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1. Manolis AJ, Ambrosio G, Collins P, et al. Impact of stable angina on health status and quality of life perception of currently treated patients. The BRIDGE 2 survey. Eur J Intern Med 2019;70:60-67. 2. Alexopoulos D, Kochiadakis G, Althonidis D, et al. Ranolazine reduces angina frequency and severity and improves quality of life: Observational study in patients with chronic angina under ranolazine treatment in Greece (OSCAR GR). Int J Cardiol. 2016;205:111–116. 3. Ranexa. Summary of Product Characteristics. Last update 10/2020



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## THE SILENT EPIDEMIC: THE NEED FOR GREATER FOCUS ON MAFLD

Dear Editor,

I am writing to draw attention to the growing concern of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), a new term for an old multisystem disorder, a term that replaced NAFLD in early 2020 (1). The global prevalence of MAFLD is estimated to be around 25- 32% of the adult population (2). This makes it one of the most common chronic liver diseases worldwide. The most common cause of MAFLD is primary NAFLD, a condition where excess fat accumulates in the liver without alcohol consumption, associated with insulin resistance and its manifestations: obesity, visceral adiposity, type 2 diabetes mellitus, hypertriglyceridemia, and arterial hypertension. Thus, up to 95% of obese persons and 75% of patients with type 2 diabetes mellitus are likely to have NAFLD. NAFLD is one of the major causes of chronic liver disease that starts with steatosis, the development of fibrosis, and progress to cirrhosis and hepatocellular carcinoma. NAFLD among patients with T2DM is 2-3-fold higher than that in the general population, or between 60-70% (3). The diagnostic criteria of MAFLD have been defined as: 1. the presence of hepatic steatosis diagnosed by ultrasound AND either a 2a. diagnosis of obesity, 2b. a diagnosis of diabetes mellitus, or 2c. metabolic dysfunction, which may include one or more of the following criteria: waist circumference greater than 102 cm (cm) in males and 88 cm in females, blood pressure greater than 130/85 mmHg or under medication, triglyceride content above 150 mg/dL or with treatment, HDL-C content less than 40 mg/dL in males and less than 50 mg/dL in females, prediabetes or diabetes mellitus, insulin resistance scores (HOMA-IR) more significant or equal to 2.5, or C-Reactive Protein levels above 2 mg/L (4). The shift to MAFLD highlights the importance of addressing metabolic risk factors in treating liver disease, emphasizing lifestyle changes, weight management, and managing comorbid conditions like diabetes and hypertension. The prevalence of MAFLD is increasing in pediatrics, also. The estimated prevalence of MAFLD in the general pediatric population is between 5% and 11%. However, this rate increases to 30% to 50% in children and adolescents who are obese (5), so it is imperative to facilitate better and improve the liver health and management of pediatric patients with obesity.

The cornerstone of managing MAFLD is weight loss, as even a 5-10% reduction in body weight can significantly reduce liver fat and inflammation (6). Currently, there are no FDA-approved medications specifically for MAFLD, but drugs used to manage related conditions can help manage the disease. Efforts to address the underlying metabolic dysfunction, promote healthier lifestyles, and improve early detection and management are crucial to curbing the prevalence and impact of MAFLD.

Detailed studies on MAFLD are essential to advancing our knowledge of the disease and improving both individual patient outcomes and public health strategies. From improving early diagnosis to developing effective treatments and preventive measures, comprehensive research will pave the way for better management of MAFLD and its related complications. It also provides an opportunity to address the growing global burden of metabolic and liver diseases, ultimately leading to more personalized and practical approaches to tackling this increasingly prevalent condition.

Thank you for considering this important issue.

Sincerely,
Assoc. Prof. Ergita Nelaj

## References


1. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1):202-209. https://doi.org/10.1016/j.jhep.2020.03.039
2. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7(9):851-861. https://doi.org/10.1016/S2468-1253(22)00165-0
3. Ajmera, Veeral et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. Journal of Hepatology, 2023;78(3): 471 – 78. http://doi.org/10.1016/j.jhep.2022.11.010
4. Lin S, Huang J, Wang M, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int. Off. J. Int. Assoc. 2020; 40(9):2082–9. https://doi.org/10.1111/liv.14548
5. Jennifer Panganiban, Mohit Kehar, Samar H. Ibrahim, Phillip Hartmann, Marisa Censani, et.al. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in Children with Obesity: An Obesity Medicine Association (OMA) and Expert Joint Perspective 2025, Obesity Pillars, 2025, 100164, ISSN 2667-3681, https://doi.org/10.1016/j.obpill.2025.100164
6. Beygi M, Ahi S, Zolghadri S, Stanek A. Management of Metabolic-Associated Fatty Liver Disease/Metabolic Dysfunction-Associated Steatotic Liver Disease: From Medication Therapy to Nutritional Interventions. Nutrients. 2024;16(14):2220. Published 2024 Jul 11. https://doi.org/10.3390/nu16142220

# DERMATOLOGIC DISEASES IN GERIATRIC PATIENTS

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**Abstract**
**Introduction:** The global growth of the elderly population has prompted an increased awareness of the health of this age group, especially in the treatment and prevention of dermatological disorders. The skin, as the largest organ of the body, is affected by aging processes, which can be accelerated by environmental factors.
**Purpose:** To analyze the frequency and characteristics of dermatological diseases in geriatric patients in the Dermatology Service, QSUT, as well as to assess the need for specialized hospital services for this population.
**Methodology:** This is a retrospective and prospective study, where 103 patients over the age of 60 were included. For its realization, medical data extracted from the medical records of patients who were previously treated in the ward were used, as well as through direct interviewswith patients during the study period.
**Results & Conclusions:** Our study showed that the majority of geriatric patients admitted to the Dermatology Service, QSUT, were in the age group of 66-70 years, with male dominance. Pruritus was the most common dermatological symptom, reported by 79% of patients, while immunological diseases, eczematous dermatitis, cutaneous neoplasms and psoriasis wereamong the most frequent diagnoses.
This study highlights the importance of providing specialized care to geriatric patients, emphasizing the need for a multidisciplinary approach to the effective treatment of dermatological diseases and comorbidities.

**Keywords**: global growth, dermatological diseases, geriatric patients, diagnose, treatment.

# SËMUNDJET DERMATOLOGJIKE NË PACIENTËT GERIATRIKË.

**Abstrakt**
**Hyrje:** Rritja globale e popullsisë së moshuar ka nxitur një ndergjegjësim të shtuar për shëndetin e kësaj grupmoshe, veçanërisht në trajtimin dhe parandalimin e çrregullimeve dermatologjike. Lëkura, si organi më i madh i trupit, është e ndikuar nga proceset e plakjes, të cilat mund të përshpejtohen nga faktorët mjedisorë.
**Qëllimi:** Analizimi i frekuencës dhe karakteristikave të sëmundjeve dermatologjike te pacientët geriatrikë në Shërbimin e Dermatologjisë, QSUT, si dhe të vlerësojë nevojën për shërbime të specializuara spitalore për këtë popullatë.
**Metodologjia:** Ky është një studim i tipit retrospektiv dhe prospektiv, ku janë përfshirë 103 pacientë mbi moshën 60 vjeç. Për realizimin e tij u shfrytëzuan të dhënat mjekësore të nxjerra

nga kartelat mjekësore të pacientëve që ishin trajtuar më parë në pavion, si dhe nëpërmjet intervistave të drejtpërdrejta me pacientët gjatë periudhës së studimit.
**Rezultate & Konkluzione:** Nga studimi jonë doli që shumica e pacientëve geriatrikë të shtruar ne Shërbimin e Dermatologjisë, QSUT, ishin të grupmoshës 66 – 70 vjeç, me dominim të meshkujve. Pruriti ishte simptoma më e zakonshme dermatologjike, e raportuar nga 79% e pacientëve, ndërsa sëmundjet imunologjike, dermatitet ekzematoze, neoplazitë kutane dhe psoriasis ishin ndër diagnozat më të shpeshta.
Ky studim nënvizon rëndësinë e ofrimit të kujdesit të specializuar për pacientët geriatrikë, duke theksuar nevojën për një qasje multidisiplinare për trajtimin efektiv të sëmundjeve dermatologjike dhe sëmundjeve shoqëruese.

**Fjalë kyçe:** rritje globale, sëmundje dermatologjike, pacientë geriatrikë, diagnose, trajtim.

## Introduction

Changing population demographics around the world, resulting in an increasing elderly population, lead to heightened awareness of health issues in this portion of the population. Among these, prevention and treatment of the highly prevalent skin disorders constitute a major concern [1]. The skin is the largest organ and has a key protective role. Similar to any other tissue, the skin is influenced not only by intrinsic/chronological aging, but also by extrinsic aging, triggered by environmental factors that contribute to accelerating the skin aging process [2].
The skin exhibits multiple functions, among them it serves as a protective barrier between internal organs and the environment, but is also a complex organ with multiple cell types and structures. It is divided into four major compartments: epidermis, dermis, appendages and subcutaneous tissue. With increasing age the epidermis, the dermis and the skin appendages progressively lose their youthful characteristics and abilities; the skin gradually loses its structural and functional characteristics. Consequently, the skin becomes more fragile and vulnerable to damage which may lead to major aging-associated diseases [3].

**Table 1.** Function of human skin that decline with age [1]

| **Barrier recovery** | **Wound healing** |
|---|---|
| **Cell proliferation** | **Vitamin D production** |
| **Thermoregulation** | **Sweat production** |
| **Lymphatic drainage** | **Sebum production** |
| **Immune responsiveness** | **DNA repair** |

Disorders of the skin are known to be common and bothersome in the elderly, and some occur predominantly in this age group. Such disorders often appear to be the consequence of age-associated intrinsic losses of cutaneous cellular function. However, many dermatoses observed more commonly in the elderly reflect the higher prevalence of systemic diseases, such as diabetes, vascular insufficiency, and various neurologic syndromes, that compound physiologic changes in the skin itself [4]. Furthermore, factors that are more common in the elderly, such as decreased mobility, the increase of certain chronic diseases or an increase in adrug that can cause skin disorders as a side effect, all increase the risk of developing many dermatological diseases. Disorders which hinder vascular efficiency and immune response, such as diabetes mellitus, HIV, congestive heart failure and artherosclerosis, are all examples of diseases that can often cause skin disease or exacerbate already detrimental skin conditions [5].

**The most frequent dermatological diseases in geriatric patients**

Common dermatoses in this population include xerosis, skin cancer, eczematous conditions, fungal infections, and chronic wounds [6].

**Table 2.** Classification of common gerodermatoses [7].Physical factors

| |
|---|
| Pressure sores (decubitus ulcers) |
| Xerosis |
| Pruritus |
| Asteatotic dermatitis |
| Infections Bacterial |
| Impetigo/folliculitis |
| Cellulitis |
| Viral |
| Herpes Zoster |
| Molluscum Contagiosum |
| Fungal |
| Onychomycosis |
| Tinea pedis |
| Tinea corporis |
| Intertrigo |
| Infestations |
| Pediculosis |
| Scabies |
| Eczematous reactions |
| Nummular eczema |
| Sebarrhoic dermatitis |
| Contact dermatitis |
| Psoriasis |
| Photodermatoses |
| Solar elastosis |
| Nodular elastoidosis |
| Cutis rhomboidalis nuchae |
| Poikilodermic changes |
| Neoplastic changes |
| Benign |
| Seborrheic keratosis |
| Skin tags |
| Cherry angiomas |
| Leukoplakia |
| Actinic keratosis |
| Malignant |
| Actinic cheilitis |
| Basal cell carcinoma |

| |
|---|
| Squamous cell carcinoma |
| Malignant melanoma |
| Immunological |
| Bullous pemphigoid |
| Psychodermatoses |
| Lichen simplex chronicus |
| Prurigo nodularis |
| Neurotic excoriations |
| Delusion of parasitosis |
| Dermatitis artefacta |
| Vascular compromise |
| Chronic venous insufficiency (stasis dermatitis) |
| Cutaneous drug reactions |
| Nutritional changes |

**Material and method**

This study aims to investigate and analyze the frequency of dermtological diseases among geriatric patients at the "Mother Teresa" University Hospital Center in Tirana. It seeks to assess the needs and examine the importance of specialized hospital services for this age group. Initially, the distribution of patients is analyzed according to general demographics, age, gender, profession, and accompanying diseases. The presented study also aims to correlate thepatients' subjective clinical data with their accurate final diagnosis.

This study is of a cross-sectional retrospective and prospective type, collecting data from patients treated at the Dermatology Service of the "Mother Teresa" University Hospital Centerin Tirana during the period from October 2023 to May 2024. The study included 103 geriatricpatients admitted to the dermatology ward during the study period. All patients included in thestudy were 60 years and older. Patients who refused to participate in the study or did not providesufficient information for statistical analysis were excluded.

Data collection was conducted through two approaches:

1. Retrospective Data: Medical records of previously treated patient in the dermatology ward were reviewed to extracy relevant information, including dermatological diagnoses, medical history, and treatment details.
2. Prospective Data: Structured interviews were conducted with patients during their hospitalization, documenting information such as dermatological diagnoses, detailed medical history, past and ongoing treatments.

All procedures followed ethical standards, ensuring confidentiality and protection of personal data. Participation was voluntary, and informed consent was obtained from all patients. Data were exclusively for scientific purposes.

This study had two primarly limitations:

A relatively small sample size.

Data limited to patients treated exclusively at the "Mother Teresa" University Hospital Center.

Statistical analysis:

Collected data were organized using Microsoft Excel and analyzed statistically using SPSS BMI

Version 27.

## Results

### Distribution of Patients by Age

The majority of patients (37%) belong to the age group of 66-70 years, followed by 31% in the60-65 age group. Patients aged 71-75 years account for 14% of the sample, while 9% fall withinthe 76-80 age range, and another 9% are over 80 years old.

**Table 3.** Distribution patients by age

| Age group (years) | Male | Female | Total (N) | Percentage (%) |
|---|---|---|---|---|
| 60-65 | **20** | **12** | **32** | **31%** |
| 66-70 | 18 | 20 | 38 | **37%** |
| 71-75 | 9 | 6 | 15 | **15%** |
| 76-80 | 8 | 1 | 9 | **9%** |
| >80 | 5 | 4 | 9 | **9%** |
| Total (103) | **60** | **43** | **103** | |

### Distribution of Patients by Gender

In the study group, there was a predominance of males, who constitued 58% of the total, while females accounted for 42%.

**Table 4.** Distribution of patients by gender

| Gender | Total (N) | Percentage (%) |
|---|---|---|
| Male | **60** | **58%** |
| Female | 43 | **42%** |
| Total | **103** | |

### Distribution of Patients by Profession

The majority of study population comprises pensioners, accounting for 71% of the total, inlcuding both males and females. Following them, 12% of the population conisists of active individuals. Patients recieving economic assistance make up 9%, while self-employed individuals and the unemployed each represent 4% of the total. Additionally, one veteran wasincluded among the patients.

**Table 5.** Distribution of patients by profession

| Profession | Male | Female | Total (N) | Percentage (%) |
|---|---|---|---|---|
| Pensioners | **38** | **35** | **73** | **71%** |
| Active Ind. | 11 | 1 | 12 | **12%** |
| Economic Assistance | 4 | 5 | 9 | **9%** |
| Self-employed | 3 | 1 | 4 | **4%** |
| Unemployed | 3 | 1 | 4 | **4%** |
| Veteran | 1 | 0 | 1 | **1%** |
| Total | **60** | **43** | **103** | |

### Distribution of Patients by Comorbidities

Out of the 103 pacients, 79 had comorbid conditions. The most common comorbidity was hypertension, with 31 patients (30% of the total) having hypertension without any other associated conditions. The second most common comorbidity was diabetes mellitus, which was present in 10 patients (10%).
Additionally:
20 patients (19%) had both hypertension and diabtes mellitus.

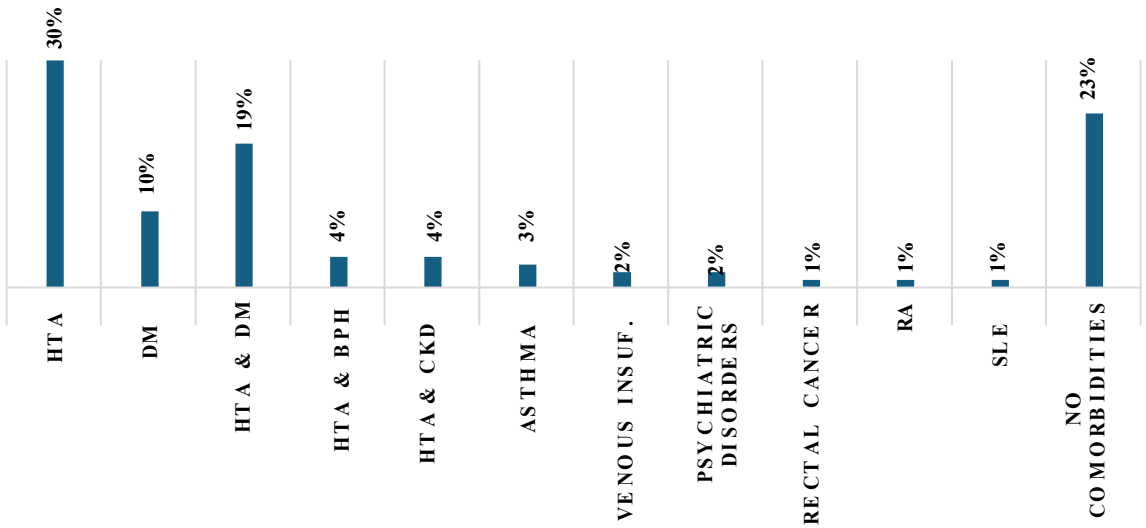
Rarer comorbidities included:
Hypertension with benign prostatic hyperplasia in 4 patients (4%).
Hypertension with chronic kidney disease in 4 patients (4%).

Other comorbidites were:
Asthma in 3 patients (3%)
Venous insufficiency in 2 patients (2%)
Psychiatric disorders in 2 patients (2%)
Rectal cancer in 1 patient (1%)
Rheumathoid arthritis in 1 patient (1%)
Systemic lupus erythematous in 1 patient (1%).
Finally, 24 patients (23%) out of 103 patients had no comorbidities.

**Table 6. Distribution of patients by comorbidities**

| **Comorbidities** | **Total (N)** | **Percentage (%)** |
|---|---|---|
| Hypertension | **31** | **30%** |
| Diabetes mellitus | 10 | **10%** |
| HTA & DM | 20 | **19%** |
| HTA & benign prostatic Hyperplasia | 4 | **4%** |
| HTA & chronic kidney disease | 4 | **4%** |
| Asthma | 3 | **3%** |
| Venous Insufficiency | 2 | **2%** |
| Psychiatric disorders | 2 | **2%** |
| Rectal cancer | 1 | **1%** |
| Rheumathoid arthritis | 1 | **1%** |
| Systemic lupus erythematous | 1 | **1%** |
| No comorbidities | **24** | **23%** |

## COMORBIDITIES




**Distribution of Patients by Primary Complaints**

In the dermatology ward, pruritus (itching) was the most common complaint among geriatric patients, with 79% patients (81 out of 103) reporting this symptom. Among this patients, 42% (43 patients) experienced pruritus without any other associated symptoms, 37% (38 patients) had pruritus accompanied by pain. 12% (12 patients) complained solely of pain. 10% (10 patients) had asympyomatic lesions that were not associated with any symptoms, such as pruritus or pain.

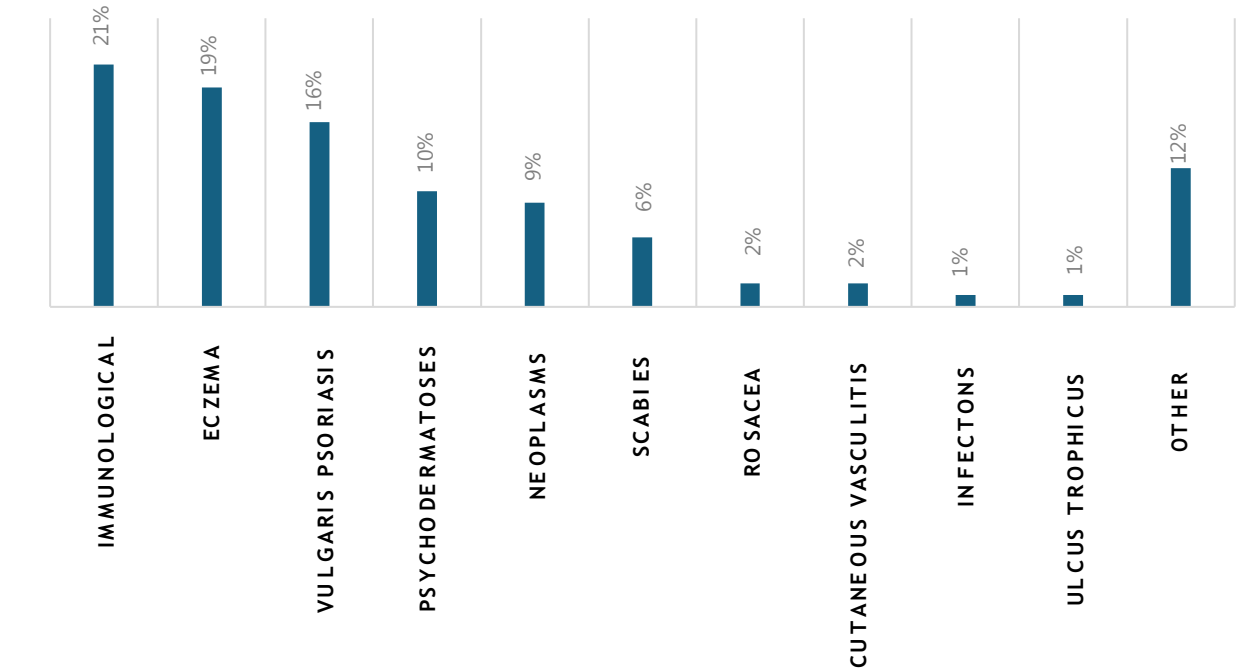
**Table 7.** Distribution of patients by primary complaints

| Complaints | Total (N) | Percentage (%) |
|---|---|---|
| Pruritus | **43** | **42%** |
| Pruritus & pain | 38 | **37%** |
| Pain | 12 | **11%** |
| Asymptomatic | 10 | **10%** |
| Total | **103** | |

**Correlation Between Pruritus and Major Dermatological Diseases**

Pruritus was reported by 81 patients in the study, a variety of dermatological conditions were identified among them. The most common dermatological diseases associated with pruritus included immunological dermatological diseases in 21% (17 patients) of cases, and eczema dermatitis in 19% (15 patients). Vulgar psoriasis was diagnosed in 16% (13 patients), while psychodermatoses were present in 10% (8 patients). Additionally, neoplasms were identified in 9% (7 patients), and scabies in 6% (5 patients). Rosacea and leukocyclastic vasculitis were each found in 2% (2 patients), with 1% having a cutaneous infection and another 1%diagnoseed with ulcus trophicus. The remaning 12% (10 patients) presented with other dermatological conditions.

This distribution highlights the diverse range of dermatological diseases that can be associated with pruritus in geriatric patients.




**Prevalence of Common Dermatological Diseases in Geriatric Patients**

Among the most common dermatological diseases observed in geriatric patients were immunological diseases, eczema dermatitis, cutaneous neoplasms, and vulgar psoriasis. In the study group of 103 patients, 17 were diagnosed with immunological diseases, 15 with eczema dermatitis, 14 with cutaneous neoplasms, and 12 with vulgar psoriasis.

Other prevalent conditions included psychodermatoses in 8 patients, scabies and leukocytoclastic vasculitis, each in 5 patients, and morphea in 3 patients. Infections, ulcers, and rosacea were each identified in 2 patients.

Among the immunological diseases, bullous pemphigoid was the most common, diagnosed in12 patients. Following this, vulgar pemphigus was identified in 5 patients, and vegetative pemphigus in 1 patient.

As for the cutaneous neoplasms, basal cell carcinoma was the most frequent, present in 4 cases. Other cutaneous neoplasms included mycosis fungoides, Kaposi sarcoma, and cutaneous lymphoma, each affecting 2 patients, while squamous cell carcinoma, Sezary syndrome, Queyrat erythroplasia, and keratoacanthoma were each diagnosed in 1 patient.

In the category of eczema dermatitis, which was diagnosed in 15 patients, chronic eczema was identified in 4 cases, generalized eczema in 3 cases, allergic contact dermatitis in 4 cases, and nummular eczema, annular eczema, stasis dermatitis, and psoriasiform eczema, each in 1 case.

Vulgar psoriasis was identified in 14 patients, while psychodermatoses included prurigo nodularis in 7 patients and lichen simplex chronicus in 1 patient.

Infections were relatively rare, with 1 patient diagnosed with tinea corporis and another with impetigo. Other diseases included lichen planus in 2 patients, parapsoriasis in 2 patients, and lichen planopilaris, lichen scleroatrophic, aphthous stomatitis, granuloma annulare, pityriasis rosea, polymorphous light eruption, photodermatitis, discoid lupus, glandular hyperplasia, necrobiosis lipoidica, and cutaneous sarcoidosis, each present in 1 patient.

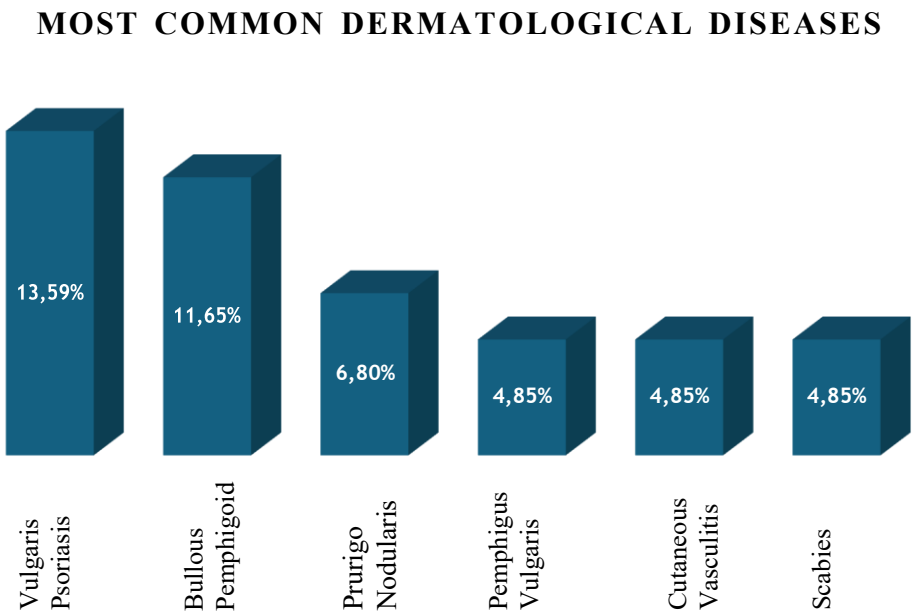
**Table 8.** Distribution of patients based on final diagnosis

| Dermatological diseases | Total (N) | Percentage (%) |
|---|---|---|
| **ULCUS TROPHICUS** | 2 | **1.94%** |
| **INFECTIONS (2)** | | |
| **Impetigo** | 1 | **0.97%** |
| **Tinea Corporis** | 1 | **0.97%** |
| **INFESTATIONS (5)** | | |
| **Scabies** | 5 | **4.85%** |
| **ECZEMATOUS DERMATITIS (15)** | | |
| **Chronic eczema** | **4** | **3.88%** |
| **Generalized eczemaContact dermatitis** | **3** | **2.91%** |
| **Nummular eczema Anular** | **4** | **3.88%** |
| **eczema Stasis dermatitis** | **1** | **0.97%** |
| **Psoriasisform eczema** | **1** | **0.97%** |
| | **1** | **0.97%** |
| | **1** | **0.97%** |
| **CUTANEOUS NEOPLASMS (14)** | | |
| **Basal cell carcinoma** | 4 | **3.88%** |
| **Cutaneous lymphoma** | 2 | **1.94%** |
| **Mycosis fungoides** | 2 | **1.94%** |
| **Kaposi sarcoma** | 2 | **1.94%** |
| **Squamous cell carcinoma** | 1 | **0.97%** |
| **Ceratoacanthoma** | 1 | **0.97%** |
| **Sezary syndrome** | 1 | **0.97%** |
| **Erythroplasia Queyrat** | 1 | **0.97%** |
| **IMMUNOLOGICAL (18)** | | |
| **Bullous pemphigoid** | 12 | **11.65%** |
| **Pemphigus vulgaris** | 5 | **4.85%** |
| **Pemphigus vegetans** | 1 | **0.97%** |
| **PSORIASIS VULGARIS** | 14 | **13.59%** |
| **PSYCHODERMATOSES (8)** | | |
| **Prurigo Nodularis** | 7 | **6.80%** |
| **Lichen Simplex Chronicum** | 1 | **0.97%** |
| **LEUKOCYTOCLASTIC VASCULITIS** | 5 | **4.85%** |
| **MORPHEA** | 3 | **2.91%** |
| **ROSACEA** | 2 | **1.94%** |

| | | |
|---|---|---|
| **TË TJERA (15)** | | |
| **Parapsoriasi** | **2** | **1.94%** |
| **s Lichen** | **2** | **1.94%** |
| **Planus** | **1** | **0.97%** |
| **Lichen** | **1** | **0.97%** |
| **Scleroatrophicus** | **1** | **0.97%** |
| **Lichen Planopilaris** | **1** | **0.97%** |
| **Aphtous stomatitis** | **1** | **0.97%** |
| **Anular granuloma** | **1** | **0.97%** |
| **Pityriasis Rosea** | **1** | **0.97%** |
| **Polymorphous Light** | **1** | **0.97%** |
| **EruptionPhotodermatitis** | **1** | **0.97%** |
| **Discoid Lupus** | **1** | **0.97%** |
| **Glandular** | **1** | **0.97%** |
| **hyperplasia** | **1** | **0.97%** |
| **Necrobiosis** | **1** | **0.97%** |
| **Lipoidica** | | |
| **Sarcoidosis Cutis** | | |

**Most Common Dermatological Diseases in Geriatric Patients**

Among the 103 patients in the study, six dermatologic diseases were found to be the most common among the cohort. The most prevalent condition was vulgar psoriasis, affecting 13.59% of patients, followed by bullous pemphigoid at 11.65%. another frequent condition wasprurigo nodularis, present in 6.80% of the patients. In addition, vulgar pemphigus, leukocytoclastic vasculitis, and scabies were each identified in 4.85% of the patients, with theseconditions having equal frequency in the studied population.




**Discussion**

The clinical study reveals a higher prevalence of dermatological conditions in male patients

(58%) compared to females (42%). A study conducted by Leena R et al. [8] examined 200 patients aged between 65 and 85 years. Of these, 142 (72%) were male and 58 (29%) were female. This result suggests that men are more prone to developing dermatological diseases in this age group.

The most affected age group is 66-70 years (37%), followed by 60-65 years (31%). In the study by Agarwal R et al. [9], most patients were in the 60-69 age group (342 cases), which accounted for 68.4%. This age distribution suggests a significant burden of skin diseases in the early elderly population, likely due to cumulative sun exposure, reduced immune function, and otherage-related skin changes.

A high percentage of retirees (71%) reflects the expected professional status in this age group, with a smaller proportion of active individuals (12%) and those receiving economic aid (9%).

Seventy-seven percent of the patients had comorbid conditions, with hypertension (30%) and diabetes mellitus (10%) being the most common. The coexistence of hypertension and diabetes mellitus in 19% of patients highlights the need for integrated care treatments to manage these chronic diseases alongside dermatological conditions. The presence of other comorbidities, such as chronic kidney disease, prostatic hypertrophy, and psychiatric disorders, furthercomplicates the clinical picture and underscores the necessity of comprehensive medical evaluations for geriatric patients.

In their study, Polat M et al. [10] observed hypertension (29.58%), diabetes mellitus (19.6%), and heart diseases (15.41%) as the most prevalent systemic diseases among patients. Mponda K et al. [11] noted that the most common associated systemic disease was hypertension (30%)and diabetes (7%).

In this study, pruritus emerged as the most frequent complaint, affecting 79% of the patients. Patange & Fernandez [12] also observed pruritus in 78.5% of their patients. Leena E et al. [109] reported pruritus in 44% of subjects. Polat M et al. [10] observed pruritus in 51.8% of elderly cases, while Mponda K et al. [11] reported pruritus in 61% of cases. This high prevalence indicates that pruritus is a significant concern among the elderly, potentially affecting their quality of life and leading to secondary skin lesions due to scratching. The fact that 42% of patients experience pruritus without other symptoms suggests that it is often a primarycondition and not a symptom of an underlying issue.

The study identifies several common dermatological conditions in the geriatric population. Immunological diseases (17%) – with bullous pemphigoid making up 11.65%, vulgar pemphigus 4.85%, and pemphigus vegetans 0.97% – are the most widespread. In contrast, in the study by Kandwal M et al. [13], immunological disorders accounted for only 4% of geriatric dermatoses (2% bullous pemphigoid, 0.8% vulgar pemphigus, 0.6% herpetiform dermatitis, and 1 case of paraneoplastic pemphigus).

Immunological diseases are followed by eczematous dermatitis, which was seen in 15% of patients. In the study by Mponda K et al. [11], the eczematous disorders group (43.7%) was the primary category of diseases. Vulgar psoriasis was observed in 13.59% of patients. In KandwalM et al.'s study [13], 11 patients (9.4%) had psoriasis out of 117 patients.

Psychodermatoses were present in 8% of patients, with prurigo nodularis (6.80%) and lichen simplex chronicus (0.97%) being the most common. Compared to this study, Patange & Fernandez [12] (12%) and Leena R et al. [109] (10%) observed a higher incidence of Lichen Simplex Chronicus.

The incidence of scabies in this study was 4.85%. Polat M et al. [10] observed a prevalence of scabies at 1.3%, while Leena R et al. [8] reported a prevalence of 3%.

Cutaneous vasculitis (leukocytoclastic) was seen in 4.85% of cases. In the study by Kandwal M et al. [13], cutaneous vasculitis accounted for 2.6% of cases.

