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**MEDICINE DOMAIN**

**THE IMPACT OF ORGAN FAILURE AND METASTASES ON THE  
QUALITY OF LIFE OF PATIENTS WITH BREAST CANCER**

**DOCTORAL THESIS SUMMARY**

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## MULȚUMIRI

Motto-ul meu de absolvire al Facultății de Medicină a fost scris pe tocă ”**Atinge steaua de neatins și nu-i uita pe cei ce au crezut în tine**”. Realizarea acestei teze de doctorat reprezintă ”**încă o atingere a unei stele de neatins**” cu ajutorul lui Dumnezeu și al unor oameni dragi sufletului meu.

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# ***"THE IMPACT OF ORGAN FAILURE AND METASTASIS ON THE QUALITY OF LIFE OF BREAST CANCER PATIENTS"***

## **Introduction**

The current PhD thesis focuses on one of the most common malignancies worldwide, breast cancer, motivated by the need to better understand the impact of subclinical organ failure syndrome on patients' quality of life and survival. Organ failure, both subclinical and clinical, represents a major challenge in the treatment of cancer patients, having a significant impact on their prognosis and quality of life. This study is motivated by gaps in the literature regarding the diagnosis and management of these conditions in breast cancer patients. [1]

Late diagnosis of breast cancer is driven by the insidious onset of the disease and lack of effective national screening programs. These factors lead to the disease being identified at advanced stages, when therapeutic options are limited and the chances of survival are considerably reduced. This context is reflected in the high values of morbidity and mortality associated with breast cancer, observable both in Romania and globally. [2, 3].

The topic of our research is of particular relevance, given that breast neoplasm is one of the most common malignancies among women and a major cause of death. The novelty of this research lies in the application of advanced artificial intelligence technologies to analyze data from the literature, facilitating the identification of predictive models for disease progression from subclinical organ failure to overt clinical organ failure.

The contemporary relevance of the topic is amplified by the close link between inflammation, altered immune responses and subacute organ failure, aspects prevalent in the context of both cancer and multiple organ failure syndromes. Chronic inflammation and impaired immune responses play a crucial role in cancer-associated organ dysfunction, contributing to tumor development and progression, impairing cellular and tissue functionality. Starting from the multiple organ failure syndrome, known and studied for several decades, a retrospective analysis of its evolutionary processes can be performed, trying to describe or observe the syndrome of infraclinical organ failure, the starting point of an organ failure. The difference between these two conditions lies in the severity and manifestation of symptoms. Subclinical organ failure syndrome is a subtler and less obvious form of multiple organ failure, potentially

reversible, compensated by the body's own homeostasis. Thus, symptoms are not obvious enough to be detected by routine clinical tests.

Quantification of this syndrome proves challenging because of the absence of overt symptoms, leading to discrete progression through different stages until reaching the state of multiple organ failure. Diagnosis of subclinical organ failure syndrome requires extensive use of laboratory examination, medical investigations, imaging techniques and advanced innovative tools such as artificial intelligence (AI) to detect those subtle changes related to organ dysfunction before the patient presents with visible symptoms and, through a domino effect, develops multiple organ failure. This approach would contribute significantly to improving survival and quality of life of breast cancer patients, emphasizing the importance of early diagnosis and early therapeutic interventions. [4,5].

International and national concerns aim to improve cancer patient care and reduce breast cancer-related mortality. At the international level, there are numerous studies investigating the issue of organ failure in oncology, but many aspects are unresolved. At the national level, current research can contribute to the development of pilot strategies for the management of breast cancer patients with the aim of increasing their survival and quality of life.

The present research aims to study the impact of multiple organ failure (MOF) and metastasis on the quality of life and survival of breast cancer patients.

The thesis is structured in two parts. The general part consists of a single chapter in which artificial intelligence (AI) techniques have been used to synthesize the most relevant data from a large number of articles, providing a new perspective on multiple organ failure (MOF) and describing the existence of subclinical organ failure syndrome in breast cancer patients. The special part is composed of the results of 3 studies performed on 981 breast cancer patients hospitalized in the Colțea Clinical Hospital between January 1, 2019 and October 1, 2023.

