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Longitudinal Clinical and Ultrasonographic Characterization of Hemiplegic Shoulder Pain After Stroke: Early Pathophysiological Mechanisms, Temporal Trajectories, and Predictive Factors

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PART I: CHAPTER 1 — STROKE: EPIDEMIOLOGY, BURDEN, AND NEUROREHABILITATION RATIONALE

1.1 Definition and Classification of Stroke

Stroke is defined as a pathological condition characterized by the sudden onset of focal and/or global neurological signs and symptoms resulting from an alteration of cerebral blood flow, persisting for more than 24 hours or leading to death, and not attributable to causes other than cerebrovascular disease (World Health Organization, 1978; Sacco et al., 2013). This definition highlights three fundamental elements: abrupt onset, vascular etiology, and structural or functional brain injury.

From a clinical and pathological standpoint, stroke encompasses a heterogeneous group of disorders that are traditionally classified into two major categories: ischemic stroke and hemorrhagic stroke. Ischemic stroke, results from arterial occlusion due to thrombosis or embolism, leading to focal cerebral ischemia and infarction. Hemorrhagic stroke, comprising intracerebral hemorrhage and subarachnoid hemorrhage, arises from rupture of cerebral vessels and is associated with higher early mortality but lower recurrence rates (Feigin et al., 2017).

Within each major category, further etiological subtypes can be identified. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification distinguishes ischemic strokes into large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology (Adams et al., 1993). This etiological heterogeneity has important implications for acute management, secondary prevention, prognosis, and long-term functional outcome.

Although stroke shares many risk factors and pathophysiological mechanisms with cardiovascular diseases, such as atherosclerosis and thromboembolism, the brain as the target organ confers distinctive features. Neurons exhibit high metabolic demand, limited anaerobic capacity, and minimal energy reserves, rendering cerebral tissue particularly vulnerable to ischemia. Consequently, even brief interruptions of cerebral perfusion may result in irreversible neuronal injury, accounting for the abrupt clinical presentation and often severe consequences of stroke (Weih et al., 1999).

1.2 Global and European/Italian Epidemiology: Incidence, Prevalence, and Mortality

Stroke represents one of the leading causes of death and disability worldwide. According to the Global Burden of Disease (GBD) Study, stroke is currently the second leading cause of death and the third leading cause of disability-adjusted life years (DALYs) globally (GBD 2019 Stroke Collaborators, 2021). Each year, approximately 15 million individuals experience a stroke, of whom nearly 5 million die and another 5 million are left permanently disabled.

Despite advances in primary prevention and acute management, the absolute number of stroke cases continues to increase, largely due to population ageing and the persistence of vascular risk factors. Projections based on demographic trends indicate that the global burden of stroke will continue to rise over the coming decades, particularly in low- and middle-income countries but also in high-income regions (Feigin et al., 2014).

In Europe, stroke remains a major public health concern. Epidemiological analyses across multiple European countries indicate substantial geographic variability in incidence and mortality, but uniformly high levels of long-term disability. A large modelling study conducted by King's College London across 35 European nations estimated that between 2015 and 2035 the number of stroke cases in the European Union will increase by approximately 34%, with a concomitant 45% increase in stroke-related deaths and a 25% increase in the number of individuals living with permanent disability (Wafa et al., 2020).

In Italy, stroke represents the third leading cause of death, following cardiovascular diseases and cancer, and the leading cause of permanent disability in adults (ISTAT; SPREAD, 2007). Approximately 157,000 first-ever strokes occur each year, rising to nearly 196,000 cases when recurrent events are included. The estimated prevalence is around 800,000 individuals, with an age-adjusted annual incidence of approximately 220 cases per 100,000 inhabitants.

Regional data further underscore the burden of stroke. In the Liguria region, approximately 4,000 new stroke cases are recorded annually. In 2022 alone, more than 700 patients were admitted to the Stroke Unit of the Policlinico San Martino Hospital in Genoa, reflecting the substantial demand placed on specialized acute stroke services.

1.3 Burden of Stroke: Disability, Healthcare Costs, and Quality of Life

Beyond mortality, stroke imposes a profound and long-lasting burden in terms of disability, healthcare utilization, and quality of life. Approximately one third of stroke survivors experience severe residual disability, requiring assistance in activities of daily living and long-term support (Feigin et al., 2017).

Motor deficits, particularly involving the upper limb, are among the most common sequelae and frequently persist despite rehabilitation. Cognitive impairment, aphasia, mood disorders, and fatigue further contribute to functional dependence and reduced participation. As a result, stroke survivors often experience a marked decline in health-related quality of life, with increased rates of depression, social isolation, and reduced reintegration into work and community life (Donnan et al., 2014).

From an economic perspective, stroke is among the most costly neurological conditions. In Italy, the average cost of care during the first three months after stroke has been estimated at approximately €6,000 per patient, increasing to nearly €10,000 within the first six months (Grieve et al., 2001; Gerzeli et al., 2005). At a regional level, this translates into tens of millions of euros per year for acute management alone.

At the national level, direct healthcare and social costs attributable to stroke amount to approximately €16 billion annually, with an additional €5 billion in indirect costs related primarily to loss of productivity (Osservatorio Ictus Italia, 2018). Importantly, these figures underestimate the true societal burden, as they do not fully account for informal caregiving provided by family members, nor for the psychological and social costs borne by patients and caregivers.

1.4 Functional Outcomes and Recovery: Acute, Subacute, and Chronic Phases and Windows of Plasticity

Recovery after stroke is a dynamic and time-dependent process that unfolds over distinct phases. The acute phase, spanning the first hours to days, is dominated by emergency management and prevention of secondary brain injury. The subacute phase, typically encompassing weeks to months after stroke, is characterized by spontaneous neurological recovery and heightened responsiveness to rehabilitation interventions. The chronic phase, extending beyond six to twelve months, is generally associated with stabilization of residual deficits (Langhorne et al., 2011).

Neurobiological mechanisms underlying recovery include resolution of cerebral edema, reperfusion of ischemic penumbra, synaptic plasticity, cortical reorganization, and recruitment of alternative neural networks. These processes are particularly active during the early post-stroke period, giving rise to so-called windows of plasticity, during which rehabilitation interventions may exert maximal effects (Krakauer et al., 2006).

Despite these mechanisms, functional recovery is often incomplete. Upper limb recovery remains limited in a substantial proportion of patients, with only 30–40% achieving useful hand function at six months' post-stroke (Kwakkel et al., 2003). This discrepancy highlights the need to identify factors that constrain recovery beyond the central nervous system lesion itself.

1.5 Post-Stroke Complications Relevant to Rehabilitation

Stroke is frequently complicated by a wide range of secondary conditions that negatively affect rehabilitation outcomes. These include medical complications such as infections, malnutrition, and thromboembolic events, as well as neurological and musculoskeletal complications.

From a rehabilitation perspective, particularly relevant complications include spasticity, joint contractures, pain syndromes, sensory deficits, cognitive impairment, neglect, and mood disorders. These complications often interact synergistically, amplifying disability and limiting participation in rehabilitation programs (Dobkin, 2005).

Musculoskeletal complications are especially common and frequently under-recognized. Altered motor control, prolonged immobility, abnormal loading patterns, and improper handling of the paretic limb predispose stroke survivors to secondary joint and soft tissue disorders. Among these, shoulder-related complications are particularly prevalent and clinically relevant.

1.6 Why the Upper Limb Represents a "Bottleneck" for Functional Recovery

Among post-stroke impairments, dysfunction of the upper limb represents one of the most significant barriers to functional recovery. While many patients regain some degree of ambulatory ability, recovery of arm and hand function is often incomplete, with persistent deficits observed in a substantial proportion of stroke survivors (Kwakkel et al., 2003).

The upper limb plays a central role in activities of daily living, self-care, and social interaction. Effective use of the hand depends critically on proximal stability and coordinated movement of the shoulder complex. Consequently, impairments at the shoulder level may have cascading effects on distal motor performance.

Pain, reduced range of motion, weakness, and altered motor control of the shoulder can severely limit the use of the paretic arm, leading to learned non-use, disuse atrophy, and further functional decline. Shoulder pain has been consistently associated with poorer functional outcomes, reduced participation in rehabilitation, and lower quality of life (Turner-Stokes & Jackson, 2002).

For these reasons, the upper limb—and particularly the shoulder—can be conceptualized as a "bottleneck" of post-stroke recovery. When shoulder dysfunction and pain are present, they may disproportionately hinder overall functional improvement despite preserved potential for neural recovery. This concept provides the rationale for focusing on shoulder-related complications in stroke survivors and sets the stage for the subsequent chapters of this thesis.

Rationale of the Thesis

Hemiplegic shoulder pain (HSP) is among the most frequent and disabling complications after stroke, with reported prevalence rates ranging from 20% to over 70% depending on the population studied and the timing of assessment. Shoulder pain interferes with rehabilitation, limits participation in therapeutic activities, reduces functional recovery of the paretic upper limb, and negatively affects quality of life. Despite its clinical relevance, HSP remains a complex and heterogeneous condition, and its pathophysiology is still incompletely understood.

A critical limitation of the existing literature lies in the predominance of cross-sectional studies and in the heterogeneity of assessment timing. Many studies investigate shoulder pain at a single time point, often in the subacute or chronic phase, when multiple pathological mechanisms may already coexist. This approach makes it difficult to disentangle cause–effect relationships and to distinguish primary post-stroke mechanisms from secondary or pre-existing shoulder pathology, which is common in the aging population.

Furthermore, although HSP is widely recognized as a multifactorial condition, clinical assessment alone often lacks sufficient specificity to identify the predominant underlying mechanism. Pain, reduced range of motion, weakness, and spasticity may result from dif-

ferent combinations of instability, capsular pathology, tendon disease, bursal inflammation, or central pain modulation. Consequently, therapeutic approaches are frequently empirical and non-targeted, with variable effectiveness.

Musculoskeletal ultrasound has emerged as a particularly suitable imaging modality for the assessment of the post-stroke shoulder. It is non-invasive, bedside-accessible, repeatable, and capable of dynamically evaluating soft tissue structures that are not adequately assessed by clinical examination alone. Importantly, ultrasound allows for quantitative and qualitative assessment of key pathological features, such as glenohumeral subluxation, capsular thickening, tendon abnormalities, bursal effusion, and synovial changes. However, despite these advantages, ultrasound has often been used in a descriptive or cross-sectional manner, and its potential role in longitudinal, mechanism-oriented assessment has not been fully exploited.

The scientific rationale of this thesis is grounded in the hypothesis that HSP is not a static condition but rather a time-dependent process, in which different pathophysiological mechanisms emerge, interact, and predominate at different stages after stroke.

The two original studies forming the core of this thesis were designed to reflect this conceptual framework. The first study focuses on the early phase after stroke, combining clinical and ultrasound assessment to identify initial risk factors and structural changes associated with the development of shoulder pain within the first months. The second study extends this approach over a longer follow-up period, aiming to characterize the trajectory of HSP, to identify clinical and ultrasonographic predictors of persistent pain, and to explore how different mechanisms may dominate at different time points.

By integrating neurological severity, clinical examination, and ultrasound findings within a longitudinal design, this thesis seeks to move beyond a purely descriptive view of HSP toward a mechanism-based and phase-specific model. Such a model has direct clinical implications, as it supports earlier identification of patients at risk, more accurate stratification of shoulder pathology, and the development of targeted preventive and therapeutic strategies tailored to the stage of recovery.

In summary, the rationale of my research lies in the need to improve understanding of HSP as a dynamic and multifactorial complication of stroke, through a rigorous, longitudinal clinical and ultrasonographic investigation. This approach aims to provide clinically meaningful insights that bridge the gap between neurological impairment and peripheral musculoskeletal pathology, ultimately contributing to more effective rehabilitation pathways and improved outcomes for stroke survivors.

CHAPTER 2 — FUNCTIONAL ANATOMY AND BIOMECHANICS OF THE SHOULDER: FOUNDATIONS FOR POST-STROKE PAIN

2.1 Functional Anatomy of the Shoulder

The shoulder is the most mobile joint complex of the human body and plays a fundamental role in positioning the hand in space for functional activities. This remarkable mobility is achieved at the expense of intrinsic stability, making the shoulder highly dependent on coordinated neuromuscular control and therefore particularly vulnerable to dysfunction in neurological conditions such as stroke (Veeger et al, 2007).

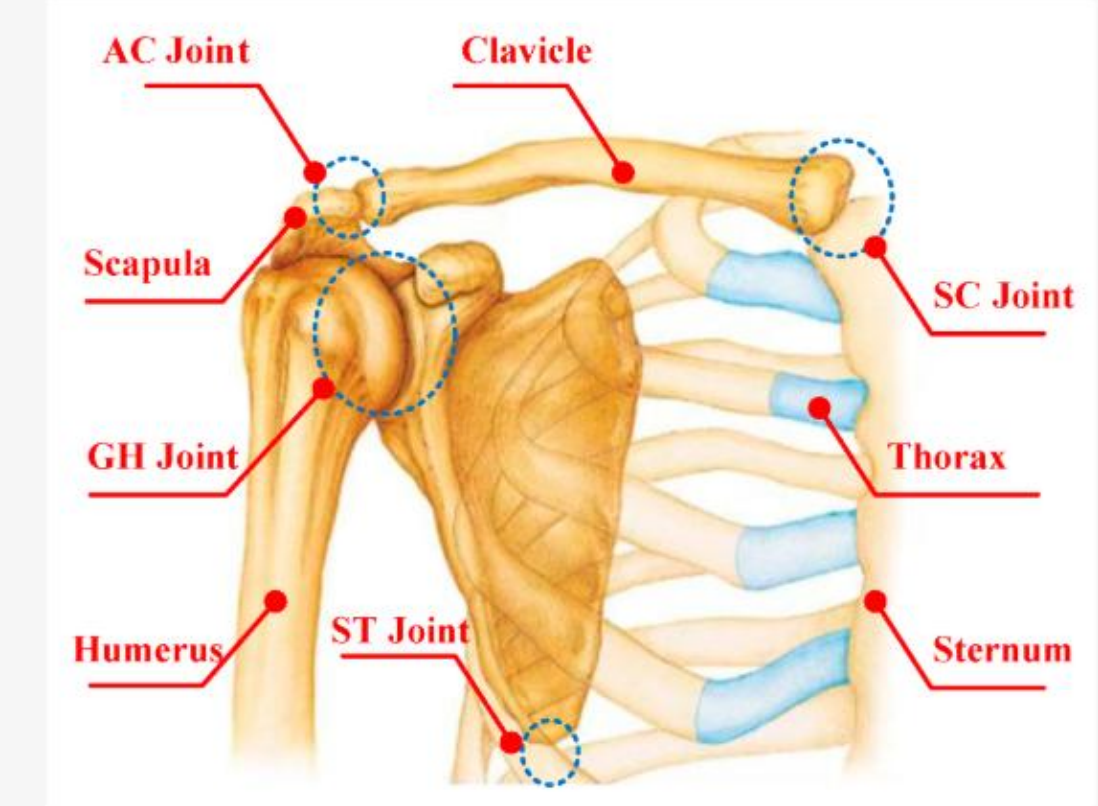
From a functional perspective, the shoulder should not be considered a single joint but rather a scapulohumeral complex, composed of four distinct articulations:

1. the glenohumeral joint,
2. the acromioclavicular joint,
3. the sternoclavicular joint, and
4. the scapulothoracic articulation, a functional rather than anatomical joint.