Cutaneous neoplasms comprised 14% of patients, with basal cell carcinoma being the most

common, present in 4 cases (3.88%). Mycosis fungoides, Kaposi's sarcoma, and cutaneous lymphoma were present in 2 patients each (1.94%), while squamous cell carcinoma, Sezary syndrome, Queyrat erythroplasia, and keratoacanthoma were present in 1 patient each (0.97%). Polat M et al. [10] reported a prevalence of cutaneous neoplasms of 9.6%, which is close to the present study's findings. However, Patange & Fernandez [12] and Leena R et al. [8] did not report any cutaneous neoplasms in their studies. The higher prevalence in Western studies and lower prevalence in Eastern studies may be attributed to skin type. The diagnosis of neoplasms, including basal cell carcinoma and cutaneous lymphoma, highlights the importance of regular skin examinations in the elderly for early detection of malignant tumors.

Other diseases included lichen planus in 2 patients, parapsoriasis in 2 patients (1.94%), and lichen planopilaris, lichen scleroatrophic, aphthous stomatitis, granuloma annulare, pityriasis rosea, polymorphous light eruption, photodermatitis, discoid lupus, glandular hyperplasia, necrobiosis lipoidica, and cutaneous sarcoidosis, each present in 1 patient (0.97%).

The findings of this study emphasize the need for specialized dermatological care for geriatricpatients. The high prevalence of comorbidities and complex dermatological conditions requiresa multidisciplinary approach to treatment, including dermatologists, primary care physicians, and other specialists. The integration of patient education programs to increase treatment adherence and self-care practices also plays a crucial role in managing chronic skin diseases ingeriatric patients.

## Conclusions

This study offers a comprehensive overview of the dermatological health of geriatric patients at the Unicersity Hospital Centre "Mother Teresa" in Tirana, where:

- The majority of patients are male (58%) and aged between 66-70 years (37%).
- Most patients are retirees (71%).
- Seventy-seven percent of patients have comorbid conditions, with hypertension (30%)and diabetes mellitus (10%) being the most common.
- Pruritus is the most frequent complaint (79%), followed by pain (12%) and asymptomatic lesions (10%).
- The presence of comorbidities, particularly hypertension and diabetes, often worsens the severity and complexity of dermatological conditions, necessitating tailored treatment plans.
- Autoimmune diseases and skin neoplasms are prevalent and require regular monitoringand early intervention.
- A significant correlation is observed between pruritus and the presence of major dermatological diseases such as psoriasis and eczema.
- The study highlighted a consistency in most cases between the initial clinical diagnosesand the final diagnoses.
- The specialized healthcare needs of geriatric patients include comprehensive management of their dermatological conditions and comorbid diseases.
- The study emphasized the importance of tailored healthcare services to address the unique needs of the elderly population, including more frequent monitoring andmultidisciplinary approaches to treatment.

This study underscores the complexity of managing dermatological diseases in geriatricpatients, particularly in the presence of multiple comorbidities. The findings highlight the need for specialized healthcare services that can offer comprehensive care tailored to the unique needs of elderly patients. The study also underscores the importance of accurate diagnosis and the adaptation of treatment protocols to effectively manage common dermatological conditions, considering the impact of comorbidities. These findings can inform future healthcare strategies

and improve the quality of care for geriatric patients with dermatologicaldiseases.

**References**


1. Daniel S. Loo, Mina Yaar and Barbara. A. Gilchrest, «Skin Disorders in the Elderly,» në *Principles and Practice of Geriatric Medicine, Volume 2, Fourth Edition*, Hoboken, New Jersey, USA, John Wiley & Sons, 2006, pp. 1589-1604. DOI: 10.1002/9781119952930.ch125
2. Ana Catarina Franco, Célia Aveleira, Cláudia Cavadas, «Skin senescence: mechanisms and impact on whole-body ageing,» *Cell,* vëll. i 28, nr. 2, pp. 97-109, 2022.
3. DOI: 10.1016/j.molmed.2021.12.003
4. Evgenia Makrantonaki, Christos C. Zouboulis, «The skin as a mirror of the aging process in the human organism – State of the art and results of the aging research in the German National Genome Research Network 2 (NGFN-2),» *Experimental Gerantology,* vëll. i 42, nr. 9, p. 879, 2007. 10.1016/j.exger.2007.07.002 .
5. hal-00499025
6. Mina Yaar, MD, and Barbara A. Gilchrest, «Aging of Skin,» në *Fitzpatrick's Dermatology in General Medicine*, New York, McGraw-Hill, 2008, pp. 963-975.
7. Alan J. Sinclair, John E. Morley, Bruno Vellas, Pathy's Principles and Practice of Geriatric Medicine, Hoboken, New Jersey: Wiley-Blackwall, 2022.
8. I. Papadopoulos, «Comparative Study of Dermatological Diseases of the Elderly in Relation to the Rest Population,» *Clin Cosmet Investig Dermatol,* vëll. i 13, pp. 173-178, 2020. doi: 10.2147/CCID.S242294
9. Mohammad Jafferany, Trung V. Huynh, Melissa A. Silverman, Zohra Zaidi, «Geriatric dermatoses: a clinical review of skin diseases in an aging population,» *Internationalds*
10. *Journal of Dermatology,* vëll. i 51, nr. 5, pp. 509-522, 2012. doi: 10.1111/j.1365-4632.2011.05311.x
11. R. L., «A clinical study of geriatric dermatoses,» *Our Dermatol Online,* vëll. i 5, nr. 3, pp. 235-239, 2014. DOI:. 10.7241/ourd.20143.59
12. Agarwal R., Sharma L., Chopra A., Mitra D., & Saraswat N., «A Cross-Sectional Observational Study of Geriatric Dermatoses in a Tertriary Care Hospital of Northern India,» *Indian Dermatol Online J,* vëll. i 10, nr. 5, pp. 524-529, 2019. doi: 10.4103/idoj.IDOJ_282_18
13. P. M., «Dermatological Complaint of the Elderly Attending a Dermatology Outpatient Clinic in Turkey: A Prospective Study over a One-year Period,» *Acta Dermatovenerol Croat,* vëll. i 23, nr. 4, pp. 277-281, 2015. PMID: 26724880
14. Mponda K & Masenga J, «Skin diseases among elderly patients attending skin clinic at the Regional Dermatology Training Centre, Northern Tanzania: a cross-sectional study,» *BMC Research Notes,* vëll. i 9, nr. 119, 2016. DOI: https://doi.org/10.1186/s13104-016-1933-6
15. Patange V. S. & Fernandez R. J. , «A Study of Geriatric Dermatoses,» *Ind J Venereol Leprol,* vëll. i 61, pp. 206-208, 1995. PMID: 20952955
16. Kandwal M., Jindal R., Chauhan P., & Roy S., «Skin diseases in geriatrics and their effect on the quality of life: A hospital-based observational study,» *J Family Med Prim Care,* vëll. i 9, nr. 3, pp. 1453-1458, 2020. PMID: 32509632

# EVALUATION OF CARDIAC COMPLICATIONS IN THE POST-ACUTE PHASE OF COVID-19 PATIENTS

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**Abstract**

**Introduction.** Cardiovascular complications linked to SARS-CoV-2 infection are both frequent and varied, contributing to elevated mortality during the acute phase and significant morbidity in the chronic phase, thereby impacting quality of life and overall health outcomes.

**Objective.** To assess the incidence and type of post-acute cardiac complications in patients with and without COVID-19.

**Materials and Methods.** This is a retrospective study involving 201 patients admitted to the Cardiology Diseases Service at UHC "Mother Teresa" in Tirana, Albania, during the period January– April 2021. For each patient, data were collected onCOVID-19status, comorbidities and previous cardiovascular events. The study describes post-acute cardiac complications: myocardial infarction (MI), arrhythmia, right ventricular dysfunction, pericardial effusion, and Takotsubo cardiomyopathy.

**Results.** The study included 201 patients, of whom 77 (38.3%) were female and 124 (61.7%) were male. The average age of the patients was 64.1 (±10.6) years, ranging from 32 to 91 years. Most patients, 116 (57.7%) of them, had COVID-19 (p=0.028). A significant association was found between COVID-19 and comorbidities such as hypertension (p=0.001), diabetes (p=0.035) and previous cardiovascular events (p=0.025). The incidence of post-acute cardiac complications in COVID-19 patients was 56 (48.3%).

**Conclusions.** Understanding the interaction between cardiovascular diseases and COVID-19 is essential for several critical reasons, including diagnosis, clinical management, and improving patient outcomes.

**Keywords:** COVID-19, post-acute cardiac complications

# VLERËSIMI I KOMPLIKACIONEVE KARDIAKE POST-AKUTE NË PACIENTËT ME COVID-19

**Abstrakt**

**Hyrje**: Komplikimet kardiovaskulare të lidhura me infeksionin SARS-CoV-2 janë të zakonshme dhe të shumëllojshme, duke çuar në vdekshmëri të lartë në fazën akute dhe sëmundshmëri të lartë në fazën kronike, duke ndikuar në cilësinë e jetës dhe rezultatet shëndetësore të një individi.

**Objektivi**: Të vlerësojë incidencën dhe llojin e komplikimeve kardiake pas akute te pacientët me dhe pa COVID-19.

**Materialet dhe Metodat**: Ky është një studim retrospektiv që përfshin 201 pacientë të shtruar në Shërbimin e Sëmundjeve Kardiologjike në QSUT "Nënë Tereza" në Tiranë, Shqipëri, gjatë periudhës janar-prill 2021. Për çdo pacient janë mbledhur të dhëna për statusin e COVID-19. Komorbiditetet dhe ngjarjet e mëparshme kardiovaskulare. Studimi përshkruan komplikimet

kardiake post-akute: infarkt miokardi (MI), aritmi, mosfunksionim të ventrikulit të djathtë, efuzion perikardial dhe kardiomiopati Takotsubo.
**Rezultatet**: Në studim janë përfshirë 201 pacientë, nga të cilët 77 (38.3%) ishin femra dhe 124 (61.7%) meshkuj. Mosha mesatare e pacientëve ishte 64.1 (±10.6) vjeç, duke filluar nga 32 deri në 91 vjeç. Shumica e pacientëve, 116 (57.7%) prej tyre, kishin COVID-19 (p=0.028). U gjet një lidhje e rëndësishme midis COVID-19 dhe sëmundjeve shoqëruese si hipertensioni (p=0.001), diabeti (p=0.035) dhe ngjarjet e mëparshme kardiovaskulare (p=0.025). Incidenca e komplikimeve kardiake post-akute në pacientët me COVID-19 ishte 56 (48.3%).
**Përfundime**: Kuptimi i ndërveprimit midis sëmundjeve kardiovaskulare dhe COVID-19 është thelbësor për disa arsye kritike, duke përfshirë diagnostikimin, menaxhimin klinik dhe përmirësimin e rezultateve të pacientit.

**Fjalë kyçe:** COVID-19, komplikacioneve kardiake post-akute

## Introduction

The COVID-19 pandemic is a growing public health concern globally, with case reports continuing to rise. As our understanding of COVID-19 continues to grow, there has been considerable discussion related to the acute effects of the virus on the cardiovascular system, including myocarditis, pericarditis, and acute complications such as myocardial infarction and arrhythmias (1,2). These factors not only contribute to grave outcomes of acute infections but have also been linked to post-acute outcomes. The term post-acute is defined as a phase that extends from the time of resolution of symptoms of an acute illness to a prolonged phase of symptoms, after which it may take up to 12 or even 24 weeks for symptoms to resolve (3). Around 27% of individuals with a confirmed case of COVID-19 have symptoms of the infection that have lasted for more than 12 weeks. Symptoms of acute and post-acute cardiac complications found in individuals with COVID-19 may range from asymptomatic to death due to cardiac arrest arising from a malignant arrhythmia. Acute cardiac complications are defined as an evidenced acute change in cardiac function and structure such as cardiac dysfunction with myocarditis, myocardial infarction, or arrhythmias observed during the initial infection of COVID-19 (4,5). Although the exact prevalence of such cardiac complications is unknown, they are known to occur but are rare. Post-acute cardiac complications are defined as evidence of loss of cardiac function when compared to pre-COVID imaging or recurrence of symptoms beyond the acute phase of COVID-19 infection (6-8). Mechanisms that explain the development and persistence of such symptoms likely relate to ongoing inflammation and/or disarray that interrupt the function of the cardiomyocytes or the sympathetic nervous system innervation (9-12)). Quite disturbing is the observation that older patients or people with chronic diseases such as diabetes or high blood pressure were most likely included in the criteria for the samples of survivors under study. At these ages, with these professional post-acute problems, an important component of rehabilitation occurs before their visit.
As such, we have argued that the follow-up for these patients emphasizes that the treatment of cardiac complications, such as inflammation, remains a necessary aspect of the assessments provided following discharge for COVID-19 survivors (13). There is growing recognition of the need to study post-acute complications, especially as they have a significant impact on public health and healthcare resources. Increasing research in this area could help with developing targeted rehabilitation programs, improving quality of life for patients, and creating guidelines for long-term management (14). In this study, the incidence and type of post-acute cardiac complications in Covid-19 and non-COVID-19 patients were evaluated.

## Materials and Methods

This is a retrospective descriptive study involving 201 adult patients admitted to the cardiology Service at UHC "Mother Teresa" in Tirana, Albania, during the interval period between January and April 2021. For each patient, data were collected on COVID-19status, comorbidities and previous CV events. The study aims to describe the incidence of post-acute cardiac complications: myocardial infarction (MI), arrhythmia, right ventricular dysfunction, pericardial effusion, and Takotsubo cardiomyopathy in patients with and without history of COVID-19infection. Post acute cardiac complications were diagnosed based on established criteria from the European Society of Cardiology (ESC) guidelines, ensuring standardized and consistent evaluation of conditions such as myocardial infarction, myocarditis, arrhythmias, and heart failure (15-20).

**Statistical Analysis**

Data analysis was performed using IBM SPSS Statistical Software version 25.0. Continuous variables are reported as mean and standard deviation (SD), and categorical variables are summarized as frequencies and percentages. The chi-square test was used to compare categorical variables, with statistical significance defined as a p-value of ≤0.05.

**Results**

The study included 201 patients, of whom 77 (38.3%) were female and 124 (61.7%) were male. The average age of the patients was 64.1 (±10.6) years, ranging from 32 to 91 years. The average age of the COVID-19 patients was 65.4 ± 10.6 years, while the average age of the non-COVID-19 patients was 60.1 ± 9.7 years. In the age group ≤50 years, there were 23 (11.4%) patients, in the age group 51-70 years there were 121 (60.2%) patients, while in the age group >70 years there were 57 (28.4%).

**Table 1.** Sociodemographic and clinical characteristics of the patients

| **Variables** | **Total (n=201)** | **COVID-19(n=116)** | **Non- COVID-19 (n=85** |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| **Sex** | | | |
| **Female** | 77 (38.3) | 44 (37.9) | 33 (38.8) |
| **Male** | 124 (61.7) | 72 (62.1) | 52 (61.2) |
| **Age M (SD)** | 64.1 (10.6) | 65.4 (10.6 | 60.1 (9.7) |
| **Age group** | | | |
| **≤50** | 23 (11.4) | 11 (9.5) | 12 (14.1) |
| **51-70** | 121 (60.2) | 68 (58.6) | 53 (62.4) |
| **>70** | 57 (28.4) | 37 (31.9) | 20 (23.5) |
| **Underlying conditions** | | | |
| **Hypertension** | 155 (77.1) | 87 (75.0) | 68 (80.0) |
| **Diabetes** | 60 (29.9) | 32 (27.6) | 28 (32.9) |
| **Previous CV events** | 62 (30.8) | 36 (31.0) | 26 (30.6) |
| **Stroke** | 3 (1.4) | 1 (0.9) | 2 (2.4) |
| **Venous or arterial thrombosis** | 2 (1.0) | 2. (1.7) | - |
| **Respiratory illness** | 11 (5.4) | 8 (6.9) | 3 (3.5) |
| **Malignancy** | 1 (0.5) | 1 (0.9) | - |
| **Chronic hepatic illness** | 1 (0.5) | - | 1 (1.2) |
| **Chronic renal illness** | 9 (4.4) | 7 (6.0) | 2 (1.4) |

Out of 201 cases, 116 patients (58%) had history of recent COVID-19infection. Hypertension (HTA) was the more common comorbidity (77.1%), followed by diabetes (29.9%), previous CV events (30.8%), stroke (1.4%), venous or arterial thrombosis (1%), respiratory disease (5.4%), malignancy (0.5%), chronic liver disease (0.5%), and chronic kidney disease (4.4%). A total of 70 (34.8%) patients manifested post-acute cardiac complications. Among the post-acute cardiac complications, myocardial infarction (MI)was reported in 29 patients(14.4%), followed by arrhythmia in 14 patients (7%), right ventricular dysfunction and pericardial effusion in 7 patients (3.5%) each, and Takotsubo cardiomyopathy in 1 (0.5%) patient.

No significant difference was found between two groups of patients regarding the rate of underlying conditions. The incidence of post-acute cardiac complications in COVID-19 patients 56 (48.3%) is significantly higher as compared to patients without COVID-19,14 cases (16.5%) ($p<0.001$). The following table, shows the incidence of cardiac complications in patients regarding the Covid-19 status (Table 2).

No significant difference between two groups was found regarding the incidence of MI (15.5% vs 12.9%) ($p=0.608$) whereas the incidence of arrhythmia ($p<0.001$) right ventricular dysfunction (7, 6%) ($p=0.021$), and pericardial effusion (7, 6%) ($p=0.021$)was significantly higher among patients confirmed with COVID-19. Takotsubo cardiomyopathy was found in one (0.9%) COVID-19 patient ($p=0.392$), only.

**Table 2.** Incidence of post-acute complications according to the status of Covid-19

| **Post-acute complications** | **COVID-19(n=116)** | **Non- COVID-19 (n=85)** | **P** |
|---|---|---|---|
| | n (%) | n (%) | |
| **MI** | 18 (15.5) | 11 (12.9) | 0.608 |
| **Arrhythmias** | 23 (19.8) | 3 (3.5) | <0.001 |
| **Right ventricular dysfunction** | 7 (6.0) | - | 0.021 |
| **Pericardial effusion** | 7 (6.0) | - | 0.021 |
| **Takotsubo cardiomyopathy** | 1 (0.9) | - | 0.392 |

The incidence of all post-acute cardiac complications was higher in the period >3 months after infection, ranging from 0.9 to 12.1% (table 3).

**Table 3.** Incidence of complications from the time of infection with COVID-19

| **Post-acute complications** | **< 1 month** | **1 – 3 months** | **> 3 months** | **P** |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | |
| **MI** | 3 (2.6) | 4 (3.4) | 11 (9.5) | 0.042 |
| **Arrhythmias** | 2 (1.7) | 7 (6.0) | 14 (12.1) | 0.165 |
| **Right ventricular dysfunction** | 1 (0.9) | 2 (1.7) | 4 (3.4) | 0.008 |
| **Pericardial effusion** | 1 (0.9) | 1 (0.9) | 5 (4.3) | 0.101 |
| **Takotsubocardiomyopathy** | | | 1 (0.9) | - |

## Discussion

A year after the COVID-19 pandemic, we have acquired significant insights into the symptoms,

complications, and underlying pathophysiological mechanisms of the disease and its effects on human health. This includes not only its impact on the respiratory system but also its association with other conditions, such as alterations in the blood and changes affecting the cardiovascular system.

While respiratory illness is the primary clinical feature of COVID-19, the overall disease burden suggests that many patients either have pre-existing cardiovascular conditions or may experience new cardiac dysfunction as the disease progresses.

This study provides an in-depth evaluation of post-acute cardiac complications in COVID-19 patients, demonstrating the significant burden of cardiovascular sequelae even months after the resolution of the acute phase of the infection. Higher Incidence of Post-Acute Cardiac Complications in COVID-19 Patients: The findings reveal that post-acute cardiac complications were significantly more common in patients with a history of COVID-19 infection compared to non-COVID-19 patients (48.3% vs. 16.5%, $p<0.001$). This aligns with growing evidence suggesting that SARS-CoV-2 infection has both direct and indirect effects on cardiac health, potentially mediated by systemic inflammation, endothelial dysfunction, and direct viral invasion of myocardial cells (***21***, 2***2***). The observed increased prevalence of arrhythmias, right ventricular dysfunction, and pericardial effusion in COVID-19 patients underscores the need for targeted cardiac monitoring and intervention strategies during follow-up care (***2***3, ***2***4).

Temporal Trends in Post-Acute Complications: Interestingly, the study found a progressive increase in the incidence of post-acute cardiac complications over time, with the highest rates observed beyond three months after infection. For example, myocardial infarction was reported in 9.5% of patients more than three months post-infection compared to 2.6% within the first month ($p=0.042$). Similarly, arrhythmias and right ventricular dysfunction showed an upward trend over time. These results are consistent with other studies reporting delayed cardiac manifestations, which may result from prolonged inflammation, autoimmunity, or unresolved myocardial injury initiated during the acute phase of COVID-19 (***2***5, ***2***6).

**Specific Complications: Mechanisms and Implications**

Myocardial Infarction (MI): The comparable rates of MI between COVID-19 and non-COVID-19 groups (15.5% vs. 12.9%, $p=0.608$) suggest that traditional risk factors and comorbidities, such as hypertension and diabetes, may play a dominant role in these patients. However, systemic inflammation and pro-thrombotic states observed in COVID-19 could exacerbate pre-existing cardiovascular risks, potentially leading to MI (27, 28).A meta-analytic study has shown that the rate of myocardial infarction can reach up to 10% in some specific groups of patients with high risk factors, such as those with a previous cardiovascular history (29). These figures show high variability, which is often related to the demographic and medical factors of the patients as well as the different methodologies used in different studies.

Arrhythmias: A significantly higher incidence of arrhythmias was observed in COVID-19 patients (19.8% vs. 3.5%, $p<0.001$). This may result from direct myocardial injury, hypoxia, electrolyte disturbances, or autonomic dysfunction. Persistent arrhythmias in the post-acute phase can contribute to long-term morbidity and require careful management (30). In an international prospective study, ventricular arrhythmia accounted for the reason for echocardiographic assessment in 3% of cases(31).

In contrast, other authors have found arrhythmia complications in 9.3% of patients, mainly represented by atrial fibrillation (32). But figures in 40% and 60% of patients with severe forms of COVID-19 have also been reported in the literature (33,34).

Right Ventricular Dysfunction and Pericardial Effusion: The exclusive presence of these complications in COVID-19 patients ($p=0.021$) highlights the potential for unique pathophysiological effects of the virus, including pulmonary vascular disease, increased right heart

strain, and persistent pericardial inflammation. These findings align with other reports emphasizing the role of right ventricular dysfunction in COVID-19-related morbidity (35, 36).
Takotsubo Cardiomyopathy: Although rare, Takotsubo cardiomyopathy was observed in one COVID-19 patient. The exact mechanism remains unclear, but it may involve stress-related catecholamine surges exacerbated by COVID-19 (37).
In our study, no cases of myocarditis were identified, perhaps due to the smaller number of patients compared to studies with large patient populations in the literature. The incidence is low and very low even in studies with a large patient population and varies from 0.1% to 3% (24). In the literature, it is reported that ventricular dysfunction was detected during echocardiography evaluation in 21% (29) and in 39% of patients (38).

**Implications for Clinical Practice**
The observed burden of post-acute cardiac complications in COVID-19 survivors highlights the necessity for structured follow-up programs. Cardiac rehabilitation tailored to address arrhythmias, ventricular dysfunction, and inflammatory conditions could improve outcomes. Additionally, early identification of at-risk individuals, particularly older patients or those with pre-existing conditions, is crucial (37).

**Conclusion**
Post-acute cardiac complications in COVID-19 are an area of intensive study due to the potential long-term impacts of the virus on the cardiovascular system.
This study underscores the significant burden of post-acute cardiac complications in COVID-19 patients, with a marked increase in incidence beyond three months after infection. Understanding the interaction between cardiovascular diseases and COVID-19 is essential for several critical reasons, including diagnosis, clinical management, and improving patient outcomes.
The findings emphasize the importance of long-term cardiac monitoring and the development of rehabilitation programs to address these complications, ultimately improving patient outcomes.

**Compliance with Ethics Requirements:**
*"*The authors declare no conflict of interest regarding this article"
"All procedures performed in this study were in accordance with the ethical standards of the institutional and/ or national research committee(s) and with the Helsinki Declaration (as revised in 2013), as well as the national law. Informed consent was obtained from the patients included in the study"
"No funding for this study"

**References**
1. Chen, N., Zhou, M., Dong, X., et al. (2020b). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395, 507–513.
2. Shi, S., Qin, M., Shen, B., et al. (2020b). Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 5, 802–810
3. Kole C, Stefanou E, Karvelas N, Schizas D, Toutouzas KP. Acute and Post-Acute COVID-19 Cardiovascular Complications: A Comprehensive Review. Cardiovasc Drugs Ther. 2023 May 20:1–16. doi: 10.1007/s10557-023-07465-w. Epub ahead of print. PMID: 37209261; PMCID: PMC10199303.
4. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(11):1265-1273.

5. Chang W-T, Toh HS, Liao C-T, Yu W-L. Cardiac involvement of COVID-19: a comprehensive review. *The American Journal of the Medical Sciences.* 2021;361(1):14- 22
6. Alkodaymi MS, Omrani OA, Fawzy NA, et al. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and metaanalysis. *Clinical Microbiology and Infection.* 2022;28(5):657-666.
7. Groff D, Sun A, Ssentongo AE, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Network Open.* 2021;4(10):e2128568-e2128568.
8. Satterfield BA, Bhatt DL, Gersh BJ. Cardiac involvement in the long-term implications of COVID-19. *Nature Reviews Cardiology.* 2022;19(5):332-341.
9. Lavelle MP, Desai AD, Wan EY. Arrhythmias in the COVID-19 patient. *Heart Rhythm O2.* 2022;3(1):8-14.
10. Ghantous E, Szekely Y, Lichter Y, et al. Pericardial Involvement in Patients Hospitalized With COVID-19: Prevalence, Associates, and Clinical Implications. *Journal of the American Heart Association.* 2022;11(7):e024363.
11. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid- 19: summary of NICE, SIGN, and RCGP rapid guideline. *bmj.* 2021;372.
12. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *European heart journal.* 2022;43(11):1157- 1172.
13. Goudman L, De Smedt A, Noppen M, Moens M. Is Central Sensitisation the Missing Link of Persisting Symptoms after COVID-19 Infection? *Journal of clinical medicine.* 2021;10(23):5594.
14. Smer A, Squires RW, Bonikowske AR, Allison TG, Mainville RN, Williams MA. Cardiac Complications of COVID-19 Infection and the Role of Physical Activity. *J Cardiopulm Rehabil Prev.* 2022.
15. Caforio AL, Pankuweit S, Arbustini E, et al.; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013; 34: 2636–2648, 2648a–2648d.
16. Adler Y, Charron P, Imazio M, et al.; ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015; 36: 2921–2964.
17. Habib G, Lancellotti P, Antunes MJ, et al.; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36: 3075–3128.
18. Ponikowski P, Voors AA, Anker SD, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.
19. Roffi M, Patrono C, Collet JP, et al.; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the Management of Acute Coronary Syndromes in

Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267–315.
20. Buxton AE, Calkins H, Callans DJ, et al.; American College of Cardiology; American Heart Association Task Force on Clinical Data Standards; (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/ AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). J Am Coll Cardiol 2006; 48: 2360– 2396.
21. Xie, Y., et al. (2022). Long-term cardiovascular outcomes of COVID-19. *Nature Medicine, 28*(4), 583–590. https://doi.org/10.1038/s41591-021-01672-1
22. Shi, S., et al. (2020). Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiology, 5*(7), 802–810. https://doi.org/10.1001/jamacardio.2020.0950
23. Zheng, Y. Y., et al. (2020). COVID-19 and the cardiovascular system. *Nature Reviews Cardiology, 17*(5), 259–260. https://doi.org/10.1038/s41569-020-0360-5
24. Puntmann, V. O., et al. (2020). Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiology, 5*(11), 1265–1273. https://doi.org/10.1001/jamacardio.2020.3557
25. Guo, T., et al. (2020). Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiology, 5*(7), 811–818. https://doi.org/10.1001/jamacardio.2020.1017
26. Chouchana, P., et al. (2021). Incidence of cardiovascular complications during COVID-19 infection: A retrospective study. *Clinical Infectious Diseases, 72*(5), 874–876. https://doi.org/10.1093/cid/ciaa906
27. Fried, J. A., et al. (2020). The variety of cardiovascular presentations of COVID-19. *Circulation, 141*(20), 1648–1655. https://doi.org/10.1161/CIRCULATIONAHA.120.047164
28. Mancia, G., et al. (2020). Cardiovascular complications and mortality in patients with COVID-19. *European Heart Journal, 41*(21), 1917–1923. https://doi.org/10.1093/eurheartj/ehaa106
29. Brogi, E., Marino, F., Bertini, P. *et al.* Cardiac complications in patients with COVID-19: a systematic review. *J Anesth Analg Crit Care* 2, 18 (2022). https://doi.org/10.1186/s44158-022-00046-7
30. Siripanthong, B., et al. (2020). Recognizing COVID-19–related myocarditis: The challenge in distinguishing between this and other conditions. *Heart Rhythm, 17*(9), 1463–1471. https://doi.org/10.1016/j.hrthm.2020.03.024
31. Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, White A, SalvoGD, Sade LE, Pearce K (2020) Global evaluation of echocardiography in patients with COVID-19. Eur Heart J Cardiovasc Imag 21(9):949–958.
32. Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, Xu J, Wu Y, Huang C, Ouyang Y, Yang L, Fang M, Xiao H, Ma J, Zhu W, Hu S, Hu Q, Ding D, Hu M, Zhu G, Xu W, Guo J, Xu J, Yuan H, Zhang B, Yu Z, Chen D, Yuan S, Shang Y (2020) Patients with COVID-19 in 19 ICUs in Wuhan, China: a cross-sectional study. Crit Care 24(1):219.
33. Mahmud, E., et al. (2020). COVID-19-related cardiovascular complications: A review. *Catheterization and Cardiovascular Interventions, 96*(5), 1006–1009. https://doi.org/10.1002/ccd.28990
34. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, Peng Z, Pan H (2020) Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 127:104364.

35. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P et al (2020) Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. Am J Respir Crit Care Med 201(11):1372– 1379. https://doi.org/10.1164/rccm.202003-0543OC
36. Cremer, P. C., et al. (2020). COVID-19 and cardiovascular disease. *Journal of the American College of Cardiology, 75*(18), 2332–2334. https://doi.org/10.1016/j.jacc.2020.03.046
37. Jabri, A., et al. (2020). Incidence of Takotsubo syndrome during the COVID-19 pandemic. *JAMA Network Open, 3*(11), e2024780. https://doi.org/10.1001/jamanetworkopen.2020.24780
38. Adamo, L., et al. (2020). Interdisciplinary care of COVID-19 patients and the cardiovascular care team. *Circulation, 142*(8), 713–715. https://doi.org/10.1161/CIRCULATIONAHA.120.048365

# PRIMARY ALDOSTERONISM; ONE OF THE MOST IMPORTANT CAUSES OF SECONDARY HIPERTENSION. SURVEY IN INTERNAL MEDICINE WARD.

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**Abstract**

**Background:** Hypertension is one of the most frequent diseases in the world and risk factor for major cardiovascular events like Acute Myocardial Infarction, cerebral Ischemia, arrhythmia, hospitalization and death. It is classified in primary hypertension, when there is no identified cause and secondary hypertension, which is a result of a certain organ damage like heart, kidneys, thyroid, adrenal glands, etc. In the general population, secondary HT affects 5-11% of cases. Primary aldosteronism (PA) is a rare condition characterized by overproduction of aldosterone (mineralocorticoid hormone), as a result of a disorder in the adrenal gland.

**Aim**: To identify the number of cases with PA in hypertensive population. To determine the methods of diagnosis and treatment. To evaluate the relation between hypokalemia and PA.

**Methods**: This is an observational, prospective, single-centered study, including 80 patients admitted for secondary hypertension, from June 2016-July 2018 at University Hospital Center Mother Theresa, Internal Medicine Ward.

**Results**: The prevalence of PA in our study was 5.9%. Mean age was 48 +/- 13 years old. Male patients were more than females. BMI was 27.97+/- 12.07 kg/m2. Most frequent diseases in addition to Hypertension were: dyslipidemia (18.7%), type 2 DM (29.9%), VCA/TIA (6.2%) and arrhythmia (5%). Hypokalemia (K+ <3.5 mmol/l) was seen in 31.2% of cases. Severe hypokalemia (K+ <2.5 mm) resulted in 6.3% of cases. The Aldosterone-to-Renin Ratio (ARR) >50 was seen in 5 % of cases. ARR <30 resulted in 20 % of cases. The gold standard for diagnosis remains Radiology. 66.3% were unilateral Adenomas, 20 % bilateral Adenomas and 7.5 % adrenal hyperplasia. Adenomas of 1-2 cm had a high prevalence (50 %) against Adenomas >2 cm (18.8% ). As for the treatment, 96.2 % received conservative therapy vs 3.8 % of Surgery, followed by biopsy. Spironolactone 25 mg resulted the most used medication of his class, 53.8%. Eplerenone was used less because of its costs, but had fewer side effects.

**Conclusions**: The prevalence of PA in this 2-year study resulted in 5.9 % of cases with Hypertension. Hypokalemia it is present in most cases of PA, but does not always confirm its presence. The ranges of plasmatic Aldosterone and ARR were low or within normal limits, in very few cases ARR was higher than 50. Radiology remains the golden standard in diagnosing Adenomas and confirming them. it locates them and determines the dimensions and its types. Conservative therapy results superior vs surgical therapy. All classes of hypertensive medications were used in treating hypertension, but the most used remains Spironolactone, Verapamil and Doxazocine, because of lesser side effects during hormone dosage.

**Key words**: hypertension, primary aldosteronism, renine, aldosterone, spironolactone.

# HIPERALDOSTERONIZMI PRIMAR- NJË NGA SHKAQET MË TË RËNDËSISHME TË HTA SEKONDAR. EKPERIENCA JONË NË MJEKESINË INTERNE.


## Abstrakt

**Hyrje**: Hipertensioni arterial është një nga sëmundjet më të përhapura në botë dhe faktor risku madhor për evente si IAM, Insulte cerebrale, Aritmi, Vdekje. Klasifikohet në primar ose esencial, kur nuk ka një shkak të identifikueshëm dhe sekondar kur vjen si pasojë e prekjes së një organi të caktuar. Në popullatën e përgjithshme HTA sekondar zë rreth 5-11% të rasteve. Aldosteronizmi primar është një gjëndje që karakterizohet nga prodhimi i shtuar i aldsoteronit ( mineralokortikoid) si pasojë e një crregullimi në gjëndrën surrenale, në mënyrë të pavarur dhe autonome nga sistemi reninë-angiotenzinë.

