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JIM Journal of Interdisciplinary Medicine

Aims and scope

The Journal of Interdisciplinary Medicine aims to publish top quality papers related to any fields of medicine that present an interdisciplinary dimension.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common situations encountered in the clinical or research practice. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different pathologies from the perspective of various clinical fields.

The Journal of Interdisciplinary Medicine will publish high-quality basic and clinical research related to interdisciplinary medical fields, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to the discovery of new mechanisms involved in the development and progression of a large spectrum of diseases.

The journal will try to provide the entire medical community with the perspective of the regional specifics of Central and Eastern European countries. The journal will primarily focus on publishing original research papers, but also other types of materials (such as review articles, case reports, state-of-the-art papers, comments to editor, etc) will be extremely welcomed.

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EDITORIAL

Cardiovascular Healthcare in 2020 – Alarming Realities in Romania

Roxana Hodas

"George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

CORRESPONDENCE

Roxana Hodas
Str. Gheorghe Marinescu nr. 50
540136 Târgu Mureș, Romania
Tel: +40 372 653 100
E-mail: roxana.hodas@yahoo.ro

The unprecedented progress recorded over the last decades in the field of prevention and management of cardiovascular disease (CVD) has led to a significant reduction of premature cardiovascular (CV) mortality across Europe.[1] Despite this progress, a new reality is emerging and generates serious concerns for public health policies. The burden of CVD presents alarming inequalities among different European regions, remaining disproportionately larger in low- and middle-income countries (LMICs) compared to high-income countries (HICs). Moreover, economic constraints at local level involve substantial disparities in availability of CV care and services, with dramatic effects on the healthcare benefits of CV patients in LMICs.[2]

The recently published map of "ESC Cardiovascular Realities 2019", a map of ESC member countries based on monitoring CV health expenditure, infrastructure, and workforce across European countries, raised alarming signs for healthcare systems regarding the social and economic burden of CVD in different regions of Europe.[3]

From this point of view, Romania presents a concerning reality in all points of interest highlighted by the ESC's call to action: insufficient control of risk factors and harmful behaviors, increased burden of CVD, and disparities in availability of CV care.

Extensively investigated, the important influence of potentially reversible well-established risk factors in the determination and progression of CVD provides a strong rationale for giving a higher priority to risk reduction strategies. In HICs, the ongoing modern-day epidemics of obesity and type 2 diabetes, particularly in younger adults, represent the most serious public health challenges which threaten to erode the health gains of recent years.[4]

In this European context, Romania seems to present inadequate strategies. Besides the negligible decrease in hypertension prevalence, poor strategies for the identification and effective treatment of people with established hypertension contribute to the continuing high rates of myocardial infarction and CV death. Moreover, the daily intake of large quantities of alcohol, insufficient self-reported physical activity, and altered nutritional intake proved to be important

contributors to the national burden of CV disease encountered in this country.

Even if longitudinal data show a steady decline of CVD mortality across European regions, mortality burden continues to show large geographical inequalities. In Romania, CVD accounts for more than 50% of all recorded deaths compared with below 30% in countries from Western Europe. In terms of CVD morbidity statistics, inequalities in CVD burden are even greater among different European countries, in correlation with national economic status. A negative association between total health expenditure per capita and age-standardized CVD burden has been identified, Romania reporting a greater than two-fold difference of disability-adjusted life years (DALYs) lost to CVD, with an average of about 9,000 DALYs per 100,000 people compared with 3,500 in HIC.[5] This fact emphasizes that limited economic resources and health expenditure derive into inequitable health outcomes.

The ESC map of CVD care delivery across European countries highlights the gaps and inequalities in the availability of appropriate CV care as a consequence of the large differences in healthcare expenditure. According to recent ESC data, the Romanian healthcare system aligns with the group of countries defined by the World Health Organization as "lagging behind in infrastructure, human resource, and therapeutic procedures, mainly those with a low gross national product, typically the ESC member countries of Eastern Europe and Northern Africa".[6]

In terms of human resources, Romania reported 63.0 cardiologists per million people, an appalling number compared with other ESC countries such as Greece or the Republic of Georgia reporting >250 cardiologists per million people. This worrying situation remains the same for interventional cardiology statistics. The number of interventional cardiologists reported by Romania is 4.37 per million people, only ahead of countries such as Kyrgyzstan, Azerbaijan, or Kazakhstan, while the average number reported across ESC countries is 11.8 per million people, with an outstanding value of 30.96 per million in HICs such as Austria. The same sad reality was recorded for the density of interventional centers: 0.7 per million people in Romania compared with 6.6 per million people in Germany. The situation is even worse in the field of interventional electrophysiology, since Romania, alongside Azerbaijan and Bosnia and Herzegovina, reported less than 1 electrophysiologist per million people, while other countries, such as Poland and Sweden, have an average number of 17 electrophysiologists per million people.[3,7] The situation is identical regarding the number of centers of interventional electrophysiology, ablation procedures, and device implantations.[8]

As at this moment we face a more than 10-fold variation in healthcare expenditures compared to Western European countries, lagging behind in human and capital healthcare resources is readily apparent in the number of performed procedures.[9] With a mean number of 4,122 coronary angiograms performed across ESC member countries, Romania reported only 1,306 procedures, much behind other countries such as Germany which reported 9,392 procedures. In terms of percutaneous coronary interventions (PCIs), only 753 procedures per million people were reported in Romania, while the average number of PCIs in Europe was estimated at 2,211 per million, and Germany reported 3,975 procedures per million people. The same disparities are recorded for structural heart interventions, Romania alongside Egypt and Turkey being placed at the bottom of the list with 25 procedures per million people, while more than 150 procedures per million are performed annually in Switzerland and Germany. Even worse, Romania is on the last place in Europe in terms of both mitral valve percutaneous interventions with 0.2 procedures per million people and transcatheter aortic valve implantations with only 2.3 procedures per million people.[2]

These numbers provide a stark image of the gap in human resources needed for the effective management of diagnostic and therapeutic CV procedures in Romania. Undoubtedly, much needs to be done in order to bridge the gaps in CVD healthcare delivery and to raise the quality of care in all European countries. Besides raising measures to control the well-established risk factors and harmful behavior, it is of vital importance to raise awareness, highlight inequality, advice decision-makers, and sustain investments for proper implementation of guidelines across all regions of Europe.

CONFLICT OF INTEREST

Nothing to declare.

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REVIEW

ALTERNATIVE MEDICINE // PUBLIC HEALTH

Disease Burden, Mechanism and Management of Obesity – Where Do We Stand?

Irfan Sharif Shakoori[1], Gohar Ashraf[2], Fauzia Aslam[3], Hammad Akram[4]

[1] Family Medicine Consultant, Cort Piil Helsesenter, Bergen, Norway
[2] University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[3] Baqai Medical University, Karachi, Pakistan
[4] Independent researcher, Waco, TX, USA

CORRESPONDENCE

Hammad Akram
Independent work, 1201 S. Trl.
Waco, TX, USA
Tel: +92 335 420 0717
E-mail: hammadakram77@yahoo.com

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Irfan Sharif Shakoori • Cort Piil-smauet 7, 5005 Bergen, Norway. Tel: +47 55 23 60 10, E-mail: dr.sharif2108@gmail.com

Gohar Ashraf • 200 Meyran Ave # 318, Pittsburgh, PA 15213, USA. Tel: +1 412 647 8586, E-mail: goharashraf@gmail.com

Fauzia Aslam • Baqai Medical University, Karachi, Pakistan. E-mail: fauzia_aslam@yahoo.com

ABSTRACT

The role of increased body mass index in general morbidity and mortality is well documented. This global public health issue continues to represent a major burden and threat to health systems and the population's wellbeing. Global statistics show that the prevalence of obesity has increased about three times since the mid-1970s, and an upward trend is still observed, not only in developed but also in developing countries. We used several databases, including PubMed, ProQuest, and Google Scholar, to perform a literature search and review on obesity. Keywords such as "obesity", "overweight", and "BMI" were used in combination with multiple keywords such as "mechanism", "factors", "socio-economic", "environmental", "social determinants", "management", "treatment", "non-traditional treatment", "alternative therapies", "non-pharmaceutical treatment" etc. and related phrases. According to the literature, the management of obesity is difficult due to the complex nature of this problem in terms of its course, complications, risks, and etiological factors. The role of alternative therapies in obesity management is still unclear, and further research is needed in this area. Recently introduced weight-loss and -management devices can also help in losing excess bodyweight. The present article summarizes relevant information related to obesity, collected from different regions of the world, and discusses diverse interventional approaches to treat obesity.

Keywords: obesity, overweight, BMI, behavioral factors

INTRODUCTION

The impact of increased body weight on health outcomes and the associated morbidity and mortality are well documented.[1] Obesity (OB) is a complex community health problem connected to several physical and non-physical factors.[2] The body mass index (BMI) is a parameter that is widely used to classify overweight (OW) and OB categories by taking weight and height into account.[3] Historical trends and patterns demonstrate increasing OW and OB rates, especially in developed countries.[3] It is also evident that developing countries are also

affected by this public health issue and have been experiencing an upward trend of increased body weight and related health conditions in recent decades.[3] Another critical health issue of concern is childhood and adolescent OW and OB, with long-term psychological and physical consequences.[2,3] Many children with OB grow up to become obese adults and continue to suffer from the detrimental effects of OB.[3] In the present paper, we explore geographically unique characteristics of OW and OB while sharing relevant data and challenges of this major public health issue. Furthermore, while presenting medical and surgical remedies of OB, we examine non-pharmaceutical and alternative approaches that can help in the management of this morbid condition. The present article summarizes relevant information from different regions of the world and discusses diverse interventional approaches to treat obesity, useful for both professionals and society.

MATERIALS AND METHODS

A careful examination of existing data published in selected regions of the world was carried out. We used several databases, including PubMed, ProQuest, and Google Scholar, to perform a literature search and review. Keywords such as "obesity", "overweight", and "BMI" were used in combination with multiple keywords such as "mechanism", "factors", "socio-economic", "environmental", "social determinants", "management", "treatment", "non-traditional treatment", "alternative therapies", "non-pharmaceutical treatment" etc. and related phrases. Abstracts were reviewed to assess the appropriateness of articles for the topic of our literature review. We preferred articles published in the past 15 years; however, older articles were also considered if insufficient research was available on a given subtopic. For certain parts of the paper, we discussed characteristics of issues from selected geographical regions considering that the authors had current, recent, or past affiliations and experiences within these areas.

MECHANISM, PREDISPOSING FACTORS, AND MAGNITUDE OF THE PROBLEM

According to global statistics, the prevalence of OB has increased almost three times since the mid-70s.[3] According to the World Health Organization (WHO), in 2016, around 52% of adults and 18% of children aged 5–19 years were overweight and obese.[3] The associated mortality was higher than the one of individuals who died because of problems associated with lower than normal body weight (underweight).[3] Compared to the global prevalence of 13% in 2016, 39.8% of adults were suffering from OB in the US in 2015–2016.[4] In the last decades, the prevalence of OB presented increasing trends in all regions of the world, Europe, America, and Eastern Mediterranean regions showing the highest prevalence and exhibiting an upward trend between 2000 and 2016 (Figure 1).[5]

The mechanisms and underlying phenomena behind OW and OB have been explored before.[1–4] There is, however, variation in causes found in different cultures and regions of the world. For example, in the US, Hispanic and African-American individuals have the highest prevalence

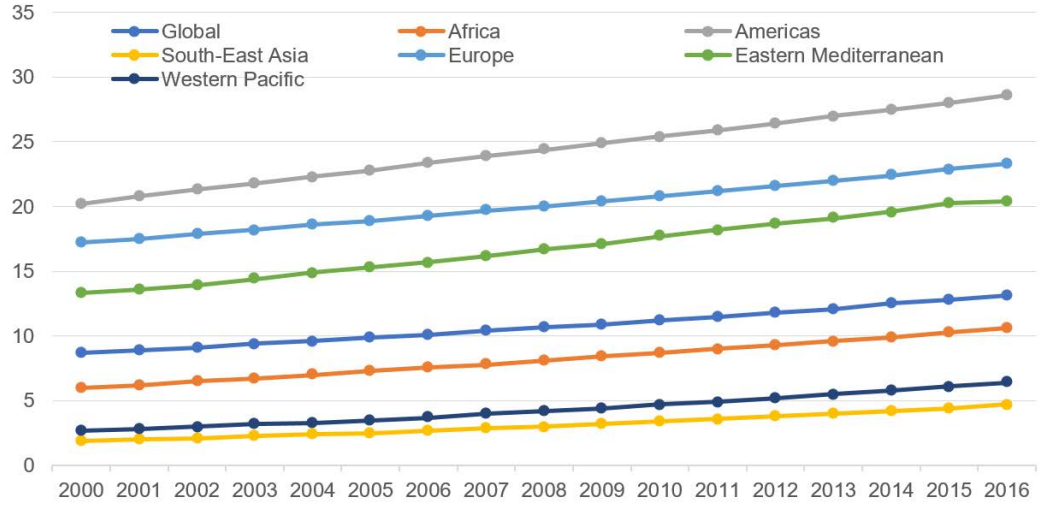

FIGURE 1. Prevalence of obesity among adults, BMI ≥ 30, age-standardized. Estimates by WHO region (2000-2016). Source: WHO, Global Health Observatory data repository[5]

of OB.[4] Furthermore, the prevalence of OB is lower among individuals with higher educational and/or socioeconomic status.[4] Among men, however, the lowest income groups are also less likely to have OB.[4]

Studies show that the prevalence of OW and OB has also increased among children and adults living in the Middle East.[6,7] In the Persian Gulf region, this increase can be attributed to major changes in the population's lifestyle over the past few decades.[6–8] In Qatar for example, the prevalence of OB has increased due to the recent industrialization and socioeconomic progress along with cultural factors, transition to a sedentary lifestyle, popularity or acceptance of fast food as a norm, and environmental factors such as extremely hot weather most of the year.[7] In a 2012 survey, over 70% of Qatari nationals were found to be overweight and obese, with 41% having a BMI in the obese category.[7] The survey also showed that around 91% of adults were not consuming enough fruits and vegetables, and 71% were not fulfilling recommended vigorous activity requirements as well.[7] Furthermore, related health problems such as high blood pressure (~33%), high blood glucose or diabetes (16.7%), and hypercholesterolemia (~22%) were also alarming.[7] Further analysis of this data showed that nutritional factors were impacting OB rates among young adults versus physical activity among older adults. Also, generalized and abdominal types of OB were significantly associated with diabetes among Qatari citizens.[7,9] OW/OB is linked to the consumption of energy-rich food items, and the Qatari population is consuming higher-than-recommended amounts of energy-dense food items.[3,10,11] OW/OB prevalence is also documented to be high among children and adolescents in Qatar.[12–14]

Population dynamics, especially immigration, can impact the health of migrant populations by adopting behaviors and experiencing opportunities that were not common in their country of origin. Recent immigrants to communities with high prevalence of OB can lead to the so-called healthy migrant effect. However, after residing in new countries for a longer duration of time, immigrants also tend to experience unhealthy weight gain.[15] In Norway, OW/OB has been an emerging issue among immigrant populations. A study carried out in 2010 with a sample comprising of 208 Somali immigrants showed that both generalized and abdominal OB had a direct positive association with the length of residence in Norway. By gender, the prevalence of OB was higher among Somali (immigrant) female respondents vs. males, similarly to the Qatari population.[7,16]

The challenges in OB prevention and reversal can be related to multiple factors. A 2013 article reveals that the study participants were not able to follow healthy diet plans due to stress, depression, cravings, and social situations where they could not avoid certain foods.[17] Respondents felt challenged by the cost, time, and motivation associated with maintaining healthy dietary habits.[17] Adherence to physical activity was found to be difficult due to various reasons such as lack of time and motivation, or not having a partner to perform exercise with.[17] Cultural norms and environmental factors can also impact the adherence to health programs; for example, a study from the Arab Gulf region showed that the main issues in sustaining healthy eating were due to unwillingness, family norms, and social gathering, where it was difficult to avoid certain food items.[18] Moreover, lack of time, underlying health conditions, and extreme weather were found to represent the main challenges in performing regular exercise.[18] Other factors include easy access to low-cost high-calorie food items such as fast food, limited access to healthier food items, increased screen time especially among youth, sedentary work environment, lack of information, skills, and interest in certain exercise/sports, not having support (family- or costs-related) to be physically active etc.[19–21]

MANAGEMENT

OW and OB can be prevented or reduced by changing lifestyle, e.g. performing physical activities and modifying the diet by including more fruits, vegetables, or other aliments with high fiber content, and by avoiding high energy foods such as sugar and fats etc.[3] Dietary modification and caloric monitoring may help in maintaining a healthy body weight. Incorporating fruits, vegetables, and whole grains in the di*et al*ong with physical activity can help in weight loss if practiced as a routine behavior. The impact of weight-loss diets, especially if followed for a shorter duration of time, is variable. Exercise can certainly help in weight loss and maintenance of a healthy weight if practiced continuously, and can play an important role in the improvement of both physical and mental wellbeing.[3,7,22] The aim is to reduce energy intake and increase energy expenditure. In certain situations, OW and OB can be managed by using pharmaceutical agents. These medicines are usually recommended if physical activity and/or dietary measures are not efficient, and the BMI is higher than 30 or 27 with underlying medical conditions.[23,24] Table 1 lists the types of approaches used in the management of OB based on our literature review.[22–28]

The role of alternative and herbal therapies in the reduction or prevention of OB requires further scientific exploration. Triphala, which is a combination of three plant

TABLE 1. Different types of management approaches for obesity

Non-pharmaceutical	Pharmaceutical (mechanism)	Surgical
Physical activity	Orlistat (inhibits gastric lipases)	Sleeve gastrectomy
Diet	Sibutramine (satiety, metabolic)	Laparoscopic adjustable gastric banding (LAGB)
Transcranial direct current stimulation	Diethylpropion (appetite suppressant)	Roux-en-Y gastric bypass (RYGB)
Cognitive behavioral interventions	Phentermine (appetite suppressant)	Single anastomosis gastric bypass (SAGB)
	Liraglutide (satiety, (GLP-1 receptor agonist)	Biliopancreatic diversion/duodenal switch (BPD/DS)
	Lorcaserin (satiety)	

species (Indian gooseberry, *Terminalia bellirica*, and *Terminalia chebula*), has shown some evidence in reducing body fat.[29,30] In addition to decreasing body fat percentage, body weight, and energy intake in mice, it also helped lower blood cholesterol and sugar levels.[29,30] In a 12-week randomized double-blinded placebo-controlled trial with 62 participants, the treatment group experienced a significant decline in mean weight and waist circumference.[31]

Nigella sativa (black cumin) was found to have mixed effects on OB and metabolic syndrome. Findings from 11 studies showed that *Nigella sativa* had some positive role in reducing body weight, BMI, and waist circumference.[32] Furthermore, clinical trials have shown that it also helped in reducing blood sugar, lipids, and body weight among study participants; however, more research is needed to understand this relationship.[33] *Garcinia cambogia* inhibits the citrate lyase enzyme and can help in reducing appetite.[34] *Camellia sinensis* may have some role in appetite suppression, enhanced energy use, and decrease absorption of nutrients.[34] Chromium picolinate is a quite common supplement known to help in glucose metabolism and food behavior, leading to possible weight loss; however, its long-term impacts on OB prevention and remission are unclear.[34,35]

Allison *et al*. reviewed the impact of 18 different alternative or non-traditional therapies on body weight and found that there is not enough evidence that these treatments are effective.[35] There is some reasonable evidence from well-designed studies suggesting that compounds containing ephedrine and caffeine may have some benefits.[35] Caffeine has been found to be beneficial in weight maintenance and appetite suppression in another study.[36] The role of alternative therapies in OB management is still unclear and further research is needed in this area.

Recently introduced weight-loss and weight-management devices can be used for patients in whom lifestyle modification approaches are not working.[37] Some examples of these devices are: gastric bands, gastric emptying system, and gastric balloons. Preliminary data show that there is reasonable benefit seen among patients who have used these devices.[37] Body countering through noninvasive methods, such as high intensity focused ultrasound, low-level laser therapy, cryolipolysis, or radiofrequency, and invasive approaches, such as liposuction, could also be beneficial but costly alternatives.[34]

SUMMARY AND CONCLUSIONS

Increased body weight and waist circumference are associated with several diseases and health conditions. OB has become a significant public health concern that can lead to diverse types of chronic diseases. High morbidity and mortality associated with body weight-related health issues exert tremendous economic burden on health systems and communities. The complex nature of this issue can be managed only by applying multi-dimensional well-researched strategies as provision of complex care needs can be challenging, especially in the presence of additional co-morbidities.[38] Programs targeted at youth can certainly help as the behavioral modification is easier if started earlier; hence, school-based programs can play an essential role in the long-term management of this issue. Incorporating recommended levels of physical activity and opting for healthier food choices in the daily routine can help reduce the incidence of chronic diseases such as heart disease, stroke, diabetes, and some cancers through reducing body weight.[7,39–41] Since OB is associated with other chronic health problems, it may also aggravate the prognosis of patients who are suffering from the novel COVID-19 infection. The mechanism of this is not yet clear, as the COVID-19 infection is relatively new and has not been sufficiently studied yet; however, OB can exert increased burden on breathing mechanics and could have a negative impact on disease course.[42,43]

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

CARDIOLOGY // SURGERY

Effects of Pirfenidone on Echocardiographic Parameters of Left Ventricular Structure and Function in Patients with Idiopathic Pulmonary Fibrosis

Shehab Al-Ansari[1], Allen Borowski[2], Ali Fuad[3], Omar Alawadhi[4], Haris Riaz[2], Vikram Sharma[1], Nauman Khan[1], Brian D. Southern[5], W.H. Wilson Tang[2]

[1] Department of Hospital Medicine, Medicine Institute, Cleveland Clinic, Cleveland, OH, USA
[2] Department of Cardiovascular Medicine, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA
[3] Royal College of Surgeons in Ireland, Dublin, Ireland
[4] Department of Surgery, Tawam Hospital, Abu Dhabi, United Arab Emirates
[5] Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA

CORRESPONDENCE

Shehab Al-Ansari
Department of Hospital Medicine
M75. 9500 Euclid Avenue
Cleveland, OH 44195, USA
Tel: +1 216 218 5795
E-mail: alansas@ccf.org

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Allen Borowski • Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA. Tel: +1 216 444 2200

Ali Fuad • 123 St Stephens Green, Dublin, Ireland. Tel: +353 1 402 2100

Omar Alawadhi • Tawam Hospital, Abu Dhabi, United Arab Emirates. Tel: +971 3 767 7444

Haris Riaz • Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel: +1 216 444 2200

Vikram Sharma • Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel: +1 216 444 2200

Nauman Khan • Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel: +1 216 444 2200

Brian D. Southern • Cleveland Clinic, 9500 Euclid Avenue OH 44195, USA. Tel: +1 216 444 2200

W.H. Wilson Tang • Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel: +1 216 444 2200

ABSTRACT

Aim: Pirfenidone is a novel anti-fibrotic agent utilized in the treatment of idiopathic pulmonary fibrosis (IPF). It has been implicated in mitigating myocardial fibrosis and left ventricular (LV) systolic and diastolic dysfunction in animal models. However, its impact on LV mechanics in humans remains unknown. The aim of this study was to retrospectively evaluate the effects of pirfenidone on echocardiographic parameters of LV function and structure in patients with IPF. **Methods:** A total of 124 patients with IPF were included in this study: 64 patients treated with pirfenidone (treatment group) and 60 patients not taking pirfenidone (control group), who had serial pretreatment/baseline and posttreatment/follow-up echocardiograms done within a time frame of four years. Changes in the means of parameters of LV function (systolic, diastolic, and global longitudinal strain) and LV structure (mass and indexed volume indices) were compared between the treatment and control groups. This was followed by a subgroup analysis that included only 88 patients (47 treated, 41 controls) with echocardiographic evidence of myocardial dysfunction at baseline (defined as an ejection fraction of ≤45, or diastolic dysfunction stage 1 or more) in addition to a known clinical diagnosis of congestive heart failure. To account for potential confounders, a secondary adjusted analysis by way of 1:1 propensity score matching (PSM) was carried out. This yielded a sample consisting of 62 patients with 56 patients in the subgroup cohort. **Results:** Patients in the treatment group were significantly younger (69.4 vs. 77 years, $p<0.001$) and had relatively lower forced vital capacity (69.9% vs. 80.6%, $p = 0.005$) in comparison to the control group. However, after PSM, the age demographics were comparable between both groups (72.18 vs. 72.15, $p = 0.9$). In the primary unadjusted analysis, there was no statistically significant change in any of the mean parameters of LV function and structure after pirfenidone administration when compared to the control group. Furthermore, no significant differences were noted in the subgroup cohort. Such findings were re-demonstrated after a secondary analysis with PSM. **Conclusion:** From an echocardiographic perspective, pirfenidone had no significant effects on LV structure and function in patients with IPF, even in patients with more overt cardiac dysfunction.

