A, Zur Hausen H, de Villiers EM. Epstein-Barr virus stimulates torque teno virus replication: a possible relationship to multiple sclerosis. PLoS One. 2012;7:(2)e32160.
43. Shackelton LA, Parrish CR, Holmes EC. Evolutionary basis of codon usage and nucleotide composition bias in vertebrate DNA viruses. J Mol Evol. 2006;62:(5)551–63.
44. Ninomiya M, Takahashi M, Nishizawa T, et al. Development of PCR assays with nested primers specific for differential detection of three human anelloviruses and early acquisition of dual or triple infection during infancy. J Clin Microbiol. 2008;46:(2)507–14.
45. Van Doorslaer K. Evolution of the papillomaviridae. Virology. 2013;445:[1-2]11–20.
46. Spandole S, Cimponeriu D, Berca LM, Mihescu G. Human anelloviruses: an update of molecular, epidemiological and clinical aspects. Arch Virol. 2015;160:(4)893–906.
47. Takahashi K, Iwasa Y, Hijikata M, Mishiro S. Identification of a new human DNA virus (TTV-like mini virus, TLMV) intermediately related to TT virus and chicken anemia virus. Arch Virol. 2000;145:(5)979–93.
48. Erker JC, Leary TP, Desai SM, Chalmers ML, Mushahwar IK. Analyses of TT virus full-length genomic sequences. J Gen Virol. 1999;80:(7)1743–50.
49. Sarker S, Terron MC, Khandokar Y, et al. Structural insights into the assembly and regulation of distinct viral capsid complexes. Nat Commun. 2016;7:(1)1–7.
50. Zheng H, Ye L, Fang X, et al. Torque teno virus (SANBAN Isolate) ORF2 protein suppresses NF-κB pathways via interaction with IκB kinases. J Virol. 2007;81:(21)11917–24.
51. Kakkola L, Hedman K, Qiu J, Pintel D. Replication of and protein synthesis by TT viruses. In: TT Viruses. 2009:53–64.
52. Nishizawa T, Okamoto H, Tsuda F, et al. Quasispecies of TT virus (TTV) with sequence divergence in hypervariable regions of the capsid protein in chronic TTV infection. J Virol. 1999;73:(11)9604–8.
53. Peng YH, Nishizawa T, Takahashi M, et al. Analysis of the entire genomes of thirteen TT virus variants classifiable into the fourth and fifth genetic groups, isolated from viremic infants. Arch Virol. 2002;147:(1)21–41.
54. Bendinelli M, Pistello M, Maggi F, et al. Molecular properties, biology, and clinical implications of TT virus, a recently identified widespread infectious agent of humans. Clin Microbiol Rev. 2001;14:(1)98–113.
55. Mankertz A, Persson F, Mankertz J, Blaess G, Buhk HJ. Mapping and characterization of the origin of DNA replication of porcine circovirus. J Virol. 1997;71:(3)2562–6.
56. Meehan BM, Creelan JL, McNulty MS, Todd D. Sequence of porcine circovirus DNA: affinities with plant circoviruses. J Gen Virol. 1997;78:(1)221–7.
57. de Villiers EM, Kimmel R, Leppik L, Gunst K. Intragenomic rearrangement in TT viruses: a possible role in the pathogenesis of disease. In: TT Viruses. 2009:91–107.

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ORIGINAL ARTICLE

Bronchial stenosis secondary to lung adenocarcinoma

Thomas Saliba, Denis Tack

Background

Lung adenocarcinoma is a common type of cancer, with signs sometimes visible on chest x-rays.

Case presentation

A 66-year-old male smoker presented with coughing. Chest x-rays were ordered, showing multiple signs of bronchial stenosis, adenopathy, and a lung nodule. These findings were correlated with a chest CT-exam and PET-CT, with biopsy confirming the diagnosis.

Conclusion

This case demonstrates multimodal correlation of adenocarcinoma signs visible on chest x-rays, in particular bronchial stenosis.