These components act synergistically to allow large ranges of motion while maintaining joint congruence and load distribution. Alteration of motion or stability at any level affects the entire system, with consequences that may propagate distally along the upper limb (Ludewig & Braman, 2011).

The glenohumeral joint is the primary contributor to upper limb mobility and represents the core of shoulder function. The sternoclavicular joint serves as the only true skeletal connection between the upper limb and the axial skeleton, allowing clavicular rotation and elevation that are essential for full arm elevation. The acromioclavicular joint enables fine-tuning of scapular motion, while the scapulothoracic articulation provides a stable base for glenohumeral movement through coordinated scapular rotation and translation.

Figure 1. Functional anatomy of the scapulohumeral complex



Li, J.; Zhang, C.; Dong, M.; Cao, Q. A Kinematic Model of the Shoulder Complex Obtained from a Wearable Detection System. *Appl. Sci.* 2020, *10*, 3696. https://doi.org/10.3390/app10113696

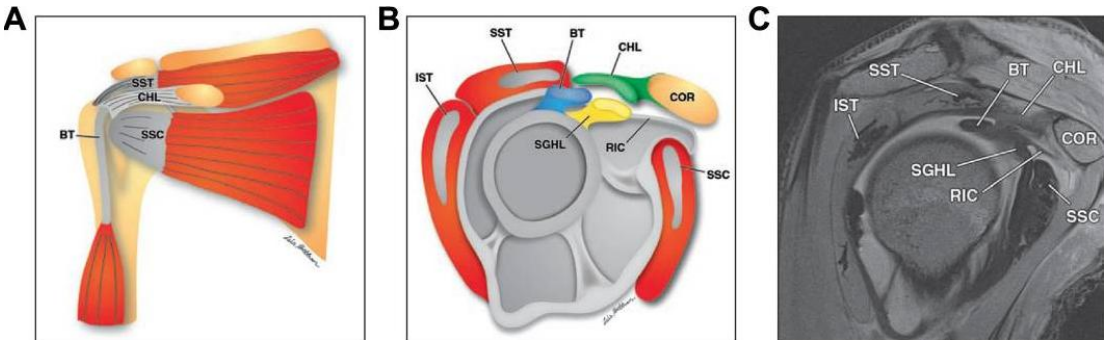
Legend:
This figure illustrates the four components of the shoulder complex—glenohumeral, acromioclavicular, sternoclavicular, and scapulothoracic articulations—and their coordinated contribution to upper limb motion. The functional integration of these joints is essential for shoulder stability and mobility and is critically dependent on neuromuscular control.

The stability of the glenohumeral joint is provided primarily by soft tissues rather than bony congruence. The joint capsule is a fibrous envelope that surrounds the articulation and allows a wide range of motion while limiting excessive translation. Capsular thickness and compliance are not uniform; the axillary recess represents the most distensible portion and is particularly important for abduction and elevation (Neviaser, 1987).

The glenohumeral ligaments (superior, middle, and inferior) contribute to passive stability, particularly at end ranges of motion. Among these structures, the inferior glenohumeral ligament complex plays a key role in preventing inferior and anterior translation of the humeral head.

The coracohumeral ligament (CHL) and the rotator interval region are increasingly recognized as critical stabilizing structures, particularly in controlling external rotation and superior translation. (Culham et al., 1993; Khan et al., 2009).

Figure 2. – Capsular anatomy and key stabilizing structures



Frank RM, Taylor D, Verma NN, Romeo AA, Mologne TS, Provencher MT. The Rotator Interval of the Shoulder: Implications in the Treatment of Shoulder Instability. Orthop J Sports Med. 2015 Dec 29;3(12):2325967115621494. doi: 10.1177/2325967115621494.

Petchprapa CN, Beltran LS, Jazrawi LM, Kwon YW, Babb JS, Recht MP. The rotator interval: a review of anatomy, function, and normal and abnormal MRI appearance. AJR Am J Roentgenol. 2010 Sep;195(3):567-76. doi: 10.2214/AJR.10.4406.

Legend:

Anatomy of the rotator interval, including illustrations in (A) coronal and (B) sagittal planes and (C) corresponding sagittal magnetic resonance proton density–weighted arthrogram show boundaries of the rotator interval, which are defined by the coracoid process (COR) at its base, superiorly by the anterior margin of supraspinatus tendon (SST), and inferiorly by the superior margin of the subscapularis tendon (SSc). Contents of the rotator interval include the long head of biceps tendon (BT), coracohumeral ligament (CHL), superior glenohumeral ligament (SGHL), and rotator interval capsule. The rotator interval capsule (RIC) is the anterosuperior aspect of the glenohumeral joint capsule, which merges with CHL and SGHL insertions medial and lateral to the bicipital groove. The CHL arises from the base of coracoid process, traverses through the subcoracoid fat, and inserts on the anterior humerus. IST, infraspinatus tendon. Alterations of these

regions are central to the pathophysiology of adhesive capsulitis and are particularly relevant in post-stroke patients exposed to immobilization and altered loading.

2.2 Rotator Cuff and Long Head of the Biceps: Stabilizing Role and Common Pathologies

The rotator cuff is a highly specialized musculotendinous complex composed of four muscles—the supraspinatus, infraspinatus, teres minor, and subscapularis—that surround the glenohumeral joint and play a fundamental role in maintaining joint stability during both static postures and dynamic movements. The rotator cuff muscles act predominantly as dynamic stabilizers, generating compressive forces that center the humeral head within the glenoid fossa. (Halder et al., 2001; Burkhart et al., 2003).

This stabilizing action is achieved through finely tuned force coupling mechanisms, whereby opposing muscle groups generate balanced forces that counteract translational movements of the humeral head. In particular, the posterior rotator cuff (infraspinatus and teres minor) counterbalances the anterior and superior forces produced by the subscapularis and the deltoid, respectively. This dynamic equilibrium is essential to prevent superior and anterior migration of the humeral head during arm elevation (Poppen & Walker, 1976).

The importance of the rotator cuff becomes particularly evident during shoulder elevation, when the deltoid generates substantial superior shear forces. In physiological conditions, the rotator cuff offsets these forces by exerting an inferiorly directed compressive vector, thereby preserving subacromial clearance and minimizing stress on passive stabilizing structures. Disruption of this force couple results in superior humeral head migration, increased strain on the joint capsule and coracohumeral ligament, and progressive overload of subacromial tissues, including the supraspinatus tendon and the subacromial–subdeltoid bursa (Ludewig & Cook, 2000; Michener et al., 2003).

The long head of the biceps tendon (LHBT) contributes to glenohumeral stability through its intra-articular course and its attachment to the superior glenoid labrum. Although its exact biomechanical role remains debated, the LHBT is believed to assist in anterior stabilization and humeral head depression, particularly during overhead activities and when rotator cuff function is compromised (Warner & McMahon, 1995). In this context, the LHBT may act as a secondary stabilizer, becoming more mechanically relevant in pathological conditions.

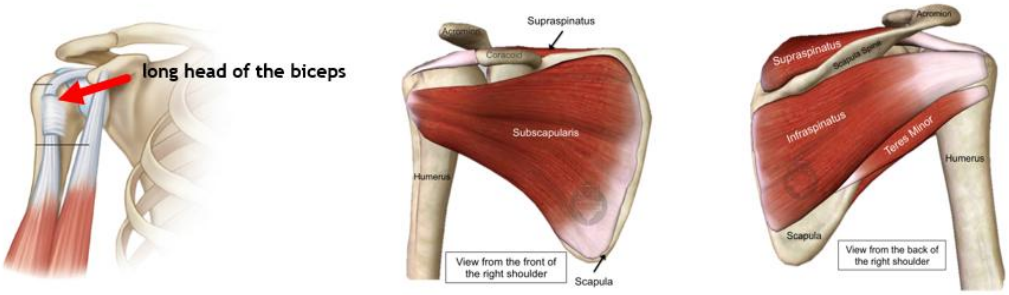
Degenerative changes of the rotator cuff and LHBT are highly prevalent in the general population and increase with age, often occurring in asymptomatic individuals. Imaging studies have demonstrated a high prevalence of partial- and full-thickness rotator cuff tears, tendinopathy, and LHBT degeneration in older adults, complicating the interpretation of imaging findings in patients with shoulder pain (Yamamoto et al., 2010; Gurney et al., 2016). These pre-existing alterations may remain clinically silent until neuromuscular control is disrupted, as occurs after stroke.

In post-stroke patients, several mechanisms converge to impair the stabilizing function of the rotator cuff and LHBT. Paresis reduces the ability of these muscles to generate sufficient compressive force, while abnormal muscle activation patterns and co-contractions further compromise the fine-tuned coordination required for dynamic stabilization. Additionally, spasticity, particularly involving the subscapularis and pectoralis major, may impose persistent internal rotation and adduction forces, alter humeral head positioning and increase capsular and tendinous stress (Ada & Foongchomcheay, 2002; Marciniak et al., 2011).

Over time, these neuromuscular alterations expose the rotator cuff tendons and LHBT to repetitive microtrauma and abnormal loading. This process may promote tendinopathy, partial tearing, and inflammatory changes, which in turn contribute to pain and further functional limitation. Importantly, these peripheral structural changes should not be viewed as isolated lesions but rather as secondary manifestations of a primary central neurological impairment.

From a clinical and rehabilitative perspective, understanding the altered role of the rotator cuff and LHBT after stroke is essential. Shoulder pain in this population often reflects the combined effect of pre-existing degenerative changes and post-stroke biomechanical dysfunction. Consequently, accurate assessment requires integration of clinical examination with imaging modalities capable of visualizing soft tissue structures dynamically, such as musculoskeletal ultrasound. This approach allows differentiation between incidental age-related findings and clinically relevant pathology that emerges as part of the post-stroke cascade

Figure 3. – Rotator Cuff and Long Head of the Biceps



2.3 Subacromial–Subdeltoid Bursa and Synovium: Physiology and Inflammation

The subacromial–subdeltoid (SASD) bursa is a synovial-lined structure that facilitates smooth gliding between the rotator cuff and the overlying acromion and deltoid muscle. Under physiological conditions, the bursa minimizes friction during arm movement and contributes to painless shoulder motion.

Inflammation of the SASD bursa may result from mechanical overload, altered kinematics, or adjacent tendon pathology. Bursal thickening and effusion are frequently observed on ultrasound, both in symptomatic and asymptomatic individuals, complicating clinical interpretation (Girish et al., 2011).

The synovium of the glenohumeral joint plays a central role in joint homeostasis. Synovial inflammation may occur secondary to capsular pathology, immobilization, or repetitive microtrauma and contributes to pain through nociceptive and inflammatory mechanisms. In post-stroke shoulders, synovial changes may coexist with capsular stiffness and instability, forming part of a multifactorial pain syndrome.

2.4 Biomechanics and Scapulohumeral Rhythm

Normal shoulder elevation results from a coordinated interaction between glenohumeral motion and scapular rotation, commonly referred to as the scapulohumeral rhythm. Classical descriptions suggest a progressive contribution of scapular upward rotation as arm elevation increases, although individual variability is considerable (Inman et al., 1944; McClure et al., 2001).

Scapular motion serves several biomechanical functions: maintaining glenoid alignment, optimizing muscle length–tension relationships, and preserving subacromial clearance. Proper rhythm reduces stress on passive structures and enhances movement efficiency.

Neurological impairment disrupts this finely tuned coordination. After stroke, altered muscle recruitment, trunk instability, and abnormal tone frequently result in delayed or reduced scapular rotation, increasing mechanical demands on the glenohumeral joint and its passive stabilizers (Ludewig et al., 2009).

2.5 Biomechanical Vulnerability of the Shoulder: Why It "Breaks" Easily

The shoulder's reliance on dynamic stabilization makes it inherently vulnerable to neurological injury. Following stroke, multiple factors converge to destabilize the system: loss of voluntary motor control, impaired proprioception, abnormal tone, prolonged immobilization, and suboptimal handling of the paretic limb.

In this context, passive structures such as the capsule, ligaments, and tendons are exposed to abnormal loading patterns for which they are not designed. Over time, this may lead to capsular fibrosis, tendon degeneration, bursal inflammation, and joint malalignment.

This biomechanical vulnerability explains why post-stroke shoulder pain is rarely attributable to a single lesion and why its clinical presentation is often heterogeneous and time-dependent. Understanding these mechanisms is essential to interpret imaging findings and to design preventive and therapeutic strategies.