Keywords: pirfenidone, idiopathic pulmonary fibrosis, heart failure, myocardial dysfunction

INTRODUCTION

Pirfenidone, a novel anti-fibrotic agent, has been shown to reduce the rate of pulmonary function decline and improve disease-free progression in patients with idiopathic pulmonary fibrosis (IPF).[1] Although its precise mechanism of action remains to be deciphered, pirfenidone inhibits transforming growth factor-beta (TGF-β)-mediated fibroblast activation and collagen synthesis,[2] one of the key pathways in the pathogenesis of myocardial fibrosis.[3] Myocardial fibrosis is known to occur in both subtypes of heart failure, being more pronounced in heart failure with reduced (HFrEF) rather than preserved ejection fraction (HFpEF).[4] However, in patients with HFpEF, the degree of myocardial fibrosis is significantly correlated to the severity of diastolic dysfunction.[4]

In pre-clinical studies, pirfenidone was found to mitigate myocardial fibrosis and attenuate left ventricular (LV) remodeling and diastolic and systolic dysfunction in animal models,[5–9] suggesting the possibility of a mechanistic overlap between cardiac and pulmonary fibrosis. This may prove beneficial in the treatment of congestive heart failure (CHF), and in particular HFpEF, where disease-specific therapy is lacking and thus carries a poor prognosis.[10]

To date, the effects of pirfenidone on LV mechanics in humans remains unknown. We therefore sought to investigate this further by retrospectively examining the effects of pirfenidone on echocardiographic parameters of LV structure and function in patients with IPF. This was followed by a subgroup analysis to only include patients with more overt cardiac dysfunction. We hypothesize that patients taking pirfenidone will have more favorable changes in markers of LV function and structure compared to the control group.

Such a hypothesis-generating study from an already existing patient cohort could elucidate the implications of pirfenidone on human myocardial mechanics and potentially lead to newer indications.

MATERIALS AND METHODS

Patient selection

In this single-center retrospective study, 900 consecutive patients with an International Classification of Diseases (ICD)-10 diagnosis code of IPF were initially identified between June 1, 2014 and June 1, 2018. Electronic medical records were then reviewed for clinical and echocardiographic data. Patients were included if they had a confirmed radiological or histological diagnosis of IPF in addition to serial baseline and follow-up echocardiograms, both done after the diagnosis was established. In patients who were on pirfenidone (treatment group) we defined baseline/pretreatment echocardiograms as those done within two years before treatment and follow-up/posttreatment echocardiograms as those done within two years after treatment. Only patients taking pirfenidone continuously throughout the defined time interval were included. The control group consisted of patients with IPF not taking pirfenidone or any other pulmonary disease modifying medications and who had two serial echocardiograms done within four years of each other. Patients with mitral stenosis or mitral valve surgery, severe mitral regurgitation, severe aortic stenosis or regurgitation, and atrial fibrillation at the time of echocardiographic analysis were excluded. Of note, patients who had a history of atrial fibrillation were only included if they were in normal sinus rhythm during echocardiographic analysis, to allow for detailed diastolic assessment.

Sequentially, a total of 124 patients with IPF were included in the primary analysis, 64 treated with pirfenidone and 60 controls not on pirfenidone. This was followed by a subgroup analysis that included only 88 patients (47 treated, 41 controls) with echocardiographic evidence of myocardial dysfunction at baseline (defined as either EF of ≤45% or grade 1 or more diastolic dysfunction) in addition to a known clinical diagnosis of CHF. In this study, the clinical diagnosis of CHF was established if a patient fulfilled the well-validated Framingham criteria.[11] Clinical data pertaining to the diagnosis was obtained from electronic medical records of patient encounters with internists or cardiologists within our institution.

Institutional Review Board approval was granted for retrospective collection of data and informed consent was waived. This study complied with the Declaration of Helsinki.

Statistical considerations

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS v26 for Windows, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation if normally distributed, and as mean (median, interquartile range) if non-normally distributed, as determined by the Shapiro-Wilk W test. Independent t test score and Mann-Whitney U test were utilized to assess for any statistical significance for normal and non-normally distributed variables, respectively. Categorical variables were expressed as a percentage, and the Chi-squared test was used to ascer-

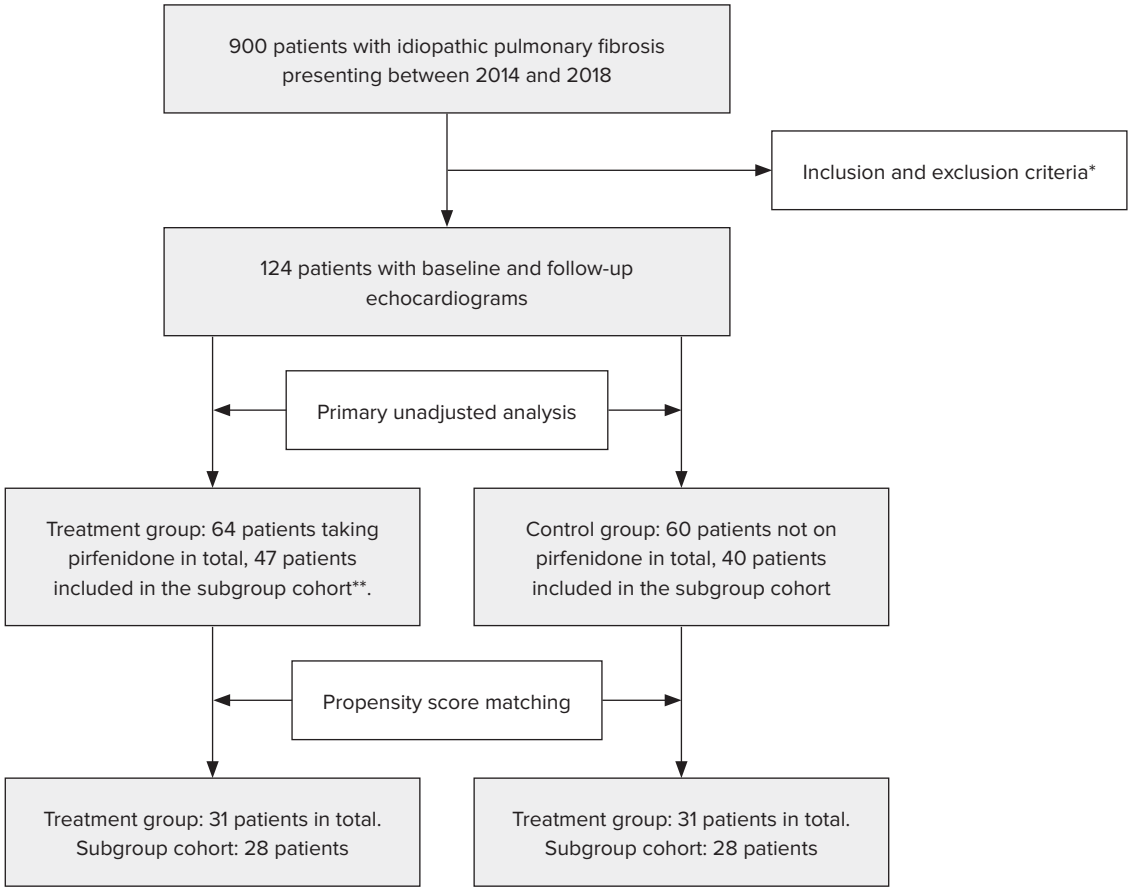

FIGURE 1. Patient selection process and statistical methodology

tain any statistical significance. A two-tailed p value of less than 0.05 was considered significant. In the primary unadjusted analysis, changes in the means of echocardiographic parameters of LV structure and function were compared between the treatment and control groups. This was followed by a subgroup analysis to only include patients with more overt echocardiographic evidence of myocardial dysfunction at baseline in addition to an established clinical diagnosis of heart failure.

To account for confounding variables that can potentially impact changes in parameters of LV function and structure, an adjusted secondary analysis was carried out by way of 1:1 propensity score matching (PSM). To estimate the propensity score, a set of variables (including

TABLE 1. Baseline demographic and clinical characteristics

	Treatment group (n = 64)	Control group (n = 60)	p value
Age (years)	69.4 ± 7	77 ± 8.8	<0.001
Male % (n)	71.9 (46)**	65 (39)	0.4
Body surface area (m^2)	2 ± 0.2	1.9 ± 0.3	0.1
Body mass index (kg/m^2)	30.1 ± 4.8	28.2 ± 6	0.1
Systolic blood pressure (mmHg)	122.6 ± 14.9	127.9 ± 16.5	0.2
Diastolic blood pressure (mmHg)	73 ± 7.3	76 ± 6.2	0.2
Cardiac risk factors and co-morbidities % (n)			
Hypertension	68.7 (44)	56.6 (34)	0.2
Diabetes	21.9 (14)	15 (9)	0.5
Hyperlipidemia	67.2 (43)	51.2 (31)	0.08
Chronic kidney disease	31.3 (20)	45 (27)	0.07
Atrial fibrillation	17.2 (11)	30 (18)	0.09
Coronary artery disease	42.2 (27)	41.7 (25)	0.6
Cardiac medications % (n)			
Beta-blockers	43.8 (26)	35 (21)	0.6
Diuretics	34.3 (22)	33.3 (20)	0.9
Renin-angiotensin-aldosterone inhibitors	39.1 (25)	35 (21)	0.5
Pulmonary function testing			
Baseline predicted forced vital capacity (%)	69.9 ± 18.2	80.6 ± 42.8	0.005
Laboratory testing			
Serum creatinine (mg/dL)	1.1 ± 0.4	1.2 ± 0.7	0.2
Time interval between baseline and follow-up echocardiogram (years)	1.7 ± 1.3	1.5 ± 1.1	0.2

n, number of patients; **numbers within the brackets represent absolute figures

age, gender, body mass index, history of coronary artery disease, chronic kidney disease, diabetes, hypertension, atrial fibrillation, use of beta blockers, and use of renin-angiotensin-aldosterone inhibitors) that could potentially impact the degree of myocardial fibrosis and thus LV function and structure were selected. Such variables were then included in a multi-variable logistic regression model which produced a propensity score for each of the 124 patients included in the primary analysis. Taking the estimated propensity score of each patient, a 1:1 match analysis without replacement was carried out using the nearest-neighbor matching technique, with a match tolerance of 0.2 of the pooled standard deviation of the logit of the propensity score, as previously described in the literature.[12] This yielded a sample consisting of 62 patients with IPF in total (31 treated, 31 controls), all of which were included in the secondary adjusted analysis. Finally, the process was repeated once more to only include the matched subgroup cohort, which resulted in 56 patients with relatively more severe cardiac dysfunction (28 treated, 28 controls). The C-statistic of the propensity score models was approximately 0.8, which is considered an adequate model fit.[12]

Figure 1 summarizes the patient selection process according to the aforementioned inclusion criteria, exclusion criteria, and statistical methodology.

Echocardiographic analysis

Comprehensive echocardiographic data extracted from a total of 248 echocardiograms (two echocardiograms per patient) were reviewed for parameters of LV structure, systolic function and diastolic function. Missing data, including detailed diastology analysis and global longitudinal strain, were obtained by directly performing measurements on stored images offline. This was performed by an experienced research sonographer in a blinded manner, using commercially available software from Siemens Healthcare (Syngo Dynamics 9.0). LV ejection fraction (EF) and cardiac volumes (indexed LV end-systolic volume, LV end-diastolic volume, and left atrial volume) were calculated using the modified Simpson bi-plane method in the apical 2- and 4-chamber views. In the parasternal short axis view, LV mass was estimated utilizing the Devereux formula after measuring the LV end-diastolic dimension, interventricular septal thickness, and posterior wall thick-

TABLE 2. Baseline echocardiographic characteristics

Baseline echocardiographic parameter	Treatment group (n = 64)	Control group (n = 60)	p value
LV structure			
Indexed LV mass (gm^2)	91.6 ± 31.2	94.1 ± 30.1	0.7
LV diastolic internal dimension (cm)	4.5 ± 0.7	4.4 ± 0.8	0.6
LV systolic internal dimension (cm)	3.3 ± 1.9	3.12 ± 0.7	0.6
Intraventricular septal wall thickness (cm)	1.12 ± 0.1	1.19 ± 0.2	0.2
Posterior wall thickness (cm)	1.03 ± 0.1	1.11 ± 0.2	0.1
Indexed LV end-systolic volume (mL/m^2)	17.8 ± 9.5	20.4 ± 9.6	0.2
Indexed LV end-diastolic volume (mL/m^2)	44.5 ± 20	45.6 ± 12.9	0.8
LV systolic function			
EF (%)	60.1 ± 6.2	60.2 ± 10.4	0.7
Patients with EF ≤45% (n)	9.4% (6)	15% (9)	0.5
LV diastolic function			
Indexed left atrial volume (mL/m^2)	27.3 ± 10	31.2 ± 13.3	0.1
Mitral valve E wave	67 (73, 37.5)	76 (65, 19)	0.1
Mitral valve A wave	81 ± 9.6	88 ± 21.1	0.1
Mitral valve E/A ratio	0.89/0.4	0.88/0.4	0.1
Mitral valve deceleration time (ms)	43 (226, 72)	38 (203, 74)	0.1
Septal e´ (cm/s)	6.3 ± 1.3	5.8 ± 1.6	0.1
Septal E/e´	11.8 ± 4.4	13.1 ± 4.7	0.1
Lateral e´ (cm/s)	8.2 ± 2.1	8.1 ± 2.9	0.8
Lateral E/e´	8.9 ± 3.2	9.94 ± .1	0.1
Pulmonary vein systolic wave (cm/s)	52 ± 15.1	56 ± 15.3	0.3
Pulmonary vein diastolic wave (cm/s)	40.3 (40, 12.5)	42.7 (38, 13.5)	0.8
Pulmonary vein systolic wave to diastolic wave ratio	1.4 (1.5, 0.4)	1.4 (1.5, 0.4)	0.9
Diastolic stage % (n)			
0	26.5% (17)	33.3% (20)	0.9
1	67.2% (43)	51.7% (31)	0.1
2	6.3% (4)	15% (9)	0.2
3	0	0	1
LV global longitudinal strain (%)	–16.5 (–16.5, 1.09)	–15.6 (16, 2.8)	0.1

n, number of patients; LV, left ventricle; EF, ejection fraction

ness. In this study, several parameters of diastolic function measured in the apical 4-chamber view were obtained by placing the sample volume at the mitral annulus as well as the tip of the mitral valve leaflets; peak mitral inflow velocities during early and late atrial filling (E and A waves), mitral valve deceleration time and peak early velocity (e´) measured at both septal and lateral locations. Subsequently, pulmonary vein systolic wave and diastolic wave were measured by placing the sample volume at the right upper or lower pulmonary vein, and the systolic to diastolic wave ratio was then calculated.

The severity of diastolic dysfunction was graded in accordance to the American Society of Echocardiography/European Association of Cardiovascular Imaging.[13] Global longitudinal strain was assessed using velocity vector imaging; strain contours were drawn from the apical 4-chamber, 2-chamber, and the apical long axis view in those with adequate frame-rate capture, respectively. Endocardial borders were automatically generated by the software and were manually adjusted as needed.

RESULTS

As illustrated in Table 1, patients in the treatment group were significantly younger (69.4 vs. 77 years, p <0.001) and had relatively lower forced vital capacity (69.9% vs. 80.6%, p = 0.005) in comparison to the control group. Other baseline clinical and echocardiographic variables were statistically comparable between the two groups (p >0.05). Moreover, after PSM, the age demographics of both groups were comparable as well (72.18 vs. 72.15 years, p = 0.9).

TABLE 3. Mean change in echocardiographic parameters

Mean change in echocardiographic parameter	Treatment group (n = 64)	Control group (n = 60)	p value
LV structure			
Indexed LV mass (gm^2)	–4.1 ± 30.3	–8.2 ± 50	0.1
LV diastolic internal dimension (cm)	-0.1 ± 0.6	+0.3 ± 0.2	0.1
LV systolic internal dimension (cm)	-0.1 ± 0.8	+0.1 ± 1.4	0.4
Intraventricular septal wall thickness (cm)	0 ± 0.3	+0.3 ± 1.3	0.3
Posterior wall thickness (cm)	0 ± 0.2	–0.1 ± 0.3	0.4
Indexed LV end-systolic volume (mL/m^2)	–1.4 (0.1, 9.8)	–1.6 (0, 15)	0.8
Indexed LV end-diastolic volume (mL/m^2)	–0.3 ± 19	+2.7 ± 20.8	0.5
LV systolic function			
EF (%)	+7 (3, 10.75)	+4 (3.5, 9.75)	0.3
LV diastolic function			
Indexed left atrial volume (mL/m^2)	+3 (4, 11.6)	+6 (4, 18.6)	0.5
Mitral valve E wave	–3.3 (2, 19.5)	–0.1 (–2.5, 33.2)	0.4
Mitral valve A wave	–0.12 (–2, 22)	–0.3 (–2, 24)	0.8
Mitral valve E/A ratio	0 ± 0.3	–0.1 ± 1	0.3
Mitral valve deceleration time (ms)	–11.6 ± 58	–12.6 ± 133.1	0.1
Septal e´ (cm/s)	–0.1 (0, 2)	–2 (0, 3)	0.3
Septal E/e´	–0.6 (0.6, 4.5)	–0.6 (–0.4, 6.2)	0.9
Lateral e´ (cm/s)	–0.3 ± 2.8	–0.4 ± 3.3	0.2
Lateral E/e´	–0.5 ± 4.9	–0.4 ± 5.3	0.9
Pulmonary vein systolic wave (cm/s)	–3.1 ± 11.1	–6.8 ± 34.5	0.6
Pulmonary vein diastolic wave (cm/s)	–0.9 ± 14.2	–2.8 ± 29	0.8
Pulmonary vein systolic wave to diastolic wave ratio	–0.7 ± 0.7	–0.5 ± 0.7	0.3
LV global longitudinal strain (%)	+0.5 ± 3.1	–0.2 ± 1.7	0.2

n, number of patients; LV, left ventricle; EF, ejection fraction

Of note, baseline and follow-up echocardiograms were done at similar time intervals in treatment and control groups, respectively: 1.7 vs. 1.5 years (p >0.05).

Table 2 summarizes the various baseline echocardiographic parameters measured in this study, all of which were comparable between the treatment and the control group, respectively (p >0.05): mean baseline LVEF was 61% vs. 62%, 9.4% vs. 15% of patients had an impaired LVEF ≤45%, 51.7% vs. 67.2% of the patients had grade 1 diastolic dysfunction, 6.3% vs. 15% grade 2 and 0% grade 3. Global longitudinal strain was –16.5% vs. –15.6%, mean indexed end-diastolic volume was 44.5 mL/m^2 vs. 45.6 mL/m^2, and mean indexed end-systolic volume was 17.8 mL/m^2 vs. 20.4 mL/m^2.

As shown in Table 3, in the primary unadjusted analysis, there was no statistically significant change in the means of any of the echocardiographic parameters of LV structure, diastolic function, systolic function, and global longitudinal strain post pirfenidone administration when compared to the control group.

In addition, we observed no significant difference in the mean change of any of the echocardiographic parameters between the treatment and control groups included in the subgroup cohort (Table 4).

After accounting for confounding variables by means of PSM, the aforementioned findings were re-demonstrated in the secondary adjusted analysis (please refer to Table S1 and Table S2 in the supplemental section).

DISCUSSION

The key finding of our study is that pirfenidone did not significantly impact echocardiographic parameters of left ventricular structure, diastolic function, systolic function, and global longitudinal strain in patients with IPF when compared to a control group of patients not on any disease-modifying medications. Furthermore, there were no significant changes in any of the echocardiographic parameters, not even in patients who had more overt echocardiographic evidence of myocardial dysfunction in addition to a clinical diagnosis of CHF. Contrary to our hypothesis, from an echocardiographic perspective, pirfenidone did not seem to improve LV function or attenuate the degree of myocardial dysfunction in patients with IPF.