# I. GENERAL PART

## Chapter 1. Artificial intelligence in early detection of clinical multiple organ failure in breast cancer patients

The aim of the present research was to highlight the existence of subclinical organ failure syndrome and to propose a novel perspective on clinical multiple organ failure in breast cancer patients. The precursor lesions of breast cancer (typical ductal hyperplasia, atypical ductal/lobular hyperplasia) and the infraclinical multiple organ failure syndrome are early stages in certain diseases. These stages are characterized by changes that manifest before apparent symptoms become clinically evident or identifiable by conventional diagnostic methods. Similarly, cancer and multiple organ failure syndrome (MOFS) are progressive diseases. Initially, the body's homeostasis is not altered by infectious or non-infectious factors, thus the onset of pathophysiologic changes, which may start from genetic to clinical manifestation, causes IMO to progress from an infraclinical organ failure syndrome, through the domino effect, to acute, clinical multiple organ failure, leading to severe disease or even death. Breast cancer progresses progressively through genetic and molecular alterations from the initial, hyperplasia stage to advanced metastatic breast cancer (Figure 1.).

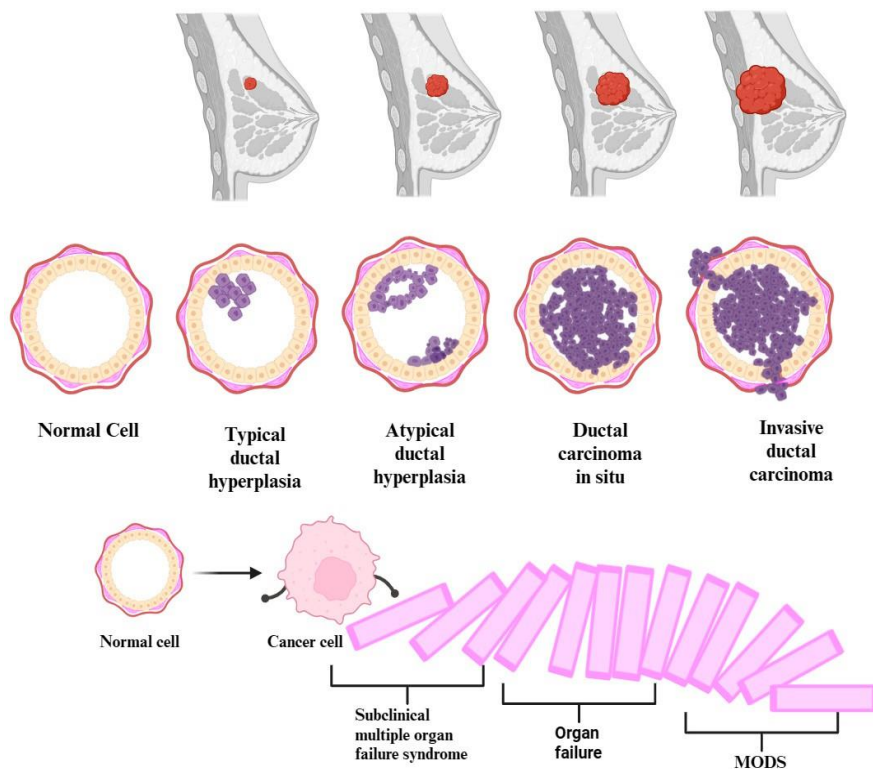


Figure 1. IMO development from multiple organ subclinical multiple

**organ failure syndrome in the context of the natural evolution of breast cancer.-  
Image drawn in BioRender.**

This paper used artificial intelligence (AI) techniques to cluster and analyze research articles related to multiple organ dysfunction syndrome (MODS). By using clustering techniques, AI allowed the identification of groups of articles with high similarities within each group, thus facilitating a clearer understanding of topics and trends in the literature. This analysis provides valuable information about specific genes, molecular markers and biochemical parameters associated with multiple organ failure in breast cancer patients. It also illustrates data on the epidemiology of breast cancer both worldwide and in Romania in recent years, as well as the epidemiology, pathogenesis, clinical syndromes and management of oncologic patients with IMO. The pathogenesis pathways have been extensively studied lately, seeking a deeper understanding of the cells and molecules that could benefit from novel therapies. The results highlight a significant gap in the management of IMO, underscoring the continued need for research to provide adequate treatment, to stop the process of chain degradation of organ systems, to improve both oncologic and non-oncologic treatment and to increase the quality of life of patients. Despite the efforts made, quality of life among breast cancer patients remains unchanged and in Romania is lower than the European average. Although the existence of subclinical organ failure syndrome is recognized in practice, current diagnostic methodologies prove insufficient for its accurate identification. Therefore, we conclude that new diagnostic methods are needed to enable physicians to effectively diagnose and manage this syndrome.

