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**Multidimensional assessment of upper limb dysfunction in breast
cancer-related lymphedema patients: integration of rehabilitation and
wearable technologies**

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ABSTRACT

Introduction

Breast cancer (BC) is one of the most common malignancies among women worldwide. Although, advances in early diagnosis and multidisciplinary treatments have significantly improved survival rates, long-term complications such as upper limb dysfunction and breast cancer-related lymphedema (BCRL) remain frequent. These conditions are considered multifactorial involving structural changes, neuromuscular adaptations, altered motor control, and may cause chronic swelling, pain, reduced mobility, and impaired quality of life.

Traditional rehabilitation methods are effective but often rely on limited assessment tools. In recent years, wearable technologies such as surface electromyography (sEMG) and inertial measurement units (IMUs) have emerged as promising tools for objective and quantitative evaluation of motor function. The aim of this study is to investigate upper limb impairment in breast cancer survivors with BCRL using a multidimensional rehabilitation-oriented approach. In this context have been integrated structural, functional, neuromuscular, and patient-reported assessments, while also exploring the feasibility of wearable technologies in rehabilitation settings.

Methods

This prospective observational study included 13 female breast cancer survivors with upper limb lymphedema undergoing outpatient rehabilitation at the Azienda Ospedaliera Universitaria of Alessandria. Assessments were performed before (T0) and after rehabilitation (T1). Structural evaluation included circumferential and volumetric measurements of the upper limbs, while functional performance was assessed through handgrip strength testing. Patient-reported outcomes included the DASH questionnaire, the LLISv2, and the EORTC QLQ-C30.

Neuromuscular evaluation was performed using wireless sEMG during standardized upper limb movements. Additionally, IMU sensors were tested in healthy volunteers to evaluate the feasibility of quantitative motion analysis through a dedicated Python®-based computational workflow.

Results

Rehabilitation was associated with improvements in structural, functional, and subjective outcomes. Mean inter-limb volume asymmetry decreased from 1269.3 ± 1584.1 mL at T0 to 686.6 ± 575.4 mL at T1, corresponding to an average reduction of 582.7 ± 1060.7 mL. Handgrip strength improved moderately after rehabilitation. Mean right-hand grip strength increased from 22.5 ± 6.0 kg to 23.6 ± 5.2 kg, while left-hand grip strength increased from 22.7 ± 4.9 kg to 25.1 ± 4.6 kg. Patient-reported outcomes also improved:

LLISv2 scores decreased from 40.4 ± 8.0 to 30.2 ± 7.1 , and DASH scores improved from 75.0 ± 23.0 to 58.7 ± 21.3 . EORTC QLQ-C30 scores showed a smaller reduction, from 53.8 ± 10.2 to 49.7 ± 4.6 . Correlation analysis demonstrated only a weak association between volumetric reduction and subjective symptom improvement. Qualitative sEMG analysis showed heterogeneous muscle activation patterns at baseline, with more coordinated activation observed after rehabilitation in several patients. The IMU-based analysis demonstrated stable signal acquisition and reproducibility, supporting the feasibility of wearable inertial sensors for quantitative movement assessment.

Discussion

The study supports the beneficial role of rehabilitation in improving upper limb function and quality of life in breast cancer survivors with BCRL. The findings highlight the multidimensional nature of upper limb dysfunction, involving structural impairment, neuromuscular adaptation, and psychosocial consequences.

The integration of wearable technologies such as sEMG and IMUs appears promising for objective rehabilitation assessment and monitoring. Although further validation in larger populations is needed, these technologies may contribute to the development of personalized and data-driven rehabilitation strategies for breast cancer survivors.

RIASSUNTO

Il carcinoma mammario è una delle condizioni maligne più diffuse tra le donne a livello mondiale. Nonostante gli avanzamenti in termini di diagnosi precoce e trattamenti multidisciplinari hanno aumentato in modo significativo i tassi di sopravvivenza, le complicanze a lungo termine causate dai trattamenti come disfunzioni dell'arto superiore e il linfedema correlato al carcinoma mammario (BCRL) rimangono frequenti. Queste condizioni sono considerate multifattoriali coinvolgendo modifiche strutturali, adattamenti neuromuscolari, controllo motorio alterato, e possono causare rigonfiamenti cronici, dolore, mobilità ridotta, e qualità della vita alterata.

I metodi riabilitativi tradizionali sono efficaci ma spesso si affidano a strumenti di valutazione limitati. Negli ultimi anni, le tecnologie indossabili come l'elettromiografia di superficie (sEMG) e le Unità Inerziali di Misura (IMU) sono emersi come strumenti promettenti per la valutazione oggettiva e quantitativa delle funzioni motorie. L'obiettivo di questo studio è di investigare la compromissione dell'arto superiore nelle pazienti sopravvissute al carcinoma mammario con BCRL utilizzando un approccio multidisciplinare orientato alla riabilitazione. In questo contesto, è stata integrata la valutazione strutturale, funzionale, neuromuscolare, e riferite dai pazienti esplorando nello stesso momento la fattibilità dell'utilizzo di tecnologie indossabili nel contesto riabilitativo.

Il seguente studio prospettico osservazionale include 13 pazienti di sesso femminile sopravvissute al carcinoma mammario con linfedema dell'arto superiore che sono sottoposte alla riabilitazione ambulatoriale presso l'Azienda Ospedaliera Universitaria di Alessandria. Le valutazioni sono state effettuate prima (T0) e dopo (T1) la riabilitazione. La valutazione strutturale ha incluso misurazioni circonferenziali e volumetriche dell'arto superiore, mentre la valutazione della performance funzionale è stata valutata tramite i test di forza di presa. I risultati riferiti dai pazienti includono la compilazione dei questionari DASH, LLISv2, e EORTC QLQ-C30. La valutazione neuromuscolare è stata effettuata utilizzando sEMG wireless durante movimenti standardizzati dell'arto superiore. Inoltre, i sensori IMU sono stati testati in volontari sani per valutare la fattibilità dell'analisi quantitativa del movimento attraverso un flusso di lavoro computazionale dedicato basato su Python®.

La riabilitazione è risultata con miglioramenti a livello strutturale, funzionale, e soggettivo. L'asimmetria media del volume tra gli arti è diminuita da 1269.3 ± 1584.1 mL in T0 a 686.6 ± 575.4 mL in T1, corrispondendo a una riduzione media di 582.7 ± 1060.7 mL. La forza di presa della mano è migliorata moderatamente dopo la riabilitazione. La forza della presa media della mano destra è aumentata da 22.5 ± 6.0 kg in T0 a 23.6 ± 5.2 kg in T1, mentre la forza della presa della mano sinistra è aumentata da 22.7 ± 4.9 kg in T0 a 25.1 ± 4.6 kg in T1. Anche gli esiti dichiarati dai pazienti sono migliorati: i punteggi del questionario LLISv2 è diminuito da 40.4 ± 8.0 a 30.2 ± 7.1 , quelli del questionario DASH sono migliorati da 75.0 ± 23.0 a 58.7 ± 21.3 . I punteggi del questionario EORTC QLQ-C30 hanno visto una piccola riduzione da 53.8 ± 10.2 a 49.7 ± 4.6 .

Le analisi di correlazione hanno dimostrato solo una debole associazione tra la riduzione volumetrica e il miglioramento soggettivo dei sintomi. L'analisi qualitativa sEMG ha dimostrato un modello muscolare di attivazione eterogeneo a livello basale, con un'attivazione più coordinata osservata dopo la riabilitazione in diverse pazienti. L'analisi basata sui sensori IMU ha dimostrato stabilità nell'acquisizione e riproducibilità dei segnali. Supportando la fattibilità dei sensori inerziali indossabili per la valutazione quantitativa del movimento.

Lo studio supporta il ruolo benefico della riabilitazione nel migliorare la funzione dell'arto superiore e la qualità della vita nelle sopravvissute al carcinoma mammario con BCRL. I risultati evidenziano la natura multidimensionale della disfunzione dell'arto superiore, che coinvolge alterazioni strutturali, adattamenti neuromuscolari, e conseguenze psicosociali.

L'integrazione di tecnologie indossabili come sEMG e IMU sembra promettente per la valutazione e il monitoraggio oggettivo della riabilitazione. Nonostante siano necessarie ulteriori validazioni su popolazioni più ampie, queste tecnologie possono contribuire allo sviluppo di strategie riabilitative personalizzate e guidate dai dati per le pazienti sopravvissute al carcinoma mammario.

INTRODUCTION

1. Breast Cancer epidemiology

Breast cancer (BC) is the most common type of cancer diagnosed among women worldwide. Global Cancer Observatory 2024 reported 2.3 million cases of BC and continues to be an important public health problem due to its high incidence, uncertainties in terms of survival, and complex epidemiological routes of development of BC. In addition to being the most commonly diagnosed cancer among females, BC continues to be the cause of the most deaths associated with cancer in the female population (followed by lung and colorectal cancers), as almost 1 out of every 4 cancer diagnoses in women are from BC [1]. The incidence of BC differs across countries (see Figure 1), with many high-income nations (USA; Countries of Western Europe; Australia) experiencing a greater incidence due to extensive screening practices and other lifestyle factors (BMI ≥ 30 kg m²; low levels of physical activity; high levels of alcohol consumption). On the opposite, despite low and middle-income countries are noted to have lower incidence rates, these regions often encounter an extremely high mortality burden as a result of delayed diagnosis and limitations on adequate treatment protocols [2]. Despite the actual decrease on breast cancer mortality rate by nearly 20% compared to the late 1980s and early 1990s, mostly in high-income countries, breast cancer remains the primary cause of women cancer-associated fatalities [3].

Age-Standardized Rate (World) per 100 000, Incidence, Females, In 2022
Breast

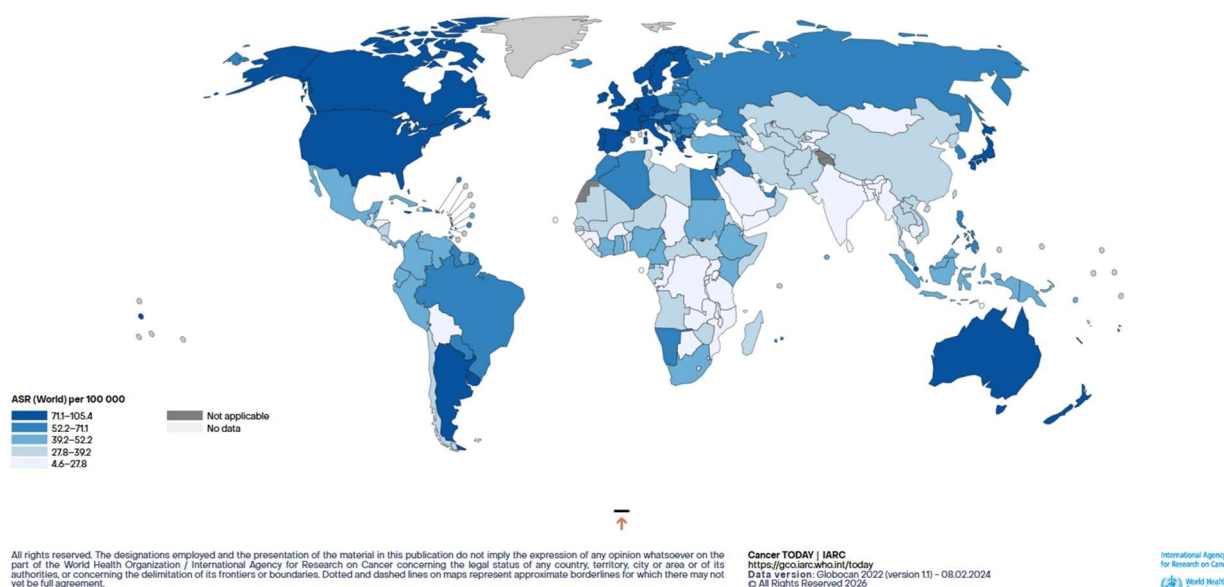


Figure 1. Age-standardized rate (world) per 100 000, incidence, females, in 2022. Image adapted from International Agency for Research on Cancer, World Health Organization.

In terms of survival, breast cancer outcomes have enhanced over the past decades. Five-year overall survival rates in well-established healthcare system countries now exceeds 85%, showing advances in early detection through mammographic screening and progress in multidisciplinary treatment approaches [4]. The benefits of these applications include breast-conserving surgery, systemic therapies, hormone-targeted treatments, and precision oncology interventions. Survival, as almost for every type of cancer, is highly stage-dependent; diagnosis at stage I present a five-year survival exceeding 95%, whereas those in metastatic stage IV face considerably poorer outcomes with almost 30% survival [5]. As explained before, also survival disparities are strictly related to socioeconomic conditions, emphasizing the role of healthcare accessibility and early detection programs on clinical outcomes.

2. Etiopathogenesis of Breast Cancer

Breast cancer develops through a heterogeneous multifactorial process that combine genetic susceptibility, epigenetic modifications, endocrine influences, environmental exposure, and alterations of the mammary microenvironment [6]. The biological diversity of BC reflects the interplay of a series of disruption of regulatory pathways responsible for cell proliferation, differentiation, and survival, across the lifespan, from early development to adulthood [7]. Understanding the mechanisms underlying the etiopathogenesis of breast cancer is crucial for clear up disease history and heterogeneity, and for identifying preventive strategies and improving effective therapies.

2.1 Genetic susceptibility and genomic instability

2.1.1 Germline mutations

Almost 5-10% of breast cancers originate from high-penetrance germline mutations responsible for alteration of pathways involved in genomic stability maintenance [8]. In this context the most well studied susceptibility genes include BRCA1 and BRCA2. These tumour suppressor genes encode proteins essential for the repair of double-strand DNA breaks through homologous recombination [9]. Loss of function mutations in these genes lead in a situation of defective genomic stability, chromosomal aberration, and oncogenic transformation susceptibility [10]. Moreover, germline mutations in PTEN, TP53 [8], PALB2, and genes involved in the development of Fanconi anemia [11] contribute to breast cancer initiation. Even though these alterations disrupt the DNA damage detection and cell cycle control, they do not initiate cancer autonomously. They make the breast more susceptible to the acquisition of somatic mutations and highlight the importance of DNA repair pathways in preserving the integrity of the mammary environment.

2.1.2 Somatic alterations

In general, most breast cancers develop in a sporadic way. They progressively accumulate somatic mutations caused by impaired metabolic processes and defects in cell replication [12]. These alterations directly impact mitogenic signalling pathways, apoptosis, and dis-regulate the cell cycle. Examples of somatic mutations in this case include TP53 mutations, promoting the block of the cell cycle arrest and apoptosis. Moreover, alterations in the PI3K/AKT/mTOR signalling pathway, particularly alterations in PIK3CA, induce proliferative signalling and metabolic reprogramming [13]. Mutations in genes responsible for transcriptional regulation and chromatin modification, along with amplifications of the HER2/ERBB2 receptors, which induce significant mitogenic signalling, further contribute to tumour initiation and progression [14]. Epigenetic disfunctions are also key factors in BC tumorigenesis. Altered hypermethylation by promoters can silence tumor-suppressor genes, instead histone modifications can activate proto-oncogenes promoting genomic instability [15]. Moreover, modified non-coding RNAs like microRNAs and long non-coding RNAs can reorganize post-transcriptional networks accelerating tumor evolution [16].

2.2 Hormonal and reproductive determinants

2.2.1 Estrogen as a central driver of mammary carcinogenesis

Hormone exposure is one of the main risk factors in breast carcinogenesis. Estrogens are among the most potent endogenous mitogens affecting the mammary epithelium. Their action on carcinogenic development can occur through two main mechanisms. The first acts through the estrogen receptor alpha (ER α), suppressing apoptotic pathways and stimulating cell cycle progression, exposing DNA to potential damage during replication [17]. The second mode of action is through estrogen metabolites, which can directly induce genotoxic lesions by generating oxidative stress and leading to mutagenesis [18]. Prolonged exposure to estrogens results in conditions such as premature menarche, late menopause, and nulliparity. These conditions are established risk factors for the development of breast cancer.

2.2.2 Progesterone and prolactin

The presence of progesterone in the system increases the development of lobulo-alveolar mammary glands (MG). Long-term increases in serum progesterone could lead to a proliferation of epithelial progenitor cells. This proliferation also increases the risk for oncogenic change [19]. Progesterone and its receptor interact with estrogen signalling pathways as well as promoting mammary epithelial proliferation, particularly during the menstrual cycle and throughout gestation.

The prolactin hormone activates the JAK2/STAT5 signalling pathway responsible for lactation. Activation of this pathway by prolactin is necessary for proper cell survival and differentiation of MG cells. Dysregulation of prolactin signalling in the context of oestrogen and progesterone may contribute to the development of breast cancer by establishing an environment conducive to tumor development [20].

2.3 Environmental, lifestyle, and metabolic influences

There is significant literature supporting the idea that ionizing radiation is considered a carcinogenic risk factor during periods of mammary gland activity [21]. Environmental carcinogens act as exogenous factors that alter cell's endogenous susceptibility. In this case, ionizing radiation induces a break of the DNA double strand, generating mutations capable of triggering carcinogenesis. Exposure to chemicals can induce alterations in hormonal signalling or damage DNA integrity, further contributing to the development of BC.

Lifestyle, as with any disease in general, influences risk factors that contribute to whether or not a person develops breast cancer. Some of the most common lifestyle risk factors that we can mention are alcohol consumption and obesity. Alcohol, even when consumed moderately, can cause oxidative damage to DNA, through increasing levels of estrogen [22]. These levels are shown to be increased also in obese patients through high aromatase expression, increasing the risk of developing breast cancer. Obesity also affects the body through chronic inflammation of adipose tissue and promotes metabolic disorders such as hyperinsulinemia and elevated levels of the growth factor IGF-1 [23].

Recent studies highlight the role of the estrobolome in modulating systemic estrogen levels [24]. The estrobolome is the set of genes in gut bacteria involved in estrogen metabolism. Its action affects the regulation of enzyme activity, and alterations in it may contribute to the development of conditions such as endometriosis and hormonal problems, potentially contributing to the risk of breast cancer.

2.4 Cellular origin, tumor microenvironment, and immune dysregulation

Modern medicine increasingly supports evidence that deregulated transformations of mammary stem or progenitor cells are the initiators of breast cancer [25]. These cells are highly susceptible to the accumulation of genetic and epigenetic mutations due to their intrinsic longevity, self-renewal, and proliferative potential. The tumor resulting from this transformation will have specific molecular and pathological identities depending on the epithelial population undergoing transformation, so, luminal progenitors, basal cells, or stem cells. Disturbances in the signaling pathways that control stem cell behaviour can initiate tumorigenesis and promote the maintenance and progression of malignancy.

This cellular origin theory provides biologically consistent evidence for the diversity of tumor behaviours observed clinically.

The breast tumor microenvironment plays a fundamental role in actively organizing tumor initiation and progression [26]. Fibroblasts, adipocytes, immune cells, and other components of a complex work together to modulate the way BC develops, either suppressing or promoting its development. For example, cancer-related fibroblasts send signal to the other cells by providing extracellular matrix macromolecules, growth factors, and cytokines, all of which lead to the growth and spread of cancer cells. Additionally, immune cells, such as tumor-associated macrophages (TAM), produce cytokines that also participate in the promotion of angiogenesis, suppression of the immune system's ability to kill cancer cells, and promotion of the invasion of cancerous cells into new areas of the body. By reorganization of the extracellular matrix, the overall physical structure of tissue is altered, which also creates new pathways that can allow for the growth and movement of cancerous cells to other places within the body.

In addition, other inflammatory mediators such as IL-6, TNF- α , and COX-2-derived prostaglandins are involved in the promotion of the development of a microenvironment that promotes the development of BC [27]. Their action promotes DNA damage, angiogenesis, and immune system evasion. TAMs, for example, promote extracellular tissue remodelling and suppress immune responses. In this way, they allow pro-tumor cells to escape immune detection.

3. Pathology and subtypes of Breast Cancer

The complex heterogeneity features of the breast cancer disease overwhelm an extensive pathological features and molecular subtypes expressing different biological behaviour, prognosis, and therapeutic involvement. From a pathological point of view, breast cancer develops from the epithelial cells that connects the ducts and the lobules of the mammary gland. The involvement of these two mammalian sites on the cancer origin, leads us to an important classification:

- a. Ductal Carcinoma In Situ (DCIS) or intraductal carcinoma, is a non-invasive or pre-invasive breast cancer. It is responsible for about 1 out of 5 new breast cancer development and is commonly known as a stage 0 cancer. These types of carcinomas are characterised by cells present in the ducts that have changed to cancer cells but, in many cases, they have not spread through the walls of the ducts into the nearby breast tissue, staying confined within the milk duct. However, reported cases shown that, in some cases, the malignant cells spread out of the ducts invading nearby breast tissue, and this is well depicted in Figure 2/a [28].

Through this process, the DCIS becomes an invasive carcinoma tissue having the ability to spread and metastasize (to disseminate) to distant sites in the body.

- b. The most prevalent form of breast cancer is Invasive Ductal carcinoma (IDC), also known as infiltrating ductal carcinoma; IDC accounts for approximately seventy to eighty percent of all diagnosed breast cancers [29]. IDC, similar as DCIS, starts in the cells present in the milk duct in the breast. From there, the cancer breaks through the wall of the duct and grows into the nearby breast tissues (Figure 2/a). At this point, it may be able to spread to other parts of the body through the lymph system and bloodstream. It represents the invasive progression of the Ductal Carcinoma in Situ.
- c. Invasive Lobular Carcinoma (ILC), shown in Figure 2/b, starts in the breast glands accounting for milk production (lobules) and represent about 1 out of 10 invasive breast cancers. Like IDC, it can spread into surrounding breast tissue and metastasize to other part of the body. Compared to other types of invasive carcinoma, ILC may be harder to detect on physical examinations and image screening like mammograms, and it is more likely to affect both breasts [30]. About 1 in 5 women with ILC might have cancer in both breasts at the time of diagnoses.

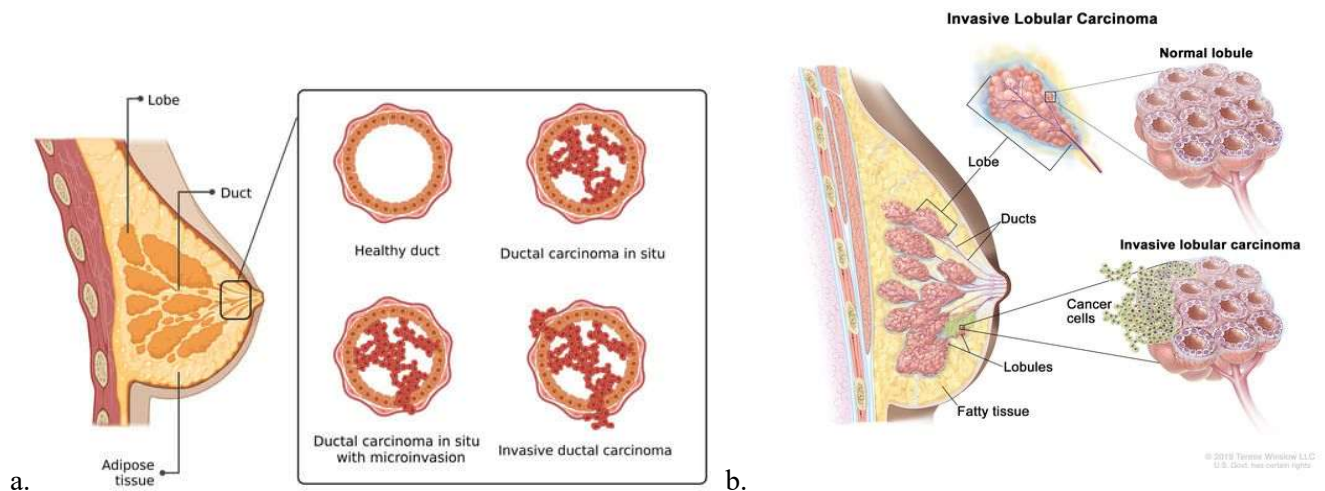


Figure 2. Pathological classification of breast cancer. a. Ductal carcinoma progression from in situ to invasive; b. Invasive Lobular Carcinoma evolution [28].

The Nottingham histological score is used to assess breast tumor grade by evaluating three characteristics of tumor aggressiveness: tubule formation, nuclear pleomorphism, and mitotic index [31]. The score provides prognostic information to supplement the histological stage of the tumor.

3.1 The Nottingham Scoring System

The Nottingham Scoring System is a breast cancer related system score able to deliver information's about how cancer cells look and how they grow compared to normal healthy breast cells. Its main role is to indicate how much aggressive a tumor may be. The score results give a grade to the breast tumor that is written in Arabic numbers. The grade of the cancer together with the cancer's size, its hormone receptor status, and other determinants, are essential on the determination of cancer stage. Cancer's characteristics involved in the formulation of the Nottingham score are:

1. Tubule formation: how much the tumor cells are similar to the normal cell structure.
2. Nuclear polymorphism: how much different are the tumor cells compared to the normal ones
3. Mitotic activity: status of cells division and reproduction.

Each of the mentioned characteristics is given a score from 1 to 3, from 1 being similar to normal and 3 being the mos abnormal. The sum of these scores is resulted to Nottingham score, with a minimum score of 3 and the maximum score of 9. The total score is assigned to a grade:

- Grade 1 breast cancer: have a score of 3 to 5 and is a well-differentiated cancer that tend to be less aggressive. Cancer cells looks just less different from normal cells, and grow in slow.
- Grade 2 breast cancer: have a score of 5 6 to 7 and it is a moderately differentiated cancer. Its cells look different from normal ones and tend to grow and divide faster than the healthy ones.
- Grade 3 breast cancer: have a score from 8 to 9 and comprises poorly differentiated cancers whose cells looks much different from normal cells that grow quickly in disorganized irregular patterns.

3.2 Molecular subtypes of breast cancer

Evolutions on immunohistochemical analysis and molecular profiling, revealed the understanding of breast cancer intrinsic subtypes. These subtypes are characterised by the expression of the estrogen receptor (ER) and progesterone receptor (PR) [32]. The receptor presence is evaluated during the biopsy, where cancer cells are taken and assessed for their presence.

The expression of hormone receptors means that the binding of the estrogen and progesterone to the receptors results in cancer grow stimulation and spread. Statistics shows that about 3 out of 4 breast cancers (75%) have at least one of these receptors [33]. This percentage is higher in older women than in younger women. Another subtype is determined based on whether or not the human epidermal growth factor receptor 2 (HER2) is expressed. HER2+ is found in 15-20% of breast cancers with high proliferation rates. The integration of ER, PR, and HER2 expression levels, along with the Ki-67 proliferation marker, allows for the categorization of breast cancer into four molecular subtypes [34]:

Luminal A, Luminal B, HER2-enriched, and Basal-like. The clinical classification of molecular subtypes of breast cancer has been summarized in Table 1 adapted from [35].

Molecular subtypes	Biomarkers	Frequency of cases	Histological grade	Prognosis	Response to therapies
Luminal A	ER+ HER2- PR+ Ki67 low	40-50	Well differentiated (Grade I)	Good	Endocrine
Luminal B [HER2+]	ER+ HER2+ PR+/- Ki67 low/high	20-30	Moderately differentiated (Grade II)	Intermediate	Endocrine Chemotherapy Target therapy
Luminal B [HER2-]	ER+ HER2- PR- Ki67 high				Endocrine Chemotherapy
Her 2+	ER- HER2+ PR- Ki67 high	15-20	Poorly differentiated (Grade III)	Poor	Chemotherapy Target therapy
Triple negative	ER- HER2- PR- Ki67 high	10-20	Poorly differentiated (Grade III)	Poor	Chemotherapy PARP inhibitors

Table 1: Classification of the molecular subtypes of Breast Cancer [35].

Luminal A tumors, the most common type, harbours some of the most significantly mutated genes, most frequent ones being the PIK3CA (45%) followed by MAP3K1, GATA3, TP53, CDH1 and MAP2K4, which take part in the p38-JNK1 stress kinase pathway [36]. They are usually ER-positive, PR-positive, and HER2-negative. The lower levels of the Ki-67 proliferative marker specify their low growing rates [37]. This kind of tumors are associated with a better prognosis and responsiveness to endocrine therapy.

Luminal B subtype, more aggressive than Luminal A, is characterized by higher mutations in TP53 than in Luminal A subtype, PIK3CA mutations (29%) and a number of pathway-inactivating events including ATM loss and MDM2 amplification along with GATA3 [38]. It is either HER2 negative with ER positive with high Ki67 (>14%) and low PR or Luminal B-like which has the same characteristics as Luminal B but with HER2 overexpressed [39]. For its treatment usually is essential to combine both hormonal therapy and chemotherapy, often requiring tailored treatments that target its specific markers. Either Luminal A or Luminal B subtypes are regarded to have the best prognostic and predictive factors [40].

HER2 enriched subtype (Amplification of Human Epidermal Growth Factor Receptor 2) represents 11-30% of all breast tumors and it is mostly defined by immunohistochemistry. It is recognized by the lack of ER and PR. HER2-E shows the highest levels of ErB-B2 mRNA and TP53 (72%) with PIK3CA

(39%), and is considered as the subtype with excessive activation of the EGFR-HER2 signalling pathway. Until now, there is no other biomarker for this class of BC except HER2 and HR status. It is also known that HER2 enriched subtype is associated with a poorer prognosis due to high cancer cell proliferating rates, increased metastatic potential, and failure of chemotherapy. The advent of targeted anti-HER2 therapies, such as trastuzumab and pertuzumab, has improved outcomes for this subgroup [41-42].

Basal-like breast cancers present an increased incidence in patients containing germline BRCA1 mutations. These tumors are also referred to as triple-negative breast cancers (TNBCs) because of the lack of ER, PR and HER2 (The Cancer Genome Atlas Network 2012). This subtype has a high frequency of TP53 mutations (80%) and loss of RB1 gene with PI3KCA being the upcoming most mutated gene. Hence, the lack of a target makes it intractable and contributes to poor prognosis and short term disease-free and overall survival [43]. Triple-negative breast cancers are subdivided into six unique groups, that are BL1, BL2, mesenchymal, MSL, IM and LAR [44]. Other rare less prevalent subtypes of BC carry unique clinical and pathological characteristics. They include:

- a. Medullary Carcinoma, a high-grade histologic tumor but adversely with a better prognosis [45];
- b. Mucinous Carcinoma, known for extracellular mucin production and better outcomes [46];
- c. Metaplastic Breast Carcinoma, an extremely aggressive form, and unmanageable through conventional treatment methods [47].

The proper identification of these unusual variants of breast cancers is essential because misidentification may result in inappropriate treatment.

Molecular techniques (gene expression profiling and NGS) yield information regarding the tumor's biology, treatment options, and prognosis when combined with standard histopathologic analyses. A number of different tests, such as Oncotype DX, MammaPrint, and Prosigna, measure the expression of many breast cancer-related genes to assist clinicians in determining whether adjuvant chemotherapy is appropriate for reducing the risk of recurrence. They are also important on guiding adjuvant therapy decisions, especially for early-stage, hormone receptor-positive subtypes [48]. In this way it is comprehensive that the integration of pathology and molecular diagnostics highlights the importance of an overall approach to BC management, confirming that therapy is proposed considering, for each case, both the morphological and molecular characteristics. Stromal cells, immune cells, and extracellular matrix make up the Tumor Microenvironment (TME), which is an important factor contributing to breast cancer's development and treatment responses. The interaction between breast cancer and their TME during metastasis will lead to a higher incidence of blood vessel formation (angiogenesis) and increased resistance to treatment [49]. In this way, pathology should be considered more broadly than just the structures of individual cells and as the result of complex biological systems.