TABLE 4. Mean change in echocardiographic parameters of patients in the subgroup cohort

Mean change in echocardiographic parameter	Treatment group (n = 47)	Control group (n = 41)	p value
LV structure			
Indexed LV mass (gm^2)	–8.5 ± 30.3	+7.7 ± 53.5	0.1
LV diastolic internal dimension (cm)	–0.9 ± 5.8	–0 ± 1.5	0.3
LV systolic internal dimension (cm)	–0.2 ± 0.9	–0.1 ± 1.2	0.7
Intraventricular septal wall thickness (cm)	+0.1 ± 0.3	–0.1 ± 0.5	0.5
Posterior wall thickness (cm)	0 ± 0.2	0 ± 0.4	0.6
Indexed LV end-systolic volume (mL/m^2)	+0.6 ± 12.9	+0.7 ± 11.3	0.9
Indexed LV end-diastolic volume (mL/m^2)	+3.4 ± 22.7	–2.1 ± 21.6	0.3
LV systolic function			
EF (%)	+4.5 (5, 10.5)	+2.7 (4, 13)	0.5
LV diastolic function			
Indexed left atrial volume (mL/m^2)	+3 ± 9.6	+6.9 ± 21.7	0.3
Mitral valve E wave	+6.3 (3, 22.5)	+0.4 (–3, 35)	0.2
Mitral valve A wave	–2 (–2, 20)	–7.3 (–6, 23)	0.6
Mitral valve E/A ratio	+0.1 (0, 0.31)	+0.1 (0, 0.5)	0.5
Mitral valve deceleration time (ms)	–6.3 ± 66.2	–34.9 ± 129.2	0.4
Septal e´ (cm/s)	+0.1 ± 1.8	+0.4 ± 2.8	0.5
Septal E/e´	+0.8 ± 5.1	+0.1 ± 5.8	0.6
Lateral e´ (cm/s)	+0.5 ± 2.6	–0.7 ± 2.7	0.1
Lateral E/e´	+0.9 (0.2, 3.2)	–0.5 (–0.3, 3.3)	0.6
Pulmonary vein systolic wave (cm/s)	–2.9 (–2, 14.5)	–5.9 (0, 62)	0.8
Pulmonary vein diastolic wave (cm/s)	+2.1 (–0.5, 21.2)	+0.7 (0, 56)	0.9
Pulmonary vein systolic wave to diastolic wave ratio	0 ± 0.5	–0.3 ± 0.7	0.2
LV global longitudinal strain (%)	+0.7 (0.3, 3.9)	+0.7 (0, 1.7)	0.7

n, number of patients; LV, left ventricle; EF, ejection fraction

Several factors may have contributed to our findings. First, the study design was retrospective in nature, with a small sample size and inherited selection bias based on availability of echocardiograms and pirfenidone. Although PSM did statistically adjust for potential confounders (such as age, gender, history of coronary artery disease etc., mentioned previously), there are unmeasurable confounding factors that could not have been accounted for. Second, approximately 60% of the entire study sample had grade 1 dysfunction, and only 9.4% of the patients in the treatment group vs. 15% of patients in the control group had LVEF ≤45%, suggesting that most patients included in the study did not have echocardiographic evidence of severe cardiac dysfunction. Third, the pathophysiology of heart failure is complex, multi-modal, and unique; myocardial fibrosis represents one component only, and we do not have direct assessments to quantify fibrosis.[14] Changes in echocardiographic parameters of LV structure and function serve as indirect markers of myocardial fibrosis. It is possible that some patients may have subclinical evidence of myocardial fibrosis that could not have been detected on serial echocardiography. Finally, there is evidence suggesting that some patients with heart failure may not have myocardial fibrosis, thus an anti-fibrotic is not applicable in this context.[10]

Larger prospective studies and randomized control trials (such as the ongoing PIROUETTE study[15]) in patients with known heart failure are therefore needed to assess the impact of this novel agent on myocardial fibrosis, utilizing cardiac magnetic resonance imaging. Findings should then be correlated to clinical outcomes to ascertain any benefit this anti-fibrotic agent may have in the context of heart failure. It would also be interesting to examine the effects of this novel agent on right-sided cardio-mechanics.

CONCLUSION

In conclusion, in our retrospective single-center study of idiopathic pulmonary fibrosis patients, treatment with pirfenidone was not associated with any significant changes in echocardiographic parameters of left ventricular structure and function. Our findings therefore caution the implications that pirfenidone may have anti-fibrotic properties that extend beyond its pulmonary indications. To our

knowledge, this is the first study in humans reviewing the implications of this novel agent outside the field of pulmonary medicine.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

EPIDEMIOLOGY // INFECTIOUS DISEASES

Malaria and HIV Infection among Febrile Patients in a Large Area of Southwestern Nigeria

Oyetunde T. Oyeyemi[1], Edet J. Etim[2]

[1] Department of Biological Sciences, University of Medical Sciences, Ondo, Nigeria

[2] Department of Biosciences and Biotechnology, Babcock University, Ilishan-Remo, Ogun State, Nigeria

CORRESPONDENCE

Oyetunde Oyeyemi
University of Medical Sciences
Laje Road, Ondo, Nigeria
Tel: +23 481 635 467 87
E-mail: zootund@yahoo.com, ooyeyemi@unimed.edu.ng

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ABSTRACT

Background: Malaria and HIV/AIDS are two major diseases that represent serious public health threats in Nigeria. They have been ascribed diseases of poverty, and therefore their distribution is expected to be overlapping. **Aim:** The aim of this study was to determine the prevalence of malaria parasites and HIV among febrile patients in the Ikeja area of Lagos State, Nigeria. **Materials and Methods:** The study was conducted on 300 patients attending medical consultation and referred to blood screening for malaria parasites at Reddington Hospital, Lagos State. Malaria parasites were identified microscopically, and HIV screening was carried out using rapid diagnostic tests (RDT). **Results:** The prevalence of malaria and HIV was 98.7% and 3.7%, respectively. All HIV-positive individuals were also infected by malaria parasites. Mean parasitemia was significantly higher in HIV-positive individuals (16,507.9 ± 2,280.7 P/μL) than in HIV-negative subjects (3,252.505 ± 236.3 P/μL) ($p < 0.05$). **Conclusions:** Our results suggest that HIV-infected individuals are more susceptible to infection with malaria parasites. Prompt HIV management is necessary in malaria-endemic areas to reduce disease severity in case of coinfection with HIV.

Keywords: malaria, HIV/AIDS, association, morbidity, Nigeria

BACKGROUND

Malaria and HIV/AIDS are two major diseases with serious public health implications in Nigeria. Globally, Nigeria is ranked number one and two in the total number of people affected by malaria and HIV/AIDS, respectively.[1,2] Both diseases are poverty-related, as the poorest segment of the population is the most vulnerable due to the lack of access to information, quality education, and good health facilities.[3] Each year, malaria and HIV cause over 2 million deaths globally.[4] Children under the age of 5 and pregnant women have the highest morbidity associated with malaria parasites infection,[5,6] while women and adolescent girls have the highest risk of HIV infection.[7] During concurrent malaria parasites and HIV infections, approximately 1 million pregnant women experience vari-

Edet J. Etim • Babcock University, Ilishan-Remo, Ogun State, Nigeria. Tel. +23 470 320 494 18, E-mail: sotisfavoured@yahoo.com

ous degrees of complications in countries of sub-Saharan Africa,[8] thus endangering the lives of both the mothers and the fetuses.

The geographical overlap between malaria parasites and HIV infections has generated research interest in terms of co-morbidity impact of concomitant infections. Some studies have suggested that there is no association between malaria parasites and HIV infection,[9] especially in populations where the prevalence of HIV is low.[10] However, others have reported a bidirectional and synergistic interaction.[11] Evidence has implicated concomitant malaria parasite and HIV infection in facilitating the progression of malaria. Importantly, malaria and HIV coinfection has been linked to an increased risk of severe malaria in adults, congenital infection, and increased transmission dynamics of the two diseases.[12–14] On the other hand, malaria has been reported to cause a reduction in CD4 cell count, thus exacerbating the clinical course of those infected with HIV.[15] Another study showed a significant rise in HIV-1 plasma load in individuals infected with malaria parasites compared to those without infection, even after up to 10 weeks of treatment.[16] Factors influencing the clinical impact of these interactions could include extent of malaria transmission in the area, host immunity, and the individual affected (e.g., adult, child, or pregnant woman).[17]

The aim of this study was to determine the prevalence of malaria and HIV among febrile patients in the Ikeja area of Lagos State, Nigeria. The study also sought to gather more evidence on the susceptibility of individuals to malaria parasites infection in case of concomitant infection with HIV.

MATERIALS AND METHODS

The study was carried out in Ikeja, a city with a population of about 437,400 people, located in Lagos State, Nigeria. The city is close to the popular Murtala Muhammad International Airport. It is the capital of Lagos State with a very large residential zone, and it is set near the Lagos Lagoon. There were over 60,000 cases of malaria in Ikeja in 2013.[18] The closeness of the city to Lagos Lagoon and the poor drainage system found in some of its areas could provide suitable breeding sites for mosquito malaria parasite vectors, enabling stable transmission of malaria. As far as HIV/AIDS is concerned, its transmission is largely associated with large population sizes and fluid movement of people in and out of the state.[19]

A descriptive cross-sectional study was conducted among febrile patients who presented themselves for medical examination at Reddington Hospital, one of the many hospitals in Ikeja receiving malaria patients. To calculate our sample size, we used the prevalence of malaria and HIV coinfection (2.9%) previously reported in Ikeja,[20] and a precision (d) of 2%. Using the method of Daniel,[21] a minimum sample size of approximately 270 participants was calculated. The study included 300 subjects, regular dwellers of the area or Lagos. Only febrile patients with signs and symptoms of uncomplicated malaria, such as fever ≥40°C, chill, headache, rigor, and joint pain, were included.[22]

Venous blood samples were obtained from the subjects by a trained laboratory staff on duty. Clean and grease-free labeled glass slides were prepared, and then thick and thin blood films were made by spreading a drop of blood on the slides. The blood was allowed to dry and then stained with 10% Giemsa stain solution. After 10 min, the stain was washed with clean running water and then dried. A drop of immersion oil was applied to each slide and was examined under ×100 objective lens for malaria parasites. Parasitemia was estimated using the methods described by Cheesbrough.[23]

All subjects were screened using Determine (DT) HIV-1/2 test kits (Alere Medical Company Limited, Chiba, Japan). About 3–5 mL of blood was collected by venipuncture and transferred to an EDTA bottle. The blood was properly mixed and then centrifuged at 1,500 rpm for 10 min. The plasma was stored in a plain tube and kept at −20°C until used. For testing, 50 μL of the plasma was added to the test spot on the kit, and the result was read after 15 min. The result was interpreted according to the kit instructions.

All kits were purchased centrally and were stored at the temperature specified by the manufacturer. Malaria and HIV tests were performed independently and were confirmed by another trained personnel. Participation in the study was voluntary, and only those who gave their consent were included. Children were included based on their parents' consent. Institutional ethical approval was obtained from Olabisi Onabanjo University Teaching Hospital (OOUTH), Ogun State, Nigeria.

Data were analyzed using SPSS for Windows version 22.0 (IBM Corp, Armonk, NY, USA). Counts and percentages were used to summarize categorical variables, and the mean ± SE was used to summarize numerical variables. Differences in prevalence by subject categories were analyzed using the chi-square and Fisher's exact test, while malaria parasitemia was analyzed using one-way ANOVA. Tukey's post-hoc test was used to compare significant differences between groups. Significant differences in malaria parasitemia in relation to the participant's HIV status was tested using Student's t-test. A p value less than 0.05 ($p < 0.05$) was considered statistically significant.

TABLE 1. Characteristics of the subjects

Variables	Number	Proportion (%)
Age		
Children (1–17 years)	93	31.0
Adults (18-59 years)	160	53.3
Elderly (≥60 years)	47	15.7
Gender		
Male	153	51.0
Female	147	49.0

RESULTS

The study population comprised children (n = 93, 1–17 years; 31%), adults (n = 160, 18–59 years; 53.3%), and elderly subjects (n = 47, ≥60 years; 15.7%) (Table 1). The mean age of the participants was 32.3 ± 22.8 years. The overall prevalence of malaria parasites was 98.7%, and mean parasitemia was 3,695.2 ± 281.2 parasites/μL of blood (P/μL). The prevalence of malaria in children (95.7%) was not significantly different from that of adult (100%) and elderly subjects (100%) ($p > 0.05$). There was also no significant variation in the prevalence of malaria in male (98.7%) and female subjects (98.6%) ($p > 0.05$). However, the intensity of infection due to malaria parasites varied significantly by age and gender ($p < 0.05$). The mean parasitemia (5,012.7 ± 807.1 P/μL) of elderly subjects was significantly higher than that of adults (4,273.0 ± 424.7 P/μL) and children (2,035.1 ± 287.4 P/μL) ($p < 0.05$) (Table 2). Also, male subjects had significantly higher parasitemia (3,722.4 ± 411.0 P/μL) than female participants (3,666.8 ± 384.1 P/μL) ($p < 0.05$).

The prevalence of HIV in the population was 3.7%. Although the prevalence of HIV was higher in adults (5.6%) than in the elderly (4.3%) and in females (4.1%) compared to males (3.3%), the prevalence of HIV was neither age- nor gender-dependent ($p > 0.05$) (Table 3). All HIV-positive subjects were infected with malaria parasites, while 98.6% of HIV-negative individuals had malaria. Also, mean parasitemia was significantly higher in HIV-positive individuals (16,507.9 ± 2,280.7 P/μL) than in HIV-negative subjects (3,252.505 ± 236.3 P/μL) ($p < 0.05$).

DISCUSSION

The study has shown that malaria is still a major problem in Lagos despite all efforts put in place to curtail the spread of the disease. Generally, the prevalence of malaria is higher among febrile patients, and malaria is the most common cause of fever in Nigeria, especially in children.[24] The prevalence reported in this study was the highest ever recorded in

TABLE 2. Prevalence and intensity of malaria parasite

Variables	Number examined	Number infected	Proportion (%)	Parasitemia (P/μL)
Age				
Children (1–17 years)	93	89	95.7	2,035.1 ± 287.4[a]
Adults (18-59 years)	160	160	100.0	4,273.0 ± 424.7[b]
Elderly (≥60 years)	47	47	100.0	5,012.7 ± 807.1[c]
Gender				
Male	153	151	98.7	3,722.4 ± 411.0[a]
Female	147	145	98.6	3,666.8 ± 384.1[b]

Different superscripts denote significant differences by Tukey's post-hoc test ($p < 0.05$). Similar superscripts denote no significant difference by Tukey's post-hoc test ($p > 0.05$).

TABLE 3. HIV status among febrile patients

Variables	Number examined	Number infected	Proportion (%)	p value
Age				
Children (1–17 years)	93	0	0.0	0.287
Adults (18-59 years)	160	9	5.6	
Elderly (≥60 years)	47	2	4.3	
Gender				
Male	153	5	3.3	0.766
Female	147	6	4.1	

any region of Nigeria among febrile patients. Previous studies reported a prevalence of 7.4% in Ilorin,[25] 29.7% in Oyo town,[26] and 37.6% in Ikare-Akoko, Ondo.[27] Higher prevalences of 54%,[28] 56%,[29] 63%,[30] 56.8%,[31] and 65.5%[32] were reported in Jos, Sokoto, Simawa Ogun State, Keffi, and Birnin Kudu in Kano State, respectively. In Lagos, our previous study found a prevalence of 39.5%, 61% and 61.3% among febrile infants, non-pregnant women, and pregnant women, respectively.[22] Another study in Lagos reported a very high prevalence (92.1%) among febrile infants (age 0–5 years).[24]

This study confirmed that Lagos State is a suitable region for stable transmission of malaria. Evidence from the State's report on malaria cases showed that malaria transmission is far from being under control. Reports have shown an increase in malaria cases from 488,780 in 2012 to 547,150 in 2014.[33] The probable reasons for this unabated increase in transmission include the presence of abundant water bodies in close proximity to human dwellings, suitable for the breeding of mosquitoes and subsequent transmission of malaria parasite to humans. Due to poor draining systems in many areas, this expanse of water bodies sometimes finds its way into canals and drainage systems, especially during flooding, to create further temporary breeding sites for these mosquitoes. Another possible reason could be the very low utilization of long-lasting insecticide-treated nets (LLIN) in Lagos, with a reported utilization rate of 18%.[34] This value is significantly lower than the 59% and 67.6% LLIN utilization rates recorded in Osun and Ekiti State, respectively.[34,35] Lagos is a megacity, and LLIN distribution through the government's malaria control program may pose some difficulties. In another study, adherence to current malaria treatment guidelines in Lagos was generally poor, as only 7% of people were using an artemisinin-based combined therapy in their last malaria episode; the majority of patients still preferred sulphadoxine-pyrimethamine and chloroquine.[36] This could increase the development of resistant parasite strains, especially in the case of chloroquine.

Although there was no significant difference in the prevalence of malaria among different population groups, parasitemia varied significantly, with the older population carrying the higher burden of the disease. It is usually expected that children, especially infants, would bear the greatest burden of malaria, because acquired immunity may still be not well developed. However, advocacy for malaria prevention in children and pregnant women has been strong recently in Nigeria. This may yield a better adherence to malaria control in these groups. Even with limited resources, children (0–5 years) and pregnant women are given priority in malaria control programs in every state of Nigeria. These programs may have an impact by reducing the extent of exposure to mosquitoes and subsequently lowering the intensity of malaria parasites infection in these groups. Nevertheless, the mean parasitemia recorded in children was very high in our study, and efforts towards abating transmission should be further strengthened, not only in children, but also in the adult population (age 18–59 years) that has a significant number of pregnant women.

In our study, the prevalence of HIV was lower than in many studies reported elsewhere in Nigeria. A prevalence of 4.9% was reported in Osogbo,[37] 6.2% in Abeokuta,[38] 24.1% in Borno,[39] 10% in Benin, and 16% in Zaria.[40] The low prevalence we found in Lagos could represent the positive impact of the various HIV/AIDS prevention programs in the state. Of importance is the possible contribution of HIV infection to increasing susceptibility to malaria parasites infection. This was demonstrated by the increased prevalence and intensity of malaria parasites infection in HIV-positive subjects compared to HIV-negative individuals. While earlier studies have shown no relationship between HIV and the severity of malaria in children and adults,[41,42] our results seem to confirm the findings of studies that have linked HIV infection to a predisposition to more frequent episodes of symptomatic and severe malaria.[43] It is possible that by suppressing the immune system, HIV favors the multiplication and proliferation of malaria parasites.

CONCLUSION

This study has shown that malaria was hyperendemic among febrile patients, while HIV had a low incidence in Ikeja, Lagos. Due to the possible interactions between malaria and HIV/AIDS, the presence of one can influence the morbidity associated with the other. HIV increases susceptibility to malaria parasites and could therefore aggravate the burden associated with malaria in infected individuals, with more serious consequences in pregnant women and infants. In order to minimize the impact of HIV on malaria, malaria and HIV control programs should be integrated into one another. The distribution of LLIN and promotion of their usage should be incorporated into voluntary counselling and testing programs in malaria endemic areas. Prompt treatment of malaria confirmed febrile patients is also highly recommended, especially in HIV/AIDS endemic areas.

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STATEMENT OF ETHICS

Informed consent was obtained from the participants. Ethical approval with approval number OOUTH/DA.326/899 was obtained from Olabisi Onabanjo University Teaching Hospital, Ogun State, Nigeria.

CONFLICT OF INTEREST

None declared.

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ORIGINAL RESEARCH

RADIOLOGY // ANATOMICAL PATHOLOGY

Ultrasound-Guided Core-Needle Biopsy of Suspicious Breast Lesions

Kincső-Zsófia Lőrincz[1], Zsuzsánna Pap[2], Simona Lileana Mocan[3,4], Csanád-Endre Lőrincz[5], Beáta-Ágota Baróti[6]

[1] Radiology and Medical Imaging Laboratory, Mureș County Emergency Clinical Hospital, Târgu Mureș, Romania
[2] Department of Anatomy and Embryology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[3] SC Morphomed SRL, Târgu Mureș, Romania
[4] Department of Pathology, Mureș County Emergency Clinical Hospital, Târgu Mureș, Romania
[5] Hungarian Department of Biology and Ecology - Medical Biology, Babeș-Bolyai University, Cluj Napoca, Romania
[6] Department of Radiology and Medical Imaging, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

CORRESPONDENCE

Zsuzsánna Pap
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureş, Romania
Tel: +40 265 215 551
E-mail: zsuzsanna.pap@umfst.ro

ARTICLE HISTORY

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Kincső-Zsófia Lőrincz • Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureş, Romania. Tel: +4,0 372 653 100. E-mail: bencso@rocketmail.com

Simona Lileana Mocan • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureş, Romania. Tel: +40 265 215 551, E-mail: slmocan70@gmail.com

Csanád-Endre Lőrincz • Str. Mihail Kogălniceanu nr. 1, 400000 Cluj-Napoca, Romania. Tel: +40 264 405 300, E-mail: lendre1992@yahoo.com

Beáta-Ágota Baróti • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureş, Romania. Tel: +40 265 215 551, E-mail: beata.baroti@umfst.ro

ABSTRACT

Background: Breast cancer is the female cancer with the highest mortality. While early detection is a public health priority in Western European countries, a screening program in our country has yet to be implemented. The best diagnostic accuracy is achieved through the use of triple assessment: clinical examination, imaging, and core-needle biopsy where indicated. Prognosis is influenced by clinical, histological, and biological factors, and therapy is most effective when individually tailored. **Aim of the study:** To analyze the clinical, histological, and immunohistochemical characteristics of the biopsied nodules and summarize our experience from the last three years. **Material and Methods:** We retrospectively analyzed data from 137 patients who underwent core-needle biopsy between 2017 and 2019. Imaging score was assigned based on ultrasound examination or mammography. Clinical and pathological parameters were recorded, followed by statistical processing of the data. **Results:** The mean age of the patients was 58 ± 14 years, lesions had a mean size of 22.83 ± 14.10 mm. Most nodules (n = 63, 47.01%) were located in the upper-outer quadrant, and bilateral presence was found in 4 (3.08%) cases. We found a significant positive correlation between lesion size and the patients' age (Spearman r = 0.356; 95% CI 0.186, 0.506; p = 0.000). The malignancy rates within the Breast Imaging Reporting and Data System (BI-RADS) categories were as follows: 0% for „4a", 31.58% for „4b", 71.42% for „4c", and 97.72% for „5". Most malignancies (n = 73, 78.35%) were represented by invasive ductal carcinoma of no special type, 58.43% (n = 52) were grade 2, 89.13% (n = 82) were estrogen receptor positive, and Luminal B-like type was the most common (n = 63, 78.75%). **Conclusions:** The mean size of tumors was larger than the average size at discovery described in the literature. In our region, age and tumor size are positively correlated. Preoperative histological results may indicate the reliability of the imaging risk stratification system. Most cases can benefit from adjuvant endocrine therapy.

Keywords: breast cancer, screening, imaging, biopsy, immunohistochemistry

INTRODUCTION

Breast cancer accounts for a quarter of all female cancers and is among the leading causes of cancer deaths. In Romania, its general mortality is lower than in Western European countries, with an age-standardized incidence of 54.5 cases per 100,000 and a 15.5 mortality rate in 2018.[1]

While national mortality has decreased in the younger population over the last two decades, it is still rising in the 65+ age group, suggesting that information about the necessity of screening has not reached the target population.[2] On the other hand, screening carries the risk of overdiagnosis, followed by overtreatment, and can lead to a 20% increase in mastectomies and more use of radiotherapy, according to a Danish study.[3] Cancer experts from several countries advise making early detection a public health priority and taking action to decrease the number of false positive diagnoses, which could be facilitated by the use of core-needle biopsy in the evaluation process.[4,5]

In multidisciplinary breast clinics, lumps undergo a triple assessment consisting of clinical examination, imaging, and preoperative biopsy, where needed.[6] While the Breast Imaging Reporting and Data System (BI-RADS) developed by the American College of Radiology approximates the risk of malignancy in breast lumps, ultrasound-guided core-needle biopsy provides gold-standard histological results, with a sensitivity of 97–99%.[7] Therapy is most effective when individually tailored; as a result, in addition to histological classification, it is of great importance to establish hormone-receptor status and the molecular subtype of each tumor. The urge to request the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status of all invasive breast cancers is included in the United Kingdom National Health Service guidelines for the diagnosis and management of early and locally advanced breast cancer.[8] The traits that characterize the different subtypes are pathological grade and proliferation, response to chemotherapy, and response to endocrine therapy.[9] In addition, Ki-67 protein status is possibly a prognostic and predictive factor for adjuvant chemotherapy.[10–12]

In the effort to diagnose breast cancer in its early stages, we have been performing core-needle biopsies as part of the triple assessment used in multidisciplinary breast clinics. The aim of this study is to analyze the clinical, imaging, histological, and immunohistochemical characteristics of the biopsied nodules and summarize our experience from the last three years.