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Lung adenocarcinoma is the most common type of lung cancer, with over 220 000 new cases in 2015, and the most common cause of cancer death.[1] Due to its non-specific symptoms, chest x-rays are often requested for these patients.[2] Therefore, the ability to detect this pathology on initial chest x-rays is essential in guiding follow-up exams. Although signs on chest x-rays are often subtle and non-specific, they can be an essential first step in making the diagnosis. As the symptoms are often late to present, an early radiological diagnosis is crucial.[3] This case demonstrates the correlation between X-ray, CT and PET-CT findings in a 66-year-old smoker presenting with a cough in whom lung cancer was suspected on an initial chest X-ray.

CASE REPORT

A 66-year-old male smoker presented with cough, resulting in a chest x-ray being ordered. The postero-anterior chest X-ray revealed a thickening of the right laterotracheal stripe and a right hilar opacity. The lateral chest X-ray showed a narrowing of the right intermediate bronchus alongside a thickening of its posterior wall (Figure 1). Furthermore, an opacity was found overlaying the spine (spine sign). A follow-up non-contrast CT-exam was ordered, revealing the cause of the thickening of the laterotracheal stripe and the thickening of the posterior wall to be due to hilar lymphadenopathy, causing bronchial constriction (Figure 2, 3, 4). The opacity overlaying the spine was found to be a lung nodule found in the superior segment of the right lower lobe. A PET-CT scan was performed to search for metastases, hypermetabolic lymph nodes were found in the supraclavicular and mediastinal regions alongside a liver metastasis (Figure 5 and 6). A percutaneous transthoracic biopsy of the lung nodule was performed, with anatomopathology discovering histological diagnosis of an adenocarcinoma with 60% PDL1 expression, confirming the diagnosis of stage IV lung adenocarcinoma. The patient is currently undergoing treatment.

DISCUSSION

Lung adenocarcinoma is the most common primary pulmonary cancer in the United states, being classed as a non-small cell lung cancer.[1] In Belgium, lung cancer represents the third most common cause of cancer, with an incidence of 98 per 100,000 and 57 per 100,000 in 2020 in men and women respectively.[4] Despite a strong association with smoking it is also the most common cancer in non-smokers, representing around 40% of all cancers.[1] When lung cancers become symptomatic, most patients present with coughing, shortness of breath, chest pain, recurring infections or haemoptysis.[3]

Adenocarcinomas frequently present on imaging as nodules or masses within the lung parenchyma, but can also appear as an opacity producing a