**Qëllimi**: Të identifikohet numri i rasteve me hiperaldosteronizëm primar në popullatën hipertensive. Të përcaktohen mënyrat e diagnostikimit dhe trajtimit të tij. Të vlerësohet lidhja e AP me hipokaleminë.

**Metoda**: Në këtë studim u përfshinë 80 pacientë të hospitalizuar në pavionin e MI, në periudhën qershor 2016 - korrik 2018, me diagnozë: suspekt HTA me natyrë sekondare. Studimi është prospektiv, rast kohort.

**Rezultatet:** Prevalenca e AP në studimin tone rezultoi 5.9 %. Mosha mesatare e pacientëve ishte 48+/- 13 vjec, meshkuj më tepër se femra. BMI rezultoi 27.97 +/- 12.07 kg/m2. Sëmundjet shoqëruese me frekuencë më të lartë përmenden: Dislipidemia (18.7%), DM tip 2 ( 29.9%), AVC/TIA (6.2) dhe Aritmia (5%). Hypokalemia ( K+ <3.5 mmol/l) u pa në 31.2% të rasteve, hipokalemi severe (K+<2.5 mmol/l ) në 6.3% të rasteve. Raporti RAA >50 u pa në 5 % të rasteve. RAA<30 u pa në 20% të rasteve. Imazheria ishte me rëndësi të madhe në vendosjen e diagnozës. 66.3% të rasteve rezultuan adenoma unilaterale, 20 % bilaterale dhe 7.5% hiperplazi e surrenales. U pa prevalencë e lartë e adenomave 1-2 cm (50%) dhe >2 cm (18.8%). Përsa i përket trajtimit, 96.2% morën terapi medikamentoze dhe 3.8% kirurgji të shoqëruar me biopsi. Spironolactoni 25 mg rezultoi medikamenti më i përdorur i klasës së tij, në 53.8%. Eplerenoni u përdor më pak për shkak të kostos së tij, por pati më pak efekte anësore.

**Konkluzione**: Prevalenca e AP në këtë studim dy-vjecar rezultoi 5.9% e rasteve me HTA. Hipokalemia është bashkëshoqëruese e AP, por nuk e vërteton gjithmonë atë. Vlerat e aldosteronit plazmatik dhe RAA kanë qënë normale ose të ulta, dhe në shumë pak raste RAA>50. Imazheria mbetet gold standart në vendosjen dhe konfirmimin e diagnozës së AP. Ajo lokalizon adenomat, hiperplazinë, përcakton përmasat dhe llojin e tyre. Terapia medikamentoze rezultoi superiore ndaj asaj kirurgjikale. U përdorën të gjitha klasat e antihipertensivëve në trajtimin e HTA, por kryesorët mbeten Spironolactoni, Verapamili dhe Doxazocina.



**Fjalë kyçe**: HTA, hiperaldosteronizmi, Reninë, Aldosteroni, spironolakton.


## Introduction

Arterial hypertension (HTN) is one of the most frequent cardiovascular diseases in the world, defined as increased SBP >140 mmHg and DBP >90 mmHg (1). The latest global prevalence is almost 1 billion people, and about 150 millions are registered in Central and East Europe (2). The prevalence of hypertension in the adult population rates among 20-45% (2). It is evaluated as the most important risk factor of global mortality and morbidity and the most related with cardiovascular diseases because of the high risk of acute myocardial infarct, VCA, heart failure and renal disease. In 95% of cases the causes remain unknown and it is known as essential or primary hypertension (3). 5 % of cases are identified as secondary hypertension (4). This is important because knowing the cause helps curing the HTN. The most frequent causes of

secondary HTN are renovascular diseases and endocrine disorders like primary aldosteronism (PA), pheochromocytoma, Cushing disease, etc (5). Despite the improvement in controlling HTN during the last 3 decades and the wide range of available antihypertensive medications, 5-30 % of patients are not in the recommended values of blood pressure, according to the latest guidelines. As such, blood pressure (BP) monitoring is important to avoid the possible complications (6).

**Aim**

To identify the prevalence of PA in hypertensive population. To determine the methods of diagnosis and treatment. To evaluate the relationship between hypokalemia and PA, and Aldosterone-to-Renin Ratio (ARR) with PA.

**Materials and Methods**

This is an observational, prospective, single-centered study including 80 patients admitted for secondary hypertension, from June 2016 - July 2018, at University Hospital Center "Mother Theresa", Internal Medicine Ward. In this study were included all patient suspected for PA, and all the other causes of hypertension were excluded.

A special database was created for gathering general information from the patients, including risk factors, other diseases, familiar cases, lifestyle, medication taken by the patient, surgeries. A consent paper from the patient was signed before each procedure.

**Results**

80 patients hospitalized in Internal Medicine Ward, "Mother Teresa" hospital, were included in the study with suspected diagnosis of PA. The prevalence of PA, according to our study and the statistics, resulted 5.9%. Mean age was 48 +/- 13 years old. BMI ranges were between 18-40 kg/m$^2$, mean BMI was 27.96 +/-12.07 kg/m$^2$. BMI > 30 was observed in 8.7% of cases. The most frequent comorbidities were dyslipidemia in 18.7 % of cases, type 2 diabetes mellitus in 29.9% of cases and cerebrovascular accident (CVA) and transient ischemic attack (TIA) before hospitalization were present in 6.2 % of cases. Cardiac arrhythmias consisted in only 5 % of cases.

According to the lab analysis, the most important indicator for diagnosing PA were the levels of blood potassium. In our study, 93.8% of cases had $K^+$ >3.0 mmol/L and in 6.3 % of cases we had severe hypokalemia. Hormone levels measurements showed ARR >50 in 5 % of patients, ARR >15 in 12.5 % and 20 % of cases had normal values. 62.5 % of patients couldn't measure the hormone levels for different reasons. During hospitalization echocardiography and 24 hours automatic blood pressure monitoring (ABPM) were performed. Mild left ventricle (LV) hypertrophy was seen in 40 % of cases and 35% of them had severe LV hypertrophy. 24 h ABPM showed 36.2% grade I hypertension, 18.8 % grade II, 7.5 % grade III and 13.7 % isolated high systolic blood pressure. Imaging related with types of PA and their dimensions showed that: 66.3 % were unilateral adenomas, 20 % bilateral and 7.5 % were classified as adrenal gland hyperplasia. In this study we evaluated that the majority of patients get medical conservative treatment, 96.2 % of cases, and only 3.8 % of patient are treated in surgery department, with adrenalectomy and respective biopsy.

**Discussion.**

Considering the global impact it has on health, the control of HTN is of extreme importance. Great efforts are made and continue to control and treat secondary forms of HTN, including PA (7,8). According to different studies, PA is evaluated as 5-11 % of worldwide hypertensive population (9). In our 2-year period study, 80 patients with PA, were included and based on the statistical data of Statistic Service, in 'Mother Teresa' University Hospital, the prevalence was 5.9 % among all

hypertensive population (10.11). This figure is within the range mentioned by international studies. First of all, the predominance of male patients versus female was observed, respectively 57.5 % vs 42.5%. Mean age was 48+/- 13 years old, almost the same limits as in international studies (12). Mean BMI was 27.96 +/- 12.07 kg/$m^2$. In relation with comorbidities, the most significant are dyslipidemia (18.7 %), type 2 Diabetes Mellitus (29.9 %), CVA and TIA (6.2 %). 5% of cases had cardiac arrhythmias, such as atrial fibrillation and sinusal tachycardia, these events happened during hospitalization (13.14). One of the purposes of our study was to evaluate the correlation between hypokalemia and PA. According to the lab database, 31.2 % of cases had $K^+ < 3.5$ mmol/l and 6.3 % severe hypokalemia ($K^+ \leq 2.5$ mmol/l). Considering the number of patients included in the study, we must emphasize that these values are statistically significant ($p < 0.05$) (15). We can determine that hypokalemia accompanies PA, but does not prove it, which means that its presence it is not related with the presence of adenomas. There are patients with normal ranges of potassium, but had adrenal adenomas (16). These results are almost equivalent to those mentioned by European studies and published in various journals. Hormonal level measurements like plasma aldosterone, rennin activity and their ratio have a more important role (17). What is worth emphasizing in this study, there are very few cases where ARR was above the normal limits, respectively 5 % of cases. 20 % were within normal ranges or lower, if we take the latest guidelines as a base, these values would definitely exclude primary aldosteronism (18). So, just as with potassium, we confirmed the presence of adrenal adenoma through imaging or biopsy, but with lower ARR. We must remember that hormonal levels are highly influenced by plasmatic potassium, as well as the right correction of mild/severe hypokalemia (19). Certain antihypertensive medications, levels of plasmatic sodium, and the procedure of blood collection play a significant role (20).

Radiology results proved once again its importance in diagnosing early cases of primary aldosteronism. 66.3 % were unilateral adrenal adenomas, 20 % bilateral adenomas and 7.5% adrenal hyperplasia (21). Through imagery we can determine their size and localization, and whether or not it will be subjected to surgery (22). 1-2 cm adenomas had the highest prevalence, 50 % of cases, statistically important (p – 0.031). 18.8 % are adenomas > 2 cm and 17.5 % less than 1cm (23).

Lastly, conservative management of primary aldosteronism predominates in 96.2 % of our patients (24). Only 3.8% were subject to surgery for adrenalectomy and follow-up biopsy (25). Regarding drug treatment, Spironolactone is the most used of the class of mineralocorticoid receptor inhibitors, at almost 53.8 % of cases (26). Its dosage depending on BP values, plasmatic levels of $K^+$ and other antihypertensive drugs. Eplerenone, another one from the mineral corticoid inhibitors, has fewer side effects than spironolactone. It is rarely used because of higher financial cost, compared to spironolactone. Doxazocine 2 mg (22.5 %) and Verapamil 80 mg (21.3 %) are two antihypertensive medications used, especially in the period before hormonal dosing, for keeping BP under control and because they don't influence hormonal levels (27). Their dosage is dependent on the severity of blood pressure; they can be given alone or combined with other antihypertensive drugs. Every patient has its individual dosage related to the BP and other comorbidities (28.29).

**Limitations**

A major limitation of this study was the high financial cost, related with hormonal level measurements. This laboratory tests are done privately by patients and not all of them had the financial possibilities.

Second, the limited number of patients included in the study. This comes as a result of not being able to dose the hormonal levels privately and the lack of an accurate database for hypertension from all causes.

In the third place, unlike the guidelines, that recommended in the first place hormonal level

measurements and then radiology, we do the opposite. We perform Angio-CT or MRI, confirm the presence of adenomas or hyperplasia and after that the hormonal dosing (30).

**Conclusions**

PA prevalence studied in the two- year period June 2016 – July 2018, at Internal Medicine Ward, resulted 5.9 %. Hypokalemia accompanies PA but does not always prove it. Having mild or severe hypokalemia does not mean we have PA, but it doesn't exclude it either. According to our results the same can be said for the hormonal level measurements. In most of our cases, the ARR was within normal limits, or lower and we had PA proven by radiology. Radiology remains the gold standard for the diagnosis of primary aldosteronism, for localizing unilateral or bilateral adenomas, or adrenal hyperplasia and defining their size. Unilateral aldosterone-secreting adenomas have higher prevalence than other types. Follow-up every six months with lab tests and radiology is done for every patient diagnosed with PA that is not subjected to surgery.

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**References**


1. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA) [published correction appears in J Hypertens. 2024 Jan 1;42(1):194. doi: 10.1097/HJH.0000000000003621]. J Hypertens. 2023; 41(12):1874-2071. doi:10.1097/HJH.0000000000003480
2. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334-1357. doi:10.1161/HYPERTENSIONAHA.120.15026
3. Mulatero P, Monticone S, Deinum J, et al. Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. J Hypertens. 2020;38(10):1919-1928. doi:10.1097
4. Käyser SC, Deinum J, de Grauw WJ, et al. Prevalence of primary aldosteronism in primary care: a cross-sectional study. Br J Gen Pract. 2018;68(667):e114-e122. doi:10.3399/bjgp18X694589.
5. Rossi GP, Bisogni V, Rossitto G, et al. Practice Recommendations for Diagnosis and Treatment of the Most Common Forms of Secondary Hypertension. High Blood Press Cardiovasc Prev. 2020;27(6):547-560. doi:10.1007/s40292-020-00415-9
6. Lamirault G, Artifoni M, Daniel M, Barber-Chamoux N, Nantes University Hospital Working Group On Hypertension. Resistant Hypertension: Novel Insights. Curr Hypertens Rev. 2020;16(1):61-72. doi:10.2174/1573402115666191011111402
7. Indra T, Holaj R, Štrauch B, et al. Long-term effects of adrenalectomy or spironolactone on blood pressure control and regression of left ventricle hypertrophy in patients with primary aldosteronism. J Renin Angiotensin Aldosterone Syst. 2015;16(4):1109-1117. doi:10.1177/1470320314549220

8. de Silva T, Cosentino G, Ganji S, Riera-Gonzalez A, Hsia DS. Endocrine Causes of Hypertension. Curr Hypertens Rep. 2020;22(11):97. Published 2020 Oct 20. doi:10.1007/s11906-020-01108-3

9. Brown JM, Siddiqui M, Calhoun DA, et al. The Unrecognized Prevalence of Primary Aldosteronism: A Cross-sectional Study. Ann Intern Med. 2020;173(1):10-20. doi:10.7326/M20-0065

10. Ruhle BC, White MG, Alsafran S, Kaplan EL, Angelos P, Grogan RH. Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives. Surgery. 2019;165(1):221-227. doi:10.1016/j.surg.2018.05.085;

11. Rossi GP, Cesari M, Cuspidi C, et al. Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism [published correction appears in Hypertension. 2014 Dec;64(6):e7]. Hypertension. 2013;62(1):62-69. doi:10.1161/HYPERTENSIONAHA.113.01316

12. Hypertension in adults: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2023 Nov 21. (NICE Guideline, No. 136.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK547161/

13. Korah HE, Scholl UI. An Update on Familial Hyperaldosteronism. Horm Metab Res. 2015;47(13):941-946. doi:10.1055/s-0035-1564166

14. Born-Frontsberg E, Reincke M, Rump LC, et al. Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: results of the German Conn's Registry. J Clin Endocrinol Metab. 2009;94(4):1125-1130. doi:10.1210/jc.2008-2116

15. Hundemer GL, Imsirovic H, Vaidya A, et al. Screening Rates for Primary Aldosteronism Among Individuals With Hypertension Plus Hypokalemia: A Population-Based Retrospective Cohort Study. Hypertension. 2022;79(1):178-186. doi:10.1161/ HYPERTENSIONAHA. 121.18118

16. Montori VM, Young WF Jr. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism. A systematic review of the literature. Endocrinol Metab Clin North Am. 2002;31(3):619-xi. doi:10.1016/s0889-8529(02)00013-0

17. Yozamp N, Hundemer GL, Moussa M, et al. Intraindividual Variability of Aldosterone Concentrations in Primary Aldosteronism: Implications for Case Detection. Hypertension. 2021;77(3):891-899. doi:10.1161/ HYPERTENSIONAHA. 120. 16429.

18. Morera J, Reznik Y. MANAGEMENT OF ENDOCRINE DISEASE: The role of confirmatory tests in the diagnosis of primary aldosteronism. Eur J Endocrinol. 2019;180(2):R45-R58. doi:10.1530/EJE-18-0704

19. Leung AA, Symonds CJ, Hundemer GL, et al. Performance of Confirmatory Tests for Diagnosing Primary Aldosteronism: a Systematic Review and Meta-Analysis. Hypertension. 2022;79(8):1835-1844. doi:10.1161/ HYPERTENSIONAHA 122.19377

20. Stowasser M, Ahmed AH, Pimenta E, Taylor PJ, Gordon RD. Factors affecting the aldosterone/renin ratio. Horm Metab Res. 2012;44(3):170-176. doi:10.1055/s-0031-1295460

21. Patel SM, Lingam RK, Beaconsfield TI, Tran TL, Brown B. Role of radiology in the management of primary aldosteronism. Radiographics. 2007;27(4):1145-1157. doi:10.1148/rg.274065150

22. Kempers MJ, Lenders JW, van Outheusden L, et al. Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. Ann Intern Med. 2009;151(5):329-337. doi:10.7326/0003-4819-151-5-200909010-00007

23. Dekkers T, Prejbisz A, Kool LJS, et al. Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: an outcome-based randomised diagnostic trial. Lancet Diabetes Endocrinol. 2016;4(9):739-746. doi:10.1016/S2213-8587(16)30100-0

24. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059-2068. doi:10.1016/S0140-6736(15)00257-3

25. Flammia RS, Anceschi U, Tufano A, et al. Minimally Invasive Partial vs. Total Adrenalectomy for the Treatment of Unilateral Primary Aldosteronism: A Systematic Review and Meta-Analysis. J Clin Med. 2022;11(5):1263. Published 2022 Feb 25. doi:10.3390/jcm11051263

26. Patibandla S, Heaton J, Kyaw H. Spironolactone. [Updated 2023 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554421/

27. Katabami T, Fukuda H, Tsukiyama H, et al. Clinical and biochemical outcomes after adrenalectomy and medical treatment in patients with unilateral primary aldosteronism. J Hypertens. 2019;37(7):1513-1520. doi:10.1097/ HJH. 0000000000002070

28. Tan YK, Kwan YH, Teo DCL, et al. Improvement in quality of life and psychological symptoms after treatment for primary aldosteronism: Asian Cohort Study. Endocr Connect. 2021;10(8):834-844. Published 2021 Jul 26. doi:10.1530/EC-21-0125

29. Velema M, Dekkers T, Hermus A, et al. Quality of Life in Primary Aldosteronism: A Comparative Effectiveness Study of Adrenalectomy and Medical Treatment. J Clin Endocrinol Metab. 2018;103(1):16-24. doi:10.1210/jc.2017-01442

30. Willenberg HS, Vonend O, Schott M, et al. Comparison of the saline infusion test and the fludrocortisone suppression test for the diagnosis of primary aldosteronism. Horm Metab Res. 2012;44(7):527-532. doi:10.1055/s-0032-1314786.

# UNDERSTANDING OCCULT HEPATITIS B IN BLOOD DONORS

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**Abstract**
Understanding and diagnosing occult hepatitis B infection (OBI) still presents an obstacle in managing HBV infection. OBI poses a problem in screening blood donors and managing transfusion procedures. The key identifier of OBI is the presence of HBV-DNA that can only be detected using DNA assays. Nucleic acid testing (NAT) or Real Time Polymerase Chain Reaction (PCR) quantifies HBV-DNA levels in units per ml [IU/ml] or copies, per ml to assess the amount. Even if the donor is HBsAg negative, they can transmit OBI to the recipient by their viremic status (detection of HBV DNA). As a result, it is well worth developing strict screening criteria and reliable tests to identify suspected OBI in blood donors and avoid the chance of HBV transmission through unscreened blood transfusion. In all, we need to consider how prevalent OBI may be among blood donors. Moreover, continuous monitoring is required because the prevalence rates differ across studies conducted in different populations. Furthermore, many infected individuals will eventually manifest liver damage and progress to cirrhosis and hepatocellular carcinoma. Accordingly, OBI is not only important in terms of transmission of infection through blood transfusion, but also has other clinical significance.

**Key words:** Occult hepatitis B infection, Polymerase Chain Reaction, blood donors, Nucleic acid testing

# HEPATITI B OKULT NË DHURUESIT E GJAKUT; ÇFARË DUHET TË DIMË

**Abstrakt**
Diagnostikimi I infeksionit okult të virusit të hepatit B (VHB) ende paraqet një aspekt të rëndësishëm në menaxhimin e tij. Infeksioni okult I hepatitit B (IOB) merr rëndësi veçanërisht në ekzaminimin e dhuruesve të gjakut dhe menaxhimin e procedurave të transfuzionit. Identifikuesi kryesor I IOB është prania e HBV-AND, që mund të zbulohet vetëm duke përdorur analizat e I-së. Testimi I acidit nukleik (TAN) ose Reaksioni Zinxhiri I Polimerazës në kohë reale (RZP) përcakton nivelet e HBV-I-së në njësi për ml [IU/ml], ose kopje për ml. Edhe nëse dhuruesi është HbsAg negativ, ata mund të transmetojnë IOB te marrësi në varësi të statusit të tyre viremik (zbulimi I I-së së VHB). Zhvillimi I kritereve të rrepta të depistimit dhe testeve të besueshme për të identifikuar IOB të dyshuar te dhuruesit e gjakut mbetet I rëndësishëm dhe I domosdoshëm për të shmangur mundësinë e transmetimit të VHB përmes transfuzionit të gjakut. Në përgjithësi, ne duhet të vlerësojmë prevalencën e IOB midis dhuruesve të gjakut. Për më tepër, kërkohet monitorim I vazhdueshëm, sepse prevalence e IOB ndryshon sipas studimeve të kryera në popullata të ndryshme. Veç kësaj, disa individë të infektuar mund të manifestojnë dëmtime të mëlçisë, të cilat progresojnë në cirrozë dhe karcinomë hepatocelulare. Rrjedhimisht, IOB nuk është

I rëndësishëm vetëm për sa I përket transmetimit të infeksionit përmes transfuzionit të gjakut, por edhe aspektit klinike dhe impaktit në shëndetin publik.

**Fjalë kyçe**: infeksion okult I hepatitit B, Reaksion zinxhir polimerazë, dhurues gjaku, testimi I acidit nukleik

## Introduction

According to the World Health Organization (WHO) 2024 for the European Region 10.6 million people are living with hepatitis B virus (HBV). If absent from proper medical treatment, the infection may lead to severe clinical outcomes such as cirrhosis or Hepatocellular Carcinoma (HCC) (1). It belongs to the Hepadnaviridae family and the main route of transmission is through the infected fluid containing either blood, or semen (2). Through studying the structure and epidemiology of the hepatitis B virus, it becomes clear how its strains and clinical forms alter approaches to prevention and treatment.

- Regarding structure, HBV belongs to the group of double-stranded DNA viruses that have an incomplete internal structure made up of essential surface antigens (HbsAg) for infectivity and immunogenic purposes that are externalized. The core antigen known as HbcAg is found within the viral envelope in the form of a nucleocapsid that encases the viral DNA polymerase and parts of the viral DNA (3).
- In accordance with the transmission section, routes for the potential transfer of HBV include unprotected sexual contact, use of non-sterile syringes or other medical equipment, or transmission from mother to child during birth. More importantly, this virus can survive outside the body for more than seven days without decomposing (4).
- In addition, HBV also possesses additional types of genotypes A through H, bearing in mind their geographical ranges and clinical relevance. Such types of genotypes can affect condition progress, treatment responsiveness, and even the responses to vaccines. For instance, genotype C has a worse liver disease and a higher risk of hepatocellular carcinoma (5).
- In relation to clinical manifestations, infection with HBV can be avirulemic with spontaneous resolution or become chronic. Many of the patients will, at the time of diagnosis, not be symptomatic during the productive phase of the infection, while many others may experience nausea, jaundice, abdominal discomfort, or flu-like illness. Chronic infection with HBV is associated with the development of complications such as liver cirrhosis, liver failure, and HCC (2, 6).
- Furthermore, concerning prevention and treatment, the definite and most effective method for preventing the population from HBV is vaccination. The vaccine is effective against all the well-known genotypes of the virus (1). Antiviral agents can be given to infected patients to control viral replication and prevent the complications (1). There are many strategies that can be employed, but will be influenced greatly by the phase of infection (acute or chronic) and the patient's clinical state (7).

### What is occult hepatitis B virus infection and why is it a concern in blood donation?

Occult hepatitis B virus infection (OBI) according to the statements from the Taormina expert meeting, is a form of HBV infection defined by the presence of HBV DNA in the liver, which can be undetectable or detectable in the serum by molecular testing in patients who test negative for the hepatitis B surface antigen (HbsAg), which represents a standard marker for HBV infection (8). In the context of a positive HBV DNA result, a low viral load in the serum (usually <200 or even below 20 IU/ml) in an individual negative for HbsAg is indicative of an OBI (8). HBV DNA

load—amount of HBV genetic material in a blood sample usually is measured as international units per mL (IU/mL) or copies per mL (9). This happens in those who are either positive or negative for HBV antibodies, and according to serologic patterns, OBI is divided into seropositive OBI and seronegative OBI (8). The difference between seropositive and seronegative OBI is clinically important. Seropositivity of OBI could represent a cleared HBV infection, where HBV is no more replicative but HBV DNA remains in the liver. They may be at reduced risk for liver-related complications compared with patients, who may have an active HBV infection, but might benefit from follow-up to monitor for disease progression or the emergence of potential reactivation. By contrast, seronegative OBI demands novel diagnostic strategies in that these individuals are negative for HBV antibodies and therefore not detected by standard serology. Yet they have hepatitis B virus DNA (viral replication) in their blood and can still potentially infect others, particularly via blood transfusion or organ donation (9).

Interest in occult hepatitis B, especially in relation to blood donation, stems from a theoretical risk of transmitting the HBV to recipients by transfusion. Although the HbsAg test for blood donors is a routine introductory screening, it may not be able to identify individuals with occult hepatitis B (10). On the subject of transmissibility, individuals with occult hepatitis B can still transmit the infection through blood transfusions, organ transplants, and other routes of exposure. (11, 12, 13) Others may be at risk for developing chronic HBV infection if they receive blood that contains occult HBV, especially those with compromised or suppressed immune systems (14). Concerning the risk of disease progression, cirrhosis and HCC are two serious liver problems that can result from a persistent HBV infection (15).

Implementation of extra steps by blood banks in the screening of blood donation to lower the risk of occult hepatitis B, included nucleic acid testing (NAT) for HBV DNA in association to the screening for the presence of HbsAg (16). Since NAT can detect HBV DNA in blood samples when no HbsAg is present, it can be used to identify individuals with occult hepatitis B and prevent the transmission of HBV via blood component transfusion.

**Epidemiology insights of occult hepatitis B infection**

The prevalence of occult hepatitis B infection in blood donors shows significant variability depending on the population and geographical location. Variations in OBI prevalence have been found by epidemiological studies across different locations and populations. OBI occurred more frequently in areas with high HBV endemicity, such as sub-Saharan Africa and parts of Asia (17). Some populations are at an increased risk of OBI due to their prior exposure history to HBV, including health workers, drug abusers, and those who have undergone organ transplantation or blood transfusion. In addition, a higher prevalence of OBI was also evidenced in people whose immune responses are depressed, as seen in HIV-infected patients and organ transplant recipients (1). The rates of occult hepatitis B in blood donors have been variably reported from as low as 0.2 % in some areas to as high as 1 to 10 % or greater in others (18). Assuming the prevalence of hepatitis B among blood donors in Albania, the findings presented at the Transfusiology Conference on New Pathogens and Transfusion Safety in 2023 indicate that the prevalence of infections detected through NAT has raised from 0.24% in the first year of implementation in 2016 to 0.65% in 2022, resulting in an average prevalence of 0.49%. Additionally, at the First International Conference of the Balkan Consortium of Transfusion Medicine, rates for our neighboring country, Kosovo, were reported as dHBV at 0.3%, dHCV at 0.01%, and dHIV at 0.009% for 2023 (19). These findings highlight a concerning trend in transfusion-transmissible infections, particularly with regard to hepatitis B, emphasizing the necessity for ongoing vigilance and improvements in blood testing methodologies to ensure transfusion safety. Among a review of all studies we found that Leontari et al. (2024) reported an occult hepatitis B infection rate of 5.4% among blood donors from northwest Greece, while Manzini et al. (2007) made an estimate

of about 4.86% in Italian blood donors in northwestern Italy (20, 21). So, the prevalence of occult hepatitis B may depend on the HBV prevalence in the general population, sensitivity of screening tests, and demographic features of blood donors (22). As the detection is difficult and diagnostic criteria keep varying, OBI underestimation can occur. More sensitive screening methods, such as nucleic acid testing, identified occult hepatitis B in blood donors and perhaps contributed to a better understanding of its prevalence (23). Understanding the epidemiology of OBI is critical to implementing targeted screening and prevention strategies in high-risk populations and informing public health policy aimed at reducing hepatitis B infections in transmission and burden.

**Risk factors for occult hepatitis B infection**

Risk factors associated with OBI span a broad spectrum influenced by various demographic, behavioral, and medical factors. Age is an important factor, with people of older ages being more likely to have been exposed to HBV throughout their lives, increasing their risk of OBI, according to Jürgen Ott's study (24) on the global epidemiology of hepatitis B virus infection and new estimates of HbsAg seroprevalence for age. Gender may also play a role, as some studies indicate a higher prevalence of OBI in men compared to women, possibly due to differences in occupational exposure or health care-seeking behavior (25). Geographic location is another crucial factor, with higher prevalence rates observed in regions with endemic HBV transmission, such as parts of sub-Saharan Africa and Asia. Occupational hazards remain important determinants to mention as they include healthcare workers and laboratory personnel at increased risk of OBI due to possible exposure to HBV-contaminated blood or body fluids (26). Behaviors like injecting drug users and high-risk sexual behavior are recognized major behavioral risk factors of OBI since these increase the chances of transmitting HBV. Besides, the risk groups, which have a higher susceptibility to OBI, are the immunocompromised hosts, either through a co-infection, for instance with the hepatitis C virus (HCV) or the human immunodeficiency virus (HIV), or immunosuppression therapy, which can all impair their immune responses (14). Medical case history: including blood transfusions, organs transplantations, or dialysis, further increase the risks in OBI (27, 28). A family history of HBV infection or liver disease may represent familial genetic susceptibility and may mean there is a higher probability for OBI development (29). Furthermore some medical conditions such as thalassemia, hemophilia, cryptogenic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) are also risk factors attached to a significantly increased chance of having OBI (30). Lifestyle factors may aggravate its degree of liver injury in those with OBI and lead to higher morbidity and mortality.

**Clinical significance of occult hepatitis B infection**

The potential for donors with undeclared infections to have low blood levels of HBV DNA increases the risk of HBV transmission during transfusion. The precise transmission risk from occultly infected donors is still poorly understood, and could lead to a variety of potentially fatal outcomes, including acute HBV infection, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (30, 31). Furthermore, recipients of blood transfusions may themselves be immunocompromised or have underlying liver disease, which increases the risk of serious consequences in the event of HBV infection (32). If there is occult HBV DNA in the liver without detectable HbsAg in the blood, it is probable that there is viral replication and liver damage. This could indicate that individuals with OBI have a higher likelihood of developing liver disease as time goes on (33). The risk of infection by transfusion justifies the need for strict screening and sensitive tests for the detection of latent HBV infection in blood donors. In order to guarantee that, in the unlikely event of the worst occurring HBV transmission the individuals in question will be recognized early and treated right away to protect all transfusion recipients must also be the subject of ongoing monitoring and follow-up.

## Occult hepatitis B diagnosis

### Challenges in diagnosing occult hepatitis B due to absence of HbsAg

Occult hepatitis B is very challenging to diagnose since HbsAg is absent. Its absence makes conventional diagnosis methods very cumbersome, because HbsAg is one of the principal markers in the identification of active HBV infection (34). In diagnosis, OBI cases need special molecular and serological testing methods since they have undetectable HbsAg, but have HBV DNA circulating within the bloodstream (35). The above-identified challenges are therefore in need of sensitive molecular techniques and expansive serological testing methods so that occult hepatitis B cases are identified correctly for relevant management to be instituted (32).

### Laboratory detection tests

Laboratory assessments consist of molecular methods that provide screening such as nucleic acid testing (NAT), real-time and quantitative polymerase chain reaction (qPCR), and transcription mediated amplification (TMA) for OBI detections, and measuring, HBV DNA copies (8). NAT is a direct method of detection of HBV DNA in blood samples through amplification of viral DNA with the use of polymerase chain reaction or other similar methods (36). Real-time PCR is a method that measures DNA during its process of amplification and therefore accurately measures the HBV DNA levels. On the other hand, TMA represents a highly sensitive tool for which many studies have been performed for the detection of HBV DNA, and quantitative PCR quantifies an amount of amplified DNA, thus giving quantitation of HBV DNA load (37, 38). These are supplemented by molecular tests for anti-HBc (hepatitis B core antibodies) and anti-HBs (hepatitis B surface antibodies) serological tests, which have an important role in defining OBI. These tests can make out seropositive and seronegative cases of occult hepatitis B. Seropositive OBI has been defined by the presence of HBV core antibodies (anti-HBc) and/or positive HBV surface antibodies (anti-HBs), which testify to a previous exposure to HBV. In contrast, seronegative OBI is an occult hepatitis B infection characterized by the absence of both anti-HBc and anti-HBs antibodies (8, 39). Given this, a multifaceted approach is needed to diagnose occult hepatitis B infection and prescribe the proper treatment.

### Potential role of NAT to improve blood safety

According to the consensus conference Taormina 2018 the gold standard for OBI diagnosis is the detection of HBV DNA in the liver (39). Since, standardised and valid assays for HBV DNA detection in the liver are not yet available; the most commonly used method is detection of HBV DNA in the blood. NAT serves as a critical tool to increase blood safety by significantly reducing the risk of transfusion-transmissible infections, including occult hepatitis B. It was introduced for screening blood donors during the mid to late 1990s (16). This method lets us spot and measure viral nucleic acids. Assays used for NAT in blood products screening have high specificity (99.9%) and a limit of detection of 2–4 IU/ml HBV DNA when applied to individual units (40). NAT can find viral nucleic acids early in the infection process. This makes blood screening more accurate and adds an extra safety step in managing blood supplies. As a result, using NAT has helped reduce HBV infections from transfusions. These methods contribute to understanding the severity of infection and the magnitude of disease transmission risk because they accurately quantify the HBV DNA load in the blood (36). Early diagnosis and timely intervention and appropriate management strategies are thus possible to prevent disease progression and reduce the risk of transmission to others by using sensitive molecular techniques (38).

### Management Strategies

The management of occult hepatitis B includes a number of measures that are directed towards the

safety of blood transfusions and reduction of risk for HBV infection. Introduction of NAT reduced the risk of transfusion-transmitted viruses through identification of donors with low HBV DNA levels (16). While, combined screening by highly sensitive serological and molecular assays is warranted in minimizing transfusion transmission risk of HBV (41, 42). Robust screening protocols should be in place to ensure that potentially infectious blood samples are discarded, thereby reducing the risk of HBV transmission through transfusions. Deferral criteria are also helpful in improving the safety of donation by admitting only those who do not have OBI but who are at high risk from other factors such as intravenous drug users or sexual activity that put them at higher risk of contracting OBI entail (43). With these criteria, it is easy to exclude people who are more likely to transmit HBV, thereby keeping infected blood out of the donor pool.