CHAPTER 3 — STROKE AND MOTOR CONTROL OF THE SHOULDER: FROM CENTRAL LESION TO PERIPHERAL DAMAGE

3.1 Negative and Positive Signs of the Upper Motor Neuron Syndrome

Stroke leads to a characteristic constellation of motor impairments collectively referred to as the upper motor neuron (UMN) syndrome, which encompasses both negative and positive signs (Lance, 1980; Ivanhoe & Reistetter, 2004). This distinction is not merely descriptive but has substantial implications for the temporal evolution of shoulder dysfunction after stroke.

Negative signs reflect a loss of normal motor function and include paresis, loss of dexterity, impaired selective motor control, and, in the early phase, hypotonia. These deficits dominate the acute and early subacute stages and directly compromise the ability of shoulder muscles to generate and finely modulate stabilizing forces.

Positive signs, conversely, arise from disinhibition of spinal and brainstem motor circuits and include spasticity, exaggerated stretch reflexes, clonus, involuntary co-contractions, and pathological movement synergies. These features typically emerge gradually during the subacute phase and may persist into the chronic stage, progressively reshaping movement patterns and joint loading.

Crucially, negative and positive signs coexist and interact rather than replacing one another. Their relative predominance changes over time, giving rise to phase-specific biomechanical challenges for the shoulder.

Table 1 summarizes the temporal evolution of UMN signs and their relevance to shoulder biomechanics.

Post-stroke phase	Predominant UMN signs	Impact on shoulder biomechanics
Acute (0–7 days)	Paresis, hypotonia, loss of selective control	Loss of dynamic stabilization, inferior humeral translation
Early subacute (1–6 weeks)	Emerging spasticity, reduced motor selectivity	Altered joint loading, inefficient movement
Late subacute–chronic (>6 weeks)	Spasticity, co-contractions,	Capsular stress, reduced ROM, chronic pain

3.2 Paresis, Hypotonia, and Early Shoulder Instability

In the immediate aftermath of stroke, paresis and hypotonia represent the dominant impairments affecting the upper limb. Reduced activation of key stabilizing muscles leads to a profound loss of dynamic glenohumeral stability (Ada & Foongchomcheay, 2002). Because the shoulder relies minimally on bony congruence and heavily on muscular forces for stability, the absence of active control allows gravitational forces acting on the paretic arm to induce inferior translation of the humeral head**.** Clinically, this may manifest as glenohumeral subluxation, which can develop within days after stroke onset and is strongly associated with severe motor impairment.

Early instability exposes the joint capsule and periarticular soft tissues to sustained tensile stress. Even in the absence of overt structural lesions, repetitive traction may induce microvascular changes, synovial irritation, and nociceptive sensitization, creating a fertile ground for subsequent pain development.

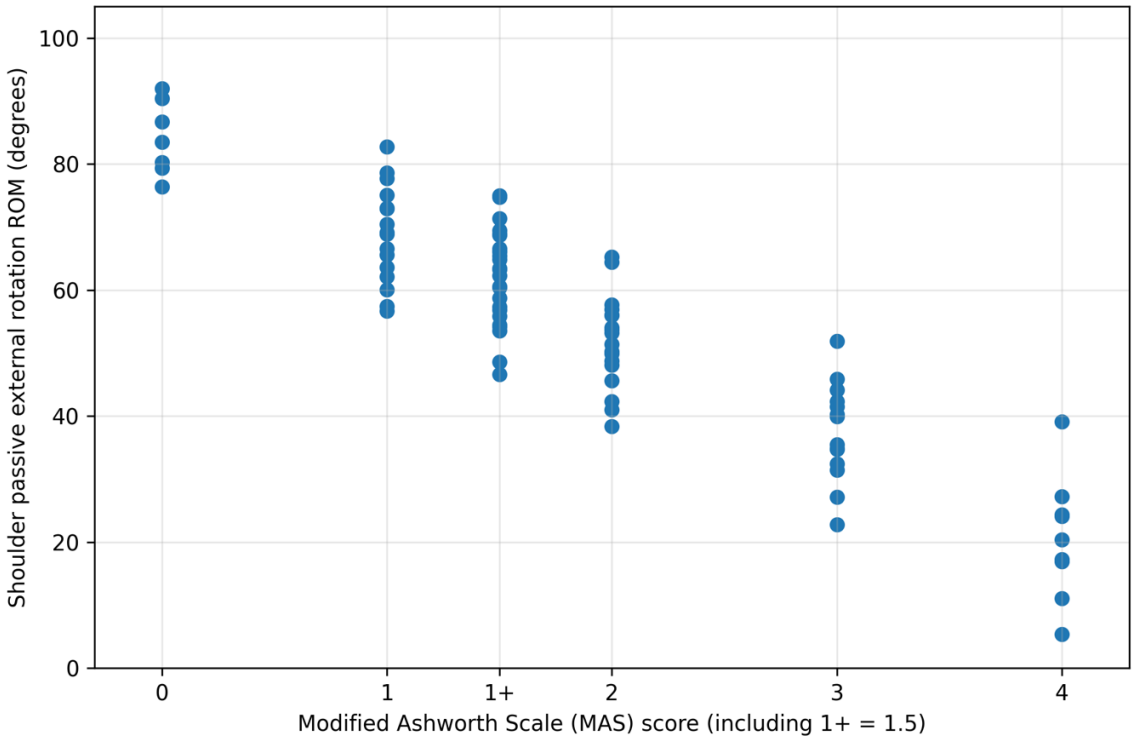
3.3 Spasticity, Co-Contractions, and Pathological Synergies: Impact on the Scapulohumeral Complex

As recovery progresses, hypotonia is often replaced or accompanied by spasticity and abnormal muscle activation patterns. Spasticity is classically defined as a velocity-dependent increase in muscle tone associated with hyperexcitable stretch reflexes (Lance, 1980), but its functional consequences extend beyond passive resistance to movement.

At the shoulder level, spasticity frequently involves the internal rotators and adductors, particularly the subscapularis, pectoralis major, and latissimus dorsi. This imbalance promotes a stereotyped posture characterized by internal rotation and adduction, which alters glenohumeral alignment and reduces external rotation and abduction.

Co-contractions, defined as simultaneous activation of agonist and antagonist muscles, further reduce movement efficiency and increase joint compressive forces. Pathological synergies, such as the flexor synergy of the upper limb, constrain voluntary movement into rigid, stereotyped patterns and disrupt normal scapulohumeral rhythm (Sheng et al., 2022).

Graph 1. – Relationship between spasticity severity and shoulder range of motion



Scatter plot created by the author to visually represent the commonly reported inverse association between upper-limb spasticity (Modified Ashworth Scale) and passive shoulder range of motion, particularly external rotation. This schematic figure is grounded in the clinical definition of spasticity and in studies reporting restricted shoulder external rotation in spastic hemiplegic patients. (Lance, 1980; Yelnik et al., 2006).

3.4 Sensory and Cognitive Alterations as Risk Factors: Proprioception and Neglect

Motor impairment after stroke is frequently accompanied by sensory and cognitive deficits, which significantly contribute to shoulder dysfunction but are often under-recognized in clinical practice.

Proprioceptive deficits, affecting up to 50–65% of stroke survivors, impair joint position sense and movement perception, reducing the effectiveness of both reflexive and voluntary stabilization mechanisms. Patients with impaired proprioception are more likely to adopt maladaptive limb positions and to experience excessive traction during transfers and caregiving activities (Moore et al., 2024)

Unilateral spatial neglect**,** particularly following right hemispheric stroke, further increases the risk of shoulder injury by reducing awareness of the paretic limb. Neglect is associated with decreased spontaneous use, poor positioning, and inadequate protection of the shoulder during daily activities (Jehkonen et al., 2006).

Table 2 summarizes sensory and cognitive factors associated with shoulder injury risk.

Deficit	Estimated prevalence	Mechanism of injury
Proprioceptive loss	50–65%	Poor joint positioning, unsafe handling
Spatial neglect	20–30%	Reduced limb awareness, traction injuries
Attention deficits	Variable	Reduced adherence to protective strategies

3.5 The Cascade Mechanism: From Central Deficit to Peripheral Soft Tissue Damage

The interaction of motor, sensory, and cognitive impairments gives rise to a cascade mechanism linking central neurological injury to peripheral musculoskeletal pathology. In this model, the initial central deficit—characterized by paresis, hypotonia, and sensory loss—leads to altered shoulder biomechanics, including instability, abnormal joint loading, and disrupted scapulohumeral coordination. Over time, these biomechanical abnormalities result in secondary damage to peripheral tissues, such as capsular fibrosis, tendon degeneration, bursal inflammation, and joint malalignment.

Importantly, this cascade is time dependent. Early instability may evolve into stiffness and capsular pathology, while chronic abnormal activation patterns may sustain pain and functional limitation even in the absence of ongoing structural progression.

CHAPTER 4 — HEMIPLEGIC SHOULDER PAIN: CLINICAL FEATURES, IMPACT, AND PATHOGENETIC MODELS

4.1 Definition of Hemiplegic Shoulder Pain and Clinical Criteria

Hemiplegic shoulder pain (HSP) is defined as pain perceived in the shoulder region of the paretic upper limb following stroke, occurring in the absence of pre-existing traumatic injury and not attributable to other non-neurological conditions. Although seemingly straightforward, this definition encompasses a broad spectrum of clinical presentations and underlying mechanisms (Turner-Stokes & Jackson, 2002).

Clinically, HSP is characterized by:

- pain at rest and/or during movement,
- pain provoked by passive mobilization,
- reduced active and passive range of motion,
- functional limitation of the paretic upper limb.

Importantly, no universally accepted diagnostic criteria exist. Most studies rely on patient-reported pain combined with clinical examination, leading to substantial heterogeneity across studies. This lack of standardization complicates comparison of prevalence estimates and therapeutic outcomes (Dyer et al., 2017).

4.2 Epidemiology of Hemiplegic Shoulder Pain: Prevalence, Incidence, and Timing

HSP is one of the most frequent complications after stroke. Reported prevalence varies widely, ranging from 20% to over 70%**,** depending on study design, population, and timing of assessment (Paci et al., 2007; Ratnasabapathy et al., 2003).

A landmark systematic review and meta-analysis by Dyer et al. (2017), including more than 30 studies, reported a pooled prevalence of HSP of approximately 34%, with substantial heterogeneity across studies (I^2 >80%). Importantly, the authors highlighted that the prevalence of shoulder pain increases over time after stroke, underscoring the dynamic and time-dependent nature of the condition rather than a static complication.

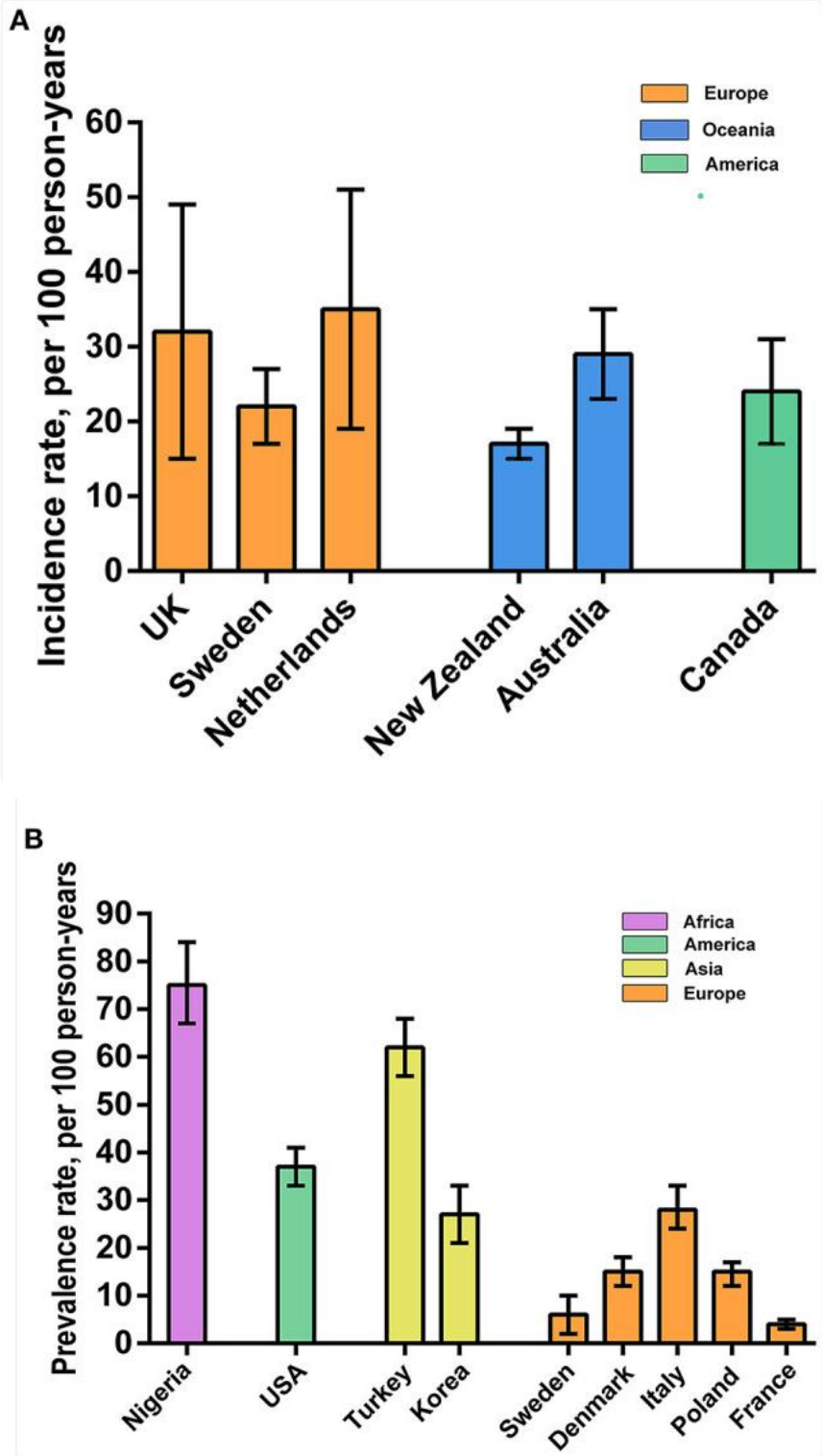
More recently, these findings have been corroborated and further refined by a systematic review and meta-analysis conducted by Zhang et al. (2021), which specifically quantified the prevalence of post-stroke shoulder pain across 10 cross-sectional studies including over 3,700 patients. Zhang and colleagues reported a pooled prevalence of 33% (95% CI: 22–43%), highly consistent with the estimate provided by Dyer et al., despite differences in study selection and analytical approach. However, heterogeneity remained high (I^2

>90%), reflecting substantial variability in study populations, timing of assessment, and diagnostic criteria for shoulder pain.