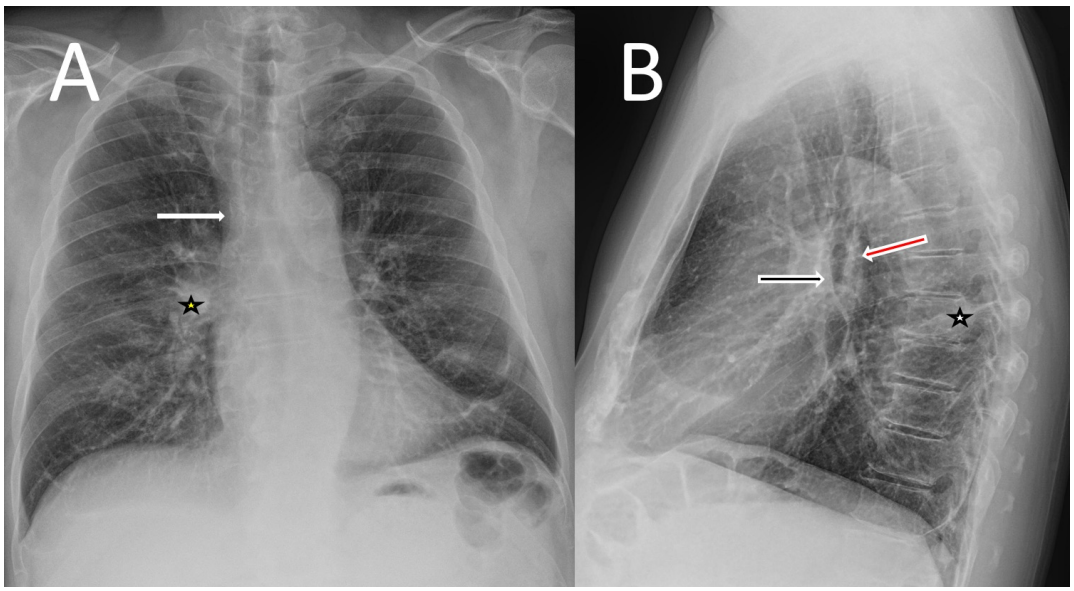


Figure 1 *Postero-anterior chest x-ray (A) showing a right hilar opacity corresponding to a lymph node (yellow star) and a thickening of the right laterotracheal stripe (white arrow). The lateral chest x-ray (B) demonstrates narrowing of the right intermedius bronchus (black arrow) alongside thickening of its posterior wall (red arrow). The primary cancer appears as a nodule overlaying the spine (white star).*



Figure 2 *Juxtaposition of the lateral chest-ray and a sagittal CT image showing right intermediate bronchus constriction between a lymph node (black arrow) anteriorly infiltration of its posterior wall (red arrow), demonstrating modality correlation. The nodule is also visible (white star).*

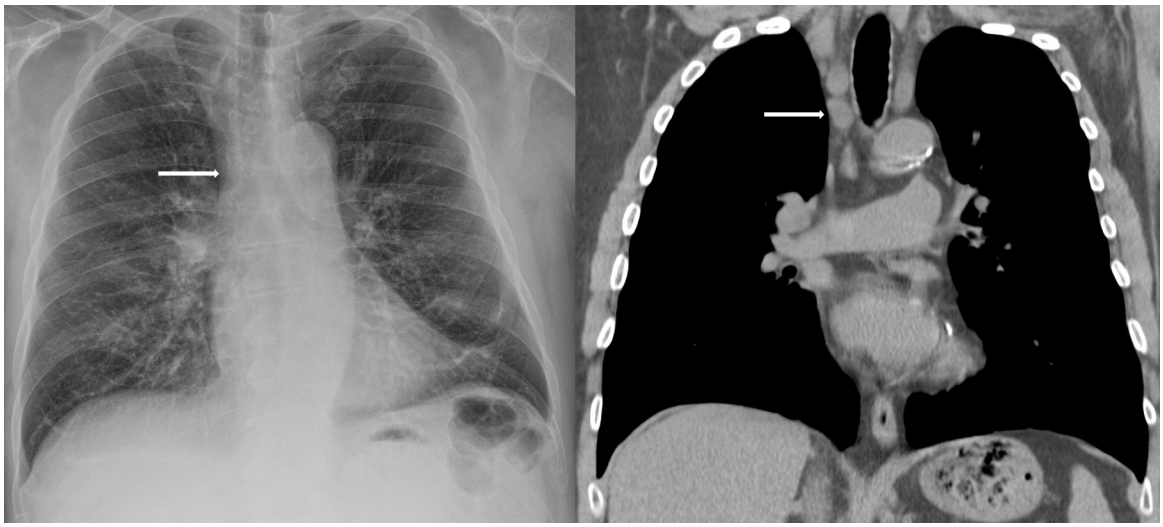


Figure 3 *Juxtaposition of the postero-anterior chest x-ray and a coronal CT image showing the correlation of hilar lymphadenopathy (yellow star) between the two modalities.*