4. Standard treatments (surgery, chemotherapy, radiotherapy)

The multidisciplinary approaches applied on breast cancer treatment evolution, combines different therapeutic protocols able to maximize survival and, at the same time, minimize morbidity. The usual clinical protocols for breast cancer treatment involves surgery, chemotherapy, radiotherapy, and hormonal therapy as shown in Figure 3. All these techniques are often combined, not only between each other but, also with targeted agents for specific molecular subtypes. Treatment assessments are based on tumour characteristics such as dimensions, stage, grade, lymph node involvement, and metastases development. In this context also, patient-related factors play an important decisive role including age, comorbidities, and lifestyle.

All these applications have mainly three common primary objectives: achieve complete extinction of the tumour, prevent reappearance, and improve the quality of life in general. Over the past decades, advances in diagnostic imaging, molecular profiling, and surgical techniques have enabled a more personalized approach, allowing clinicians to customize treatment intensity to different individual risk profiles, based on their clinical course [50].

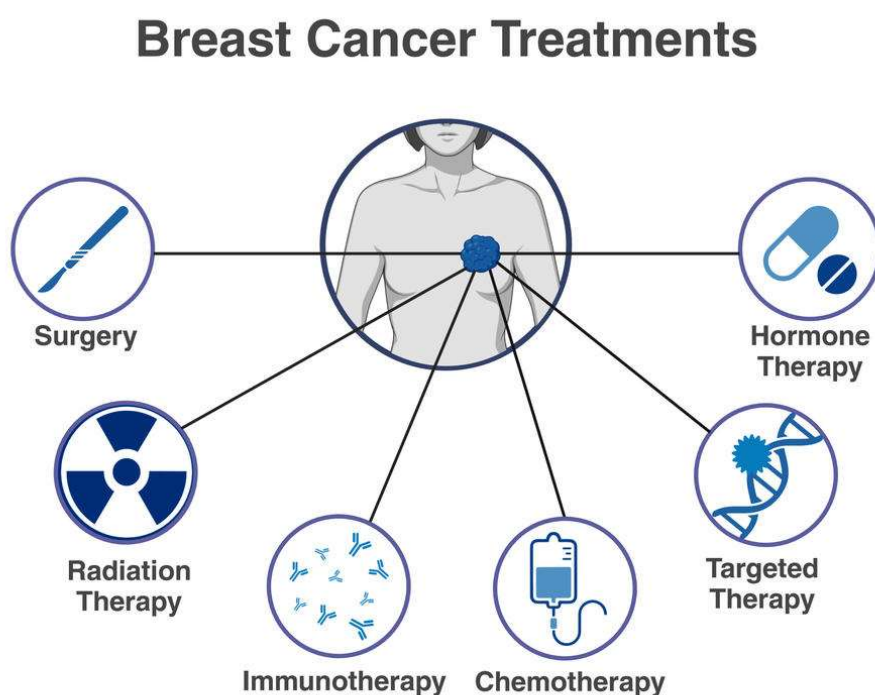


Figure 3. Representation of the different breast cancer treatments. Adapted from National Cancer Institute.

4.1 Chemotherapy

Chemotherapy, as a systemic therapy, uses anti-cancer drugs able to travel through the bloodstream to reach the active site of the cancer cells. These drugs may be administered intravenously or by mouth targeting rapidly dividing cells and plays a pivotal role in both early-stage and advanced breast cancer. Chemotherapeutic approaches are not applied in every breast cancer treatment. The principal conditions in which these drugs are recommended can be before surgery (neoadjuvant) or after surgery (adjuvant) [51].

In the first case, neoadjuvant chemo drugs might be given to try to decrease tumour's size so it can be removed with less extensive surgery. Because of this, neoadjuvant chemotherapy is often used to treat cancers that either are too big to be removed by surgery when first diagnosed and have many lymph nodes involvement, or are inflammatory breast cancers [52]. Instead, adjuvant chemotherapeutic drugs administration tries to kill any cancer cells that might have been left behind after surgery or have spread but can't be seen even on image screening. Is important to underly that chemotherapy can be used as the main treatment for patients in which cancer has spread outside the breast and underarm area to distant organs like liver or lungs [53].

Standard chemotherapeutic agents include anthracyclines (doxorubicin and epirubicin), taxanes (paclitaxel and docetaxel), cyclophosphamide, carboplatin, capecitabine, and fluorouracil, which are usually administered in combination prescription to improve efficacy [54]. For HER2-positive tumours, modern clinical approaches involve also targeted drug therapies such as trastuzumab and pertuzumab that target proteins on cancer cells responsible for cell, spread, and longevity, improving in this way survival outcomes and limiting systemic toxicity. The commitment of chemotherapeutic regimens depends by the molecular profile of the tumour considering its morphological characteristics, proliferation rate, and hormone receptor status [55]. While chemotherapy can cause adverse effects such as myelosuppression, alopecia, and gastrointestinal toxicity, supportive care measures and dose adjustments have improved tolerability and patient quality of life [56].

4.2 Surgery

Surgery remains still the fundamental technique for localized breast cancer treatment. Different types of breast surgery are performed according to the tumour expansion and marginal definition. The principal goal of this treatment is to remove completely the tumour while preserving the healthiest tissue that is possible. Breast-conserving surgery (BCS) known also as lumpectomy, quadrantectomy, or partial mastectomy, removes the cancer as well as some surrounding breast normal tissue containing that.

This technique is usually the best option for early-stage cancers because it allows the preservation of the breast and cosmetic appearance. However, almost always, patients that are subjected to this surgery requires radiation therapy. On the other hand, mastectomy surgery removes the entire breast and sometimes removes also nearby tissues, and it is performed for large, multifocal tumours. The second techniques may be chosen or recommended due to an advanced tumour stage or for personal decisions considering radiation exposure after BCS [57-58].

4.2.1 Surgery to remove nearby lymph nodes.

In order to figure out the stage of the cancer, the patient is subjected to the removal and studying of one or more lymph nodes. These techniques are important for understanding if the breast cancer has spread to underarm (axillary) lymph nodes. In that context, lymph nodes may be removed either as part of the surgery to remove the breast cancer or as a separate operation [59]. The two main types of surgery to remove lymph nodes are:

- a. Sentinel lymph node biopsy, a procedure in which the surgeon injects a radioactive substance or a blue dye and then removes only the lymph nodes under the arm that have taken up the dye (sentinel node). These lymph nodes cover the location in which the cancer would likely spread first.
- b. Axillary lymph node dissection, in which the surgeon removes usually less than 20 lymph nodes from the area under the axilla and check them for cancer spread. It is usually performed at the same time as a mastectomy or breast-conserving surgery.

4.3 Radiation therapy

The radiation therapy involves high-energy rays or particles that destroy cancer cells. Depending on the tumour's stage, radiotherapy can be used in several situation. As we mentioned before, most of the patients that undergo breast-conserving surgery, requires radiation therapy next, to reduce the chances for local recurrence in the same breast or nearby lymph node and improve survival [60]. The therapy can be also applied after a mastectomy of large size cancers that involves many lymph nodes, and in cases where it spreads to other parts of the body, like bones spinal cord, and brain. The main types of radiation therapy that can be used to treat breast cancer are external beam radiation therapy (EBT) and brachytherapy. The first one is the most common radiation therapy for BC. It is performed by a machine from outside the body that focuses the radiation on the area affected by the cancer. The areas that need radiation depends on the surgery type that patient had. If the patient had a mastectomy, radiation will be focused on the chest wall, the mastectomy scar, and the places where any drains exited the body after surgery.

Instead, if it is performed a BCS, the patient will most likely have radiation to the entire breast. EBT after surgery do not start usually until the surgery site has healed, and this may take a month or longer [61]. The second type of radiation therapy is the brachytherapy also known as internal radiation. It consists of the use of a device containing radioactive seeds or pellets placed into the breast tissue for a short time in the area where the cancer had been removed (tumour bed). For certain patients who had breast-conserving surgery (BCS), brachytherapy can be used by itself (instead of radiation to the whole breast) as a form of accelerated partial breast irradiation. Tumour size, location, and other factors may limit who can get brachytherapy [62].

4.4 Hormonal therapy

Hormonal or endocrine therapy is a main treatment that block the attachment of estrogens and progesterone respectively to estrogen receptor and progesterone receptor breast cancer cells. In this way the therapy is recommended only for patients affected by hormone receptor-positive tumours, and it is able to reach cancer cells almost anywhere in the body and not just in the breast. Hormone therapy, even though it can start before surgery, it is often prescribed after that, as an adjuvant therapy to reduce the risk of cancer recurrence [63]. There are several types of endocrine therapy for breast cancer. Most types of them either lower estrogen levels in the body or stop estrogen from helping breast cancer cells grow. The drugs that block estrogen receptors, stop estrogen from fuelling breast cancer cells to grow. They can be divided in two major categories: selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs). SERM drugs are pills taken by mouth that block estrogen from connecting to the cancer cells and induce them to grow and divide. While they have anti-estrogen effects in breast cells, they act like an estrogen in other tissues, like the uterus and the bones [64]. On the other hand, SERDs attach to estrogen receptors more tightly and cause them to be broken down. These drugs are mainly used in women who are in post menopause. When given to pre-menopausal women, they need to be combined with a luteinizing-hormone releasing hormone (LHRH) agonist to turn off the ovaries [65]. Differently, the drugs that lower estrogen levels induce a slow of the cancer's grow and help to prevent it from coming back. Before menopause, most estrogen is made by the ovaries. But in women whose ovaries are not working, either because they have gone through menopause or because of certain treatments, estrogen is still made in body fat by an enzyme called aromatase. Aromatase inhibitors (AIs) are drugs that stop most estrogen production in the body from aromatase enzyme [66]. Hormonal therapy is usually administered for at least 5 years. Treatment longer than 5 years might be prescribed to patients who have a higher chance of recurrences. This therapy is associated with mild side effects compared to chemotherapy, though long-term use can be linked to bone density loss and cardiovascular effects.

Endocrine therapy is also effective in the metastatic setting, often combined with targeted agents such as CDK4/6 inhibitors to enhance efficacy [67].

4.5 Integration and personalization

The therapeutic techniques described above are rarely applied individually in breast cancer treatment. The protocols of treatment are formulated according to the physical and biological characteristics of the tumour. They take in consideration also patient preferences, and risk stratification. Multidisciplinary oncology committees composed of oncology experts and support teams are the cornerstone of major cancer centres, ensuring effective treatment and optimizing quality of life. The use of molecular techniques and biomarkers in treatment applications has significantly improved the personalization of therapy [68]. These techniques help to characterised patients who could benefit from more effective treatment and those in whom overtreatment could be avoided. The personalized treatments applied have significantly improved survival rates and quality of life, reduced recurrences, and diminished long-term post-treatment side effects.

5. Functional consequences of treatment

In the recent past, advancements in breast cancer treatment have led to an increase in survival rates. However, as the number of patients living through recovery from breast cancer is growing significantly, there has been a corresponding increase in functional effects from oncologic treatment. These treatments can cause structural, neuromuscular, and functional alterations that persist in long-term beyond the nearest post-surgical period. The main concern that emerges from these changes, can significantly affect upper limb function, resulting in breast cancer-related lymphedema (BCRL).

BCRL is one of the most common post-surgical complications for patients who have undergone breast cancer surgery. The patient may complain of shoulder pain, limitation of movements, weakness and swelling of the limbs. These changes persist long after the completion of treatment. In fact, it has been observed that these changes can significantly affect the quality of life [69].

It is important to note that upper limb dysfunction is more than a mechanical problem. In fact, it is a complex multifactorial condition that results from changes affecting tissue re-modelling, neuromuscular activity, and inflammatory pathways that occur during breast cancer treatment. These changes are multidimensional and must be considered as such if effective rehabilitation strategies are to be developed to deal with upper limb dysfunction.

5.1 Structural and biological disruptions

Breast cancer surgery and axillary lymph node dissection trigger an inflammatory response and healing process, leading to tissue re-modelling [70]. Fibroblast proliferation and extracellular matrix hyperproduction may cause scar tissue development, decreased flexibility of the fascial layers, and diminished tissue extensibility. These conditions may impact the biomechanical characteristics of the shoulder joint and restrict normal joint range of motion.

Radiation therapy may also play a role in decreasing tissue extensibility through the long-term activation of fibrotic pathways and vascular alterations. These changes may cause a reduced vascularization and increased density of the connective tissue layers, leading to a compliance and functional restriction.

In this way, these processes can create a biological environment with altered mechanical characteristics and a pro-inflammatory environment, which may impact tissue function and neuromuscular mechanisms.

5.2 Neuromuscular alterations

In addition, there are significant neuromuscular adaptations that can occur in breast cancer patients [71]. For example, pain, stiffness, and sensory feedback can affect motor control strategies, forcing to adaptations in muscle recruitment.

Research has shown that breast cancer patients can have alterations in the activation of shoulder stabilizer muscles, delayed muscle recruitment, and increased co-contraction patterns in the upper limb. These adaptations occur due to compensatory mechanisms that aim to protect the affected areas. These adaptations, therefore, can result in decreased movement efficiency.

In this way, even if there is an adequate amount of joint movement, there can be alterations in movement coordination. These alterations cannot be easily determined unless advanced methods of biomechanical and neuromuscular assessments are performed.

5.3 Lymphedema and functional limitations

Upper limb breast cancer-related lymphedema is one of the most frequent side effects that breast cancer patients suffer because of treatment methods that involve the removal or irradiation of lymph nodes [72]. Lymphedema is caused by an impairment in the process of normal drainage, causing an accumulation of protein-containing fluid in the affected limb. It develops through a combination of inflammation, adipose tissue formation, and fibrosis. These conditions can result in alterations of the upper limbs' biomechanics and weight. Cancer patients who suffer from lymphedema complain

feelings of heaviness and discomfort in the upper limbs, and these feelings can affect the utilization of upper limbs [73].

5.4 Impact on daily activities and Health-Related Quality of Life

The functional limitations that have been described can have a significant impact on the execution and completion of everyday activities. For example, some normal, usual activities, like reaching near places or moving objects, can become a challenge due to pain and weakness.

Patient's psychosocial state is another limitation resulting from the conditions explained before [74]. For instance, cancer-related discomfort and disability can have a negative impact on the patient's self-confidence. Fatigue related to cancer may also exacerbate the disability [75].

Therefore, in assessing the rehabilitation outcomes of breast cancer survivors, it is important to use assessment tools not only capable of measuring functional outcomes objectively but also those able to measure the patient's perception of disability or quality of life.

6. Conventional physiotherapy approaches and limitations

Conventional physiotherapy techniques remain the gold standard treatment in the rehabilitation of upper limbs in breast cancer survivors. Conventional physiotherapy for breast cancer survivors includes a variety of clinical interventions such as range of motion, progressive strengthening, postural re-education, scar mobilization techniques, manual therapy techniques, and management techniques for lymphedema. These clinical interventions over the years have shown clear efficacy in breast cancer survivors in terms of shoulder range of motion, reduction in pain levels, and achievement of functional independence in daily activities [76].

Randomized controlled trials and systematic reviews have shown positive outcomes in shoulder flexion and abduction movements, muscular strength in the scapulohumeral rhythm, and reduction in perceived disability after exercise programs [77]. These outcomes are associated with significant improvements in health-related quality of life in breast cancer survivors.

Nevertheless, in spite of its proven efficacy, traditional models of rehabilitation have inherent methodological and structural limitations. Among these, an important limitation is that related to assessment strategies. In fact, clinical evaluation is often performed at distinct time points, and methods like goniometry, manual stretching, measurement of limb circumference, and patient-based questionnaires are employed. Though useful, these methods only give an incomplete account of functional capability and can be insensitive in identifying small neuromuscular and kinematic changes [78]. Thus, in range-of-motion testing, although joint movement can be quantified, no information is provided on movement quality, speed, and coordination.

Manual muscle testing provides an estimate of muscle strength, but no information is provided on muscle recruitment timing and coordination. Likewise, limb circumference provides information on volume changes in patients with lymphedema but does not give any information on composition and motor implications.

Another limitation is related to ecological validity. Rehabilitation is usually conducted in a clinical environment that may not accurately represent the demands placed on movement in daily activities. Rehabilitation gains may not necessarily equate to optimized movement strategies in daily activities. As such, compensatory movements may be present without recognition in daily activities [79].

Compliance with exercise programs carried out at home is another limitation. After patients leave the clinical environment to practice on their own, there is limited ability to monitor their activities. Clinicians are forced to rely on patient reports on exercise compliance. This may be subject to bias or motivational effects. Lack of sufficient exercise may limit the efficacy of the program, while excessive or improper exercise may lead to discomfort or exacerbation of symptoms [80].

Furthermore, there is often an emphasis on subjective clinical judgment in determining how rehabilitation is progressing, instead of quantification in terms of motor function. For example, how intense an exercise regimen is, or how much load an individual can manage, might differ between practitioners due to the lack of digital monitoring frameworks.

The above limitations should not, in any way, undermine the efficacy of traditional physiotherapy. Instead, they underscore the importance and benefits that could be realized from an integration with objective measurement technologies. This, in fact, could lead to an improvement in the degree of precision in physiotherapy, in addition to quantification and measurable recovery.

In this regard, it is possible to affirm that there is a harmonious relationship between traditional physiotherapeutic applications and digital technologies, mainly those related to wearable sensors.

7. Functional evaluation questionnaires in post-mastectomy rehabilitation

Assessment of quality of life (QoL) is a crucial component of the post-mastectomy rehabilitation program, as surgery has a significant effect on the physical, psychological, and social well-being of the individual. Though assessments of range of motion, muscle strength, and activation of muscles provide vital and critical pieces of information concerning physical status, no such scale can measure the subjective experience of disability, pain, or psychosocial challenges [81]. In this context, Patient-Reported Outcome Measures (PROMs) questionnaires play an integral role in the assessment of QoL in post-mastectomy patients, as it will help clinicians and researchers quantify disabilities, complications arising from disease and rehabilitation, and overall health status [82].

Therefore, it will be easier to assess and evaluate the efficacy of telerehabilitation programs. Some of the most common questionnaires used in this context are explained above.

7.1 DASH

The Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire is one of the most common methods for evaluating the capacity of a patient with musculoskeletal or post-surgical disorders of the upper limb (Figure 4). A better representation of the questionnaire is shown on Appendix 1. The results of the tests provide an assessment of the patient's physical capacity, the presence of symptoms, and their ability to function. These results are provided using a series of test items and are normalized within an overall score representing the perceived disability of the affected patient. Following mastectomy, the DASH test provides a critical tool when monitoring shoulder movements, patient arm strength, as well as any post-surgery or treatment disorders. By providing continuous results, clinicians are able to effectively evaluate the success of an exercise routine and make any necessary adaptations with respect to an individual's needs [83-84].

As a result of wearable technology, explained later, the results of the DASH test provide a subjective extension of the quantitative results provided through such devices.

Questionario per l'arto superiore DASH
(Disability of the Arm, Shoulder and Hand) Italian Version

Istruzioni: Il presente questionario riguarda i Suoi sintomi e la Sua capacità di compiere alcune azioni. Risponda a ogni domanda facendo riferimento al Suo stato durante l'ultima settimana. Se non ha avuto l'opportunità di eseguire una delle azioni durante l'ultima settimana, risponda alla domanda **provando a immaginare** come avrebbe potuto eseguirle. Non importa con quale mano o braccio Lei esegue l'azione; risponda in base alla Sua capacità di compierla e senza tenere conto del modo in cui la compie.

Valuti la sua capacità di eseguire le seguenti azioni durante l'ultima settimana.

	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non ci sono riuscito
1. Svitare il coperchio di un barattolo ben chiuso o nuovo.	1	2	3	4	5
2. Scrivere.	1	2	3	4	5
3. Girare una chiave.	1	2	3	4	5
4. Preparare un pasto.	1	2	3	4	5
5. Aprire spingendo una porta pesante.	1	2	3	4	5
6. Pesare un oggetto su uno scaffale al di sopra della propria testa.	1	2	3	4	5
7. Fare lavori domestici pesanti (es. lavare i pavimenti o i vetri).	1	2	3	4	5
8. Fare lavori di giardinaggio.	1	2	3	4	5
9. Rifare il letto.	1	2	3	4	5
10. Portare la borsa della spesa o una ventiquattrina.	1	2	3	4	5
11. Portare un oggetto pesante (oltre 5 Kg).	1	2	3	4	5
12. Cambiare una lampadina posta al di sopra della propria testa.	1	2	3	4	5
13. Lavarsi le mani e asciugarsi i capelli.	1	2	3	4	5
15. Infilarsi un maglione.	1	2	3	4	5
16. Usare un coltello per tagliare del cibo.	1	2	3	4	5
17. Attività ricreative che richiedono poco sforzo (es. giocare a carte, lavorare a maglia).	1	2	3	4	5
18. Attività ricreative nelle quali si fa forza o si prendono colpi sul braccio, sulla spalla o sulla mano (es. usare il martello, giocare a tennis o a golf, ecc.).	1	2	3	4	5
19. Attività ricreative che richiedono un movimento libero del braccio (es. giocare a football, a badminton, ecc.).	1	2	3	4	5
20. Far fronte alle necessità di spostamento (andare da un posto ad un altro).	1	2	3	4	5
21. Attività sessuale.	1	2	3	4	5

Questionario per l'arto superiore DASH
(Disability of the Arm, Shoulder and Hand) Italian Version

Durante la settimana passata, in che misura il suo problema al braccio, alla spalla o alla mano ha interferito con le normali attività sociali con la famiglia, gli amici, i vicini di casa i gruppi di cui fa parte?

	Per nulla	Molto poco	Un po'	Molto	Moltissimo
22.	1	2	3	4	5

Durante la settimana passata è stato limitato nel suo lavoro o in altre attività quotidiane abituali a causa del suo problema al braccio, alla spalla o alla mano?

	Non mi ha limitato per nulla	Mi ha limitato leggermente	Mi ha limitato discretamente	Mi ha limitato molto	Non ci sono riuscito
23.	1	2	3	4	5

Valuti l'intensità dei seguenti sintomi durante l'ultima settimana.

	Nessuno	Lieve	Discreto	Forte	Estremo
24. Dolore al braccio, alla spalla o alla mano	1	2	3	4	5
25. Dolore al braccio, alla spalla o alla mano nel compiere una qualsiasi attività specifica	1	2	3	4	5
26. Formicolio (sensazione di punture di spillo) al braccio, alla spalla o alla mano	1	2	3	4	5
27. Debolezza al braccio, alla spalla o alla mano	1	2	3	4	5
28. Rigidità del braccio, della spalla o della mano	1	2	3	4	5

Durante l'ultima settimana quanta difficoltà ha incontrato nel dormire a causa del dolore al braccio, alla spalla o alla mano?

	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non sono riuscito a dormire
29.	1	2	3	4	5

Mi sento meno capace, meno fiducioso o meno utile a causa del mio problema al braccio, alla spalla o alla mano?

	Non sono assolutamente d'accordo	Non sono d'accordo	Non saprei	Sono d'accordo	Sono assolutamente d'accordo
30.	1	2	3	4	5

Questionario per l'arto superiore DASH
(Disability of the Arm, Shoulder and Hand) Italian Version

MODULO LAVORATIVO (OPZIONALE)
Le seguenti domande si riferiscono all'impatto del suo problema al braccio, alla spalla o alla mano sul suo lavoro (compreso il lavoro in casa se questa è la sua attività principale).
Indichi qual è il suo lavoro/attività: _____

Indichi su ogni riga il numero che meglio descrive la sua capacità fisica durante l'ultima settimana.

Ha avuto difficoltà:

	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non ci sono riuscito
31. A utilizzare la Sua tecnica abituale per lavorare?	1	2	3	4	5
32. A svolgere il Suo lavoro abituale a causa del dolore al braccio, alla spalla o alla mano?	1	2	3	4	5
33. A fare il lavoro bene come vorrebbe?	1	2	3	4	5
34. A dedicare al Suo lavoro la consueta quantità di tempo?	1	2	3	4	5

MODULO ATTIVITÀ SPORTIVE/RECREATIVE (OPZIONALE)
Le seguenti domande si riferiscono all'impatto del Suo problema al braccio, alla spalla o alla mano sulla Sua capacità di suonare il Suo strumento musicale o praticare il Suo sport, o su entrambe le attività.
Se pratica più di uno sport o suone più di uno strumento (o fa entrambe le cose) risponda facendo riferimento all'attività che è più importante per lei.
Indichi quale sport o strumento è il più importante per lei: _____

Indichi su ogni riga il numero che meglio descrive la sua capacità fisica durante l'ultima settimana.

Ha avuto difficoltà:

	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non ci sono riuscito
35. A utilizzare la Sua tecnica abituale per suonare il suo strumento o praticare il suo sport?	1	2	3	4	5
36. A suonare il suo strumento o praticare il suo sport a causa del dolore al braccio, alla spalla o alla mano?	1	2	3	4	5
37. A suonare il suo strumento o praticare il suo sport bene come vorrebbe?	1	2	3	4	5
38. A dedicare al suo strumento o al suo sport la consueta quantità di tempo?	1	2	3	4	5

Figure 4. Disabilities of the Arm, Shoulder, and Hand questionnaire.

7.2 Lymphedema Life Impact Scale, version 2 (LLISv2)

A disease-specific tool, LLISv2 (Figure 5) is designed to assess physical, functional, and psychosocial consequences of lymphedema, a common health concern often experienced in different individuals undergoing mastectomies [85]. As an extensive measurement tool, LLISv2 targets and assesses specific symptoms such as swelling, heaviness, and discomfort. Additionally, it measures the consequences of such disease manifestations on the ability of an individual to participate in daily activities, work, and other psychosocial events.

In the context of rehabilitation, it is used to recognize individuals who are vulnerable to deterioration, track the progression of the illness, and measure the effectiveness of treatment targeting swelling reduction and functional improvement. In conjunction with the potential of wearable technologies for monitoring activity and usage patterns of the limbs, LLISv2 presents a complete understanding of the physiological and psychosocial consequences of a specific illness. A better representation of the questionnaire is shown on Appendix 1

LLIS Lymphedema Life Impact Scale									
Version 1									
Cognome e Nome _____					Data _____				
Qui di seguito sono elencati i sintomi o i disturbi che vengono descritti da molti pazienti che hanno un linfedema. Per favore indichi quanto questi disturbi associati al suo linfedema sono stati per lei un problema durante le ultime 2 settimane . Se entrambi gli arti sono gonfi, giudichi i disturbi degli arti gonfi rispetto a qualsiasi arto non gonfi. Faccia un cerchio sul numero che meglio descrive l'entità del disturbo.									
• DISTURBI FISICI									
1. L'intensità del dolore associato al linfedema è: 12345 nessun doloredolore fortissimo					5. Rispetto all'arto sano, la pelle dell'arto gonfi sembra al tatto: 12345 ugualeestremamente diversa				
2. L'intensità del senso di pesantezza associato al linfedema è: 12345 nessuna pesantezzaestremamente pesante					6. Il linfedema limita i movimenti dell'arto gonfi: 12345 movimenti normaliestremamente limitati				
3. L'intensità di ingrossimento cutaneo associato al linfedema è: 12345 nessun ingrossimentoestremamente ingrossito					7. Rispetto all'arto sano, la forza dell'arto gonfi è: 12345 stessa forzaestremamente debole				
4. Rispetto all'arto sano, la dimensione dell'arto gonfi sembra: 12345 dimensione normaleestremamente grande					8. Negli ultimi 2 anni, quante volte ha dovuto prendere antibiotici per bocca o essere ricoverato per infezione all'arto gonfi? 12345 mai<1 volta per anno1-3 volte per anno4-6 volte per anno>6 volte per anno				
• DISTURBI PSICOSOCIALI									
9. Il linfedema condiziona la mia immagine corporea (cioè come penso di sembrare): 12345 per nullagravemente									
10. Il linfedema condiziona la socializzazione con gli altri: 12345 nessuna interferenzainterferisce totalmente									
11. Il linfedema condiziona le mie relazioni intime: 12345 nessuna interferenzainterferisce totalmente									
12. Il linfedema mi fa sentire più (cioè mi sento depresso, frustrato o arrabbiato per colpa del linfedema): 12345 maicostantemente									
14. Il linfedema condiziona la capacità di eseguire le cose che devo fare a lavoro (se applicabile): 12345 nessuna interferenzainterferisce totalmente									
15. Il linfedema condiziona la prestazione nelle mie preferite attività ricreative: 12345 nessuna interferenzainterferisce totalmente									
16. Il linfedema condiziona la giusta taglia di vestiti/scarpe: 12345 per nullaimpossibile da indossare									
17. Il linfedema condiziona il mio sonno: 12345 nessuna interferenzainterferisce moltissimo									
18. Devo contare sull'aiuto di altri per colpa del mio linfedema: 12345 per nullatotalmente									
• DISTURBI FUNZIONALI									
13. Il linfedema condiziona la capacità di eseguire le cose che devo fare a casa: 12345 nessuna interferenzainterferisce totalmente									

Figure 5. Lymphedema Life Impact Scale, version 2 questionnaire.

7.3 EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire (Figure 6) is used to assess the quality of life in patients with cancer [86]. It includes domains that assess the health status of the patient, physical functions of patients, fatigue, pain, and emotional as well as role functions. Using this instrument, one can obtain a comprehensive view of the quality of life of the patient. When used with breast cancer patients, it will show the impact of surgery and rehabilitation on their quality of life, as well as the impact of therapy and all that it entails as the patient comes to terms with her new condition and rehabilitation. By using the QLQ-C30 on breast cancer patients longitudinally, medical professionals can follow improvements or negative changes in the quality of life and track these with measurable data collected using wearable devices such as IMUs and REMO. A better representation of the questionnaire is shown on Appendix 1

Together, DASH, LLISv2, and EORTC QLQ-C30 will present a multidimensional picture of recovery concerning upper limb, the impact of lymphedema, and overall health-related quality of life. Such tools, in conjunction with objective monitoring via wearable technologies, will enable clinicians to make an exhaustive evaluation of the efficiency of telerehabilitation approaches. This way, personalized rehabilitation will be achieved, and the intensity of exercise, compliance, and any potential complications can be managed to improve the outcome for the patient.



EORTC QLQ-C30 (versione 3)

Con questo questionario vorremmo sapere alcune cose su di Lei e sulla Sua salute. La preghiamo di rispondere a tutte le domande selezionando il numero che meglio corrisponde alla Sua risposta. Non esiste una risposta "giusta" o "sbagliata". Le Sue informazioni verranno tenute strettamente riservate.