Notably, Zhang et al. emphasized that prevalence estimates were strongly influenced by the time elapsed since stroke onset, with higher prevalence rates observed in studies assessing patients in the subacute and chronic phases. This temporal effect reinforces the concept that HSP evolves over time and likely reflects the progressive interplay of different pathophysiological mechanisms, rather than a single early-onset phenomenon.

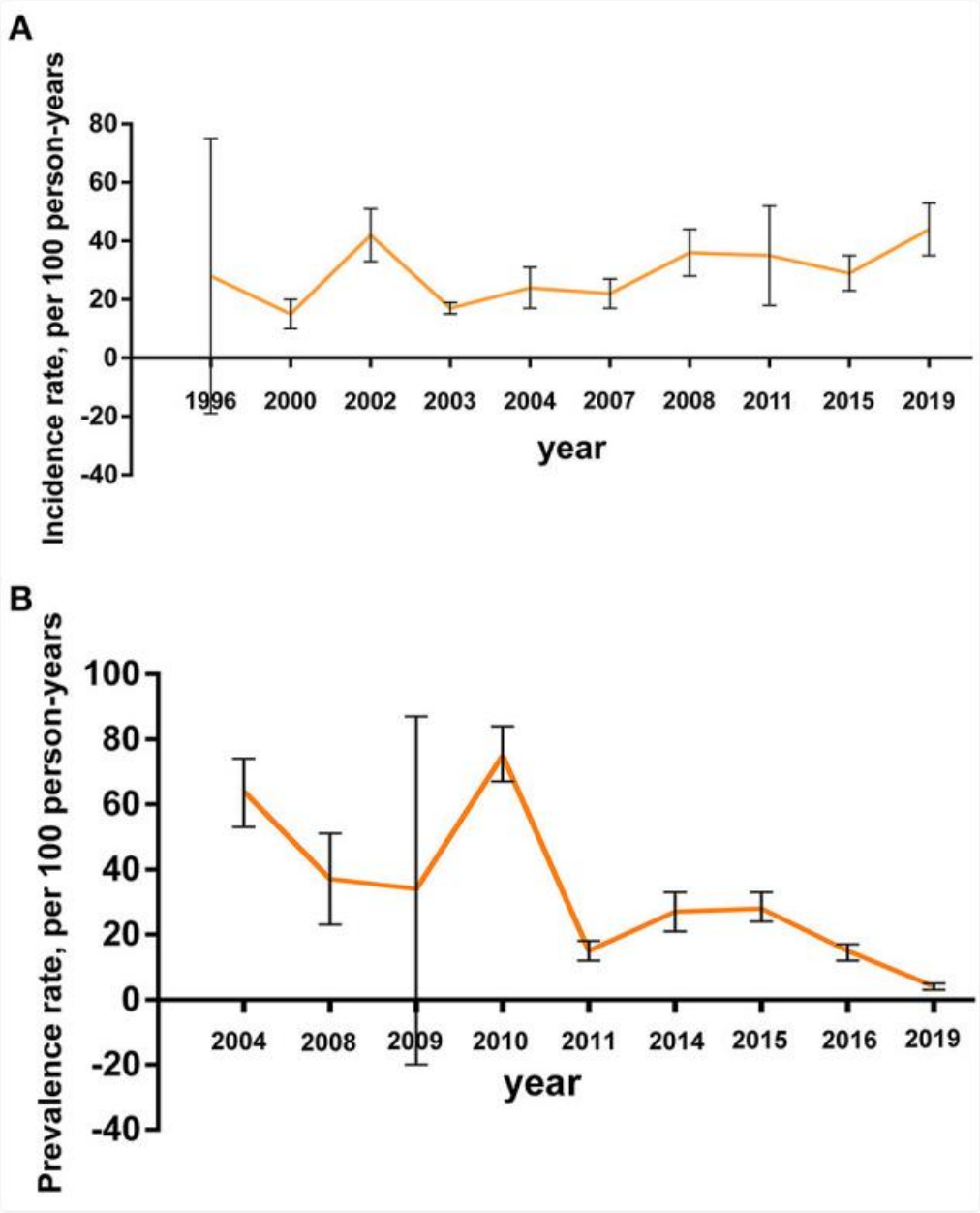
Taken together, the converging evidence from these meta-analyses supports a prevalence of HSP of approximately one third of stroke survivors, while simultaneously highlighting the limitations of cross-sectional estimates and the critical importance of considering the temporal dimension when interpreting epidemiological data.

Figure 4 A, B. Geographical regions. **(A)** Incidence of HSP on different geographical regions; **(B)** Prevalence of HSP on different geographical regions.



Zhang Q, Chen D, Shen Y, Bian M, Wang P, Li J. Incidence and Prevalence of Poststroke Shoulder Pain Among Different Regions of the World: A Systematic Review and Meta-Analysis. Front Neurol. 2021 Nov 4;12:724281. doi: 10.3389/fneur.2021.724281. PMID: 34803873; PMCID: PMC8600331.

Figure 5 A, B. Annual trend. **(A)** The annual incidence rate of HSP; **(B)** The annual prevalence rate of HSP



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4.3 Impact of Hemiplegic Shoulder Pain on ADL, Participation, and Rehabilitation Outcomes

HSP has a profound impact on functional recovery and quality of life. Multiple studies have demonstrated that patients with shoulder pain show:

- reduced independence in activities of daily living (ADL),
- lower participation in rehabilitation programs,
- decreased intensity and tolerance of therapeutic interventions,
- poorer motor recovery of the upper limb (Lindgren et al., 2007; Gamble et al., 2002).

A systematic review by Adey-Wakeling et al (2013) found that HSP is consistently associated with worse functional outcomes and longer rehabilitation stays. Pain limits both active use of the paretic arm and passive mobilization by therapists, reinforcing learned non-use and contributing to secondary complications such as stiffness and contracture.

Table 3. summarizes the functional consequences of HSP.

Domain	Effect of Hemiplegic Shoulder Pain (HSP)
Activities of daily living (ADL) independence	Reduced
Rehabilitation intensity and tolerance	Decreased
Upper limb motor recovery	Impaired
Length of hospital stay	Increased
Health-related quality of life	Lower

4.4 Pathogenetic Mechanisms of Hemiplegic Shoulder Pain: An Integrated Model

Post-stroke shoulder pain is best conceptualized as a multifactorial and time-dependent syndrome arising from the interaction between neurological impairment, altered biomechanics, and peripheral and central pain mechanisms. The literature consistently indicates

that no single lesion explains most cases; rather, different mechanisms may coexist, overlap, and dominate at different time points after stroke (Turner-Stokes & Jackson, 2002; Dyer et al., 2016).

To increase clinical interpretability, a mechanism-based framework is useful, grouping patients into dominant phenotypes while acknowledging that mixed presentations are common. The main pathophysiological contributors include peripheral structural disorders (instability, capsular pathology, tendinopathy, bursitis/effusion), neuromuscular abnormalities (spastic hypertonia and abnormal activation patterns), and central pain mechanisms (central post-stroke pain and sensitization). In addition, a subset of patients may develop complex pain syndromes such as complex regional pain syndrome**.**

In the early post-stroke phase, paresis and hypotonia reduce dynamic stabilization of the glenohumeral joint, allowing gravitational forces to induce inferior humeral head translation. Clinically, this may present as glenohumeral subluxation. While subluxation is not invariably painful, it increases capsular strain and may contribute to nociceptive input and inflammatory responses, particularly when combined with improper handling and immobility (Ada & Foongchomcheay, 2002; Dyer et al., 2016).

Capsular fibrosis and adhesive capsulitis represent key contributors to persistent pain and progressive restriction of passive range of motion. Thickening of the joint capsule, involvement of the rotator interval, and changes in the coracohumeral ligament have been implicated in the pathophysiology of stiffness-associated shoulder pain (Bunker, 2009; Do et al., 2021). In post-stroke patients, immobilization, altered loading, and pain-related avoidance behaviors may accelerate capsular remodeling.

Rotator cuff tendinopathy, partial tears, and long head of the biceps tendon (LHBT) abnormalities are frequently detected by ultrasound in post-stroke shoulders. However, these findings are also common in asymptomatic older adults, complicating causal attribution (Yamamoto et al., 2010). In the post-stroke setting, abnormal biomechanics and altered scapulohumeral rhythm may increase tendon overload and contribute to symptom persistence (Pong et al., 2009).

Subacromial–subdeltoid bursitis and glenohumeral effusion may reflect secondary inflammatory responses to mechanical overload and microtrauma. Ultrasound studies often report higher prevalence of bursal effusion in painful compared with painless shoulders, although specificity is limited and findings must be interpreted in clinical context (Snels et al., 2002; Dyer et al., 2016).

Spasticity and spastic hypertonia are frequent after stroke and can contribute directly and indirectly to shoulder pain. Spasticity is traditionally defined as a velocity-dependent increase in muscle tone due to hyperexcitability of the stretch reflex (Lance, 1980). In the upper limb, spastic hypertonia typically affects shoulder adductors and internal rotators (e.g., pectoralis major, subscapularis), promoting a posture of adduction and internal rotation with reduced external rotation and abduction. This abnormal positioning alters joint alignment and increases stress on passive structures, contributing to capsular shortening, pain during mobilization, and progressive stiffness (Pandyan et al., 2005; Malhotra et al., 2011).

Beyond passive resistance, abnormal co-contractions and pathological synergies constrain selective motor control and disrupt scapulohumeral coordination, increasing joint reaction forces and reducing movement efficiency. Clinically, this phenotype is often characterized by pain exacerbated by stretching, reduced passive external rotation, and difficulty achieving functional arm positioning during rehabilitation (Turner-Stokes & Jackson, 2002).

A minority of stroke survivors develop a complex pain syndrome consistent with complex regional pain syndrome (CRPS), historically referred to as shoulder-hand syndrome. CRPS is characterized by disproportionate pain, swelling, trophic changes, abnormal sweating, temperature asymmetry, and motor dysfunction, typically affecting the distal limb but often involving the shoulder and upper limb function as a whole (Zangrandi et al., 2021).

Post-stroke CRPS is clinically relevant because pain may be severe and disabling and may not correlate with focal structural abnormalities of the shoulder. Early recognition is essential, as delayed diagnosis may lead to persistent pain and functional deterioration. Proposed mechanisms include neurogenic inflammation, altered sympathetic function, and central sensitization, often triggered by immobilization and peripheral injury in the context of neurological impairment (Pertoldi et al., 2005; Harden et al., 2010)

In a subset of patients, shoulder pain may reflect central post-stroke pain (CPSP) or central sensitization mechanisms rather than (or in addition to) peripheral nociceptive input. CPSP is a neuropathic pain condition resulting from lesions of central somatosensory pathways and is characterized by burning pain, allodynia, hyperalgesia, and sensory abnormalities (Klit et al., 2009).

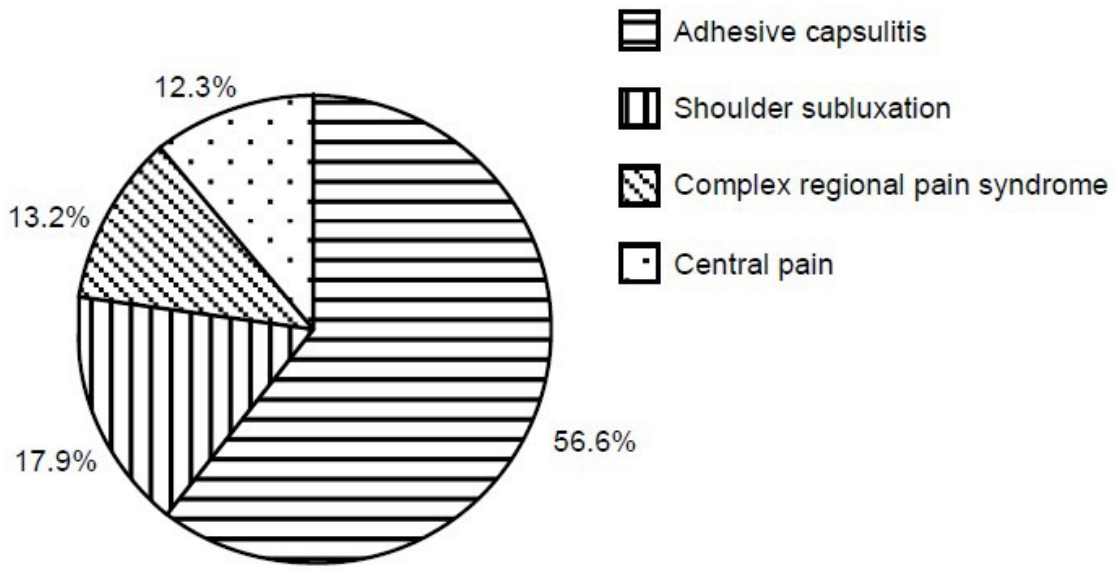
Although CPSP is often discussed in relation to thalamic lesions, it may occur with lesions at different levels of the somatosensory system. Importantly, central mechanisms can coexist with peripheral shoulder pathology, amplifying pain perception and reducing

responsiveness to purely mechanical interventions. This aligns with contemporary concepts of nociplastic pain, in which altered pain processing contributes to chronicity and disproportionate symptom severity (Klit et al., 2009; Nicholas et al., 2019).