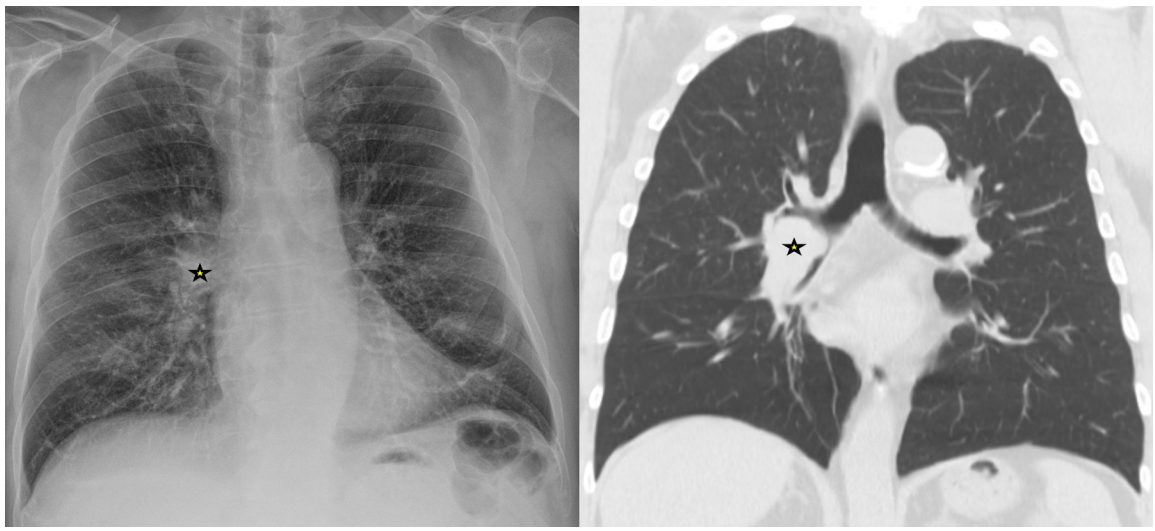


Figure 2 *Juxtaposition of the postero-anterior chest x-ray and a coronal CT image showing the correlation of right laterotracheal stripe thickening (white star) between the two modalities.*

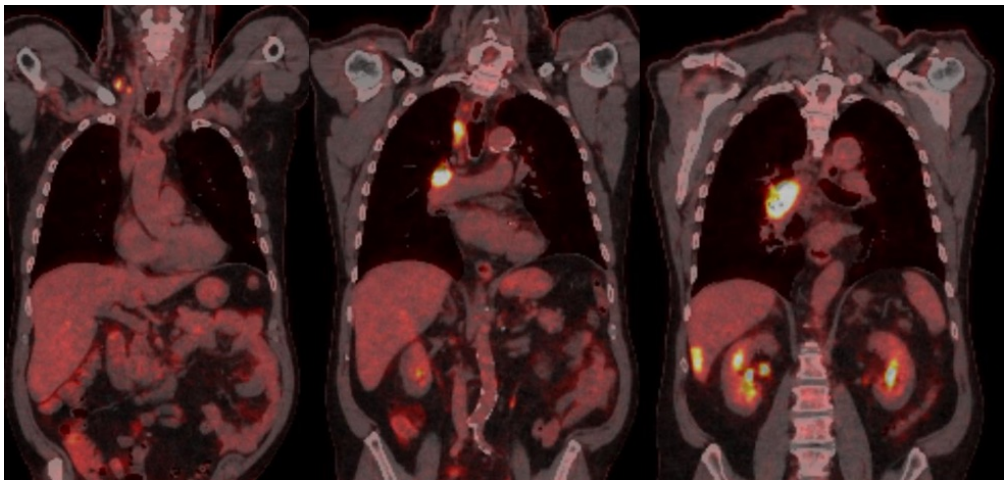


Figure 5 *Axial fusion image of CT and PET-CT showing zones of high activity both anterior and posterior to the right intermediate bronchus*

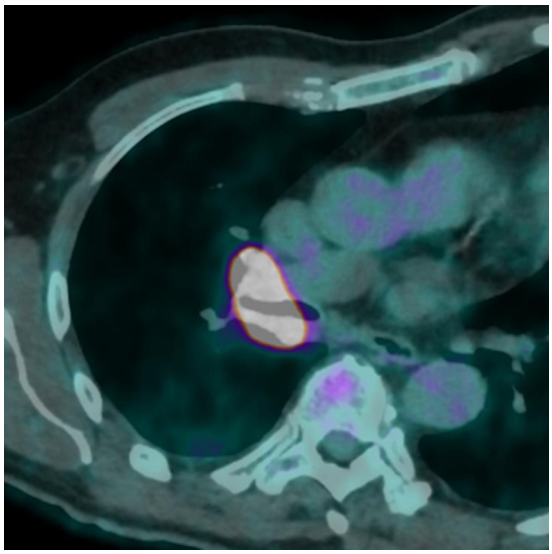


Figure 6 *Coronal PET-CT images demonstrating high activity of the supraclavicular lymphadenopathies, liver metastasis and mediastinal lymphadenopathies and lesions*