MATERIAL AND METHODS

We retrospectively analyzed the case records of 137 patients with breast lesions who underwent triple assessment consisting of clinical examination, imaging, and core-needle biopsy between January 2017 and December 2019. During the selection of the cases, we divided the patients into two groups. The first one was formed of 130 female patients, of all ages, with no personal medical history of breast malignancies. The second group of 7 patients was formed of special cases which corresponded to one of the following criteria: male; previous treatment for breast cancer; metastasis found in the breast, with the primary tumor located in other organs. Bilateral breast nodules were catalogued as two separate cases. Clinical information included the patients' sex, age, and relevant personal and family medical history. During ultrasound examination, the location and size of the lump, morphologic features, imaging characteristics, and presence of suspicious lymph nodes were noted. The risk of breast cancer was determined by mammography and ultrasound in the majority of cases; for patients younger than 35 only ultrasonography was used. Cancer risk was estimated using the BI-RADS risk stratification tool: 0 – incomplete; 1 –negative; 2 – benign; 3 – probably benign; 4 – suspicious for malignancy, where 4a represents a probability of 2–9%, 4b 10–49%, 4c 50–94%; 5 – highly suspicious of malignancy, with a probability of over 95%. The core-needle biopsy was performed with ultrasound guidance, under local anesthesia with 1% lidocaine using a Bard Magnum biopsy gun with a 14-gauge needle. Histopathological examination of the bioptic material delivered information about the histological type and grade of malignancy of the tumor. We used the protocol of the College of American Pathologists (CAP) for the examination of biopsy specimens from patients with invasive carcinoma of the breast to report every malignant specimen; we also included current WHO classification of breast tumors and the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system).[13–16] A surrogate molecular breast cancer classification was used based on immunohistochemical assessment of biomarkers (ER, PR, HER2, and Ki-67) and in situ hybridization confirmation, adopted by the 13th St. Gallen International Breast Cancer Conference (2013).[17–19] The five categories were: Luminal A-like (ER positive, PR positive, HER2 negative, Ki-67 low), Luminal B-like (HER2-negative) (ER positive, HER2 negative, and at least one of the following: Ki-67 high, or PR negative or low), Luminal B-like (HER2-positive) (ER positive, HER2 overexpressed or amplified, PR any), HER2-positive (non-

luminal) (HER2 overexpressed or amplified, ER negative, PR negative), and Triple-negative (ER negative, PR negative, HER2 negative). Cut-off values were set according to the guideline of the American Society of Clinical Oncology/College of American Pathologists for immunohistochemical testing.[20]

Statistical analysis was performed using Microsoft Excel Professional Plus 2010 (version 14.0.7116.5000) and Graph Pad Prism (version 8.4.0.671). Numerical data were expressed as mean ± standard deviation. Categorical data were expressed as frequency and percentage. Associations between age and other prognostic factors were evaluated by Chi square tests. P values smaller than 0.05 were considered statistically significant.

The study was conducted in accordance with the principles stipulated in the Declaration of Helsinki. Informed consent was waived by the ethics committee of the institution, as the study was retrospective.

RESULTS

The study population consisted of 137 patients with breast lumps who underwent core-needle biopsy, 136 (99.27%) of which were females. The mean age of the patients was 58 ± 14 years. Malignant tumors were found in 97 (80.17%) cases, and 24 (19.83%) cases were benign. In 17.05% (n = 15) of breast cancer cases, family history was positive for breast cancer, and two of these patients were younger than the recommended screening age for normal risk of breast cancer.

Upon presentation, the lesions had an overall mean size of 22.83 ± 14.10 mm, malignant lesions being slightly larger (23.46 ± 10.75 mm) (Table 1). Nodules were most frequently located in the upper-outer quadrant (UOQ) (n = 63, 47.01%), and bilateral presence was found in 4 cases (Table 1). Tumor frequency for each site and BI-RADS scores are listed in Table 1, along with size and age distributions. We found a significant positive correlation between lesion size and the patient's age (Spearman r = 0.356; 95% CI 0.186, 0.506; p = 0.00), suggesting an increase in tumor size with the advancement of age (Figure 1).

The malignancy rates within the BI-RADS categories were as follows: 0% for „4a", 31.58% for „4b", 71.42% for „4c" and 97.72% for „5".

Tumor histological types for each category are listed in Table 2.

The occurrence of benign/malignant tumor types was significantly different (p <0.0001) in patients aged 40 or younger, mostly diagnosed with benign nodules (n = 8, 88.89%), compared to older patients whose nodules were mostly malignant (n = 92, 85.19%). Malignancy rates based on age categories are presented in Figure 2. The cancer-free biopsies were mostly fibroadenomas (n = 15, 62.5%), normal breast tissue being found in 4 cases (16.67%). Most malignancies (n = 73, 78.35%) were represented by invasive ductal carcinoma (IDC) of no special type, followed by lobular (n = 9, 9.28%), mucinous (n = 5, 5.15%), papillary (n = 4, 4.12%), tubular (n = 1, 1.03%), cribriform (n = 1, 1.03%), and neuroendocrine (n = 1, 1.03%) types. No cases of carcinoma with medullary pattern were found. The histological type of the tumors showed a correlation of statistical significance with the patient's age, as IDC was the most frequently diagnosed type in all age categories, except the last one (81 and older), where the mucinous type was the most common (p = 0.044). The rates of tumor types found in each age category are presented in Figure 3. The distribution of malignancy grades across age groups is

TABLE 1. Clinical and imaging data

		n	%
Laterality	Left	61	44.53
	Right	72	52.55
	Bilateral	4	2.92
Location	UOQ	63	47.01
	LOQ	6	4.48
	UIQ	18	13.43
	LIQ	7	5.22
	CC	18	13.43
	U	10	7.46
	L	7	5.22
	I	0	0
	O	5	3.73
Size	<10 mm	18	14.52
	10.1–20 mm	50	40.32
	20.1–30 mm	32	25.81
	31–40 mm	12	9.68
	41–50 mm	10	8.06
	>50 mm	2	1.61
Age (years)	<20	2	1.50
	20-30	2	1.50
	31-40	6	4.51
	41-50	32	24.06
	51-60	22	16.54
	61-70	37	27.82
	71-80	24	18.05
	>80	4	3.01
BI-RADS	4a	7	5.79
	4b	19	15.70
	4c	7	5.79
	5	88	72.73

UOQ, upper-outer quadrant; LOQ, lower-outer quadrant; UIQ, upper-inner quadrant; LIQ, lower-inner quadrant; CC, central; U, limit of upper quadrants; L, limit of lower quadrants; I, limit of inner quadrants; O, limit of outer quadrants

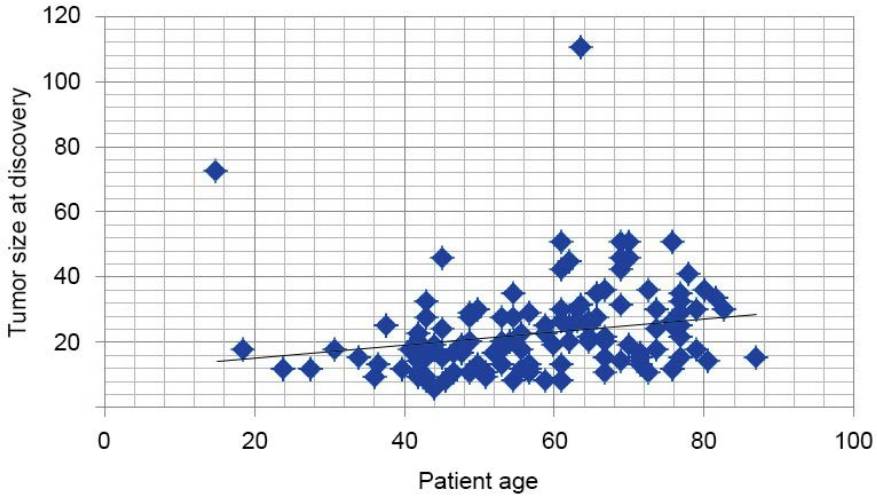

FIGURE 1. Patient age and tumor size correlation

presented in Figure 4. Grade 2 tumors were the most common (n = 52, 58.43%), especially in the 61–70 and 41–50 age groups. Grade 1 tumors were observed in patients aged 41 and older, becoming more and more frequent until the age of 70. Grade 3 tumors were present in patients aged between 41 and 80, most of them occurring in the 61–70 age group. There was no statistically significant correlation between age and grade of malignancy (p >0.05).

The immunohistochemistry assays concluded that 89.13% (n = 82) of lesions were ER-positive with all specimens above 10% staining, 67.03% (n = 61) were PR positive, and 80.43% (n = 74) expressed high Ki-67 levels. HER-2 positivity was 26.09% (n = 24). Luminal B-like (HER2-negative) type was the most common (n = 45, 56.25%), followed by Luminal B-like (HER2-positive) (n = 18, 22.5%), Luminal A-like (n = 8, 10%), and HER2-positive (n = 6, 7.5%). Triple-negative tumors (TNBC) were the least common, accounting for 3.75% (n = 3) of all cases. Luminal B-like (HER2-positive) tumors were more frequent in patients under 50 years, Luminal B-like (HER2-negative) tumors being dominant above this age. The largest triple-negative tumor rate was observed in the 80+ age category. There was no statistically significant correlation between age and tumor molecular type (p >0.05).

A number of 7 cases were not included in the calculations above. One male patient underwent biopsy for a BI-RADS 4c lesion, which proved to be gynecomastia with normal breast tissue. Two female patients, already surgically treated for breast cancer, were found with suspicious lesions. Histopathological examination found no sign of recurrence, the ultrasonographic appearance being due to scar tissue. There were two cases of recurrence, one intramammary lymph node metastasis involving IDC of no special type, and one case of metastatic melanoma.

TABLE 2. Tumor histological type by BI-RADS categories

	BIRADS 4a (n)	BIRADS 4b (n)	BIRADS 4c (n)	BIRADS 5 (n)
Benign				
FA	4	10	1	0
Other	3	3	1	2
Malignant				
IDC	0	5	3	68
Lobular	0	0	0	9
Papillary	0	0	2	2
Mucinous	0	0	0	5
Other	0	1	0	2

FA, fibroadenoma; IDC, invasive ductal carcinoma

DISCUSSIONS

In the European Union (EU), the breast is the most common site of cancer among women, whereas male breast cancer represents approximately 1% of all breast cancer cases.[21,22] Recommendations of the European Commission (EC), last updated in 2020, include biannual mammography screening for women aged between 45 and 69 years.[23]

Over the last two decades, the median tumor size has been decreasing, reaching 11–15 mm with the use of radiological screening methods, but remains between 19–21 mm when discovered by self-detection or clinical examination.[24,25] The mean age of patients in our study (58 ± 14 years) fits the target age group for screening; however, the mean size at discovery was above average (23.46 vs. 11–15 mm/19–21 mm). The 2017 EC Eurostat report regarding

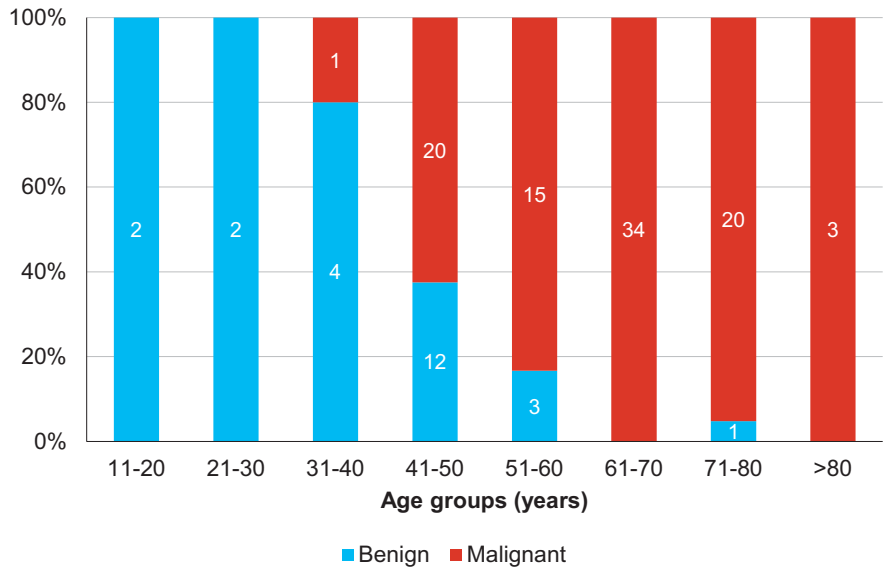

FIGURE 2. Rate of benign and malignant lesions within age groups

breast cancer screening places Romania last among EU member states with 0.2% participation in 2015.[26] According to data collected in 2016, participation reached 6%.[21] By contrast, in Western member states, participation is above 75%.[26] This discrepancy in screening participation rates and median tumor size suggest that either self-detection or clinical examination applied to the majority of our cases. Multiple studies have concluded that tumor size at discovery is correlated with lymph node status and the presence of metastases, and it is an independent predictor for mortality.[27–31] In a cohort study of 819,647 women, published in 2018, for tumors from 9 to 20 mm, mortality increased from 7.0 to 22.3%.[32] We found a statistically significant positive correlation between lesion size and the patients' age. Although slower growing tumors are diagnosed in elderly women, this category of patients is often less informed than the younger population and is reluctant to seek medical help. Studies from other geographical regions have reached opposite conclusions, suggesting that size decreases with advancement of age or have not found any significant correlation.[33–35]

General screening recommendations apply to women aged 45 to 69 with normal risk for breast cancer, but in many cases individual risk factor identification is neces-

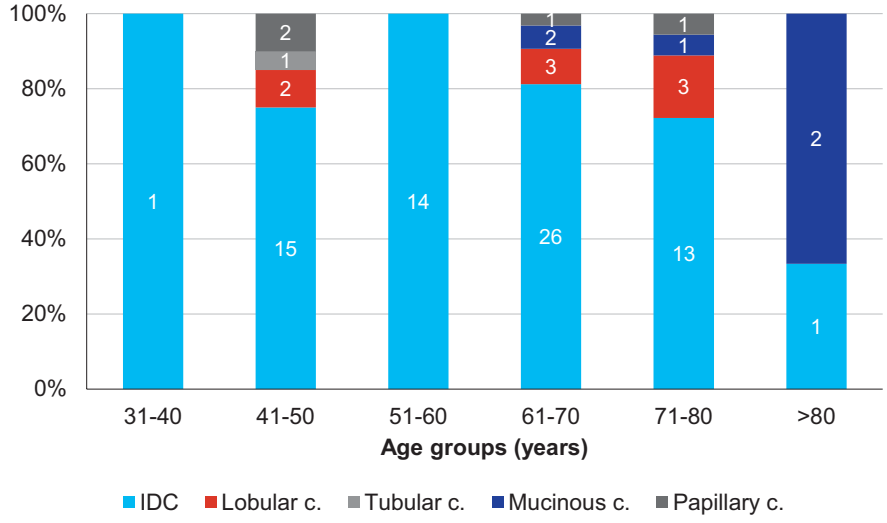

FIGURE 3. Tumor histological types within age groups

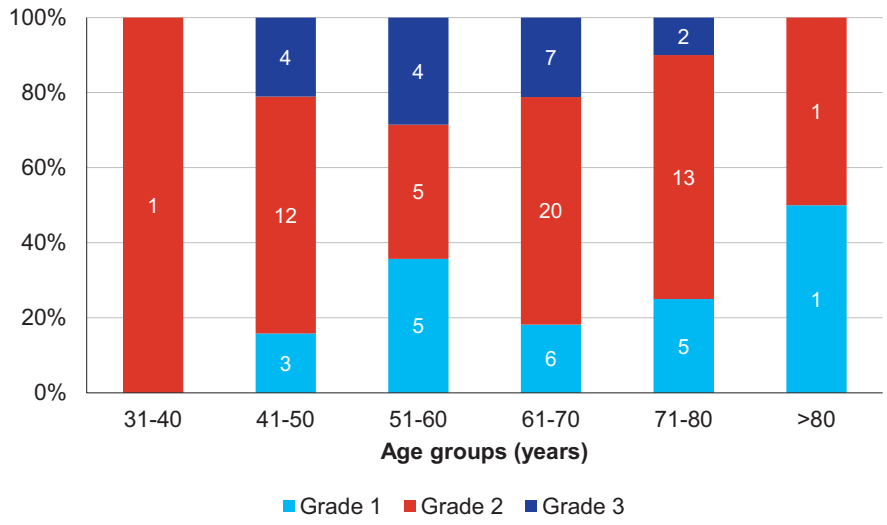

FIGURE 4. Tumor malignancy grades within age groups

sary to provide personalized suggestions such as screening from a younger age. Patients whose first- or second-degree relatives have been diagnosed with breast cancer have a twofold risk or higher, according to a systematic review.[36] Similarly to other results,[37] among our patients with malignant tumors, 15 (17.05%) had a positive family history, two of whom were under the age of 45.

Tumors are located most frequently in the UOQ across multiple populations, which is also our case (47.01%). Although tumor location is not an independent prognostic factor, central tumors are more difficult to evaluate mammographically, and as a result, they may be discovered in more advanced stages.[38] Other studies have discovered an increasing trend in mortality with increasing distance from the axilla, regardless of axillary lymph node invasion, concluding that survival is significantly better for UOQ tumours.[39,40]

Screening mammography can be very useful for detecting cancer in early stages; however, it has a major downside: overdiagnosis. Supplemental ultrasound breast screening can be used when breast density is high, but its specificity is low compared to mammography.[41] Overdiagnosis is defined as the discovery of breast lesions that would never cause symptoms or harms in the absence of screening.[42] These represent 0–54% of all cases, according to a systematic review.[43] Consequential overtreatment can be limited by adding the third step to the diagnostic process, represented by histopathological evaluation and proposing all suspicious lesions (BI-RADS 4 and 5 categories) for core-needle biopsy. In our study, malignancy rates, confirmed by histopathological examinations, were in the estimated range for each category, except BI-RADS 4a (0% vs. estimated 2–10%).

Most tumors (n = 73, 78.35%) were represented by IDC of no special type, with the highest frequency in all age categories, with the exception of patients over 80 years, who were mostly diagnosed with the mucinous type. This supports data from international literature, where the rate of IDC is estimated to 40–75%, and mucinous carcinoma is associated to elderly patients.[44] Preoperative histopathological examination is not only useful for avoiding unnecessary treatment of benign tumors, but also for improving surgical results, including margin negativity, in malignant tumors.[45]

Once the need for treatment is confirmed, evaluation of prognostic factors is a key part of defining a personalized therapeutic strategy. Practitioners rely on the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) for malignancy stratification and decision making regarding treatment.[46] The Nottingham combined histologic grade evaluates the amount of tubule formation, the extent of nuclear pleomorphism, and the mitotic count. Tumor grade proportion is variable in the literature, but grade 2 tumors are the most frequent in the majority of studies.4[47–51] In our study, grade 2 tumors were observed in more than half of the cases.

Besides tumor grade, the molecular subtype of the tumor strongly influences survival.[52–54] Breast cancer is heterogeneous at the molecular level, with different patterns of gene expression leading to differences in behavior and prognosis. Due to time and cost constrains, a surrogate molecular breast cancer classification is used, based on immunohistochemical assessment of biomarkers (ER, PR, HER2, and ki-67).[18] Approximately 75% of breast cancers express estrogen and progesterone receptors, which indi-

cates responsiveness to hormonal therapy. In our study, 89.13% of lesions were ER-positive and 67.03% PR-positive.[46] Estrogen expression rate is based on the percentage of cells staining by immunohistochemistry, but in the clinical practice the response of low positive (1–10% staining) ER cancers is uncertain. The 2020 guideline of the American Society of Clinical Oncology (ASCO)/CAP recommends reporting these cases in a new category, ER low positive.[55] In order to predict the benefit of hormonal therapy, the Allred score combines both the percentage and intensity of staining.[20] Luminal B-like subtype was dominant in this study, which means that most of our patients will need additional chemotherapy, compared to luminal A, where hormonal therapy is sufficient in most cases.[46] The least favorable cases, HER2-positive and TNBC, were found predominantly in the older age groups; however, we have found no significant association between age and molecular subtype. Some studies have reached the same conclusion; at the same time, it is widely recognized in the literature that younger women present with more aggressive tumors.[51,56]

CONCLUSIONS

Most of the newly diagnosed breast cancers in our region are localized in the upper-outer quadrant, the 61–70 age group being most affected. At the time of discovery, these tumors are larger than the average size at discovery described in the literature, and they also show a positive correlation with age. The introduction of triple assessment to our routine was successful; however, it cannot compensate the lack of screening participation. Preoperative histological results suggest the BI-RADS risk stratification system's reliability and appropriate use. Most tumors express both ER and PR, and these patients can benefit from adjuvant endocrine therapy.

CONFLICT OF INTEREST

Nothing to declare.

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PLASTIC SURGERY // GENERAL SURGERY

Proper Surgical Treatment of Small and Medium Size Umbilical Hernias. A Single Surgeon Experience

Etele Élthes[1,2], Daniela Sala[1,2], Radu Mircea Neagoe[1,2], János Székely[1], Márton Dénes[1,2]

[1] "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[2] 2nd Department of Surgery, Emergency County Clinical Hospital, Târgu Mureş, Romania

CORRESPONDENCE

Daniela Sala
Str. Nicolae Grigorescu nr. 15, ap. 11
540095 Târgu Mureș, Romania
Phone number: +40 726 167 557
E-mail: salatatiana@yahoo.com

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Etele Élthes • Str. Păcii nr. 68B, ap.14, 540118 Târgu Mureș, Romania. Tel: +40 746 556 355, E-mail: elthesetele@yahoo.com

Radu Mircea Neagoe • Str. Gheorghe Marinescu nr. 38, 540136 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: neagoerm@gmail.com

János Székely • Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 372 653 100, E-mail: egyjanek@yahoo.com

Márton Dénes • Aleea Carpați nr. 29, Ap. 65, 540336 Târgu Mureș, Romania. Tel: +40 744 509 214, E-mail: denesmatyi@yahoo.com

ABSTRACT

Introduction: Minimally invasive surgical procedures have become routine interventions nowadays and represent an effective therapeutic option even for small umbilical hernias, providing favorable postoperative and aesthetic results. **Aim of study:** To determine the most appropriate minimally invasive treatment option for small and medium size umbilical hernias. **Materials and methods:** We conducted a prospective study on 50 patients with small or medium umbilical hernia (<4 cm). All patients benefited of minimal invasive surgery with mesh implantation. Depending on the surgical procedure, two major groups were defined: group A – patients with open surgical approach (n = 24) and group B – patients undergoing laparoscopic surgery (n = 26). Clinical, surgical, postoperative, and follow-up data were analyzed. **Results:** Mesh replacement via open approach through the umbilicus was associated with significantly reduced surgical time (p = 0.0359), administration of painkillers (p = 0.0461), and use of anticoagulants (p = 0.0404). Hospital stays (p = 0.0001) and costs (p = 0.0005) were also significantly lower in this group. After 6 months of follow-up, no recurrence was observed, and no significant differences were detected regarding postoperative pain and the patients' professional reintegration. Patient satisfaction regarding postoperative scar was superior in the open group. **Conclusion:** The present study indicates that the ventral patch technique is a safe and effective method for the treatment of small and medium size umbilical hernias.