Integrative interpretation

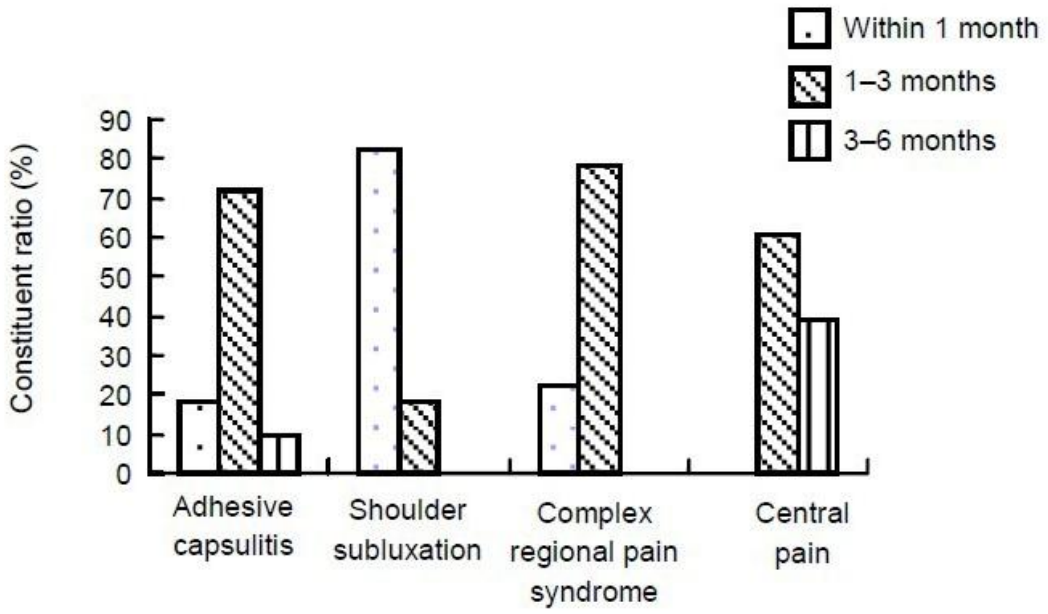
Overall, the expanded framework emphasizes that post-stroke shoulder pain may arise from (i) peripheral structural pathology**,** (ii) neuromuscular dysfunction (including spastic hypertonia and abnormal activation)**,** (iii) complex pain syndromes such as CRPS, and (iv) central/neuropathic mechanisms. Clinically, this supports the need for time-sensitive phenotyping and integrated assessment (clinical + ultrasound + neurological pain profiling) to guide targeted interventions and to interpret longitudinal trajectories.

Figure 6. Constituent ratio (%) of classification of hemiplegic shoulder pain in 106 stroke patients



Zhu Y, Su B, Li N, Jin H. Pain management of hemiplegic shoulder pain post stroke in patients from Nanjing, China. Neural Regen Res. 2013 Sep 5;8(25):2389-98. doi: 10.3969/j.issn.1673-5374.2013.25.010. PMID: 25206549; PMCID: PMC4146042.

Figure 7. Constituent ratio (%) of onset period of hemiplegic shoulder pain in 106 stroke patients. As only a few patients developed shoulder pain after 6 months, they were not included in the statistical analysis.



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4.5 Why Hemiplegic Shoulder Pain Is Multifactorial and Why Phenotyping Matters

The coexistence of multiple mechanisms explains why single-modality treatments often yield inconsistent results. Clinical trials targeting only one presumed mechanism (e.g., subluxation or spasticity) frequently show modest or variable effects.

Phenotyping HSP—integrating clinical features, timing, and imaging findings—offers a framework for:

- individualized treatment selection,
- improved prognostic stratification,
- more meaningful interpretation of clinical trials.

Table 4. summarizes proposed HSP phenotypes.

Phenotype	Dominant mechanisms	Typical timing after stroke	Key clinical features
Mechanical (early instability)	Paresis, hypotonia, loss of dynamic stabilization, glenohumeral subluxation	Acute–early subacute	Inferior humeral translation, pain with traction or positioning, minimal ROM limitation initially
Capsular (adhesive capsulitis / stiffness)	Capsular fibrosis, rotator interval and coracohumeral ligament involvement	Subacute–chronic	Progressive loss of passive ROM, pain
Tendinous (rotator cuff / LHBT)	Tendinopathy, partial tears, altered scapulohumeral biomechanics	Subacute–chronic	Movement-related pain, weakness, positive impingement-like signs
Inflammatory (bursal/synovial)	Subacromial–subdeltoid bursitis, joint effusion, secondary inflammation	Variable	Pain at rest and with movement, night pain, ultrasound evidence of effusion
Neuromuscular (spastic hypertonia)	Spasticity of internal rotators/adductors, co-contractions, pathological synergies	Subacute–chronic	Pain during stretching, reduced passive movements, increased tone, abnormal posture
Complex regional pain syndrome (CRPS)	Neurogenic inflammation, autonomic dysfunction, central sensitization	Subacute	Disproportionate pain, edema, trophic skin changes, temperature asymmetry
Central / nociplastic	Central post-stroke pain, altered pain modulation, sensitization	Chronic	Burning pain, allodynia, sensory abnormalities, poor correlation with peripheral findings

CHAPTER 5 — CLINICAL ASSESSMENT OF THE SHOULDER IN POST-STROKE PATIENTS

A standardized clinical assessment is essential in HSP for three reasons: (i) it quantifies symptom severity and functional impact, (ii) it improves longitudinal comparability across time points, and (iii) it provides the necessary clinical context to interpret ultrasound findings. However, because post-stroke shoulders are influenced by weakness, abnormal tone, sensory deficits, and pain-related guarding, clinical measures must be collected with explicit operational definitions and awareness of potential sources of bias.

5.1 Pain Assessment (NRS/VAS): Rest vs Movement-Evoked Pain

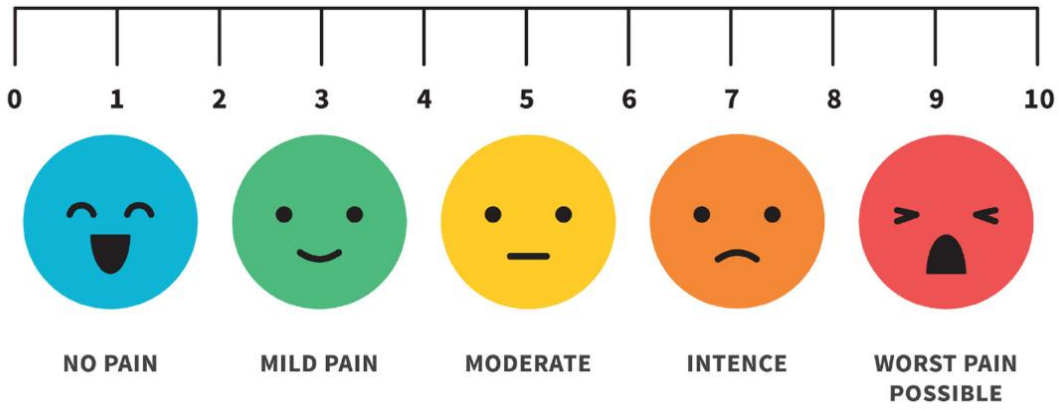
Pain is the defining symptom of HSP, yet it is heterogeneous and often mechanism dependent. Separating pain at rest from movement-evoked pain increases interpretability because these dimensions frequently map onto different underlying drivers (e.g., inflammatory/central pain at rest vs capsular/tendinous pain at end-range, traction pain during handling). Turner-Stokes and Jackson (2002) emphasized that clinical patterns of HSP vary across phases and may not be captured by a single global pain score.

The Numeric Rating Scale (NRS/NPRS, 0–10) and Visual Analogue Scale (VAS, 0–10 cm) are widely used for pain intensity measurement. Their use in stroke requires attention to cognitive–communicative limitations: Price et al. (1999) showed that many stroke patients can use VAS appropriately, but a meaningful minority cannot, especially when there is aphasia or cognitive impairment.

Additional work on pain assessment in communication-impaired populations supports the need to consider simplified self-report tools and feasibility screening when aphasia is present. (De Vries et al. 2024)

For HSP specifically, is demonstrated inter- and intra-rater reliability of clinician-administered vertical VAS ratings for post-stroke shoulder pain (intensity, frequency, affective response), supporting VAS as a repeatable outcome when used by trained staff and standardized procedures.

Figure 8. Pain Measurement Scale



A pragmatic and reproducible approach is to collect two pain scores at each visit:

1. Rest pain: patient seated or supine, paretic arm fully supported, no movement for ≥60 s; record NRS/VAS.
2. Movement-evoked pain: record NRS/VAS immediately after standardized passive maneuvers (e.g., PROM abduction and PROM external rotation performed at low velocity).

5.2 Passive and Active ROM: Meaning, Limitations, and Bias (Pain-Limited ROM)

Range of motion (ROM) is central to HSP assessment but highly vulnerable to measurement bias because post-stroke movement limitation may be driven by pain**,** spastic hypertonia**,** mechanical stiffness**,** or impaired motor control.

ROM is commonly measured using manual goniometry (or digital inclinometers), with standardized patient positioning and consistent anatomical landmarks. Evidence from musculoskeletal populations shows generally high intra- and inter-rater reliability for many shoulder planes when protocols are standardized, though reliability varies across movements and clinical settings (Fieseler et al., 2017).

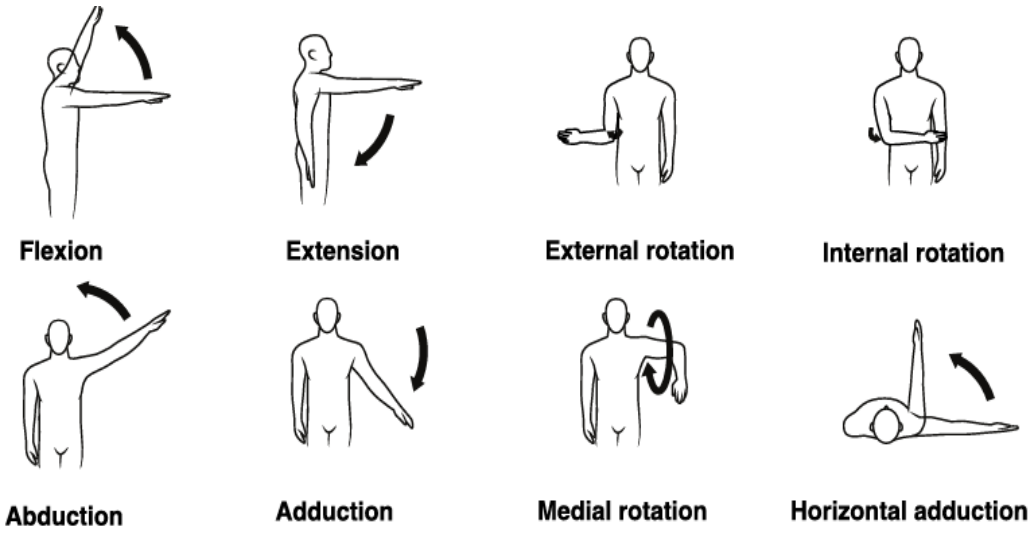
Recent work comparing measurement approaches continues to emphasize that reliability depends on rater training and consistent technique.

For post-stroke shoulder phenotyping, the most clinically informative PROM/AROM planes are:

- External rotation (ER): particularly sensitive to capsular involvement and clinically important for functional reach.

- Abduction (ABD) and flexion: integrate scapulohumeral rhythm and often reflect pain avoidance/guarding.

Figure 9. Main axes of shoulder movement



A key methodological point is to record not only the angle, but also what limited ROM**:**

- pain (patient reports pain and guards),
- firm capsular end-feel (mechanical stiffness),
- velocity-dependent “catch” (spastic hypertonia).

This qualitative annotation helps distinguish capsular vs neuromuscular limitation and increases interpretability when correlated with ultrasound findings.

Table 5 — ROM interpretation in HSP

Pattern	Most likely dominant contributor	Practical clue
PROM ER markedly reduced + painful end-range	Capsular phenotype	Terminal stiffness + pain at the end of range of motion
PROM reduced with velocity-dependent "catch"	Neural hypertonia	Resistance increases with speed (see §5.4)
AROM ≪ PROM	Motor control deficit	Weakness/synergy rather than structural block

5.3 Strength (MRC) and Proximal Motor Control

Post-stroke shoulders often deteriorate functionally because proximal motor control is compromised before distal recovery is achieved, resulting in impaired stabilization and inefficient movement patterns. For this reason, muscle strength should be assessed pragmatically using bedside-feasible and widely validated scales that allow repeated evaluation across different phases of recovery.

The Medical Research Council (MRC) scale (0–5) is extensively used in neurological and rehabilitation settings to assess voluntary muscle strength across the entire upper limb, providing a simple ordinal quantification of force generation. Although not specific to the shoulder, the MRC scale allows a global characterization of motor impairment, which is essential to contextualize shoulder dysfunction within the broader pattern of post-stroke motor recovery (James et al., 2007).

Within HSP assessment pathways, particular attention is often given to shoulder abductors and external rotators, as this muscle groups are crucial for dynamic glenohumeral stabilization and are strongly implicated in early post-stroke instability models. However, MRC testing is not limited to these movements and should be systematically applied to proximal and distal muscle groups, including elbow flexors/extensors and wrist muscles, to capture the overall severity of paresis.

This integrated use of the MRC scale supports both local interpretation of shoulder biomechanics and global interpretation of neurological recovery, reinforcing its relevance in longitudinal post-stroke shoulder assessment.

Figure 10. Medical Research Council

Score	Muscle Response
0	No muscle contraction is seen or identified with palpation. Generally seen in case of complete paralysis.
1	Muscle contraction is identified or seen with palpation but the muscle is insufficient to produce joint movement. Only flicking or twitching is seen even with the elimination of gravity.
2	The muscle can move the joint it crosses through a full range of motion but only if the part is positioned in such a way that the force of gravity is eliminated.
3	The muscle can move the joint it crosses through a full range of motion against the gravity but without applying any resistance.
4	The muscle can move the joint it crosses through a full range of motion, against the gravity as well as against some amount of resistance applied by the examiner.
5	The muscle can move the joint it crosses through a full range of motion, against the gravity as well as against full resistance applied by the examiner.