**Conclusion**

To summarize, OBI is a major blood transfusion risk due to its potential for HBV transmission by infected donors. Global OBI rates are inconsistent, and therefore we need careful review and more research. We have to determine better how the screening can be improved and the blood safer as the OBI rates vary in different groupings or localities. To detect low levels of HBV DNA among blood donors, we should use sensitive molecular tests such as NATs, which minimizes chances of transfusing OBI. Therefore, it is increasingly important to diagnose OBI by reliable molecular and serological methods that are capable of identifying those with a real risk of latent and occult HBV transmission. Moreover, awareness campaigns will guarantee an all-inclusive screening protocol in place, which will maintain the high quality of the blood donated to patients. The prospective working agenda needs researchers, physicians, and policymakers' concerted efforts aimed at understanding occult hepatitis B further and ensuring safety for blood recipients. Ultimately, this will contribute towards faster patient recovery and enhanced public health outcomes.

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**References:**

1. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection: World Health Organization; 2024 [cited 2024 Nov 28]. Available from: https://www.who.int/publications/i/item/9789240090903
2. Liang TJ. Hepatitis B: The Virus and Disease. Hepatology. 2009 May; 49(5 Suppl). doi: 10.1002/hep.22881. PMID: 19399811; PMCID: PMC2809016. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2809016/
3. Zhao F, Xie X, Tan X, Yu H, Tian M, Lv H, et al. The Functions of Hepatitis B Virus Encoding Proteins: Viral Persistence and Liver Pathogenesis. Front Immunol. 2021 Aug 12; 12:691766 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8387624/
4. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67:1560–99. https://doi.org/10.1002/hep.29800
5. Araujo NM, Teles SA, Spitz N. Comprehensive Analysis of Clinically Significant Hepatitis B Virus Mutations in Relation to Genotype, Subgenotype and Geographic Region. Front Microbiol. 2020; 11:616023. https://doi.org/10.3389/fmicb.2020.616023
6. Mehta P, Grant LM, Reddivari AK. Viral Hepatitis. Treasure Island (FL): Stat Pearls Publishing; Jan 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554549/
7. Kramvis A, Kostaki EG, Hatzakis A, Paraskevis D. Immunomodulatory Function of HBeAg

Related to Short-Sighted Evolution, Transmissibility, and Clinical Manifestation of Hepatitis B Virus. Front Microbiol. 2018 Oct 24; 9:2521. doi: 10.3389/fmicb.2018.02521. PMID: 30405578; MCID:PMC6207641. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6207641/
8. Raimondo G, Allain JP, Brunetto MR, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. J Hepatol. 2008; 49:652-657. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0168827808004790
9. Hep B Blog. Diagnosed with Chronic Hepatitis B? What Does Your HBV DNA Test (Viral Load) Tell You? 2016 Feb 15. Available from: https://www.hepb.org/blog/diagnosed-with-chronic-hepatitis-b-what-does-your-hbv-dna-test-tell-you/
10. Sofian M, Aghakhani A, Izadi N, Banifazl M, Kalantar E, Eslamifar A, et al. Lack of occult hepatitis B virus infection among blood donors with isolated hepatitis B core antibody living in an HBV low prevalence region of Iran. Int J Infect Dis. 2010;14(4). Available from: https://pubmed.ncbi.nlm.nih.gov/19656713/
11. Candotti D., Assennato S.M., Laperche S., Allain J.P., Levicnik-Stezinar S. Multiple HBV transfusion transmissions from undetected occult infections: Revising the minimal infectious dose. Gut. 2019;68:313–321. doi: 10.1136/gutjnl-2018-316490.
12. Cheung C.K., Lo C.M., Man K., Lau G.K. Occult hepatitis B virus infection of donor and recipient origin after liver transplantation despite nucleoside analogue prophylaxis. Liver Transpl. 2010;16:1314–1323. doi: 10.1002/lt.22169.
13. Walz A, Wirth S, Hucke J, Gerner P. Vertical transmission of hepatitis B virus (HBV) from mothers negative for HBV surface antigen and positive for antibody to HBV core antigen. J Infect Dis. 2000; 200:1227-1231. https://doi.org/10.1086/605698
14. Motswedi A., Bonolo B. P., Basetsana K. P., Mbatshi M., Lynnette N. B., Girlie N. G., et al. Persistence and risk factors of occult hepatitis B virus infections among antiretroviral therapy-naïve people living with HIV in Botswana. Frontiers in Microbiology Volume 15 - 2024 URL=https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2024.1342862. DOI=10.3389/fmicb.2024.1342862
15. Yi Mak L., Ka-Ho Wong D., Pollicino T., Raimondo G., Hollinger B., Yuen M. Occult hepatitis B infection and hepatocellular carcinoma: Epidemiology, virology, hepatocarcinogenesis and clinical significance. Journal of Hepatology 2020 vol. 73 j 952–964. https://doi.org/10.1016/
16. Roth WK. History and Future of Nucleic Acid Amplification Technology Blood Donor Testing. Transfus Med Hemother. 2019 Apr;46(2):67-75. doi: 10.1159/000496749.
17. Allain JP. Global epidemiology of occult HBV infection. Ann Blood. 2017; 2. Available from: https://aob.amegroups.org/article/view/3915/html
18. Takuissu GR, Kenmoe S, Amougou Atsama M, Atenguena Okobalemba E, Mbaga DS, Ebogo-Belobo JT, et al. (2022) Global epidemiology of occult hepatitis B virus infections in blood donors, a systematic review and meta-analysis. PLoS ONE 17(8): e0272920. https://doi.org/10.1371/journal.pone.0272920
19. Mahmutaj H. Quality and safety of blood: Overview of testing algorithms in NBTC Pristina. Presented at: 1st International Conference of the Balkan Consortium of Transfusion Medicine; 2024 Oct 3-4; Tirana, Albania. Available from: https://mtsh.al/
20. Leontari M, Mousavere I, Fousekis FS, Kalampoki A, Baltayiannis G. Occult Hepatitis B Infection among Blood Donors in Northwestern Greece. Maedica (Bucur). 2024;19(1):17–22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11079725/
21. Manzini P, Girotto M, Borsotti R, Giachino O, Guaschino R, Lanteri M, et al. Italian blood donors with anti-HBc and occult hepatitis B virus infection. Haematologica. 2007; 92:1664-1670. Available from: https://pubmed.ncbi.nlm.nih.gov/18055990/
22. Gerlich WH. Medical virology of hepatitis B: how it began and where we are now. Virology Journal. 2013 Jul 20; 10:239. doi: 10.1186/1743-422X-10-239. Available from:

https://virologyj.biomedcentral.com/articles/10.1186/1743-422X-10-239
23. Wu D, Feng F, Wang X, Wang D, Hu Y, Yu Y, et al. The impact of nucleic acid testing to detect human immunodeficiency virus, hepatitis C virus, and hepatitis B virus yields from a single blood center in China with 10-years review. BMC Infect Dis. 2022;22(279). Available from: https://pubmed.ncbi.nlm.nih.gov/35321684/
24. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30(12):2212-2219. Available from: https://pubmed.ncbi.nlm.nih.gov/22273662/
25. Liu M, Li L, Zhao J, Ungvari GS, Ng CH, Duan Z, et al. Gender differences in demographic and clinical characteristics in patients with HBV-related liver diseases in China. PeerJ. 2022;10. https://doi.org/10.7717/peerj.13828
26. Mossburg S, Agore A, Nkimbeng M, Commodore-Mensah Y. Occupational hazards among healthcare workers in Africa: A systematic review. Ann Glob Health. 2019;85(1):78. https://doi.org/10.5334/aogh.2434
27. Bernieh B. Viral hepatitis in hemodialysis: An update. J Transl Intern Med. 2015;3(3):93-105. https://doi.org/10.1515/jtim-2015-0018
28. Mussa A., Ismail H., Syed N. H., Talib M., Siddig A., Hassan R., et al. Immune response to occult hepatitis B virus infection among hemodialysis patients: A review, The Microbe, Volume 5, 2024, 100176, ISSN 2950-1946, https://doi.org/10.1016/j.microb. 2024.100176.
29. Zhenhua Z., Changtai W., Zhongping L., Guizhou Z., Jun L., Mengji L. Host Genetic Determinants of Hepatitis B Virus Infection. Frontiers in Genetics. Volume 10 – 2019. https://doi.org/10.3389/fgene.2019.00696
30. Weng C, Kumar R, Sultana R, Chow WC. Occult hepatitis B virus infection and the risk of hepatocellular carcinoma: A systematic review and meta-analysis. Cells. 2020;9(10):2233. https://doi.org/10.3390/cells9102233
31. Saitta C, Pollicino T, Raimondo G. Occult Hepatitis B Virus Infection: An Update. Viruses. 2022 Jul 8;14(7):1504. doi: 10.3390/v14071504.
32. Xiao Y, Thompson AJ, Howell J. Point-of-care tests for hepatitis B: An overview. Cells. 2020;9(10):2233. https://doi.org/10.3390/cells9102233
33. Raimondo G, Caccamo G, Filomia R, Pollicino T. Occult HBV infection. Semin Immunopathol. 2013;35:39-52. Available from: https://pubmed.ncbi.nlm.nih.gov/22829332/.
34. Allain JP, Opare-Sem O. Screening and diagnosis of HBV in low-income and middle-income countries. Nat Rev Gastroenterol Hepatol. 2016; 13:643-653. https://doi.org/10.1038/nrgastro.2016.138
35. Candotti D, Assennato SM, Laperche S, Allain JP, Levicnik-Stezinar S. Multiple HBV transfusion transmissions from undetected occult infections: revising the minimal infectious dose. Gut. 2019 Feb;68(2):313-321. doi: 10.1136/gutjnl-2018-316490.
36. Arora S, Doda V, Kirtania T. Sensitivity of individual donor nucleic acid testing (NAT) for the detection of hepatitis B infection by studying diluted NAT yield samples. Blood Transfus. 2015;13(2):227-232. https://doi.org/10.2450/2014.0048-14
37. Akram A., Islam S.M.R., Munshi S.U., Tabassum S. Detection of hepatitis B virus DNA among chronic and potential occult HBV patients in resource-limited settings by loop-mediated isothermal amplification assay. J Viral Hepat, 25 (2018), pp. 1306-1311
38. Caviglia G.P., Abate M.L., Tandoi F., Ciancio A., Amoroso A., Salizzoni M., *et al.* Quantitation of HBV cccDNA in anti-HBc-positive liver donors by droplet digital PCR: a new tool to detect occult infection. J Hepatol, 69 (2018), p. 301-7
39. Raimondo G, Locarnini S, Pollicino T, Levrero M, Zoulim F, Lok AS. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. J Hepatol. 2019; 71:397-408. https://doi.org/10.1016/j.jhep.2019.03.034

40. Busch MP. Should HBV DNA NAT replace HBsAg and/or anti-HBc screening of blood donors? Transfus Clin Biol. 2004;11(1):26-32. https://doi.org/10.1016/j.tracli.2003.12.003
41. Damiani AS, Holzmayer V, Galli C, De Nuzzo M, Anderson M, Cloherty G, Di Renzo N. Serological and Molecular Characterization of Occult HBV Infection in Blood Donors from South Italy. Viruses. 2023 Dec 31;16(1):71. doi: 10.3390/v16010071.
42. Athalye S, Patil A, Khargekar N, Shinde S, Chavan S, Dixit A, Shankarkumar A, Madkaikar M, Banerjee A. Efficacy of combined HBsAg, anti-HBc and anti-HBs screening in minimizing transfusion transmission risk of hepatitis B infection in low resource setting. Heliyon. 2024 Feb 3;10(3):e25805. doi: 10.1016/j.heliyon.2024.e25805.
44. European Association for the Study of the Liver (EASL). Hepatitis B: The Burden of Disease in Europe. Published 2018. Available from: https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf

# APPLICATION OF MOLECULAR CYTOGENETIC TEST IN HAEMATOLOGICAL MALIGNANCIES FOR THE FIRST TIME IN ALBANIA

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**Abstract**

Genetic Characterization and changes in genome organization are crucial in the clinical evaluation of almost every form of hematological malignancy. Studies has shown that Fluorescence In Situ hybridization has made possible to determine the genetic abnormalities and estabilish their and frequency. After great efforts and challenges, this technology was applied for the first time in the Molecular Cytogenetic Laboratory, Clinical Genetic Laboratory Service, University Hospital Center "Mother Teresa." The aim was to use proper probes as a diagnostic tool to understand the pathophysiology, diagnosis, treatment, prognosis, and monitoring of the disease activity. Thanks to simple procedure is possible to recognize hematological malignancy abnormality. Screening by in situ hybridization plays a supportive role in personalized medicine. The images captured using fluorescently labeled probes allow the confirmation of genetic abnormalities such as deletions, translocations, or break-apart rearrangements using Meta Class software. According to the European recommendations for probes in malignant hemopathies, these probes are available for diagnosis and classification of the diseases, providing important prognostic and therapeutic information, monitoring disease response to treatment, Assessment of minimal residual disease, and identification of an early relapse stage of the disease. The use of this technology for the first time in Albania in the molecular cytogenetics laboratory is an important achievement that contributes to the advancement of diagnostic and personalized medicine for hematology patients. It can provide a powerful tool for diagnosing these diseases with a very high level of accuracy and precision. This also increases the quality of health care and brings opportunities for further progress in scientific and medical research in the country. Accurately knowing the genetic characteristics of a hematological disease can help determine the best treatments for patients.

**Keywords:** Fluorescence in situ hybridization, probes, personalized medicine; targeted treatment, prognostic factor.

# APLIKIMI I TESTIT TË CITOGJENETIKËS MOLEKULARE NË PATOLOGJITË HEMATOLOGJIKE MALINJE PËR HERË TË PARË NË SHQIPËRI

**Abstrakt**

Ndryshimet gjenetike në organizimin e gjenomës janë vendimtare në vlerësimin klinik të patologjive hematologjike. Hibridizimi me fluoreshencë In Situ ka mundësuar një përcaktim më të saktë të pranisë dhe shpeshtësisë së anomalive gjenetike. Pas përpjekjeve dhe sfidave të mëdha, aplikimi i kësaj teknologjie ka filluar të aplikohet për herë të parë në Laboratorin e Citogjenetikës Molekulare, Shërbimi i Laboratorit të Gjenetikës Klinike, Qëndra Spitalore Universitare "Nënë Tereza". Qëllimi është përdorimi i sondave të duhura si një mjet diagnostikues për të përcaktuar

patofiziologjinë, diagnozën, trajtimin, prognozën dhe monitorimin e aktivitetit të sëmundjes. Ekzaminimi me hibridizimin in situ luan një rol mbështetës në mjekësinë e personalizuar. Imazhet e kapura duke përdorur sondat e markuara me fluoreshencë, lejojnë konfirmimin e anomalive gjenetike si delecionet, translokacionet ose thyerjet duke përdorur softuerin MetaClass. Sipas rekomandimeve evropiane për hemopatitë malinje, këto sonda janë të disponueshme për diagnostikimin dhe klasifikimin e sëmundjeve, duke ofruar informacione të rëndësishme prognostike dhe terapeutike, monitorimin e përgjigjes së sëmundjes ndaj trajtimit, vlerësimin e mbetjeve minimale dhe identifikimin e një faze të hershme të rikthimit të sëmundjes. Përdorimi i kësaj metode për herë të parë në Shqipëri në laboratorin e citogjenetikës molekulare është një arritje e rëndësishme që kontribuon në avancimin e mjekësisë diagnostike dhe të personalizuar për pacientët. Ai mund të sigurojë një mjet të fuqishëm për diagnostikimin e këtyre sëmundjeve me një nivel shumë të lartë saktësie. Ky test gjithashtu rrit cilësinë e kujdesit shëndetësor dhe sjell mundësi për përparim të mëtejshëm në kërkimin shkencor dhe mjekësor në vend. Njohja e saktë e karakteristikave gjenetike të një sëmundje hematologjike mund të ndihmojë në përcaktimin e trajtimeve më të mira dhe të personalizuara për pacientët.

**Fjalë kyçe:** Hibridizimi In Situ me fluoreshencë, sonda, mjekësi e personalizuar; trajtim “target”, faktor prognostik.

## Introduction

Malignant hemopathies are a group of neoplasms of hematopoietic cells, characterized by their disrupted differentiaon and multiplication (1). Hematological malignancies have historically been a pioneer among cancers in the use of genetic analysis, particularly for diagnosis and classification. Genetic Characterization and changes in genome organization are crucial in the clinical evaluation of almost every form of hematological malignancy. Molecular diagnosis is an important diagnostic tool in the diagnosis and their management (2).

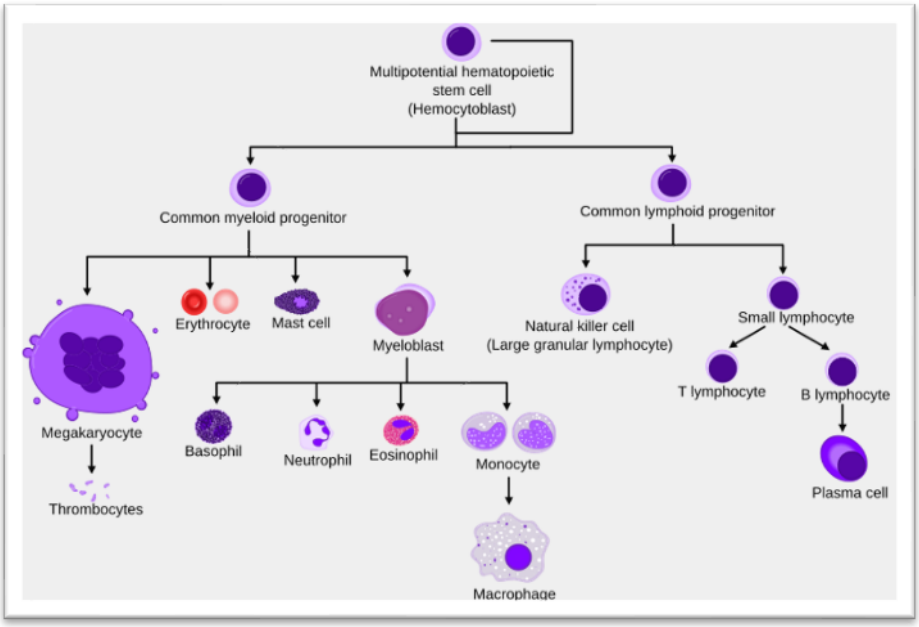



**Figure 1.** The development from hematological stem cell to mature cell of different blood cell lines(A. Rad and M. Häggström. CC-BY-SA 3.0 license." Image: Hematopoiesis (human) diagram)

The hematological diseases have been shown to be associated with a variety of genetic aberrations,

from a single base-pair substitution to whole chromosomal abnormalities. This characterisation at the molecular level of those recurrent nonrandom cytogenetic abnormalities has specifically identified different disease-related genes being involved in myeloid and lymphoid malignancies. Molecular cytogenetic analysis has become essential for disease diagnosis, classification, prognostic stratification, and treatment guidance (3). Fluorescence In Situ hybridization (FISH) has augmented the enhancement in this field making more precise to determine the presence and frequency of genetic abnormalities. After great efforts and challenges, the application of FISH technology has started to be applied for the first time in the Molecular Cytogenetic Laboratory, Clinical Genetic Laboratory Service, UHC "Mother Teresa ."The aim was to use proper FISH probes such as BCR/ABL, AML1/ETO, PML/RARA, IGH/MYC, P53 etc, as a diagnostic tool to understand the pathophysiology, diagnosis, treatment, prognosis, and monitoring of the disease activity in Chronic Myeloid Leukemia (CML), Acute Myeloid Leukemia (AML), Chronic Lymphoblastic Leukemia (CLL), Acute Lymphoblastic Leukemia (ALL), Myelodysplasia (MDS), Multiple myeloma and Lymphoma cases. FISH has some advantages compared to standard cytogenetic analysis, such as being able to identify too small genetic changes difficult to be detected under a microscope, not requiring cell culture, and being able to be applied directly for a quick evaluation of interphase nuclei. The application of FISH involving an enormous variety of chromosome-specific DNA probes helps to further determine the molecular subclasses and also estabilish the cytogenetic risk categories for the patients with some particular hematologic malignancies. It is also useful in identifying the undetectable by conventional chromosomal analysis of some genetic abnormalities and also it can monitor the residual disease during treatment and follow-up (4).

**FISH methodology**

FISH as a technique makes possible the detection of the DNA sequences in interphase nuclei starting from fixed samples. The technique uses DNA probes that hybridize into single unique sequences. After fixation and denaturation, target DNA is available for annealing to a similarly denatured, fluorescently labeled DNA probe, which has a complementary sequence. Following hybridization, an unbound and nonspecifically bound DNA probe is removed, and the DNA is counterstained for visualization with an anti-fade solution containing DAPI (4′,6-diamidino-2-phenylindole) applied to the slide, and a coverslip must be added. For FISH analysis, fluorescence microscopy with specific filters for identifying fluorochromes and a charge-coupled device (CCD) camera that captures the images allows the visualization of the hybridized probe on the target material (6).

Thanks to simple FISH procedure is possible to recognize hematological malignancy abnormality. Screening by in situ hybridization plays a supportive role in personalized medicine. The images captured using fluorescently labelled DNA probes, allow the confirmation of genetic abnormalities such as deletions, translocations or breakapart rearrangements using MetaClass software (5).

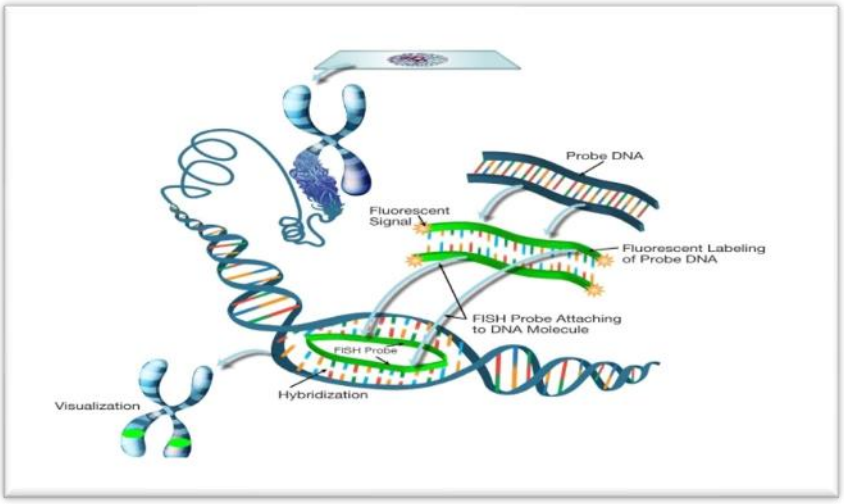



**Figure 2.** Sample and slide preparation, denaturation of DNA, hybridization and slide analyses (Arun Kumar, Mar 17, 2020)

FISH using specific probes that are capable of defining these stereotypic structural rearrangements has now become a routine diagnostic test in our molecular cytogenetic laboratory, and the technique has been shown to be useful in the management of our hematological malignancies patients. We use a range of FISH probes, specific for a number of hematological malignancies like Chronic Myeloid Leukemia (CML), Acute Myeloid Leukemia (AML), Chronic Lymphoblastic Leukemia (CLL), Acute Lymphoblastic Leukemia (ALL), Myelodysplasia (MDS), Multiple myeloma and Lymphoma cases. The names of the probes, chromosome regions, and probe types are shown in the table below.

**Table 1.** A range of FISH probes optimized for haematological malignancies in Albania

| Probe name | Chromosome region | Probe type | Diagnoses |
|---|---|---|---|
| **BCR/ABL (ABL1) Dual Fusion** | 22q11.22-q11.23/9q34.11-q34.12 | Translocation | CML, ALL |
| **AML1/ETO (RUNX1/RUNX1T1) Dual Fusion** | 21q22.12/8q21.3 | Translocation | AML |
| **TEL/AML1 (ETV6/RUNX1) Dual Fusion** | 12p13.2/21q22.12 | Translocation | ALL |
| **PML/RARα (RARA) Dual Fusion** | 15q24.1/17q21.1-q21.2 | Translocation | AML |
| **IGH/CCND1 Dual Fusion** | 14q32.33/11q13.3 | Translocation | CLL, Limphoma |
| **IGH/MYC Dual Fusion** | 14q32.33/8q24.21 | Translocation | ALL, Limphoma |
| **Del(5q)** | 5p15.31-5q13.2 | Deletion | AML, MDS, MPN |
| **Del(7q)** | 7q22.1-q22.2/7q31.2 | Deletion | AML, MDS |
| **Del(20q)** | 20q12/20q13.12 | Deletion | AML, MDS, MPN |
| **P53 (TP53)** | 17p13.1 | Deletion | ALL, AML, CLL, Limfoma, MDS, MM |
| **ATM** | 11q22.3 | Deletion | CLL |
| **D13S319** | 13q14.2-q14.3 | Deletion | CLL |
| **P16 (CDKN2A)** | 9p21.3 | Deletion | ALL, AML |
| **E2A (TCF3)** | 19p13.3 | Breakapart | ALL |
| **MLL (KMT2A)** | 11q23.3 | Breakapart | ALL, AML |

## Interpretation of results

When we use a translocation probe such as: BCR/ABL (ABL1) Dual Fusion, AML1/ETO (RUNX1/RUNX1T1) Dual Fusion, TEL/AML1 (ETV6/RUNX1) Dual Fusion, PML/RARα (RARA) Dual Fusion, IGH/CCND1 Dual Fusion, IGH/MYC Dual Fusion expected results of a normal and abnormal signals are shown below.

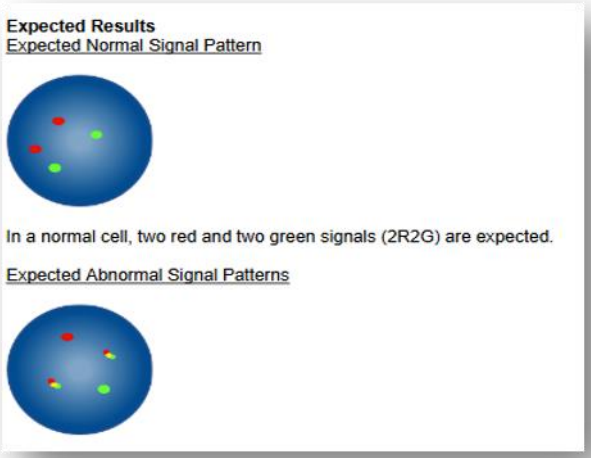



**Figure 3.** Analysis guidelines of one translocation probe (55)

When we use a deletion probe such as: Del(5q), Del(7q), Del(20q), ATM deletion, D13S319 deletion, P16 (CDKN2A) deletion and P53 (TP53) deletion expected results of a normal and abnormal signals are shown below.

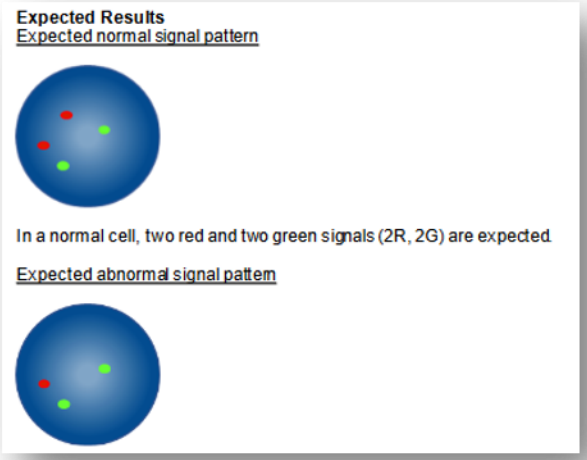



**Figure 4.** Analysis guidelines of one deletion probe (55)

When we use a breakapart probe such as: E2A (TCF3) or MLL (KMT2A) expected results of a normal and abnormal signals are shown below (55).

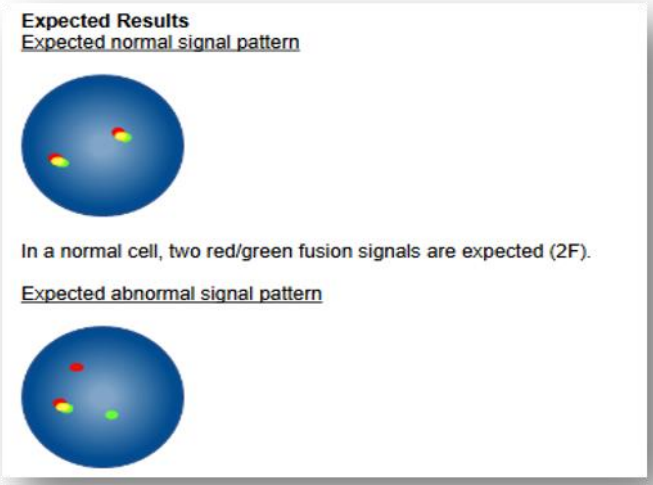



**Figure 5.** Analysis guidelines of one breakapart probe (55)

## Discussion

According to the European recommendations for FISH probes in malignant hemopathies, these probes are available for diagnosis and classification of the diseases, providing important prognostic and therapeutic information, monitoring disease response to treatment, Assessment of minimal residual disease, and identification of an early relapse stage of the disease (7).
Below, we present some of the important information for each probe used in our service.

BCR/ABL (ABL1) Translocation, Dual Fusion Probe
Tthe location of the BCR (BCR activator of RhoGEF and GTPase) gene is found at 22q11.2, and speaking of the ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase, his gene is located at 9q34.1. Translocation between these two genes gives rise to the BCR-ABL1 fusion gene and produces a Philadelphia chromosome, the visible result of this translocation. The translocation t (9;22) (q34.1;q11.2) is the hallmark of the diagnosis of the chronic myeloid leukemia and is found in around 90-95% of these cases. The remaining 5-10% of patient cases diagnosed with CML present a variant translocation or a cryptic rearrangement involving 9q34.1 and 22q11.2 that cannot be identified by routine cytogenetic analysis. The BCR-ABL1 fusion can also be found in 25% of adult acute lymphoblastic leukemia and in 2-4% of childhood ALL. The presence of a BCR-ABL1 fusion has been shown to confer a poor prognosis in ALL in both adults and children (8, 9). The detection of abnormalities is, therefore, of high importance for risk stratification, which will influence treatment and management decisions (9). In a small number of ALL cases, the translocation [Philadelphia chromosome] is not cytogenetically visible. In these cases, FISH is essential for detectig the presence of the fusion gene (10).
This rearrangement is also seen in some rare cases of acute myeloid Leukemia, characterized by its resistance to conventional standard chemotherapy and poor prognosis, so accurate and rapid identification of this chromosomal abnormality is vital (11).

AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion
The AML1/ETO (RUNX1/RUNX1T1) translocation, also known as the dual fusion test, is a FISH (Fluorescence In Situ Hybridization) test used to detect rearrangements involving the AML1 (RUNX1) region on chromosome 21 at location 21q22.1 and the ETO (RUNX1T1) region on

chromosome 8 at location 8q21.3. Acute Myeloid Leukemia (AML) with a RUNX1-RUNX1T1 fusion, resulting from a translocation t(8;21)(q22;q22), is recognized as a distinct disease entity in the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. (12).

The cytogenetically cryptic t(12;21)(p13;q22) translocation occurs between ETV6 (ETS variant 6) at 12p13 and RUNX1 (RUNX family transcription factor 1) at 21q22, resulting in the formation of the ETV6-RUNX1 chimeric fusion gene (13).The cytogenetically cryptic translocation t(12;21)(p13;q22) involves a rearrangement between the ETV6 gene located at 12p13 and the RUNX1 gene at 21q22. This translocation leads to the formation of the ETV6-RUNX1 chimeric fusion gene. Both ETV6 and RUNX1 encode transcription factors. ETV6 is essential for proper transcription processes during hematopoiesis in the bone marrow. (13, 14). B-lymphoblastic leukemia and lymphomas with t(12;21)(p13;q22) translocations are recognized as a distinct disease entity according to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. This group represents approximately 25% of childhood B-acute lymphoblastic leukemia (B-ALL) cases. (15). As the t (12;21) (p13; q22) translocation is cytogenetically-cryptic, FISH is an important diagnostic tool for this type of leukemia (16). B-ALL with ETV6-RUNX1 is considered to have a favorable outcome with cure rates of more than 90%. Studies demonstrate late relapses of the disease is attributed to the presence of a persistent preleukaemic clone escaping chemotherapy (15, 17).

PML/RARa (RARA) Translocation, Dual Fusion

The PML (promyelocytic leukemia) gene is located at 15q24.1, and the RARA (retinoic acid receptor, alpha) gene is located at 17q21.2. The translocation t (15:17) (q24;q21) gives rise to the PML-RARA fusion gene and is the diagnostic hallmark of more than 90% of cases of acute promyelocytic Leukemia. PML and RARA have both been implicated in normal hematopoiesis. PML possesses growth suppressor and proapoptotic activity, whereas RARA is a transcription factor that mediates the effect of retinoic acid at specific response elements (18). PML-RARA fusion protein behaves as an altered retinoic acid receptor with the ability to transmit oncogenic signaling (19).

IGH/CCND1 Translocation, Dual Fusion

The t (11;14) (q13;q32) translocation involving the CCND1 (cyclin D1) gene at 11q13.3 and the IGH (immunoglobulin heavy locus) gene at 14q32.33 is associated with cell lymphoma. IGH-CCND1 translocation status would be important for clinical management in recognized diagnostic and clinical care pathways (20).

IGH/MYC Translocation, Dual Fusion

The IGH/MYC translocation, dual fusion is a FISH test used to detect rearrangement involving the IGH (immunoglobulin heavy locus) gene at 14q32.33 and the MYC (v-myc avian myelocytomatosis viral oncogene homology) oncogene at 8q24 is a recognized recurrent abnormality commonly seen in patients with B-cell malignancy. The (8,14) (q24,q23) translocation is the most common and is found in approximately 85% of patients with Lymphoma (21).

Del(5q) Deletion probe

Deletions in the long arm of chromosome 5 are among the most common genetic abnormalities observed in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) with myelodysplasia-related changes. The EGR1 gene (early growth response 1), a tumor suppressor

located at 5q31.2, has been shown to contribute to the development of MDS and AML through haploinsufficiency. Loss of the 5q31.2 region, which includes the EGR1 gene, is associated with a more aggressive form of MDS and AML. This deletion is often accompanied by additional cytogenetic abnormalities and correlates with a poorer prognosis. This probe can also detect some deletions that are associated with 5q- syndrome. However, the probe does not cover the critical deleted region for 5q33 and is not intended to detect all deletions associated with 5q- syndrome (22, 23).