## **II. PERSONAL CONTRIBUTIONS**

### **Chapter 2. Working hypothesis and general research objectives**

The main hypothesis of the thesis is that subclinical organ failure is a pathologic state, but clinically unrecognized due to the fact that the body's homeostasis compensates for the deficit by its own mechanisms, but over time, through domino effect, it reaches acute, clinical, multiple organ failure, with negative effects on the quality of life and survival of patients. It is hypothesized that the use of artificial intelligence (AI) techniques to analyze data from the literature will allow the identification of models describing this pre-clinical organ failure state, as well as to diagnose and manage clinical multiple organ failure in breast cancer patients. In addition, treatment with CDK4/6 inhibitors in combination with hormone therapy as first-line therapy for HR+/HER2- metastatic breast cancer patients may influence the monitoring and management of organ dysfunction, thereby improving the prognosis and quality of life of these patients. Also, pairwise analysis of organ failures, such as cardiopulmonary and cardio-renal syndromes, emphasizes the importance of a multidisciplinary approach to oncology patients. The use of the EORTC QLQ-C30 and EORTC QLQ-BR45 questionnaires, provides a more accurate assessment of the impact of treatment and organ failure on these patients, thus improving clinical management and quality of life.

#### **Overall research objectives**

1. Use artificial intelligence techniques to cluster and analyze the literature describing subclinical organ failure syndrome and studying clinical organ failure in breast cancer patients.
2. To assess the influence of organ failure on survival among HR+ and HER2- metastatic breast cancer patients undergoing treatment with CDK4/6 inhibitors in combination with hormonal therapy.
3. Pairwise analysis of organ failures, identifying cardiopulmonary syndrome, cardio-renal syndrome, cardio-hepatic syndrome, hepato-renal syndrome, hepato-pulmonary syndrome and reno-pulmonary syndrome in breast cancer patients.
4. Use of the EORTC QLQ-C30 and EORTC QLQ-BR45 questionnaires for a thorough and comprehensive assessment of the QoL of breast cancer patients in Romania



5. Assessment of organ dysfunctions (cardiac, respiratory, renal, neurologic, hepatic, gastrointestinal) and their correlation with QoL data.
6. Evaluation of the survival rate of breast cancer patients in the study group.

### **Chapter 3. General research methodology**

The special part of this PhD thesis was carried out in the Medical Oncology Clinic of the Colțea Clinical Hospital, including a total cohort of 981 patients with breast cancer in different stages of development treated between January 1, 2019 and October 1, 2023. Also, the total cohort of 981 patients was analyzed in 3 research studies, two retrospective between January 1, 2019- March 30 and one prospective between August-September 2023 including 874 patients with breast cancer in different stages of evolution.

The research method adopted for the prospective study was observational, using validated quality of life questionnaires translated into Romanian (EORTC QLQ-C30 and EORTC QLQ-BR45). Each patient was fully informed about the details and objectives of the study and signed the informed consent to participate (Appendix 1 of the PhD thesis).

The 3 studies had their own research protocol, inclusion and exclusion criteria. All patients were Caucasian and of Romanian ethnicity.