5.4 Tone and Spasticity Assessment (MAS and MTS): Distinguishing Hypertonia from Mechanical Stiffness

Tone abnormalities contribute substantially to HSP but are frequently misinterpreted in clinical practice. A critical goal of tone assessment is to distinguish spastic hypertonia (spasticity-related resistance) from non-neural mechanical stiffness due to capsular fibrosis, muscle shortening, or connective tissue changes. Failure to make this distinction may lead to inappropriate attribution of pain and to suboptimal treatment strategies (Lance, 1980; Pandyan et al., 2005).

The Modified Ashworth Scale (MAS) is one of the most commonly used clinical tools for the assessment of increased muscle tone in neurological populations due to its simplicity and feasibility at the bedside. The MAS evaluates resistance encountered during

passive movement of a limb through its range of motion at a single, non-specified velocity**,** typically described as a “fast but comfortable” stretch. (Meseguer et al., 2018)

Modified Ashworth Scale (MAS): procedure and interpretation

Procedure:

- The patient is positioned in a relaxed posture, with the tested limb adequately supported.
- The examiner passively moves the joint through its available range of motion, attempting to minimize voluntary activation.
- Resistance to movement is graded on a 6-point ordinal scale (0, 1, 1+, 2, 3, 4), where higher scores indicate greater resistance to passive movement.

Interpretation:

MAS scores reflect overall resistance to passive movement, which may result from both neural (reflex-mediated) and non-neural (mechanical) components. As such, MAS does not isolate spasticity in the strict sense but rather quantifies hypertonia as a composite phenomenon**.**

Reliability of the MAS varies by muscle group and rater experience. In a recent stroke-focused reliability study, Vidmar et al. (2023) reported good-to-excellent intra-rater reliability for upper-limb muscles but only poor-to-good inter-rater reliability, underscoring the importance of standardized procedures and rater training in research and clinical settings.

Figure 11. MAS and modified-modified Ashworth scale (m-MAS)

MAS	*m-MAS*	*Description*
0	0	No increase in muscle tone
1	1	Slight increase in muscle tone, manifested by a catch and release
1+	2	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance
2	3	More marked increased in muscle tone through most of the ROM, but affects part(s) easily moved
3	4	Considerable increase in muscle tone, passive movement difficult
4	5	Affected part(s) rigid in flexion or extension

Modified Tardieu Scale (MTS): procedure and interpretation

The Modified Tardieu Scale (MTS) was developed to better align clinical assessment with the classical, velocity-dependent definition of spasticity. Unlike MAS, the MTS explicitly compares muscle responses to passive stretch performed at different velocities, allowing partial differentiation between neural and mechanical contributors to resistance.

Procedure:

- The joint is passively moved at two standardized velocities:
    - V1: as slow as possible, intended to assess the full passive range of motion and mechanical stiffness.
    - V3: as fast as possible, intended to elicit stretch reflex activity.
- Two angles are recorded:
    - R2: the angle of full passive range achieved during slow stretch (V1).
    - R1: the angle at which a "catch" or clonus is felt during fast stretch (V3).
- The difference between R2 and R1 (R2–R1) provides an estimate of the dynamic, velocity-dependent component of resistance.

Interpretation:

- A large R2–R1 difference suggests a predominantly neural component (spasticity).
- A small R2–R1 difference with reduced R2 indicates predominantly mechanical stiffness.

This conceptual framework makes the MTS particularly valuable in distinguishing spastic hypertonia from fixed contracture, although its clinical execution is more demanding than MAS (Haugh et al., 2006).

A rehabilitation-focused reliability study by Li et al. (2014) found that both MAS and MTS can demonstrate acceptable reliability under standardized conditions, but that reliability varies across muscles and raters, reinforcing the need for training and protocol consistency.

Figure 12. Modified Tardieu Scale

Tardieu scale	
Velocities	
V1	As slow as possible, slower than the natural drop of the limb segment under gravity
V2	Speed of limb segment falling under gravity
V3	As fast as possible, faster than the rate of the natural drop of the limb segment under gravity
Scoring	
0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of passive movement, no clear catch at a precise angle
2	Clear catch at a precise angle, interrupting the passive movement, followed by release
3	Fatigable clonus with less than 10 s when maintaining the pressure and appearing at the precise angle
4	Unfatigable clonus with more than 10 s when maintaining the pressure and appearing at a precise angle
5	Joint is immovable

Clinical integration and limitations

In practice, MAS and MTS should not be viewed as interchangeable but rather as complementary tools. MAS provides a rapid, global estimate of resistance to passive movement, while MTS offers additional insight into the velocity-dependent neural component of hypertonia. However, both scales remain ordinal and examiner-dependent, and neither directly quantifies muscle or capsular stiffness.

Therefore, tone assessment should always be interpreted in conjunction with:

- passive ROM and end-feel characteristics,
- pain behavior during stretch,
- functional movement patterns,
- and, where available, imaging findings.

This integrated approach is particularly important in HSP, where spastic hypertonia and mechanical stiffness often coexist and interact over time.

5.5 Functional Scales and Disability (DASH and Others): Why They Matter

Pain intensity and range of motion (ROM) provide only a partial representation of disability in HSP. While pain and ROM quantify symptom severity and biomechanical impairment, they do not capture the patient's ability to perform meaningful tasks, participation restrictions, or functional capacity during daily life—domains that are central in neurorehabilitation. Therefore, combining patient-reported and performance-based outcomes is recommended to obtain a multidimensional profile of post-stroke upper-limb dysfunction. The Disabilities of the Arm, Shoulder and Hand (DASH) is a self-administered patient-reported outcome measure designed to quantify upper-limb disability and symptoms. It consists of 30 items; each scored on a 5-point scale (1 = no difficulty to 5 = unable). Item responses are converted to a 0–100 total score**,** where higher scores indicate greater disability. In practical terms, completion usually requires approximately 5–10 minutes**,** supporting feasibility in clinical settings.

In adults following stroke, the DASH has shown acceptable validity and has been perceived by clinicians as quick and simple to administer. (Dalton et al., 2017). The Fugl-Meyer Assessment—Upper Extremity (FMA-UE) is a stroke-specific, performance-based instrument widely regarded as a gold standard for quantifying upper-limb sensorimotor impairment after stroke. The FMA-UE comprises 33 items scored on a 3-point ordinal scale (0 = cannot perform, 1 = performs partially, 2 = performs fully), yielding a maximum total score of 66 points.

The FMA-UE has strong evidence for reliability, validity, and responsiveness across stroke populations. Hernandez et al. (2019) provided evidence supporting the FMA-UE as a reliable and valid instrument and also reported a clinically important difference estimate in their cohort, reinforcing its utility for longitudinal measurement in rehabilitation research.

In the context of HSP, the FMA-UE is valuable because it anchors shoulder pain findings to the severity of central motor impairment and proximal control deficits, which are major determinants of biomechanics and secondary musculoskeletal complications.

The Action Research Arm Test (ARAT) is a performance-based measure designed to evaluate upper-limb activity capacity following cortical injury and is widely used in stroke rehabilitation trials. It includes 19 items grouped into four subscales **(**grasp, grip, pinch, gross movement**)**. Each item is scored from 0 to 3, for a maximum total score of 57 points, with higher scores indicating better arm-hand function. Typical administration time is approximately 10–15 minutes, depending on impairment severity.

Classic validation work by Hsieh et al. (1998) demonstrated very high inter-rater reliability and good validity of the ARAT in stroke patients, supporting its suitability for measuring functional recovery of the upper limb.

More recently, Fernández-Solana et al. (2022) provided an updated psychometric evaluation, reporting good validity and reliability indicators and reinforcing the ARAT as a robust tool for post-stroke upper-limb function assessment.

Table 6. — Suggested functional battery for HSP cohorts

Construct	Measure	What it captures
Disability (patient-reported)	DASH	Self-perceived difficulty in daily arm use
Motor impairment	FMA-UE	Stroke-specific sensorimotor impairment severity
Arm-hand activity	ARAT	Performance-based functional capacity

5.6 Limits of Isolated Clinical Assessment: Low Etiological Specificity

Even a rigorous clinical examination often has limited specificity for identifying the dominant pain mechanism in HSP. Several factors explain this: symptom overlap among capsular, tendinous, and inflammatory disorders; confounding effects of weakness, synergy, neglect, and sensory deficits; and the high prevalence of degenerative shoulder findings in older adults. Additionally, the time-dependent evolution of mechanisms means that single time-point evaluations can misrepresent causality (Turner-Stokes & Jackson, 2002).

Therefore, clinical assessment should be considered necessary but not sufficient, and it achieves its greatest value when combined with imaging (particularly ultrasound) and repeated longitudinally with standardized procedures—exactly the rationale supporting clinical–ultrasound longitudinal designs in HSP research.

CHAPTER 6 — MUSCULOSKELETAL ULTRASOUND OF THE POST-STROKE SHOULDER: STATE OF THE ART AND STANDARDIZATION

Musculoskeletal ultrasound (MSK-US) has progressively emerged as a key imaging modality in the assessment of HSP. Its unique combination of accessibility, dynamic assessment, and ability to visualize soft tissues makes it particularly suited for the post-stroke population, in whom shoulder pathology is often multifactorial, time-dependent, and poorly characterized by clinical examination alone.

6.1 Why Ultrasound? Bedside, Dynamic, Repeatable, and Contralateral Comparison

Ultrasound offers several advantages over other imaging modalities in the evaluation of the post-stroke shoulder. First, it is bedside-accessible, allowing assessment of patients with severe disability, limited mobility, or acute medical conditions who may not tolerate magnetic resonance imaging (MRI). This is particularly relevant in the early post-stroke phase, when patients are often hospitalized and medically unstable (Pong et al., 2012).
Second, ultrasound enables dynamic assessment, allowing real-time evaluation of tendon motion, impingement phenomena, and joint behaviour during movement. This dynamic capability is especially valuable in HSP, where altered biomechanics, abnormal muscle activation, and movement-related pain are central features (Doğun et al., 2014).
Third, MSK-US is repeatable and radiation-free, making it suitable for longitudinal follow-up studies. This characteristic is essential for investigating the temporal evolution of shoulder pathology after stroke, a dimension that has been largely neglected in previous cross-sectional research (Doğun et al., 2014).
Finally, ultrasound allows direct comparison with the contralateral, non-paretic shoulder, which serves as an internal control. This is particularly useful in older patients, in whom age-related degenerative changes are common and may be bilateral. Contralateral comparison improves interpretability by helping to distinguish pre-existing or incidental findings from stroke-related pathology (Yamamoto et al., 2010).

6.2 Scanning Protocol: Overview of What to Assess and How

A standardized ultrasound scanning protocol is fundamental to ensure reproducibility, reliability, and meaningful comparison across time points and studies, particularly in the context of HSP, where pathological findings may evolve dynamically. Inadequate standardization of scanning technique and patient positioning represents one of the main sources of variability in musculoskeletal ultrasound research and may significantly limit interpretability, especially in longitudinal designs (Jacobson, 2018).

Most authors recommend a systematic, multiplanar approach, incorporating anterior, lateral, and posterior views of the shoulder. Examinations are typically performed with the patient in a seated position, allowing easier access to most anatomical landmarks; however, a supine position may be required in severely impaired or acute post-stroke patients. Regardless of position, the key requirement is that the patient be comfortable, relaxed, and adequately supported, minimizing involuntary muscle activation and postural compensation (Pong et al., 2012).

The transducer should be oriented consistently according to anatomical landmarks, with careful attention to probe pressure to avoid compression of superficial structures, particularly the subacromial–subdeltoid bursa and joint recesses.

A comprehensive post-stroke shoulder ultrasound protocol should include the following structures, each assessed according to established musculoskeletal ultrasound guidelines.

<u>Rotator cuff tendons</u>

The supraspinatus, infraspinatus, teres minor, and subscapularis tendons should be examined in both longitudinal and transverse planes. Physiologically, normal rotator cuff tendons appear as fibrillar, hyperechoic structures with uniform thickness and smooth bony insertion. Dynamic assessment during gentle arm movement may be used to confirm tendon continuity and to exclude impingement-related abnormalities

In post-stroke patients, attention should be paid not only to focal defects or hypoechogenicity suggestive of tendinopathy or tears, but also to global tendon thickening or altered echotexture, which may reflect chronic overload or disuse-related changes (Desmeules et al., 2025)

Long head of the biceps tendon (LHBT)

The LHBT should be visualized within the bicipital groove in both short- and long-axis views. In physiological conditions, the tendon appears oval to round, hyperechoic, and centred within the groove, with a thin surrounding hypoechoic halo representing the synovial sheath. Dynamic internal and external rotation of the arm may be used to assess tendon stability.

Key pathological features include tenosynovial fluid, tendon thickening, loss of fibrillar pattern, or dynamic subluxation. In post-stroke shoulders, even subtle abnormalities may become clinically relevant due to impaired dynamic stabilization (Gupta et al., 2015).

Subacromial–subdeltoid (SASD) bursa

The SASD bursa is best evaluated in the lateral view, with the arm in slight abduction. Under normal conditions, the bursa is barely visible or measures less than 2 mm in thickness. Excessive hypoechoic or anechoic fluid, bursal thickening, or increased compressibility are suggestive of bursitis.

Care should be taken to avoid excessive transducer pressure, which may artificially displace bursal fluid and lead to underestimation of pathology (Gupta et al., 2015).

Glenohumeral joint effusion

Effusion is typically assessed in the posterior or anterior recess, depending on patient positioning. Physiologically, minimal or no fluid is visible. Anechoic or hypoechoic fluid collections exceeding the expected physiological amount should be documented and, where possible, measured.