Del 7q deletion Probe

Monosomy of chromosome 7 and deletions of the long arm of chromosome 7 are common chromosomal abnormalities often observed in myeloid disorders, such as myelodysplastic syndrome and acute myeloid leukemia. The presence of monosomy 7 or deletion of the long arm of chromosome 7 (del(7q)) as identified through karyotyping is associated with a poorer prognosis in myeloid malignancies. These deletions are typically extensive, and there is considerable variability in the breakpoints found in myeloid diseases, which complicates the mapping of common deleted regions.

Del 20q deletion probe

Deletions of the long arm of chromosome 20 are recognized as recurrent chromosomal abnormalities associated with myeloid malignancies, particularly myeloproliferative neoplasms, myelodysplastic syndromes, and acute myeloid leukemia. Deletion of the long arm of chromosome 20 occurs in 4% of Myelodysplastic Syndromes (MDS) cases and in 1-2% of Acute Myeloid Leukemia (AML) cases. When the deletion of chromosome 20q is the only abnormality present in MDS, the prognosis is generally good. However, the presence of additional secondary abnormalities may indicate disease progression.

P53 deletion probe

The TP53 gene, located at 17p13.1, is a crucial tumor-suppressor gene that is often deleted in various types of human cancers. It is one of the most significant tumor suppressor genes, functioning as a powerful transcription factor that plays a vital role in maintaining genetic stability.

Screening for the loss of TP53 is essential because deletions or losses on the short arm of chromosome 17, which encompasses the TP53 region, are frequently observed in many cancers. These changes are often linked to disease progression, a poorer response to treatment, and an unfavorable prognosis. Specifically, loss of TP53 is found in 10% of patients with chronic lymphocytic leukemia and is regarded as the most concerning prognostic marker for this disease. (27, 28). In acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), the loss of the TP53 gene is linked to a poor prognosis and is frequently considered an indicator of disease progression or the development of secondary disease. In patients with multiple myeloma, TP53 loss occurs later in the disease course and serves as a marker of progression, which is associated with a very poor prognosis. (32, 33).

ATM deletion probe

The protein kinase ATM (ATM serine/threonine kinase) gene at 11q22.3 is frequently deleted in cases of B-cell chronic lymphocytic leukemia. ATM is an important checkpoint gene involved in the management of cell damage. Its function is to assess the level of DNA damage in the cell and attempt repair by phosphorylating key substrates involved in the DNA damage response pathway (34). Screening for deletions of ATM and/or TP53 is vital to allow informed therapy choices for B-CLL patients, as deletions of TP53 and ATM confer poorer prognosis in this disease (37)

therefore, the use of FISH has proved to be a powerful tool in both the diagnosis and management of patients with B-CLL (34,35,36). Analysis of the ATM/TP53 interaction in B-CLL has shown that TP53 and ATM play an important role in the proliferation of lymphoid cancer (34). In the absence of ATM, damaged cells are allowed to continue to proliferate (38).

D13S319 deletion probe

Rearrangements leading to the loss of all or part of the long arm of chromosome 13 are seen frequently in a wide range of hematological disorders. Chromosome 13q aberrations occur in 16-40% of multiple myeloma cases. Historically, deletions of 13q have been associated with poor prognosis in MM, but it is believed that its prognostic relevance may be related to its association with other concurrent genetic lesions (39, 40). Deletions affecting 13q14 are also the most frequent structural genetic aberrations in chronic lymphocytic Leukemia (41, 42, 43). This region is found to be heterozygously deleted in 30-60% and homozygously deleted in 10-20% of CLL patients (44).

P16 deletion probe

The CDKN2A (cyclin-dependent kinase inhibitor 2A) gene at 9p21 is a tumor suppressor gene that has been shown to be deleted in a wide range of human malignancies. Loss of the CDKN2A gene results in cellular proliferation and dysregulation of proapoptotic pathways. Deletions of 9p that include the CDKN2A gene are frequently reported in patients with acute lymphoblastic leukemia in approximately 30% of adult B-cell ALLs, 30% of childhood ALLs, and up to 50% of T- cell ALLs. In adult B-cell ALL, CDKN2A deletions are frequently acquired in disease progression (45, 46, 47, 48). CDKN2A loss has been implicated with shorter overall survival in ALL patients.

E2A (TCF3) Break-apart Probe

The TCF3 (transcription factor 3) gene is located at 19p13.3. Translocations involving TCF3 are some of the most common rearrangements in childhood B-cell acute lymphoblastic leukemia.
According to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, B lymphoblastic leukemia/Lymphoma with t (1;19) (q23;p13) TCF3-PBX1 is recognized as a distinct (49, 50).

MLL (KMT2A) breakapart probe

The KMT2A (lysine methyltransferase 2A) gene at 11q23.3 is commonly rearranged in acute leukemias, especially in infant leukemia and secondary leukemia (51). KMT2A rearrangements can be detected in approximately 80% of infants with acute lymphoblastic leukemia and in 5-10% of pediatric and adult ALLs (52, 53). They can also be found in 60% of infant acute myeloid leukemia in 3% of de novo and 10% of therapy-related adult AML cases (52, 54). Historically, KMT2A rearrangements in acute leukemia were associated with a poorer outcome, but recent studies have shown that the prognosis is highly dependent on the fusion partner, and it may differ between children and adults (51).

**Conclusions:**

The use of FISH for the first time in Albania in the molecular cytogenetics laboratory is an important achievement that contributes to the advancement of diagnostic and personalized medicine for hematology patients. It can provide a powerful tool for diagnosing these diseases with a very high level of accuracy and precision. This also increases the quality of health care and brings opportunities for further progress in scientific and medical research in the country. Accurately knowing the genetic characteristics of a hematological disease can help determine the best

treatments for patients..

**Conflicts of Interest:** No conflict of interest.

**References:**


1. Ngo Sack Françoise, Lontsi Sonkwa Edgard, Chetcha Tchemegni Bernard. Clinical, biological, therapeutic and evolving profile of malignant hemopathies in adults at the central hospital of Yaounde. JMR 2021; ISSN:2395-7565.
2. Sevgi Gezici, Molecular Mechanisms of Immune Checkpoints as an Immunotherapy Tool in Hematological Malignancies. Comprehensive Hematology and Stem Cell Research, 2024, 366-372.
3. Radhakrishnan Ramchandren, Tarek Jazaerly, Ali M. Gabali. Molecular Diagnosis of Hematopoietic Neoplasms. Clin Lab Med, 2013, 33(4):817-833.
4. Mi-Ae Jang. Genomic technologies for detecting structural variations in hematologic malignancies. Blood Res, 2024 Feb 13;59(1):1.
5. Natalia Magdalena Chrzanowska, Janusz Kowalewski , Marzena Anna Lewandowska. Use of Fluorescence In Situ Hybridization (FISH) in Diagnosis and Tailored Therapies in Solid Tumors.Molecules. 2020 Apr 17;25(8).
6. Rasime Kalkan. The Use of Molecular Cytogenetic Techniques for the Identification of Chromosomal Abnormalities. Chromosomal Abnormalities, August 2017.
7. K A Rack, E van den Berg, C Haferlach. European recommendations and quality assurance for cytogenomic analysis of haematological neoplasms. Leukemia, 2020 Feb 7;34(8):2262–2264.
8. Swerdlow, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, France. IARC:2008.
9. Harrison, et al. Guidelines for the laboratory investigation of heritable disorders of platelet function. Br J Haematol, 2010;151:132-142.
10. Van Rhee, et al. Detection of the BCR-ABL gene by reverse transcription/polymerase chain reaction and fluorescence in situ hybridization in a patient with Philadelphia chromosome. Br J Haematol. 1995; 90:225-8.
11. Soupir, et al. Philadelphia chromosome-positive acute myeloid leukemia: a rare aggressive leukemia with clinicopathologic features distinct from chronic myeloid leukemia in myeloid blast crisis. Am J ClinPathol. 2007; 127:642-650.
12. Joseph D. Khoury, Eric Solary, OussamaAbla et. al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 36, (2022), 1703–1719.
13. Charles G Mullighan. Molecular genetics of B-precursor acute lymphoblastic leukemia**.** The Journal of Clinical Invest. 2012;122(12):3407-3415.
14. Wang et al. The TEL/ETV6 gene is required specifically for hematopoiesis in the bone marrowGenes Dev 1998;12(15):2392-2402.
15. Swerdlow et al., WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue, Lyon, France, 4th edition, IARC, 2017.
16. Borkhardt et al., Incidence and Clinical Relevance of TEL/AML1 Fusion Genes in Children with Acute Lymphoblastic Leukemia Enrolled in the German and Italian Multicenter Therapy Trials, Blood. 1997;90(2):571-577.
17. E. Mosad et al., Persistence of *TEL-AML1* fusion gene as minimal residual disease has no additive prognostic value in CD 10 positive B-acute lymphoblastic leukemia: a FISH study. Journal of Haematology & Oncology 2008; 1:17.

18. Grimwade et al., Characterization of acute promyelocytic leukemia cases lacking the classic t (15;17) Blood 2000;96(4):1297-1308.
19. Francesco Lo-Coco, Syed Khizer Hasan. Understanding the molecular pathogenesis of acute promyelocytic leukemia. Best Pract Res Clin Haematol, 2014 Mar; 27(1):3-9.
20. AK Ho et.al., Small B-cell neoplasms with typical mantle cell lymphoma immunophenotypes often include chronic lymphocytic leukemias. Am J ClinPathol 2009; 131:27-32.
21. Ronald Hoffman et.al., Basic Principles and Practice, Expert Consult Premium Edition. Hematology (2009); 1304–1305.
22. Benjamin L Ebert, Genetic deletions in AML and MDS. Best Pract Res Clin Haematol. 2010 Nov 4;23 (4):457–461.
23. Swerdlow SH, Campo E, et.al., WHO Classification of Haematolymphoid tumours. Leukemia. 2022 Nov; 36(11):2748-2749.
24. Alex Pezeshki, Shreya Podder, Ralph Kamel, Seth J Corey. Monosomy 7/del (7q) in inherited bone marrow failure syndromes: A systematic review. Pediatr Blood Cancer. 2017 Jul 14; 64(12):10.
25. A D Trobaugh-Lotrario, et al. Monosomy 7 associated with pediatric acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS): successful management by allogeneic hematopoietic stem cell transplant (HSCT). Bone Marrow Transplant, 2005 Jan; 35(2):143-9.
26. Jana Březinová, et al. Prognostic significance of del (20q) in patients with hematological malignancies, Cancer Genetics and Cytogenetics, Volume 160, Issue 2, 2005, 188-192.
27. Rossi D, et al., Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia, Blood. 2013 Feb 21;121(8):1403-12.
28. Baliakas P, et al., Clinical effect of stereotyped B-cell receptor immunoglobulins in chronic lymphocytic leukaemia: a retrospective multicentre study. Leukemia. 2014;(April):1-8.
29. Grimwade D, et al., Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials Blood, 2010 Jul 22;116(3):354-65.
30. Seifert H, et al., The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. Leukemia. 2009;23(4):656-63.
31. Stengel A, et al., TP53 mutations occur in 15.7% of ALL and are associated with MYC-rearrangement, low hypodiploidy, and a poor prognosis. Blood. 2014;124(2):251-8.
32. Palumbo A, et al., Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group, J ClinOncol. 2015 Sep 10;33(26):2863-9.
33. Fonseca R, et al., International Myeloma Working Group molecular classification of multiple myeloma: spotlight review, Leukemia. 2009 Dec;23(12):2210-21
34. Stankovic et al., Microarray analysis reveals that *TP53*- and *ATM*-mutant B-CLLs share a defect in activating proapoptotic responses after DNA damage but are distinguished by major differences in activating prosurvival responses**,** Blood 2004;103(1):291-300
35. Dohner et al., Genomic aberrations and survival in chronic lymphocytic leukemia N Eng J Med 2000;343:1910-1916.
36. Zent et al., Assessment of p53 and ATM functionality in chronic lymphocytic leukemia by multiplex ligation-dependent probe amplification, Blood 2010;115(21):4154-4155.
37. Rossi et al., Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. Blood 2013;121(8):1403-1412.
38. Khanna et al., ATM associates with and phosphorylates p53: mapping the region of interaction, Nature Genetics 1998;20(4):398-400.
39. Jeffrey R. Sawyer, The prognostic significance of cytogenetics and molecular profiling in multiple myeloma, Cancer Genetics 2011;204:3-12.

40. Shaughnessy J et al., Molecular aspects of multiple myeloma. Blood 2000; 96:1505-11.
41. Juliusson G et al., Prognostic subgroups in B-cell chronic lymphocytic leukemia defined by specific chromosomal abnormalities, N Eng J Med 1990;323:720-4.
42. Puiggros et al., Genetic abnormalities in chronic lymphocytic leukemia: where we are and where we go, Biomed Res Int 2014;1-13.
43. Kasar et al., Whole-genome sequencing reveals activation-induced cytidine deaminase signatures during indolent chronic lymphocytic leukaemia evolution, Nature Communications 2015;6:1-12.
44. Hammarsund M et al., Characterization of a novel B-CLL candidate gene – *DLEU7* – located in the 13q14 tumor suppressor locus, FEBS Letters 2004;556:75-80.
45. Moorman A V, et al., Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial, Blood. 2007;109(8):3189-97.
46. Anu Usvasalo , Suvi Savola et.al., CDKN2A deletions in acute lymphoblastic leukemia of adolescents and young adults: an array CGH study. Leuk Res, 2008 Aug;32(8):1228-35.
47. Schwab CJ, et al., Genes commonly deleted in childhood B-cell precursor acute lymphoblastic leukemia: association with cytogenetics and clinical features, Haematologica. 2013 Jul; 98(7):1081-8.
48. E.C. Smyth, M. Verheij et.al, Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology. **2016**, Volume 27, Supplement 5V38-V49.
49. Van der Burg et al., Split-signal FISH for detection of chromosome aberrations in acute lymphoblastic leukemia. Leukemia 2004;18(5):895-908.
50. Swerdlow et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms 4th edition, Blood, 2016, volume 127.
51. Tomizawa D et. al., Recent progress in the treatment of infant acute lymphoblastic leukemia Pediatr Int. 2015; 4:811–9.
52. Mateusz Górecki et.al., Updates in KMT2A Gene Rearrangement in Pediatric Acute Lymphoblastic Leukemia, Biomedicines 2023, 11(3), 821.
53. Alberto Hernández-Sánchez et. al., Rearrangements involving 11q23.3/KMT2A in adult AML: mutational landscape and prognostic implications – a HARMONY study. Leukemia volume 38, pages 1929–1937 (2024).
54. Super HJ et al., Rearrangements of the MLL gene in therapy-related acute myeloid leukemia in patients previously treated with agents targeting DNA-topoisomerase II, Blood. United States; 1993 Dec;82(12):3705–11.
55. OGT Product Catalogue 2017-2018.

# DYING WITH DIGNITY, A MISSING DEBATE IN ALBANIA

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**Abstract**
In our daily work as clinicians, we have all faced the moment when the patient no longer benefits from the therapy defined according to medical protocols and the patient's treatment plan must change from therapeutic to palliative or supportive. The medical progress of the chronically ill will inevitably lead to the patient's death. The way the patient and his family members will face death is directly related to the work of the physician and the medical staff and also to the explanation of the prognosis of the disease and the expectations from the therapy or medical equipment to help the therapy. As a function of this process, concepts (new or not) such as: actively dying, end of life care, terminal patient, which help in determining the stages of a chronic disease with an inevitable end, come to the aid of the physician and the staff. This text is not intended to serve as a guide, but aims to raise a debate that is missing in Albania regarding ethical, medical, practical aspects of the daily work of the clinician (internist) regarding patients in the terminal stage of the disease, the approach to death from both the doctor's point of view and that of the patient and his family members.

**Keywords**: actively dying, end of life care, terminal patient

# TË VDESËSH ME DINJITET, NJË DEBAT I MUNGUAR NË SHQIPËRI

**Abstrakt**
Në punën e përditshme si mjekë klinicistë, të gjithë jemi përballur me çastin kur pacienti nuk përfiton më nga terapia e përcaktuar konform protokolleve mjekësore dhe plani i trajtimit të pacientit duhet të ndryshojë nga terapeutik në paliativ apo suportiv. Ecuria mjekësore e të sëmurëve kronikë, do shkojë në mënyrë të pashmangshme në drejtim të vdekjes së pacientit. Mënyra se si pacienti dhe familjarët e tij do të përballen me vdekjen, është e lidhur drejtpërdrejtë me punën e mjekut dhe stafit mjekësor dhe po ashtu me sqarimin e prognozës së sëmundjes dhe pritshmëritë nga terapia apo paisjet mjekësore në ndihmë të terapisë. Në funksion të këtij procesi vijnë në ndihmë të mjekut dhe stafit edhe koncepte (të reja ose jo) të tilla si: vdekje aktive, kujdesi në fund të jetës, pacient terminal, të cilat ndihmojnë në përcaktimin e stadeve të sëmundjes kronike me një përfundim të pashmangshëm. Ky material nuk ka për qëllim të shërbejë si udhërrëfyes, por synon të ngrejë një debat të munguar në Shqipëri, në lidhje me aspekte etike, mjekësore, praktike, të punës së përditshme të mjekut klinicist (internist), në lidhje me pacientët në stad terminal të sëmundjes, qasjen ndaj vdekjes si nga këndvështrimi i mjekut, ashtu edhe nga ai i pacientit dhe familjarëve të tij.
**Metoda**: Rishikim i literaturës dhe aspekte nga përvoja e punës në pavionin e Mjekësisë Interne dhe HTA, QSUT.
**Përfundim**: Ekziston nevoja e ndërtimit të protokolleve mjekësore dhe juridike në lidhje me kujdesin shëndetësor në fund të jetës. Gjithashtu nevojitet ngritja e qendrave të përkujdesit për të

sëmurët terminal.

**Fjalë kyç:** në fazën e vdekjes aktive, kujdesi në fund të jetës, pacienti në fazën terminale.

## Introduction

More and more deaths, especially in developed and developing countries, are occurring as a result of the slow progression of chronic diseases. Such a thing is inevitably associated with a long and sometimes slow process of the final period of life where vital functions gradually decrease and the patient can become dependent on medical devices and therapies, which often do not bring health benefits. Prolonging life with pain and suffering is unbearable for many patients and humanly and medically senseless. In order to adapt to the new situations with which reality confronts us, a not only practical but also logical and humane approach is needed in the treatment of the patient.

## Concepts

In order to have a widely accepted understanding of the stages in which the chronic patient will pass on the way to the inevitable end, a standardization of terminology and concepts is needed for an easier communication between the physician and the patient and/or family members. Although a universally accepted definition of the following terms does not exist, I will try to give the most frequent meaning based on the reviewed literature.

*Actively dying*: the days or hours before imminent death, during which the patient's vital functions decline (1, 2).

*Terminally ill* is generally accepted as: life expectancy of 6 months or less (3).

*Terminal care*: medical care for individuals with a terminal illness from which death is expected within the next 12 months. Terminal care is about alleviating suffering (physical, spiritual, emotional, social) in the last phase of their life (3).

*Palliative care* is a medical service that improves the quality of life of patients (adults and children) and their families who face problems related to life-threatening illnesses. Palliative care prevents and alleviates suffering through early identification, assessment and accurate treatment of pain and other problems, whether physical, psychosocial or spiritual (4). Care provided to patients with symptoms resulting from incurable disease or a progressive disease with a short life expectancy. Palliative care is an active and comprehensive care model built on a clearly defined philosophy with the aim of meeting quality of life (QOL) requirements when curative therapy is no longer possible (5).

*Hospice care*: Hospice services provide supportive care in the home for patients with a life expectancy of less than 6 months. The focus of hospice care is patient comfort; treatment to extend life is not included (6). In providing active care of patients with advanced, progressive, and incurable diseases, hospice care: provides relief from pain and other distressing symptoms; enhances the quality of life when the length of life is limited; regards dying as a normal process; does not intend to hasten or postpone death; incorporates psychological and spiritual aspects of patient care; uses a team approach to provide a support system for patients and their families (7).

*Dying with dignity*: the most difficult concept to evaluate, because there are many definitions, from: an ethical concept aimed at avoiding suffering and maintaining control and autonomy in the end-of-life process. In general, it is usually treated as an extension of the concept of dignified life, in which people retain their dignity and freedom until the end of their life (8). up to euthanasia. Personally, I conceive dying with dignity as the patient's right to choose to die naturally, without pain, sometimes away from medical devices (pacemaker, ventilator, medical monitor), the right to choose not to perform life-saving maneuvers (do not resuscitate) and not to die in the hospital. The latter is also related to a widespread custom among Albanians not to let their family member die

in the hospital, but at home surrounded by close family members and friends.

**What are the pathologies that deserve palliative treatment?**

When it comes to palliative care for patients, many people think of advanced cancer patients. But in today's medical understanding of palliative treatment, this concept is expanding more and more, either in the way of pathologies that deserve palliative treatment in the advanced stages of the disease or in terms of the time when this treatment can be started during the evolution of the chronic disease.

The National Institute for Clinical Excellence (NICE) emphasizes the importance of not only the best possible control of symptoms but also psychological, social and spiritual support for patients and their families (9). Today's view is that access to palliative care should focus on need and not diagnosis and on that criterion many patients with non-malignant diseases qualify as candidates for palliative treatment (10, 11).

Currently, palliative care, especially in developed countries, includes the treatment of advanced stages of the disease (and not only) in pathologies such as:

*Oncological diseases:* In advanced or metastatic stages, especially when they cause pain, fatigue, nausea, or other severe symptoms.

*Cardiovascular diseases*: Chronic heart failure. Cardiomyopathies in advanced stage.

*Chronic pulmonary diseases:* Chronic obstructive pulmonary disease (COPD). Pulmonary fibrosis. Severe pulmonary hypertension.

*Neurological diseases*: Alzheimer's disease and other forms of dementia. Parkinson's disease in advanced stages. Amyotrophic lateral sclerosis (ALS).

*Cerebrovascular diseases* (for example: the consequences of a severe stroke).

*Hepatic and renal diseases:* End-stage liver cirrhosis. Chronic renal failure, especially when dialysis is no longer effective.

*Chronic or incurable infectious diseases* HIV/AIDS in advanced stages. Incurable or drug-resistant tuberculosis.

*Advanced rheumatological or autoimmune diseases:* Severe systemic lupus. Rheumatoid arthritis in terminal stages.

*Hematological diseases:* Leukemias and lymphomas in incurable stages. Advanced myelodysplastic syndromes.

*Pediatric incurable conditions.*

*Severe genetic metabolic diseases.*

*Congenital syndromes causing severe disability or limited life expectancy.*

Because in the ward of Internal Medicine (UHC), the main focus is on the treatment of patients with heart failure, I will dwell a little longer on the palliative treatment of this chronic pathology with an inevitable fatal outcome.

*Chronic heart failure*

Anderson and colleagues compared symptoms in stage IV heart failure with those in advanced cancer and found that the most distressing were dyspnea and pain, respectively. (12) Various studies have shown that pain and dyspnea in end-stage heart failure patients are poorly controlled, even in hospitalized patients (13). Although the disease course of each patient with HF is unique, there is a general pattern of gradual decline, marked by episodes of acute worsening leading to either sudden death or death due to progressive HF. Communication about the inevitable progress of the disease and advance planning should begin as soon as a patient is diagnosed with advanced HF. Medical team-based approaches to palliative and end-of-life care have been proposed for patients with HF. Specific models of palliative care have been developed for patients with advanced HF. These initiatives aim to reduce hospitalizations, without a clear effect on survival, and have some effects on QOL and symptom burden (14). Progressive functional decline (physical

and mental) and/or dependence in most activities of daily living accompanied by severe heart failure symptoms with poor QOL despite optimal pharmacological and non-pharmacological therapies are clear signs of end of life. Frequent hospital admissions or other serious episodes of decompensation despite optimal treatment constitute a clear indication to consider (14).
The main elements of palliative care service in patients with advanced heart failure focus on improving or maintaining the QOL of a patient and his/her family as much as possible until the patient dies. Frequent assessment of symptoms (including dyspnea and pain) is the main goal of medical treatment at this stage of the illness (14). It is important at this stage to discuss issues such as the place of death and life-saving maneuvers, which may also include the deactivation of medical devices such as: ICD (implantable cardioverter-defibrillator) and MCS (mechanical circulatory support) (14).

**The difference between the terminal oncological and cardiac patient**

Society's model of death originates in the trajectory of most cancer patients cancer: a long period of good vital functions, followed by a relatively short period of weight loss, and decreased vital functions. With the classic course of cancer, the average patient usually lives relatively well for up to two months before death. Once cancer becomes terminal, declines in vital functions and well-being is evident on a weekly basis, and death becomes quite predictable (15).
Patients with heart failure have a very different course at the end of life. Unlike cancer patients, these chronic patients have long-term limitations in functions with occasional early deteriorations, with hospitalizations where the clinical situation improves with treatment and a return to almost previous functional status is often observed (16). Doctors find it difficult to predict when a patient will deteriorate or, which episode will be fatal. Death in this course may seem sudden and unexpected for any patient, even though predictive models can derive an accurate survival curve for a large group of people with heart failure (15).
Perhaps also because the trajectory of heart disease is marked by many deteriorations and then improvements in the clinical condition, which makes the prognosis difficult, doctors rarely communicate with their patients about how they would like to live until at the end of life. This lack of comprehensive medical care planning causes patients to receive treatments such as intensive care and mechanical ventilation, even if they would have preferred otherwise (15). Determining the goal of treatment is particularly important for patients with heart failure, as, as the patient's disease worsens, the use of new technologies such as implantable cardioverter-defibrillators (ICD), resynchronization therapy, left ventricular assist devices, artificial hearts and even heart transplants all become therapeutic options. Clinicians must help patients weigh the benefits and burdens of medical interventions and devices in the impact they have on their lives (15).
In addition, as the clinical course of patients deteriorates, their cardiac function may deteriorate and cause multiple ICD shocks. Due to the progression of co-morbidities such as cancer or chronic pulmonary disease which will inevitably lead to death, continuous defibrillation can be distressing and pointless (17). Considering the likelihood that continued use of the ICD will become ineffective in prolonging life to an acceptable quality and providing workload while the chronic disease worsens, some patients may choose to deactivate their devices at the moment when their life is judged to be coming to an end (15).

**When is the moment when the patient no longer benefits from medical treatment and should switch to palliative care?**

In all the literature reviewed, there is no correct and exhaustive answer to this question. Although there are palliative treatment protocols for cancerous and non-cancerous diseases (National Consensus Project for Quality Palliative Care NCP, European Association for Palliative Care EAPC) which also provide an expanded panorama of clear end-of-life signs such as: decreased

food intake and impaired hydration, death rattle, terminal delirium (without going into more detail as it is not in the focus of this material), no one defines exactly when it is the moment that medical treatment to go into palliative care. It should be emphasized that such a moment cannot be determined since in the concept of palliative medicine it can begin in the early stages of the treatment of the disease and can coexist with medical therapy for the purpose of recovery.

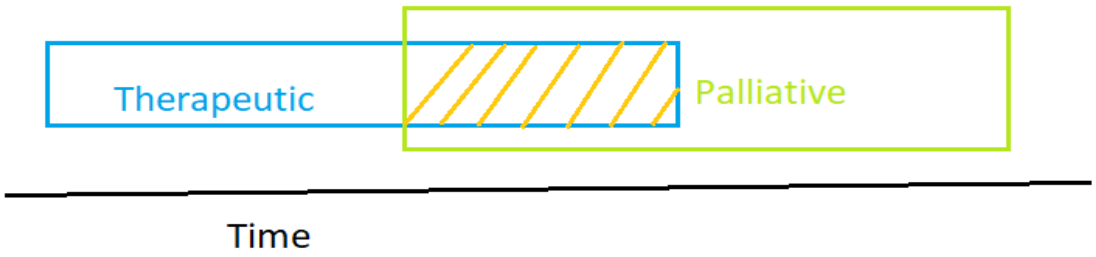



**Figure 1.** Therapies of terminal patient

**Who does the assessment and where is it based?**

Best practices based on the protocols of the American and British Palliative Care Associations emphasize the importance of decision-making by a multidisciplinary medical team in collaboration with the patient (when possible) and/or family members. The decision whether the patient should be transferred to hospice care centers for the continuation of palliative therapy, when it is judged that the further continuation of medical therapy with a therapeutic purpose is futile, should be taken by a group of experienced doctors.

**The concept of hospice care: history, evolution and can it be applied in Albania**

The concept of hospice care is closely related to the life and work of Cicely Saunders. Trained as a nurse during the Second World War in England, she then devoted her work to establishing care centers for cancer patients, to help relieve pain and make life as easy as possible and the easiest transition to the afterlife. Her work was sparked by an episode in her personal life where she cared intensely for her fiancé (a Polish immigrant with cancer) in the years immediately following the war (18).

In the following years, the objective of hospice care centers treatment was expanded to include, in addition to oncology patients, terminal cardiac patients and those with AIDS.

In Albania, to our knowledge, there was a hospice care center within a non-profit organization for a short period of time, which was then closed due to lack of funds. Currently, in our country, only a few centers of the Oncology Service at Home (SOB) (state) and some non-profit organizations are operating only for the help of the terminal patient treated at home. Regarding the palliative treatment of patients with non-cancerous diseases, there is no state medical organization or non-profit organization in this field.

**Conclusion**

With the increase in life expectancy and increasingly efficient treatments of various chronic pathologies, the number of non-oncological terminal patients has also increased. Such a situation has brought as the need of the time the medical and legal definition of new concepts regarding the treatment of patients at the end of life as well as medical protocols for treatment when medical therapy is judged to be worthless. Communication with the patient and/or family members of the diagnosis and its consequences, as well as the patient's life expectancy, are extremely important in

relation to the progress of the treatment as well as the impact that the loss of a loved one can have on his family. The lack of hospice care centers where terminal patients can die with dignity and assisted by qualified medical staff (doctor, nurse) brings, in addition to the social and psychological traumas of the patients' families, an overload in the hospitals, especially in the capital. This is often associated with a deterioration of the doctor's image in general (especially in cases where terminal patients are not accepted for hospitalization).

**Recommendation**

The authors of this text recommend the definition of a legal framework related to the concepts discussed above to improve the approach, assessment and treatment of the non-oncological terminal patient as controlled as possible. This initiative requires the widest possible involvement of professionals from many disciplines (clinical doctors, nurses, psychologists, and lawyers, sociologists) in order to have a product as close as possible to the countries of the European Union, considering the customary, religious and social features of our country. The establishment and operation of hospice care centers for terminal oncological and non-oncological patients, to assist in the last stages of life. To introduce into the work practice in wards (Internal Medicine, Cardiology, Nephrology), making collegial decisions regarding the determination of patients who no longer benefit from curative medical therapy and can be transferred to palliative treatment at home.

**References**


1. Hui D, Nooruddin Z, Didwaniya N, et al. Concepts and definitions for "actively dying," "end of life," "terminally ill," "terminal care," and "transition of care": a systematic review. J Pain Symptom Manage. 2014;47(1):77-89. doi:10.1016/j.jpainsymman.2013.02.021
2. Hui D, Mori M, Parsons H, et al. The lack of standard definitions in the supportive and palliative oncology literature. J Pain Symptom Manage 2012; 43:582e592..
3. Proot IM, Abu-Saad HH, ter Meulen RH, Goldsteen M, Spreeuwenberg C, Widdershoven GA. The needs of terminally ill patients at home: directing one's life, health and things related to beloved others. Palliat Med. 2004;18(1):53-61. doi:10.1191/0268216304pm818oa
4. https://www.who.int/news-room/fact-sheets/detail/palliative-care WHO palliative care definition 2020
5. Hansen MJ, Enright RD, Baskin TW, Klatt J. A palliative care intervention in forgiveness therapy for elderly terminally ill cancer patients. J Palliat Care. 2009;25(1):51-60.
6. Hill RR, Martinez KD, Delate T, Witt DM. A descriptive evaluation of warfarin use in patients receiving hospice or palliative care services. J Thromb Thrombolysis. 2009;27(3):334-339. doi:10.1007/s11239-008-0210-5
7. Buescher PA, Brunger JB. Hospice in North Carolina. N C Med J. 2009;70(2):187-188.
8. Qué es muerte digna?". *Fundación Pro Derecho a Morir Dignamente*. Archived from the original on 2021-01-25.
9. NICE. Improving Supportive and Palliative Care for Adults with Cancer. [www.nice.org.uk/page.aspx?o=110005]. Accessed 16 March 2005
10. NHS Executive. A Policy Framework for Commissioning Cancer Services: Palliative Care Services. London: NHS Executive, 1996
11. Addington-Hall J. Reaching Out: Specialist Palliative Care for Adults with Non-malignant Disease. London: National Council for Hospices and Specialist Palliative Care
12. Anderson H, Ward C, Eardley A, et al. The concerns of patients under palliative care and a heart failure clinic are not being met. Palliat Med 2001;15:279–86
13. Ward C. The need for palliative care in the management of heart failure. Heart 2002;87:294–8

14. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy) et al. European Heart Journal (2021) 42, 3599-3726
15. Trajectory of End-Stage Heart Failure *the influence of technology and implications for policy change* Nathan E. Goldstein* and Joanne Lynn†
16. Lunney, Lynn, and Hogan 2002; Lunney et al. 2003
17. Eckert dhe Jones 2002; Glikson dhe Friedman 2001; Sears dhe Conti 2002
18. https://en.wikipedia.org/wiki/Cicely_Saunders

# CARDIAC SURGERY IN OCTOGENARIANS IN ALBANIA

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**Abstract**

**Introduction:** For many years, surgical treatment of cardiac pathologies in subjects over 80 years of age has been viewed with great skepticism. Old age as a significant risk factor for cardiovascular diseases has also been considered an indicator of high surgical risk, being influenced by the progressive increase in comorbidities with increasing age. However, with the increase in quality of life and at the same time average life expectancy, an ever-increasing trend has been observed in patients over 80 years of age who have shown the need for cardiac surgical treatment.

**Methods:** In this retrospective study based on hospital registry data, we analyzed all patients over 80 years of age who were hospitalized in the cardiac surgery service in the period January 2021-December 2024 with a focus on the short-term results of surgical treatment, mortality and morbidity. Patients who, after evaluation by the cardiosurgical and cardio-anesthetic medical staff, were considered inoperable were excluded from the study.