Patient ID: CH - ____ - ____ - ____

Date: _____

	No	Un po'	Parecchio	Moltissimo
1. Ha difficoltà nello svolgere attività faticose, come portare una borsa della spesa pesante o una valigia?	1	2	3	4
2. Ha difficoltà nel fare una <u>lunga</u> passeggiata?	1	2	3	4
3. Ha difficoltà nel fare una <u>breve</u> passeggiata fuori casa?	1	2	3	4
4. Ha bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4
Durante gli ultimi sette giorni:				
6. Ha avuto limitazioni nel fare il Suo lavoro o altre attività quotidiane?	1	2	3	4
7. Ha avuto limitazioni nel praticare i Suoi passatempi-hobby o altre attività di divertimento o svago?	1	2	3	4
8. Le è mancato il fiato?	1	2	3	4
9. Ha avuto dolore?	1	2	3	4
10. Ha avuto bisogno di riposo?	1	2	3	4
11. Ha avuto difficoltà a dormire?	1	2	3	4
12. Ha sentito debolezza?	1	2	3	4
13. Le è mancato l'appetito?	1	2	3	4
14. Ha avuto un senso di nausea?	1	2	3	4
15. Ha vomitato?	1	2	3	4
16. Ha avuto problemi di stitichezza?	1	2	3	4

	No	Un po'	Parecchio	Moltissimo
17. Ha avuto problemi di diarrea?	1	2	3	4
18. Ha sentito stanchezza?	1	2	3	4
19. Il dolore ha interferito con le Sue attività quotidiane?	1	2	3	4
20. Ha avuto difficoltà a concentrarsi su cose come leggere un giornale o guardare la televisione?	1	2	3	4
21. Si è sentito/a teso/a?	1	2	3	4
22. Ha avuto preoccupazioni?	1	2	3	4
23. Ha avuto manifestazioni di irritabilità?	1	2	3	4
24. Ha avvertito uno stato di depressione?	1	2	3	4
25. Ha avuto difficoltà a ricordare le cose?	1	2	3	4
26. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con la Sua vita <u>familiare</u> ?	1	2	3	4
27. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con le Sue attività <u>sociali</u> ?	1	2	3	4
28. Le Sue condizioni fisiche o il Suo trattamento medico Le hanno causato difficoltà finanziarie?	1	2	3	4

Per le seguenti domande ponga un cerchio intorno al numero da 1 a 7 che meglio corrisponde alla Sua risposta:

29. Come valterebbe in generale la Sua <u>salute</u> durante gli ultimi sette giorni?	1	2	3	4	5	6	7
Pessima							Ottima

30. Come valterebbe in generale la Sua <u>qualità di vita</u> durante gli ultimi sette giorni?	1	2	3	4	5	6	7
Pessima							Ottima

Figure 6. EORTC QLQ-C30 questionnaire

8. Motor rehabilitation and assistive technologies

Motor rehabilitation is a key aspect of breast cancer survivorship care. As mentioned before, the dysfunction of the upper limbs of breast cancer patients goes beyond the limitation of the joint and weakness of the muscles. It results from a complex interplay of tissue remodelling, inflammatory responses, neuromuscular adaptations, and motor compensation. Rehabilitation of the upper limbs of post-treatment breast cancer patients consists, in this way, not only on the rehabilitation of the range of motion. It involves a multidimensional rehabilitation approach that aims to promote the improvement of functional performance, biological recovery, and quality of life [87]. From a clinical point of view, rehabilitation of breast cancer patients includes a combination of different techniques, like early mobilization, progressive range of motion, resistance training, and postural re-education. Improvement on biological conditions, instead, is due to neuromuscular retraining, and various techniques of lymphatic management [78, 88]. There is now considerable evidence that the rehabilitation of breast cancer patients through physiotherapeutic interventions could lead to the improvement of the range of motion of the shoulder joints and the muscles.

In fact, resistance training, which has previously been believed to be contraindicated in patients at risk of developing lymphedema, is now believed to be safe and may be beneficial [89]. The effects of rehabilitation go beyond the mechanical and biomechanical improvements. Today it is quite clear from a clinical point of view that physical activity and exercise interventions could positively influence inflammatory mediators, endothelial function, lymphatic circulation, and muscle metabolism in skeletal muscles [90]. At the neuromuscular level, repetitive and well performed exercise interventions may have an impact on motor coordination and reduce abnormal compensatory mechanisms. These findings support the idea of a multidimensional model of rehabilitation in which physical, biological, and psychosocial domains interact dynamically [91]. It is important to reiterate that, as mentioned before, even though the benefits of conventional physiotherapy have been well established, some limitations associated with rehabilitation interventions are challenging clinicians. These limitations have led to the advancement of technology-assisted rehabilitation strategies, especially in the realm of telerehabilitation. Indeed, it is believed that the application of technology may enhance the continuity of care, accessibility, and objective monitoring of recovery processes [92-93].

In this regard, assistive and wearable technologies have been identified as a promising means of supporting rehabilitation processes and outcome measurement. In greater detail, wearable technologies may be used for providing quantified information regarding the performance of patients during functional tasks, thereby enhancing the application of conventional clinical assessments.

Indeed, wearable technologies may be used for monitoring physiological and biomechanical responses during movement and task execution, thereby enhancing the sensitivity of rehabilitation processes [94]. The application of wearable technologies in clinical settings has led to the advancement of the concept of digital functional biomarkers, which are quantified and objective measures of recovery processes. Digital biomarkers are particularly relevant in oncological rehabilitation because there is a chance to identify trends, asymmetries, and compensatory strategies in recovery processes that are not visible through clinical observation alone. In addition, there is a chance to individualize exercise intensity and progression through data-driven approaches, which is particularly important in rehabilitation processes [95]. However, the clinical application of assistive and wearable technology in breast cancer rehabilitation is still in its development stage. In particular, standardization methods are still to be addressed in breast cancer populations. In addition, much of the literature has been focused on individual technology or outcome measures, whereas the application of multiple methods is less well represented. From this perspective, the application of assistive technology in motor rehabilitation should be seen not as a substitute for conventional methods of physiotherapy, but as a step forward to more accurate, objective, and individualized approaches to patient care.

8.1 The RESTORE-MAM Project within the NODES Ecosystem

The growing interest in digital health technologies and personalized rehabilitation strategies has promoted the development of innovative research programs dedicated to technology-assisted healthcare approaches. In this context, the present work was developed within the framework of the RESTORE-MAM project (“TeleRiabilitazione con interfaccia Elettromiografica e SupportO multimediale per tumore MAMario”), an academic initiative belonging to the NODES ecosystem (“Nord Ovest Digitale e Sostenibile”). NODES is an innovation ecosystem funded by the Italian Ministry of University and Research (MUR) through the National Recovery and Resilience Plan (PNRR) under the NextGenerationEU initiative. The ecosystem promotes collaboration between universities, healthcare institutions, research centres, and industrial partners with the objective of supporting digital and sustainable innovation across different strategic sectors in Northwestern Italy. In particular, RESTORE-MAM is included within Spoke 5 – Industry for Health and Silver Economy, which focuses on the development of innovative healthcare technologies, digital medicine, and rehabilitation solutions. The RESTORE-MAM project was conceived to support the development of innovative rehabilitation strategies for breast cancer survivors, with particular attention to upper limb dysfunction and breast cancer-related lymphedema. The project promotes the integration of wearable technologies, electromyographic interfaces, and digital rehabilitation approaches in order to improve functional assessment, rehabilitation monitoring, and patient support.

Within recent years, wearable technologies have progressively attracted attention in rehabilitation medicine because of their potential to provide objective and quantitative information regarding movement quality, neuromuscular activation, and functional recovery. In oncological rehabilitation, these technologies may contribute to the identification of compensatory strategies and functional alterations that are not always detectable through conventional clinical evaluation alone. Furthermore, the possibility of integrating wearable sensors into telemedicine and telerehabilitation frameworks may improve continuity of care and facilitate personalized rehabilitation interventions. In this perspective, the RESTORE-MAM project reflects the growing transition toward multidimensional and technology-assisted rehabilitation models aimed at improving functional recovery and quality of life in breast cancer survivors.

9. Emerging role of wearable devices in telerehabilitation after breast mastectomy

Telerehabilitation, a milestone of the modern medicine, has become an essential component of the healing process for those patients that have undergone mastectomies due to breast cancer. For such individuals, challenges emerge, not only targeting their movements by causing discomfort and pain in the shoulders, but also decreasing their physical strength. The traditional style of rehabilitation was not considered to be effective due to the presence of logistical, geographical, and physical barriers [96]. However, the role of wearable technology in the success of telerehabilitation cannot be overemphasized with regard to the case [97]. Wearable devices comprise different types of equipment used for activity tracking. Inertial Measurement Units (IMUs), surface electromyography (sEMG) trackers like the REMO armband, and smartwatches. These instruments can track not only physical activities, but also detect specific movements like upper limb activities and symmetries, making available precise information for clinicians about patients' motor activities. Real-time tracking allows flexible modifications, improving so patient comfort and rehabilitation outcomes [98].

Systemic reviews and meta-analyses have identified the positive impact of the incorporation of wearable technology in physical activity interventions to favourably increase physical activity. It is also fundamental on health outcomes such as health-related quality of life (HRQoL), physical function, musculoskeletal pain, as well as reduce sedentary behaviour, with continuous feedback aiding the patients in staying engaged with their rehabilitation activities [99].

The development in sensor fusion technology and algorithmic analytics has enabled the accurate characterization of specific patterns of movement. This further allows clinicians to gain knowledge that may not be gained by traditional clinical assessments.

The measurement aspect of wearable sensors can assist in the detection of impairments and the precise application of rehabilitation protocols. This precision can aid in a more accurate classification of motor performance and rehabilitation progress, thereby improving recovery outcomes in breast cancer survivors.

9.1 REMO®: a wearable sEMG-based device for rehabilitation monitoring

The REMO system (Figure 7/a and mode of action 7/b) is a type of wearable electromyogram-based technologies dedicated to extracting signals specifically regarding muscle activity within the upper part of the human body. The system of sEMG of traditional technologies targets individual muscle groups of specific interest and provides desirable informations for the rehabilitation process [100]. Differing from this is the REMO® system, a circumnavigator armband consisting of multiple bipolar surface electrodes dedicated to extracting and detecting global muscle activity within the forearm area of the human body.

Furthermore, it is worthwhile noting that the inertial measurement unit plays a significant and essential role in standardization and standard reference within the context of this specific device. First proposed as a rehabilitation method following stroke [101], REMO® has been investigated and applied as an interface for motor training using biofeedback technology. The interface, is able to wirelessly connect via Bluetooth technology to a host interface like a computer, a smartphone or a tablet. From this application, it facilitates an interactive rehabilitation training session in which the feedback from the individual muscles is used by visual feedback components [102]. This is an integral aspect of motor training, as it enhances the continuous processes of motor learning by providing insights into muscle activation, as it is being used. This aspect of feedback, therefore, becomes important as a closed-loop system, through tests, while engaging an individual in a rehabilitation session.

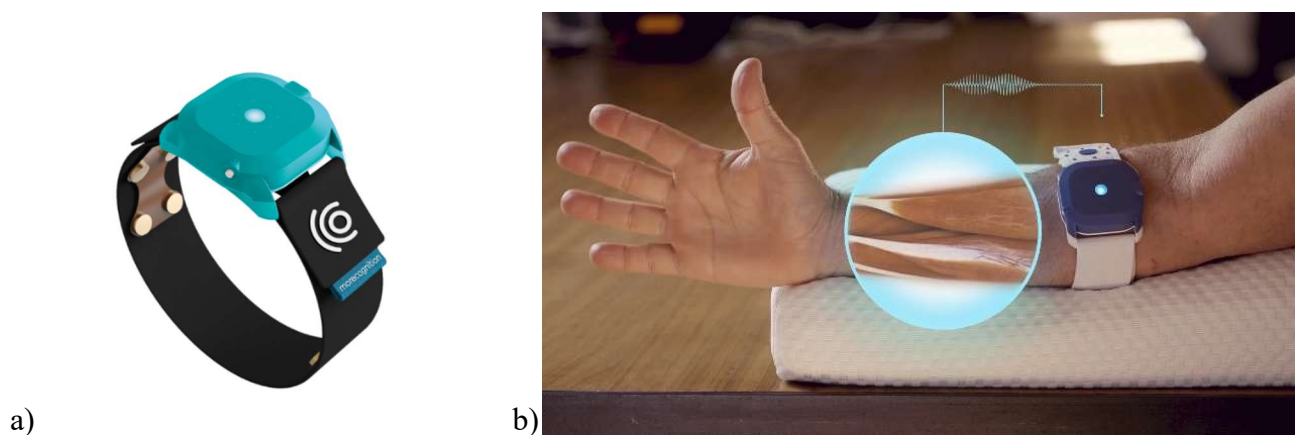


Figure 7. a) s-EMG REMO Device; b) s-EMG REMO Device mode of action

Preliminary clinical testing of REMO® in upper-limb rehabilitation settings has shown that it can detect clinically relevant differences in the motor control capability of individuals with central motor impairments. For instance, in one sample of individuals post-stroke, the device's performance—namely, the number of different hand movements that this device was able to successfully control—was significantly associated with conventional clinical measures of upper-limb motor function, including the Fugl-Meyer Assessment and Box and Blocks Test [103]. These correlations suggest that REMO® may offer subjective motor control feedback and objective metrics of residual functional capacity, enhancing traditional assessments, which are often subjective or limited to discrete clinical tests. Another important characteristic of REMO® deals with its multichannel surface EMG acquisition, providing an overall record of muscle activity across the forearm circumference, rather than acquiring single-muscle signals in isolation.

It is conceivable that this comprehensive capture could lead to increased robustness for dynamic tasks, where co-activation patterns and synergistic muscle recruitment play a critical role in functional movement. Moreover, the integrated IMU enables the calibration of armband orientation, thereby indirectly enhancing the reliability of muscle activation patterns because device positioning will be consistent across sessions and individuals [104-105].

Despite these advantages, clinical research using REMO® is still in its infancy, with a number of limitations that need to be overcome by future studies. For example, pattern recognition algorithms for classifying different motor tasks are still being developed [106]. The currently used implementations have not yet automated hand movement classification, which could further improve the accuracy of rehabilitation protocols. Moreover, due to the limited number and placing of electrodes, the number of degrees of freedom that can actually and effectively be controlled with an armband remains intrinsically limited [107].

9.2 Inertial Measurement Units (IMUs) in rehabilitation monitoring

Inertial Measurement Units (Figure 8) have now become one of the cornerstones in modern rehabilitation research. They are able to provide objective, continuous, and quantitative measures of human movement out of traditional laboratory or clinical settings. A typical IMU usually integrates a combination of accelerometers, gyroscopes, and sometimes magnetometers in order to capture data on linear acceleration, angular velocity, and orientation [108]. Miniaturization and cost reduction of this sensor packages have allowed the widespread adoption across a wide array of fields including in rehabilitation science: for motor assessment after neurological injury, orthopaedic recovery, and management of chronic conditions.



Figure 8. *Inertial Measurement Unit (IMU)*

The value of IMUs applications lies in the notion that while goniometric measures amount to a sporadic assessment of patient function, the data provided by the IMU can be employed to identify and quantify physical parameters. These parameters include the angle of joints, the velocity of movement, as well as the symmetry of the movement patterns. In this way, it becomes easier to identify motor functions from the patient even if the functions are sporadic. The use of IMUs in the post-treatment motor assessment is growing in the field of oncology rehabilitation. For instance, research that focuses on the sensorimotor control of upper limb symmetry in survivors of breast cancer even utilized IMU sensors in measuring the angular velocities of the functional reach task. The results of the research have revealed detectable differences in the execution of movement between the operated and non-operated sides, which may be attributed to functional sequelae following the operation, variables that might not be detected using traditional methods of assessing movement, like range of motion and strength [109].

Furthermore, there is increasing consideration given to the integration of IMUs into telerehabilitation systems in which it is necessary to monitor the patients remotely due to the nature of the rehabilitation process. The validation study on the low-cost IMU system revealed favourable agreement in the segmentation algorithms used in rehabilitation repetitions and calculation of the descriptive metrics, thus proving the feasibility of the low-cost IMU system in the rehabilitation process. Apart from the personal monitoring activities mentioned above, IMUs have been used in the context of wearable networks, where several IMUs are attached to distinct parts of the body in order to achieve more comprehensive movement analysis [110]. Such networks are useful in conducting more advanced biomechanical analyses, which include the extraction of more discriminative parameters, e.g., smoothness, segment coordination, and compensatory movement.

These parameters would prove useful in more investigation-based scenarios where the qualitative component of motor rehabilitation is considered equally important. Despite the extensive potential of the IMU technologies, challenges abound for their application in a clinical setting. For example, consistency in placement, sensor drift, and the importance of powerful algorithms in interpreting clinical metrics out of sensor data represent an area of ongoing development. Additionally, there remains an important prerequisite requirement in standardizing outcomes across different studies, particularly in establishing cross-study comparability and normative databases [111]. A comparison of these two wearable technologies is summarised in table 2.

Characteristics	REMO® Armband	IMU Wearable
Primary Signal	Muscle electrical activity (sEMG) + IMU data	Kinematic data (acceleration, magnetometro, gyroscope)
Purpose	Detection of muscle activation patterns and biofeedback	Quantitative assessment of movement and range of motion
Typical Placement	Forearm circumference (around muscles of interest)	Shoulder, upper arm, forearm, wrist
Output	Gesture recognition, activation levels, biofeedback signals	Joint angles, velocity, movement symmetry, smoothness
Clinical Use	Interactive rehabilitation, motor control feedback, objective assessment of residual function	Remote monitoring of range of motion, functional asymmetries, exercise adherence
Advantages	Real-time biofeedback; robust multichannel sEMG; supports neuromuscular training; can quantify functional capacity	Continuous, ecologically valid data; portable; integrates into telerehabilitation platforms
Limitations	Pattern recognition algorithms still evolving; limited degrees of freedom; early-stage clinical research	Sensor placement consistency; signal drift; requires algorithms to translate raw data
Complementarity	Provides neuromuscular insights; can be combined with IMUs for comprehensive monitoring	Provides objective kinematic data

Table 2. Comparison between IMU Wearables and REMO® Armband characteristics.

AIM OF THE STUDY

The primary objective of this study is to investigate the neuromuscular, functional, and structural characteristics of the upper limb in breast cancer survivors with breast cancer-related lymphedema who are undergoing an outpatient rehabilitation program. It is important to mention that the current study is conducted in accordance with a multidimensional approach, including objective and subjective instrumental measures in order to obtain an extensive evaluation of upper limb impairment. Two different approaches have been evaluated in parallel for the monitorization of rehabilitation techniques. The neuromuscular function has been evaluated through surface electromyography, while the REMO® system was applied in post-treatment breast cancer patients. This method permitted the analysis and assessment of muscle activation and motion during upper limb movements. Functional evaluation is established through handgrip strength measurement, while structural characteristics related to upper limb lymphedema are evaluated through circumferential and volumetric measurements. Apart from objective functional assessment and structural appraisal, the study also comprises valid patient-reported outcome measures to evaluate the impact of upper limb impairment on daily activities and quality of life. This was performed through the use of the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH), Lymphedema Life Impact Scale version 2 (LLISv2), and the EORTC QLQ-C30.

Moreover, the study investigates the feasibility of inertial measurement unit (IMU) technology in the quantitative evaluation of upper limb movements. IMUs technology have been validated as an effective technique on healthy subjects, but they have not been applied on patient cohorts. IMUs are employed as an overall reference to evaluate the feasibility of wearable technology in the context of upper limb rehabilitation in breast cancer survivors.

Our work intends to contribute to the development of a comprehensive framework for the upper limb evaluation of breast cancer survivors with lymphedema by integrating neuromuscular, functional, structural, and patient-reported outcome measures, as well as the evaluation of the feasibility of wearable technology in the objective evaluation of upper limb movements.

METHODOLOGY

The current research is designated as a prospective observational study aimed at investigating the neuromuscular, functional, and structural characteristics of the upper limb in breast cancer survivors with BCRL undergoing an outpatient rehabilitation program. The project follows a multidimensional approach using clinical assessment tools, and patient-reported outcome measures in order to achieve a complete evaluation of the impaired upper limb affected.

The clinical part of the research project is focused on investigating the neuromuscular activity of the muscles of the upper limb through the use of surface electromyography (sEMG) with the REMO® technology. This technology allows the assessment of muscle activity and coordination during the performance of standardized movements of the upper limb under rehabilitation program. Besides the patient population being investigated, a group of healthy subjects was also recruited in order to establish a reference framework of neuromuscular activity and functional performance.

In addition to the clinical component of the research, the study also presented a methodological component that focused on the assessment of the wearable inertial technology. Specifically, the reliability of the inertial measurement unit (IMU) system was tested on a population of healthy volunteers. The IMU system consists of accelerometers, gyroscopes, and magnetometers, allowing respectively the measurement of linear acceleration, angular velocity, and spatial orientation. The methodological validation of the IMU system was based on the assessment of the reliability of the acquired signal and the pre-processing of the data and the extraction of the variables related to the kinematics of the upper limbs' movements.

The combination of the two methodological components of the research allowed the assessment of the neuromuscular and functional changes occurring in patients suffering from BCRL and the exploration of the potential use of wearable technology in the objective assessment of the rehabilitation outcomes.

11.1 Study population

11.1.1 Patients cohort

A group of 13 female patients between 18 and 75 years old with clinical diagnosis of upper limb lymphedema following breast cancer treatment were selected from patients referred to an outpatient rehabilitation program from Azienda Ospedaliera Universitaria of Alessandria. Patients had previously undergone breast surgery for breast cancer treatment, including mastectomy or quadrantectomy, with or without reconstructive techniques on one or both breasts. The clinical diagnosis of upper limb lymphedema was confirmed by measurement of the volume of the upper limb through circumferences. Patients were considered eligible if they were able to actively perform upper limb movements required for the experimental procedure and did not present any contraindications to rehabilitation activities.

Exclusion criteria involves severe musculoskeletal disorders in the shoulder girdle region, neurological disorders of central or peripheral nervous systems, cognitive disorders that could interfere with understanding of the procedures, or any other conditions that could interfere with the safe execution of upper limb movements required by the study protocol.

11.1.2 Healthy subjects

A group of 52 healthy female subjects between the ages of 18 and 75 was chosen as the reference population for neuromuscular and functional assessments and for the methodological validation of the inertial measurement system.

Healthy subjects were those without any history of breast cancer, upper limb lymphedema, neurological disorders, and musculoskeletal disorders of the upper limbs. This group of subjects was chosen to be able to identify physiological movement strategies and muscle activation strategies for standardized movements.

Additionally, the group of volunteer healthy subjects from the Translational Research Centre for Autoimmune and Allergic Diseases (CAAD), Novara, was chosen as the experimental population for the validation of the inertial measurement unit system and the development of the data processing procedures for kinematic analysis.

11.2 Clinical and functional assessment

A complete clinical and functional assessment of the upper limb is carried out to evaluate the impact of breast cancer-related lymphedema on physical, functional, and subjective parameters. This type of multidimensional assessment allows us to simultaneously analyze the physiological and functional limitations experienced by the participants.

At the beginning of the rehabilitation program (T0), and after the end of the treatment program (T1), all participants were subjected to a clinical evaluation that consisted of collecting medical history data, functional assessment, volume measurement, and completing questionnaires. This kind of clinical evaluation allow us to identify possible changes in functional capacity and symptom perception related to the effects of the rehabilitation program.

The muscle strength of upper limbs is measured by performing handgrip strength using a Jamar Plus Digital Dynamometer. The participants sit in a standardized position with their back supported, feet flat on the floor, shoulder in a neutral position, elbow flexed at 90 degrees, forearm in a neutral rotational position, and wrist slightly extended. Three measurements of handgrip strength for each hand are taken at a resting interval of at least thirty seconds to avoid fatigue.

The mean of the measurements is used for further analysis. The structural assessment of upper limbs is conducted by measuring circumferences at predefined anatomical landmarks. The circumferences of upper limbs are measured at various levels by using a flexible measuring tape. The circumferences measured are those of the hand, wrist, forearm, and upper arm. The volume of upper limbs is calculated by considering upper limbs as geometric truncated cones. The volume difference between the affected and unaffected limbs was also computed to measure the severity of the lymphedema. Based on the accepted clinical criteria, the volume difference of more than 200 mL between the two limbs was an indication of clinically significant lymphedema.

Apart from the clinical assessment of the patients, patient-reported outcomes are used to measure the functional and psychological impact of the upper limb disability. The Disabilities of the Arm, Shoulder, and Hand (DASH) outcomes measures the functional disability and limitation of the patient's upper limbs. The Lymphedema Life Impact Scale version 2 (LLISv2) assessed the impact of the patient's lymphedema on the patient's physical, functional, and psychosocial status. The EORTC QLQ-C30 was considered to measure the health-related quality of life of patients suffering from cancer.

The combination of clinical measurements, functional strength testing, and patient-reported outcomes formed a framework for a multidimensional assessment of the consequences of upper limb lymphedema. This method facilitated the correlation of objective physiological parameters with the subjective experience of symptoms and functional consequences of the disorder from the patients' perspective.

11.3 Instrumental assessment of upper limb function

To achieve an objective measurement of upper limb neuromuscular function, instrumental measurements were collected using a wireless surface electromyography system, REMO®. This technology is able to record the electrical signals of the muscles during the performance of standardized functional movements, providing information about the characteristics of muscle activation and coordination strategies.

Surface electromyography is a non-invasive application that is commonly used in biomechanical and rehabilitation research to examine the physiological mechanisms underlying movement control. This method can record the electrical signals of the muscles during movement, providing information about the coordination of different muscle groups and the characteristics of muscle activation. In the case of breast cancer-related lymphedema, it can provide valuable information regarding the neuromuscular adaptations that may be related to biomechanical changes in limb function.

Before the placement of the sensors, the skin surface was well prepared to minimize impedance. This was done by cleaning the skin using alcohol. Additionally, hair was also removed if necessary. Finally, the REMO® sensors were placed on the muscles of interest based on the standardized anatomical position that is most frequently used in surface electromyography research.

The sensors were placed in the direction of the muscle fibres. This was done to increase the sensitivity of the sensors and minimize the interference that could be caused by the muscles adjacent to the muscles of interest. A simple verification procedure was conducted. The subjects were asked to make simple movements. This was done to confirm the position of the sensors and the nature of the signals that were being produced. During the signal acquisition, the participants were asked to perform a set of standardized motor activities that were meant to engage the major muscles of the upper limbs. The movements included functional movements such as hand opening and closing, wrist flexion and extension, forearm pronation and supination, and anterior shoulder elevation. The movements were done slowly and in a controlled way to avoid movement artifacts and to allow the recording of the electromyographic signals. The movements were repeated five times with short pauses between the repetitions. The participants were also required to undertake the Five Times Sit to Stand Test (FTSST), which is a functional test intended to measure the strength of the lower limbs and the functional ability of the participants. For the test, the participants were required to stand up and sit down five consecutive times as fast as possible while seated on a chair with their arms crossed on their chest. The use of standardized movements and controlled acquisition procedures was useful in ensuring the consistency of the results from the electromyographic recordings. These instrumental measurements were useful in obtaining objective information on neuromuscular function and identifying any potential changes in muscle activation patterns between the two assessments.

11.4 Morphological assessment

In addition to the clinical and functional assessment of the patient, the morphological assessment of the upper limb was also conducted to evaluate the structural changes that occur as a result of breast cancer-related lymphedema. The morphological assessment of the upper limb was conducted using three-dimensional scanning of the upper limb. This method of assessment was effective in obtaining the necessary morphological and volumetric details of the upper limb of the patient. Three-dimensional scanning of the upper limb is considered an effective non-invasive method of assessment that allows the digital reconstruction of the upper limb. The advantage of using three-dimensional scanning of the upper limb is that it provides the complete circumference of the upper limb.

This method of assessment of lymphedema is considered effective because it provides crucial details regarding the changes that occur in the morphology of the upper limb. Throughout the acquisition process, the participants were placed in a standardized posture to ensure that measurements are consistent throughout different participants and assessment time points. The participants were asked to stand upright while keeping their upper limb at a standard position by flexing the shoulder by 90 degrees, extending the elbow fully, keeping the wrist straight, and extending and abducting the fingers slightly. The upper limb was completely visible during the scanning process by keeping it at this position to avoid occlusion or distortion during digital reconstruction. The scanning process created a three-dimensional digital reconstruction of the upper limb that could be utilized for morphometric assessment at a later time point. Volumetric and geometric data could be derived from this reconstruction to compare different time points.

The combination of the use of 3D scanning and the traditional method of clinical measurement provided a more comprehensive assessment of the structural characteristics of the upper limb. This method was also useful in the identification of the potential changes that might affect the morphology of the upper limb due to lymphedema and the multi-dimensional assessment method that was followed.

11.5 IMU-based motion analysis

In addition to neuromuscular analysis, motion analysis was carried out with the help of inertial measurement units, with the aim of examining the viability of wearable technology for movement analysis. Inertial measurement units are small devices that can measure movement through the assistance of various sensors.

An inertial measurement unit consists of various sensors of three types, respectively accelerometers, gyroscopes, and magnetometers. Each of these sensors is of the tri-axial type.

The accelerometers measure linear accelerations along various axes. They measure the changes in the velocity of movement and the orientation of the movement with respect to gravity. The gyroscope is able to detect rotational movements of the limb segments with the help of a measure of angular velocity. The magnetometer is able to detect the orientation of the sensor with respect to the Earth's magnetic field.

With the integration of data from these three sensors, it is possible to reconstruct the orientation and movement of body segments in three-dimensional space. This is usually done through sensor fusion algorithms that integrate data from accelerometer, gyroscope, and magnetometer signals to obtain a more stable estimation of segment orientation.

With regard to the advantages that IMU sensors present over other systems used to analyse movement, these types of devices are lightweight and portable, and their cost is relatively low. These features allow for the application of these types of sensors in clinical and rehabilitation settings without needing to resort to special equipment or laboratories. Additionally, these types of sensors allow for the registration of movement in a more natural state.

In this regard, within the framework of this research, IMU sensors were applied to a healthy volunteer group to assess the feasibility and reliability of this system in relation to its application in movement analysis. The purpose of this methodological component was to assess the quality of signal acquisition and to investigate the prospects of this technology for quantitative description of upper limb movement patterns.

The data collected from the inertial sensors were then analysed through a computational algorithm implemented in a specific computational workflow written in Python®. This allowed for the extraction of kinematic parameters related to movement dynamics.

11.6 IMU data acquisition and computational processing (Python®)

The signals that were collected from the inertial measurement devices were then processed by a computational flow that was created by utilizing a programming language called Python®. The purpose of this computational flow was to allow for data acquisition, data storage, signal inspection, and data preparation for subsequent kinematic analysis.

Scripts were written to enable the management of data acquisition as well as the management of sensor data that registered from IMU system. The script (figure 9/a and 9/b) allows the acquisition of raw signals that were collected from a tri-axial accelerometer, a gyroscope, a magnetometer, and other sensors that are integrated into the inertial measurement unit. The data acquisition program enabled the management of sensor signals that were streamed over time. The signals that were transmitted from the sensors were stored appropriately.

The acquired signals were exported and stored in a CSV file. This data management and compatibility with data analysis environments were facilitated using the CSV format. Each data file contained synchronized time series data from the three components of the IMU sensors, enabling the reconstruction of movement dynamics in the three dimensions of space.

A second set of Python® scripts was also created for the visualization and inspection of the recorded signals (figure 9/c). This script produced a graphical representation of the recorded signals, enabling the inspection and analysis of the acquired data. This visualization step was particularly crucial in detecting potential artifacts in the recorded data, allowing for further processing techniques.

After the preliminary inspection of the collected signals, the signal pre-processing procedures were conducted in order to enhance the quality and reliability of the collected signals. The procedures included the application of filtering techniques that were intended to minimize noise and enhance the reliability of the sensor signals. Additionally, the normalization procedures were applied to the accelerometer and magnetometer signals in order to enhance the analysis of the collected data.

The processed signals were then employed to calculate the descriptive kinematic variables that were intended to describe the dynamics of the collected movements. The combination of the collected accelerometer, gyroscope, and magnetometer signals was employed to calculate the kinematics of the sensor movements in three-dimensional space. The resulting kinematic variables were intended to describe the movements and were considered the basis of the exploration of the potential use of wearable inertial sensors in rehabilitation assessment.