In post-stroke patients, effusion may represent a secondary inflammatory response rather than primary joint pathology and should be interpreted in conjunction with other findings (Gupta et al., 2015).

Capsular structures: rotator interval, coracohumeral ligament, and axillary pouch

Evaluation of capsular structures is increasingly recognized as important in HSP. The rotator interval and coracohumeral ligament (CHL) are examined in the anterior shoulder, typically with the arm in neutral or slight external rotation. In physiological conditions, the CHL appears as a thin, hyperechoic band, and the rotator interval contains minimal hypoechoic tissue.

Capsular thickening at the axillary pouch is considered a diagnostic hallmark of adhesive capsulitis. Hypoechoic tissue proliferation, or increased CHL thickness, provides complementary information on inferior capsular involvement (Gupta et al., 2015).

Quantitative assessment of glenohumeral subluxation

Inferior subluxation is quantified by measuring the acromion–greater tuberosity (AGT) distance in a standardized coronal plane. Under physiological conditions, AGT measurements are symmetrical between sides or show minimal asymmetry. Increased AGT distance on the paretic side reflects inferior humeral head displacement.

Consistent patient posture, arm position, and probe orientation are essential to ensure measurement reliability (Idowu et al 2018).

Standardization and longitudinal consistency

To minimize artefacts and improve inter-rater agreement, standardized patient positioning, probe orientation, and scanning sequence should be strictly adhered to. In longitudinal studies, maintaining the same scanning protocol, anatomical landmarks, and examiner whenever possible further reduces variability and enhances sensitivity to true biological change rather than measurement error (Pong et al., 2012).

This level of methodological rigor is particularly critical when ultrasound findings are used not merely descriptively, but as outcome measures or predictors in longitudinal clinical research on HSP.

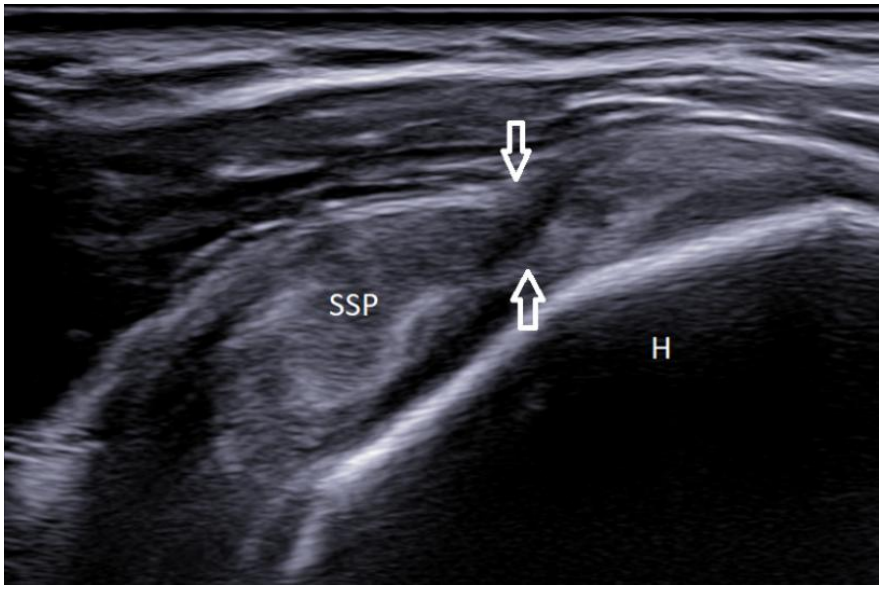
6.3 Key Ultrasound Findings and Diagnostic Criteria

Rotator Cuff and LHBT Pathology

Ultrasound is highly sensitive for detecting rotator cuff tendinopathy, partial-thickness tears, and full-thickness tears, as well as LHBT abnormalities such as tenosynovitis, degeneration, and instability. Diagnostic criteria include tendon thickening, hypoechogenicity, loss of fibrillar pattern, focal defects, and dynamic subluxation for the LHBT (Jacobson, 2018).

In post-stroke populations, several studies have reported a high prevalence of cuff and LHBT abnormalities in painful shoulders compared with painless ones (Pong et al., 2009; Snels et al., 2002). However, similar abnormalities are also common in asymptomatic older adults, highlighting the importance of clinical correlation and contralateral comparison (Yamamoto et al., 2010).

Figure 13. Longitudinal 12–3 MHz US scan, shows a partial tear through the entire thickness of the pre-insertional portion of the supraspinatus tendon (arrows). Note the loss of the normal convexity of the peribursal fat at the site of the tear. H: humeral head; SSP: supraspinatus tendon

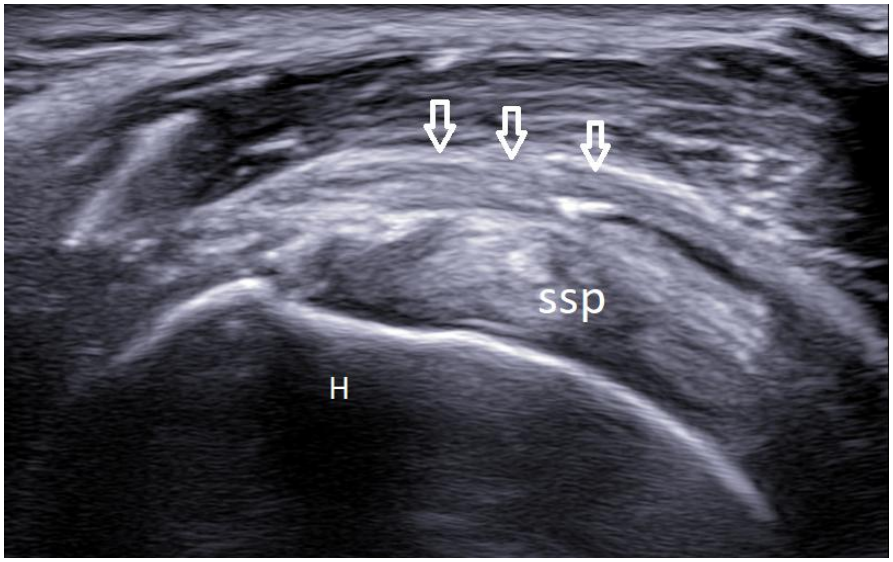


Subacromial–Subdeltoid Bursitis

SASD bursitis is identified sonographically by bursal thickening (>2 mm), hypoechoic or anechoic fluid accumulation, and increased compressibility. Inflammatory changes may be static or dynamic, becoming more evident during arm elevation.

Several observational studies have reported a higher frequency of SASD bursitis in painful hemiplegic shoulders, suggesting a role for secondary inflammatory processes related to abnormal biomechanics and overload (Lee et., 2009).

Figure 14. Longitudinal 12-3 MHz US scan along the supraspinatus tendon shows increased thickening of the bursa walls (arrows) associated with hyperechoic content, consistent with chronic bursitis. H: humeral head; SSP: supraspinatus tendon



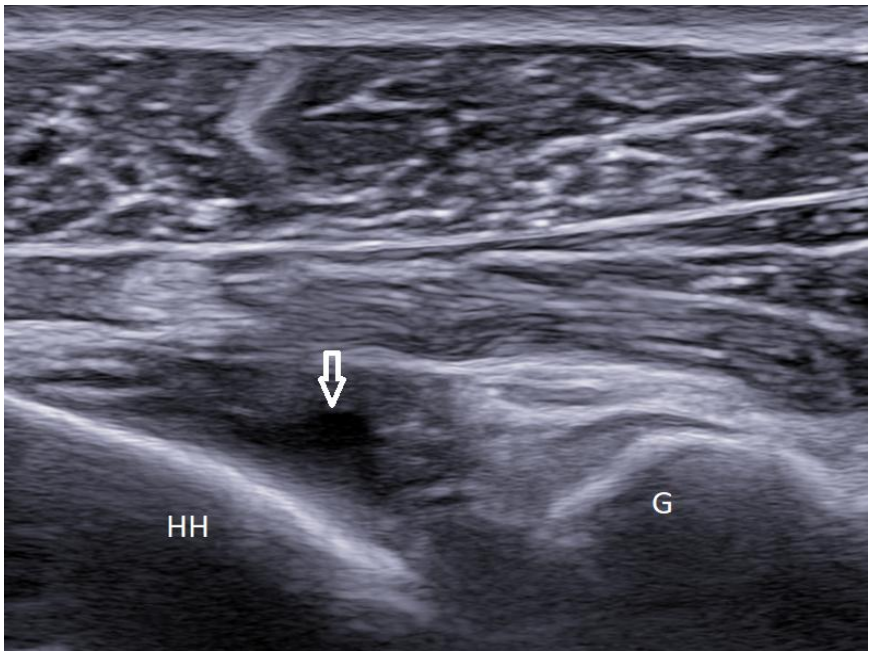
6.3.3 Glenohumeral Joint Effusion

Joint effusion appears on ultrasound as anechoic or hypoechoic fluid within the posterior or anterior recess of the glenohumeral joint. Effusion may reflect synovial inflammation, capsular irritation, or secondary changes due to instability and microtrauma.

Effusion has been reported more frequently in painful than painless post-stroke shoulders (Pong et al., 2009). As with bursitis, effusion should be interpreted as a marker of inflammatory response rather than a primary diagnosis.

Figure 15. Longitudinal 12-3 MHz US scan over the posterior shoulder demonstrates a hypoechoic effusion (arrow), distending the posterior gleno-humeral recess. This recess is located between the humeral head and the posterior aspect of bony glenoid, deep to the infraspinatus tendon and muscle.

HH: humeral head; G: bony glenoid



6.3.4 Adhesive Capsulitis: Capsular Thickness, Rotator Interval, and CHL

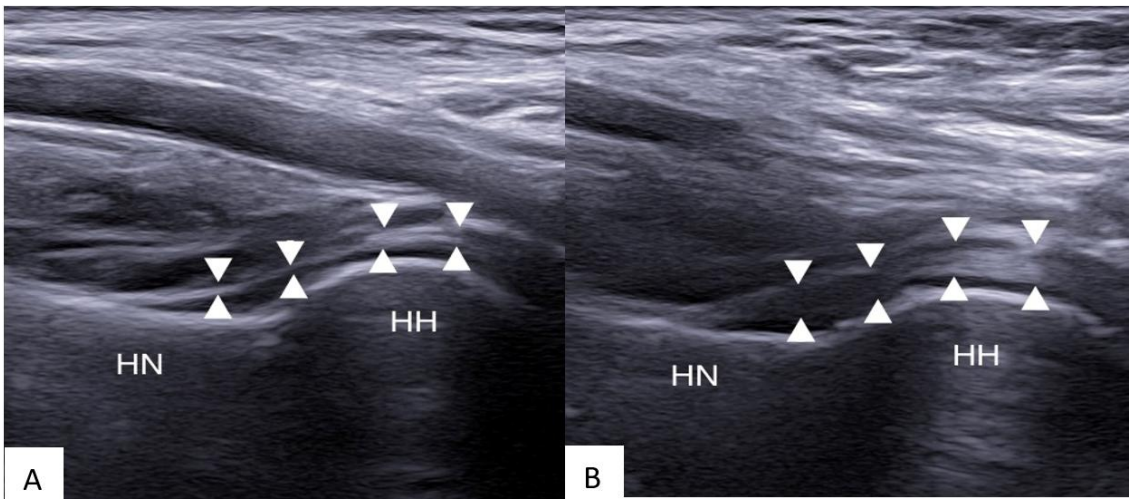
In post-stroke patients, capsular changes may develop progressively due to immobilization, altered loading, and pain-related avoidance, reinforcing the need for longitudinal assessment.

Capsular pathology represents a key mechanism in post-stroke shoulder stiffness and pain. On ultrasound, capsular thickening at the axillary pouch is considered a diagnostic hallmark of adhesive capsulitis, reflecting inferior capsular contracture and reduced joint volume. Increased thickness of the axillary recess, typically assessed in the inferior glenohumeral joint, has been consistently associated with restricted passive external rotation and shoulder stiffness. (Stella et al., 2021; Picasso et., 2024)

Additional sonographic features, such as hypoechoic tissue proliferation within the rotator interval and increased thickness of the coracohumeral ligament (CHL), may further support the diagnosis of capsular involvement. However, these findings should be regarded as complementary rather than diagnostic in isolation, as they may vary with disease stage and patient positioning (Stella et al., 2021; Picasso et., 2024)

When technically feasible, combined assessment of the axillary pouch (diagnostic) and rotator interval/CHL (complementary) provides a more comprehensive evaluation of inferior and anterior capsular involvement, enhancing diagnostic confidence and allowing better correlation with clinical measures of stiffness and pain.