Keywords: small umbilical hernia, ventral patch, minimally invasive, esthetics

INTRODUCTION

Abdominal wall hernias are quite common surgical conditions affecting all ages and both genders. A hernia represents an abnormal protrusion of a peritoneum-lined sac through the muscular covering of the abdomen. The umbilicus is one of the weak points of the abdominal wall and a relatively common site for herniations. Nowadays, umbilical hernias still represent an important medical issue, affecting a significant part of the population. Because of the increased recurrence rates following suture repair, closure of the abdominal wall defect using a synthetic prosthesis has been shown to be superior to other surgical techniques, even for

small size hernias. The outcome of hernia repair may also be affected by the surgical approach. Minimally invasive techniques for mesh placement have been shown to reduce postoperative complications and may offer a satisfying esthetic result as well. Synthetic patches are particularly suitable for small hernias because they require a smaller dissection; however, it is still unclear whether the results of this procedure are at least equal to other minimally invasive techniques.[1–3]

The aim of the study was to assess the efficacy of two minimally invasive (open versus laparoscopic) surgical options in treating small and medium size umbilical hernias.

MATERIALS AND METHODS

Patient selection

Between January 1, 2018 and June 30, 2019 we conducted a prospective study at the 2nd Department of General Surgery of Mureș County Emergency Clinical Hospital on 50 patients diagnosed with small or midsized umbilical hernias. All patients underwent surgical treatment and benefited of minimally invasive care of the abdominal wall defect.

The laparoscopic approach was performed using the standard three-trocar method, and reinforcement of the abdominal wall was carried out with composite surgical mesh fastened with surgical tacks. For the open surgical procedure, a single microincision was performed at the level of the umbilicus. After careful dissection, the parietal defect was identified, and the hernia content was reintroduced in the peritoneal cavity. Succeeding cautious examination of possible adhesions around the abdominal wall defect, a ventral patch-type synthetic mesh (Figure 1) was introduced through the umbilicus and fastened with two separate sutures. The abdominal wall defect and the skin incision were closed with separate sutures.

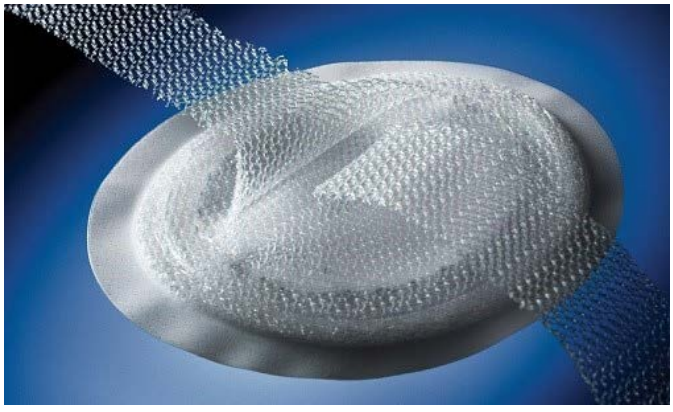

FIGURE 1. Ventral patch for hernia repair

The surgical procedures were performed by a single surgeon, with competency and experience in minimally invasive hernioplasty. Follow-up for these patients was performed at 6 months after surgical treatment. Patients requiring hernia repair in emergency conditions, those with increased size umbilical defects, advanced stages of obesity, or undergoing other surgical treatment options than minimally invasive techniques were excluded from the study.

Subdivision of patients and collected data

Based on the surgical intervention performed, the patients were divided into two groups: 1) a study group (SG), with open approach, including 24 patients who underwent open surgical treatment of the umbilical hernia; 2) a control group (CG), with laparoscopic approach, including 26 patients who benefited of reinforcement of the abdominal wall with composite surgical mesh via laparoscopic repair. All patients were carefully questioned and examined. At the same time, data was gathered from medical charts and operatory protocols.

The first subanalysis of the study compared the two surgical procedures analyzing clinical, surgical, and postoperative data. Clinical characteristics included the patients' gender, age, weight, and size of umbilical defect. For interpretation of age, three subgroups were defined: young adults (<44 years), middle-aged adults (45–69 years), and elderly adults (>70 years). For obesity assessment, the internationally applied body mass index (BMI) was calculated. For categorization of the abdominal wall defect, we used the classification proposed by the European Hernia Society: hernias with diameters <2 cm were defined as small sized, and hernias with diameters between 2–4 cm were defined as medium sized. Regarding surgical and postoperative data, the following variables were examined: number of abdominal incisions, mesh fixation method, duration of surgical intervention, mobilization after surgery, postoperative medication (painkillers, anticoagulants, and antibiotics), length of hospital stay, and hospitalization costs. For easier assessment of surgical time, short surgical interventions (<60 minutes) and prolonged operations (>60 minutes) were defined. The early mobilization subgroup contained patients who sustained physical effort (walking) on the day of surgical intervention, while those with delayed mobilization performed physical activity later during the postoperative recovery. Regarding the postoperative medication, three subgroups were distinguished, based on the length of medicine intake (without treatment, treatment only on the day of surgical intervention, and more than one-day treatment).

During the second subanalysis we mainly focused on statistical analysis of data gathered throughout patient follow-up. These aspects included evaluation of postoperative pain, the patients' professional reintegration, and assessment of recurrence rate. For the evaluation of postoperative pain, the following numerical rating scale was applied: 0 = no pain, 1–3 = reduced pain, 4–6 = moderate pain, 7–9 = significant pain, 10 = worst pain ever. Professional reintegration was measured in time (weeks) spent from surgical intervention until return to work.

Esthetic results were assessed in the third subanalysis, through which the following aspects were analyzed: number of abdominal incisions, wound closing methods, and the patients' satisfaction on wound healing. Postoperative scar healing results were analyzed with the Vancouver Scar Scale (VSS), which is widely used in clinical practice and research.

Statistical analysis

The collected information was processed using Microsoft Excel. The statistical analysis of the database was performed using GraphPad InStat software (GraphPad Software, Inc., San Diego, USA). Quantitative variables were presented by mean and median, while qualitative and categorical variables were expressed both as integer and percentage values. A normality test was applied for all variable groups in order to determine the distribution of values. Furthermore, for the quantitative statistical analysis, Student's t-test was applied for groups with Gaussian distribution of values, while the Mann-Whitney nonparametric test was used for groups with non-Gaussian distribution. The level of statistical significance for the present research was set at a p value of 0.05, while the confidence interval was 95% for all calculated parameters.

RESULTS

Basic comparison of the surgical procedures

The results of the first subanalysis comparing patients undergoing the two studied procedures is presented in Table 1, which indicates that male patients were present in a higher proportion in both of the studied groups (SG – 79.17%, CG – 65.38%), but without statistically significant difference. Analysis of age indicated a majority of middle-aged adults (n = 26), followed by young adults (n = 20) and elderly patients (n = 4). However, age-related data did not show any significant differences between the groups. Regarding obesity, the majority of patients (SG – 70.83%, CG – 50%) had a BMI in the normal range; overweight patients were present in a higher proportion in the laparoscopic group, while obese patients were present in just a small percentage. Neither of these data showed significant differences during statistical analysis. The last investigated clinical aspect was the size of the parietal defect. Abdominal wall defects smaller than 2 cm benefited mainly of classic approach (SG – 54.17%, p = 0.0938), while umbilical hernias with

TABLE 1. Clinical characteristics of the study population

	Study group Open approach n = 24 (%)	Control group Laparoscopic approach n = 26 (%)	p value
Gender			
Male	19 (79.17)	17 (65.38)	0.3
Female	5 (20.83)	9 (34.62)	0.3
Age (years)			
25–44	11 (45.83)	9 (34.61)	0.4
45–69	10 (41.67)	16 (61.54)	0.2
>70	3 (12.5)	1 (3.85)	0.5
BMI			
Normal (18.5–24.9)	17 (70.83)	13 (50)	0.2
Overweight (25–29.9)	7 (29.17)	11 (42.31)	0.4
Obese (30–34.9)	0 (0)	2 (7.69)	–
Severely obese (35–39.9)	0 (0)	0 (0)	–
Morbidly obese (40+)	0 (0)	0 (0)	–
Size of hernia defect (cm)			
<2 cm	13 (54.17)	7 (26.92)	0.09
2–4 cm	11 (45.83)	19 (73.08)	

TABLE 2. Surgical and postoperative data in the study population

	Study group Open approach n = 24 (%)	**Control group Laparoscopic approach n = 26 (%)**	**p value**
No. of abdominal incisions			
One	24 (100)	0 (0)	–
Three	0 (0)	26 (100)	–
Wound closing technique			
Simple interrupted suture	24 (100)	8 (30.77)	0.0001
Intradermal suture	0 (0)	18 (69.23)	
Mesh fixation method			
Separate sutures	24 (100)	0 (0)	–
Tacks	0 (0)	26 (100)	–
Duration of surgery (min)			
Average	45 minutes	70 minutes	–
Short (<60 min)	22 (91.67)	15 (57.69)	0.03
Prolonged (>60 min)	2 (8.33)	11 (42.31)	
Mobilization			
Early (Day 0)	23 (95.83)	22 (84.62)	0.4
Delayed (Day 1)	1 (4.17)	4 (15.38)	
Use of painkillers (days)			
Average	1.33 days	2.80 days	
Without treatment	4 (16.67)	0 (0)	0.04
Only one day of treatment	9 (37.5)	1 (3.85)	0.004
More than one day of treatment	11 (45.83)	25 (96.15)	0.0001
Use of anticoagulant (days)			
Average	0.95	2.34	–
Without treatment	13 (54.17)	6 (23.08)	0.04
One day of treatment	0 (0)	0 (0)	–
More than one day of treatment	11 (45.83)	20 (76.92)	0.04
Use of antibiotic (days)			
Average	0.72	0.92	–
Without treatment	0 (0)	5 (19.23)	0.05
One day of treatment	21 (87.5)	18 (69.23)	0.1
More than one day of treatment	3 (12.5)	3 (11.54)	1.0
Average length of hospital stay (days)	2.65	4.19	0.0001
Average hospitalization costs (EUR)	718.23	1185.08	0.0005

diameters between 2–4 cm were predominantly treated via laparoscopic approach (CG – 73.08%, p = 0.0938).

Surgical and postoperative details are presented in Table 2. Patients who benefited of abdominal reinforcement with ventral patch composite synthetic mesh needed a single abdominal microincision, while patients from the CG had at least three abdominal microincisions. For wound closure during classic surgical intervention, exclusively simple interrupted sutures were utilized, while in case of laparoscopic surgery, significantly more patients benefited of intradermal suture (p = 0.0001). In case of the ventral patch method, mesh fixation happened via separate sutures, while in case laparoscopic hernioplasty, metallic or absorbable tacks were used in order to fix the composite surgical mesh. No significant differences were observed during the analysis of these data. Regarding the duration of surgical intervention, patients from the SG had a significantly shorter operation compared to patients who benefited of laparoscopic intervention (p = 0.0359). Early postoperative mobilization was encouraged for all patients, and statistical analysis of these characteristics did not indicate any significant difference for neither of the studied groups.

Postoperative medication represented an important part of our investigation, and we noticed that patients with classic hernioplasty benefited of significantly less painkillers and anticoagulant therapy. There were no statistically significant differences between the study groups in terms of antibiotic

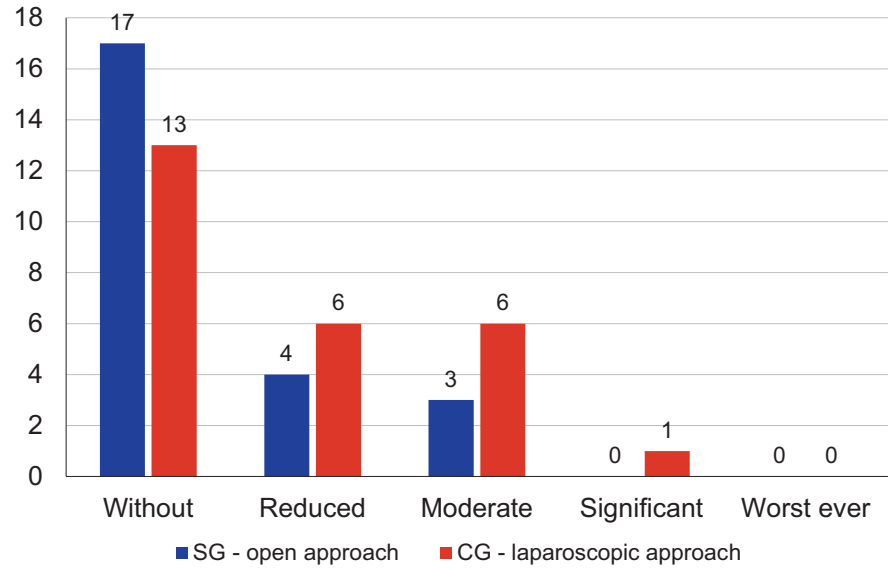

FIGURE 2. Distribution of postoperative pain

use. On the other hand, the length of hospital stay seemed to be significantly longer for patients with laparoscopic hernioplasty ($p = 0.0001$), while hospitalization costs were significantly higher in patients from the CG ($p = 0.0005$).

Follow-up

The second subanalysis in our study focused on patient follow-up. Figure 2 presents the distribution of postoperative pain among patients, which showed no significant differences between the two studied groups. The professional reintegration of the patients is illustrated in Figure 3, where a slightly difference can be observed between the two studied groups. Ventral patch-type hernioplasty seemed to assure faster return to work, but with no statistical significance ($p = 0.0944$). As for hernia recurrence, no reappearance of umbilical defects was registered in neither group during the six months of follow-up.

Esthetic issues after minimally invasive hernioplasty

The open surgical approach required a single incision, while in order to perform laparoscopic hernioplasty, the patients suffered at least three incisions in the abdominal wall. Regarding wound closing technique, the majority of patients from the CG benefited of intradermal suture. Furthermore, VSS assessment indicated a significantly higher

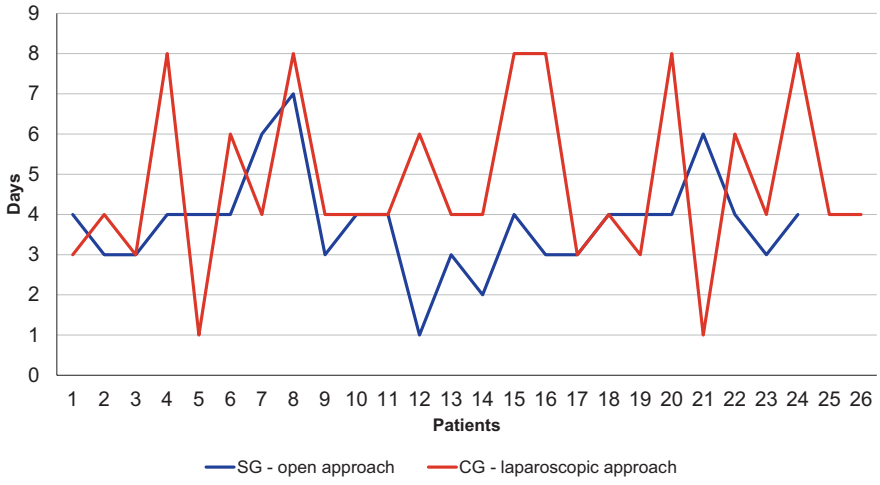

FIGURE 3. The professional reintegration of patients

index for patients from the CG (mean = 4 points), while ventral patch-type hernioplasty seemed to yield higher satisfaction among patients (mean = 2.5 points, p = 0.0109).

DISCUSSION

Primary considerations

There is no consensus on the ideal technique for repairing small and medium size umbilical hernias in adults, both presented surgical procedures representing current options for minimally invasive hernioplasty. The laparoscopic repair of parietal defects has been widely applied, and several studies have confirmed the procedure's benefits; the patch-type surgical mesh represents a new open-technique solution for small and medium size umbilical hernias, with at least similar efficacy as other treatment options.[4,5]

Choosing the right surgical intervention is not always easy, and the surgical decision should be guided by the general condition of the patients, as well as the clinical considerations. Regarding age and gender, the current literature is vague.[6] However, in our experience, advanced age associated with comorbidities requires cautious decision and a careful analysis of the risk-benefit ratio.

Obesity is a well-known risk factor for abdominal wall defects, but an excessive amount of adipose tissue can also cause difficulties during surgical interventions.[7] Therefore, patient selection had an important role in our study. Bonomo *et al.* also highlighted the importance of patient selection during minimally invasive surgery.[8] In many cases, the current literature recommends laparoscopic treatment of umbilical hernia in obese patients; contrariwise, Wassenber *et al.*, in a single center experience, highlighted the benefits of the ventral patch technique.[9,10]

The size of the parietal defect should also be considered when opting for the right surgical technique. Due to the technical difficulty of retro-rectus and preperitoneal dissection for these small abdominal wall defects, effective alternative approaches seem to be the use of a self-expanding mesh device introduced into the peritoneal cavity through a single microincision (open ventral patch method), or laparoscopic abdominal wall reinforcement. Results similar to ours can be found in the literature.[11,12]

Regarding mesh fixation, the two surgical procedures are completely different. During open surgical intervention, the composite patch is fastened with separate sutures in a few key points, while laparoscopic surgery requires surgical tacks in order to secure the composite mesh. Fixation of the synthetic patch seemed more easy to perform, a fact underlined by other researchers as well.[13]

There is a strong relationship between mesh fixation methods and surgical time, since laying and fastening the composite surgical mesh during laparoscopic hernioplasty requires additional minutes. In a multicenter prospective study, Berrevoet *et al.* assessed surgeon satisfaction related to ease of mesh use in 95% of surgeries and reported an average surgical time of 36.2 minutes, favoring the open ventral patch technique.[14]

Both surgical procedures represent minimally invasive techniques, therefore early mobilization of the patients is characteristic for these type of interventions. Vychnevskaia *et al.* and Vorst *et al.* highlighted the benefits of minimally invasive procedures.[15,16] The shorter operation time and the integrity of the abdominal wall allow patients to perform physical effort on the day of surgical intervention.

Medication after surgery is essential in avoiding serious complications and granting comfort in the postoperative period. In the present study, similar medication has been utilized for both of the studied groups, with slightly better results for patients from the open group regarding painkillers and anticoagulant therapy. As for antibiotic use, no differences worth mentioning were registered. The majority of patients benefited of prophylactic, single-dose antibiotic treatment prior to surgical intervention. Prolonged antibiotic intake was registered only in case of patients with high BMI who are more prone to wound complications. In a randomized controlled, multicenter trial, Ponten *et al.* mentioned similar considerations regarding postoperative medication.[17]

Both surgical interventions were generally associated with a short hospital stay. The minimally invasive approach assured patients early hospital discharge after a short postoperative recovery, and the ventral patch technique seems to ensure an even more reduced hospitalization. For instance, Zarmpis *et al.* reported an average hospital stay of 4 days.[18]

In the modern era of medical care, the financial aspects of therapeutic methods cannot be ignored. According to Roumm *et al.*, the costs of laparoscopic surgery are frequently high.[19] The present article identified an average hospitalization cost of 718.23 euro per patient with the composite ventral patch technique, while the mean cost of laparoscopic surgery was 1.65 time higher.

Follow-up

Postoperative pain represented the first aspect followed during the 6-month follow-up. Most of the time, minimally invasive surgical procedures are associated with reduced perioperative pain, a fact also confirmed during the pres-

ent study, both surgical methods being linked with a low pain index during postoperative recovery.

In general, less invasive surgical treatments ensure an early possibility for work resumption. Based on our experience, patients who benefited of the open approach and reinforcement of the abdominal wall defect with the ventral patch technique presented a slightly faster professional reintegration. However, Agca *et al*. found that this type of surgical intervention does not influence postoperative pain and early return to work significantly.[20]

During the follow-up period, no recurrence was registered for either of the studied groups. However, we must underline that the follow-up period was relatively short. Further studies with longer follow-up periods are needed to draw conclusions. Venclauskas *et al*. reported that laparoscopic surgery for umbilical hernia repair can be safely applied with favorable long-term outcomes regarding recurrence.[21] As for open repair with synthetic patch implantation, Ambe *et al*. reported a low recurrence rate for this type of intervention.[22]

Esthetics after umbilical hernioplasty

Nowadays, esthetic results are an important issue in general surgery. During our research, the following aspects were followed for defining an esthetic result: the number of abdominal incisions, wound closure techniques, and patient satisfaction regarding scar healing.

Regarding the number of incisions, the open technique with ventral patch implantation offers a more satisfying result, with a single microincision at the level of umbilicus (Figure 4), compared to laparoscopic hernioplasty, which requires at least three abdominal incisions.

As far as wound closing methods are concerned, the majority of patients from the laparoscopic group benefited of intradermal closure of the incisions. Being a more delicate area, we exclusively used separate surgical sutures for closing umbilical wounds.

Patient satisfaction regarding scar healing was estimated using the Vancouver Scar Scale, our results showing a lower VSS index during follow-up for the open hernioplasty group. In 2019, Berrevoet *et al*. published a large multicenter prospective study about the ventral patch technique, with results similar to our study. They concluded that open hernioplasty with ventral patch implantation offers satisfying results.[23]

LIMITATIONS OF THE STUDY

Our study has several limitations. Firstly, the fact that no recurrence was observed may be related to the relatively short follow-up period of 6 months; a longer follow-up period may identify several long-term complications. Secondly, the sample size was relatively small, and statistical significance had not been reached in several parts of the study. With a larger sample size, probably some of the statistical analysis would have reached significant thresholds.

CONCLUSION

Placement of a synthetic patch through a minimally invasive open approach as treatment for umbilical defects is associated with low recurrence rate, low postoperative pain, lower hospitalization costs, and high esthetic satisfaction. These confirm that hernioplasty with the ventral patch technique via open procedure is an effective option for small and medium size hernia repair.

CONFLICT OF INTEREST

Nothing to declare.