The use of a computational pipeline based on a Python® programming environment was beneficial in the sense that it enabled the automation of some steps in the data analysis process. Additionally, the use of an open-source programming environment is beneficial in the sense that it allows for the extension and development of other tools for data analysis in the context of motion analysis and wearable sensors.

```
IMU_2_sens_video6.py - C:\restoreMAM\IMU_2_sens_video6.py (3.12.4)
File Edit Format Run Options Window Help

import os
import sys
import pygame as pg
import pyvdpplayer2 as pv
import csv
from time import sleep
from mbientlab.metawear import MetaWear, libmetawear, parse_value
from mbientlab.metawear.cbindings import *

#####
#param_a,param_b,param_c,param_d=7.5, 1000, 0, 6000
param_a,param_b,param_c,param_d=7.5, 7.5, 0, 6000
#param_a,param_b,param_c,param_d=750.0, 1000.0, 128, 16384
#####

# --- Configuration ---
# Update with the correct paths and addresses for your system.
PATH_VIDEO_FOLDER = "C:/restoreMAM/Video/VideoEdited/VideoIMU/"
PATH_FFMPEG = "C:/restoreMAM/CodiceApp/ffmpeg/ffmpeg/bin/"

# Add FFMpeg to the system path
sys.path.insert(0, PATH_FFMPEG)
os.environ["PATH"] += f";{PATH_FFMPEG}"

# Define the MAC addresses of the two MetaWear IMU devices
DEVICE_ADDRESSES = ['EB:04:47:A2:9E:69', 'FF:69:DC:7A:ED:AD']

# --- IMU State Management Class ---
class State:
    """Manages the state of a single MetaWear device and its data logging."""
    def __init__(self, device):
        self.device = device
        self.samples = 0
        self.callback = FnVoid_VoidP_DataP(self.data_handler)
        self.video_object = None
        self.csv_file = None
        self.csv_writer = None
        self.csv_filename = "" # Filename is generated in setup_csv

    def setup_csv(self):
```

a)

Ln: 1 Col: 0

```
*IDLE Shell 3.12.4*
File Edit Shell Debug Options Window Help

Python 3.12.4 (tags/v3.12.4:8e8a4ba, Jun 6 2024, 19:30:16) [MSC v.1940 64 bit (AMD64)] on win32
Type "help", "copyright", "credits" or "license()" for more information.
>>>

===== RESTART: C:\restoreMAM\IMU_2_sens_video6.py =====
pygame 2.5.2 (SDL 2.28.3, Python 3.12.4)
Hello from the pygame community. https://www.pygame.org/contribute.html
--- IMU and Video Synchronization Script ---
Attempting to connect to EB:04:47:A2:9E:69 (Attempt 1/3)...
[SUCCESS] Connected to EB:04:47:A2:9E:69
Attempting to connect to FF:69:DC:7A:ED:AD (Attempt 1/3)...
[SUCCESS] Connected to FF:69:DC:7A:ED:AD

All devices connected. Now configuring...
Configuring EB:04:47:A2:9E:69...
Configuring FF:69:DC:7A:ED:AD...
All devices configured successfully.

Please select a video to play:
[1] alzata sedia.MP4
[2] braccio penzoloni.mp4
[3] gomiti testa.MP4
[4] laterale muro.MP4
[5] palmo su muro.MP4
[6] rotazione spalle.MP4
[7] saltelli.mp4
[8] sbarra davanti.MP4
Enter number (1-8):
```

Ln: 5 Col: 0

b)

c)

```

IMU_Time_Series_and_Video_Viewer2.py - C:\restoreMAM\IMU_Time_Series_and_Video_View...
File Edit Format Run Options Window Help

import cv2
import pandas as pd
import matplotlib.pyplot as plt
from matplotlib.widgets import Slider
import numpy as np
import sys
import os

PATH_FFMPEG = "C:/restoreMAM/CodiceApp/ffmpeg/ffmpeg/bin/"

# Add Ffmpeg to the system path
sys.path.insert(0, PATH_FFMPEG)
os.environ["PATH"] += f";{PATH_FFMPEG}"

# --- Configuration ---
# Ensure these files are in the same directory as the script, or provide full pa
myfolder="C:/restoreMAM/Video/VideoEdited/VideoIMU/"
VIDEO_PATH = 'palmo su muro.mp4'
#VIDEO_PATH = 'collo.mp4'
CSV_PATH1 = 'imu_data_patient2_palmo su muro1.csv'
#CSV_PATH1 = 'imu_data_EB_04_47_A2_9E_69_collo.csv'
CSV_PATH2 = 'imu_data_patient2_palmo su muro2.csv'
#CSV_PATH2 = 'imu_data_FF_69_DC_7A_ED_AD_collo.csv'
# --- Load and Prepare Data ---
try:
    # Load the video
    cap = cv2.VideoCapture(myfolder+VIDEO_PATH)
    if not cap.isOpened():
        raise IOError(f"Cannot open video file: {VIDEO_PATH}")

    # Get video properties
    total_frames = int(cap.get(cv2.CAP_PROP_FRAME_COUNT))
    fps = cap.get(cv2.CAP_PROP_FPS)
    if fps == 0:
        print("Warning: Video FPS is 0. Defaulting to 30.")
        fps = 30 # Set a default FPS if it's not available
    video_duration_s = total_frames / fps

    # Load the CSV files
    dfl = pd.read_csv(CSV_PATH1)

```

Ln: 1 Col: 0

Figure 9. a) The main script created from signal acquisition permitted the selection of the exercise to be performed by the patient. B) After running the system an interface is opened allowing the initiation of signal recording that finish with a CSV file creation. c) The second script allows the visualization of the stored CSV file.

11.7 Data management

All the data collected throughout the research was structured within a structured research database that was intended to guarantee consistency and traceability of the collected data. Additionally, the collected data was intended to be safely stored. Each participant was given a unique anonymized identification code to maintain the confidentiality of the collected data and to comply with the current data protection regulations. For the collected data, demographic factors, clinical factors, and the medical history of the subjects were considered. Additionally, the clinical and functional data collected throughout the assessment sessions were also considered. The clinical and functional data included the measurement of the circumferences of the limbs and the calculation of the volumes of the limbs. Additionally, the handgrip strength of the subjects was considered.

The instrumental data were stored in specific files linked to the participant identification code. The electromyographic data acquired through the REMO system were stored as raw files, whereas the kinematic data acquired through the IMU sensors were stored as structured data in CSV format. This allowed for the efficient integration of clinical and instrumental data within a single analytical framework.

All the datasets were stored on secure storage systems with limited access. The personal identifiers were removed from the analytical dataset to ensure the confidentiality of the participants. The structured database allowed for the systematic organization of the acquired data and the subsequent performance of statistical analyses to investigate the correlations between the clinical characteristics, neuromuscular activity, functional performance, and patient-reported outcomes.

11.8 Statistical analysis

Statistical analysis was performed in a descriptive point of view. It is aimed at characterizing the study population and evaluating differences in clinical, functional, and morphological parameters during the rehabilitation process. Furthermore, it is used to shed light on the influence of different clinical treatment that patients underwent. Variables were expressed as mean $\pm$ standard deviation (SD), while categorical variables, including type of surgery, chemotherapy regimen, radiotherapy exposure, hormone therapy, and other treatment-related variables, are designed as absolute frequencies. For graphical representation, we choose to express data as mean $\pm$ standard error of the mean (SEM), in order to illustrate the validity of the mean of the cohort. Sample sizes are reported for each subgroup. Comparison between pre-rehabilitation (T0) and post-rehabilitation (T1) conditions were performed descriptively to assess changes in limb volume difference (between affected limb and the sane one), handgrip strength as a functional parameter and patient-reported outcomes from the questionnaires.

To better represent the effect of the rehabilitation, the Δ volume difference was calculated and expressed as the difference between T1 and T0 volume values. The clinical variables taken in consideration for the analysis concern type of axillary surgery, chemotherapy regimen, radiotherapy exposure, hormonal therapy, and the number of lymph node dissection.

11.9 Ethical considerations

All the participants were educated on the objectives, procedures, and possible implications of the study before they were recruited. Written consent from all the participants was sought before any procedure was performed. The study was conducted in accordance with the ethical guidelines proposed in the Declaration of Helsinki. The study was conducted in a manner that conformed to the regulations on the handling of personal data as proposed in the General Data Protection Regulation (GDPR).

The relevant ethics committee reviewed the study before the collection of the data. Participation in the study was voluntary. The participants were allowed to withdraw from the study at any time without any effect on their care.

The study has been approved by the Comitato Etico Territoriale (CET) Interaziendale AOU Maggiore della Carità di Novara, Prot. n°114/CE, of 28/02/2025. The document is found on Appendix 2.

RESULTS

12.1 Study population

The study population was comprised of breast cancer survivors suffering from breast cancer-related lymphedema and who were enrolled in an outpatient rehabilitation program. In addition, two groups of normal subjects were included in the study.

Thirteen women with lymphedema of the upper limbs from breast cancer made up the clinical trial population. The mean age of the women in this study was 66.1 ± 12.5 years (range: 43 to 85 years), and their mean BMI was 25.6 ± 3.8 kg/m². This indicates that the patients were from a heterogeneous population of normal weight, overweight, and obese patients. Patients in this study were also assessed for the presence of coexisting medical conditions using the Cumulative Illness Rating Scale (CIRS). With a mean CIRS score of 7.9 plus or minus 3.9, it was apparent that all participants had multiple comorbidities based on their CIRS score alone, as all the patients had previously undergone some form of surgical intervention as treatment for their breast cancer. The procedures included quadrantectomy, mastectomy, and modified radical mastectomy. The procedures were sometimes combined with reconstructive procedures. Axillary procedures were also performed on the patients. The procedures included sentinel node biopsy and axillary lymphadenectomy. Additionally, the patients had undergone various modalities of cancer therapy. The therapies included chemotherapy, radiotherapy, hormone therapy, and sometimes a combination of the therapies. This was due to the multifaceted nature of breast cancer and its potential impact on the upper limbs.

The control group was comprised of 52 healthy female subjects, who were included in order to provide reference data on upper limb function and neuromuscular parameters. The results from this reference population is used for comparison with the functional and neuromuscular data recorded on breast cancer patients during the study. This control group is comprised of healthy female subjects in order to ensure that there was no history of breast cancer, lymphedema, neurological disorders, and/or significant upper limb musculoskeletal disorders.

There was also one last cohort of subjects that were included as a separate group for the methodological validation of the inertial measurement unit (IMU) systems in use for motion analysis, consisting of 22 healthy volunteer participants who voluntarily agreed to participate at the Center for Autoimmune and Allergic Diseases (CAAD) Research Center in Novara. The purpose of this cohort was to determine feasibility, signal reliability and the computational processing pipeline related to the wearable inertial sensor system. The use of a healthy cohort allowed for the testing and optimization of the IMU data acquisitions, signal pre-processing methods, and algorithms for extracting kinematic parameters to occur in controlled experimental conditions.

The combination of the three cohorts enabled the integration of a clinical investigation, comparative functional evaluations, and methodological validation of the wearable motion analysis technology. This approach supported a multidimensional assessment of the upper extremity function of breast cancer survivors with lymphedema.

12.2 Functional assessments

The functional assessment of the upper limb was conducted through objective measurement of handgrip strength and volumetric assessment of the limb, as shown in Table 3. These methods enable the quantification of both muscular performance and alterations related to breast cancer-related lymphedema.

12.2.1 Handgrip strength

The muscular function of a person's upper extremities, overall, was measured through a standardised means of measuring grip strength, which involves using a dynamometer to get comprehensive grip strength measurements. At baseline (T0), the mean for grip strength on the right side of the body was 22.5 ± 6.0 kg; however, the mean for grip strength on the left was slightly higher at 22.7 ± 4.9 kg. Large differences in muscular strength within this patient population were indicated by the data. After having completed the rehabilitation process (T1), overall grip strength in all patients have increased. The mean value for grip strength in the right had at T1 was 23.6 ± 5.2 kg, while the left had averaged 25.1 ± 4.6 kg at T1. Consequently, while a mean increase in grip strength had been demonstrated, to what degree, and if there was consistency, were dependent on the subject. This can be related to the functional goals of physiotherapeutic intervention, in which there is an improvement in upper limb function, reduction in muscle recruitment, and alleviation of functional limitations related to breast cancer and lymphedema.

12.2.2 Limb volume assessment

The structural involvement in the upper limb was evaluated in terms of circumferential measurements at predefined anatomical landmarks. Limb volume was determined by the truncated cone method, in which it is possible to estimate total limb volume from sequential measurements of circumference. On the initial evaluation, there were variations in the degree of asymmetry between an affected and that limb. The patients had a mean volume discrepancy of 1269.3 ± 1584.1 mL, with considerable differences in severity of lymphedema present among patients.

After completion of the rehabilitation program, patients demonstrated a mean limb volume difference of 686.6 ± 575.4 mL and an average decrease of 582.7 ± 1060.7 mL in overall limb volume asymmetry from T0 to T1. Despite the large inter-individual variability, the majority of patients with paired data exhibited a reduction/stabilization of limb volume over time.

The results of the study show that the rehabilitation program was associated with significant changes in limb volume in several patients, which could be a potential benefit for the improvement of the distribution of fluid through the lymphatic system.

Parameter	T0	T1
Handgrip Right (kg)	22.5 ± 6.0	23.6 ± 5.2
Handgrip Left (kg)	22.7 ± 4.9	25.1 ± 4.6
Limb Volume Difference (mL)	1269.3 ± 1584.1	686.6 ± 575.4

Table 3. Functional assessment outcomes. Results are expressed as mean $\pm$ standard deviation. the rehabilitation program resulted to moderate levels of improvement in muscular strength and a reduction in volume asymmetry in the limbs in most of patients. However, the degree of response was highly variable among individuals, considering the diverse clinical background in breast cancer survivors with lymphedema.

12.3 Questionnaire outcomes

Patient-reported outcome measures were collected to evaluate the impact of upper limb impairment on daily functioning, burden associated with lymphedema, and quality of life (Table 4). Three measures were selected: Disabilities of the Arm, Shoulder and Hand questionnaire (DASH), the Lymphedema Life Impact Scale version 2 (LLISv2), and the EORTC QLQ-C30 questionnaire.

12.3.1 LLISv2 results

The multidimensional impact of lymphedema on the patient's physical, functional, and psychosocial health status was evaluated using the LLISv2 questionnaire. The mean value of the total score of the LLISv2 questionnaire among the patient cohort at T0 was 40.4 ± 8.0 . This suggests a significant perceived burden associated with upper limb swelling and functional limitations. At the end of the rehabilitation program (T1) this value has decreased to 30.2 ± 7.1 . This decrease may be linked to the improvement in the perceived impact of the patient's daily activities.

The decrease in the total value of the LLISv2 questionnaire for the subgroup of breast cancer-related lymphedema patients may be linked to the decrease in the perception of the feeling of heaviness or discomfort in the limbs.

12.3.2 DASH outcomes

The second method for measuring the disabilities of the upper limbs was the DASH questionnaire. This questionnaire was used for measuring the functional limitations and the perceived symptoms that affect the upper limbs during daily activities.

The mean value for the total DASH questionnaire for the baseline data at T0 is 75.0 ± 23.0 . This indicates a significant level of upper limb disability for the patients. At the end of rehabilitation program at T1 this value decreased to 58.7 ± 21.3 .

The decrease in the DASH value shows that there is improvement in the perceived level of ability in doing daily tasks for the upper limbs. These daily tasks include grip strength, reaching, lifting, and coordination. This decrease in the level of disability is in line with the improvements observed from the objective measurements.

12.3.3 EORTC QLQ-C30 outcomes

The cancer-related quality of life was also assessed by means of the EORTC QLQ-C30 questionnaire for multiple dimensions.

The mean total score for the EORTC QLQ-C30 was 53.8 ± 10.2 for the patient population at the initial evaluation at T0. This value decreased to 49.7 ± 4.6 at the end of rehabilitation program at T1.

The results from the comparison between the EORTC QLQ-C30 questionnaire and the more specific questionnaires on upper limb disability and burden of lymphedema showed that the first one was less sensitive to the functional changes that occur during the rehabilitation period. This could be due to the fact that the former measures general dimensions of cancer-related quality of life.

Questionnaire	T0	T1
LLISvc2	40.4 ± 8.0	30.2 ± 7.1
DASH	75.0 ± 23.0	58.7 ± 21.3
EORTC QLQ-C30	53.8 ± 10.2	49.7 ± 4.6

Table 4. Patient-reported questionnaires' outcomes. Results are expressed as mean $\pm$ standard deviation and they reflect a parallel improvement in the burden of lymphedema and upper extremity disability.

12.4 Systemic and multimodal treatment exposure

The treatment of the participants had been multimodal in the majority of cases and had been representative of modern standard-of-care in management of breast cancer. In the surgical procedure, quadrantectomy or mastectomy and modified radical mastectomy was done along with axillary staging through sentinel lymph node biopsy or axillary lymph node dissection.

All the patients have taken chemotherapy drugs in their treatment process. However, the vast majority of these individuals took treatment with an anthracycline regimen, mostly with taxanes. There was also a small group that received platinum-based chemotherapy. Two-thirds of all patients had undergone endocrine therapy using aromatase inhibitors (letrozole/anastrozole); there had also been some patients having undergone tamoxifen-based treatment. In certain cases, targeted therapies had been used, namely trastuzumab for HER2-positive tumors and CDK4/6 inhibitors in case of luminal metastatic disease or high-risk conditions. Radiotherapy had been applied to the majority of participants either in adjuvant or combined setting.

Thus, the group under analysis is heterogeneous both in terms of treatment intensity and biological subtypes, and there had been a lot of differences regarding the sequence of therapies used.

Due to that, the effects of particular treatment regimens could only be assessed in a descriptive way (Table 5).

Type of treatment	Subtype/Regimen	Patients (n)
Surgery	Quadrantectomy	6
	Mastectomy (total/mod)	7
	Axillary lymph node dissection	9
	Sentinel lymph node biopsy	4
Chemotherapy	Any	13
	Anthracycline-based (Epirubicin / AC / EC)	10
	Taxane-based (Paclitaxel / Docetaxel)	8
	Platinum-containing (Carboplatin)	2
	Capecitabine	1
Radiotherapy	Adjuvant / combined RT	10
Endocrine therapy (HT)	Aromatase inhibitors (Letrozole / Anastrozole)	7
	Tamoxifen	1
	Sequential / combined HT strategies	2
Targeted therapy	Trastuzumab	2
	CDK4/6 inhibitors (Abemaciclib / Ribociclib)	2
Other systemic therapy	Immunotherapy (e.g. Pembrolizumab)	1

Table 5: *Oncological Treatment Exposure in the Study Cohort.*

12.5 Influence of axillary surgery on rehabilitation

The cohort was stratified according to the type of axillary surgical procedure: Axillary Lymph Node Dissection (ALND) versus Sentinel Lymph Node Biopsy (SLNB).

Patients who underwent ALND (n=9) exhibited markedly higher baseline inter-limb volume differences compared to those treated with SLNB (n=4), respectively 1470 mL vs 540 mL, indicating a greater severity of lymphedema in this subgroup. This finding is consistent with the more extensive disruption of lymphatic drainage associated with ALND (Figure 5/a).

Following rehabilitation, both groups showed reductions in limb volume asymmetry. At T1, the inter-limb volume difference was 850 mL in the ALND group and 330 mL in the SLNB group. In this way, ALND patients demonstrated greater absolute reductions (−620 mL vs −210 mL), suggesting a larger margin for improvement (Figure 5/b). Despite this, variability remained high, particularly in the ALND group.

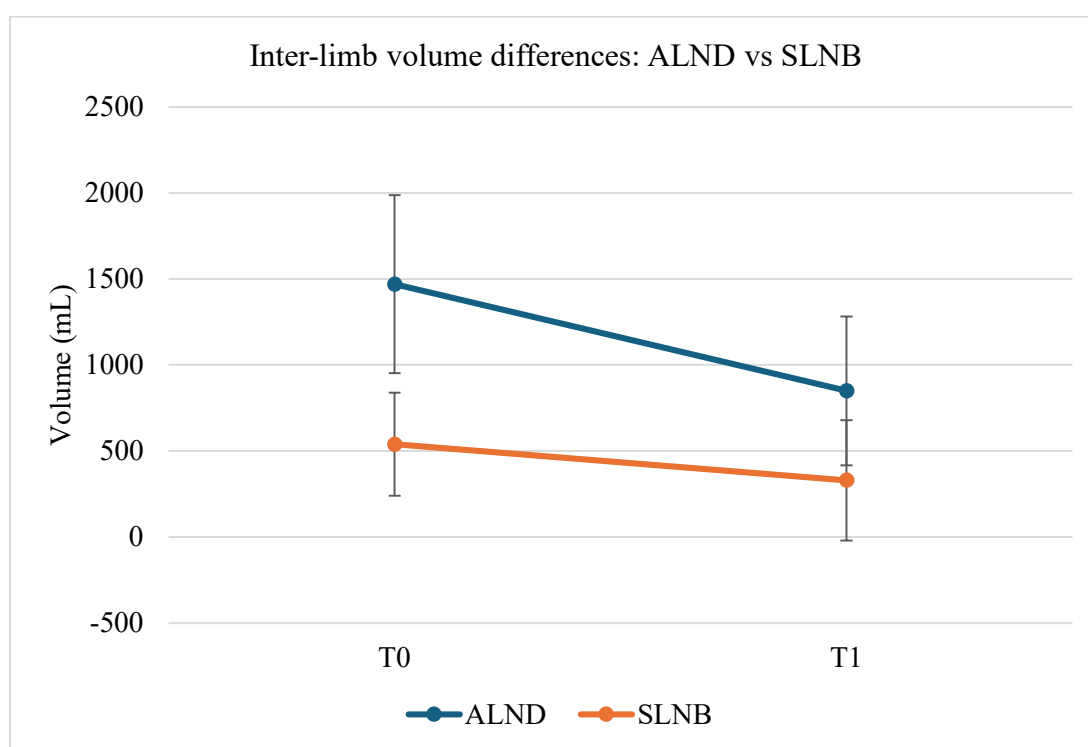


Figure 5/a: Inter-limb volume comparison between BC patients that have undergone Axillary Lymph Node Dissection (ALND) and Sentinel Lymph Node Biopsy (SLNB), before rehabilitation (T0) and at the end of it (T1). Data are presented as mean $\pm$ standard error of the mean (SEM). ALND (n=9), SLNB (n=4).

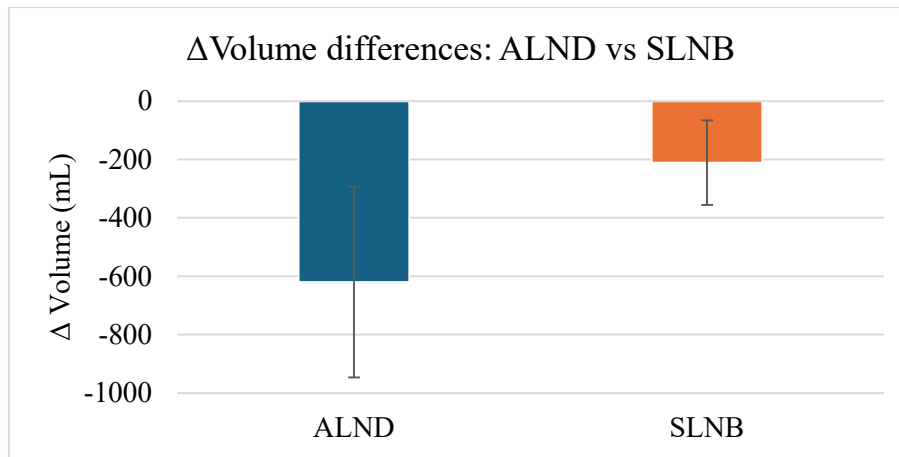


Figure 5/b: Inter-limb Δ Volume reduction in Axillary Lymph Node Dissection (ALND) and Sentinel Lymph Node Biopsy (SLNB) groups at the end of rehabilitation. Δ Volume is measured as a difference of T1-T0. Data are presented as mean $\pm$ SEM. ALND (n=9), SLNB (n=4).

Regarding functional assessment, handgrip strength was slightly lower in the ALND group at baseline compared to the SLNB group (21.8 kg vs 23.9 kg). Following rehabilitation, a modest but consistent improvement was observed in both cohorts, with values reaching 23.2 kg for ALND and 24.8 kg for SLNB patients (Figure 6). A detailed analysis of the ALND cohort revealed a significant functional outlier (Patient ID 04). Despite the extensiveness of the axillary dissection, this patient maintained a baseline handgrip strength significantly above the group mean (>30 kg). The presence of such outliers contributes to the high variability observed in the functional outcomes of the more invasive surgical group.

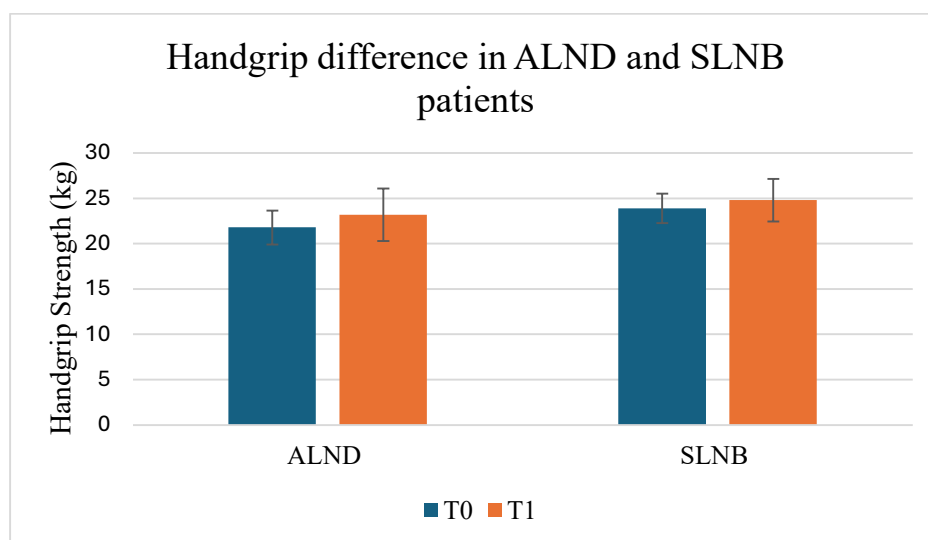


Figure 6: Handgrip strength differences in ALND and SLNB patients before (T0) and after (T1) rehabilitation process. Data are presented as mean $\pm$ SEM. ALND (n=9), SLNB (n=4).

12.6 Influence of chemotherapy regimens on rehabilitation

Taxane exposure was selected as the reference chemotherapy stratification due to its variability across patients and its role as an indicator of systemic treatment intensification beyond standard anthracycline-based regimens, which were administered to the majority of the cohort and therefore did not allow meaningful subgroup discrimination. The evaluation of volumetric outcomes according to this chemotherapy regimen is presented in Figure 7/a and 7/b. Analysis of the cohort showed that patients treated with Taxanes (n=8) exhibited a higher baseline inter-limb volume difference (1300 mL) compared to the No Taxane (n=5) group (1220 mL). However, the Taxane group also demonstrated a more pronounced response to rehabilitation, achieving a mean volume reduction of 590 mL compared to 470 mL in the non-exposed group. When normalized to baseline values, this resulted to an approximate relative reduction of 45% in the Taxane group compared to 38% in the non-exposed group. Parallel to these volumetric changes, functional grip strength followed a positive recovery trend in both subgroups. Despite Taxane-treated patients starting from a slightly lower baseline (21.9 kg at T0), they successfully reached 23.4 kg at T1, mirroring the improvement seen in the No Taxane cohort (23.6 kg to 24.9 kg). These findings suggest that while Taxane-based regimens are associated with greater initial lymphatic impairment, they do not negatively impact the potential for significant functional and volumetric gains through targeted rehabilitation.

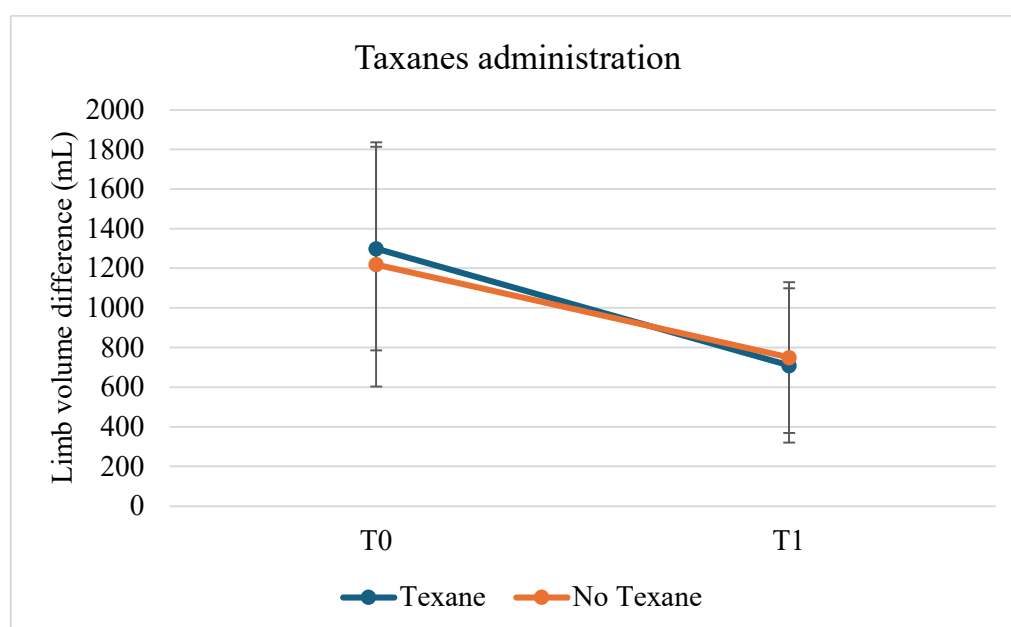


Figure 7/a: Inter-limb volume difference in T0 before the rehabilitation start and at the end of that, based on the administration or not of the Taxane chemotherapeutic drugs. We can confirm that the Taxane group had more pronounced response. Data are presented as mean $\pm$ SEM. Taxanes (n=8), No Taxanes (n=5).

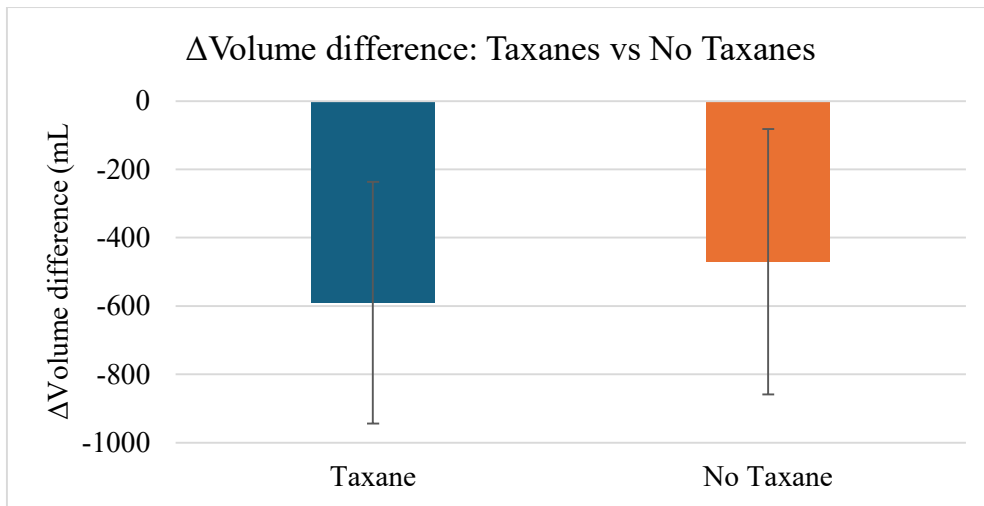


Figure 7/b: Inter-limb Δ Volume reduction in Taxane administered group and in the one that did not administer it at the end of the rehabilitation process. Data are presented as mean $\pm$ SEM. Taxanes ($n=8$), No Taxanes ($n=5$).