consolidation of an entire lobe or lung.[3] This tumour often metastasises, particularly to the liver, bone, central nervous system, adrenal glands or the same or contralateral lung.[3] When imaged using CT-exams, lung adenocarcinoma can present as ground-glass nodules or consolidations with a ground-glass halo.[3] If mediastinal lymph nodes are involved they may be seen on chest x-rays as mediastinal enlargement or hilar masses, as seen here.[3] Our patient had both a lung nodule overlaying the spine, the spine sign, and mediastinal enlargement. Furthermore, one can see the stenosis of the right intermediate bronchus due to it being encircled by enlarged hilar lymph nodes, causing extrinsic compression, accompanied by tumoral infiltration of the bronchial wall. Although extrinsic central airway obstruction was common, reported in 20-30% of lung cancer cases, modern lung cancers have shifted to favouring peripheral development.[5] A recent study of lung cancer patients showed that around 13% of their patients had signs of central airway obstruction on their baseline CT-exam.[5] The phenomenon of tumour-related airway obstruction is classed into extrinsic, intrinsic or mixed depending on the aetiology.[5] Of the patients that develop central airway obstruction a third will die of asphyxia, haemoptysis or post-op obstructive pneumonia.[5]

The treatment of airway stenosis can involve bronchoscopic treatments, for which the best candidates are lesions less than a centimetre, without extra-cartilaginous invasion.[2] For the 20-30% of patients with central airway obstruction, the bronchoscopic tools that can be used will depend on the mechanism of the stenosis.[2] For intraluminal lesions, mechanical debulking, as well as thermal techniques can be attempted amongst others.[2,6] For extrinsic compressions, airway stenting is used.[2] However, as interventional bronchoscopy is not without risk, it is only indicated in symptomatic cases with viable tissue downstream of the lesion.[2]

The treatment of bronchial stenosis is essential, even in a palliative setting, due to the fact that it may stave off imminent suffocation, as well as severe dyspnoea.[6] This is essential to improve the quality of life of the patients as well as possibly providing extra time for additional therapy to take effect.[6]

CONCLUSION

Lung adenocarcinomas are common and frequently fatal. Chest x-rays, often the first exam patients will undergo, can show signs of adenocarcinoma, allowing follow-up exams. This case demonstrates multiple x-ray signs, with their CT and PET-CT correlations.

REFERENCES

1. Bhimji SS, Wallen JM. Lung Adenocarcinoma. StatPearls StatPearls Publishing; 2022.
2. Guibert N, Mhanna L, Droneau S, Plat G, Didier A, Mazieres J, Hermant C. Techniques of endoscopic airway tumor treatment. Journal of Thoracic Disease AME Publishing Company; 2016; 8: 3343–60.
3. Panunzio A, Sartori P. Lung Cancer and Radiological Imaging. Current Radiopharmaceuticals Bentham Science Publishers; 2020; 13: 238.
4. Sciensano. Non-Communicable Diseases: Cancer, Health Status Report. 2023.
5. Guedes F, Branquinho M V., Sousa AC, Alvites RD, Bugalho A, Maurício AC. Central airway obstruction: is it time to move forward? BMC Pulmonary Medicine BioMed Central Ltd; 2022; 22: 1–16.
6. Saji H, Furukawa K, Tsutsui H, Tsuboi M, Ichinose S, Usuda J, Ohira T, Ikeda N. Outcomes of airway stenting for advanced lung cancer with central airway obstruction. Interactive CardioVascular and Thoracic Surgery Oxford Academic; 2010; 11: 425–8.

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CASE REPORT

Drug-Induced Hyperlipidaemia in a Paediatric Patient with B-Cell Acute Lymphoblastic Leukaemia

Sophie Hackenbruch, Jessica Coppini, Paula Gauci

Dyslipidaemias are rarely encountered in the paediatric age group and may be primary, secondary or multifactorial. Secondary causes include endocrinological and chronic inflammatory disorders, renal disease, liver disease, and medications. We report a case of hypertriglyceridaemia in a 3-year-old girl receiving chemotherapy for B-cell acute lymphoblastic leukaemia.