**Results:** During the 4-year study period, 3001 patients were hospitalized in the Cardiac Surgery Service, of whom 80 patients were over 80 years old. 18 patients considered inoperable were excluded from the study. Of the 62 patients in the study, 25 were female and 37 were male. The average age was 81.46 years old (minimum 80, maximum 86). Hospitalization of patients was in emergency n=3 patients and elective in n=59 patients. The interventions performed in these patients were simple (n=50): CABG (n=30); AVR (n=13); MVR (n=4); Mitral Valve Plastic (n=1); AAR(n=2); and complex n=12 such as: AVR and CABG (n=6); MVR and CABG (n=2); Mitral Valve Plastic and CABG (n=1); AVR and MVR and ASD Closure (n=1); AVR and AAR (n=1); CABG and ASD Closure (n=1);. The average length of stay of these patients in the cardiac surgery service was 14.5 days (minimum 1 day, maximum 40 days). The postoperative course was without complications in most patients. Postoperative mortality during this period was 8 %. All patients were discharged in improved clinical condition, NYHA II-III functional class.

**Conclusions:** Although age is a significant indicator of increased morbidity and hospital stay in patients suffering from cardiac pathology and consequently undergoing cardiac surgery, it does not result in a significant factor of mortality in these patients. On the other hand, it results that cardiac surgery in these patients has brought significant improvement in clinical condition and quality of life. Based on the ever-increasing presentation of these patients in hospital clinics seeking treatment for these pathologies, cardiac surgery is considered a relatively safe definitive treatment method with good results.

**Keywords:** cardiac, surgery, high risk, octogenarians

# KIRURGJIA KARDIAKE GJATË TË TETËDHJETAVE NË SHQIPËRI

**Abstrakt**

**Hyrje;** Prej shumë vitesh, trajtimi kirurgjikal i patologjive kardiake te subjektet mbi 80 vjeç është parë me shumë skepticizëm. Mosha e madhe, si një faktor rrisku i rëndësishëm për sëmundjet

kardiovaskulare, është konsideruar gjithashtu dhe si një tregues i rriskut të lartë kirurgjikal, duke u influencuar nga rritja progresive e sëmundjeve bashkeshoqëruese me rritjen e moshës. Megjithatë, me rritjen e cilësisë së jetës dhe në të njëjtën kohë dhe e jetëgjatësisë mesatare, është vënë re një tendencë gjithnjë në rritje e pacientëve mbi 80 vjeç, të cilët kanë shfaqur nevojën e trajtimit kardiokirurgjikal.
**Metodat**: Në këtë studim retrospektiv bazuar në të dhënat e regjistrit spitalor, ne analizuam të gjithë pacientët mbi 80 vjeç të shtruar në shërbimin e kardiokirurgjisë në periudhën janar 2021-dhjetor 2024 me fokus në rezultatet afatshkurtra të trajtimit kirurgjikal, vdekshmërisë dhe sëmundshmërisë. Pacientët të cilët, pas vlerësimit nga stafi mjekësor kardiokirurgjikal dhe kardio-anestetik, u konsideruan të paoperueshëm, u përjashtuan nga studimi.
**Rezultatet**: Gjatë periudhës 4-vjeçare të studimit, në Shërbimin e Kardiokirurgjisë janë shtruar 3001 pacientë, nga të cilët 80 pacientë ishin mbi 80 vjeç. 18 pacientë të konsideruar inoperabel u përjashtuan nga studimi. Nga 62 pacientët në studim, 25 ishin femra dhe 37 ishin meshkuj. Mosha mesatare ishte 81.46 vjeç (minimumi 80, maksimumi 86). Hospitalizimi i pacientëve ishte në urgjencë n=3 pacientë dhe elektiv në n=59 pacientë. Ndërhyrjet e kryera në këta pacientë ishin të thjeshta (n=50): CABG (n=30); ZVA (n=13); ZVM (n=4); Plastike e Valvulës Mitrale (n=1); ZvAoAsc (n=2); dhe komplekse n=12 si: ZVA dhe CABG (n=6); ZVM dhe CABG (n=2); Plastike e valvules mitrale dhe CABG (n=1); ZVA, ZVM dhe Mbyllje e DIA (n=1); ZVA dhe ZvAoAsc (n=1); CABG dhe Mbyllje e DIA (n=1);. Kohëzgjatja mesatare e qëndrimit të këtyre pacientëve në shërbimin e kardiokirurgjisë ishte 14.5 ditë (minimumi 1 ditë, maksimumi 40 ditë). Ecuria postoperative ishte pa komplikime në shumicën e pacientëve. Vdekshmëria pas operacionit gjatë kësaj periudhe ishte 8 %. Të gjithë pacientët dolen nga spitali në gjendje të përmirësuar klinike, me funksion kardiak NYHA II-III.
**Konkluzione**: Edhe pse mosha është një tregues domethënës i rritjes së sëmundshmërisë dhe qëndrimit në spital në pacientët që vuajnë nga patologjia kardiake dhe për pasojë që i nënshtrohen kardiokirurgjisë, ajo nuk rezulton në një faktor të rëndësishëm vdekshmërie tek këta pacientë. Nga ana tjetër rezulton se kardiokirurgjia tek këta pacientë ka sjellë përmirësim të ndjeshëm në gjendjen klinike dhe cilësinë e jetës. Bazuar në paraqitjen gjithnjë në rritje të këtyre pacientëve në klinikat spitalore që kërkojnë trajtim për këto patologji, kardiokirurgjia konsiderohet një metodë trajtimi përfundimtare relativisht e sigurt dhe me rezultate të mira.

**Fjalë kyçe:** kardiak, kirurgji, rrezik i lartë, tetëvjeçarë

## Introduction

Age is an important factor of cardiovascular function deterioration, increasing the risk of cardiovascular disease (CVD) in older people (1). Along with atherosclerosis, stroke, and myocardial infarction, CVD prevalence increases with age in both men and women. The American Heart Association AHA indicates that CVD incidence in US men and women is ~40% from 40-59 years, ~75% from 60-79 years, and ~86% beyond 80 years (2).
Most algorithms employed to assess the cardiac surgical risk indicate that octogenarians consistently receive high scores for estimated mortality risk due to age and co-morbidity factors. Therefore, for a long time this has resulted in challenges in consultation and hesitation in both offering and accepting the surgical treatment (3).

## Methods

We designed the following retrospective study assessing the outcome of cardiac surgical treatment in octogenarians presented to our clinic. Based on hospital registry data, we analyzed all patients over 80 years of age who were hospitalized in the cardiac surgery clinic in the period January 2021-December 2024, excluding the patients considered inoperable from the cardiosurgical and

cardio-anesthetic medical staff and the patients denying consent for the surgical intervention. The patients undergoing cardiac surgery were classified according to age, gender, mode of admission, diagnosis, complexity of the intervention, length of hospital stay, postoperative course, and postoperative mortality.

**Results**

During the 4-year study period, 3001 patients were hospitalized in the Cardiac Surgery Service, of which 80 patients (2,7%) were over 80 years old. 18 patients, considered inoperable from the cardio-surgical and cardio-anesthetic teams or not willing to undergo such indicated surgery, were excluded from the study. Of the 62 patients in the study, 25 (40%) were female and 37 (60%) were male. The average age was 81,46 years (minimum 80, maximum 86). Hospitalization of patients was in emergency n=3 patients and elective in n=59 patients. The interventions performed in these patients were simple (n=50): CABG (n=30); AVR (n=13); MVR (n=4); Mitral Valve Plasty (n=1); AAR(n=2); others and complex n=12 such as: AVR and CABG (n=6); MVR and CABG (n=2); Mitral Valve Plastic and CABG (n=1); AVR and MVR and ASD Closure (n=1); AVR and AAR (n=1); CABG and ASD Closure (n=1);.

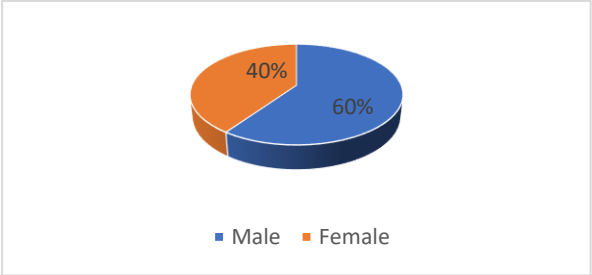



**Figure 1**. Division of the patients according to sex

| ***Simple Surgery*** | **No of Patients** |
|---|---|
| **CABG** | 30 |
| **AVR** | 13 |
| **MVR** | 4 |
| **MVP** | 1 |
| **AAR** | 2 |
| ***Combined Surgery*** | |
| **CABG+AVR** | 6 |
| **CABG+MVR** | 2 |
| **CABG+MVP** | 1 |
| | |
| **AVR+MVR+ASD** | 1 |
| **AVR+AAR** | 1 |
| **CABG+VSD** | 1 |

**Table1.** Type of operations CABG coronary artery bypass grafting, AVR aortic valve replacement, MVR mitral valve replacement, MVP mitral valve plastiy, AAR ascending aorta replacement, ASD atrial septal defect, VSD ventricular septal defect.

| CABG No of grafts | Patients No(percentage) |
|---|---|
| **1** | 1(1,9%) |
| **2** | 17(32,7%) |
| **3** | 10(19,2%) |
| **4** | 2(3,8%) |

**Table 2.** Number of the grafts during coronary bypass surgery

In surgical cases of valve replacement, all the patients received a biological prostheses Epic St Jude Medical either mitral in 7 patients or aortic17 patients.
One patient was re-operated for pericardial tamponade by opening a pleuro-pericardial window in thoracotomy and another one for sternal dehiscence with reconstruction of the wound. The average length of stay of these patients in the cardiac surgery service was 14.5 days (minimum 1 day, maximum 40 days). The postoperative course was uneventful in most patients.
The postoperative mortality during this period was 8 %. 5 patients with fatal postoperative events were recorded (intraoperative n=0, first postoperative day n=1, first postoperative week n=2, first postoperative month n=2). All the patients who survived, were discharged from the hospital with significant improvement in clinical condition, marking NYHA II and II-III heart failure, along with the other comorbidities.

**Discussions**

In Albania, coronary artery diseases alone, contribute to 40% of the national mortality. According to INSTAT (Institute of Statistics in Albania), there were 11,500 deaths from these diseases in 2015 and approximately 11,000 deaths in 2016.
Due to the aging of the population, but also the increase in life expectancy, the number of citizens older than 80 years, in Albania has more than doubled the last two decades according to INSTAT data in 2020 (their number was around 82.000 compared to 38.000 people over 80 years old in 2001). Seniors over 80 accounted for 2.9% of the total population in 2020, up from 1.3% in 2011. About 53% of them are women, for the reason that women live on average 3-4 years longer than men.

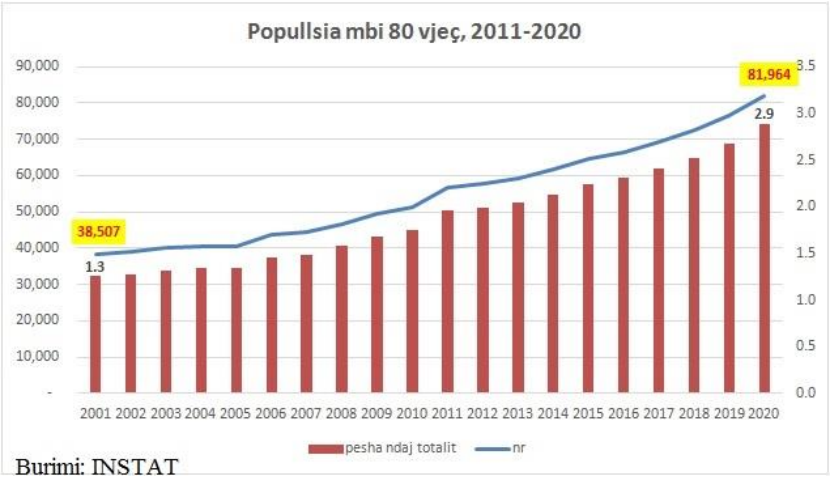



**Figure 2.** Population over 80 years old increase during the last 20 years in Albania Institute of Statistics in Albania INSTAT

As a result, during the last decade, the number of older patients needing heart surgery has progressively increased. Octogenarians have a particularly challenging place because of their

specific age-related physiology, various comorbidities, and exposure to complex chronic medications. These lead to a decompensated condition of general health. Cardiovascular disease, in particular, is the cause for the decline in the overall health of octogenarians (4).

The recent years our clinic has met a notable increase in the number of patients over 80 years old needing cardiac surgery. There are concerns and hesitation among patients, their family but also the medical team whether to operate this group of people or not. They represent only 2% of the total patients operated in the cardiac surgery clinic compared with 11% of patients undergoing adult cardiac surgery by the end of the 15-year study published by Jones et al about the situation in the United Kingdom. During this period, they observed almost a three-fold increase from the start of it (5). So, we must predict also a furthermore increase in the number of patients over 80 years to be operated in the following years in Albania.
Most of the octogenarians (around 80 %) needing cardiac surgery at the public hospital were operated with good results after careful selection by a dedicated cardio-surgical team. The hospital mortality, as the main indicator of the surgical outcome was 8%. It is almost the double of the overall mortality of 3-4 %, which is a well-established result at our clinic from many years, but it is an excellent result for this group of patients compared with other reports from different groups in Europe (3,5).
Stoica et al reports an in-hospital mortality rate of 3.9% for all patients and 9.8% for octogenarians (predicted 14.1%). Long bypass time and non-elective surgery were identified as risk factor for death above the Euro-SCORE prediction in both groups (3).
Postoperatively, a greater proportion of patients stayed in intensive care more than 48 hours as it is the general protocol for our clinic but it is comprehensible and does not affect the outcome, although it resulted in higher costs and demands in the intensive care unit and ward, reflected by a high median hospital stay for these patients.
Long term survival is significantly better, as reported in different studies with octogenarians, than in a general population with the same age–sex distribution (3,5). We have to follow this group of patients and have a clear panorama of intermediate and long-term results in order to confirm the present suggestion for surgery in this group of patients presenting at our public hospital.

**Conclusions**

Although age is a significant indicator of increased morbidity and hospital stay in patients suffering from cardiac pathology and consequently undergoing cardiac surgery, it does not result in a significant factor of mortality in these patients. On the other hand, it results that cardiac surgery in these patients has brought significant improvement in clinical condition and quality of life. Based on the ever-increasing presentation of these patients in hospital clinics seeking treatment for these pathologies, cardiac surgery is considered a relatively safe definitive treatment method with good results.

**Conflict of interest:** Nothing to declare

**References:**

1. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res. 2012 Apr 13;110(8):1097-108. doi: 10.1161/CIRCRESAHA.111.246876. PMID: 22499900; PMCID: PMC3366686.
2. Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, Karia K, Panguluri SK. Cardiovascular Risks Associated with Gender and Aging. J Cardiovasc Dev Dis. 2019 Apr 27;6(2):19. doi: 10.3390/jcdd6020019. PMID: 31035613; PMCID: PMC6616540.

3. Stoica SC, Cafferty F, Kitcat J, Baskett RJ, Goddard M, Sharples LD, Wells FC, Nashef SA. Octogenarians undergoing cardiac surgery outlive their peers: a case for early referral. Heart. 2006 Apr;92(4):503-6. doi: 10.1136/hrt.2005.064451. Epub 2005 Aug 23. PMID: 16118240; PMCID: PMC1860849.
4. Taghizadeh-Waghefi A, Petrov A, Arzt S, Alexiou K, Tugtekin SM, Matschke K, Kappert U, Wilbring M. Clinical Outcomes after Multivalve Surgery in Octogenarians: Evaluating the Need for a Paradigm Shift. J Clin Med. 2024 Jan 27;13(3):745. doi: 10.3390/jcm13030745. PMID: 38337441; PMCID: PMC10856504.
5. James Mark Jones, Mahmoud Loubani, Stuart W Grant, Andrew T Goodwin, Uday Trivedi, Simon Kendall, David P Jenkins, Cardiac surgery in older patients: hospital outcomes during a 15-year period from a complete national series, *Interactive CardioVascular and Thoracic Surgery*, Volume 34, Issue 4, April 2022, Pages 532–539, https://doi.org/10.1093/icvts/ivab320

# EXTRANODAL DIFFUSE LARGE B CELL LYMPHOMA WITH ADDITIONAL SPREAD TO THE BREAST: A CASE REPORT

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**Abstract**
**Introduction**. Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of lymphoid malignancies with significant clinical, morphological, and genetic diversity. The most common subtype, Diffuse Large B-Cell Lymphoma (DLBCL), typically involves lymph nodes, spleen, or bone marrow, but can also present at extranodal sites. Extranodal involvement occurs in about 30% of cases, with the skin being a frequent site. Breast involvement, however, is rare.
**Objectives**. To describe the clinical case of a patient with primary cutaneous DLBCL and concurrent breast involvement, emphasizing the importance of detailed clinical examination and timely treatment.
**Materials and Methods.** A detailed clinical examination revealed a primary skin lesion on the thigh and a mass in the breast in a patient presenting to the QSUT Consultation Center. The patient underwent biopsy and imaging, and was treated with six cycles of the R-CHOP chemotherapy regimen. Hospital records were used to track the progression of the disease and treatment response.
**Results.** After completing the R-CHOP regimen, both the thigh and breast lesions completely regressed. Follow-up imaging and clinical evaluation confirmed complete remission, and the patient has remained in remission for two years.
**Conclusions**. This case highlights the clinical diversity of DLBCL and underscores the critical role of a comprehensive clinical examination in detecting extranodal involvement. The patient's complete remission following R-CHOP therapy further demonstrates the efficacy of this regimen in managing extranodal lymphoma.

**Keywords**. Non-Hodgkin Lymphoma, DLBCL, extranodal involvement, breast lymphoma, clinical examination.

# LIMFOMA ME QELIZA B TË MËDHA DIFUZE EKSTRANODALE ME PËRHAPJE EDHE NË MAME: RAST KLINIK

**Abstrakt**
**Hyrje**. Limfoma Jo-Hodgkin (NHL) është një grup heterogjen i neoplazive limfoide me diversitet të rëndësishëm klinik, morfologjik dhe gjenetik. Nëntipi më i zakonshëm, Limfoma Difuze me Qeliza të Mëdha B (DLBCL), zakonisht përfshin nyjet limfatike, shpretkën ose palcën e kockave, por mund të paraqitet edhe në vende ekstranodale. Përfshirja ekstranodale ndodh në rreth 30% të rasteve, ku lëkura është një vend i shpeshtë. Megjithatë, përfshirja e gjirit është e rrallë.
**Qëllimi.** Të përshkruhet rasti klinik i një pacienti me DLBCL primare të lëkurës dhe përfshirje të njëkohshme të gjirit, duke theksuar rëndësinë e ekzaminimit të detajuar klinik dhe trajtimit në kohë.
**Materiale dhe Metoda**. Një ekzaminim i detajuar klinik zbuloi një lezion primar të lëkurës në kofshë dhe një masë në gji te një paciente që u paraqit në Qendrën e Konsultave QSUT. Pacientja iu nënshtrua biopsisë dhe ekzaminimeve imazherike dhe u trajtua me gjashtë cikle të regjimit të kimioterapisë R-CHOP. Regjistrat spitalorë u përdorën për të ndjekur progresionin e sëmundjes

dhe përgjigjen ndaj trajtimit.
**Rezultatet**. Pas përfundimit të regjimit R-CHOP, lezionet në kofshë dhe gji regreduan plotësisht. Imazheria dhe vlerësimi klinik gjatë ndjekjes konfirmuan remision të plotë, dhe pacientja ka qendruar në remision për dy vjet.
**Përfundime**. Ky rast nënvizon diversitetin klinik të DLBCL-së dhe thekson rolin thelbësor të një ekzaminimi të plotë klinik në zbulimin e përfshirjes ekstranodale. Remisioni i plotë i pacientes pas terapisë R-CHOP gjithashtu demonstron efikasitetin e këtij regjimi në menaxhimin e limfomës ekstranodale.

**Fjalë kyçe:** Limfoma Jo-Hodgkin, DLBCL, përfshirje ekstranodale, limfoma e gjirit, ekzaminim klinik

## Introduction

Non-Hodgkin's Lymphoma (NHL) comprises a diverse group of lymphoproliferative disorders, characterized by significant clinical, morphological, histological, biological, genetic, and molecular variability (1). The annual incidence of NHL ranges from 14 to 19 cases per 100,000 individuals (2). NHL is generally categorized into B-cell and T-cell types, with approximately 90% of cases being of B-cell origin, which includes various subtypes, among which Diffuse Large B-Cell Lymphoma (DLBCL) is the most prevalent.

DLBCL is an aggressive lymphoma characterized by rapidly enlarging tumors, typically found in lymph nodes, spleen, liver, or bone marrow. It accounts for 20-50% of malignant NHL cases in adults (3) and has an annual incidence of 3-4 cases per 100,000 people (2). While DLBCL is commonly associated with nodal involvement, it can also arise in extra - nodal locations, with approximately 30% of cases exhibiting extra - nodal presentation. The gastrointestinal tract is the most common extra - nodal site, followed by the skin. At diagnosis, skin involvement may present as plaques, papules, nodules, or ulcers. Other extra - nodal sites may include the central nervous system (CNS), bone, thyroid, reproductive organs, and breast (4-7).

This article reports the case of a patient diagnosed with extra - nodal DLBCL, with initial presentation in the skin of the thigh and additional involvement of the breast. The patient was diagnosed with hematological malignancy for the first time and received treatment accordingly. Clinical data and imaging findings were obtained from hospitalization records in the Hematology clinic.

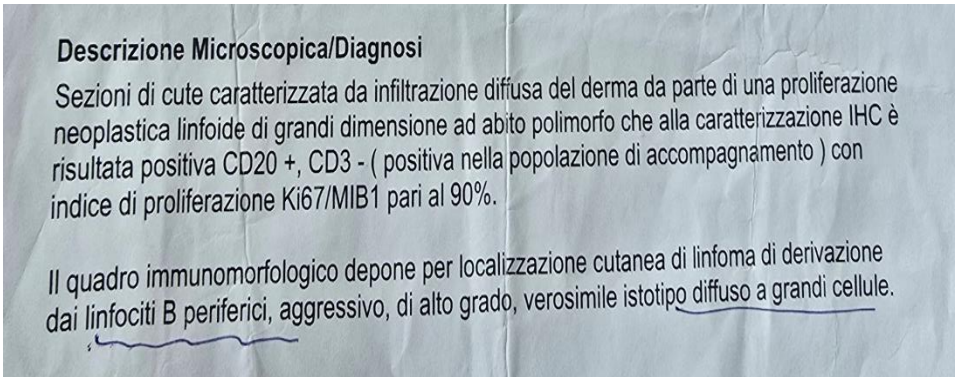
## Clinical Presentation

A 48-year-old patient, V.K., presented to the Hematology Consultation Center at QSUT in June 2022 for initiation of treatment for lymphoma. The patient exhibited a large lesion on the right thigh extending into the inguinal region, accompanied by significant edema in the right leg. The disease had first manifested five years earlier as a localized skin lesion on the right thigh, progressively enlarging over the following year (Fig.1 a,b). Approximately three to four months before seeking consultation, the lesions expanded rapidly, and the patient developed severe lower-extremity edema.



**Figure 1 (a, b).** Thigh lesions at the onset of treatment (June 2022). The images depict papulomatous, nodular, and ulcerative lesions on the skin, along with pronounced edema in the right leg.

The patient initially sought medical attention in her district of Durrës, where imaging studies were conducted. Subsequently, she visited a private hospital in Tirana, where a biopsy of the skin lesion on the right thigh was performed. The biopsy confirmed the diagnosis of Non-Hodgkin's Lymphoma (NHL), specifically Diffuse Large B-Cell Lymphoma (DLBCL). Following this, the patient was referred to the Hematology Consultation Center at QSUT to begin specific treatment.
*Diagnostic Findings.* On physical examination, no significant peripheral lymphadenopathy was observed, except for small inflammatory lymph nodes on MRI. Imaging studies revealed no thoraco-abdominal lymphadenopathy. The skin biopsy revealed diffuse infiltration of the dermis by a large lymphoid neoplastic proliferation with polymorphic characteristics. Immunohistochemistry (IHC) findings were CD20 positive, CD3 negative, and a Ki-67 proliferation index of 90%, confirming the diagnosis of DLBCL (Fig. 2).



**Descrizione Microscopica/Diagnosi**

Sezioni di cute caratterizzata da infiltrazione diffusa del derma da parte di una proliferazione neoplastica linfoide di grandi dimensione ad abito polimorfo che alla caratterizzazione IHC è risultata positiva CD20 +, CD3 - ( positiva nella popolazione di accompagnamento ) con indice di proliferazione Ki67/MIB1 pari al 90%.

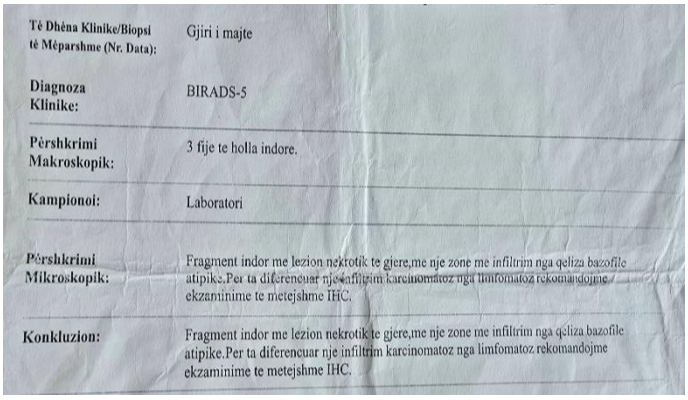
Il quadro immunomorfologico depone per localizzazione cutanea di linfoma di derivazione dai linfociti B periferici, aggressivo, di alto grado, verosimile istotipo diffuso a grandi cellule.

**Figure 2.** Biopsy result of thigh lesions. The skin section shows diffuse infiltration of the dermis by a large lymphoid neoplastic proliferation with polymorphic characteristics. Immunohistochemistry (IHC) reveals CD20 positivity, CD3 negativity, and a Ki67 proliferation index of 90%. **Conclusion**: Malignant Non-Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma (DLBCL).

During the treatment process, a detailed physical examination identified a palpable mass in the left breast. Ultrasound examination categorized the mass as BI-RADS 5, indicating a high likelihood of malignancy. A biopsy of the breast mass revealed tissue fragments with extensive necrotic lesions and areas of infiltration by atypical basophilic cells (Fig.3). Immunohistochemical analysis demonstrated no nuclear staining for estrogen receptor (ER), slight nuclear staining in 30% of cells for progesterone receptor (PGR), and positivity for CD45 and CD20, confirming the diagnosis of NHL, consistent with DLBCL (Fig. 4 a,b)



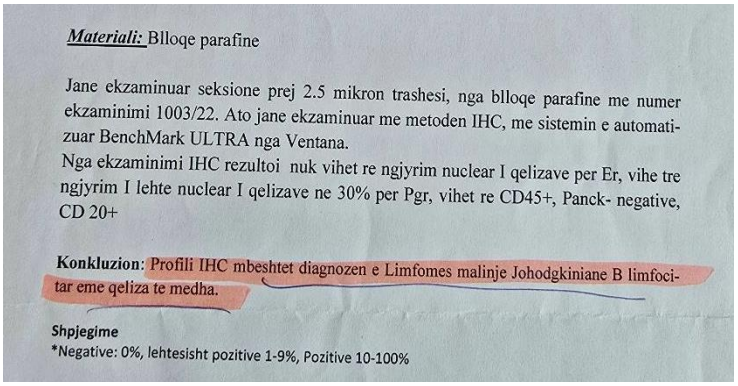
**Figure 3.** The mass in the left breast, following biopsy. The image shows the scar from the aspiration procedure.



| | |
|---|---|
| Të Dhëna Klinike/Biopsi të Mëparshme (Nr. Data): | Gjiri i majte |
| Diagnoza Klinike: | BIRADS-5 |
| Përshkrimi Makroskopik: | 3 fije te holla indore. |
| Kampionoi: | Laboratori |
| Përshkrimi Mikroskopik: | Fragment indor me lezion nekrotik te gjere,me nje zone me infiltrim nga qeliza bazofile atipike.Per ta diferencuar nje infiltrim karcinomatoz nga limfomatoz rekomandojme ekzaminime te metejshme IHC. |
| Konkluzion: | Fragment indor me lezion nekrotik te gjere,me nje zone me infiltrim nga qeliza bazofile atipike.Per ta diferencuar nje infiltrim karcinomatoz nga limfomatoz rekomandojme ekzaminime te metejshme IHC. |

**Figure 4 a.** Breast Biopsy Result: Tissue fragment showing extensive necrotic lesions, along with

an area of infiltration by atypical basophilic cells. Immunohistochemistry (IHC) examinations are recommended to differentiate between carcinomatous and lymphomatous infiltration.



***Materiali:*** Blloqe parafine

Jane ekzaminuar seksione prej 2.5 mikron trashesi, nga blloqe parafine me numer ekzaminimi 1003/22. Ato jane ekzaminuar me metoden IHC, me sistemin e automatizuar BenchMark ULTRA nga Ventana.
Nga ekzaminimi IHC rezultoi nuk vihet re ngjyrim nuclear I qelizave per Er, vihe tre ngjyrim I lehte nuclear I qelizave ne 30% per Pgr, vihet re CD45+, Panck- negative, CD 20+

**Konkluzion**: Profili IHC mbeshtet diagnozen e Limfomes malinje Johodgkiniane B limfocitar eme qeliza te medha.

**Shpjegime**
*Negative: 0%, lehtesisht pozitive 1-9%, Pozitive 10-100%

**Figure 4 b**. Immunohistochemistry Result of the Breast Mass: Immunohistochemistry findings: No nuclear staining of cells for estrogen receptor (ER), slight nuclear staining observed in 30% of cells for progesterone receptor (PGR). CD45 positive, PanCK negative, and CD20 positive.

**Conclusion:** Non-Hodgkin Lymphoma (NHL), Diffuse Large B-Cell

Lymphoma (DLBCL).

*Treatment*. The patient began treatment with the R-CHOP protocol, which includes Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, and Prednisolone. After the initial two cycles of treatment, there was a pronounced regression of the thigh lesions, with most of the lesions disappearing (Fig. 5a). By the fourth cycle, only scars remained (Fig. 6b). Upon completing six cycles of treatment, the lesions in both the thigh and breast had completely resolved.



**Figure 5 a.** Thigh Lesions After Two Cycles of Treatment (July 2022):
Significant regression observed, with the disappearance of most of the lesions.




**Figure 6 a,b**. Lesions after 4 treatment cycles (September 2022). Only scars remain

*Outcome*. Currently, the patient remains in complete remission, with no recurrence of lesions for over two years. The patient's psychological well-being was also addressed during the treatment process, given her history of depressive disorder. She continues follow-up evaluations to monitor her long-term remission status.

**Discussion**

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of Non-Hodgkin's Lymphoma (NHL), representing an aggressive malignancy with diverse clinical presentations. While nodal involvement remains the predominant site of disease, approximately 30% of DLBCL cases exhibit extranodal manifestations. Extranodal DLBCL can affect nearly any organ, with the gastrointestinal tract being the most frequent site, followed by other less common locations such as the skin, central nervous system, bone, and breast (2, 4-7). The case presented here highlights the significance of extranodal DLBCL involving the skin and breast, illustrating the diagnostic and therapeutic challenges associated with such presentations.

The patient's initial presentation with a large, ulcerated lesion on the thigh, along with extensive edema, underscores the variability in lymphoma manifestations. Skin involvement in lymphoma is uncommon but not rare, typically presenting as papules, nodules, or ulcers, and often mimicking other dermatologic or oncologic conditions (4). In this case, the delayed progression from localized skin lesions to more extensive involvement of the thigh over five years exemplifies the often insidious nature of the disease.

Of particular note is the involvement of the breast in this case, which is a rare extranodal site for DLBCL. Breast lymphoma accounts for less than 1% of all breast malignancies and is most frequently associated with NHL. The presence of a palpable breast mass, confirmed to be DLBCL via biopsy and immunohistochemistry, reinforces the need for thorough and systematic clinical examinations, especially in patients with known or suspected lymphoproliferative disorders (6).

Histopathological and immunohistochemical evaluations were pivotal in establishing the diagnosis. CD20 positivity and a high Ki-67 proliferation index supported the classification of this malignancy as DLBCL, distinguishing it from other lymphoid or carcinomatous infiltrations. The biopsy results from both the thigh and breast were concordant, affirming the diagnosis of extranodal DLBCL with multifocal involvement (5).

The successful response to R-CHOP therapy, with complete remission achieved after six cycles, highlights the efficacy of this standard treatment protocol. R-CHOP remains the cornerstone for managing DLBCL, offering a high likelihood of durable remission even in advanced or extranodal cases. The pronounced regression of lesions after the initial cycles and the absence of residual disease after treatment underscore the importance of timely and appropriate therapeutic interventions (3).

This case also underscores the psychological impact of a lymphoma diagnosis and the critical role of mental health support during treatment. The patient's history of depressive disorder necessitated a multidisciplinary approach, integrating psychological support with oncologic care. Addressing the emotional and psychological well-being of patients is integral to achieving holistic and effective treatment outcomes.

**Conclusion**

This case highlights the diagnostic challenges posed by extranodal DLBCL and emphasizes the value of a comprehensive clinical examination, systematic diagnostic workup, and multidisciplinary care. The rare presentation of DLBCL involving both the skin and breast serves as a reminder of the disease's diverse manifestations and underscores the importance of individualized patient management.