Parallel to these volumetric changes, functional grip strength followed a positive recovery trend in both subgroups. As shown in Figure 8, despite Taxane-treated patients starting from a slightly lower baseline (21.9 kg at T0), they successfully reached 23.4 kg at T1, mirroring the improvement seen in the No Taxane cohort (23.6 kg to 24.9 kg). These findings suggest that while Taxane-based regimens are associated with greater initial lymphatic impairment, they do not negatively impact the potential for significant functional and volumetric gains through targeted rehabilitation.

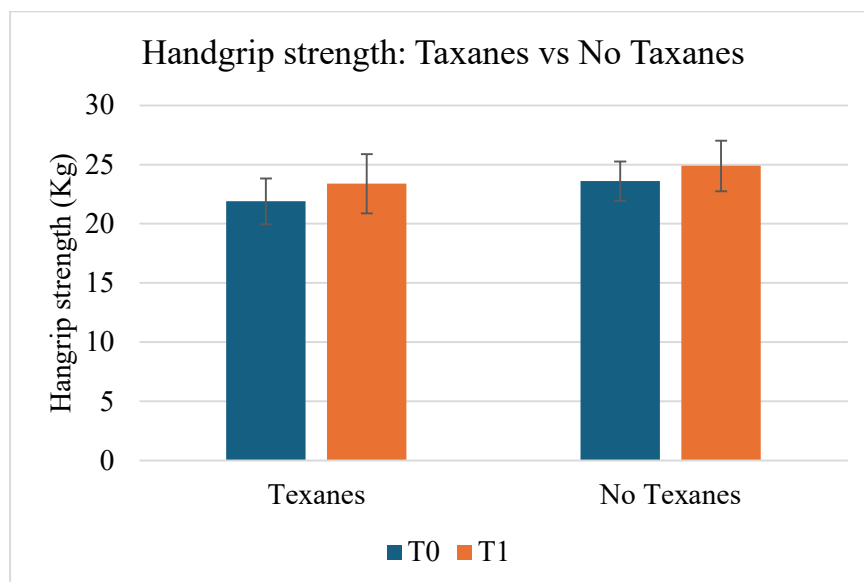


Figure 8: Handgrip strength recovery based on Taxane administration or not patients, before rehabilitation (T0) and at the end of that (T1). Data are presented as mean $\pm$ SEM. Taxanes ($n=8$), No Taxanes ($n=5$).

12.7 Influence of radiotherapy on rehabilitation

Patients were stratified according to exposure to radiotherapy (n=10) and not exposure (n=3). At baseline, patients treated with radiotherapy showed higher inter-limb volume differences (1350 mL) compared to those who did not receive RT (820 mL), suggesting a potential contribution of radiotherapy to lymphatic impairment.

Following rehabilitation, both groups demonstrated reductions in limb volume asymmetry. At T1 the inter-limb volume differences decreased to 790 mL in the RT group and to 390 mL in the No RT group (Figure 9/a). In this way is comprehensible that, as shown in Figure 9/b, the RT group exhibited greater variability in response (−560 mL), whereas non-RT patients showed a more homogeneous trend (−430 mL).

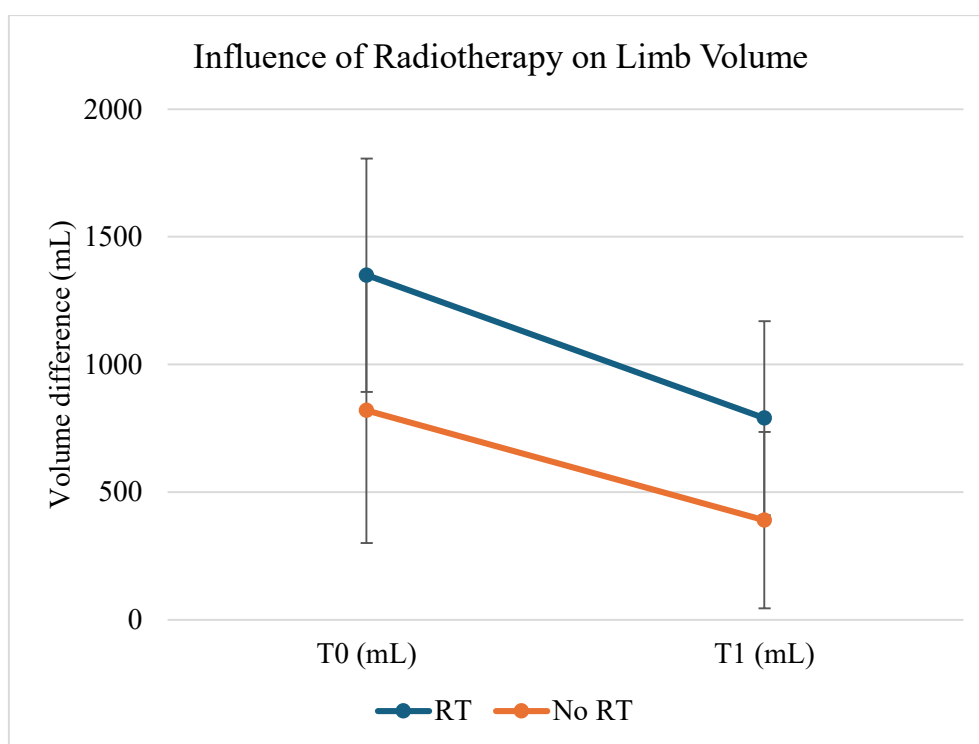


Figure 9/a: The effect of the Radiotherapy exposure in the inter-limb volume difference before rehabilitation (T0) and at the end of the process (T1). Data are presented as mean $\pm$ SEM. RT Yes (n=10), RT No (n=3).

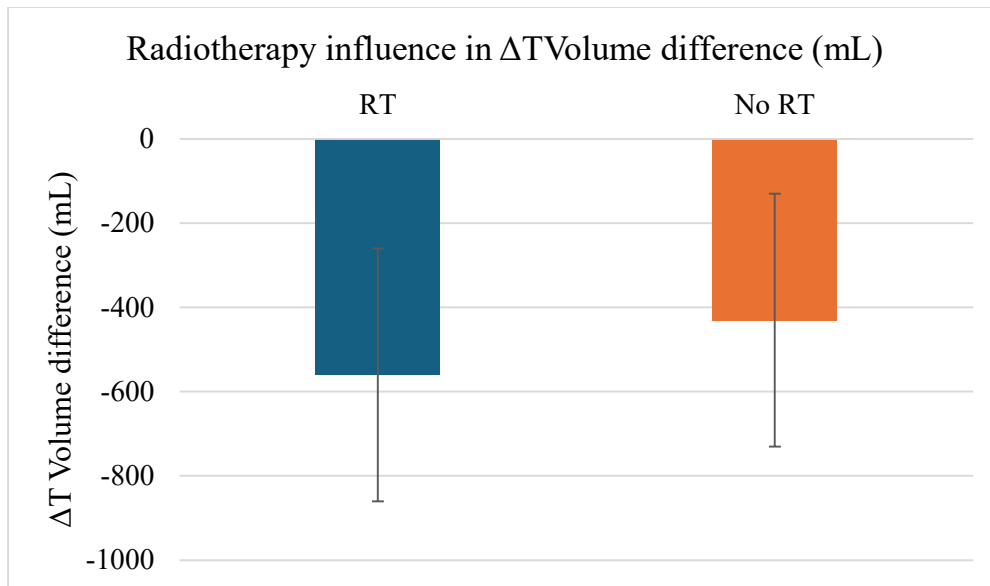


Figure 9/b: Inter-limb Δ Volume reduction in RT exposure group and in the not exposure one at the end of the rehabilitation process. Data are presented as mean $\pm$ SEM. RT Yes ($n=10$), RT No ($n=3$).

We also analysed the impact of radiotherapy (RT) on functional recovery. Patients in the RT Yes group showed an increase in handgrip strength from 22.1 kg at T0 to 23.8 kg at T1. Similarly, the RT No group improved from 23.4 kg to 24.5 kg. Although radiotherapy is often associated with increased tissue fibrosis, these results suggest that both subgroups achieved functional gains through the rehabilitation program (Figure 10).

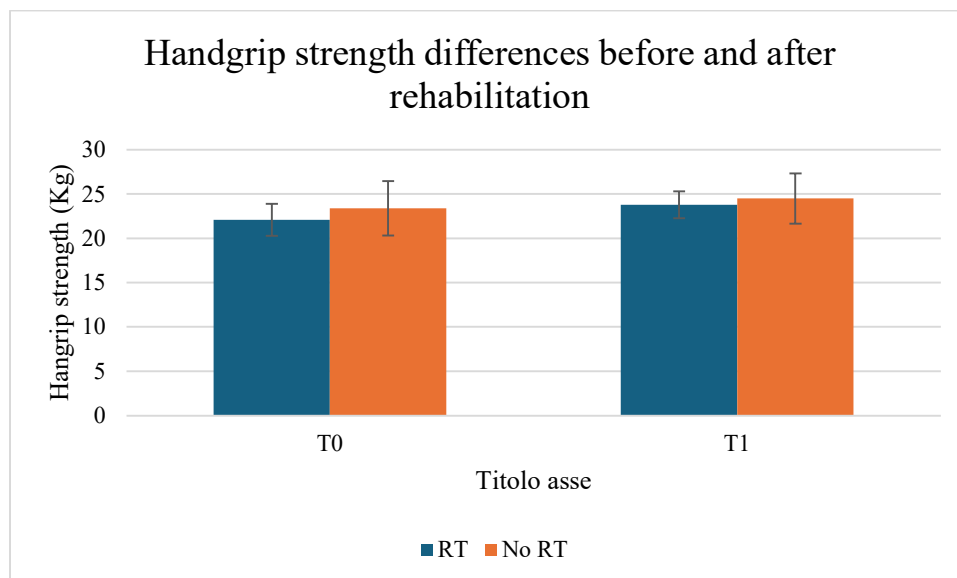


Figure 10: Handgrip strength recovery in RT and non-RT patients, before (T0) rehabilitation and after it (T1). Data are presented as mean $\pm$ SEM. RT Yes ($n=10$), RT No ($n=3$).

12.8 Influence of hormone therapy on rehabilitation

The impact of hormone therapy (HT) was evaluated descriptively, as shown in Figure 11/a and 11/b. Given the high prevalence of HT in the cohort, no clear subgroup differences could be identified. At baseline of the rehabilitation program, patients that had administered a hormonal therapy showed a limb volume difference of 1280 mL, compared to 1180 mL in the non-HT group. Both subgroups achieved similar volume reductions respectively -550 mL and -480 mL, with final volumes at T1 of 730 mL in the HT group and 700 mL in the non-HT one. The high variability observed in both functional and volumetric outcomes suggests that hormone therapy alone is unlikely to be a primary determinant of upper limb impairment or recovery in this specific cohort.

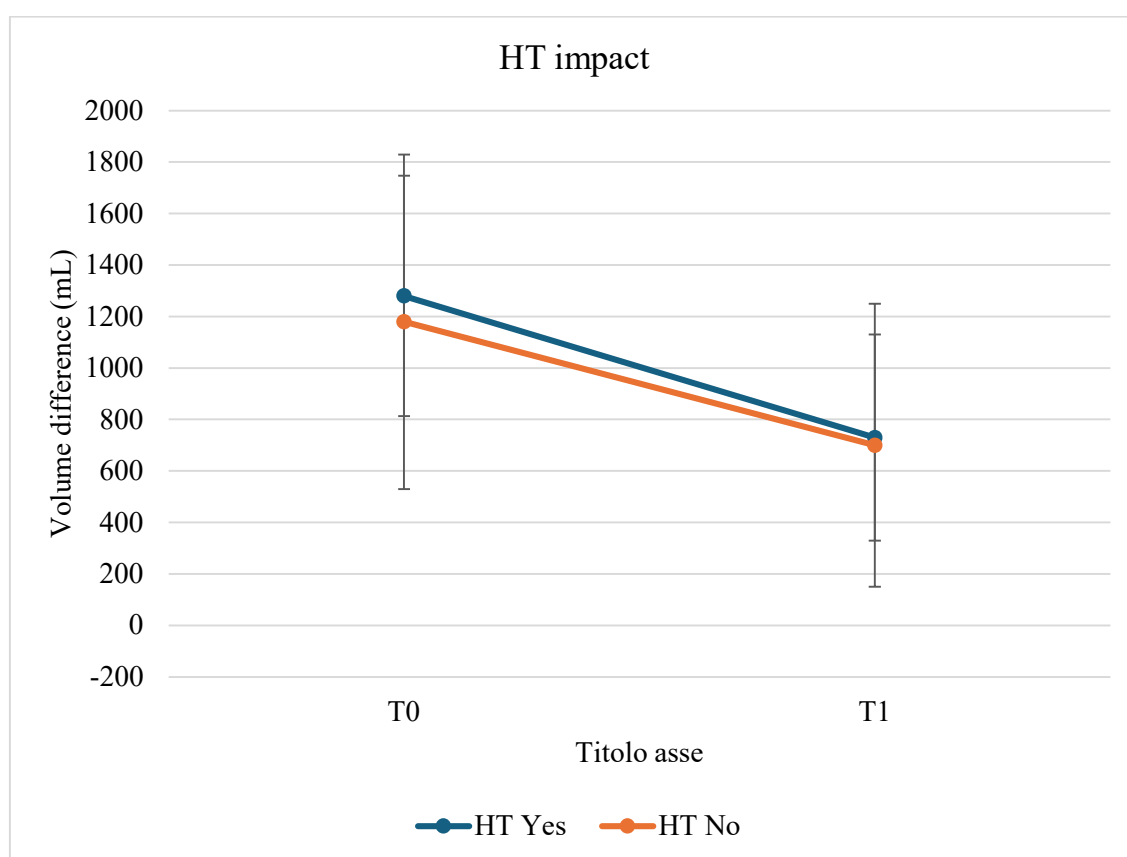


Figure 11/a: Inter-limb volume difference in T0 before the rehabilitation start and at the end of that in T1, based on hormone therapy followed or not. Data are presented as mean $\pm$ SEM. HT Yes ($n=9$), HT No ($n=4$).

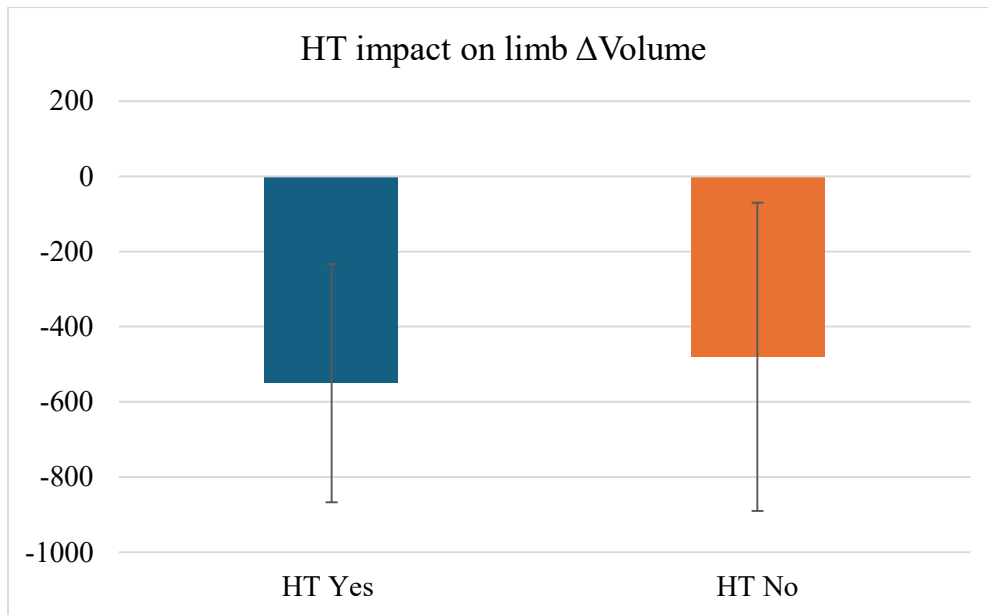


Figure 11/b: Inter-limb Δ Volume reduction in hormonal therapy exposed group and in the one that was not exposed on it at the end of the rehabilitation process. Data are presented as mean $\pm$ SEM. HT Yes (n=9), HT No (n=4).

Functional assessment based on handgrip strength evaluation mirrored this trend, with both groups showing a steady improvement (HT Yes: 22.0 to 23.6 kg; HT No: 23.3 to 24.7 kg), represented in Figure 12.

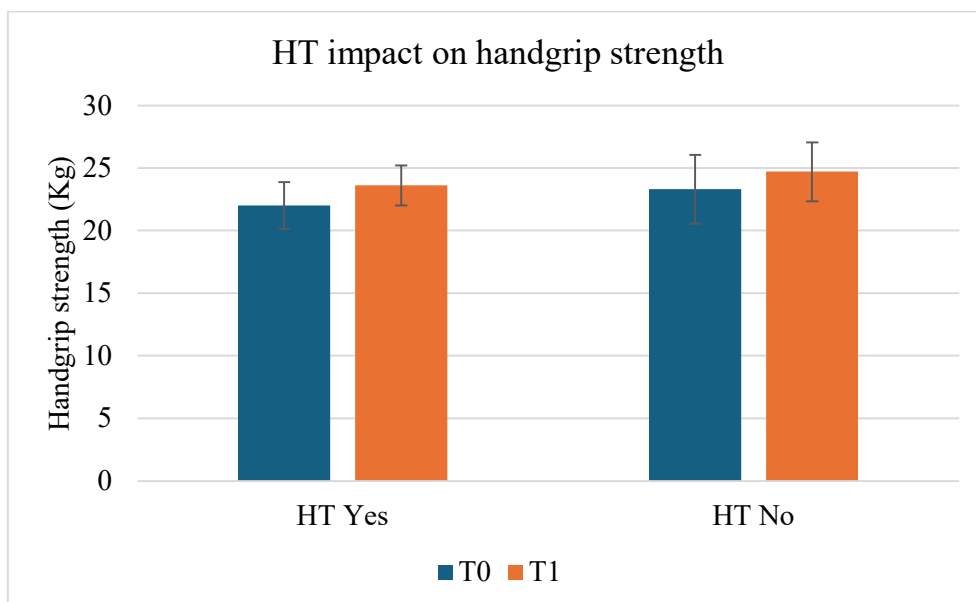


Figure 12: Handgrip strength recovery based on hormone therapy exposure or not patients, before rehabilitation (T0) and at the end of that (T1). Data are presented as mean $\pm$ SEM. HT Yes (n=9), HT No (n=4).

12.9 Influence of lymph node dissection extent

Patients were stratified based on the number of dissected lymph nodes (<10 vs. ≥ 10), as showed in Figure 13. A marked difference in baseline limb volume asymmetry was observed: patients in the ≥ 10 group showed significantly higher initial values (1680 mL) compared to the <10 group (680 mL). This finding strongly supports the association between surgical burden and the severity of secondary lymphedema.

Following the rehabilitation protocol at T1, the <10 group had a mean limb volume of 420 mL showing a relatively lower reduction of Δ Volume -260 mL. Instead, the ≥ 10 group had a mean limb volume difference of 970 mL in T1, demonstrating a more pronounced absolute reduction in volume (Δ Volume -710 mL), although individual variability remained high (Figure 13). These results indicate that while extensive lymphadenectomy is a major risk factor for severe edema, these patients may also experience the greatest absolute benefit from intensive physical therapy.

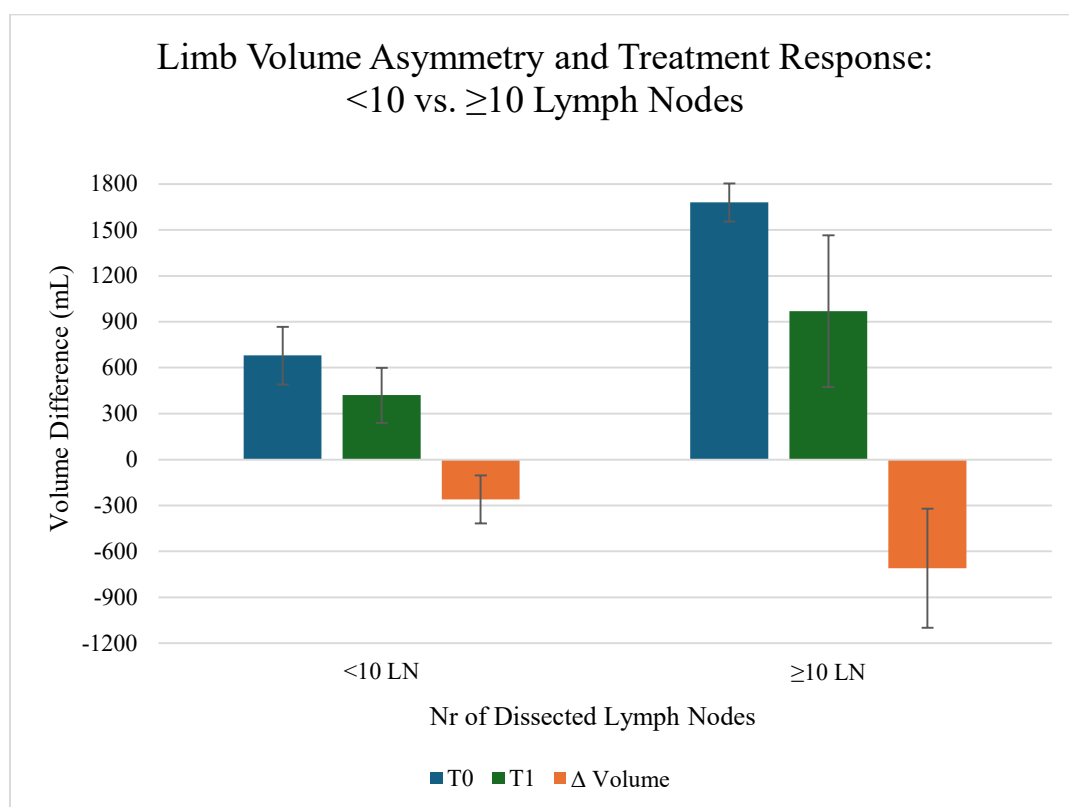


Figure 13: Number of lymph node dissection influence on the rehabilitation program progress at baseline before it starts (T0) and at the end of that (T1). The Δ Volume is expressed to show the final difference. Data are presented as mean $\pm$ SEM. <10 LN (n=5), ≥ 10 LN (n=8)

12.10 Correlation between changes in limb volume and perceived lymphedema impact

The relationship between structural changes and patient-reported outcomes was evaluated and it is illustrated in Figure 14. In it is shown the distribution of individual patients according to changes in limb volume (Δ Volume) and perceived lymphedema impact (Δ LLIS). While all patients reported an improvement in symptoms (Δ LLIS < 0), volumetric changes were heterogeneous, highlighting a partial dissociation between objective morphological changes and subjective perception.

However, quantitative morphological analysis was based exclusively on circumference-derived measurements, while the three-dimensional reconstruction was used as a complementary tool for visual assessment.

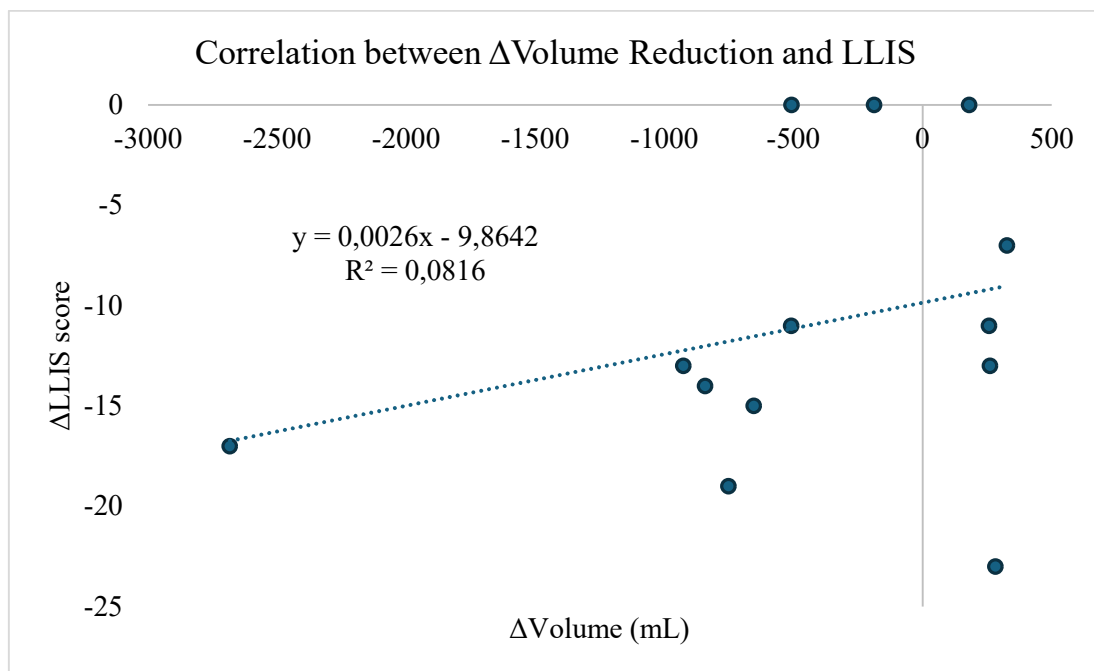


Figure 14. Relationship between changes in limb volume (Δ Volume) and patient-reported lymphedema impact (Δ LLIS). Each point represents an individual patient. Negative Δ LLIS values indicate improvement. While all patients showed a reduction in perceived lymphedema burden, volumetric changes were heterogeneous.

12.11 sEMG analysis (REMO® System)

The neuromuscular functions of the upper limbs were evaluated with the help of surface electromyography. This has been done with the help of the REMO(R) wireless electromyographic system. This helps in the measurement of the electrical signals that are emitted from the muscles during the execution of standardized movements. The sEMG signals were recorded during a series of controlled movements of the upper limbs that involved the activation of the major muscle groups that are involved during functional movements of the upper limbs. The movements included hand opening and closing, wrist flexion and extension, forearm pronation and supination, and anterior shoulder elevation. The movements were executed in a slow manner.

The electromyographic signals obtained during baseline evaluation (T0) showed that the patient group presented heterogeneous patterns of muscle activation during movement. This is likely due to the complex neuromuscular compensations that take place after breast cancer treatment and development of upper limb lymphedema. Indeed, surgical interventions, axillary treatments, pain, and protective movement strategies could all contribute to changes in patterns of muscle activation during movement of the upper limbs.

The electromyographic signals recorded during the performance of the standardized movement tasks indicated that several muscle groups are activated in a coordinated sequence of activations in order to perform even simple movement tasks. In some patients, electromyographic signals indicated that compensatory movement strategies are present, which is a common feature of individuals who have undergone changes in upper limb biomechanics following oncological treatment.

The results from the comparison between the baseline and post-rehabilitation tests revealed changes in the neuromuscular activation patterns. The electromyogram patterns for the patients who underwent repeated tests revealed a trend towards consistent and coordinated neuromuscular activation patterns during the execution of tasks. The changes observed in the neuromuscular coordination and control can be attributed to the rehabilitation process.

The analysis undertaken in the current study is mainly aimed at interpreting the results from a qualitative perspective. The REMO system has shown its capability in detecting neuromuscular signals that can be effectively utilized for analyzing the functional movements. The use of wireless surface electromyography in the study has shown its potential in providing valuable information regarding the neuromuscular component of upper extremity function in breast cancer survivors with lymphedema. The inclusion of sEMG in the study provided a multidimensional assessment of upper extremity impairment by interpreting neuromuscular activity in the context of overall functional recovery and rehabilitation.

12.12 Kinematic analysis and IMU data processing

Kinematic analysis of the upper limb was conducted using an inertial measurement unit (IMU) system, and the results were obtained from a group of healthy volunteers. The main idea behind this experiment was to assess the technical feasibility and reliability of wearable motion analysis, especially in a rehabilitation setting.

The inertial measurement unit system helped in obtaining signals, and then the signals were processed using a computational framework. The signals were processed using a Python-based framework, and this helped in converting the signals into kinematic information, especially about the upper limb. One example of the screening acquisition is shown on Figure 15. The signals were consistent and showed similar patterns during repeated attempts. This indicates that the signals were acquired properly and were consistent during the execution of the tasks. The signals also showed smooth changes over time, and this indicates that there were no issues with the signals. In this case, each signal was associated with a particular action, and this indicates that there was no noise interference. The integration and processing of multi-sensor data made it possible to reconstruct limb orientation over time and provide a continuous and coherent representation of movement in three-dimensional space. This allowed for movement phase identification and for better understanding movement execution pattern, emphasizing the possibilities offered by IMUs in capturing relevant movement features.

Signal visualization and pre-processing was also instrumental in validating the reliability of the acquired signals. The application of filters and normalization ensured the stabilization and reduction of variability in signals, thus contributing to the improvement and robustness of extracted kinematic features. The features provided quantitative information regarding movement dynamics, including temporal and coordination aspects in repeated movements.

Moreover, the similarity in signals across subjects and repetitions also validates the technical reliability of the system. Specifically, the ability to capture stable orientation and signal profiles across repetitions and subjects indicates that the IMU system is technically adequate for capturing and measuring controlled movements in the upper limb in a standardized experimental context.

Significantly, this was done on healthy subjects only and therefore does not provide direct clinical information on the patient population. Instead, it provides a methodological validation of the IMU system, which can be used for future clinical populations.

Overall, the integration of wearable IMU technology and a computational pipeline provides a foundation for the potential integration of quantified kinematic assessment into the rehabilitation process. Although further work is necessary to determine its potential applicability to the patient population suffering from upper limb impairment, the current work provides a solid foundation for future clinical implementation.

In Appendix 1 (Figures 16-21) are shown the acquisition of the four exercises selected for our IMU system performed by 6 of our volunteers.