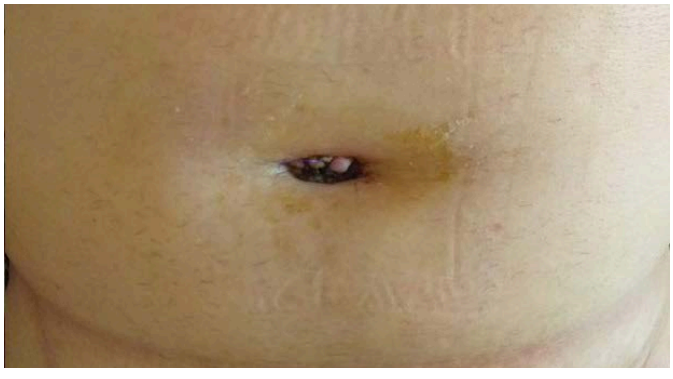

FIGURE 4. Postoperative esthetic results with the ventral patch technique

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ORIGINAL RESEARCH

CARDIOLOGY // IMAGING

Epicardial Fat Volume as a New Imaging-Based Feature Associated with Risk of Recurrence after Pulmonary Veins Ablation in Atrial Fibrillation

Emanuel Blîndu[1,2], Szilamér Korodi[3,4], Lehel Bordi[1,2,3], István Kovács[1,2,3], Imre Benedek[1,2,3]

[1] Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Târgu Mureș, Romania
[2] Clinic of Cardiology, Emergency Clinical County Hospital, Târgu Mures, Romania
[3] "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[4] Clinic of Cardiology, Emergency County Hospital, Miercurea Ciuc, Romania

CORRESPONDENCE

Szilamér Korodi
Str. Doctor Dénes László nr. 2
530173 Miercurea Ciuc, Romania
Tel: +40 266 324 193
E-mail: szilamerkorodi@yahoo.com

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Emanuel Blîndu • Str. 22 Decembrie 1989 nr. 76, 540124 Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail: emi.blindu@yahoo.com

Lehel Bordi • Str. Gheorghe Marinescu nr. 38, 540138 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: bordi_lehel@yahoo.com

István Kovács • Str. Gheorghe Marinescu nr. 38, 540138 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: kov_istvan@yahoo.com

Imre Benedek • Str Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: imrebenedek@yahoo.com

ABSTRACT

Background: Atrial fibrillation (AF), a common arrhythmia in clinical practice, is associated with a high rate of complications and an increased risk for thromboembolic events. Pulmonary vein ablation is a new therapeutic option to cure AF; however, it remains associated with a high rate of recurrence. In this study we aimed to identify the clinical characteristics and imaging-based features that may predict the risk of recurrence after pulmonary veins ablation in atrial fibrillation. **Materials and method:** Twenty-four patients with paroxysmal and persistent AF, who underwent radiofrequency catheter ablation and a 12-month follow-up were included in the study. Group 1 included 8 patients with AF recurrence, and group 2 included 16 patients with no AF recurrence. In all cases, cardiovascular risk factors, ejection fraction, left atrial diameter, atrial volumes, and epicardial fat volume were analyzed. **Results:** CT analysis revealed that patients with AF recurrence presented a significantly larger mean index of left atrial volume (59.57 ± 8.52 mL/m2 vs. 49.99 ± 10.88 mL/m2, p = 0.04), right atrial volume (58.94 ± 8.37 mL/m2 vs. 43.21 ± 6.4 mL/m2, p<0.0001), and indexed bi-atrial volume (118.5 ± 15.82 mL/m2 vs. 93.19 ± 16.42 mL/m2, p = 0.005). At the same time, CT analysis of the epicardial adipose tissue volume indicated that patients with AF recurrence have a larger amount of epicardial fat than those without AF recurrence (176.4 ± 100.8 mL vs. 109.8 ± 40.73 mL, p = 0.02). **Conclusion:** Left atrial diameter, indexed atrial volumes, and epicardial fat volume may be used as factors to identify patients at risk for developing recurrence after pulmonary vein ablation.

Keywords: AF recurrence, pulmonary vein ablation, indexed atrial volumes, epicardial adipose tissue

INTRODUCTION

Atrial fibrillation (AF) is the most common type of atrial rhythm disturbances, being associated with an increased risk for thromboembolic complications and heart failure. The increased incidence of this rhythm disorder can be attributed to an increased life expectancy and to a higher rate of predisposing factors. Although AF is not life-threatening, it significantly influences the quality of life through a series of anatomical and hemodynamic changes. A study published in 2014 has shown that AF affects 8 million patients in Europe, and these numbers are expected to increase to about 18 million by 2060, with higher incidence and prevalence rates in developed countries.[1] Estimates suggest a prevalence of AF of approximately 3% among adults aged 20 years or older, with a higher prevalence in the elderly and in patients with obesity, high blood pressure, heart failure, ischemic heart disease, valvulopathy, diabetes, or chronic kidney disease.[2–4] As the incidence of AF continues to increase, it is very important to identify therapies that are safe and effective, improving patients' symptoms and daily life.

Radiofrequency pulmonary vein (PV) ablation is a novel and complex procedure that has encountered increasing interest in the last decade. The exponential development of new techniques and the innovation of existing ones are reflected in clinical practice in a continuously increasing number of PV ablation procedures performed. This also leads to an increasing need to establish predictive factors for the success of PV ablation in AF.[5] To date, the success rates of ablation are not very satisfactory, reaching only 70% in patients with paroxysmal AF and 60% in patients with persistent AF.[6] Recurrences still remain a common problem after the ablation, affecting quality of life through symptomatic episodes and high readmission rates. The recurrence rate after AF ablation has been reported up to 45% in a study published in 2017.[7] Therefore, there is considerable clinical interest to identify factors that can predict the success of PV ablation, in order to develop personalized therapeutic strategies for each patient.

Several clinical characteristics have been described as being associated with an increased recurrence rate after ablation procedures such as age, gender, comorbidities (hypertension, obesity, diabetes mellitus, heart failure), or imaging-derived features of cardiac volumes, mainly the diameter or volume of the left atrium.[7–15] More recently, the amount of epicardial adipose tissue, assessed either by its thickness via echocardiography, or by its volume via cardiac computed tomography (CT), has been described as a reliable predictor for the risk of AF development or recurrence.[16,17] Given the heterogeneous clinical profile of patients with AF or with AF recurrence after PV isolation, identification of those factors that can predict maintenance of sinus rhythm after ablation could help the clinicians to better select the patients for this complex and expensive procedure. Furthermore, an optimal patient selection for interventional AF therapies could reduce the costs of care and avoid to expose them to unnecessary interventions.

In the present study, we sought to identify clinical and imaging-based predictors for the risk of recurrence at one year following radiofrequency catheter ablation in patients with paroxysmal and persistent atrial fibrillation.

MATERIALS AND METHOD

We analyzed 24 patients with paroxysmal and persistent AF, who underwent radiofrequency catheter ablation in the 2015–2018 period. All patients underwent radiofrequency ablation for AF using the PV isolation method and presented to follow-up at 1, 3, 6, and 12 months after the intervention. Prior to the procedure, all patients underwent contrast-enhanced cardiac CT for assessment of left and right atrial volumes, as well as for quantification of the epicardial adipose tissue using manual tracing.

Patients were divided into two groups, according to the presence or absence of AF recurrence during follow-up. Group 1 included 8 patients who presented AF recurrence in the first year after ablation, and group 2 included 16 patients without any sign of recurrence during the 12-month follow-up.

The study was approved by the Ethics Committee of the institution where the procedures were performed and was conducted in compliance with the ethical principles stated in the Declaration of Helsinki. All patients gave informed consent for their participation in the study.

Ablation Protocol

After venous access using the Seldinger technique, one sheath was placed in the left femoral vein and two sheaths in the right femoral veins. A 6F decapolar diagnostic catheter was placed in the coronary sinus, one non-steerable sheath was used for positioning the mapping catheter (Lasso) and the other steerable sheath for placing an externally irrigated contact force-sensing ablation catheter. Interatrial septal puncture was performed using transesophageal echocardiography guidance. 3D electroanatomically mapping of the left atrium and PVs was performed using the EnSiteTM NavXTM system, EE3000

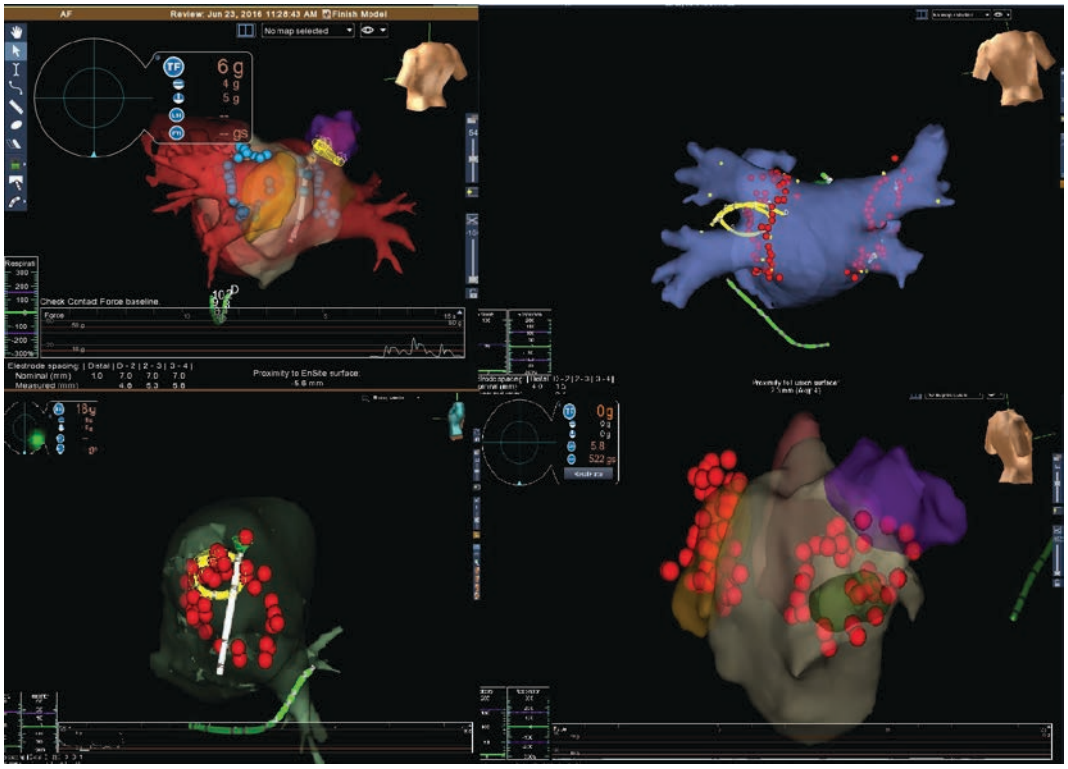

FIGURE 1. 3D maps of the left atrium and PVs. The red tags represent ablation points around the right and left pulmonary veins' ostia. The yellow catheter is the Lasso catheter, positioned in pulmonary vein. The green catheter is placed in the coronary sinus

version (St. Jude Medical, St. Paul, MN, USA), associated with advanced techniques of fusion imaging, fusing 3D mapping images with those acquired by CT. After inserting the mapping catheter in the ostium of the PV, radiofrequency catheter ablation was initiated in order to isolate the PVs. Ablation was performed by applying a 30 W energy and a 10 to 30 g pressure with temperature adjusted at 50 °C, using an irrigated contact force-sensing catheter positioned on the left atrial wall. A PV was considered electrically isolated when no electrical potentials were identified or when a successful PV potential dissociation was demonstrated.

CT Analysis

The cardiac CT acquisition was performed using 64- and 128-slice CT (Somatom Sensation 64-slice CT, Somatom Definition 128-slice CT, Siemens Healthcare, Germany), and the Syngo.via Frontier software (Siemens Healthineers, Erlangen, Germany) was used for image post-processing. Quantification of epicardial fat volume was performed by tracing and manually adjusting epicardial contours, as part of postprocessing protocols. Adipose tissue was identified using the attenuation references between –190 and –30 Hounsfield units. Atrial endocardial profiles were traced semi-automatically on the axial slices.

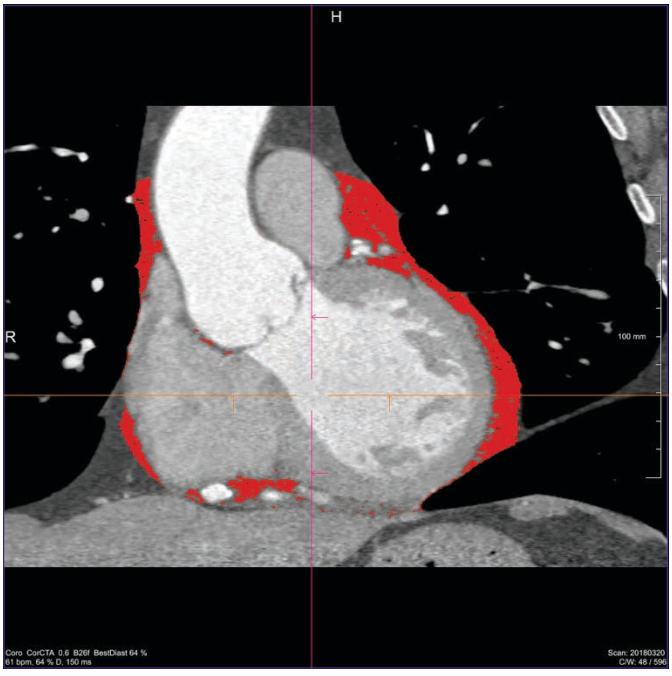

FIGURE 2. Exemplification of epicardial adipose tissue quantification using native CT

TABLE 1. Baseline characteristics of the study population

Age (years)	57.25 ± 11.72
Gender, male, n (%)	14 (58.33%)
History	
Hypertension, n (%)	17 (70.83%)
Diabetes, n (%)	7 (29.16%)
Dyslipidemia, n (%)	5 (20.86%)
Obesity, n (%)	12 (50%)
Clinical characteristics	
eGRF (mL/m²/min)	79.85 ± 17.51
Ejection fraction (%)	53.21 ± 5.09
Left atrium (mm)	41.54 ± 6.43
Heart failure, n (%)	10 (41.66%)
CAD, n (%)	10 (41.66%)
AF type	
Persistent AF	10 (41.66%)
Indexed atrial volume	
LAVI (mL/m²)	58.18 ± 10.98
RAVI (mL/m²)	48.45 ± 10.41
BAVI (mL/m²)	101.6 ± 20.02
Epicardial fat volume (mL)	132 ± 72.14

Atrial volumes were calculated by the software, interpolating the endocardial tracings. Indexed atrial volumes were calculated by indexing atrial volume to body surface area. Body surface area was calculated using the DuBois formula after recording height and weight.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). Quantitative data were expressed as mean ± standard deviation, and data were compared using Student's t test or the Mann-Whitney test when appropriate. Qualitative values were expressed as integer values and percentages, and the difference between groups was analyzed using the Chi2 test or its appropriate variants. The threshold for statistical significance was set at an alpha of <0.05.

RESULTS

Baseline characteristics of the study lot, including demographic data, medical history, comorbidities, and clinical and imaging features of the 24 patients included in the study are listed in Table 1.

There were no statistically significant differences between the two groups in respect to age, gender, or cardiovascular risk factors (Table 2). There was no significant difference between the study groups regarding the left ventricular ejection fraction evaluated by 2D echocardiography (51.88 ± 6.55% vs. 53.88 ± 4.28%, p = 0.3); however, clinical symptoms of heart failure were significantly more frequent in patients with AF recurrence following ablation (p = 0.03). Also, left atrium diameter was significantly larger in patients with AF recurrence after catheter ablation (p = 0.04) (Table 2).

CT analysis revealed that patients with AF recurrence presented a significantly larger mean index of left atrial volume (LAVI) (59.57 ± 8.52 mL/m² vs. 49.99 ± 10.88 mL/m², p = 0.04). Also, the indexed right atrial volume (RAVI) and the indexed bi-atrial volume (BAVI) were higher in the group with AF recurrence (58.94 ± 8.37 mL/m² vs. 43.21 ± 6.4 mL/m², p <0.0001 for RAVI and 118.5 ± 15.82 mL/m² vs. 93.19 ± 16.42 mL/m², p = 0.005 for BAVI). Figure 3 indicates the difference between the groups in respect to anatomic features as assessed by cardiac CT, namely calculated indexes of atrial volumes.

At the same time, CT analysis of the epicardial adipose tissue volume indicated that patients with AF recurrence have a larger amount of epicardial fat compared with patients without recurrence (176.4 ± 100.8 mL vs. 109.8 ± 40.73 mL, p = 0.02). Figure 4 represents the difference between the groups in respect to the volume of epicardial fat as computed by CT.

TABLE 2. Clinical and echocardiographic features associated to AF recurrence after ablation

	AF recurrence n = 8	No AF recurrence n = 16	p value
Heart failure, n (%)	6 (75%)	4 (25%)	0.03
Left atrium (mm)	45.25 ± 5.14	39.69 ± 6.33	0.04
LAVI (mL/m²)	59.57 ± 8.52	49.99 ± 10.88	0.04
RAVI (mL/m²)	58.94 ± 8.37	43.21 ± 6.74	<0.0001
BAVI (mL/m²)	118.5 ± 15.82	93.19 ± 16.42	0.005
Epicardial fat volume (mL)	176.4 ± 100.8	109.8 ± 40.73	0.02

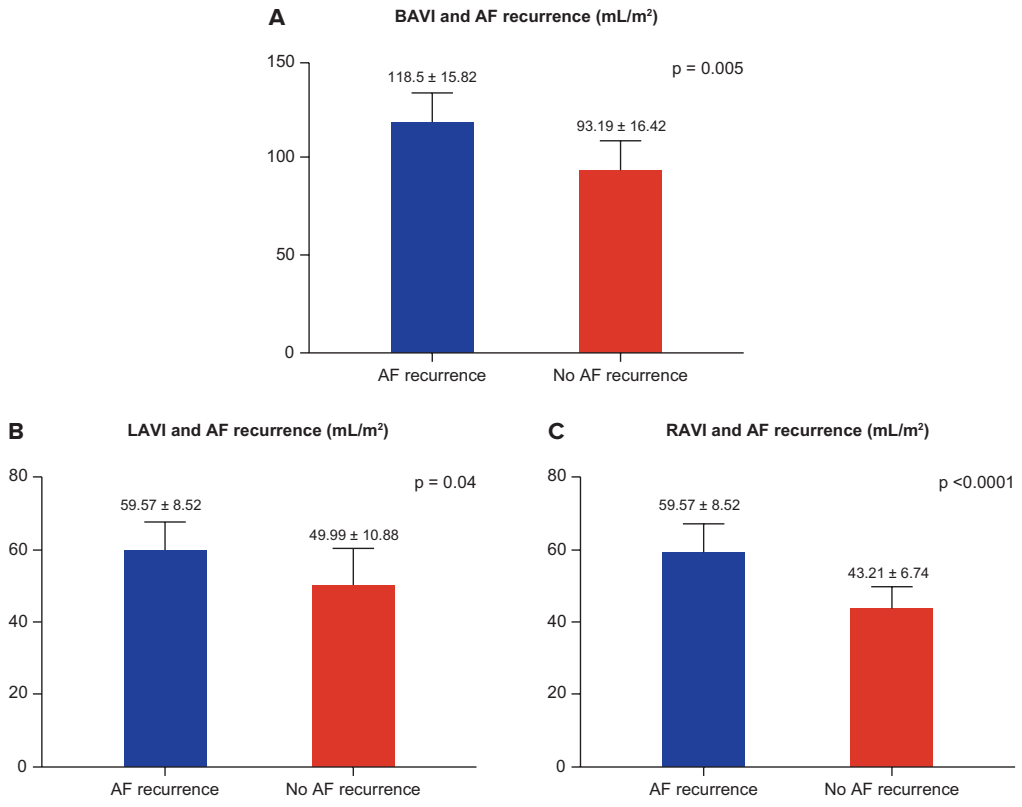

FIGURE 3. Atrial volumes and risk of recurrence after AF ablation. **A** – Bi-atrial indexed volume in the study groups; **B** – Right indexed atrial volume in study groups; **C** – Left indexed atrial volume in the study groups

DISCUSSIONS

AF is a disease with a high prevalence and is associated with increased mortality and morbidity. PV catheter ablation has emerged as a first-line treatment option, especially in cases resistant to antiarrhythmic medication.[18] Immediate success rates have been achieved using PV catheter ablation, but maintaining long-term sinus rhythm in these cases still remains a challenge. Given the average success rates, it is necessary to investigate factors associated to a lower risk of recurrence, which may facilitate a proper selection of patients for ablation. In the last years, several studies have tried to identify predictive factors for a favorable long-term outcome, but reliable markers predicting the maintenance of sinus rhythm have not been identified.[9,19,20] The contribution of this study relies on the description of the role of new imaging-based features associated with the risk of AF recurrence, such as LAVI, RAVI, BAVI, and the volume of epicardial adipose tissue, along with other factors investigated also in other studies, such as AF type, cardiovascular risk factors, left atrium diameter, ejection fraction, and renal function.

Our study aimed to identify new predictive factors for the risk of recurrence based on the differences between patients who presented AF recurrence and those who maintained sinus rhythm. The results of this study indicate that the diameter of the left atrium, the presence of heart failure, atrial volumes, and the amount of epicardial adipose tissue are predictive factors for the risk of arrhythmia recurrence at one year after radiofrequency ablation of AF.

The link between the enlargement of the left atrium and the recurrence of AF is still controversial. In the long term, an enlarged left atrium leads to cardiac remodeling,

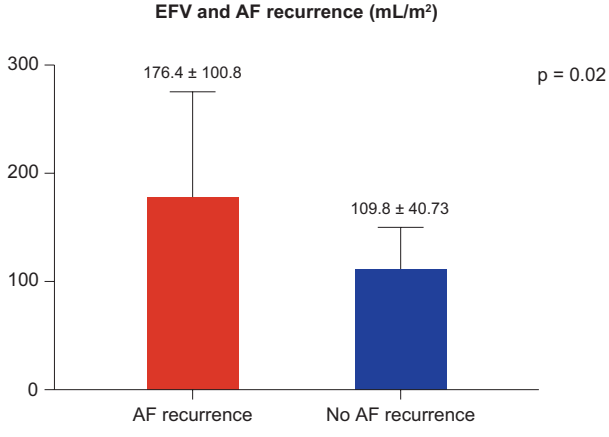

FIGURE 4. Epicardial fat volume in the study groups

manifested by reduced myocardial tissue and increased fibrosis. The increased diameter of the left atrium, reflecting diastolic dysfunction and increased filling pressure due to atrial remodeling, contributes to the vulnerability of atrial myocytes to arrhythmia.[9] As it has been shown that the size of the left atrium is an important factor in the occurrence and maintenance of AF, this could be used in the same way to predict the recurrence after intervention. In a meta-analysis on risk factors for recurrence of post-ablation arrhythmias, an increased diameter of the left atrium was found to have predictive value for AF recurrence.[13] In our study, patients who had maintained sinus rhythm had a significantly smaller left atrium diameter compared to patients with recurrence.

AF and heart failure are two linked conditions, each one predisposing to the other one, and are associated with considerable mortality and morbidity. Important changes in the prevalence of AF in patients with heart failure have been observed, AF occurrence being directly linked to the severity of heart failure, from less than 10% in patients with NYHA class I to almost 50% in patients in NYHA class IV.[21] In a recent study, patients with heart failure had an increased susceptibility to develop recurrences, compared to patients with normal left ventricular function. The main limitation for using left atrial diameter as a measure of the risk of recurrence relies on its representation as a one-dimensional value, which can underestimate or overestimate the true size of the atrium. Therefore, assessment of the atrial volume, especially body surface-related volume, is indicated for a more precise assessment of the left atrium, having a superior predictive value.[15] Comparing atrial volumes between the two groups, we observed that patients with AF recurrence had significantly larger left, right, and bi-atrial indexed volumes than patients who maintained sinus rhythm during follow-up. A number of studies found LAVI to be predictive of AF recurrence, but no consensus was reached on the predictive cut-off value.[15,22] At the same time, there are few data regarding the effect of an increased right atrial volume on the risk of AF recurrence after PV isolation. Given that ablation targets the myocardial tissue surrounding the PV, the right atrium remains "untreated", thus maintaining an increased risk of recurrence in patients with a higher right atrial volume. In one study it was found that RAVI has predictive value only for early recurrences of AF, while LAVI has predictive value in recurrences at one year.[23]

Epicardial adipose tissue is a special type of fat located in the space between the myocardium and the visceral pericardium. This tissue is not just an anatomical depot of fat, but also an active tissue that secretes cytokines and pro-inflammatory hormones, being involved in the pathogenesis of both structural heart disease and the coronary heart disease independent of body mass index.[24] Several studies have evaluated the association between pericardial fat and AF and have shown that an increased volume of pericardial adipose tissue, independent of intrathoracic or intraabdominal adipose tissue, results in a higher risk of AF.[16,17] Another important observation is that in patients with persistent AF, the volume of pericardial adipose tissue is higher than in patients with paroxysmal AF or in patients with sinus rhythm.[25] Several studies have shown that following PV ablation, patients with increased epicardial fat volume had more frequent recurrences, regardless of body mass index and body surface area.[26–28] In this paper, the volume of epicardial adipose tissue was determined using computed tomography, and a lower epicardial fat volume was associated with maintenance of the sinus rhythm one year after the intervention.