**References**


1. Ansell SM. Non-Hodgkin Lymphoma: Diagnosis and Treatment. Mayo Clin Proc. 2015;90(8):1152-1163. doi:10.1016/j.mayocp.2015.04.025
2. Hatellari A. (2021). Faktorët që influencojnë në përgjigjen dhe rezultatet e mjekimit në limfomat malinje jo hodgkiniane. http://umed.edu.al/wp-content/ uploads/2021 /04/ doktoratura.pdf
3. Wang SS. Epidemiology and etiology of diffuse large B-cell lymphoma. Semin Hematol. 2023;60(5):255-266. doi:10.1053/j.seminhematol.2023.11.004
4. Vannata B, Zucca E. Primary extranodal B-cell lymphoma: current concepts and treatment strategies. Chin Clin Oncol. 2015;4(1):10. doi:10.3978/j.issn.2304-3865.2014.12.01
5. Yang H, Xun Y, Ke C, Tateishi K, You H. Extranodal lymphoma: pathogenesis, diagnosis and treatment. Mol Biomed. 2023;4(1):29. Published 2023 Sep 18. doi:10.1186/s43556-023-00141-3
6. Guo M, Liu J, Gilmore R, et al. Primary breast diffuse large B cell lymphoma. BMJ Case Reports CP 2022;15:e250478.
7. Heckendorn E, Auerbach A. Pathology of Extranodal Lymphoma. Radiol Clin North Am. 2016;54(4):639-648. doi:10.1016/j.rcl.2016.03.001

# THE ROLE OF PULMONARY BIOPSY IN THE DIAGNOSIS OF INTERSTITIAL LUNG DISEASES

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**Abstract**
**Background.** Granulomatosis with polyangiitis (GPA) is a rare autoimmune disease characterized by diverse clinical symptoms and radiological presentations, which often make diagnosis challenging. Pulmonary nodules associated with GPA can mimic malignancies or other pulmonary conditions, necessitating thorough evaluation to achieve a definitive diagnosis.
**Case Report**. A 45-year-old female presented with a two-month history of systemic symptoms and respiratory issues. Initially followed in the infectious diseases department, she was referred to our service with suspicion of lung cancer after inconclusive laboratory and imaging studies. Contrast-enhanced computed tomography (CT) revealed two opacities in the right lung with significant enhancement. Subsequent endoscopic biopsy confirmed the diagnosis of granulomatosis with polyangiitis. Treatment with corticosteroid and immunosuppressant was initiated, leading to clinical improvement.
**Conclusion**. The differential diagnosis of pulmonary nodules encompasses a wide range of conditions, including malignant tumors, infectious or non-infectious granulomas, and other entities such as bronchiolitis obliterans organizing pneumonia (BOOP), pulmonary infarction, or arteriovenous malformations. In patients without risk factors for malignancy, such as non-smokers, systemic symptoms can guide alternative diagnostic pathways. Pulmonary biopsy remains a cornerstone in cases where clinical, laboratory, and imaging findings are inconclusive. This case highlights the importance of multidisciplinary evaluation in diagnosing complex pulmonary conditions and tailoring appropriate treatment strategies.

**Key words:** pulmonary biopsy, ILD, granulomatous polyangitis

# ROLI I BIOPSISË PULMONARE NË DIAGNOZËN E SËMUNDJES INTERSTICIALE PULMONARE

**Hyrje**. Poliangiti granulomatoz (GPA) është një sëmundje autoimune e rrallë, e karakterizuar nga simptoma klinike dhe paraqitje radiologjike të ndryshme, të cilat shpesh e bëjnë diagnostikimin të vështirë. Nodujt pulmonarë të lidhur me GPA mund të imitojnë malinje ose kushte të tjera pulmonare, duke kërkuar një vlerësim të plotë për të arritur një diagnozë përfundimtare.
**Rasti Klinik**. Një paciente 45-vjeçare u paraqit me një histori 2-mujore të simptomave sistemike dhe problemeve respiratore. Fillimisht e ndjekur në departamentin e sëmundjeve infektive, ajo u referua në shërbimin tonë me dyshimin për kancer të mushkërive pas studimeve laboratorike dhe imazherike të pasakta. Tomografia e kompjuterizuar (CT) me kontrast zbuloi dy opacitete në mushkërinë e djathtë me përmirësim të dukshëm. Biopsia endoskopike pasuese konfirmoi diagnozën e Poliangiti granulomatoz. Trajtimi me kortikosteroide dhe imunosupresantë u nis, duke çuar në përmirësim klinik.
**Konkluzion**. Diagnoza diferenciale e nodujve pulmonarë përfshin një gamë të gjerë kushtesh, si tumoret malinje, granulomat infektive ose jo-infektive, dhe entitete të tjera si bronchioliti

obliterans me pneumoni organizuese (BOOP), infarkti pulmonar, ose malformimet arterio-venoza. Tek pacientët pa faktorë rreziku për malinje, si mos-pirësit e duhanit, simptomat sistemike mund të drejtojnë shtigje diagnostikuese alternative. Biopsia pulmonare mbetet një gur themeli në rastet kur gjetjet klinike, laboratorike dhe imazherike janë të pamjaftueshme. Ky rast nënvizon rëndësinë e vlerësimit multidisiplinar në diagnostikimin e kushteve komplekse pulmonare dhe përshtatjen e strategjive të duhura të trajtimit.

**Fjalë kyçe:** biopsi pulmonare, ILD, poliangiti granulomatose.

## Introduction

Pulmonary nodules are small abnormal areas (less than 3 cm) sometimes discovered incidentally during routine chest CT scans. They are usually non-malignant, and based on a scoring system, they are monitored with follow-up CT scans after 3–6 months to assess for size changes over time. However, nodules detected during lung cancer screening are typically considered malignant and are managed differently. Granulomatosis with polyangiitis (GPA), also known as Wegener's granulomatosis, is a necrotizing systemic vasculitis (1). Although diagnosing GPA remains challenging in clinical practice, non-pulmonary manifestations, serological tests, and histopathology obtained via endobronchial, transbronchial, or transthoracic approaches can aid in reaching a diagnosis (2,3). This article presents a clinical case diagnosed and treated in our service, following a multidisciplinary approach and based on available literature from online databases, regarding the challenges of diagnostic processes and disease management.

## Case presentation

This clinical case involves a 45-year-old female patient referred to our service from the Infectious Diseases Department, where she had been hospitalized for a prolonged febrile condition initially considered a viral infection. During her stay, she underwent a pulmonary CT scan, which revealed two pulmonary opacities in the right lung, raising suspicion of a malignant process, specifically lung cancer. Her two-month clinical history included various symptoms such as jaw pain, nasal congestion, and a feeling of ear blockage accompanied by hearing loss. She also reported recurrent episodes of high fever, reaching up to 39°C over the previous two weeks, which did not respond to different antibiotic treatments, either outpatient or during hospitalization. Laboratory examinations showed microcytic hypochromic anemia and elevated inflammatory markers, including CRP, D-dimer, fibrinogen, and ferritin. A urinalysis was normal, while total IgE levels were within acceptable limits. Tests for anti-echinococcus antibodies, direct sputum analysis, and GeneXpert for tuberculosis were all negative, ruling out common infectious causes. To refine the diagnostic process, the patient underwent a contrast-enhanced CT scan, which revealed a spiculated peripheral opacity in the third segment of the right lung, measuring 21x16 mm. This opacity demonstrated increased density after contrast injection, rising from 24 HUI to 45 HUI, further reinforcing suspicions of a malignant process.

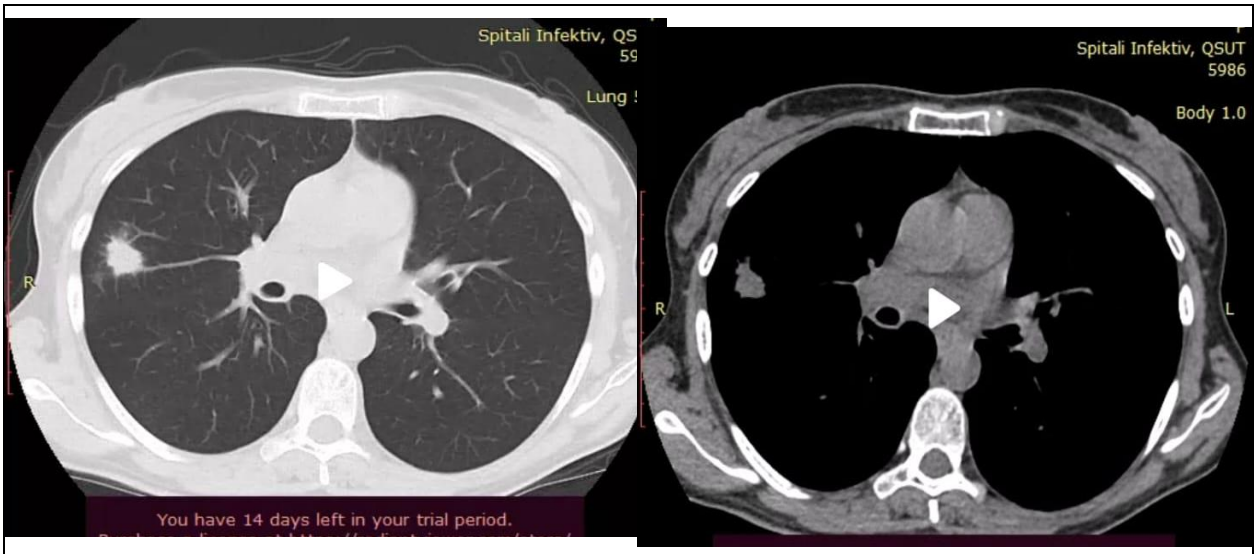



**Figure 1.** Under computerized tomography two opacities where noticed on the right lung



Figure 1. Endoscopic evaluation revealed infiltration of tracheal carina and right primary bronchus with necrotic elements on the surface.

Endoscopic evaluation identified infiltration of the tracheal carina extending toward the primary right bronchus, accompanied by visible necrotic elements on the mucosal surface. A biopsy was taken during this procedure and subsequently analyzed histopathologically. Concurrently, the patient was assessed by a rheumatologist, who requested a complete autoimmune panel. Meanwhile, treatment with Cefuroxime (750 mg), Prednisolone (50 mg daily), and supportive therapy was initiated. Within two days of starting treatment, the patient's febrile condition improved, and the fever did not recur.

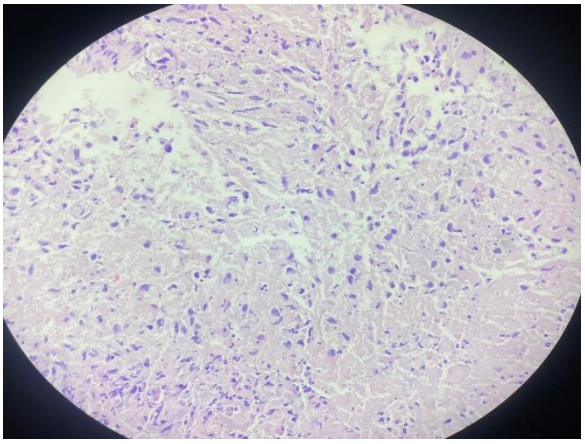


Figure 2 Pathological evaluation resulted as granulomatous necrotic inflammation with giant multinuclear cells.

The autoimmune panel was negative for ANA, RF, anti-CCP, ENA screen, anti-dsDNA, C3, and C4. However, PR3-ANCA tested positive, with a very high level of 356.09 RU/mL (normal value <20), suggesting the presence of an autoimmune pathology. Ten days later, histopathological analysis of the biopsy material revealed necrotizing granulomatous inflammation with multinucleated giant cells. These findings confirmed the diagnosis of Granulomatosis with Polyangiitis (GPA). The patient was treated with a corticosteroid regimen (75 mg daily, with a gradual dose tapering weekly) and immunosuppressants (Cyclophosphamide). Following an intensive treatment period, she was discharged from the hospital with significant improvement in her clinical and radiological condition. This case underscores the importance of a multidisciplinary approach and advanced diagnostic procedures in identifying and accurately treating rare pathologies such as Granulomatosis with Polyangiitis.

**Discussion**

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare systemic vasculitis that primarily affects small and medium-sized blood vessels, often involving the upper respiratory tract, lungs, and kidneys. It is characterized by the presence of necrotizing granulomas, vasculitis, and autoantibodies against proteinase 3 (PR3), known as anti-neutrophil cytoplasmic antibodies (ANCA). This case highlights the clinical, diagnostic, and therapeutic challenges associated with GPA, particularly in patients with overlapping characteristics that mimic malignancy (4).

**Clinical Presentation and Challenges**

The patient's presentation with prolonged fever, jaw pain, nasal congestion, and hearing loss posed an initial diagnostic dilemma. Such symptoms are nonspecific and can overlap with many conditions, including chronic infections, malignancies, or other systemic autoimmune diseases (5). GPA often manifests with upper respiratory tract symptoms that can mimic chronic sinusitis or middle ear infections, as seen in this case. Fever and systemic symptoms are also common and may lead to a misdiagnosis of infectious diseases in the early stages (6). Pulmonary involvement, as observed in this case with pulmonary nodules and infiltrates, further complicates the diagnostic process. Pulmonary nodules in GPA are usually bilateral and cavitary, but they may appear solid or spiculated, raising suspicion for malignancy, especially in patients without other risk factors for lung cancer (7). The radiological findings in this patient—spiculated opacities with contrast enhancement—highlight the overlap between the imaging characteristics of GPA and malignancies, often necessitating a tissue biopsy for a definitive diagnosis.

**Diagnostic Approach.**
The diagnostic evaluation in this case was comprehensive and systematic, involving laboratory, imaging, and histopathological investigations. Initial laboratory findings revealed anemia and elevated inflammatory markers (CRP, D-dimer, fibrinogen, ferritin), which are consistent with active inflammation but nonspecific. Notably, the autoimmune panel was crucial in narrowing the differential diagnosis. While most markers were negative, the highly elevated PR3-ANCA level (356.09 RU/mL, normal <20) strongly suggested GPA as the underlying etiology (8). Pulmonary biopsy remains the gold standard for diagnosing GPA, particularly when imaging and serological findings are inconclusive. The histopathological findings of necrotizing granulomatous inflammation and multinucleated giant cells confirmed the diagnosis in this case. The biopsy findings not only supported the diagnosis but also ruled out malignancy and infections such as tuberculosis, which were initially considered based on the patient's clinical presentation.

**Therapeutic Considerations**
The management of GPA involves immunosuppressive therapy aimed at inducing and maintaining remission. In this case, the patient was treated with high-dose corticosteroids (Prednisolone 75 mg daily) combined with Cyclophosphamide, a standard induction regimen for severe GPA (9). The patient responded well to this regimen, with rapid resolution of fever and improvement in clinical and radiological findings. Long-term management would involve transitioning to a maintenance regimen with less toxic agents, such as azathioprine or methotrexate, to minimize the risk of relapse (10).

**Importance of a Multidisciplinary Approach**
This case underscores the critical role of a multidisciplinary approach in diagnosing and managing complex cases of GPA. Collaboration among pulmonologists, rheumatologists, radiologists, and pathologists facilitated an accurate and timely diagnosis, allowing for the initiation of appropriate treatment. The involvement of a rheumatologist in the diagnostic process was particularly valuable, as it prompted the autoimmune panel testing that revealed the characteristic PR3-ANCA positivity.

**Differential Diagnosis and Broader Implications**
Pulmonary nodules and systemic symptoms require a broad differential diagnosis, including infections (e.g., tuberculosis, fungal infections), malignancies, and other autoimmune conditions such as sarcoidosis and eosinophilic granulomatosis with polyangiitis (EGPA). In this case, the absence of risk factors for malignancy (e.g., smoking history) and the presence of systemic symptoms (e.g., fever) directed clinicians toward a non-malignant etiology, further supported by PR3-ANCA positivity.
This case also highlights the need for heightened clinical suspicion for GPA in patients with unexplained systemic symptoms and multi-organ involvement. Delayed diagnosis can lead to significant morbidity, including permanent organ damage, particularly renal involvement, which fortunately was absent in this patient.

**Conclusions**
This case demonstrates the diagnostic and therapeutic challenges of GPA, particularly when presenting with features that mimic malignancy. Early recognition, multidisciplinary collaboration, and a systematic diagnostic approach were critical in achieving a favorable outcome. Future efforts should focus on improving diagnostic algorithms for systemic vasculitides to minimize delays in diagnosis and optimize patient outcomes.

**Conflict of interest**: None

**References:**


1. Puéchal X. Granulomatosis with polyangiitis (Wegener's). Joint Bone Spine. 2020 Dec;87(6):572-578. doi: 10.1016/j.jbspin.2020.06.005. Epub 2020 Jun 17. PMID: 32562697.
2. Yaseen K, Mandell BF. ANCA associated vasculitis (AAV): a review for internists. Postgrad Med. 2023 Jan;135(sup1):3-13. doi: 10.1080/00325481.2022.2102368. Epub 2022 Jul 21. PMID: 35831990.
3. Allen SD, Harvey CJ Imaging of Wegener's granulomatosis. Br J Radiol 2007;80:757–65
4. Garlapati P, Qurie A. Granulomatosis With Polyangiitis. [Updated 2022 Dec 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-
5. Witko-Sarsat V, Thieblemont N. Granulomatosis with polyangiitis (Wegener granulomatosis): A proteinase-3 driven disease? Joint Bone Spine. 2018 Mar;85(2):185-189. doi: 10.1016/j.jbspin.2017.05.004. Epub 2017 May 8. PMID: 28495524.
6. Falk, R. J., & Jennette, J. C. (2011). ANCA small-vessel vasculitis. New England Journal of Medicine, 365(19), 1785–1798. https://doi.org/10.1056/NEJMra1100352
7. King, T. E., Jr., Inoue, Y., & Lynch, D. A. (2013). Pulmonary involvement in vasculitis. European Respiratory Review, 22 (129), 131–139. https://doi.org/10.1183/09059180.00006112
8. Jennette, J. C., Falk, R. J., Bacon, P. A., Basu, N., Cid, M. C., et.al. (2013). 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis & Rheumatology, 65(1), 1–11. https://doi.org/10.1002/art.37715
9. Stone, J. H., Merkel, P. A., Spiera, R., Seo, P., Langford, C. A., et.al., & WGET Research Group. (2010). Rituximab versus cyclophosphamide for ANCA-associated vasculitis. New England Journal of Medicine, 363(3), 221–232. https://doi.org/10.1056/NEJMoa0909905
10. Yates, M., Watts, R. A., Bajema, I. M., Cid, M. C., et.al., (2016). EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Annals of the Rheumatic Diseases, 75(9), 1583–1594. https://doi.org/10.1136/annrheumdis-2016-209133

# AN ASSOCIATION OF HERPES VIRUS REACTIVATION AND ERYTHEMA MULTIFORME

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**Abstract**
**Introduction**: Erythema multiforme is a skin disease manifested with "target lesions" as an iris that affects skin and mucous system. It is an acute hypersensitivity reaction with various etiological factors and mostly due to infections such are herpes simplex virus, medications, autoimmune diseases, and malignancies. The diagnosis is based on clinical manifestations, symptoms and histopathology.
**Case Presentation**: In this article we report the case of a patient diagnosed with Erythema multiforme associated with reactivation of Herpes simplex virus. The biopsy of the skin confirmed the diagnosis of EM during the reactivation and positive serology of HSV. The treatment of the case consisted on the treatment of symptoms and the prophylactic treatment with acyclovir or valacyclovir for 6 months.
**Conclusions**: The prophylactic treatment of EM due to reactivation of HSV is a must for any clinician that treat patients with Erythema Multiforme.

**Keywords:** Erythema Multiforme, Herpes Simplex Virus, CD34+, Herpes Associated. Erythema Multiforme.

# SHOQËRIMI I RIAKTIVIZIMIT TË VIRUSIT HERPES ME ERITEMËN MULTIFORME.

**Abstrakt**
**Hyrje:** Erythema multiforme eshte nje semundje lekure qe manifestohet me 'lezione target" qe mund te prekin lekuren dhe mukozat. Eshte nje reaksion hipersensibiliteti me etiologji te ndryshme si semundje infektive, Herpes Simplex virus, medikamente, semundje autoimmune dhe semundje malinje. Diagnoza bazohet ne manifestimet klinike, simptomat dhe histopatologjine.
**Prezantim rasti**: Ne kete artikull ne raportojme nje rast klinik te diagnostikuar me Erytheme multiforme shoqeruar me riaktivizim te Herpes simplex virus. Biopsia e lekures konfirmon diagnozen e EM nderkohe qe ne serologji kemi rezultate pozitive per HSV. Trajtimi konsiston ne trajtim simptomatik dhe trajtim profilaktik me acyclovir ose valacyclovir per 6 muaj.
**Konkluzione**: Trajtimi profilaktik i EM nga ri aktivizimi i virusit HSV eshte nje domosdoshmeri per cdo mjek klinicist qe trajton pacient me EM me etiologji nga virusi HSV.

## Introduction

Erythema multiforme is a recurrent disease manifested with "target lesions" as an iris that affects skin and mucous system. It is an acute hypersensitivity reaction with various etiological factors

and mostly due to infections and drugs. Etiopathology is not well understood, but the most frequent etiologic factors reported are Herpes Simplex Virus, medicaments, autoimmune diseases, premalignancy conditions. (1,2) EM may occur at any age, and several reports suggest that males are affected more than females. (3) Clinical manifestations reported are erythema with different shades within the element, vesicula or bulla on the center. The disease affects or not oral cavity or other mucous area, genital, ocular, laryngeal, and esophageal mucosae.

**Case prescription**

A 28-year-old female patient presented to the Dermatology Department complaining of pruritic skin rashes on the face since the last 5 days after symptoms of weakness and fatigue in the prior days. On physical examination, there were multiple annular erythematous papules with central bullae and peripheral erythematous margins, localized on the face, and trunk. (Fig.1)



**Figure 1:** Erythematous papules with central bullae and peripheral erythematous margins, localized on the face and erosive lesions on the oral mucosa.

Intraoral examination revealed numerous painful erosions in the palate, buccal mucosae and on the lips. The patient referred for a history of recurrences of these oral lesions that were presented very often these last four years. Laboratory examinations showed normal levels of complete blood count, liver function, serum creatinine and electrolytes levels as well as the serological tests for Hepatitis B and C viruses and HIV infection. Serological test for Herpes Simplex Virus (HSV1) was positive. The main differential diagnosis was Erythema Multiforme, Pemphigus Vulgaris. To confirm the diagnosis a skin biopsy was performed on the oral mucosa. Direct immunofluorescence was also performed to exclude Pemphigus Vulgaris. The histological examination revealed dermal inflammatory infiltrate and edema of the lamina propria with perivascular infiltrate of mononuclear cells, features compatible with Erythema Multiforme.
Referring the anamnesis, clinical manifestations, and biopsy the diagnosis was Erythema Multiforme after the reactivation of Herpes Simplex Virus (Herpes Activation Erythema Multiforme HAEM). The patient was treated with prednisone 50 mg a day for 10 days, supportive

IV fluids, local antiseptics. Referring the history of recurrences, the patient was treated with valaciclovir 500 mg a day for 6 months. On a follow up after 3 months the patient denied any sign of recurrence.

**Discussion**

EM is diagnosed based on clinical manifestation (target lesions) and histopathology examination. Target lesions are erythematous lesions with 2-3 different concentric shades of pigment. On the center of the lesion is evident a bulla or vesicula. Based on the affection of mucous area EM is classified in EM major (with manifestations on skin & mucosa) and EM minor (without lesions on oral cavity or other mucosae). (4) Manifestations on oral cavity can be alone or may precede lesions on other sites. (3) At the beginning of the disease different differential diagnosis have to be taken in consideration; primary herpetic infection, hand-foot-and-mouth disease, erosive lichen planus, urticaria, lupus erythematosus, fixed drug eruption, cutaneous vasculitis, Sweet syndrome, mucositis due to methotrexate. (4, 5, 6,7) In cases of erosions of lips and oral mucosae direct immunofluorescence may help to differentiate with pemphigus vulgaris, paraneoplastic pemphigus, mucosal bullous pemphigoid, and linear IgA dermatosis.

Lesions may progress through erythematous macules presented to the skin and mucosae, to bullae, erosions and crusted lesions to the lips and mouth. Herpes Simplex Virus infection was reported as a most common cause in many publications. (8) Asier et al reported that 23% of patients were found to have associated HSV infection. (2, 3) EM typically follows a lesion of recurrent herpes simplex within 1 to 3 weeks. The interval usually is about 10 days. There is reported that lips are the most common site of preceding HSV infection in recurrent EM implicating HSV-1. (1) Other factors implicated in etiopathogenesis of EM are bacterial, viral, and fungal infections, drugs, radiation therapy, and emotional stress. (2,4,6)

**Table 1.** Etiological factors of Erythema Multiforme.

| **Infectious agents** | **Medications** |
|---|---|
| Herpes Simplex | Sulfonamides |
| Epstein Bar virus | Penicillins, Cephalosporins |
| Citomegalovirus | Quinolones |
| Varicella Zoster virus | Anticonvulsants |
| Mycoplasma pneumoniae | Analgesics |
| Streptococci | Anti-inflammatory Nonsteroidal |
| Fungal agents<br>Parasites | Antifungals |

The diagnosis is based on clinical view and histopathology examination as in our case report. The histopathology concluded in necrosis of some keratinocytes and epidermal damage. This damage is particularly noticed on the center of the target lesions of EM. (9, 10) In more severe cases with bulla and erosions were reported necroses of the whole dermis. (11)

The differences between EM and Steven Johnson Syndrome are not just referring the etiology where SJS is mostly caused by medicaments bur either referring the severity of the disease and the surface of the body affected in SJS that is around 10% or less. (1,6) Making the right decision for the treatment of EM is based on severity of the disease, mucosal involvement, reactivation, and risk factors. Most EM minor forms may regress within 2 to 4 weeks. If the manifestations are not severe it is recommended conservative care. In case of oral mucosal involvement, the symptomatic treatment includes topical analgesics and anesthetics and liquid foods. Patients are recommended to avoid spicy foods, acidic foods, and liquids. Systemic treatments, besides the supportive therapy

consist of corticosteroid therapy and in cases of secondarily infected lesions systemic antibiotics are also indicated.
When the suspected etiological factor is a specific medication, the main step of management is to stop the suspected drug and avoid the use of other drugs to prevent cross reactivity reactions. In cases of recurrent HSV episodes, antiviral therapy is indicated in order to prevent further recurrences. (12) In a double-blind placebo-controlled study conducted by Tatnall et al., which involved 20 patients with recurrent EM, where of 15 had a proven HSV association; it was shown superiority in the use of acyclovir in the prevention of EM episodes. Furthermore, the discontinuation of acyclovir resulted in clinical remission on some patients, instead of recurrences in all the patients treated with placebo. (13) For individuals facing HSV-related erythema multiforme (EM) who do not respond to standard antiviral treatments, alternative approaches include oral cyclosporine. Thalidomide, despite its known risk of birth defects, can also be used due to its ability to modulate TNFα. (4) Additionally, corticosteroid-sparing medications like dapsone, azathioprine, methotrexate, and mycophenolate mofetil are options worth considering for managing these difficult cases. (5) How is it explained the etiopathogenesis in the case of HSV and Herpes Associated EM? In a paper published by Miura et al 1992 was concluded that HSV persists in the skin sited of previous lesions for up to 3 months and as a conclusion was noted that the difference in Herpes Associated Erythema Multiforme HAEM patients were an inability to clear the virus. (15) A group of authors reported the implication of CD34+ cells in HAEM pathogenesis. HSV-associated EM (HAEM) lesions are virus-free (15, 16), but they contain HSV DNA fragments, most often comprising sequences that encode the viral DNA polymerase (Pol). (15, 17-23) The percentages of circulating CD34+ (and CD34+/CLA+) cells were significantly higher in HAEM patients at the time of acute lesions. A similar increase was not seen for HSV patients. (24)

**Conclusions**

The prophylactic treatment of EM due to reactivation of HSV is a must for any clinician that treat patients with Erythema Multiforme. The use of antiviral therapy minimizes the recurrences of the disease and has a great impact in the quality of life of the patients.

**Conflict of interests:** No conflict of interests is declared**.**

**References:**


1. Kokuba H, Aurelian L, Burnett JW. Herpes simplex virus associated erythema multiforme (HAEM) is mechanistically distinct from drug-induced erythema multiforme: interferon-γ is expressed in HAEM lesions and tumor necrosis factor-α in drug-induced erythema multiforme lesions. J Invest Dermatol. 1999;113(5):808-15.
2. Lamoreux MR, Sternbach MR, Hsu WT. Erythema multiforme. Am Fam Physician. 2006;74(11):1883-8.
3. P. Farthing, J. V. Bagan, and C. Scully, “Number IV erythema multiforme,” Oral Diseases, vol. 11, no. 5, pp. 61–267, 2005.
4. M. Lerch, C. Mainetti, B. T. Beretta-Piccoli, and T. Harr, “Current perspectives on erythema multiforme,” Clinical Reviews in Allergy & Immunology, vol. 54, no. 1, pp.177–184, 2018.
5. L. Ayangco and R. S. Rogers 3rd, “Oral manifestations of erythema multiforme,” Dermatologic Clinics, vol. 21, no. 1, pp. 195–205, 2003.

6. P. O. Fritsch and R. R. Maldonado, “Erythema multiforme,” in Dermatology in General Medicine, vol. 2, T. B. Fitzpatrick, A. Z. Eisen, K. Wolff, I. M. Freedberg, and K. F. Austen, Eds., pp. 636–643, McGraw-Hill, New York, NY, USA, 4th edition, 1993.
7. S. D. Helander and R. S. Rogers III, “The sensitivity and specificity of direct immunofluorescence testing in disorders of mucous membranes,” Journal of the American Academy of Dermatology, vol. 30, no. 1, pp. 65–75, 1994.
8. Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. Arch Dermatol. 1995 May;131(5):539-43. PMID: 7741539.
9. Weston WL. Herpes-associated erythema multiforme. J Invest Dermatol. 2005;124(6):xv-xvi.
10. Ng PP, Sun YJ, Tan HH, Tan SH. Detection of herpes simplex virus genomic DNA in various subsets of Erythema multiforme by polymerase chain reaction. Dermatology. 2003;207(4):349-53.
11. Nanda S, Pandhi D, Reddy BS. Erythema multiforme in a 9-day-old neonate. Pediatr Dermatol. 2003;20(5):454-5.
12. F. Drago, A. Parodi, and A. Rebora, “Persistent erythema multiforme: report of two new cases and review of literature,” Journal of the American Academy of Dermatology, vol. 33, no. 2, pp. 366–369, 1995.
13. F. M. Tatnall, J. K. Schofield, and I. M. Leigh, “A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme,” The British Journal of Dermatology, vol. 132, no. 2, pp. 267–270, 1995.
14. T. Bashir, S. Arti, G. Jyoti, Y. Monu, K. Vijay, and A. Naeem, “Erythema multiforme: a case report,” International Journal of Scientific Study, vol. 2, no. 7, pp. 249–251, 2014.
15. Miura, S., C. C. Smith, J. W. Burnett, and L. Aurelian. 1992. Detection of viral DN within skin of healed recurrent herpes simplex infection and erythema multiforme lesions. J. Investig. Dermatol. 98:68–72
16. Aurelian L, Kokuba H, Burnett JW. Understanding the pathogenesis of HSV-associated erythema multiforme. Dermatology. 1998;197(3):219-22. doi: 10.1159/000018000. PMID: 9812024.
17. Darragh TM, Egbert BM, Berger TG, Yen TS. Identification of herpes simplex virus DNA in lesions of erythema multiforme by the polymerase chain reaction. J Am Acad Dermatol. 1991 Jan;24(1):23-6. doi: 10.1016/0190-9622(91)70003-k. PMID: 1847956.
18. Aslanzadeh J, Helm KF, Espy MJ, Muller SA, Smith TF. Detection of HSV-specific DNA in biopsy tissue of patients with erythema multiforme by polymerase chain reaction. Br J Dermatol. 1992 Jan;126(1):19-23. doi: 10.1111/j.1365-2133.1992.tb08397.x. PMID: 1311188.
19. Imafuku S, Kokuba H, Aurelian L, Burnett J. Expression of herpes simplex virus DNA fragments located in epidermal keratinocytes and germinative cells is associated with the development of erythema multiforme lesions. J Invest Dermatol. 1997 Oct;109(4):550-6. doi: 10.1111/1523-1747.ep12336800. PMID: 9326389.
20. Kokuba H, Imafuku S, Huang S, Aurelian L, Burnett JW. Erythema multiforme lesions are associated with expression of a herpes simplex virus (HSV) gene and qualitative alterations in the HSV-specific T-cell response. Br J Dermatol. 1998 Jun;138(6):952-64. doi: 10.1046/j.1365-2133.1998.02260.x. PMID: 9747355.
21. Aurelian L, Ono F, Burnett J. Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): a viral disease with an autoimmune component. Dermatol Online J. 2003 Feb;9(1):1. PMID: 12639459.
22. Aurelian L, Ono F, Burnett J. Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): a viral disease with an autoimmune component. Dermatol Online J. 2003 Feb;9(1):1. PMID: 12639459.

23. Sun Y, Chan RK, Tan SH, Ng PP. Detection and genotyping of human herpes simplex viruses in cutaneous lesions of erythema multiforme by nested PCR. J Med Virol. 2003 Nov;71(3):423-8. doi: 10.1002/jmv.10502. PMID: 12966549.
24. Fumitake Ono, Bhuvnesh K. Sharma, Cynthia C. Smith, Joseph W. Burnett, Laure Aurelian. CD34+ Cells in the Peripheral Blood Transport Herpes Simplex Virus DNA Fragments to the Skin of Patients with Erythema Multiforme (HAEM), Journal of Investigative Dermatology,Volume 124, Issue 6, 2005, Pages 1215-1224, ISSN 0022-202X, https://doi.org/10.1111/j.0022-202X.2005.23712.x.

# EFFICACY OF HYDROXYCHLOROQUINE IN SYSTEMIC LUPUS ERYTHEMATOSUS WITH HEMATOLOGICAL INVOLVEMENT.

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**Abstract**

**Introduction:** Systemic Lupus Erythematosus is an autoimmune disease with systemic multiorgan involvement that requires continuous follow-up to control the clinical course of the disease. Based on the current problems in our country, this paper aims to highlight the role of Hydroxychloroquine as a highly effective immunosuppressive therapy in the treatment of SLE and the hematological complications that are caused.

**Objectives:** The aim of this study is to evaluate the effectiveness of Hydroxychloroquine in the treatment of patients with Hematological involvement. Determination of the treatment protocol based on clinical signs and current evidence according to the Eular system. Evaluation of comorbidities from Hydroxychloroquine therapy and combination therapy with Immunosuppressants such as Methotrexate, Azitropine, Mycophenolate and Corticosteroids.

**Materials and methods**: For the realization of this work, real data obtained from a contigent (group) of 120 cases (patients) hospitalized at the Rheumatology ward at the "Mother Teresa" University Hospital in Tirana. At the same time, cases presented at the Consultation Center at the QSUT in Tirana during the time period April 2021-April 2024 were also used. The data were processed according to the SPSS statistical program.

**Study results**: From the data of our study it results that in 89% of cases the patients are female, the average age of the patients is 45.2±10.2 years of patients with SLE. Based on the study of the laboratory characteristics of SLE patients with Hematological involvement we have the presence of Anemia, Chronic Anemia has appeared in 72% of the patients, that from Fe deficiency in 46.6% of the patients who have developed anemia and AIHA in 7% of them. PRCA resulted positive in 7 clinical cases, 19 patients have developed leukopenia and 50 patients developed thrombocytopenia. Description of the results of the study regarding to the effectiveness of therapy in patients with SLE resulted that the use of hydroxychloroquine as a single and combined therapy reduces the activity of the disease in 78% of cases by inhibiting clinical signs and improving the course of the disease.