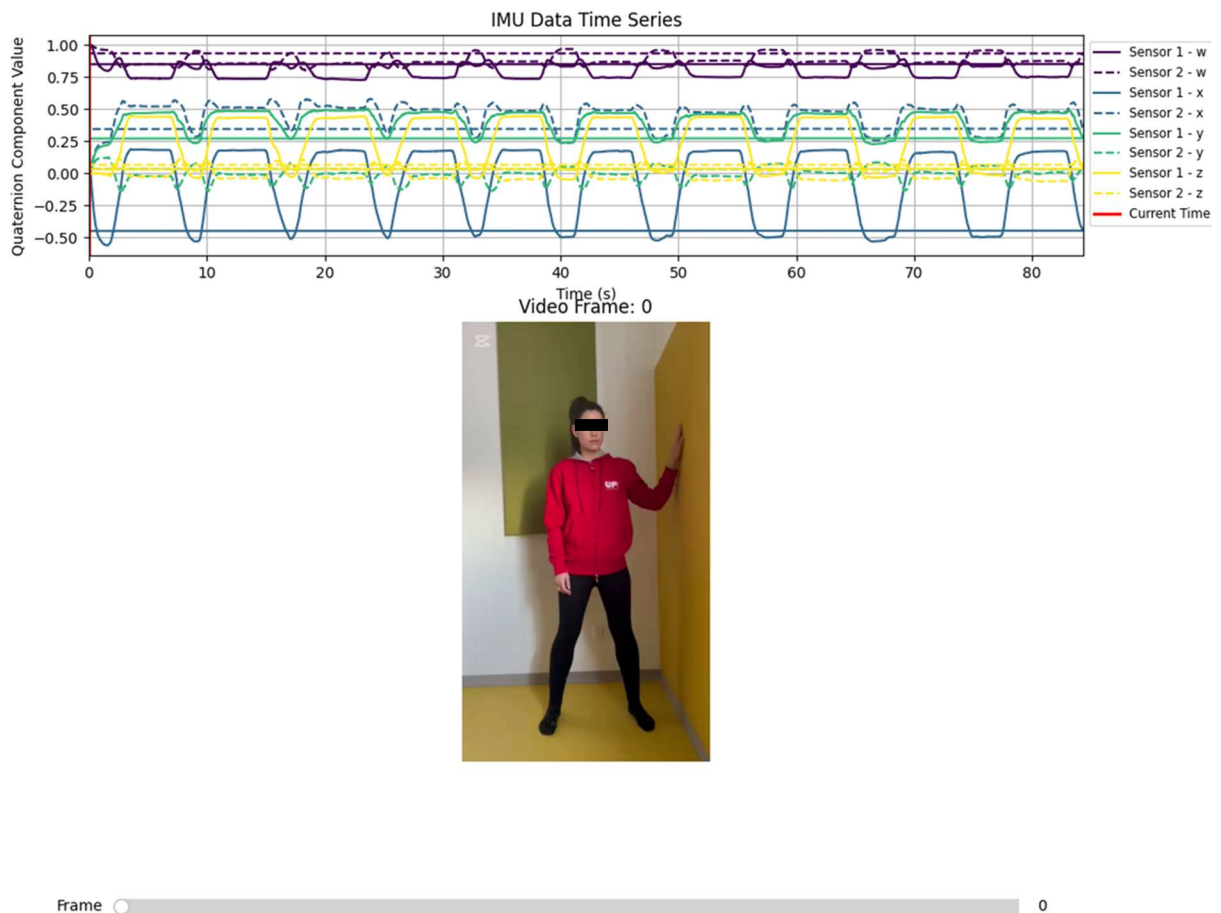


Figure 15. Example of IMU-derived kinematic signals recorded during standardized upper limb movement in a healthy subject obtained through the Python-based processing pipeline. The time-series data illustrate the temporal evolution of sensor outputs and demonstrate the consistency and stability of signal acquisition used for kinematic reconstruction.

DISCUSSION

Main Findings and clinical implications

Breast cancer (BC) is the most common type of cancer diagnosed among women worldwide. Global Cancer Observatory 2024 reported 2.3 million cases of BC and continues to be an important public health problem due to its high incidence, uncertainties in terms of survival, and complex epidemiological routes of development of BC. In this context, breast cancer-related lymphedema (BCRL) is a complicated chronic condition following breast cancer treatment among women. It is usually associated with disruption of lymphatic drainage after treatment, especially radiotherapy and surgery. This complication is characterised by an abnormal aggregation of protein-rich interstitial fluid, resulting to a progressive inflammation of the affected upper limb, heaviness, pain, and functional limitation. In addition, BCRL may permanently affect psychological wellbeing, daily activity, and overall quality of life. The multifactorial pathophysiology of BCRL involves lymphatic vessel disruption, inflammatory activation, microvascular damage, and progressive fibrotic remodelling of soft tissues [112-113].

In the present study we aimed to explore the multidimensional effects of the rehabilitation program in breast cancer survivors affected by BCRL. We have combined structural, functional, patient-reported, and neuromuscular assessments within a rehabilitation-oriented scheme. In addition, the study investigates the utility of wearable devices, including surface electromyography (sEMG) and inertial measurement units (IMUs) as complementary tools for the monitoring and evaluation of the upper limb function.

One of the main findings resulted from this study was the reduction in inter-limb volume difference observed after rehabilitation program. Before the rehabilitation initiation, patients showed substantial heterogeneity regarding the severity of the lymphedema. Different individuals presented marked volumetric asymmetry between the affected limb and the sane one. At the end of the program, most patients demonstrated stabilization or reduction of limb volume difference. This fact supports the beneficial role of rehabilitation implementation in the management of BCRL as confirmed also by Arias-Crespo et al., 2025 and Marchica et al., 2021 [114-115]. These results are coherent with the actual understanding of rehabilitation strategies in lymphedema treatment. For that, physical therapy, movement-based interventions, and lymphatic drainage approaches contribute to improvement of upper limb biomechanics and tissue mobility. Volumetric improvement and function recovery were observed in parallel in the cohort. Handgrip strength showed a modest but consistent increase between the initiation (T0) and the termination (T1) of the physiotherapy. This result suggests that rehabilitation may positively influence not only structural impairment but also muscular performance and functional activity consistent with previous evidences [116-117]. Muscular weakness and impaired hand function have a significant impact in the daily living and quality of life of BC survivors.

For this reason, the functional recovery of the upper limb is clinically relevant, and physiatrists and oncologists are really focused on the post-treatment rehabilitation. It is interesting the fact that the improvement in functional recovery appeared proportionally smaller than the reduction showed in limb volume. This type of dissociation suggests that structural recovery alone it is not a factor on the determination of functional improvement. Upper limb function after breast cancer treatment is, in different way, influenced by several additional components, including fibrosis, pain, fatigue, altered motor control strategies, compensatory muscle activation, and psychological and social adaptation. Patient-reported questionnaire outcomes showed a positive effect of rehabilitation. Both LLISv2 and DASH scores demonstrated improvement during the program, explaining the reduction in recognized disability and lymphedema-related burden. These results emphasize the necessity of an integration between subjective patient perception and rehabilitation assessment. This integration is essential also because objective structural changes do not necessarily correspond to the patient's experience of recovery. In fact, the correlation analysis between Δ Volume and Δ LLISv2 showed, from the results, only a weak association between volumetric reduction of the affected limb and perceived symptom improvement. Even though the majority of the patients reported an overall subjective improvement, volumetric changes remained heterogeneous. This discovery is particularly relevant because it admits that overall functional and psychosocial impact of BCRL is not represented only by the limb volume differences. The symptoms that these patients express, such as heaviness, discomfort, and daily functional limitations, may improve independently of large volumetric reductions. For this reason, multidimensional approach strategies combining objective measurements and patient-reported outcomes were essential for a more detailed and comprehensive evaluation of rehabilitation outcomes. Among the subgroup's evaluations, previous oncological treatments differences appeared to represent one of the most influential determinants of baseline severity. Patients who underwent axillary lymph node dissection (ALND) or were submitted to a higher number of removed lymph nodes exhibited greater volumetric asymmetry at baseline compared with less invasive surgical groups. This finding is consistent with the actual role of ALND as one of the major risk factors for the development of secondary lymphedema [112-118]. Similarly, subjects exposed to taxane-based chemotherapy or radiotherapy demonstrated more pronounced edema before rehabilitation. Nevertheless, variability remained very elevated in these groups, reflecting heterogeneous rehabilitation responses in patients with huge surgical impairments. On the other hand, functional recovery appeared to occur across both less invasive and more extensive surgical groups, supporting the utility of rehabilitation independently from the severity of previous surgical treatments.

Comparison with previous literature

The results obtained from our study confirm the increasing amount of scientific data regarding the role of rehabilitation in the treatment of BCRL [114-117]. Previous researches have provided evidence of the potential of physiotherapy treatments for decreasing limb swelling, improving function, and enhancing the quality of life in BC survivors [115-116]. The results of this study further emphasize the idea that rehabilitation might improve both structural and functional disorders.

A specific finding made during the current research is the partial dissociation between the volume decrease and the subject's functional improvement. Although a number of patients demonstrated clinically significant reduction in limb volume asymmetry, these objective structural changes do not necessarily correspond to the patient's experience of recovery [113-119]. In fact, the correlation analysis between Δ Volume and Δ LLISv2 showed only a weak association between volumetric reduction of the affected limb and perceived symptom improvement. In this connection, BCRL should not be considered just a volumetric issue, but it should be approached as a complex pathology associated with biomechanical and neuromuscular alterations as well as with inflammation and psychological factors.

The subgroup analyses additionally confirmed that patients who previously underwent axillary lymph node dissections (ALND) showed relatively higher inter-limb volume at T0 compared to patients who underwent sentinel lymph node biopsy (SLNB) [112-118]. In a similar way, patients with ≥ 10 dissected lymph nodes exhibited relatively higher initial volumetric asymmetry than patients with < 10 dissected lymph nodes, and this was also confirmed by DiSipio et al., 2013 [120]. These results are biologically coherent with the known pathophysiology of secondary lymphedema, where a significant compromised lymphatic drainage and tissue homeostasis results from the disruption of axillary lymphatic pathways.

The exploratory evaluations regarding systemic treatment and radiotherapy revealed additional clinically relevant information. Patients who were exposed to Taxane-based chemotherapy demonstrated greater inter-limb volume asymmetry at T0 prior to rehabilitation, compared to the non-exposed ones. Taxane-treated patients also showed larger volumetric reductions following rehabilitation in absolute terms compared to baseline conditions. Taxane-related conditions like neurotoxicity, inflammatory responses, and tissue alterations may contribute to greater initial upper limb impairment [121]. This may explain the more severe baseline condition observed in this subgroup. However, our findings suggest that exposure to Taxane-based drugs does not prevent clinically significant rehabilitation-related recovery.

In a similar way, radiotherapy-exposed patients showed a higher edema severity at T0 compared to non-exposed subjects. This examination is consistent with the already known fibrotic and vascular effects of radiotherapy on soft tissues and lymphatic structures [122]. However, both groups, RT and non-RT exposed patients, showed improvements in volumetric and functional parameters at the termination of the rehabilitation program. On the other hand, hormone therapy appeared to exert a less evident influence on rehabilitation results. Here, both exposed and non-exposed patients demonstrated comparable trends of recovery.

Unlike previous research found on bibliography that focused mostly on circumference measurements or self-assessment questionnaires, this work introduces a more integrated evaluation approach. The inclusion of structural measurements, physiological tests, self-assessment questionnaires, and wearables forms one of the most creative features of this research. This comprehensive approach may help achieve a more precise assessment of upper limb dysfunctions and can assist in designing personalized rehabilitation protocols for patients in the future [123].

Advantages and limitations of wearable devices

Another important aspect we have investigated in the present study regards the integration of wearable technologies within the assessment framework. Surface electromyography (sEMG) using the REMO system was used for the exploration of upper limb neuromuscular activity during standardized exercises. Prior rehabilitation, patients frequently demonstrated heterogeneous activation patterns, reflecting compensatory neuromuscular adaptation resulting from surgery, fibrosis, pain, and motor control alterations. Once rehabilitation program has finished, different patients showed to exhibit more stable and coordinated activation patterns, although the present study remained principally qualitative. These conclusions support the potential ability of sEMG in identifying neuromuscular adaptations that in some cases may not be detectable only through conventional clinical evaluation [124].

Similarly, the methodological evaluations related to inertial measurement units (IMUs) further demonstrated the usefulness of wearable devices for objective movement analysis during rehabilitative program applications. Even though IMU validation was performed exclusively in healthy subjects, the development of a computational pipeline for the acquisition of signals and data processing can serve as a methodological basis for future applications in BC rehabilitation. By quantitatively assess movement quality, velocity, symmetry, and coordination through wearable technologies may be considered as an important advancement toward a more personalized rehabilitation approach [125].

This integration is particularly relevant considering the limitations of traditional clinical evaluation methods and the physiotherapeutic gold standard in post-treatment BC patients' rehabilitation.

Conventional approaches, like circumferential measurements, manual strength assessment, and questionnaire compilation provide an incomplete information regarding upper limb function and activity. For that reason, wearable devices may contribute to a continuous, quantitative, and ecologically monitoring of neuromuscular and kinematic behaviour. In this context, our study supports the idea that rehabilitation programs in breast cancer survivors should progressively evolve and adequate toward multidimensional and technology-assisted approaches. However, some limitations should also be considered. For example, REMO and IMUs signals may be influenced by the position of the electrodes, soft tissue peculiarity, and signal variability. These situations may affect reproducibility and interpretation. Therefore, more research is needed in order to confirm the validity of these devices in clinical setting.

Overall, wearable devices may represent promising complementary tools capable of integrating traditional clinical assessments with objective and quantitative evaluations of upper limb functionality in breast cancer survivors.

Study limitations

Different limitations should though be considered. First, the study population was relatively small, particularly within subgroup analyses. And this was a major reason on limiting the possibility of performing robust inferential statistical comparisons. Secondly, the cohort was particularly heterogeneous referring to the oncological treatment they received, surgical procedures, disease severity, and rehabilitation responses. This heterogeneity increases inter-individual variability and complicates subgroup interpretation, even though it reflects real-world clinical practice. Another limitation regards the absence of long-term follow-up limits the possibility of evaluating the persistence of rehabilitation -related improvements over time. For this reason, several analyses performed in the present study should be considered exploratory and descriptive in nature. Finally, quantitative neuromuscular and kinematic evaluations remain preliminary. Neuromuscular and kinematic evaluations require further quantitative validation especially those regarding IMU applications in clinical populations.

Conclusions and future perspectives

Overall, this study supports the positive impact of rehabilitation on the quality of outcome measures in BCRL patients. Specifically, the positive effects of rehabilitation include reduction of inter-limb volume asymmetry, improvement in handgrip strength, and better patient ratings in terms of physical disabilities and lymphedema-related burden. The current findings confirm that rehabilitation plays an important role on breast cancer management when the disease results in upper limb alteration post-management. A key finding that comes out at the end of the current research is that the structural recovery process in itself is not enough to explain the functional problems associated with BCRL. The weak correlation found between volumetric reduction and subjective improvements in symptoms highlights the fact that the dysfunction occurring in the upper extremity can be understood as a multidimensional entity comprising different dimensions, such as physical, neuromuscular, biomechanical, and psychological elements.

Future investigations need to be performed by recruiting larger and more homogenous groups of patients to ensure the validity of statistical tests applied to subgroups, and to increase the potential for generalization of results. Longitudinal studies, which will assess the durability of rehabilitation-related improvements, as well as further progress in functional recovery, are needed to be further evaluated. Further study is required to investigate the application of wearable devices in the quantitative aspects of rehabilitation. An advanced analysis of signals acquired via sEMG and IMU can reveal the existence of biomarkers reflecting motor recovery, compensation mechanisms, and responsiveness to rehabilitation therapy. Moreover, wearables can become a part of personalized treatment approaches by integrating with AI-based tools that would allow selecting exercises and the level of their difficulty according to individual functional features.

To sum up, the present study gives a contribution on the growing evidence supporting personalized and multidimensional rehabilitation approaches in breast cancer survivors with upper limb dysfunction. In addition, the integration of wearable devices like sEMG and IMUs may provide a promising methodological application for future objective and technology-assisted rehabilitation strategies aimed at improving functional recovery and quality of life in BC survivors with BCRL.

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APPENDIX 1

1 / 3

Questionario per l'arto superiore DASH

(Disability of the Arm, Shoulder and Hand) Italian Version

Istruzioni: Il presente questionario riguarda i Suoi sintomi e la Sua capacità di compiere alcune azioni. Risponda a **ogni domanda** facendo riferimento al Suo stato durante l'**ultima settimana**. Se non ha avuto l'opportunità di eseguire una delle azioni durante l'ultima settimana, risponda alla domanda **provando a immaginare** come avrebbe potuto eseguirla. Non importa con quale mano o braccio Lei esegue l'azione; risponda in base alla Sua capacità di compierla e senza tenere conto del modo in cui la compie.

Valuti la sua capacità di eseguire le seguenti azioni durante l'**ultima settimana**.

	(Indichi un numero)				
	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non ci sono riuscito
1. Svitare il coperchio di un barattolo ben chiuso o nuovo.	1	2	3	4	5
2. Scrivere	1	2	3	4	5
3. Girare una chiave	1	2	3	4	5
4. Preparare un pasto	1	2	3	4	5
5. Aprire spingendo una porta pesante	1	2	3	4	5
6. Posare un oggetto su uno scaffale al di sopra della propria testa	1	2	3	4	5
7. Fare lavori domestici pesanti (es. lavare i pavimenti o i vetri)	1	2	3	4	5
8. Fare lavori di giardinaggio	1	2	3	4	5
9. Rifare il letto	1	2	3	4	5
10. Portare la borsa della spesa o una ventiquattrore	1	2	3	4	5
11. Portare un oggetto pesante (oltre 5 Kg)	1	2	3	4	5
12. Cambiare una lampadina posta al di sopra della propria testa	1	2	3	4	5
13. Lavarsi o asciugarsi i capelli	1	2	3	4	5
14. Lavarsi la schiena	1	2	3	4	5
15. Infilarsi un maglione	1	2	3	4	5
16. Usare un coltello per tagliare del cibo	1	2	3	4	5
17. Attività ricreative che richiedono poco sforzo (es. giocare a carte, lavorare a maglia)	1	2	3	4	5
18. Attività ricreative nelle quali si fa forza o si prendono colpi sul braccio, sulla spalla o sulla mano (es. usare il martello, giocare a tennis o a golf, ecc.)	1	2	3	4	5
19. Attività ricreative che richiedono un movimento libero del braccio (es. giocare a frisbee, a badminton, ecc.)	1	2	3	4	5
20. Far fronte alle necessità di spostamento (andare da un posto ad un altro)	1	2	3	4	5
21. Attività sessuale	1	2	3	4	5

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Questionario per l'arto superiore DASH

(Disability of the Arm, Shoulder and Hand) Italian Version

Durante la settimana passata, in che misura il suo problema al braccio, alla spalla o alla mano ha interferito con le normali attività sociali con la famiglia, gli amici, i vicini di casa i gruppi di cui fa parte?

	(Indichi un numero)				
	Per nulla	Molto poco	Un po'	Molto	Moltissimo
22.	1	2	3	4	5

Durante la settimana passata è stato limitato nel suo lavoro o in altre attività quotidiane abituali a causa del suo problema al braccio, alla spalla o alla mano?

	(Indichi un numero)				
	Non mi ha limitato per nulla	Mi ha limitato leggermente	Mi ha limitato discretamente	Mi ha limitato molto	Non ci sono riuscito
23.	1	2	3	4	5

Valuti l'intensità dei seguenti sintomi durante l'ultima settimana.

	(Indichi un numero per ogni riga)				
	Nessuno	Lieve	Discreto	Forte	Estremo
24. Dolore al braccio, alla spalla o alla mano	1	2	3	4	5
25. Dolore al braccio, alla spalla o alla mano nel compiere una qualsiasi attività specifica	1	2	3	4	5
26. Formicolio (sensazione di punture di spillo) al braccio, alla spalla o alla mano	1	2	3	4	5
27. Debolezza al braccio, alla spalla o alla mano	1	2	3	4	5
28. Rigidità del braccio, della spalla o della mano	1	2	3	4	5

Durante l'ultima settimana quanta difficoltà ha incontrato nel dormire a causa del dolore al braccio, alla spalla o alla mano?

	(Indichi un numero)				
	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non sono riuscito a dormire
29.	1	2	3	4	5

Mi sento meno capace, meno fiducioso o meno utile a causa del mio problema al braccio, alla spalla o alla mano

	(Indichi un numero)				
	Non sono assolutamente d'accordo	Non sono d'accordo	Non saprei	Sono d'accordo	Sono assolutamente d'accordo
30.	1	2	3	4	5

Questionario per l'arto superiore DASH

(Disability of the Arm, Shoulder and Hand) Italian Version

MODULO LAVORATIVO (OPZIONALE)

Le seguenti domande si riferiscono all'impatto del suo problema al braccio, alla spalla o alla mano sul **suo lavoro** (compreso il lavoro in casa se questa è la sua attività principale).

Indichi qual è il suo lavoro/attività: _____

Indichi su ogni riga il numero che meglio descrive la sua capacità fisica durante l'ultima settimana.

Ha avuto difficoltà:

	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non ci sono riuscito
31. A utilizzare la Sua tecnica abituale per lavorare?	1	2	3	4	5
32. A svolgere il Suo lavoro abituale a causa del dolore al braccio, alla spalla o alla mano?	1	2	3	4	5
33. A fare il lavoro bene come vorrebbe?	1	2	3	4	5
34. A dedicare al Suo lavoro la consueta quantità di tempo?	1	2	3	4	5

MODULO ATTIVITÀ SPORTIVE/RICREATIVE (OPZIONALE)

Le seguenti domande si riferiscono all'impatto del Suo problema al braccio, alla spalla o alla mano sulla Sua capacità di **suonare il Suo strumento musicale o praticare il Suo sport, o su entrambe le attività**.

Se pratica più di uno sport o suona più di uno strumento (o fa entrambe le cose) risponda facendo riferimento all'attività che è più importante per lei.

Indichi quale sport o strumento è il più importante per lei: _____

Indichi su ogni riga il numero che meglio descrive la sua capacità fisica durante l'ultima settimana.

Ha avuto difficoltà:

	Nessuna difficoltà	Lieve difficoltà	Discreta difficoltà	Notevole difficoltà	Non ci sono riuscito
35. A utilizzare la Sua tecnica abituale per suonare il suo strumento o praticare il suo sport?	1	2	3	4	5
36. A suonare il suo strumento o praticare il suo sport a causa del dolore al braccio, alla spalla o alla mano?	1	2	3	4	5
37. A suonare il suo strumento o praticare il suo sport bene come vorrebbe?	1	2	3	4	5
38. A dedicare al suo strumento o al suo sport la consueta quantità di tempo?	1	2	3	4	5

LLIS Lymphedema Life Impact Scale

Version 1

Cognome e Nome _____

Data _____

Qui di seguito sono elencati i sintomi o i disturbi che vengono descritti da molti pazienti che hanno un linfedema. Per favore indichi quanto questi disturbi associati al suo linfedema sono stati per lei un problema durante le **ultime 2 settimane**. Se entrambi gli arti sono gonfi, giudichi i disturbi degli arti gonfi rispetto a qualsiasi arto non gonfio.

Faccia un cerchio sul numero che meglio descrive l'entità del disturbo.

• DISTURBI FISICI

1. L'intensità del dolore associato al linfedema è:

1	2	3	4	5
---	---	---	---	---

nessun dolore

dolore fortissimo

2. L'intensità del senso di pesantezza associato al linfedema è:

1	2	3	4	5
---	---	---	---	---

nessuna pesantezza

estremamente pesante

3. L'intensità di ispessimento cutaneo associato al linfedema è:

1	2	3	4	5
---	---	---	---	---

nessun ispessimento

estremamente ispessito

4. Rispetto all'arto sano, la dimensione dell'arto gonfio sembra

1	2	3	4	5
---	---	---	---	---

dimensione normale

estremamente grande

5. Rispetto all'arto sano, la pelle dell'arto gonfio sembra al tatto:

1	2	3	4	5
---	---	---	---	---

uguale

estremamente diversa

6. Il linfedema limita i movimenti dell'arto gonfio:

1	2	3	4	5
---	---	---	---	---

movimenti normali

estremamente limitati

7. Rispetto all'arto sano, la forza dell'arto gonfio è:

1	2	3	4	5
---	---	---	---	---

stessa forza

estremamente debole

8. Negli ultimi 2 anni, quante volte ha dovuto prendere antibiotici per bocca o essere ricoverato per infezione all'arto gonfio?

1	2	3	4	5
---	---	---	---	---

mai

<1 volta
per anno

1-3 volte
per anno

4-6 volte
per anno

7-9 volte
per anno

- DISTURBI PSICOSOCIALI**

9. Il linfedema condiziona la mia immagine corporea (cioè come penso di sembrare):

1	2	3	4	5
----------	----------	----------	----------	----------

per nulla gravemente

10. Il linfedema condiziona la socializzazione con gli altri:

1	2	3	4	5
----------	----------	----------	----------	----------

nessuna interferenza interferisce totalmente

11. Il linfedema condiziona le mie relazioni intime:

1	2	3	4	5
----------	----------	----------	----------	----------

nessuna interferenza interferisce totalmente

12. Il linfedema mi fa sentire giù (cioè mi sento depresso, frustrato o arrabbiato per colpa del linfedema):

1	2	3	4	5
----------	----------	----------	----------	----------

mai costantemente

- DISTURBI FUNZIONALI**

13. Il linfedema condiziona la capacità di eseguire le cose che devo fare a casa:

1	2	3	4	5
----------	----------	----------	----------	----------

nessuna interferenza interferisce totalmente

14. Il linfedema condiziona la capacità di eseguire le cose che devo fare a lavoro (se applicabile):

1	2	3	4	5
----------	----------	----------	----------	----------

nessuna interferenza interferisce totalmente

15. Il linfedema condiziona la prestazione nelle mie preferite attività ricreative:

1	2	3	4	5
----------	----------	----------	----------	----------

nessuna interferenza interferisce totalmente

16. Il linfedema condiziona la giusta taglia di vestiti/scarpe:

1	2	3	4	5
----------	----------	----------	----------	----------

per nulla impossibile da indossare

17. Il linfedema condiziona il mio sonno:

1	2	3	4	5
----------	----------	----------	----------	----------

nessuna interferenza interferisce moltissimo

18. Devo contare sull'aiuto di altri per colpa del mio linfedema:

1	2	3	4	5
----------	----------	----------	----------	----------

per nulla totalmente



Patient ID: CH - ____ - ____

EORTC QLQ-C30 (versione 3)

Date:

Con questo questionario vorremmo sapere alcune cose su di Lei e sulla Sua salute. La preghiamo di rispondere a tutte le domande selezionando il numero che meglio corrisponde alla Sua risposta. Non esiste una risposta "giusta" o "sbagliata". Le Sue informazioni verranno tenute strettamente riservate.

	No	Un po'	Parec- chio	Moltis- simo
1. Ha difficoltà nello svolgere attività faticose, come portare una borsa della spesa pesante o una valigia?	1	2	3	4
2. Ha difficoltà nel fare una <u>lunga</u> passeggiata?	1	2	3	4
3. Ha difficoltà nel fare una <u>breve</u> passeggiata fuori casa?	1	2	3	4
4. Ha bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4

Durante gli ultimi sette giorni:

	No	Un po'	Parec- chio	Moltis- simo
6. Ha avuto limitazioni nel fare il Suo lavoro o altre attività quotidiane?	1	2	3	4
7. Ha avuto limitazioni nel praticare i Suoi passatempi-hobby o altre attività di divertimento o svago?	1	2	3	4
8. Le è mancato il fiato?	1	2	3	4
9. Ha avuto dolore?	1	2	3	4
10. Ha avuto bisogno di riposo?	1	2	3	4
11. Ha avuto difficoltà a dormire?	1	2	3	4
12. Ha sentito debolezza?	1	2	3	4
13. Le è mancato l'appetito?	1	2	3	4
14. Ha avuto un senso di nausea?	1	2	3	4
15. Ha vomitato?	1	2	3	4
16. Ha avuto problemi di stitichezza?	1	2	3	4

Continuare alla pagina successiva



Patient ID: CH - ____ - ____

EORTC QLQ-C30 (versione 3)

Date:

Con questo questionario vorremmo sapere alcune cose su di Lei e sulla Sua salute. La preghiamo di rispondere a tutte le domande selezionando il numero che meglio corrisponde alla Sua risposta. Non esiste una risposta "giusta" o "sbagliata". Le Sue informazioni verranno tenute strettamente riservate.

	No	Un po'	Parec- chio	Moltis- simo
1. Ha difficoltà nello svolgere attività faticose, come portare una borsa della spesa pesante o una valigia?	1	2	3	4
2. Ha difficoltà nel fare una <u>lunga</u> passeggiata?	1	2	3	4
3. Ha difficoltà nel fare una <u>breve</u> passeggiata fuori casa?	1	2	3	4
4. Ha bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4

Durante gli ultimi sette giorni:

	No	Un po'	Parec- chio	Moltis- simo
6. Ha avuto limitazioni nel fare il Suo lavoro o altre attività quotidiane?	1	2	3	4
7. Ha avuto limitazioni nel praticare i Suoi passatempi-hobby o altre attività di divertimento o svago?	1	2	3	4
8. Le è mancato il fiato?	1	2	3	4
9. Ha avuto dolore?	1	2	3	4
10. Ha avuto bisogno di riposo?	1	2	3	4
11. Ha avuto difficoltà a dormire?	1	2	3	4
12. Ha sentito debolezza?	1	2	3	4
13. Le è mancato l'appetito?	1	2	3	4
14. Ha avuto un senso di nausea?	1	2	3	4
15. Ha vomitato?	1	2	3	4
16. Ha avuto problemi di stitichezza?	1	2	3	4

Continuare alla pagina successiva

APPENDIX 2



Comitato Etico Territoriale (CET) Interaziendale AOU Maggiore della Carità di Novara



Prot. n° 114/CE

del 28/02/2025

Pratica N° CE367/2024

AOU di Alessandria

OGGETTO: Richiesta parere pervenuta in data 08/11/2024

Titolo Studio: **TeleRiabilitazione con interfaccia Elettromiografica e Supporto multimediale per tumore MAMario: Uno Studio di fattibilità**

Tipologia Studio: **noProfit**

Acronimo: **RESTORE-MAM** .-

Eudract: .-

Sperimentatore Principale: Dott. **Marco Invernizzi**

Struttura: **Rimondini Lia**

Presidio **Università del Piemonte Orientale**

DOCUMENTAZIONE PRESENTATA:

- MAIN2_2024-11-08_Modulo_sottomissione.pdf
- MAIN_2025-02-06_ricevuta_di_sottomissione_388468 (1).pdf
- ELCE_2024-11-08_Documento NA.pdf
- DNP_2024-11-08_Dichiarazione studio spontaneo.pdf
- DATI_2024-11-08_6.Strumenti_Dati clinici e demografici.pdf
- SS_2024-11-08_MbientLab EU Declaration of Conformity.pdf
- DATI_2024-11-08_8. Scale di valutazione self report.pdf
- IB_2024-11-08_MbientLab 2ACEB-MMR FCC Grant.pdf
- AMST_2024-11-08_Documento NA.pdf
- IMPD_2024-11-08_MbientLab EU Declaration of Conformity.pdf
- DATI_2024-11-08_7. SClae di valutazione esiti di fattibilità.pdf
- CDP_2024-11-08_3. Informativa e consenso trattamento dati (1).pdf
- IB_2024-11-08_11_Scheda Tecnica.pdf
- IB_2024-11-08_1_Descrizione_Specifiche.pdf
- CASS_2024-11-08_Documento NA.pdf
- DCI_2024-11-08_Signed_MI- Dichiarazione_Conflitto_Interessi_Sperimentatore.pdf
- CV_2024-11-08_Cv.INVERNIZZI.Marco.Ita.pdf
- PUCE_2024-11-08_Documento NA.pdf
- LIMC_2024-11-08_4. Lettera al medico di famiglia.pdf
- IB_2024-11-08_MbientLab 12118A-MMR ISEDC CoC.PDF
- IMPD_2025-02-06_25_Dichiarazione-Conformità (2).pdf
- IB_2025-02-06_Remo_Manuale-duso-e-manutenzione.pdf
- FICI_2025-02-06_V2_Track_SCHEDA INFORMATIVA E DICHIARAZIONE DI CONSENSO PER IL PAZIENTE_interventistico.docx
- PROT_2025-02-06_V2_Track_AOU_Protocol.docx
- FICI_2025-02-06_V2_Clean_SCHEDA INFORMATIVA E DICHIARAZIONE DI CONSENSO PER IL PAZIENTE_interventistico.docx
- PROT_2025-02-06_V2_Clean_AOU_Protocol.docx
- ADS_2024-11-08_Mod. 06 DAIRIO1_Autorizzazione Autorità competente Locale (23)-signed.pdf
- LDI_2024-11-08_Lettera di intenti_Signed.pdf



**Comitato Etico Territoriale (CET)
Interaziendale AOU Maggiore della Carità di Novara**



- LDI_2025-02-06_Lettera di risposta al parere.pdf
- SIN_2025-02-06_V2_Track_Sinossi.docx
- SIN_2025-02-06_V2_Clean_Sinossi.docx

Il Comitato Etico Territoriale (CET) denominato "Comitato Etico Interaziendale AOU Maggiore della Carità di Novara" istituito ai sensi dell'art. 2, comma 7, della legge n. 3 del 2018, dell'art. 5 del D.M. 30 gennaio 2023, dell'art.1 del D.M. 26.01.2023 e della D.G.R. 21 marzo 2023, n. 24-6629 e nominato con DPGR n° 26 del 12.06.2023; nella seduta del **28/02/2025**, esaminata la documentazione prodotta, nell'intesa che lo studio clinico sia espletato in conformità ai principi etici che traggono la loro origine dalla Dichiarazione di Helsinki nella sua ultima versione, e che rispetti le GCP e le disposizioni delle normative vigenti, ritiene di esprimere

PARERE Favorevole/Accettazione del parere unico

Eventuali note: **Formulato dopo acquisizione e valutazione della documentazione integrativa pervenuta.** -

Questo Comitato dovrà essere informato dell'inizio della sperimentazione e della sua conclusione od eventuale interruzione nonché di ogni eventuale emendamento al protocollo. Al momento della chiusura dello studio sarà cura del ricercatore inviare allo stesso Comitato, secondo quanto previsto dalla normativa vigente, una relazione sintetica dei risultati ottenuti presso il proprio ambito di sperimentazione e comunicare gli estremi bibliografici di eventuali pubblicazioni che verranno prodotte sulla base della ricerca stessa.