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Hypertryglyceridaemia is infrequently observed in children however is a rare and often asymptomatic side effect of PEG-asparaginase therapy.[1] Our patient developed hypertryglyceridaemia after the second dose of PEG-asparaginase which was given concomitantly with steroids. She presented with significant polyuria and polydipsia which resolved with treatment.

CASE REPORT

A 3 year 10-month-old girl presented in the first instance with a 1-month history of pyrexia and weight loss; on examination pallor and splenomegaly were found. Initial blood investigations showed a white cell count of 3.22 x10 ^{9}/L (normal range 4.86-13.18 x10 ^{9}/L) with a neutrophil count of 0.05 x10 ^{9}/L (normal range 1.60-8.29 x10 ^{9}/L) and a haemoglobin level of 4.2 g/dL (normal range 10.2-12.7 g/dL). The blood picture showed hypochromia with red cell

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anisocytosis. Morphology from a bone marrow aspirate reported infiltration with small to medium sized blasts with a high nuclear to cytoplasmic ratio. These blast cells were positive for CD19(++), CD10(+++), CD34(++) (on 64% of the blasts), CytCD79a(++), TdT(++), CD22(+++), CD24, CD38(++), CD81(+++), CD9(+++), CD13(+), C66c(+), CD58(+), CD123(+++), Lambda(+/-). Approximately 11% of the blast cell population expressed brighter CD81(+++), CD38(++), NG2(+) and weak CD15/CD65. These findings were consistent with a diagnosis of B-cell acute lymphoblastic leukaemia.

The patient was treated as per UK ALL 2019 regimen A protocol. Induction consisted of 28 days of dexamethasone (given per oral route) at a dose of 6mg/m^2/day tapered down over 7 days, 4 doses of vincristine (1.5mg/m^2) administered intravenously, 2 doses of PEG-asparaginase (1000 IU/m^2) given intramuscularly and intrathecal methotrexate at a dose of 12mg on day 1, 15 and 29. The child developed a hyponatremia of 127 mmol/L (normal range 136-145 mmol/L) associated with polydipsia and polyuria on day 24. No hyperglycaemia was documented, and her blood samples were noted to be grossly lipemic. Lipid indices showed a raised total cholesterol (29.29 mmol/L; normal range 2.0–5.0 mmol/L), triglycerides (19.48mmol/L; normal range 0.1-2.26 mmol/L) and LDL (2.87 mmol/L; normal range 0.1-3.88 mmol/L) with low HDL (0.10 mmol/L; normal range 1.15-1.68 mmol/L). Lipid indices were compared to a fasting lipid level taken off steroids and PEG asparaginase; total cholesterol (4.50 mmol/L), triglycerides (0.77mmol/L), LDL (2.88 mmol/L) and HDL (1.27 mmol/L).

The sudden development of hypertryglyceridaemia was likely a result of the concomitant administration of PEG asparaginase treatment and steroid therapy during induction treatment. Management involved increasing the patient's oral fluid intake, a change to a low fat and carbohydrate diet and introduction of fenofibrate at 67mg/20kg/day. Lipid indices showed a drastic improvement within two weeks of treatment with complete normalization within 1 month. Her polyuria and polydipsia resolved. Fenofibrate treatment was stopped upon normalization of lipid levels. During the first part of delayed intensification when she received her third dose of PEG-asparaginase concomitantly with dexamethasone, fenofibrate was added at the previous dose. Lipid levels were monitored closely during this period and the dyslipidemia did not recur after 3 weeks of treatment with fenofibrate. A follow up lipid profile taken when she was off steroids and PEG asparaginase was also within normal. No history of familial hypercholesterolemia was recorded. In view of this her dyslipidemia was attributed to PEG asparaginase therapy in combination with steroid therapy.