**Conclusions:** Based on the results of our study, the importance of monitoring the clinical course of patients in time is highlighted, enabling the combination of therapy in the initial phase of disease treatment and maintenance therapy.Hydroxychloroquines resulted in effective therapy both alone and in combination in the treatment of SLE patients with hematological involvement.

**Keywords:** Systemic Lupus Erythematosus, Hematological involvement, Hydroxychloroquines, Effectiveness.

# EFIKASITETI I HYDROXYCHLOROQUINES NË LUPUS ERITEMATOZ SISTEMIK ME PREKJE HEMATOLOGJIKE.

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**Abstrakt**
**Hyrje:** Lupusi Eritematoz Sistemik është një sëmundje autoimune me prekje sistemike multiorganore i cili kërkon një ndjekje të vazhdueshme për të mbajtur në kontroll dekursin klinik të sëmundjes.
Bazuar në problematikën aktuale në vëndin tonë ky punim synon të evidentojë rolin e Hydroksiklorikinës si terapi imunosupresore me efektshmëri të lartë në trajtimin e LES dhe komplikacioneve me natyrë Hematolgjike që shkaktohen.
**Objektiva:** Qëllimi i këtij studimi është vlerësimi i efektshmërisë së Hydroxychloroquinës në trajtimin e pacientëve me prekje Hematologjike. Përcaktimi i protokollit të trajtimit bazuar në shenjat klinike dhe evidencat aktuale sipas sistemit të Eularit. Vlerësimi i komobirditeteve nga terapia me Hidroksiklorikinë dhe terapia e kombinuar me Imunosupresorë si Metotrexate, Azitriopinë, Mycofenolate dhe Kortikosteroidë.
**Metodologji:** Për realizimin e këtij punimi u përdorën të dhëna reale të marra nga një kontigjent (grup) prej 120 rastesh (pacientësh) të shtruar pranë pavionit të Reumatologjisë në Spitalin Universitar "Nënë Tereza" në Tiranë. Në të njëjtën kohë, u shfrytëzuan edhe rastet e paraqitura në Qëndrën e Konsultave në QSUT në Tiranë gjatë periudhës kohore në periudhën Prill 2021-Prill 2024.Të dhënat u përpunuan sipas programit statistikor SPSS.
**Rezultatet e studimit:** Nga të dhënat e studimit tonë rezulton se në 89% të rasteve pacientët janë femra, mosha mesatare e pacientëve është 45.2±10.2 vjec të pacientëve me LES. Në bazë të studimit të karakteristikave laboratorike të pacientëve LES me prekje Hematologjike kemi prani të Anemisë, Anemia kronike është shfaqur në 72% të pacientëve, ajo nga mungesa e Fe në 46.6% të pacientëve që kanë zhvilluar anemi dhe AIHA në 7% të tyre. PRCA rezultoi pozitive në 7 raste klinike, 19 pacientë kanë zhvilluar leukopeni dhe 50 pacientë zhvilluan trombocitopeni. Përshkrimi i rezultateve të studimit lidhur me efektshmërinë e terapisë në pacientët me LE rezultoi që përdorimi i hidroksiklorikinës si terapi e vetme dhe e kombinuar ul aktivitetin e sëmundjes në 78% të rasteve duke frenuar shenjat klinike dhe duke përmirësuar ecurinë e sëmundjes.
**Konkluzione:** Në bazë të rezultateve të studimit tonë evidentohet rëndësia e ndiekjes së dekursit klinik të pacientëve në kohë duke mundësuar kombinimin e terapisë në fazën fillestare të trajtimit të sëmundjes dhe terapisë mbajtëse. Plaquenili rezultoi terapi e efektshme qoftë e vetme dhe e kombinuar në trajtimin e pacientëve LES me prekje hematologjike.

**Fjalë kyce:** Lupus Eritematoz Sistemik, prekje Hematologjike, Hydroxychloroquines, Efektshmëri.

## Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug originally used for the treatment of Plasmodium parasitic infection, from which the drug class derives its name. (1,6,8)
Beyond its initial indication as an antimalarial, HCQ has been used in autoimmune and infectious diseases, as well as in metabolic or neoplastic disorders. Based on recent studies, clear benefits were reported mainly in Systemic Lupus Erythematosus (SLE). Our article focuses on the value of

the drug in SLE patients with hematological involvement.

**Objectives**

The aim of this study is to evaluate the effectiveness of Hydroxychloroquine in the treatment of patients with Hematological involvement. Determination of the treatment protocol based on clinical signs and current evidence according to the Eular system. Evaluation of comorbidities from Hydroxychloroquine therapy and combination therapy with Immunosuppressants such as Methotrexate, Azitropine, Mycophenolate and Corticosteroids.

**Materials and methods**

Real data obtained from a contigent (group) of 120 cases (patients) admitted near the Rheumatology ward at the "Mother Teresa" University Hospital in Tirana were used for the realization of this paper. At the same time, the cases presented at the Consultation Center at the QSUT in Tirana during the period April 2021-April 2024 were used. The data were processed according to the SPSS 2022 statistical program. Based on the clinical evidence, it was possible to evaluate the clinical signs of the patients according to the SLEDAI model.

**SLEDAI** Assessment (5)

The SLEDAI assessment was performed for each patient to enable the generalization of as much real data as possible regarding the course of the disease, its management and the combination of therapy based on clinical and laboratory data. (Below is the type card, the data of which were used to carry out the statistical processing of the paper.)

**Table nr 1** The SLEDAI type card that was used in our study.

| Elements | Description | Points |
|---|---|---|
| **Convulsions** | Immediate onset, without metabolic, infectious or drug-related causes | **8** |
| **Psychosis** | Inability to reason and perceive the real surrounding environment; including hallucinations, associative disorders, illogical thinking, and catatonic or strange behavior, certainly in the absence of uremia or medications. | **8** |
| **Organic brain damage syndrome** | Alteration of mental function characterized by poor memory, clouding of consciousness accompanied by loss of ability to concentrate and react to the surrounding environment plus at least two of the following elements: loss of continuity of thought, incoherent speech, insomnia at night or being sleepy during the day, and increased or decreased psychomotor activity, in the absence of infectious, metabolic, or drug causes | **8** |
| **Visual** | Retinal changes due to LES deposits accompanied by retinal hemorrhage, serous or hemorrhagic choroid exudate, otic neuritis (in the absence of infectious, drug-related, or HTN causes) | **8** |
| **Cranial nerve** | Sudden onset of a sensory or motor neuropathy | **8** |

| | | |
|---|---|---|
| | involving the cranial nerves | |
| **Headache** | Headache in lupus is persistent, severe; may be migraine-like in nature and does not respond to analgesics. | **8** |
| **AVC** | Immediate onset; rule out atherosclerosis | **8** |
| **Vaskulitis** | Ulcerations, gangrene, soft nodules on fingers, periungual infarctions, subungual hemorrhage, vasculitis confirmed by biopsy or angiogram | **8** |
| **Arthritis** | Affection of more than two joints with inflammatory pain accompanied by swelling | **4** |
| **Myositis** | Muscle pain associated with weakness of the extremities and increased levels of aldolase/creatine phosphokinase; electromyographic changes on EMG; myositis on biopsy | **4** |
| **Crust** | Containing blood, granules, or erythrocytes | **4** |
| **Haematuria** | > 5 erythrocytes per field in complete urine (exclude causes of kidney stones) | **4** |
| **Proteinuria** | > 0.5 g in 24-hour urine | **4** |
| **Pyuria** | > 5 leukocytes per field (exclude infectious causes) | **4** |
| **Molar rash** | Sudden onset of a rash of an inflammatory nature | **4** |
| **Alopecia** | Abnormal diffuse hair loss | **4** |
| **Mukosis of nose/mouth** | Appearance of ulcerative phenomena in the mouth or nose | **4** |
| **Pleuritis** | Chest pain accompanied by pleural effusion and pleural thickening | **4** |
| **Pericarditis** | Chest pain accompanied by pericardial effusion, confirmed by ultrasound and ECG | **4** |
| **Hipokomplementemia** | Decreased levels of C3 or C4 | **2** |
| **Increase DNA binding capacity** | > 25% evidenced in laboratory techniques | **2** |
| **Temperature** | > 38 ˚C in the absence of infectious causes | **1** |
| **Thrombocitopeny** | < 100,000 platelets | **1** |
| **Leukopeny** | **< 3000/mm 3 (exclude drug causes)** | **1** |

**Study results**

Of the 120 patients included in this study, 107 (89%) individuals were female versus 13 (11%) male subjects. Overall, the mean age of the patients included in the study was 45.2 years and there was a significant difference in the mean age value according to the gender of the patients (in males, the mean age was: 56.2 years, while in females the mean age was: 39.5 years).

The mean age of male patients was 63.7±11.2 years, while the mean age of female patients was 45.3±14.5 years.

There was evidence of a statistically significant difference in the mean age value by gender: thus, the mean age value was significantly higher in males compared to females (Student's T-test: P<0.001; a similar result was obtained by the Mann-Whitney test: P<0.001).

**Table nr 2.** Age distribution among patients in the study

| Ages | | Number | Percentage |
|---|---|---|---|
| Valid | <=17 | 1 | 1.2 |
| | 18-25 | 18 | 15 |
| | 26-35 | 34 | 28.3 |
| | 36-45 | 13 | 10.8 |
| | 46-55 | 37 | 30.8 |
| | 56-65 | 15 | 12.5 |
| | 66-75 | 2 | 2.4 |
| Total | | 120 | 100.0 |

As can be seen from the results of the study, the highest frequency of cases belongs to the age group 46-55 years, 30.8%, followed by 26-35 with 28.3% patients. In a clinical surveillance based on the factors that trigger the outbreak of SLE, these age groups have the highest incidence of cases.

The average age in women is lower than in male patients and this is also due to the greater prevalence of autoimmune diseases affecting the female gender. (2)
Compared to current studies, LES appears in female patients more than males. Even in our study, the largest number of cases is in female patients 89% females. (3)
The clinical signs of the patients included in the study are presented in the table below.

**Table 3.** Clinical manifestation:

| Clinical manifestation | Raste në % | Clinical manifestation | Raste në % |
|---|---|---|---|
| Joint pain | **72%** | **Temperature** | **15%** |
| Leukopenia | **48%** | **LE cutaneous** | **11%** |
| Butterfly rash | **43%** | **Renal disfunction** | **10%** |
| Alopecia | **36%** | **'Le Diskoid' lesions** | **8%** |
| Oral ulcerations | **27%** | **Seizuritis** | **5%** |
| Lupus nephritis | **22%** | **Phericarditis** | **5%** |
| Pleural effusion /perikardial | **16%** | **Autoimun hemolysis** | **4%** |
| Thrombocytopenia | **36%** | **Psychosis** | **2%** |

The clinic of LES begins with fatigue, body weakness, temperature, fever of an unknown nature,

then the clinical signs become more evident and correlate with the diagnosis. (1,2)Thus, in our study, the most pronounced and general clinical manifestations are joint pain, leukopenia, butterfly rush, oral ulcerations, nephritis etc. As can be seen from the percentage of cases, the patients' clinic is diverse, with a combination of one or more clinical signs.This will be more explained in the material discussion.
SLE presents a diverse clinical course where clinical manifestations can orient from the beginning towards the diagnosis and on the other hand some independent clinics develop as an early sign of SLE. Based on contemporary literature (2) but also the results of the study we have treated the number of cases for each symptom that our patients have referred, which are presented below:
Systemic lupus erythematosus as a multiorgan disease exhibits extensive clinical symptomatology even in the cases taken into the study. Below are presented the secondary clinical signs that were identified in our work, not with a high frequency but are in line with the studies conducted for this diagnosis.

**Table nr 4** presents cases of the appearance of clinical symptoms in a broader spectrum of the disease and extended over time.

| The system where clinical signs developed | Symptoms | Nr of cases | Cumulative % |
|---|---|---|---|
| **Gastrointestinal** | Dysfagia | 9 | 7.5 |
| **Oral** | Ulcerations of oral mucosa | 13 | 10.8 |
| **Respirator** | Dyspnea | 15 | 12.5 |
| **Neurologic** | Numbness of the hands | 22 | 18.3 |
| **Haematologic** | Pale face, fatigue | 35 | 29 |
| **Digities** | Puffy finger | 13 | 10.8 |

**Hematological manifestations in systemic lupus erythematosus**
They are frequently encountered in the clinic and range from mild to severe. Therefore, treatment approaches are needed; biologic drug therapy has shown good results in improving hematological parameters but further studies are needed on the management modalities with Hydroxychloroquine. (3,4,6)
The most prominent hematological manifestations of SLE in our study population are anemia, leukopenia, thrombocytopenia. The bone marrow (BM) is also considered a target organ in SLE and features such as myelofibrosis, aplastic anemia, and pure red cell aplasia. Thus, we will briefly review the pathogenesis and management of specific hematological manifestations in the patients studied. (4)

**Anemia** Anemia is common, affecting more than 50% of patients throughout the clinical course. Anemia is defined as a hemoglobin level of less than 12 g/dl in women and 13.5 g/dl in men. In patients with SLE, it may be immunological or non-immunological.

**Chronic anemia** is the most common type of anemia in SLE patients studied, present in 2/3 of cases or 72%. It usually presents as normocytic and normochromic anemia, with normal or elevated serum ferritin values and a normal BM. The etiology of chronic anemia in Systemic Lupus Erythematosus is not yet fully understood, but it appears to be related to alterations in iron homeostasis, inadequate erythropoietin response or activity, and impaired erythropoiesis.

**Iron deficiency anemia,** in our study population, low blood Fe levels are common in patients with SLE, affecting about g78 patients with anemia or 46.6% of SLE patients. Based on the clinical history of the patients and the questionnaire developed for the clinical course over time, iron deficiency anemia is associated with chronic gastrointestinal bleeding as a complication in those patients who have been treated with nonsteroidal anti-inflammatory drugs and glucocorticoids.

**Autoimmune hemolytic anemia** (AIHA) Hemolytic anemia with reticulocytosis is included in both the ACR and SLICC. Autoimmune hemolytic anemia (AIHA) is caused by antibodies that damage red blood cells (RBCs) in a complement-dependent or complement-independent manner. AIHA may be the first manifestation of SLE and may occur several years before the diagnosis of SLE is made. Also in our case, in 7 patients out of 12 cases of SLE-related AIHA, anemia had begun before the patient was diagnosed with SLE. Its prevalence varies, probably due to the different diagnostic criteria for AIHA. Patients who presented with anemia before the diagnosis of SLE had severe hemolytic anemia (defined by hemoglobin <8.0 g/dl, in the presence of a positive direct antiglobulin test (DAT), an increased reticulocyte count, and a decrease in hemoglobin by 3.0 g/dl within a 1-week period (2 patients who confirmed it through hospitalization medical records, increased conjugated bilirubin and reticulocyte count >5%) was identified in 4 (%) patients.

**Pure red cell aplasia** (PRCA) Characterized by normocytic normochromic anemia and reticulocytopenia, with severe aplasia or hypoplasia of the red cell lineage, while the leukocyte and megakaryocyte lineages in the BM remain normal. In most cases, PRCA is diagnosed simultaneously with or shortly after the diagnosis of SLE. The pathogenesis of PRCA is diverse and includes genetic defects affecting the erythropoietic lineage, viral infections (such as parvovirus B19), and autoimmune factors. Aplastic anemia is characterized by pancytopenia with a low reticulocyte count. It is rare in SLE, with only 10 cases reported.

**Leukopenia** In the study population, it turns out that we have 19 cases with leukopenia, with values at levels <4000/mm3 and lymphopenia at levels <1500/mm3 in at least 12 cases. Similarly, in the SLICC classification criteria, leukopenia (<4000/mm3 in at least 5 cases) and lymphopenia (<1000/mm3 at least 2 times) are also part of the classification criteria for SLE with hematological involvement.

**Immune thrombocytopenia in SLE** Immune thrombocytopenia is an immune-mediated disorder that presents as primary (P-ITP) characterized by isolated thrombocytopenia. Immune thrombocytopenia in SLE is a common clinical manifestation, defined by a platelet count <100x109/mm3 with no other identifiable cause. In our study, 50 of 120 patients had thrombocytopenia. Of these 50 patients, 54% had platelet counts between 50 and 100 x 109/mm3, 18% had counts between 20 and 50 x 109/mm3, and 28% had platelet counts less than 20x109/mm3.
Antiplatelet autoantibodies are present in up to 60% of patients with SLE, the majority of which are IgG (60%) (23% are IgM). In P-ITP, the antigens for antiplatelet antibodies are glycoprotein IIb/IIIa (GpIIb/IIIa) and membrane glycoprotein (αIIaβ3integrin), and they can also be seen in patients with SLE. SLE patients with thrombocytopenia are more often positive for lupus anticoagulant, and higher levels of IgM ACA have been associated with a possible role of aPL in its pathogenesis.

**Table nr 5.**Thrombocytopenia in SLE patients

| | **Nr of cases** | **Nr of cases in %** |
|---|---|---|
| **Positive thrombocytopenia** | 50 | 41.6 |
| **Negative thrombocytopenia** | 70 | 58.4 |
| **Total** | 120 | 100% |

| Nr of thrombocytes | **Nr of cases in %** | **Nr of cases** |
|---|---|---|
| **50 to 100 x 109 /mm3,** | 54 | 27 |
| **20 to 50 x 109 /mm3** | 18 | 9 |
| **Less than 20x109 /mm3** | 28 | 14 |
| **Total** | 100% | 50 |

**Imunological Examinations**

The patients performed a series of laboratory examinations such as complete blood, leukocyte formula, PCR, FR, etc., in which the findings were identified, but because they are not the focus of our study, we did not stop to analyze and interpret them. Valuable examinations in the diagnosis of SLE are immunological analyzes ANA, Anti ds DNA, CD3, CD4, ENA. (16)

They are the most valuable diagnostic mediators to determine the aggressiveness and course of the disease from diagnosis, to follow-up and provide an indication regarding the benefits of drug therapy. In the patients studied, the reference examinations on which we are based are ANA, Anti ds DNA, CD3, CD4, ENA. (17)

Thus, according to clinical evidence, except the medical records, laboratory examinations ANA were performed as an examination from 120 patients, from which it resulted positive in 98 patients, negative in 22 patients.

**Anti ds DNA**, the DNA antibody, is the second immunological parameter taken in the study. As an examination, it has value in following the progress of SLE, but Anti ds DNA does not always provide information on the activity of the disease, so a negative Anti ds DNA does not exclude Lupus.(17)

Based on the data of our examination, 110 patients underwent the examination, from which 86 patients resulted positive and 24 patients negative. There is a correlation between contemporary literature and the scientific evidence of the study.

**The ENA** assessment was performed in 109 patients in total out of 120 patients included in the study, from which it resulted positive in 78 cases and 31 cases ENA resulted negative according to the data of the patient cards included in the study. The lack of assessment of this parameter in 100% of the population included in the study is multifactorial and is open to discussion.

**The assessment of monoclonal antibodies CD3, CD4** in the patients included in the study resulted in a positive result in 72% of cases 86 patients, where C3 is presented with increased values in 22 patients, C4 It is important to evaluate the antibodies as it helps in the scientific evidence on the correlation of the positive results of the immunological examinations and the progress of the disease. is presented with increased values in 18 patients.

**Treatment and complications in midterm and long term usage of medications**

In patients included in the study, the treatment protocols were applied according to the latest EULAR guidelines. The focus of the study is the use of hydroxychloroquine and its effectiveness in inhibiting the clinical course of SLE. A careful assessment has been made for each patient and

special treatment protocols have been drawn up. It is understood that difficulties have been encountered in the periodic follow-up of patients as a result of not appearing in the hospital, not performing specific examinations which hinder to some extent the accurate interpretation of the data.(7,8)
Medical therapy applied in SLE patients with Hydroxychloroquine as a single therapy and its combination with Immunosuppressants such as Methotrexate, Mycophenolate, Azathioprine and Corticosteroids Prednisone and Medrol. (3,7)

**Table nr 6.** Description of therapy

| Therapy | Patients number |
|---|---|
| **Plaquenil 200 mg** | 12 |
| **Plaquenil 200 mg + Prednisone 5 mg** | 30 |
| **Plaquenil 200 mg + Mycophenolate 500 mg+ Medrol 4 mg** | 12 |
| **Plaquenil 200 mg+ Medrol 4 mg** | 21 |
| **Plaquenil 200 mg + Azatiopinë 50mg+ Prednisone 5 mg** | 23 |
| **Plaquenil 200 mg+ Azatiopinë 50 mg + Medrol 4 mg** | 14 |
| **Prednisone 5 mg / Medrol 4 mg** | 8 |

The combination therapy was adapted based on the clinical and laboratory evidence of the patients, the international treatment protocols according to Eular and the assessment of disease activity using the SLEDAI index. In general, during the period under study, the treatment was started in low doses and remained under control; in patients who have shown a lack of response to therapy, the dose of the drug has been increased or we have combined medications with the aim of activating the inhibition mechanisms.
In addition, the treatment was carried out under medical surveillance through laboratory examinations (complete blood) in cases where we encountered thrombocytopenia, leukopenia or unjustified forms of anemia.Table nr 7 summarizes the causative mechanisms that have induced hematological abnormalities affecting RBC in the patients studied.

**Table nr 7**. Anemia in LES

| **RBC ALTERATIONS IN SLE PATIENTS** |
|---|
| **Causes of anemia** |
| • **Chronic anemia**<br>• **Low blood iron levels**<br>  ○ **Blood loss (GI, menorrhagia)**<br>  ○ **Decreased absorption of Fe in the intestines**<br>• **Autoimmune hemolytic anemia**<br>• **Microangiopathic hemolytic anemia**<br>• **Red blood cell aplasia**<br>• **Shkaqe të tjera të anemisë**<br>  ○ **Nutritional deficiencies (Vitamin B12, Folate)**<br>  ○ **Other immune blood disorders (Pernicious anemia)**<br>  ○ **Iatrogenic ASA,CYC**<br>  ○ **Anemia in pancytopenia associated with disorders: Myelofibrosis, Thrombotic thrombocytopenic purpura** |

In this spectrum of hematological changes affecting the Leukocyte formula, the treatment protocol

implemented in patients is presented in

**Table 8:**

| **Treatment of Anaemia** | | |
|---|---|---|
| **Treatment** | Indications | Discussion |
| **Glucocorticosteroids** | First-line therapy<br>Dose: 1mg/kg/day | □ After 3 weeks of treatment<br>□ Prednisone > 15 mg/day<br>□ >0.1mg/kg/day prednisone equivalent to maintenance therapy |
| **AZAs** | To promote the remission phase | We have no evidence in AIHA. |
| **CSAs** | To induce remission in refractory cases.<br>Discontinuation may be difficult. | Evidence in refractory AIHA, Immune thrombocytopenia and Evans syndrome. |
| **CYC** | Për të nxitur remisionin në rastet refraktare | In patients who underwent high-dose CYC treatment in AIHA:<br>□ All became transfusion independent.<br>□ 2/3 of patients went into complete remission (5P-AIHA and 1 S-AIHA). |
| **CNIs** | Possible adjunctive treatment when other drugs are considered with pronounced toxicity. | Immediate benefit in 1/3 of patients with AIHA.<br>Regarding the response:<br>□ Hepatomegaly.<br>□ Low pre-treatment Hb (6-7g/dl). |
| **Hydrpchlorciquine** | Sporadic adjunctive use as first line of treatment | 17 patients (10 with antibody positive AIHA, 5 who responded well to prednisone and 2 with refractory AIHA):<br>□ Better responses.<br>□ Successful as maintenance therapy. |
| **Plasma transfusion** | Pre-transfusion use of RBCs<br>without benefit. | 19 patients underwent a total of 38 plasma transfusion sessions:<br>□ There was no significant increase in Hb in patients who received plasma before red blood cell transfusion |
| **Mycophenolate** | Induces the remission phase | □ 13 patients had >1.5 g/dL increase in Hb and >50% reduction in reticulocyte count.<br>Leukocyte cell changes in patients with systemic lupus erythematosus.<br>□ 2 patients who did not respond had AIHA with<br>positive IgG autoantibodies. |
| | | |

**Table nr 9** summarizes the changes in leukocytes in SLE patients with hematological involvement.

| Changes in leukocyte formula in SLE patients |
|---|
| Factors that cause leukopenia<br>▪ Neutropenia<br>**Immune mediators**<br>**Infections**<br>**Iatrogenic (AZA, CYC)**<br>▪ Lymphopenia<br>**Immune mediators**<br>**Viral infections**<br>**Iatrogenic** |
| Factors that cause leukocytosis<br>▪ **Infections**<br>▪ **Disease activity**<br>▪ **Iatrogenic (Use of IG)** |

**Table nr 10** presents the treatment for cases with thrombocytopenia in the setting of SLE.

| Treatment | Indications | Discussions |
|---|---|---|
| **GC** | First line therapy | □ Response to treatment begins within 1-8 weeks.<br>□ No efficacy in long-term use<br><br>High-dose dexamethasone, per os<br>(40 mg/day for 4 days x 4-8 cycles<br>at 2-4 week intervals).<br><br>Prednisone (starting at 0.5-<br>1 mg/kg/day) may be used,<br>Dexamethasone responds better as long-term maintenance therapy.<br><br>Methylprednisolone presents<br>an increased risk of avascular necrosis.<br>No benefit compared with high-dose oral GCs. |
| **HCQ** | Combined with GCs when the effectiveness of first-line treatment is reduced | Variable dosage depending on the progress.<br><br>16 patients:<br>• Initially treated with 200 mg/day<br>and then the dose was increased by 200 mg every four weeks.<br>• All patients had a good response within the first two months.<br>• At a mean follow-up of 18.2<br>months, the medication was reduced<br>to 200 mg/day<br>without relapse. |

| | | |
|---|---|---|
| | | 6 patients intolerant to GCs were successfully treated with:<br>• High initial dose (800 mg/day for 8 weeks).<br>• Lower dose as maintenance therapy (ranging from 200 to 600 mg/day).<br>Hydrochlorothiazide cannot be discontinued without relapse.<br><br>Hydrochlorothiazide is safe and well tolerated.<br>• Can be used during pregnancy |
| **HCQ** | | Increased and sustained response rate. |
| **CYC** | Relapsed immune thrombocytopenia | 10-15 mg/kg CYC intravenously, every month for at least 4 months:<br>□ Platelet count increases within 2-18 weeks.<br>□ High response rate to therapy.<br>□ Long-term therapy rarely applied<br><br>Concerns about adverse effects led to the proposal of a new regimen:<br>□ Administered dose 500 mg, every two weeks for 3 months.<br>□ Followed by MMF or AZA, improves drug tolerability without loss of efficacy. |
| **MCI** | Relapsed immune thrombocytopenia. | Limits steroid use<br>Use as maintenance therapy |
| **AZA** | Limits the use of steroids | Përdorim si terapi mbajtëse |
| **CSA** | Chronic immune thrombocytopenia.<br>Limits steroid use | Risk of nephrotoxicity<br>□ Administration at lower doses has been used successfully.<br>□ Serious side effects: neuropathy and bone pain. |
| **IVIg** | Preferred if a rapid increase in platelet count is needed due to:<br>• Active bleeding.<br>• Emergency surgery. | Initial dose: 400 mg/kg per day for 5 consecutive days.<br>Maintenance: 400 mg/kg per month<br>Intermittent or continuous.<br>There was insufficient evidence to analyze long-term response |
| **Biologics preparates** | Chronic thrombocytopenia. | Significantly reduces antiplatelet antibodies, especially the IgG isotype.<br>Preferred over splenectomy because it is beneficial for other manifestations of SLE. |
| **IL-11** | life-threatening chronic thrombocytopenia | Case report of a patient with intrabronchial hemorrhage refractory to IVig, high-dose GCS, |

| | | |
|---|---|---|
| | | CYC and plasma exchange.<br>Response to IL-11 during a 5-day administration, reaching a platelet count of 50x109 /mm3 |

Based on the treatment scheme according to the categories of clinical manifestation of SLE with hematological involvement in a 3-month follow-up plan, improvements in laboratory blood values, inhibition of the progression of the disease, and successful treatment of cases identified in the initial stages of the disease were seen in the patients included in the treatment.

**Material discussion**

Of the 120 patients included in this study, 107 (89%) individuals were female versus 13 (11%) male subjects. Overall, the mean age of the patients included in the study was 45.2 years and there was a significant difference in the mean age value according to the gender of the patients (in males, the mean age was: 56.2 years, while in females the mean age was: 39.5 years). Referring to contemporary literature, there is a statistical significance between gender and autoimmune diseases such as SLE, which is most in females it is more developed in women as a result of genetic predisposition, lifestyle, stress, exposure to factors that promote se, autoimmune disorders.(3)

The clinic of LES begins with fatigue, body weakness, temperature, fever of an unknown nature, then the clinical signs become more evident and correlate with the diagnosis. (13,14,15) Thus, in our study, the most pronounced and general clinical manifestations are joint pain, leukopenia, butterfly rush, oral ulcerations, nephritis etc. SLE makes a combination of clinical signs, being a systemic disease, so patients have seen more than a few characteristic elements of the SLE clinic.As can be seen from the percentage of cases, the patients' clinic is diverse, with multiorgan effects that require a combination of objective and imaging examinations for their evidence.

The most prominent hematological manifestations of SLE in our study population are anemia, leukopenia, thrombocytopenia. The bone marrow (BM) is also considered a target organ in SLE and features such as myelofibrosis, aplastic anemia, and pure red cell aplasia. Thus, we will briefly review the pathogenesis and management of specific hematological manifestations in the patients studied. (4)

| | | |
|---|---|---|
| **Anemia** | **Chronic Anemia**<br>**Iron deficiency anemia**<br>**Autoimmune hemolytic anemia AHA** | **72%**<br>**46.6%**<br>**12%** |
| **Pure red cell aplasia PRCA** | | 10% |
| **Leukopenia** | Lymphopenia | 19% |
| **Immune thrombocytopenia in SLE** | | 41.6% |

Treatement and complications. Here are listened principles and 13 recommendations, concerning the use of hydroxychloroquine (HCQ), glucocorticoids (GC), immunosuppressive drugs (ISDs) (including methotrexate, mycophenolate, azathioprine, cyclophosphamide (CYC)), calcineurin inhibitors (CNIs), cyclosporine, tacrolimus, voclosporin) and biologics (belimumab, anifrolumab, rituximab).

Advice is also provided on treatment strategies and targets of therapy, assessment of response, combination and sequential therapies, and tapering of therapy.

HCQ is recommended for all patients with lupus at a target dose of 5 mg/kg real body weight/day,

considering the individual's risk for flares and retinal toxicity. GC are used as 'bridging therapy' during periods of disease activity; for maintenance treatment, they should be minimized to equal or less than 5 mg/day (prednisone equivalent) and, when possible, withdrawn. (6,11)
Prompt initiation of ISDs (methotrexate, azathioprine, mycophenolate) and/or biological agents (anifrolumab, belimumab) should be considered to control the disease and facilitate GC tapering/discontinuation. (9,12)
CYC and rituximab should be considered in organ-threatening and refractory disease, respectively. For active lupus nephritis, GC, mycophenolate or low-dose intravenous CYC are recommended as anchor drugs, and add-on therapy with belimumab or CNIs (voclosporin or tacrolimus) should be considered. Updated specific recommendations are also provided for cutaneous, neuropsychiatric and hematological disease, SLE-associated antiphospholipid syndrome, kidney protection, as well as preventive measures for infections, osteoporosis, cardiovascular disease. (1,18,20)

**Conclusion**

The updated recommendations provide consensus guidance on the management of SLE, combining evidence and expert opinion.
Follow-up of patients and combination of maintenance therapy depending on the clinical course.
Evidence of the effectiveness of Hydroxychloroquine in the treatment of patients with SLE, especially those with hematological involvement.
Creation of an accurate database for chronic patients with SLE to enable a real assessment of the patient's health situation. Increased cooperation between the primary, secondary and tertiary health systems.
Development of diagnostic and therapeutic protocols according to the needs and clinical presentation of the patient.

**References:**


1. Maier WP, Gordon DS, Howard RF, Saleh MN, Miller SB, Lieberman JD et al. Intravenous immunoglobulin therapy in systemic lupus erythematosusassociated thrombocytopenia. Arthritis Rheum, 2013;33:1233-9.
2. Levy Y, Sherer Y, Ahmed A, Langevitz P, George J, Fabbrizzi F et al. A study of 20 SLE patients with intravenous immunoglobulin--clinical and serologic response. Lupus, 1999;8:705-12
3. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum, 2012;64:2677-86
4. Gomard-Mennesson E, Ruivard M, Koenig M, Woods A, Magy N, Ninet J et al. Treatment of isolated severe immune hemolytic anaemia associated with systemic lupus erythematosus: 26 cases. Lupus, 2018;15:223-31.
5. Barcellini W, Fattizzo B, Zaninoni A, Radice T, Nichele I, Di Bona E et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood, 2020;124:2930-6.
6. Gómez-Almaguer D, Solano-Genesta M, Tarín-Arzaga L, Herrera-Garza JL, Cantú-Rodríguez OG, Gutiérrez-Aguirre CH et al. Low-dose rituximab and alemtuzumab combination therapy for patients with steroid-refractory autoimmune cytopenias. Blood, 2020;116:4783-5.
7. Chao MP, Hong J, Kunder C, Lester L, Schrier SL, Majeti R. Refractory warm IgM-mediated autoimmune hemolytic anemia associated with Churg-Strauss syndrome responsive to eculizumab and rituximab. Am J Hematol, 2015;90:78-81.

8. Antonis Fanouriakis-Rheumatology and Clinical Immunology Unit, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece 2023;238:227-6
9. Myrto Kostopoulou-Lupus Europe, Copenhagen, Denmark 2022; 153: 1067-1
10. Jeanete Andersen-Division of Rheumatology, Department of Medicine III, University Medical Center & Faculty of Medicine Carl Gustav Carus at the TU Dresden, Dresden, Germany 2024;75: 2390-2
11. Laurent Arnaud- Department of Rheumatology, Hôpitaux Universitaires de Strasbourg, INSERM UMR-S 1109, Centre National de Référence des Maladies Auto-immunes Systémiques Rares (RESO), Strasbourg, France
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