The present research was approved by the Ethics Committee of the Colțea Hospital Clinic-Bucharest, according to decision no. 19091/5.10.2021.

Data analysis of literature data was performed using advanced artificial intelligence techniques, and descriptive and inferential statistics to identify relevant patterns and correlations between the studied variables were performed using JASP version 0.18.2 and IBM SPSS version 29 programs.

## **Chapter 4. Actual treatment outcomes with CDK4/6 inhibitors in metastatic breast cancer in Romania: impact on survival and risk of organ failure**

This paper investigated the actual treatment outcomes of CDK4/6 inhibitors in patients with HR+ HER2- metastatic HER2- metastatic breast cancer treated at Colțea Clinical Hospital in Bucharest. The retrospective study, conducted between 2019-2023, included 107 patients who received CDK4/6 inhibitors (Palbociclib, Ribociclib and Abemaciclib) in combination with hormonal therapy. The main aim of the study was to calculate median progression-free survival (PFS) and compare it with data from other randomized clinical trials[4,5].

Study results showed a median progression-free survival of 17 months, compared with 25.3 months reported in clinical trials. Although no major differences from the results of randomized clinical trials were observed, the study highlighted the importance of rigorous monitoring of pulmonary and cardiac function, as more than half of the patients experienced respiratory and cardiac failure during treatment.

Palbociclib was frequently associated with gastrointestinal, hepatic and respiratory dysfunction compared with Ribociclib and Abemaciclib, probably due to the larger number of patients in our group treated with this inhibitor. Although no statistically significant differences were observed between the distributions of organ failures for each CDK4/6 inhibitor, the presence of multiple failures indicates a more severe prognosis and requires increased attention from medical teams[6,7].

The study suggests that patients with visceral metastases are at higher risk of developing organ failures, particularly respiratory and cardiac, highlighting the need to customize treatment strategies according to patients' individual vulnerabilities. Careful monitoring of vital functions and rapid adjustment of treatment in case of failure are essential for the effective management of these patients[8,9].

## **Chapter 5. Analysis of organ failure and organ failure-related syndromes in breast cancer patients: a retrospective observational study**

The presented study analyzes organ failures and their associated syndromes in breast cancer patients, through a retrospective observational study conducted between 2019 and 2023 at Colțea Clinical Hospital in Bucharest. Multiple organ failure syndrome (MODS) is a major cause of mortality in both oncological and non-oncological patients, characterized by simultaneous dysfunction of two or more organs, often triggered by a severe systemic inflammatory response, septic shock or hypoxia. In cancer patients, MODS can be aggravated by disease- and treatment-specific factors, including secondary infections, chemotherapy-induced toxicity and side effects of targeted therapies.

The study included 880 patients with breast cancer, analyzing the presence of cardiac, pulmonary, renal and hepatic insufficiencies, as well as combinations of these insufficiencies, such as cardio-pulmonary, cardio-renal, cardio-hepatic, hepato-renal, hepato-pulmonary and reno-pulmonary syndromes. The results showed that heart failure was the most common, being present in 45.57% of patients, followed by respiratory (20.22%), renal (20.90%) and hepatic (18.30%) failure. In particular, the study revealed that cardio-renal syndrome was the most common (12.95%), followed by cardio-pulmonary (10.57%) and hepato-renal (5.34%), emphasizing the need for strict monitoring of these complications in breast cancer treatment.

The findings emphasize the need for close monitoring of vital organ functions during oncologic treatments, especially in the context of aggressive treatments. The study also recommends a multidisciplinary approach in the management of breast cancer patients, with collaboration between oncologists, cardiologists, hepatologists and pulmonologists being essential to optimize treatment and improve prognosis. The study also emphasizes the importance of further research to better understand the pathophysiology of organ failure syndromes and to develop more effective therapeutic interventions that contribute to increased survival and improved quality of life in these patients[10-16].