CONCLUSIONS

AF is a common disorder in clinical practice and is often characterized by recurrences. Therefore, the identification of particular features that can predict the maintenance of sinus rhythm after PV ablation represents an important goal in clinical practice, allowing a more appropriate patient selection. This study shows that left atrial diameter, indexed atrial volumes, and epicardial fat volume may be used as reliable indicators of the risk to develop AF recurrence after pulmonary vein ablation.

CONFLICT OF INTEREST

Nothing to declare.

ACKNOWLEDGEMENT

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ORIGINAL RESEARCH // BRIEF REPORT

EPIDEMIOLOGY // PERIODONTOLOGY

Incidence of Periodontal Disease among Adolescents

Delia-Roxana Dicu[1], Ana Petra Lazăr[2], Luminița Lazăr[3]

[1] Faculty of Dental Medicine, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[2] Department of Oral Rehabilitation and Occlusology, Faculty of Dental Medicine, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[3] Department of Periodontology and Oral Diagnosis, Faculty of Dental Medicine, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

CORRESPONDENCE

Ana Petra Lazăr
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: analazar_mvfa@yahoo.com

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ABSTRACT

Background: Despite the scarcity of studies regarding periodontal disease in young patients (teenagers and young adults), it seems that this disorder is also affecting the young population. Risk factors for periodontal disease include older age, chronic tobacco use, male gender, habits regarding oral hygiene, educational status, ethnicity, and financial status. **Aim:** This study aimed to evaluate the periodontal health among adolescents in two high schools in Târgu Mureș that had dental practices. **Material and Methods:** An online questionnaire consisting of 16 questions was distributed among high schoolers of Târgu Mureș. Data about personal characteristics, oral hygiene habits, family history of periodontal disease, risk factors for periodontal disease, and symptoms of periodontal disease observed by the respondents were collected and analyzed. **Results:** Out of the 501 teenagers who responded to the online questionnaire, 114 (22.8%) were 18 years old and were mostly females (88.2%). Regarding oral hygiene habits, 75.8% prefer a manual toothbrush over an electric toothbrush, 66.7% brush their teeth twice a day, and 54.1% practice a horizontal method of toothbrushing. Mouthwash was the most used oral hygiene aid (58.3%). Family history of periodontal disease was observed in 21.9% of respondents. As favoring factors, nicotine addiction (23.8%), bruxism (24.4%), interposition of various objects between teeth (48.3%), past or present orthodontic treatments (38.7%) were recorded. Symptoms of gingivitis and periodontitis, such as gingival bleeding (81.4%), redness of gingiva (39.3%), increased gingival volume (44.5%), gingival retraction (22.8%), and halitosis (81%), were present in the responding teenagers. **Conclusions:** In this study, periodontal disease was affecting mostly adolescent females who are practicing inappropriate methods of toothbrushing with inadequate frequency.

Keywords: periodontal health, adolescents, gingivitis, periodontitis

Delia-Roxana Dicu • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 748 864 900, E-mail: dicu.delia@yahoo.com

Luminița Lazăr • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: luminita.lazar15@gmail.com

INTRODUCTION

Nowadays, the major focus of dental medicine is maintaining a lifelong healthy state of the hard and soft tissues. In order to achieve this goal, periodontal diseases should be diagnosed early in life, starting from childhood and adolescence, as they affect more than half of the teenage population, which are mainly asymptomatic. Bimstein (1991) stressed the importance of prevention, early diagnosis, and early treatment of periodontal diseases in children and adolescents, because the prevalence and severity of periodontal diseases is high. Also, the incipient periodontal diseases found in childhood may develop into advanced periodontal diseases during adulthood, and there is a direct association between periodontal disease and systemic conditions. Patients, families, or populations at risk could be identified and included in special prevention or treatment programs, as prevention and treatment of most periodontal diseases is relatively simple and very effective, providing lifetime benefits.[1,2]

This study aimed to evaluate periodontal health among adolescents in two high schools in Târgu Mureș that had a dental practice.

MATERIAL AND METHODS

The study was initially created as a clinical trial involving the clinical examination of teenagers from "Alexandru Papiu Ilarian" National College and "Traian Săvulescu" Agricultural College that had a dental practice. We determined that 10th and 11th graders were appropriate to be examined. The first step included a presentation concerning periodontal health and a questionnaire about personal characteristics, oral hygiene habits, family history of periodontal disease, favoring factors for periodontal disease, and symptoms of periodontal disease. Then, the next stage included an objective clinical examination in school dental practices using dental examination instruments (probe, mirror, tweezers) and a periodontal probe. We examined plaque index, tartar index, gingival index, clinical attachment loss, papillary bleeding index, mobility, furcation involvement, and periodontal probing depth on Ramfjord teeth. The study was approved by the Ethics Committee of "George Emil Palade" University of Medicine and Pharmacy, Science and Technology of Târgu Mureș was obtained. All participants gave informed consent for participation in this study and all the study procedures were conducted in accordance with the principles stated in the Declaration of Helsinki.

Due to the worldwide epidemiologic context of the time when we were about to start the study (March 2020), a safe clinical examination was not possible; therefore, we adjusted accordingly and narrowed the study down to an online questionnaire. Thus, the present study was based on a questionnaire consisting of 16 questions that was distributed among the high schoolers of Târgu Mureș. When formulating the questions, we used colloquial language in order to have a greater addressability. Data about personal characteristics, oral hygiene habits, family history of periodontal disease, risk factors for periodontal disease, and symptoms of periodontal disease observed by the respondents were collected and analyzed.

The resulting data were collected and interpreted using Google Forms and Microsoft Excel.

RESULTS

Data from 501 responding adolescents were collected and analyzed. The respondents were aged between 14 and 19 years, most of them being 18 years old. The majority of the respondents (88.2%) were female. Regarding oral hygiene habits, 75.8% stated that they prefer a manual toothbrush over an electric toothbrush, 66.7% brush their teeth twice a day, and 54.1% practice a horizontal method of toothbrushing. Mouthwash was the most used oral hygiene aid (58.3%). Data about oral hygiene habits is presented in Table 1.

Family history of periodontal disease was observed in 21.9% of the study population.

Favoring factors that play an important role in the development of periodontal diseases were also addressed in the questionnaire. The answers revealed that 23.8% of the participants were smokers, 24.4% practiced the habit of bruxism, 48.3% had viciously interposing objects between their teeth, and 38.7% were undergoing an orthodontic treatment.

Given the lack of an objective clinical examination, we focused some of the questions on the symptoms of gingivitis and periodontitis in order to have a general view regarding these pathologies. When asked about gingival bleeding, 81.4% of the respondents answered positively. A similar percentage of participants (81%) admitted to have halitosis, and 39.3% have observed redness of the gingiva. Increased gingival volume and gingival retractions were observed by 44.5% and 22.8% of respondents, respectively.

DISCUSSIONS

Despite the scarcity of studies regarding periodontal disease in young patients (teenagers and young adults), it seems that this disorder is also affecting the young popula-

TABLE 1. Distribution of oral hygiene habits among the responding adolescents

Question	Possible answers	Answered yes (%)
Type of toothbrush	Manual	75.8
	Electric	24.2
Daily toothbrushing frequency	Does not brush on a daily basis	0
	Once a day	33.1
	Twice a day	66.7
Toothbrushing method	Horizontal	54.1
	Vertical	45.9
Auxiliary method of removing dental plaque	Mouthwash	58.3
	Interdental floss	34.1
	Wooden toothpick	29.1
	Oral irrigator	13
	Interdental toothbrush	12

tion. Risk factors for periodontal disease include older age, chronic tobacco use, male gender, habits regarding oral hygiene, educational status, ethnicity, and financial status.[3,4] In the present study, we aimed to assess the prevalence of periodontal disease in the high school population of a medium-sized city in Central Romania. Although initially designed as a cross-sectional clinical study, the global COVID-19 pandemic situation has led to a drastic change in the research methodology and study design. Therefore, we conducted a questionnaire-based study on the clinical signs and symptoms of periodontal disease, and also its associated risk factors, on a population of young students aged between 14 and 19 years, from two high schools in Târgu Mureș.

Given the lack of an objective clinical examination, we considered the triad of gingival bleeding – increased gingival volume – redness of gingiva as an indicator of gingivitis, regardless of the causal factor (dental plaque, hormones, manifestation of general disease etc.). Gingivitis was present in a relatively large proportion of respondents (26.5%). Moreover, we considered the simultaneous presence of halitosis and gingival retraction as indicator of periodontitis, which was present in a lower rate (19.3%). The gender distribution of subjects with periodontitis and gingivitis in our study population was skewed towards female respondents, which was similar to a study conducted in Bucharest. On the other hand, two international studies found that males presented higher odds for periodontal disease compared to females.[5,6]

Regarding the age of the participants, there was a tendency for the prevalence of gingivitis and periodontitis to increase with age. The increasing trend of gingivitis and periodontitis during puberty and adolescence could be related to hormonal influences over dental plaque and gingival tissue.[7,8] Daily toothbrushing frequency was similar for both individuals who use a manual toothbrush or an electric toothbrush. However, regardless of the type of toothbrush used, the percentage of teenagers who brush their teeth twice a day was almost double compared to those who brush their teeth once a day. The efficiency of toothbrushing was also assessed. Gingivitis was more frequent (36.1%) among respondents who brush their teeth once a day and among those who use an electric toothbrush (28.9%). The latter result is inconsistent with other studies that report an increased dental plaque removal using an electric toothbrush by 4% to 29.6%.[9–11]

By adolescence, people should grasp the correct technique of toothbrushing, which is the vertical one. Most of the respondents were using a horizontal technique, which demonstrates the lack of oral hygiene education. The main consequence of horizontal toothbrushing is gingival retraction, which is also directly related to bristle hardness, the duration of each toothbrushing session, as well as the frequency of changing a used toothbrush.[12,13] Adolescents seem to show a great interest in auxiliary methods of removing dental plaque, using mostly mouthwash, interdental floss, and wooden toothpicks, although they are not proven to decrease dental plaque; only interdental brushes showed a decrease in dental plaque (32%) and gingivitis (34%).[14–16]

Gingivitis was predominant among respondents who reported a family history of periodontal disease, although other studies did not confirm whether the disease has a genetic transmission or it is a result of environmental factors.[17,18]

According to the World Health Organization, nicotine addiction exerts a great influence on oral health, being frequently associated with a poor oral hygiene and the pres-

ence of red complex periodontal pathogens.[19,20] Although most of the international studies agree that most smokers are males, our study shows an increased percentage of female smokers (25.4% vs. 23.5%) and consequently, an increased percentage of gingivitis and halitosis. Other major contributing factors to gingivitis and gingival retraction are bruxism and the vicious habit of interposing various objects between teeth, which were relatively frequent in the questioned population. It is proven that nocturnal bruxism is present in children and adolescents more often than in adults, but it does not cause gingivitis or gingival retraction without the presence of dental plaque.[2,21–24]

Orthodontic materials increase the retentivity of the dental arch and, consequently, dental plaque build-up and the development of periodontal disease. Gingivitis was more frequent in teenagers with orthodontic treatment (34.5%) in our study. This result is supported by other studies which state that dental plaque build-up and hyperplastic gingivitis occur in the first two months after starting the orthodontic treatment.[25,26] Patients treated with removable materials showed a decreased plaque index and gingivitis due to superior cleaning possibilities compared to fixed appliances.[27] Gingival retractions are also increased in teenagers with orthodontic treatment (24.2%), even though they are not specific to this age group.[28]

Study limitations

The major limitation of this study was the difficulty to conduct a more objective clinical examination, in the absence of which the results have only an indicative value. Other sources of error could be misinterpretation of symptoms by the respondents or truncated information, and misinterpretation of results. The study supports further additions and improvements by adding a clinical examination as it was initially intended.

Such studies are of great value in the current clinical activity because they evaluate the state of the general population, and through these studies, health education programs focused on oral health can be implemented. Furthermore, epidemiologic studies justify and support therapeutic protocols by highlighting the risk factors for the evaluated disorder.

CONCLUSIONS

In this study, periodontal disease was affecting mostly adolescent females who are practicing inappropriate methods of toothbrushing with inappropriate frequency. Although the respondents were keen on using auxiliary methods of removing dental plaque, their effectiveness has not been demonstrated. Bruxism is a major favoring factor for periodontal disease due to an increased prevalence of gingivitis and gingival retraction among adolescents that practice this habit. Another favoring factor, nicotine addiction, can cause gingivitis and halitosis among female adolescents. Orthodontic appliances cause increased dental plaque retention leading to gingivitis and gingival retraction.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH // BRIEF REPORT

PUBLIC HEALTH // EPIDEMIOLOGY

Immunosuppressive Medication and Non-Rejection-Related Complications Following Heart Transplantation

Dumitru Costel[1], Dana Ghiga[2], Simona Voidazan[3], Alexandra Grosan[4], Dan Simpalean[5], Anca Sin[6]

[1] "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[2] Discipline of Methodology of Medical Scientific Research, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[3] Discipline of Epidemiology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[4] Discipline of Pharmacology and Clinical Pharmacy, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[5] "Filantropia" Clinical Hospital, Bucharest, Romania
[6] Discipline of Cell Biology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

CORRESPONDENCE

Dumitru Costel
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: costimv@yahoo.com

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ABSTRACT

Background: Although the clinical evolution of a patient with heart failure is initially improved by transplantation, a number of potential complications may occur in the post-transplant period, which may be directly related to the effects of chronic immunosuppression. The purpose of this study was to analyze the occurrence and frequency of post-transplant complications related to immunosuppressive treatment in the Institute of Cardiovascular Diseases and Transplantation of Târgu Mureș, Romania. **Material and methods:** This is a descriptive study including 53 patients out of a total of 71 patients who underwent cardiac transplantation between 2000 and 2017 in the Institute of Cardiovascular Disease and Cardiac Transplantation in Târgu Mureș, Romania. Data were collected from the patient files and included demographic, clinical and laboratory data, as well as information about post-transplant complications related to immunosuppressive treatment. **Results:** The mean age of patients undergoing heart transplantation was 40.72 ± 14.07 years, the majority of patients being male (84.91%) and living in an urban environment (56.60%). The average length of hospital stay was 33.6 days. From the total number of patients, 7 (13.2%) presented post-transplantation bacterial infections, while antibodies indicating the presence or history of B hepatitis, toxoplasma, and cytomegalovirus infection were identified with a relatively high incidence in the study population. **Conclusions:** Infections following surgery are probably the most common post-transplant pathology, the primary reason being the administration of immunosuppressive medication.

Keywords: cardiac transplant, postoperative complications, immunosuppression

Dana Ghiga • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551

Simona Voidazan • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551

Alexandra Grosan • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551

Dan Simpalean • Blv. Ion Mihalache nr. 11, 011171 București, Romania. Tel: +40 21 318 89 37

Anca Sin • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551

INTRODUCTION

Heart transplantation is the treatment of choice in severe cases of end-stage heart failure.[1,2] In the absence of heart transplantation, the management of these critical cases is associated with a poor prognosis.[3–5] Cardiac transplantation has shown a very good long-term survival rate in patients with dilative cardiomyopathy and end-stage coronary heart disease, with up to 85% survival in the first year after transplant, 75% at 5 years, and 56% at 10 years.[6,7] Although the clinical evolution of a patient with heart failure is initially improved by transplantation, a number of potential complications may occur following the intervention, which may be directly related to the effects of chronic immunosuppression, mandatory to prevent the rejection of transplanted hearts.

AIM OF THE STUDY

The purpose of this study was to analyze the occurrence and frequency of post-transplant complications related to immunosuppressive treatment in the Institute of Cardiovascular Diseases and Transplantation of Târgu Mureș, Romania.

MATERIAL AND METHODS

This is a descriptive study including 53 patients out of a total of 71 patients who underwent cardiac transplantation between 2000 and 2017 in the Institute of Cardiovascular Diseases and Cardiac Transplantation in Târgu Mureș, Romania. Data were collected from the patient files and included demographic, clinical and laboratory data, as well as information about post-transplant complications related to immunosuppressive treatment. The collected data were analyzed using descriptive statistical methods. Continuous variables were expressed as mean ± standard deviation, and quantitative data as proportions. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, and in agreement with the good clinical practice measures. The study was approved by the local ethics committee, and all patients gave informed consent for participation in the study.

RESULTS

The mean age of patients undergoing heart transplantation was 40.72 ± 14.07 years, the majority of patients being male (84.91%) and living in an urban environment (56.60%). The average length of hospital stay was 33.6 days.

Infectious complications

From the total number of patients, 7 (13.2%) presented post-transplantation bacterial infections: *Klebsiella pneumoniae* was found in 2 cases, while *Clostridium difficile*, *Staphylococcus aureus*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* were identified in the rest of 5 cases.

Viral infections were also diagnosed with a high frequency following heart transplantation. Antibodies indicating the presence or history of B hepatitis, *Toxoplasma*, and *Cy-*

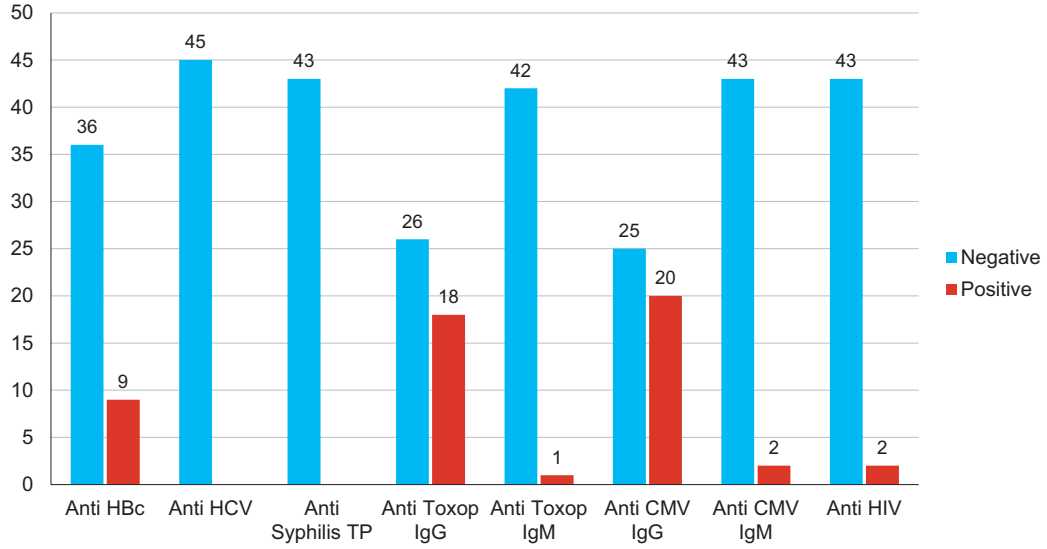

FIGURE 1. The distribution of positive-tested antibodies in the studied population

tomegalovirus (CMV) infection were identified with a relatively high incidence in the study population (Figure 1).

Renal dysfunction

Cyclosporine-induced nephrotoxicity remains a medical challenge in cardiac post-transplant management. In our study, only 1 (2%) patient out of 53 was diagnosed with renal failure post-cardiac transplant. Following heart transplantation, the mean serum levels of urea and creatinine were 61.13 ± 30.87 mg/dL and 1.002 ± 0.932 mg/dL, respectively.

Hyperlipidemia

We assessed the incidence of hyperlipidemia with multifactorial origin and found mean cholesterol values of 381.0 ± 175.0 mg/dL and mean LDL-cholesterol values post-transplant of 220.1 ± 63.38 mg/dL.

DISCUSSIONS

Post-transplant pathology – development of new clinical conditions favoring infections

According to published literature, post-transplant evolution is frequently marked by the development of new clinical conditions which, associated with immunosuppressive treatment, may favor the development of severe infections, reducing the defensive capacity of the body. These conditions include new-onset diabetes, hypertension, hyperlipidemia, renal dysfunction, tumors, or thyroid diseases.

Almost 20% of patients surviving transplant develop diabetes in the first year after the intervention, but 5 years later only 15% can be classified as diabetic. This is most likely caused by the use of decreasing doses of corticosteroids. It has not yet been proven whether transplant patients need to be managed differently in terms of blood glucose, glycated hemoglobin, or medicinal agents used in therapy.[8,9] Data from the international literature also show that hypertension after transplantation is common, with an incidence of 70–90% in patients treated with cyclosporine and 30–50% in those treated with tacrolimus.[10,11] Both tacrolimus and cyclosporine may influence blood pressure levels and favor hyperlipidemia, as shown by Han *et al.*[12]

Regarding renal dysfunction, it has been demonstrated that immunosuppressive therapy with cyclosporine has improved graft function and survival time in transplant patients. However, cyclosporine-induced nephrotoxicity remains a medical challenge for post-heart transplant management. Cyclosporine, a highly nephrotoxic immunosuppressive agent, causes an initially reversible decrease in glomerular filtration rate (GFR), possibly through arteriolar vasoconstriction. The mechanisms by which renal vasoconstriction and decreased filtration rates occur are not known, but it has been suggested that abnormalities of endogenous vasoconstrictor and vasodilator mechanisms may be responsible. In this context, an oral dose of cyclosporine (5 mg/kg) was found to strongly affect renal hemodynamics, both in patients with cardiac transplantation and chronic treatment and in healthy volunteers, in whom 10 mg/kg cyclosporine caused an 18% decrease in GFR. Increased serum creatinine levels due to cyclosporine may be associated with hypertension, a disproportionate increase in serum urea, hyperkaliemia, increased uric acid levels, mild proteinuria (usually less than 1 g/24 h), and decreased fractional sodium excretion. Increased blood pressure may be associated with decreased sodium excretion, stimulation of the renin-angiotensin system, increased local endothelin synthesis and/or decreased local nitric oxide synthesis. Treatment interruption or lowering the dose of cyclosporine may sometimes stabilize kidney function, but even when renal function remains stable, the morphological lesions and proteinuria may progress further.[13–15] Tacrolimus, another immunosuppressive agent, is also associated with a higher risk of nephrotoxicity. This reaction may be explained by the increase in the production of oxygen free radicals that induce kidney damage.[13–15]

Hyperlipidemia is one of the most common metabolic dysfunctions encountered in transplanted patients, with an incidence of 60–80%. Studies show that tacrolimus and cyclosporine can influence blood pressure (hypertension) and hyperlipidemia.[16–18] It has a multifactorial origin, with mechanisms dependent on abnormalities of the pre-existing lipid status, cyclosporine therapy, and corticosteroids. Discontinuation of corticosteroid treatment has been shown to be associated with low cholesterol. Cyclosporine A (CsA)-induced hyperlipidemia is already known and is a clinically significant problem. CsA affects the metabolism of lipids and lipoproteins; however, the basic mechanisms that cause dyslipidemia are not well known. Additional studies are needed to help identify immunosuppressive agents that do not cause hyperlipidemia, or to support the development of strategies to effectively monitor CsA-induced hyperlipidemia.[19]

Youn *et al.* performed a retrospective analysis on 17,587 patients from the International Society of Heart and Lung Transplant (ISHLT) registry over a 10-year period (2001–2011) in order to identify the occurrence of malignant tumors after heart transplantation.[20] Over 10% of the moni-

tored patients have developed de novo malignancy in 1 to 5 years after transplantation. The authors reported a 12.4% increase in de novo malignancies in patients transplanted between 2006 and 2011, compared with 10% in patients treated between 2000 and 2006, resulting in an absolute increase of 2.4%. Skin cancer accounted for most of this increase, solid organ malignancy was responsible for a small increase, and the incidence of post-transplant lymphoproliferative disease (PTLD) was low (approximately 1%) in both cohorts compared to the previously reported 3% to 9%.[21] These results are diametrically opposed to those in pediatric heart transplant patients, in whom PTLD is the major post-transplant malignancy. This low incidence may also show that PTLD related to Epstein-Barr virus infection occurs relatively early, usually in the first year after transplantation, and in this analysis, these patients were not included. Although it has been observed that the change in immunosuppression has led to a decrease in the incidence of PTLD, the prevention and more effective treatment of infectious diseases and/or under-reporting to the ISHLT registry remains unclear.[22]

Thyroid diseases can also deteriorate in most heart transplant patients. After cardiac transplant, the serum levels of TSH hormone should be monitored and controlled in all patients, especially in those with a history of thyroid disease.[23]

Post-transplant pathology – infections related to immunosuppressive treatment

In transplant patients, selective inhibitors of cytokine production and function (tacrolimus, cyclosporine), immunosuppressive antimetabolites (mycophenolate mofetil), and antivirals (valganciclovir) are frequently used to prevent graft rejection.