DISCUSSION

Although the combination of steroids and PEG asparaginase is known to rarely cause hypertryglyceridaemia, it has not shown to result in significant long-term complications.[2] A literature review revealed that although dietary care is only mildly effective in these children, it is still recommended.[3] A large study carried out by Bhojwani et al in 2018 compared 257 children with ALL who were given steroids and PEG-asparaginase in combination. Their lipid levels were checked at 4 specific points during their respective chemotherapy protocol. A total of 48 children developed hypertriglyceridaemia, 18 (7%) of which had triglyceride levels of >1000 mg/dL and were classified as severe. 17 of the 18 severely hyper triglyceridemic patients continued receiving PEG-asparaginase and steroids. Following the completion of chemotherapy, lipid levels normalised in all children. No statistically increased risk of pancreatitis or thrombosis was noted. Higher doses of steroids or PEG-asparaginase as well as older age were associated with a higher risk of developing hypertryglyceridaemia. The study highlights that fibrates may reduce the risk of hypertryglyceridaemia as well as improve symptoms. It has been proven to prevent pancreatitis in adults.[3] Our case report showed good clinical response to fenofibrate and similarly no pancreatitis occurred. Although hypertryglyceridaemia has been described in similar cases in the literature, little has been reported about the incidence and prognostic implications.[4]

In 2020 Kloos et al studied individualized therapeutic drug monitoring and adjustment of PEG-asparaginase to avoid PEG-asparaginase induced toxicities in children with ALL. The study noted no reduction in toxicity.[5]

Several studies have shown that a child with hypertryglyceridaemia induced by combined PEG-asparaginase and steroid therapy should be closely monitored for pancreatitis [1,6,7]. There is no consensus on the optimal management of hypertriglycerdiaemia in these cases. Tried treatment options have included short term fasting, low fat diet, plasmapheresis, omega-3 and oral fibrates.[6,8,9] Our case represents another successfully treated PEG-asparaginase induced hypertryglyceridaemia with an oral fibrate with no complications.

CONCLUSION

Hypertryglyceridaemia is a rare but known complication of PEG asparaginase treatment, especially when combined with steroids, however in most cases of childhood ALL the benefits of treatment outweigh any short- or long-term risks. There is little evidence on dietary modification or use of lipid lowering agents in such patients however a low-fat diet and fenofibrate therapy proved to be very effective in this case. As symptoms are very nonspecific, a low threshold for lipid investigations should be maintained in children on PEG-asparaginase and steroids. In view of the different treatment modalities that have been used to treat dyslipidaemia, a standardized management plan would aid paediatric oncologists in this potential life-threatening complication.

REFERENCES

1. Salvador C, Meister B, Crazzolara R, Kropshofer G. Management of hypertryglyceridaemia in children with acute lymphoblastic leukemia under persistent therapy with glucocorticoids and L-asparaginase during induction chemotherapy. Pediatr. Blood Cancer 2012;59:771.
2. Steinherz PG. Transient, Severe Hyperlipidemia in Patients with Acute Lymphoblastic Leukemia Treated with Prednisone and Asparaginase. Cancer 1994;12:3234-9.
3. Bhojwani D, Darbandi R, Pei D, et al/em>. Severe Hypertryglyceridaemia During Therapy For Childhood Acute Lymphoblastic Leukemia. Eur. J. Cancer, 2018;15:2685-94
4. Parsons SK, Skapek SX, Neufeld EJ et al Asparaginase-Associated Lipid Abnormalities in Children With Acute Lymphoblastic Leukemia. Blood 1997;6:1886-95.
5. Kloos RQH, Pieters R, Jumelet FMV, De Groot-Kruseman HA, Van Den Bos C, Van Der Sluis IM. Individualized Asparaginase Dosing in Childhood Acute Lymphoblastic Leukemia. J. Clin. Oncol.202;38:715–24.
6. Hijiya N, Van Der Sluis IM. Asparaginase-Associated toxicity in children with acute lymphoblastic leukemia. Leuk. Lymphoma 2016;57:748–57.
7. Tong WH, Pieters R, De Groot-Kruseman HA et al The toxicity of very prolonged courses of PEGasparaginase or Erwinia asparaginase in relation to asparaginase activity, with a special focus on dyslipidemia. Haematologica 2014;99:1716–21.
8. Berrueco R, Rives S, López-García VS, Catalá A, Toll T, Estella J. Very high hypertryglyceridaemia induced: is plasmapheresis needed? Pediatr. Blood Cancer 2011;57: 532.
9. Ridola V, Buonuomo PS, Maurizi P et al Severe acute hypertryglyceridaemia during acute lymphoblastic leukemia induction successfully treated with plasmapheresis. Pediatr. Blood Cancer 2008;50:378–80.