Il Comitato Etico ricorda altresì che deve essere garantito il diritto alla diffusione e/o pubblicazione dei risultati favorevoli o non favorevoli da parte degli sperimentatori che hanno condotto lo studio, nel rispetto delle disposizioni vigenti in tema di riservatezza dei dati sensibili e di tutela brevettuale e che non devono sussistere vincoli di diffusione e pubblicazione dei risultati da parte del Promotore.

Il responsabile dello studio dovrà, inoltre, far pervenire una relazione annuale sull'andamento dello stesso.

In ogni successiva comunicazione dovrà essere indicato il numero di pratica assegnato a questa sperimentazione.

Il Presidente
Dott.ssa Alessia Pisterna



Comitato Etico Territoriale (CET) Interaziendale AOU Maggiore della Carità di Novara



I componenti:

- Dott.ssa Pisterna Alessia Presidente (Presente)
- Avv. Valente Margherita membro (Presente)
- Avv. Giudice Lorenzo membro (Presente)
- Prof. Patti Giuseppe membro (Presente via web)
- Dott.ssa Fruttero Claudia membro (Presente via web)
- Dott. Monchiero Luca membro (Assente)
- Prof. Dal Molin Alberto membro (Presente)
- Dott.ssa Dalla Costa Cloè membro (Non convocato)
- Prof.ssa Mazzini Letizia membro (Presente)
- Dott. Fornara Savio Renato membro (Presente)
- Sig. Mari Roberto membro (Presente)
- Prof. Savarino Luca membro (Presente via web)
- Prof.ssa Rabbone Ivana membro (Assente)
- Prof. Condorelli Fabrizio membro (Presente)
- Prof. Garzaro Massimiliano membro (Presente)
- Prof.ssa D'Alfonso Sandra membro (Presente)
- Dott.ssa Sacerdote Carlotta membro (Presente)
- Ing. Morena Francesca Maria membro (Presente)

APPENDIX 3

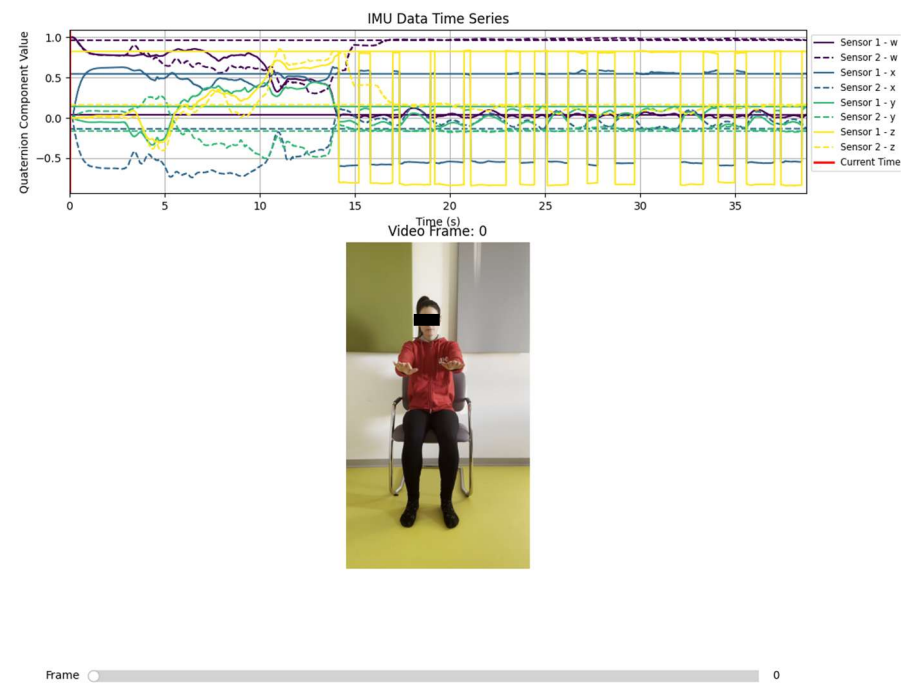


Figure 16/a: Aizata sedia, first exercise performed by the first volunteer.

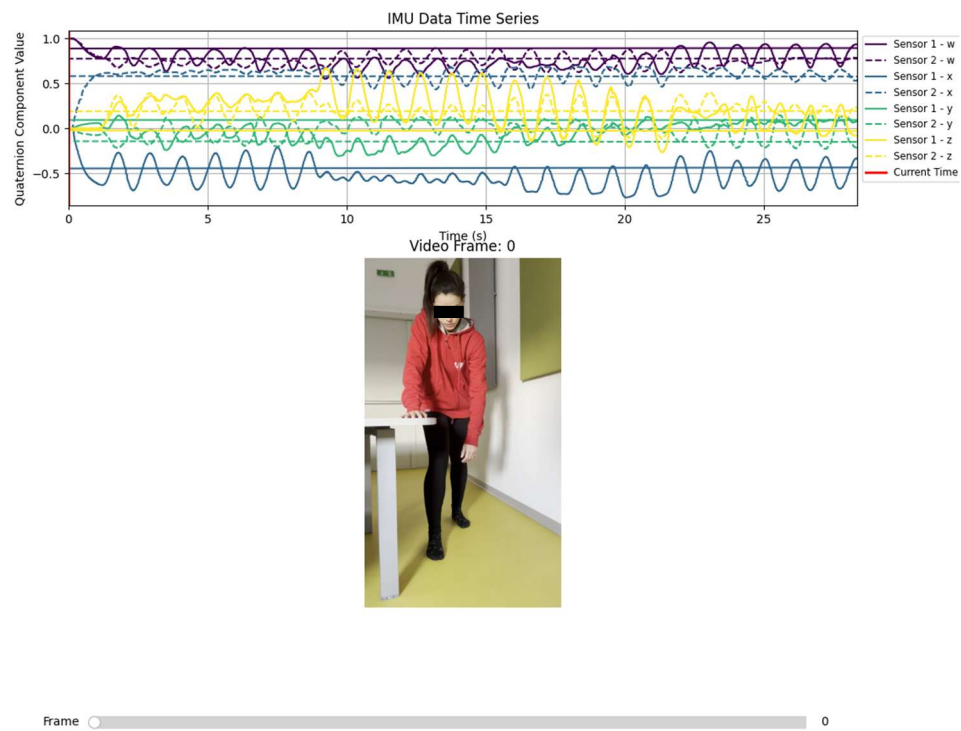


Figure 16/b: Braccio penzoloni, second exercise performed by the first volunteer.

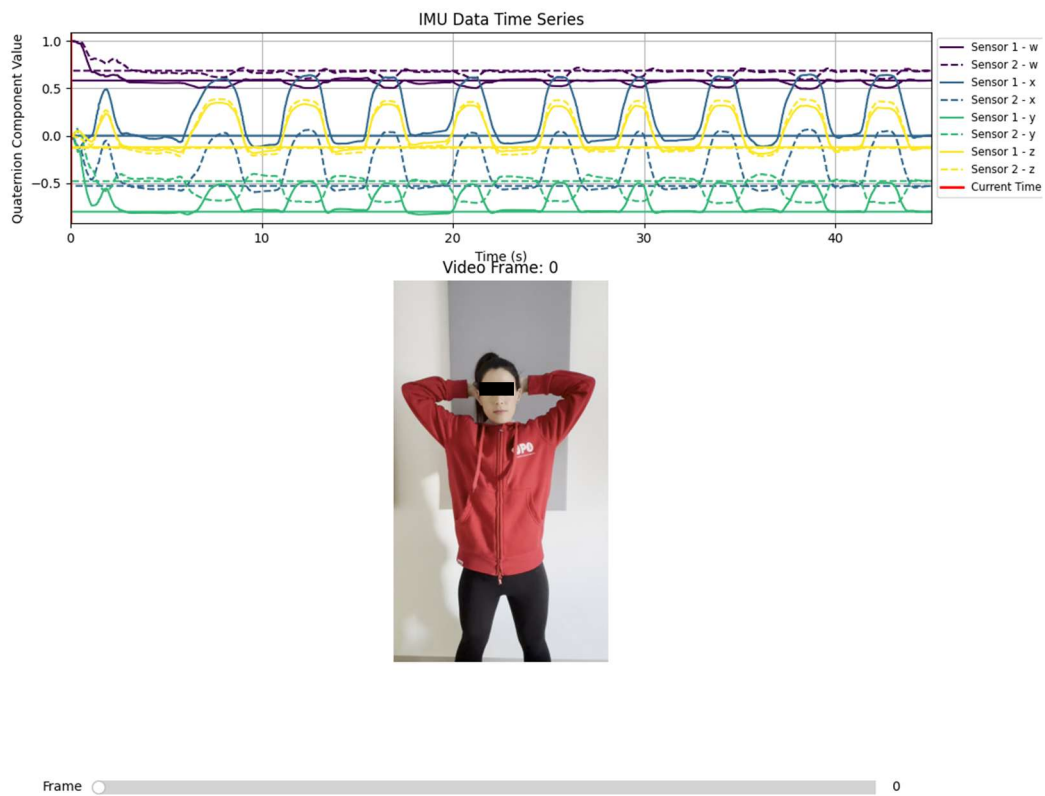


Figure 16/c: Gomiti testa, second exercise performed by the first volunteer.

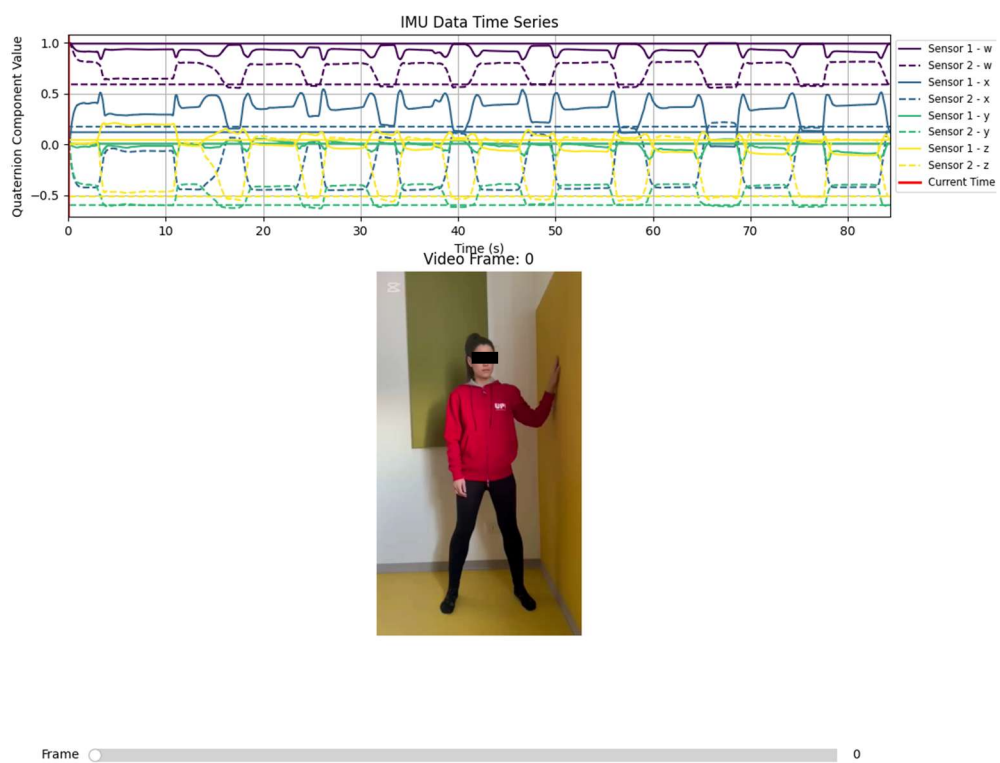


Figure 16/d: Palmo su muro, last exercise performed by first volunteer.

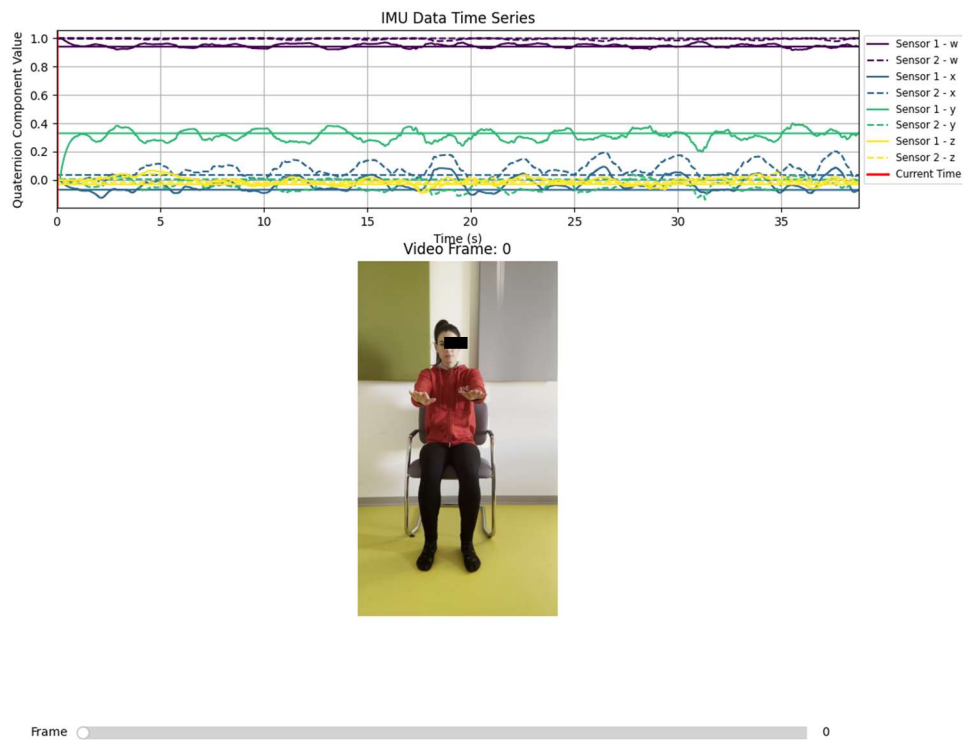


Figure 17/a: Alzata sedia, first exercise performed by the second volunteer.

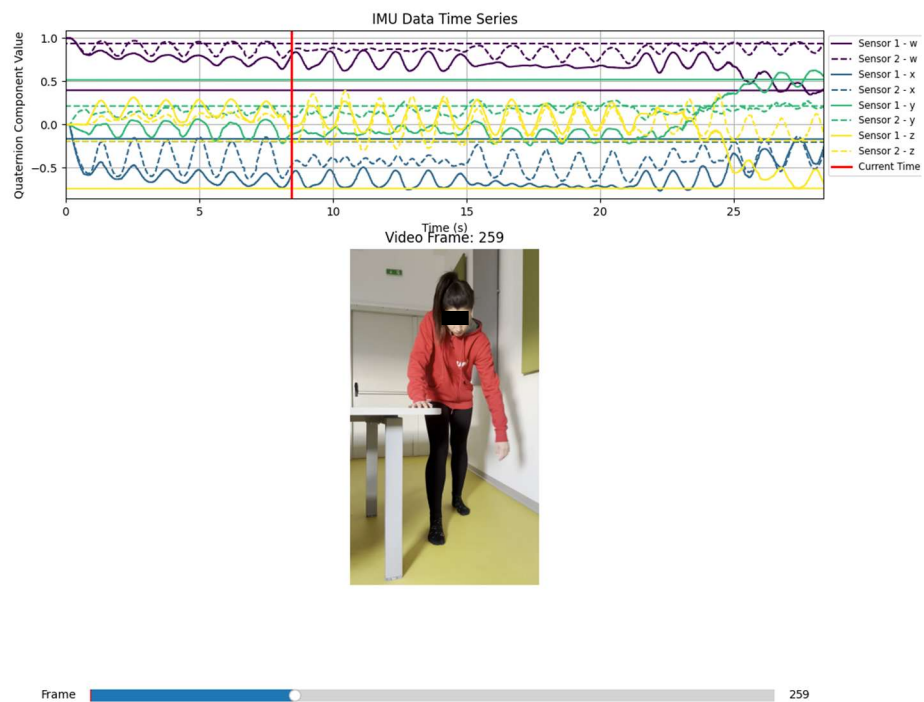


Figure 17/b: Braccio penzoloni, second exercise performed by the second volunteer.

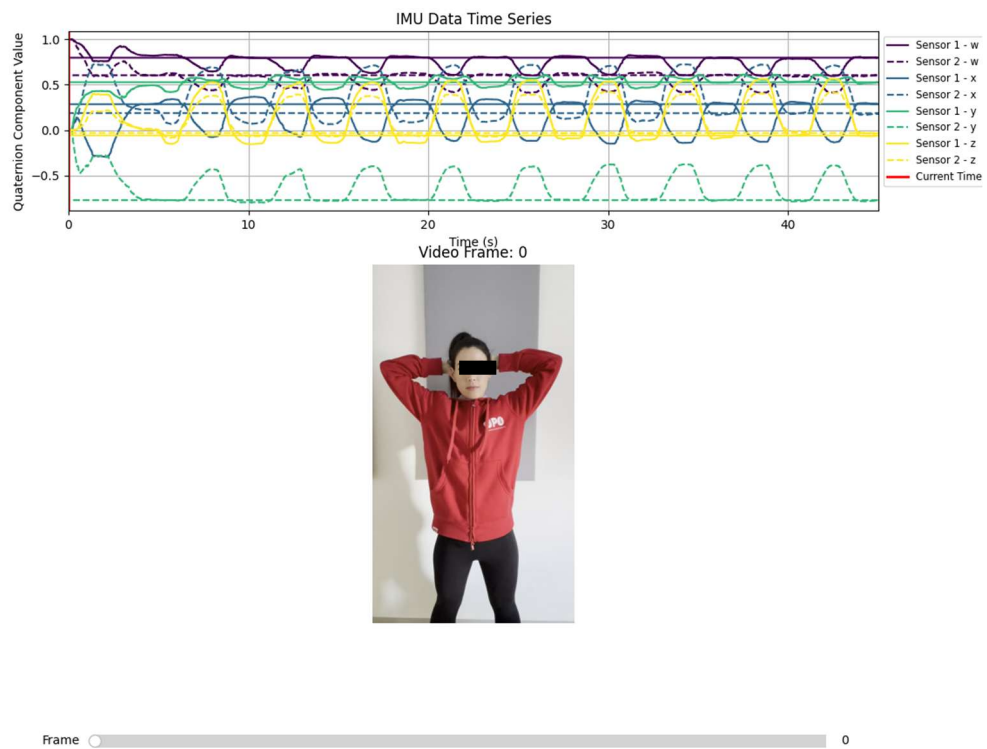


Figure 17/c: Gomiti testa, third exercise performed by the second volunteer.

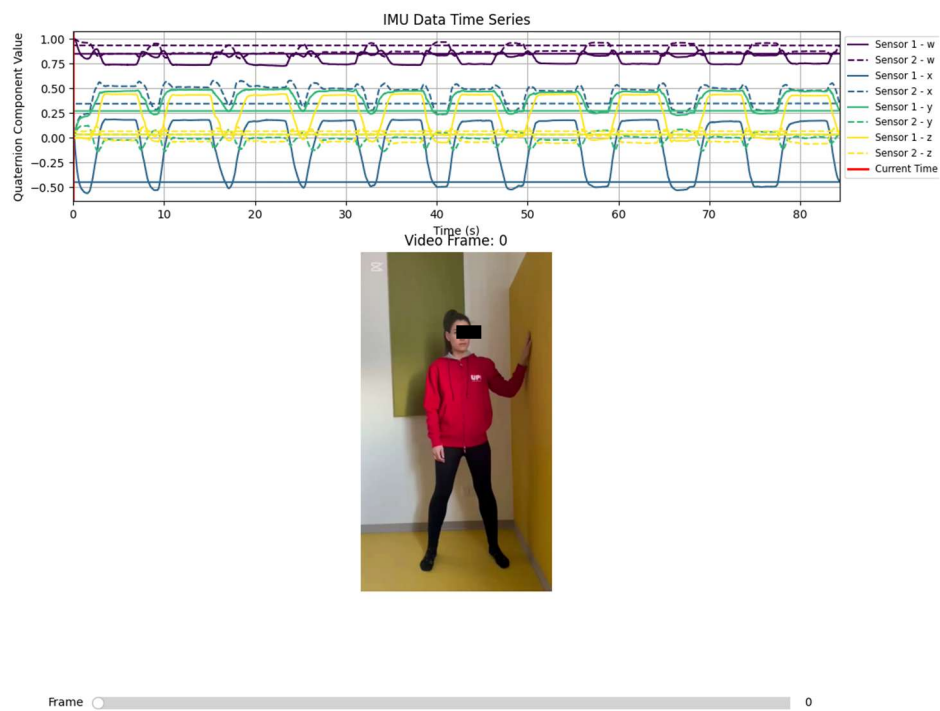


Figure 17/d: Palmo su muro, last exercise performed by the second volunteer.

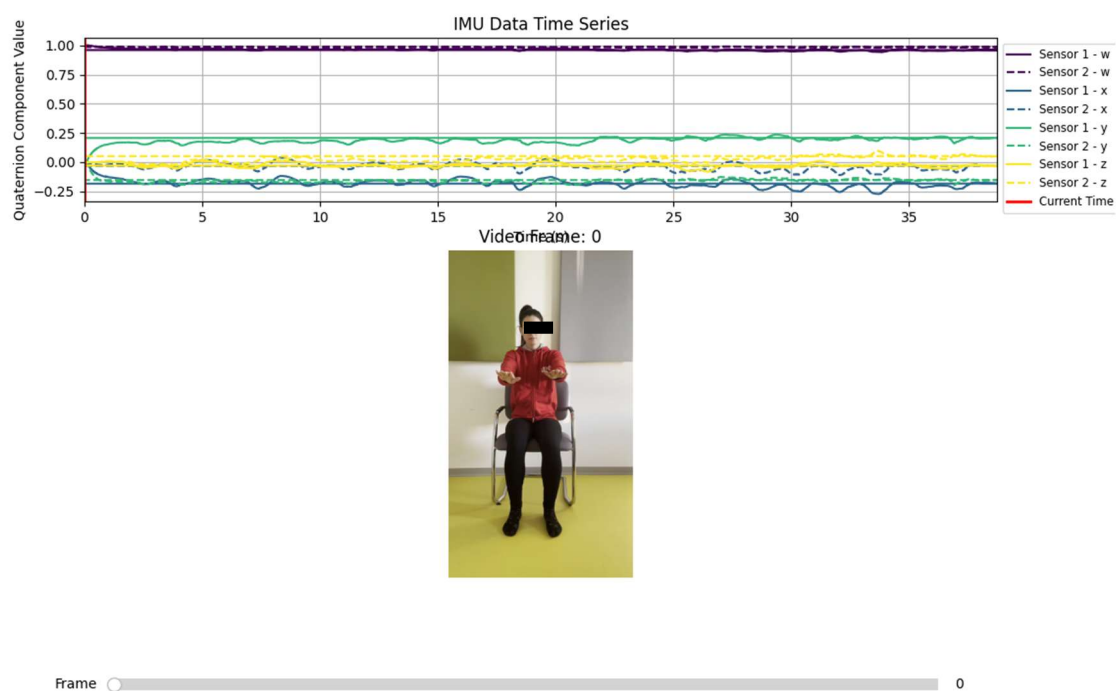


Figure 18/a: Alzata sedia, first exercise performed by the third volunteer.

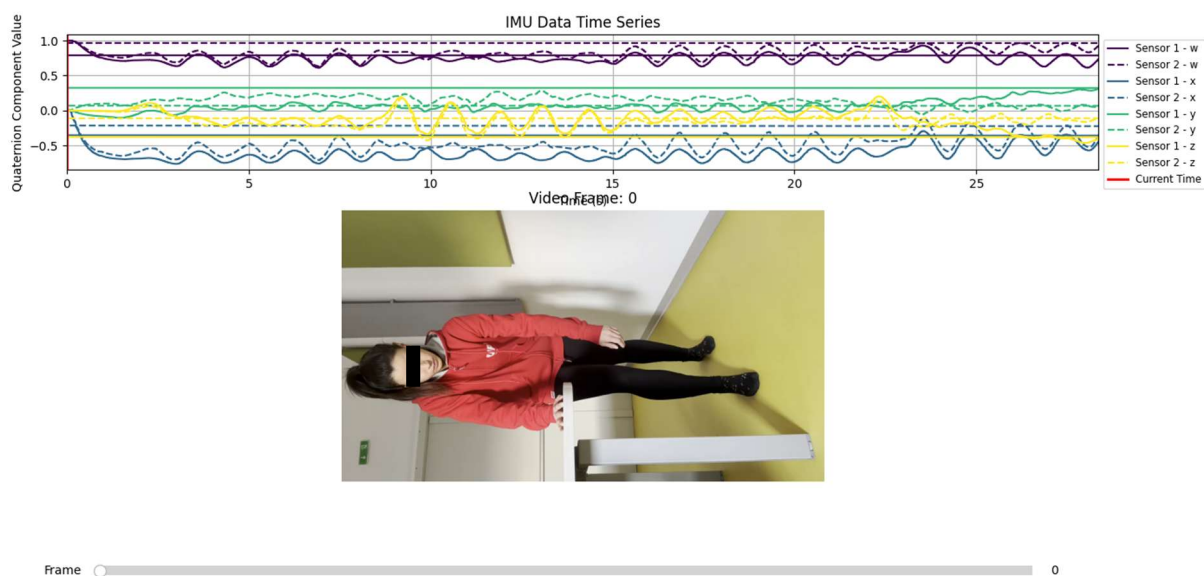


Figure 18/b: Braccio penzoloni, second exercise performed by the third volunteer.

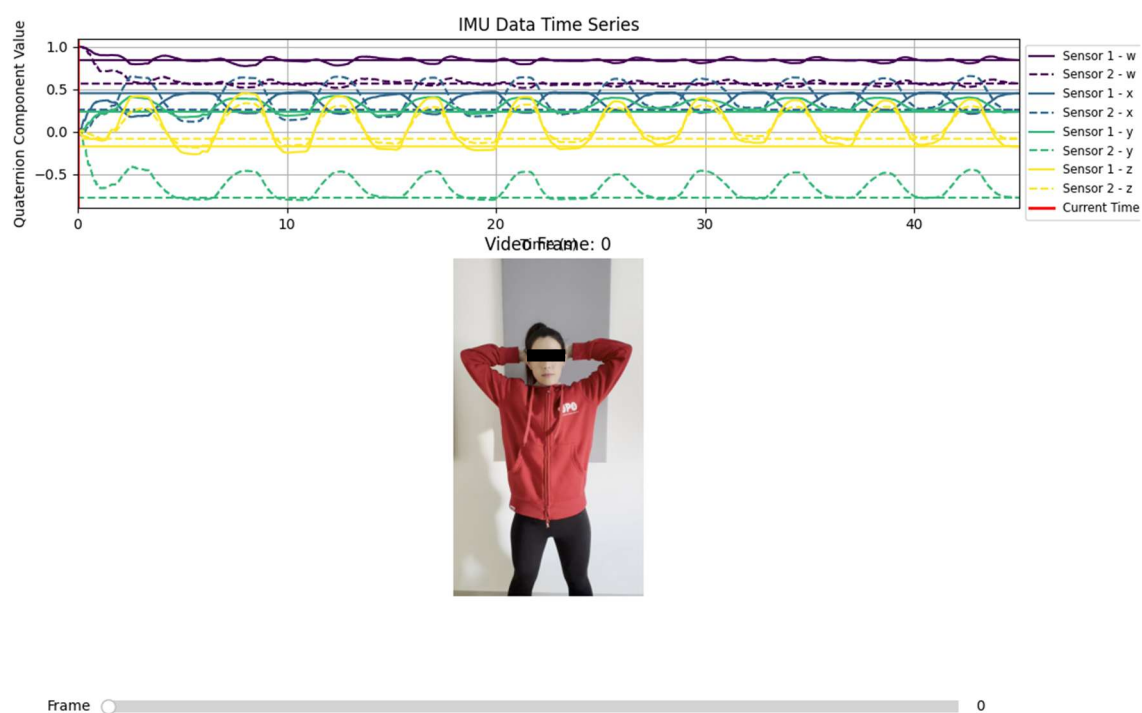


Figure 18/c: Gomiti testa, third exercise performed by the third volunteer.

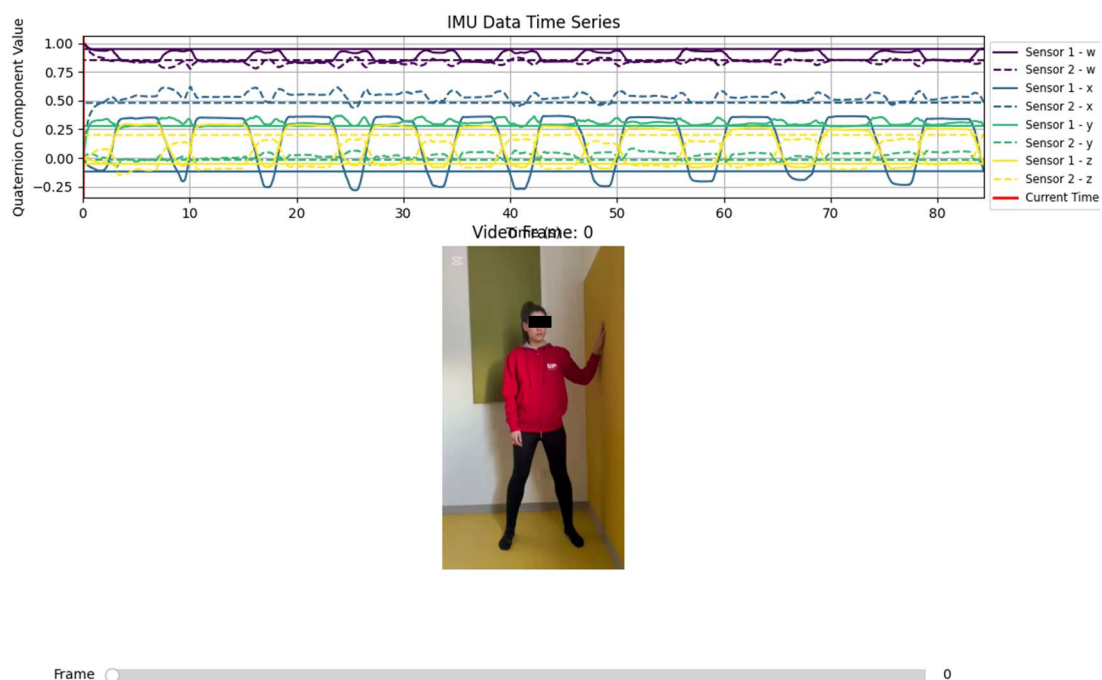


Figure 18/d: Palmo su muro, last exercise performed by the third volunteer.