## **Chapter 6. Evaluation of the influence of organ failure and metastasis on quality of life in breast cancer patients: a prospective study using EORTC QLQ-C30 and QLQ-BR45**

This study, conducted at the Colțea Clinical Hospital in Bucharest, evaluated the impact of organ failure and metastasis on quality of life (QoL) in breast cancer patients using the EORTC QLQ-C30 and EORTC QLQ-BR45 questionnaires. The prospective study, conducted between January 2019 and October 2022, included 607 eligible participants out of a total of 874, after excluding 201 deaths and 66 refusals. Results showed statistically significant differences in various aspects of QoL in heart failure patients, including physical functioning, pain, insomnia, general health, and overall health score. Renal failure significantly impaired physical functioning, body image, sexual functioning, and sexual endocrine symptoms, and respiratory failure demonstrated significant differences in several domains of QoL. Patients with bone metastases also reported reduced physical functioning and increased pain.

The study revealed a 5-year life expectancy of 68.8%, with survival rates of 93.8% for stage I, 86.3% for stage II and 77.2% for stage III breast cancer. Patients with metastatic cancer had a 45-month survival rate of 35.6%, with a median survival of 36 months.

The findings highlight the need to integrate standardized QoL assessments into clinical practice from initial diagnosis and throughout follow-up. The study highlights the significant impact of organ failures on QoL and the need for future research targeting pharmacologic and non-pharmacologic interventions to improve QoL, increase adherence to treatment and ultimately improve survival rates in breast cancer patients[17-23].

## **Chapter 7. Conclusions and personal contributions**

### **Conclusions**

The PhD thesis highlighted the link between subclinical organ failure, multiple organ failure and the impact on quality of life and survival of breast cancer patients. The research also aimed to identify potential predictive models for disease progression from subclinical to clinically manifest organ failure using advanced artificial intelligence (AI) technologies.

The study highlighted that late diagnosis of breast cancer, caused by the subtle onset of the disease and the absence of effective national screening programs, leads to the identification of the disease at advanced stages, when therapeutic options are limited and the chances of survival are considerably reduced. This contributes to the high morbidity and mortality rates associated with breast cancer both in Romania and globally.

The use of the EORTC QLQ-C30 and QLQ-BR45 questionnaires allowed a comprehensive assessment of quality of life, while artificial intelligence techniques facilitated the identification of relevant predictive models to manage information from the literature on organ failure among cancer patients. The analysis of organ syndromes emphasized the importance of continuous monitoring of breast cancer patients, especially those in advanced stages, where the risk of multiple organ failure is considerable.

The scientific objectives of the thesis were achieved by collecting and analyzing data from 981 breast cancer patients treated at the Department of Medical Oncology of the Colțea-Bucharest Clinical Hospital and by developing two retrospective studies and a prospective study with innovative results for the literature.

The results of this research highlight the need for personalized therapeutic interventions, aimed not only at treating the cancer itself, but also at preventing and managing associated organ dysfunctions. The research has provided a comprehensive perspective on organ failure in the oncologic context, emphasizing the importance of integrating advanced technologies in diagnosis and treatment. However, a major obstacle of the study was the lack of appropriate paraclinical techniques to identify and measure subclinical organ failure.

### **Personal contributions**

1. Defining subclinical organ failure syndrome in breast cancer patients
2. Recent advances in diagnostic methods of clinical organ failure in breast cancer patients
3. Use of AI that combines data from the literature, providing a new approach in the evaluation and management of the oncologic patient
4. First study in Romania with real-world data investigating the efficacy of CDK4/6 inhibitors in patients with metastatic breast cancer. Also the first worldwide study to track organ dysfunction distributions for each CDK4/6 inhibitor (Palbociclib, Ribociclib, Abemaciclib)
5. First worldwide study to use the EORTC QLQ-BR45 questionnaire, providing reliable and relevant data on a cohort of 607 patients. It is also the first to study quality of life for each organ failure
6. Significant contributions to the literature by publishing the results in prestigious journals, advancing knowledge in the field of oncology by defining subclinical organ failure syndrome as a new entity, recognized as a starting point towards multiple organ failure in oncology patients.

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