Infections following surgery are probably the most common post-transplant pathology, the primary reason for this being the use of immunosuppressive medication. The latter depends on each patient's predilection for rejection, which has been shown to decrease exponentially over time.[24] Bacteria and viruses are responsible for more than 80% of post-transplant infections.[25,26] The most common bacterial infections after cardiac transplantation are nosocomial ones, caused by intravascular catheters, infected gas lines, or occult pneumonias caused by Gram-negative germs.[27]

In our study, microbiological tests were performed in all 53 patients, starting with the 3rd postoperative day. Twelve per cent of patients developed bacterial infections from the 7th to the 9th postoperative day, manifested by fever and elevated acute phase inflammatory reactants and confirmed by microbiology.

The most common viral infections following cardiac surgery are generally caused by herpes viruses (CMV, herpes zoster, and herpes simplex).[28] Infections with CMV represent major causes of morbidity, being associated with a high rate of readmission after heart transplantation. In a recent study, data on cytomegalovirus infection were analyzed in 1,553 patients undergoing heart transplantation from 26 centers in the Cardiac Transplant Research Database Group, the results indicating 230 confirmed cytomegalovirus infections, of which 16 were proven fatal (6%).28 In the same study, 12% of the 200 patients with CMV infection had a recurrent infection during a mean follow-up of 13.9 months.[28] In our study, 44.44% of patients have developed a CMV infection, while 40.91% of them tested positive for *Toxoplasma* IgG antibodies.

CONCLUSIONS

Infections following surgery are probably the most common post-transplant pathology, the primary reason for this phenomenon being immunosuppressive medication. The administration of immunosuppressive agents is dependent on the patient's predilection for the rejection reaction, which decreases exponentially over time. Our experience has shown that bacteria and viruses are responsible for over 80% of post-transplant infections. The evaluation of post-transplant cardiac complications should be a priority, as they hold a negative impact on the post-operative evolution of heart transplant patients.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

ENDOCRINOLOGY // GASTROENTEROLOGY

Acute Drug-Induced Cholestatic Syndrome in Basedow Graves' Disease

Robert Aurelian Tiucă[1], Alina Mioara Boeriu[2], Rareș Adrian Georgescu[3], Ionela Maria Pașcanu[4]

[1] Clinic of Endocrinology, County Clinical Hospital Mureș, Târgu Mureș, Romania
[2] Department of Gastroenterology, County Clinical Hospital Mureș, "George Emil Palade" University of Medicine and Pharmacy, Science and Technology, Târgu Mureș, Romania
[3] Department of Surgery, County Clinical Hospital Mureș, "George Emil Palade" University of Medicine and Pharmacy, Science and Technology, Târgu Mureș, Romania
[4] Department of Endocrinology, County Clinical Hospital Mureș, "George Emil Palade" University of Medicine and Pharmacy, Science and Technology, Târgu Mureș, Romania

CORRESPONDENCE

Alina Mioara Boeriu
Department of Gastroenterology,
County Clinical Hospital Mureș
Str. Gheorghe Marinescu nr. 1
540103 Târgu Mureș, Romania
Tel +40 265 215 133
E-mail: aboeriu@gmail.com

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Robert Aurelian Tiucă • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 217 274, E-mail: tiuca.robert@gmail.com

Rareș Adrian Georgescu • Str. Gheorghe Marinescu nr. 1, 540103 Târgu Mureș, Romania. Tel: +40 265 215 133, E-mail: rares1geo@yahoo.com

Ionela Maria Pașcanu • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 217 274, E-mail: iopascanu@gmail.com

ABSTRACT

Introduction: Graves' disease (GD), an autoimmune disorder caused by high levels of autoantibodies against the thyroid-stimulating hormone receptor, is considered the most common cause of thyrotoxicosis, characterized by features such as goiter, ophthalmopathy and dermopathy. In our country, the administration of antithyroid drugs (ATD) is the first line of treatment in this disease. Side effects are rare but some of them, such as agranulocytosis or liver damage, may become serious. **Case presentation:** We report the case of a 20-year-old female patient who was diagnosed with GD after being previously diagnosed with viral hepatitis A. Treatment was initiated with methimazole 30 mg/day, and three weeks later she developed intense hepatic cytolysis and cholestatic syndrome, therefore the ATD was stopped. A suspicion of autoimmune liver disease was raised, and a liver biopsy was performed in order to establish the diagnosis. The next therapeutic option for hyperthyroidism was radioactive iodine (RAI). Three months following RAI, the patient presented severe hypothyroidism, thereupon treatment with levothyroxine was initiated. **Conclusions:** Although severe acute liver injury is rare, mild liver dysfunction is quite common in patients with GD. The overproduction of thyroid hormones, or the treatment with ATD through immune mediated processes or drug reactions, represent possible mechanisms responsible for liver damage.

Keywords: Graves' disease, methimazole, hepatitis, cytolysis, cholestatic syndrome

INTRODUCTION

Graves' disease (GD) is an organ-specific autoimmune disorder of unknown cause and the most common form of thyrotoxicosis. It affects women more commonly than men (5 : 1), with a peak incidence between the second and forth decade of life.[1,2] Thyrotoxicosis, goiter, ophthalmopathy, and dermopathy are features that can be typically found in a patient with GD.[1] Goiter and hyperthyroidism that appear in GD are due to a high level of circulating autoan-

tibodies that are directed against the thyroid-stimulating hormone (TSH) receptor in the thyroid cell membrane (TRAb).[1] These autoantibodies are synthesized by B lymphocytes in the thyroid gland, which were stimulated by the T lymphocytes.[1,2] A thyroid ultrasound usually describes a diffusely enlarged, hypoechoic thyroid with increased vascularity.[2] There is evidence that suggests a familial predisposition in developing GD, and environmental triggers include stress, tobacco use, pregnancy, viral or bacterial infections, and iodine exposure.[1] Treatment for GD implies the use of antithyroid drugs (ATDs) such as methimazole, carbimazole, or propylthiouracil in order to reduce the high production of thyroid hormones.[1,2] Common side effects of ATDs are itching, skin rash, and abnormal hair loss, while less common side effects include muscle and joint pain, headache, swelling, and in severe cases liver injury or agranulocytosis.[2] Another treatment option for GD, which reduces the amount of thyroid tissue, is radioactive iodine treatment (RAI) or total thyroidectomy.[1,2] This article aims to present the case of a young female patient with GD who had been previously diagnosed with viral hepatitis A and who developed acute cholestatic syndrome after ATD use.

CASE PRESENTATION

A 20-year-old female patient was admitted to the Infectious Diseases Department of Mureș Clinical County Hospital with symptoms such as nausea, vomiting, jaundice, and urinary hyperchromia. The laboratory workup revealed high values of direct bilirubin and total bilirubin, hepatic cytolysis, and positive immunoglobulin M antibody to hepatitis A virus. Abdominal ultrasound showed hepatosplenomegaly, visible intrahepatic ducts, and gallbladder wall thickening. A diagnosis of acute viral hepatitis A was established and treatment with intravenous infusions of glucose 5% and hepatoprotective agents was initiated. The patient's general status as well as the hepatic panel tests improved. During hospitalization, she presented an enlargement of the anterior cervical region, therefore, two weeks after discharge, she was evaluated by an endocrinologist.

A thyroid ultrasound was performed, which described an increased volume, with inhomogeneous structure and enhanced vascularity, suggesting an autoimmune thyroid disease. Blood test evaluation showed thyrotoxicosis with a TSH of 0.0090 µUI/mL (normal range: 0.55–4.78),

TABLE 1. The evolution of liver panel, bilirubin tests, and thyroid function

Time frame	AST (NR: 5–34 U/L)	ALT (NR: 0–55 U/L)	GGT (NR: 12–64 U/L)	DB (NR: 0.0–0.5 mg/dL)	TB (NR: 0.2–1.2 mg/dL)	Thyroid function	Treatment received
Onset of the viral hepatitis	1516	1727	–	5.22	6.28	–	Hepatoprotective drugs + infusions with glucose 5%
2 weeks after being discharged from the Infectious Diseases Department	80	150	–	0.97	1.44	Thyrotoxicosis	Hepatoprotective drugs + introduction of ATD
3 weeks later	1393	1995	275	8.98	12.39	–	Stopping methimazole Hepatoprotective drugs + prednisone + gastroprotective agents + cardioactive agents
After 10 days of treatment	259	628	238	5.24	6.44	–	
After 1 month from stopping ATD	46	166	97	1.36	2.22	Euthyroidism	
5 months later	25	38	28	–	–	Relapse of the hyperthyroidism	Hepatoprotective drugs + cardioactive agents
2 months later	34	60	36	0.44	1.1	Mild thyrotoxicosis	3 weeks after RAI Hepatoprotective drugs + cardioactive agents
3 months later	23	30	21	–	–	Severe hypothyroidism	Levothyroxine

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; DB, direct bilirubin; TB, total bilirubin

free thyroxine (FT4): 4.33 ng/dL (normal range: 0.89–1.76), free triiodothyronine (FT3): 14.68 pg/mL (normal range: 2.3–4.2), with high levels of anti-thyroid peroxidase (ATPO) of 1,571.0 UI/mL (normal range: <35) and TRAb: 33.41 UI/L (<1.75). She was eventually diagnosed with GD and treatment with 30 mg of methimazole along with 30 mg of propranolol was started.

After roughly three weeks of treatment with ATDs, the patient was admitted to the Endocrinology Department of Mureș County Clinical Hospital complaining of tiredness, fatigue, jaundice, and urinary hyperchromia. Physical examination revealed icteric sclera and skin, no signs of ascites or abdominal tenderness, negative Murphy's sign, and no ophthalmopathy. The liver blood panel described hepatic cytolysis and cholestatic syndrome on several determinations (Table 1).

While the patient was admitted to our department, treatment with hepatoprotective drugs was started, whereas the treatment with ATDs was stopped. However, the patient's general state did not improve. A suspicion of autoimmune cholangiohepatitis was raised, and the patient was transferred to the Gastroenterology Department for further medical investigations.

In the Gastroenterology Department, the physical examination revealed hepatosplenomegaly, normal heart rate and blood pressure. Liver tests showed severe cytolysis and cholestasis. Hepatitis B and C testing, and the markers for autoimmune hepatitis and primary biliary cirrhosis (anti-smooth muscle antibodies, anti-liver kidney microsomal type 1 antibodies, antimitochondrial antibodies, antinuclear antibodies, anti-soluble liver antigen antibodies) were negative, with normal serum protein electrophoresis, prothrombin time, and albumin levels. Abdominal ultrasound depicted splenomegaly, lymphadenopathy in the hepatic hilum, hepatomegaly, and gallbladder wall thickening, with no obstruction of biliary ducts. Infusions with hepatoprotective agents were initiated, as well as treatment with prednisone (1 mg/kg/day) and ursodeoxycholic acid (10 mg/kg/day).

Liver biopsy described hepatitis with minimum necrotic-inflammatory activity, and minimum inflammatory infiltrate at the portal space formed by lymphocytes, neutrophils, and eosinophilic granulocytes (Figure 1).

Under treatment with hepatoprotective, gastroprotective, and cardioactive agents, prednisone tapering regimen and ursodeoxycholic acid, the patient's liver condition progressively improved. She was retransferred to the Endocrinology Department, where the thyroid function tests were normal, while the hepatic panel described mild cytolysis and cholestatic syndrome (Table 1).

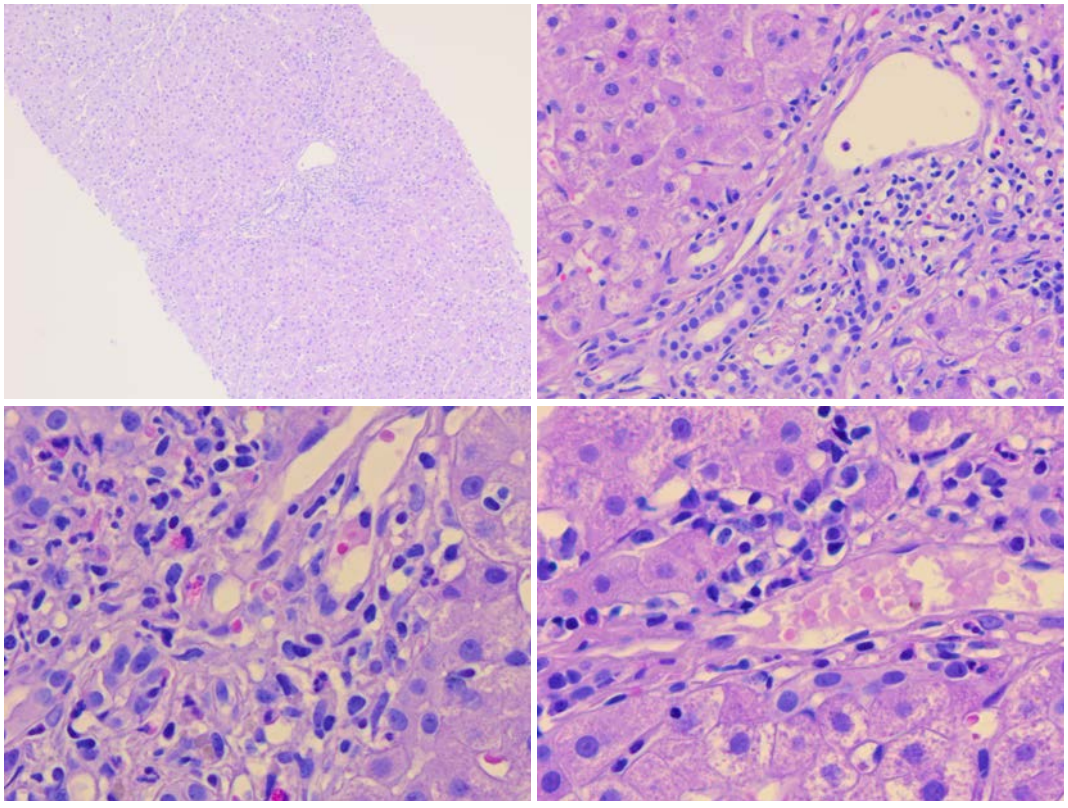

FIGURE 1. The microscopic aspect of the liver biopsy

The patient was reevaluated after five months, when the thyroid function tests revealed a relapse of the hyperthyroidism, whereas the liver function tests were normal. Given the medical history of the patient and the acute liver injury (ALI) secondary to the administration of ATDs, the patient was advised to undergo treatment with RAI. One month later, she received a therapeutic dose of 11.72 mCi of I-131. The patient was reevaluated three weeks later, when she was still in mild thyrotoxicosis, eventually being discharged without any additional ATD. Three months later, the patient presented severe hypothyroidism (TSH level of 285.746 μUI/mL and FT3 level of <0.20 pg/mL), with a low thyroid volume and normal liver functions tests, thereupon treatment with levothyroxine was initiated (Table 1).

The patient agreed to the publication of her medical information, the manuscript being written respecting the ethical principles stated in the Declaration of Helsinki.

DISCUSSIONS

We report the case of a 20-year-old female patient who was diagnosed with GD. Prior to the diagnosis, the patient had viral hepatitis A, which required the admission to the Infectious Diseases Department. ATDs are usually the first-line treatment option with remission rates ranging from 14% to 80%, the recommended duration of therapy being 12–18 months.[2,3] In our case, the treatment was started with methimazole 30 mg/day alongside with propranolol 30 mg/day. Our patient had slightly elevated liver function tests before initiating the ATD, most probably due to thyrotoxicosis; nevertheless, three weeks after starting the medication, she developed jaundice, urinary hyperchromia, and fatigue, suggesting an ALI.

The incidence of hepatotoxicity associated with the use of any ATD is low (<0.5%), propylthiouracil being the thionamide that is reported to have a higher risk of serious, non-dose related liver injury, especially in pediatric patients. The risk of liver failure is 1 in 2,000 children and 1 in 10,000 adults.[4,5] On the other hand, methimazole toxicity is found more often in patients over 40 years of age, with no reported deaths from liver failure.[4] In the literature, there are several studies that have observed the hepatotoxicity profiles of methimazole vs. propylthiouracil. A study conducted in Japan found a 6.6% incidence of methimazole-induced hepatotoxicity from 30 mg/day compared to 26.9% in case of propylthiouracil at 300 mg/day.[4,6] Wang *et al*. reported that hepatitis had a higher incidence rate than acute liver failure (ALF) when comparing methimazole vs. propylthiouracil.[7] Moreover, methimazole use, especially in high dose, associated an increased risk of hepatitis when compared with any propylthiouracil use.[7] Rivkees & Szarfman reported that methimazole had a higher rate of mild liver injury (cytolysis, jaundice, or cholestasis) but a lower rate of severe liver injury (hepatitis, ALF, or liver transplant) than propylthiouracil.[8]

A first hypothesis in the mechanism of developing an ALI in patients with GD is that hyperthyroidism can cause liver damage directly by increasing the metabolic rate, resulting in a higher oxidative capacity and oxidative tissue damage.[1] Oshima *et al*. reported in 1990 an autopsy case of death due to hyperthyroidism in which the autopsy revealed hepatic inflammation, fibrosis, and centrilobular necrosis.[9–11] Hyperthyroidism increases the production of insulin-like growth factor within the liver, resulting in a hypermetabolic state that can make the liver more prone to injury.[12]

A second hypothesis in developing an ALI after starting treatment with methimazole could be related to the implication of an immune-mediated process and/or drug reactions, though the exact mechanism is not yet fully understood.[4] In 2004, Mikhail reported a case of a 43-year-old woman who developed severe, though reversible cholestatic jaundice after 4 weeks of treatment with methimazole, with an improvement in general state after stopping the medication.[13] Drug-induced liver injury due to methimazole is reported more often in the first weeks after starting the treatment, the injury having usually a cholestatic type pattern with symptoms such as jaundice, fatigue, pruritus, and malaise.[4,13–15] Chang *et al*. reported that elevated TRAb levels might predispose the patient to carbimazole/methimazole-induced cutaneous reactions and/or hepatotoxicity.[16] Heidari *et al*. found that mice that were treated with a nonhepatotoxic dose of bacterial lipopolysaccharide (LPS) from *E. coli* as well as with ATD in nonhepatotoxic doses, presented with hepatic inflammation that eventually led to ALI.[17] LPS can stimulate toll-like receptors and activate the Kupffer cells that could damage the hepatocytes and furthermore, produce inflammatory cytokines and proteolytic enzymes.[17] After the inhibition of Kupffer cells by methyl palmitate, methimazole-induced hepatotoxicity as well as propylthiouracil-induced liver injury in LPS-treated mice diminished.[17]

A third hypothesis for the onset of an ALI is the presence of an underlying autoimmune disease that causes serious damage to the liver such as an autoimmune hepatitis. In order to diagnose an autoimmune liver disease, autoimmune markers and liver biopsy are needed.[10] In our case, biopsy found no specific microscopic features for autoimmune hepatitis, and serum tests were negative.

In our case, the most plausible hypothesis for the occurrence of ALI is that the recent history of viral hepatitis

A, concurrent with the consecutive administration of methimazole, led to the development of an acute cholestatic syndrome.

Another treatment option for hyperthyroidism is based on reduction of the amount of thyroid tissue with either RAI or thyroidectomy, especially in patients with relapsing hyperthyroidism after stopping the ATD.[2] RAI for GD is a safe form of treatment, though with a latency period that can last up to 6 months.[3] Sundaresh *et al*. conducted a retrospective study on 720 patients and reported a failure rate in correcting the hyperthyroidism of 48.3% for ATD treatment compared with 8% for RAI.[18] Nearly 3 months after RAI, our patient developed severe hypothyroidism, and treatment with levothyroxine was initiated.

CONCLUSIONS

Although severe ALI is rare, mild liver dysfunction is quite common in patients with GD. Overproduction of thyroid hormones, or treatment with ATD through immune-mediated processes or drug reactions represent possible mechanisms responsible for liver damage. Liver tests monitoring during ATD therapy is recommended, especially in patients with prior liver dysfunction. In cases where ATDs are not indicated, definitive treatment with either RAI or total thyroidectomy may represent effective therapeutic options. Although hypothyroidism is a complication of the definitive treatment, management of this condition may be easier than the one of hyperthyreosis.

CONFLICT OF INTEREST

Nothing to declare.

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Letter to the editor

Letters to the editor should address either a recently published article in the Journal of Interdisciplinary Medicine, or a new topic in the field of cardiovascular emergencies.

Concerning a letter, discussing a recently published article, the comments contained in the letter will be forwarded to the authors of the original paper who will be invited to respond. Any response will be published in the same journal issue as the letter to the editor. A letter to the

editor should be no longer than 500 words, 5 references, and three authors. No abstract is required.

Editorial

Editorials should address either a particular topic that is currently of interest in the field of interdisciplinary medicine or to an article which is published in the same issue of the journal. The number of references should not exceed twenty-five in total.

MANUSCRIPT CONTENT

Style and spelling: Authors, whose first language is not English, are requested to have their manuscripts checked carefully, preferably by an English native-speaker, before submission, to expedite the review process.

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- Title page.
- Abstract, or a summary of case reports (references should not be included in abstracts or summaries).
- Main text separated under appropriate headings and subheadings using the following hierarchy: BOLD CAPS, bold lower case, Plain text, italics.
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- Acknowledgements, Competing Interests, Funding, and all other required statements.
- Reference list.
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The journal will publish the reference list according to the style of Index Medicus (or spelled out if not listed in Index Medicus). List all the authors in each reference following the format and punctuation indicated below as examples:

Reference to an article

1. Benedek I, Gyongyosi M, Benedek T. A prospective regional registry of ST-elevation myocardial infarction in Central Romania: impact of the Stent for Life Initiative recommendations on patient outcomes. *Am Heart J*. 2013;166:457-465.

Reference to a book

2. Nichols WW, Rourke MF. Aging, High Blood Pressure and Disease in Human. 3rd ed. London/Melbourne: Lea and Febiger; 1990.

Reference to a chapter in a book

3. Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger, 1990; p. 398-420.

Reference to a webpage

4. Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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