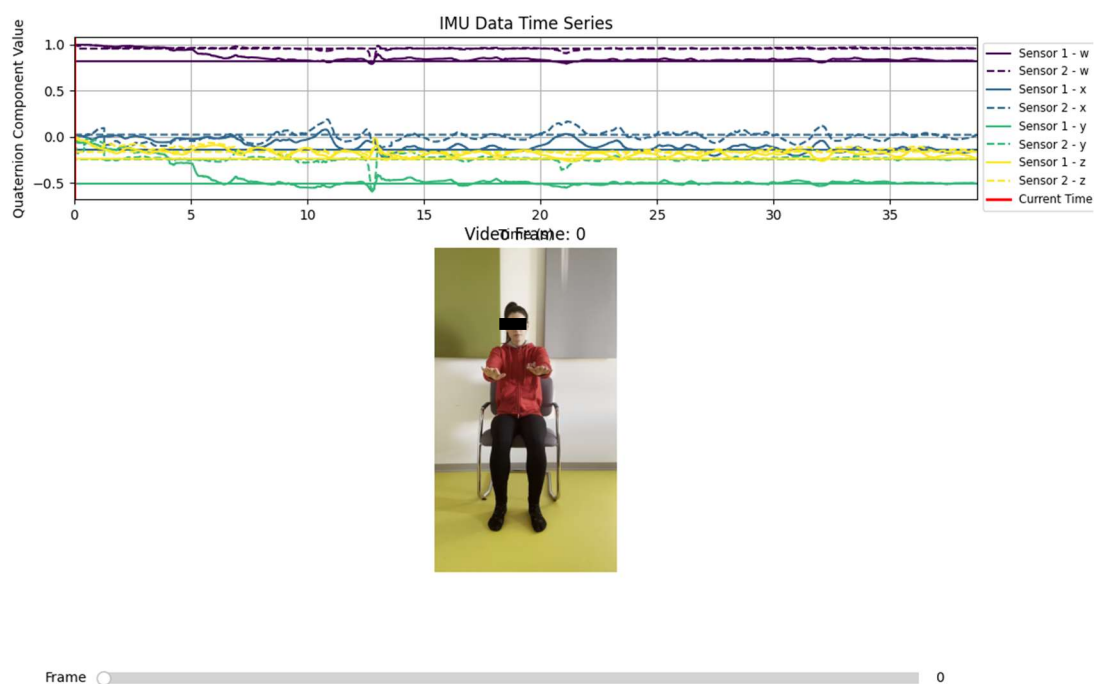


Figure 19/a: Alzata sedia, first exercise performed by the fourth volunteer.

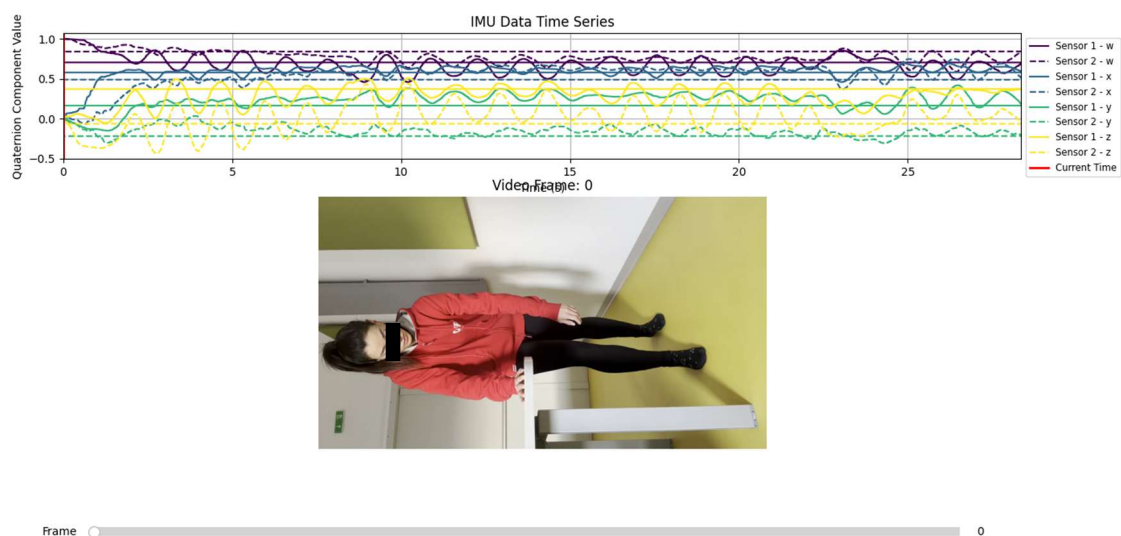


Figure 19/b: Braccio penzoloni, second exercise performed by the fourth volunteer.

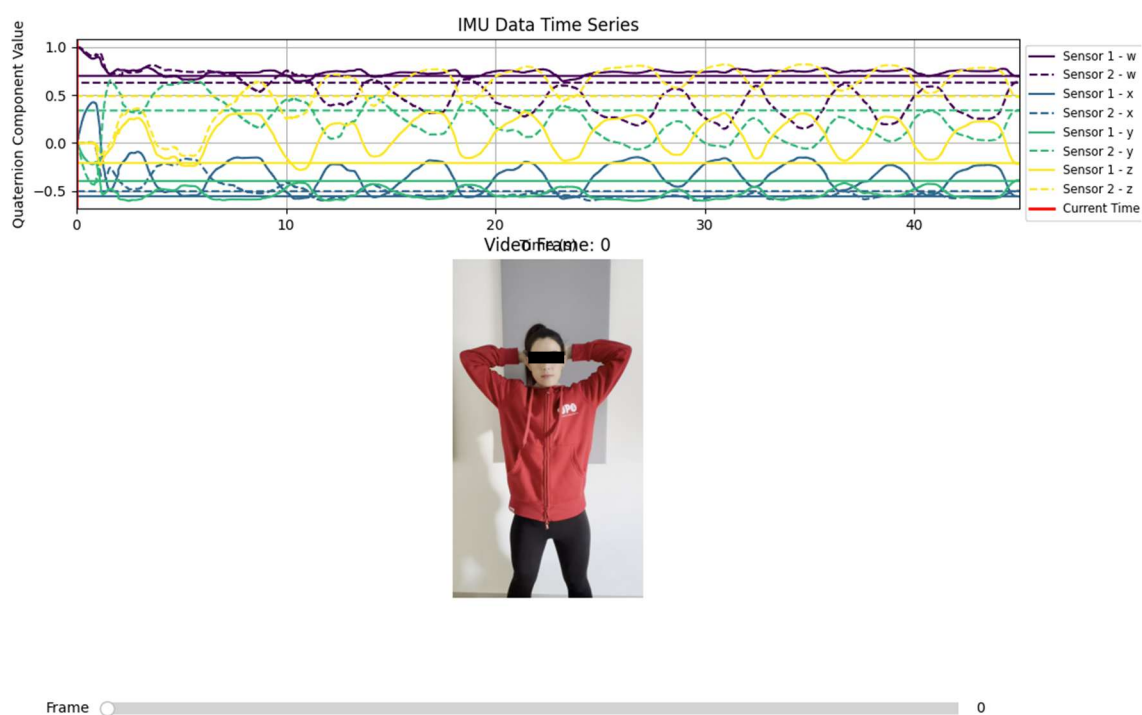


Figure 19/c: Gomiti testa, third exercise performed by the fourth volunteer.

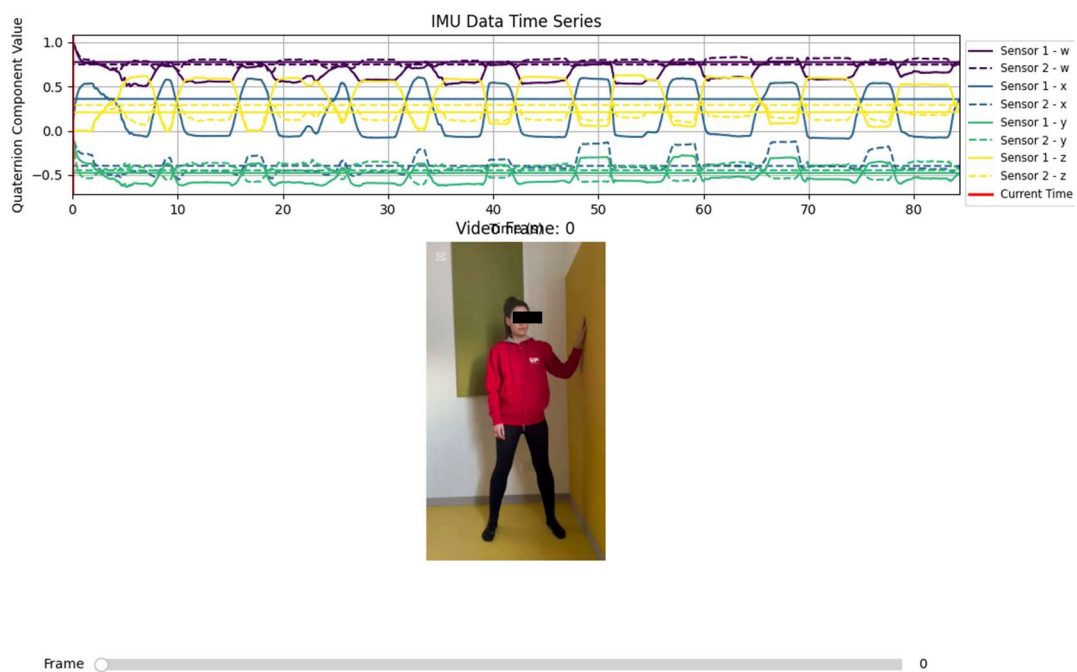


Figure 19/d: Palmo su muro, last exercise performed by the fourth volunteer.

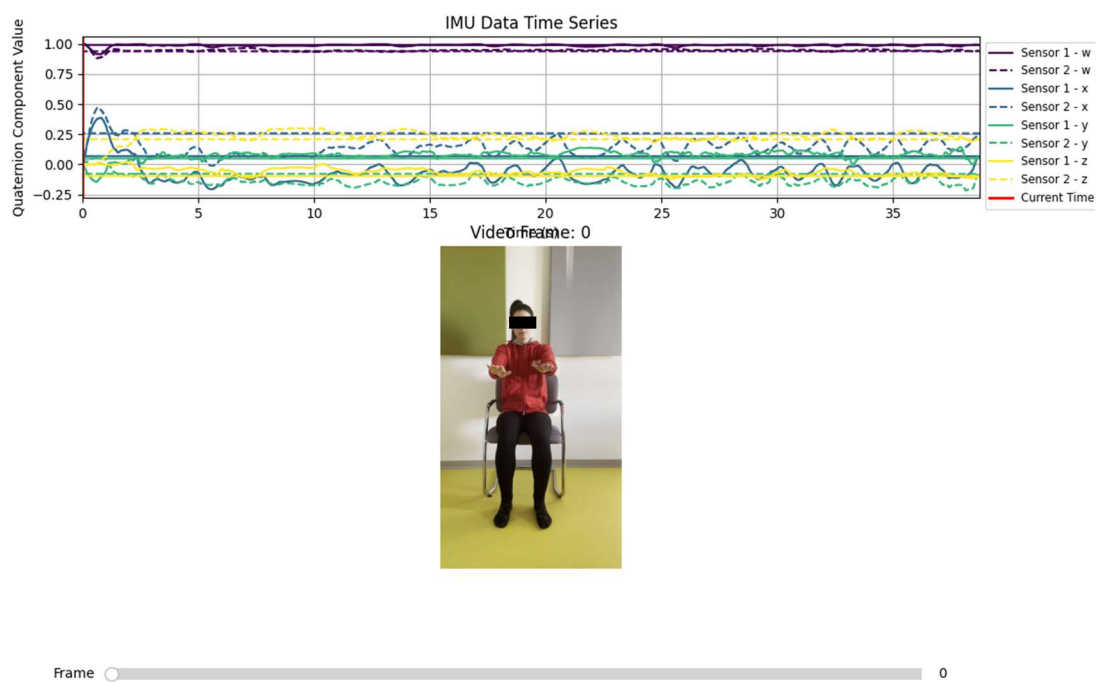


Figure 20/a: Alzata sedia, first exercise performed by the fifth volunteer.

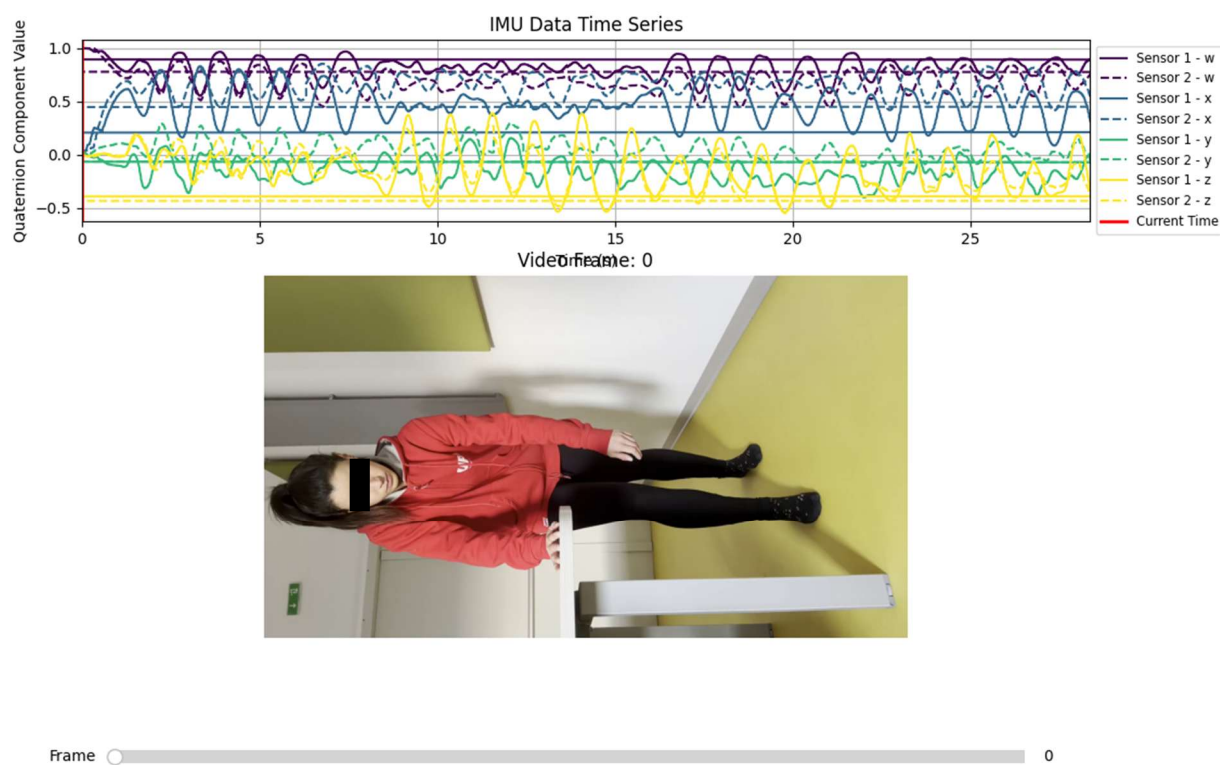


Figure 20/b: Braccio penzoloni, second exercise performed by the fifth volunteer.

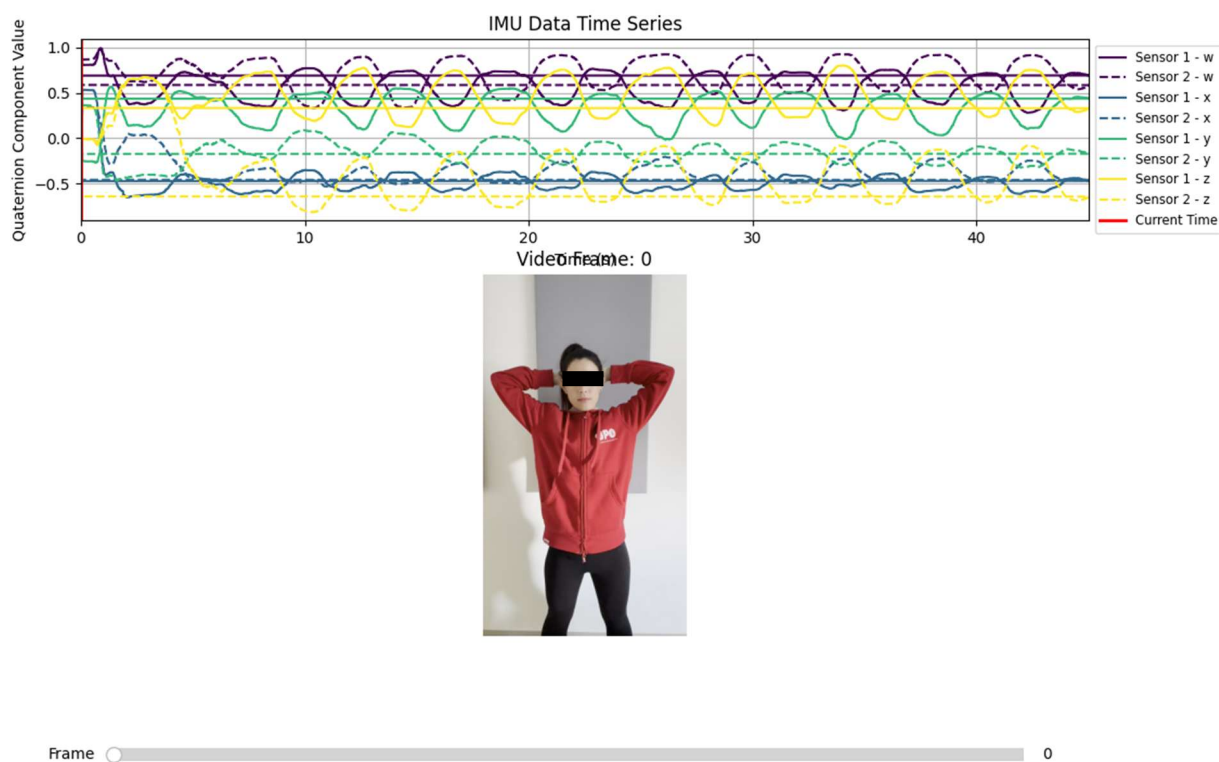


Figure 20/c: Gomiti testa, third exercise performed by the fifth volunteer.

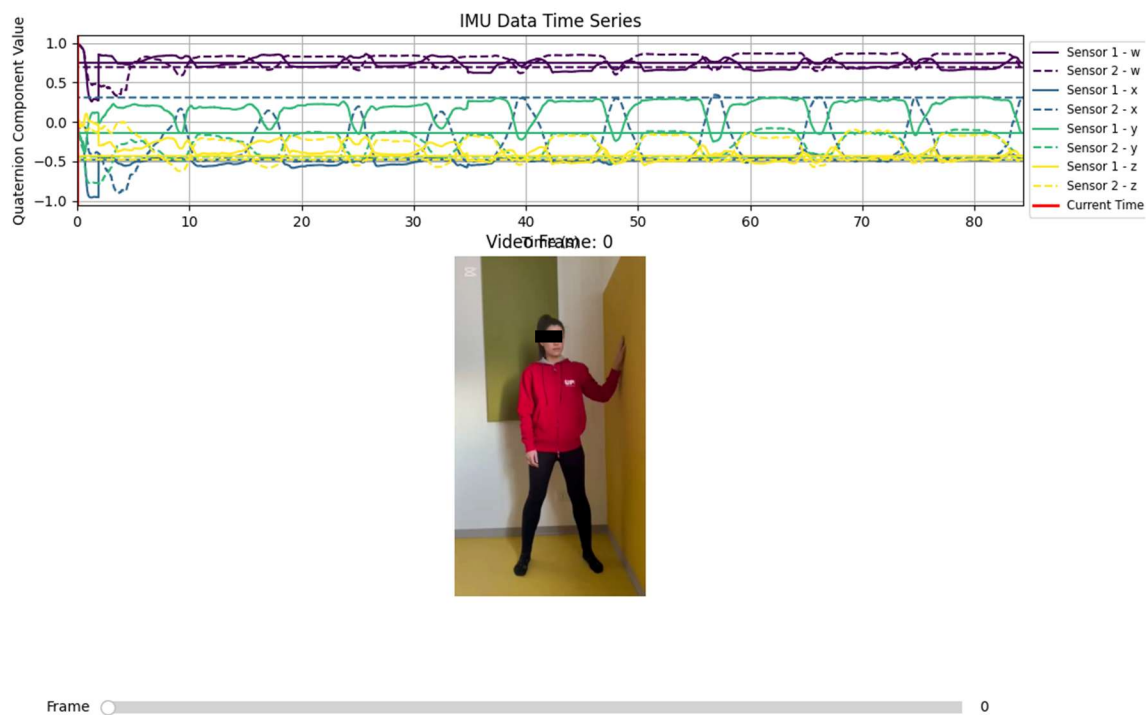


Figure 20/d: Palmo su muro, last exercise performed by the fifth volunteer.

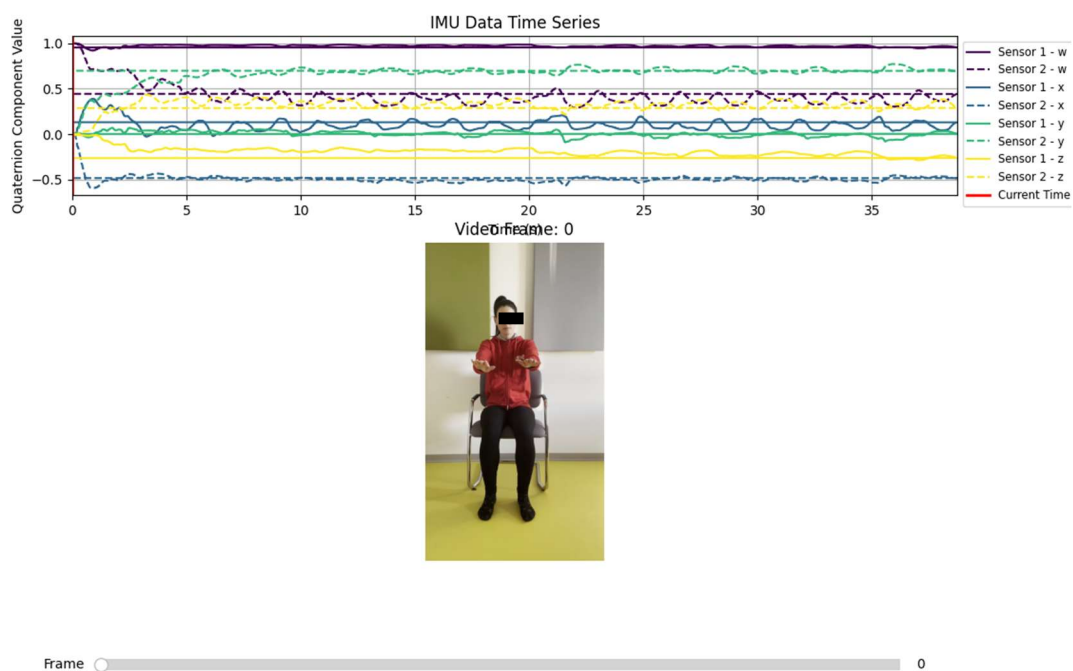


Figure 21/a: Alzata sedia, first exercise performed by the sixth volunteer.

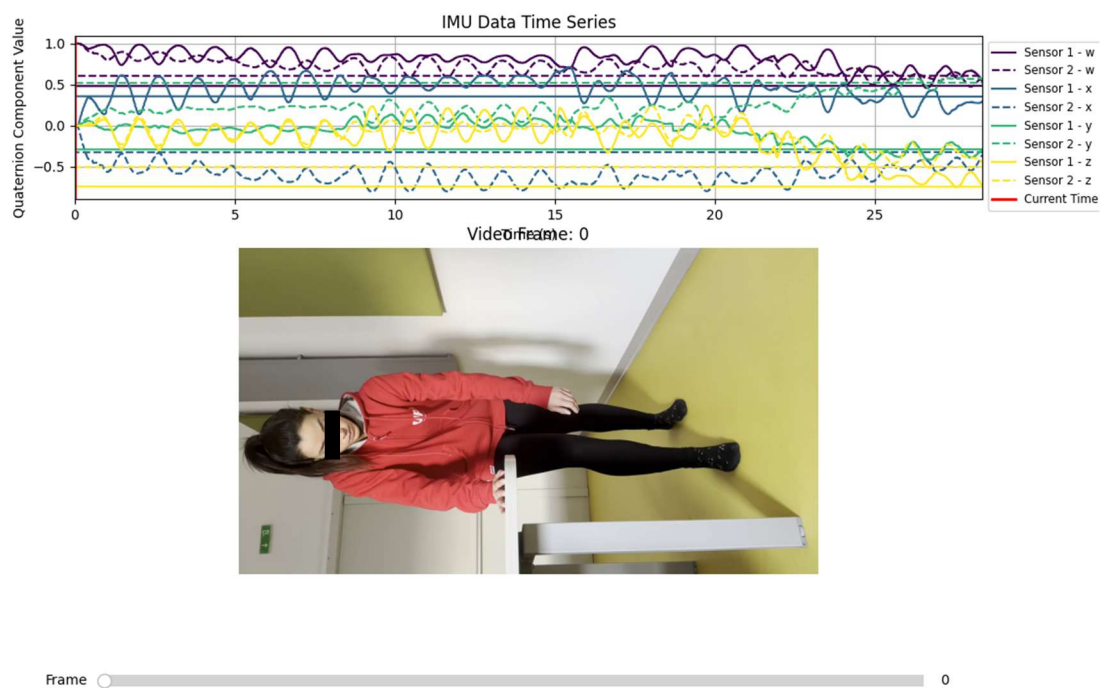


Figure 21/b: Braccio penzoloni, second exercise performed by the sixth volunteer.

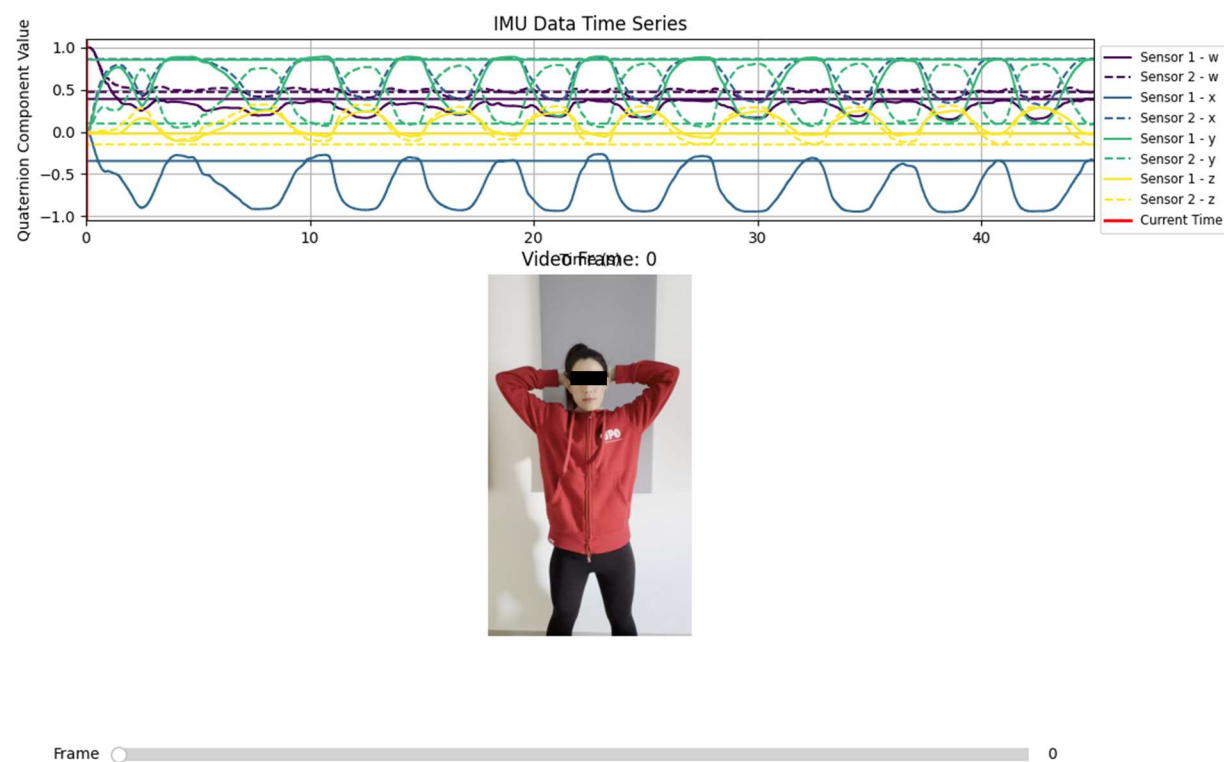


Figure 21/c: Gomiti testa, third exercise performed by the sixth volunteer.

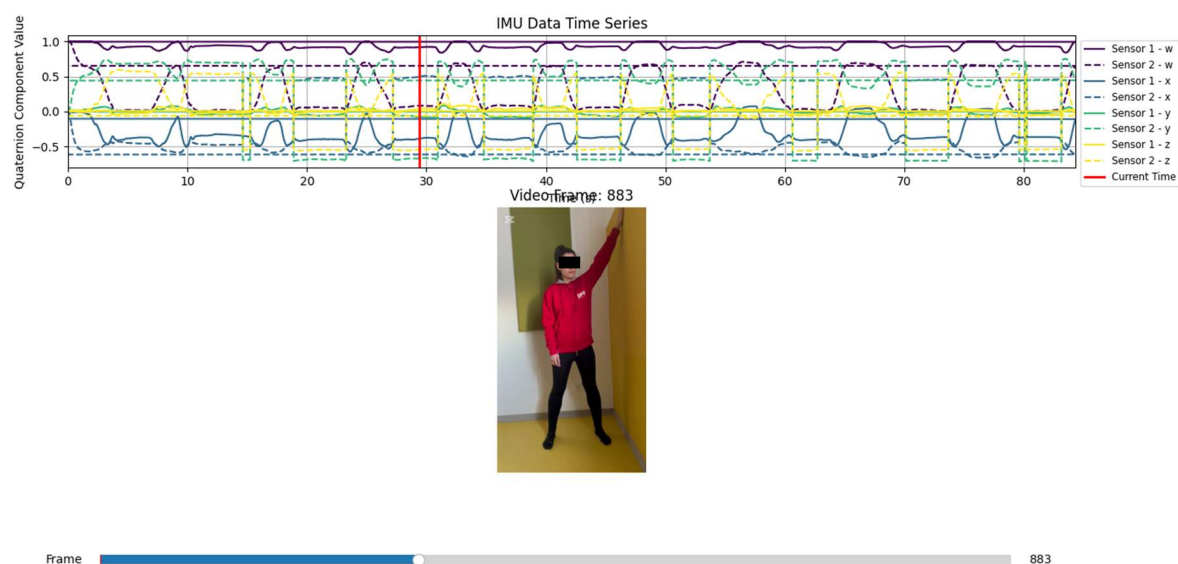


Figure 21/d: Palmo su muro, last exercise performed by the sixth volunteer.