Figure 16 a, b. Longitudinal 12–3 MHz US scans, obtained with the probe aligned parallel to the humerus in the axillary pouch. **a** normal inferior capsule (arrowheads) extending over the humeral head (HH) and draping along the humeral neck (HN); **b** evident thickening of the inferior capsule (arrowheads)

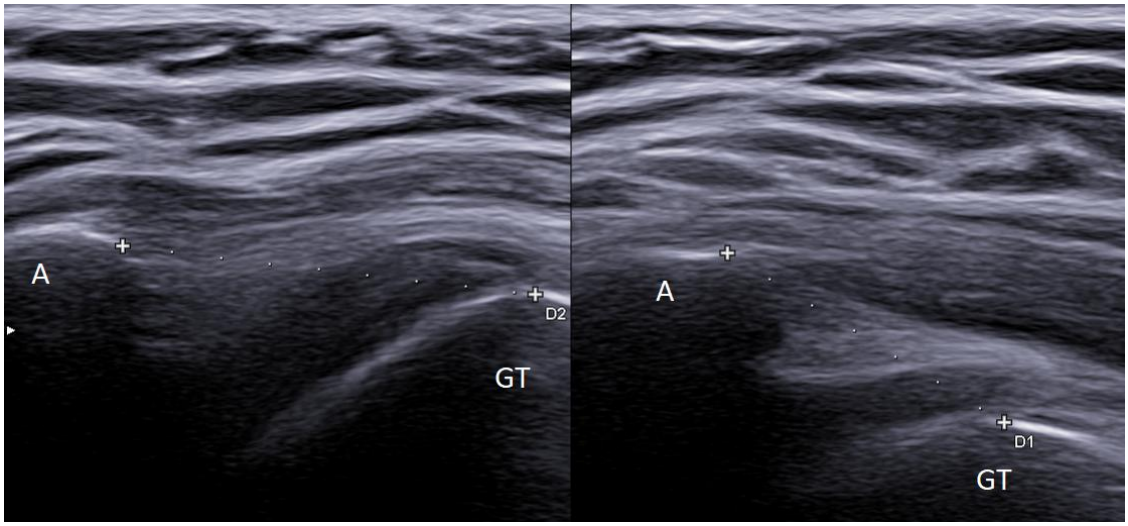


6.3.5 Glenohumeral Subluxation: AGT Distance and Reliability

Ultrasound allows quantitative assessment of inferior glenohumeral subluxation by measuring the distance between the acromion and the greater tuberosity (AGT). This measurement provides an objective estimate of humeral head descent relative to the acromion. Several studies have demonstrated good intra- and inter-rater reliability of AGT measurements when standardized protocols are used (Park et al., 2007; Pong et al., 2012; Idowu et al 2018). Ultrasound-based quantification is more sensitive than clinical palpation methods and can detect subtle asymmetries that may be clinically relevant, particularly in early post-stroke phases.

Figure 17 a, b. Longitudinal 12–3 MHz US scans, showing the Acromion–Greater Tuberosity Distance (AGTD) measurement (between cursors). **a** demonstrates a clear increase in the acromion–greater tuberosity distance; **b** normal distance

A: acromion; GT; greater tuberosity



6.4 Discordance Between Ultrasound Findings and Pain: Incidental Findings

A critical concept in MSK-US interpretation is the discordance between imaging findings and pain. Numerous studies have shown that structural abnormalities such as rotator cuff tears or tendinopathy may be present in asymptomatic shoulders, particularly with increasing age (Tempelhof et al., 1999; Minagawa et al., 2013; Lawrence et al., 2016).

In post-stroke patients, this issue is magnified by the high prevalence of pre-existing degenerative changes. Consequently, ultrasound findings should not be interpreted in isolation but integrated with clinical presentation, pain characteristics, timing after stroke, and functional impairment. This reinforces the concept that ultrasound identifies potential contributors to pain rather than definitive causes.

6.5 Reliability, Operator Dependency, and Implications for Longitudinal Studies

The reliability of musculoskeletal ultrasound depends on operator expertise, standardization of scanning protocol, and clear diagnostic criteria. When performed by trained examiners using standardized procedures, MSK-US demonstrates good to excellent intra- and inter-rater reliability for most shoulder structures (Jacobson, 2018; Pong et al., 2012).

Operator dependency remains a limitation, particularly in multicenter studies. However, this limitation can be mitigated through:

- standardized training,
- use of predefined measurement landmarks,
- blinded assessment,
- repeated measures by the same examiner in longitudinal designs.

Importantly, the repeatability of ultrasound makes it particularly well suited for longitudinal studies, where changes within the same patient over time are often more informative than cross-sectional comparisons between individuals.

Musculoskeletal ultrasound provides a powerful, versatile, and clinically meaningful tool for the assessment of the post-stroke shoulder. Its ability to visualize soft tissues dynamically, quantify instability, and be repeated over time makes it uniquely suited to investigate the evolving mechanisms of HSP. However, ultrasound findings must be interpreted within an integrated clinical framework to avoid over-attribution of incidental abnormalities. When standardized and combined with longitudinal clinical assessment, ultrasound becomes a cornerstone for mechanistic research and targeted management of HSP.

CHAPTER 7 — RATIONALE, AIMS, AND HYPOTHESES OF THE THESIS

This doctoral thesis is grounded in the need to better understand the temporal evolution and pathogenetic heterogeneity of HSP. As highlighted in the preceding chapters, HSP is a frequent, disabling, and multifactorial complication whose clinical presentation and underlying mechanisms vary substantially across time after stroke. Despite extensive literature on prevalence and risk factors, critical gaps remain in the early characterization, longitudinal evolution, and clinic–imaging integration of shoulder pathology in stroke survivors.

The two studies presented in this thesis were conceived as parts of a single, coherent research program, rather than as isolated investigations. Together, they aim to clarify *when*, *how*, and *why* specific pathological mechanisms emerge and contribute to shoulder pain after stroke.

7.1 Scientific Rationale: Why Start Within 72 Hours and Follow Patients Over Time

The rationale for initiating shoulder assessment within the first 72 hours after stroke onset is rooted in both pathophysiological and methodological considerations.

From a pathophysiological perspective, the early post-stroke phase is characterized by profound neurological changes, including paresis, hypotonia, altered muscle activation, and loss of dynamic joint stabilization. These factors precede the development of many secondary musculoskeletal alterations traditionally associated with HSP. (Turner-Stokes & Jackson, 2002; Pong et al., 2009). Early assessment allows investigation of primary biomechanical and neuromuscular contributors, before they are confounded by secondary adaptations.

From a methodological standpoint, most published studies on HSP have assessed patients weeks or months after stroke, often in the subacute or chronic phase. Consequently, they are unable to distinguish between:

- pre-existing degenerative findings,
- early stroke-related changes,
- and late secondary adaptations due to immobilization, pain, and altered use.

This limitation has been repeatedly acknowledged in systematic reviews and meta-analyses, which emphasize the heterogeneity of study timing as a major source of bias (Dyer et al., 2017; Zhang et al., 2021).

Longitudinal follow-up is therefore essential. HSP is not a static condition but rather a dynamic process, in which different mechanisms may dominate at different stages. Early instability and hypotonia may give way to glenohumeral subluxation, followed by capsular stiffness, tendinous overload and inflammatory changes, while central and nociplastic mechanisms may modulate pain perception throughout the course (Turner-Stokes & Jackson, 2002; Klit et al., 2009).

By combining early baseline assessment (≤72h) with systematic longitudinal follow-up, this research directly addresses the temporal dimension that has been largely missing in previous research.

7.2 General Objective

The general objective of this doctoral thesis is to characterize the clinical and ultrasonographic evolution of the hemiplegic shoulder after stroke, from the acute phase through subsequent recovery stages, and to identify time-dependent mechanisms associated with the development and persistence of shoulder pain.

Specifically, the thesis aims to integrate clinical examination and musculoskeletal ultrasound to improve pathogenetic understanding, phenotypization, and interpretation of HSP over time.

7.3 Specific Objectives (Study 1 and Study 2)

The present doctoral thesis is structured around two complementary studies that together form a single longitudinal research framework aimed at elucidating the temporal and pathogenetic determinants of HSP.

Study 1 — Early and Short-Term Clinical–Ultrasound Characterization

To the best of our knowledge, Study 1 represents the first investigation in which musculoskeletal ultrasound assessment of the shoulder was performed longitudinally starting in the acute phase of stroke**,** within 72 hours of stroke onset**,** while patients were still admitted to the stroke unit.

In this study, patients underwent a systematic clinical and ultrasonographic evaluation at three predefined time points:

- within 72 hours after stroke onset (acute phase),
- at one-month post-stroke, during inpatient rehabilitation (early subacute phase),
- at three months post-stroke, following discharge from the rehabilitation unit (late subacute phase).

By initiating a comparative assessment of clinical and ultrasound findings at such an early stage, this study aimed to capture the earliest biomechanical and structural alterations of the hemiplegic shoulder**,** before the confounding effects of prolonged immobilization, compensatory strategies, and chronic adaptations.

The specific objectives of Study 1 were:

1. To determine whether shoulder pain can already be detected in the acute phase after stroke and to describe its early clinical characteristics.
2. To characterize the prevalence and type of ultrasound-detected shoulder abnormalities during the first three months after stroke.
3. To explore associations between early clinical findings (e.g., paresis, tone abnormalities, subluxation) and ultrasound abnormalities.
4. To identify which ultrasound findings are associated with shoulder pain in the early post-stroke period.

Study 2 — Extended Longitudinal Trajectory and Predictive Modeling

While Study 1 established the feasibility and clinical relevance of early and short-term longitudinal ultrasound assessment, it was inherently limited by sample size and by a follow-up restricted to three months. These limitations precluded robust multivariable modeling and restricted insight into the chronic evolution of HSP.
To address these gaps, Study 2 was designed as an extension and expansion of the preliminary cohort, with both an increased sample size and prolonged follow-up to six and twelve months post-stroke. This design allowed a more comprehensive investigation of the long-term trajectory of HSP and the relative contribution of different mechanisms over time.

The specific objectives of Study 2 were:

1. To characterize the 12-month temporal trajectory of HSP, from the acute phase through subacute and chronic stages.

2. To identify the principal clinical and ultrasound predictors of shoulder pain at different time points after stroke.
3. To determine the independent contribution of clinical and ultrasound variables to pain development and persistence using multivariable statistical models.
4. To examine whether early clinical–ultrasound findings predict later shoulder pain, stiffness, or functional impairment.

By mapping how different mechanisms emerge, interact, and evolve over time, Study 2 aimed to refine the pathophysiological model of HSP, moving beyond cross-sectional associations toward a phase-specific, mechanism-based framework**.** Ultimately, this study seeks to inform early screening, risk stratification, and prevention strategies, with potential implications for timing and targeting of rehabilitative and preventive interventions.

Conceptual integration of Study 1 and Study 2

Together, Study 1 and Study 2 form a continuum of investigation, in which early pathogenetic signals identified in the acute and subacute phases are tracked and tested for their prognostic relevance over the longer term. This integrated approach strengthens causal inference and aligns with the overarching objective of the thesis: to understand HSP as a dynamic, evolving condition, rather than as a static post-stroke complication.

7.4 Main Hypotheses (Phase-Specific: Mechanical → Capsular → Tendineous)

The central hypothesis underpinning this doctoral thesis is that HSP is not attributable to a single pathological mechanism but rather reflects the interaction of multiple clinical and structural factors whose relative contribution may vary over time after stroke. This assumption is grounded in previous clinical models and observational studies suggesting that shoulder pain after stroke is heterogeneous, multifactorial, and dynamically influenced by neurological recovery, biomechanical changes, and secondary musculoskeletal adaptations (Turner-Stokes & Jackson, 2002; Snels et al., 2002; Pong et al., 2009).
Based on the existing literature and on the theoretical framework outlined in the two studies included in this thesis, the following hypotheses were formulated.

Hypothesis 1: Early post-stroke shoulder pain is associated with neuromuscular and biomechanical factors
In the acute and early post-stroke period, shoulder pain and vulnerability are hypothesized to be primarily associated with neuromuscular impairment, including paresis, hypotonia,

altered muscle activation, and loss of dynamic stabilization of the glenohumeral joint. These factors are expected to predispose the shoulder to abnormal loading, micro-instability, and increased susceptibility to pain, even in the absence of overt structural lesions detectable by imaging.

This hypothesis is supported by prior observations that shoulder pain can occur early after stroke and that mechanical factors such as subluxation and impaired motor control may play a role in its development (Turner-Stokes & Jackson, 2002; Kumar et al., 2014).

Hypothesis 2: Structural alterations detectable by ultrasound contribute to pain development during recovery

Over time, patients tend to achieve partial recovery in terms of strength; however, it is during the subacute phaseit is that structural changes of periarticular tissues**,** detectable by musculoskeletal ultrasound, increasingly contribute to shoulder pain. These may include alterations of the joint capsule, periarticular soft tissues, and intra-articular environment, potentially related to immobilization, abnormal posture, pain-related avoidance, and altered use of the paretic limb.

Previous cross-sectional and short-term longitudinal studies have suggested associations between shoulder pain and findings such as capsular involvement, joint effusion, and periarticular inflammation, although the temporal relationship between these changes and pain onset remains poorly defined (Snels et al., 2002; Pong et al., 2009; Dyer et al., 2017).

Hypothesis 3: Different ultrasound findings show distinct temporal relationships with pain

A further hypothesis of this thesis is that different ultrasound-detected abnormalities exhibit distinct temporal patterns in their association with shoulder pain. Rather than assuming a uniform contribution of all structural findings, the thesis explores whether specific abnormalities—such as glenohumeral instability, capsular changes, or tendinous alterations—are more strongly associated with pain at certain stages of recovery than others.

This hypothesis directly addresses a major limitation of previous studies, which have typically assessed patients at a single time point and therefore could not disentangle early contributors from later secondary adaptations (Dyer et al., 2017; Zhang et al., 2021).

Hypothesis 4: Early clinical–ultrasound findings have prognostic relevance

Finally, the thesis hypothesizes that clinical and ultrasound findings obtained in the acute phase may have prognostic value for the subsequent development or persistence of shoulder pain. Identifying such early markers could contribute to improved risk stratification and inform the timing of preventive or targeted interventions.

This hypothesis reflects the growing emphasis in stroke rehabilitation research on early identification of secondary complications and is consistent with calls in the literature for longitudinal, mechanism-oriented studies starting from the acute phase (Turner-Stokes & Jackson, 2002; Dyer et al., 2017).

Together, these hypotheses frame HSP as a dynamic and multifactorial condition, whose mechanisms cannot be fully understood without early and repeated assessment. Rather than presupposing phase-specific dominance, the thesis adopts an exploratory longitudinal approach to test whether and how different clinical and ultrasound factors relate to shoulder pain over time.

7.5 Added Value Compared with Existing Literature

The added value of this thesis lies in several key aspects:

1. **Very early assessment:**
   Initiating evaluation within 72 hours post-stroke minimizes confounding by secondary adaptations and allows investigation of primary mechanisms.
2. **Longitudinal design:**
   Repeated assessments enable true temporal analysis, addressing a limitation repeatedly highlighted in reviews (Dyer et al., 2017; Zhang et al., 2021).
3. **Integrated clinical–ultrasound approach:**
   The combination of standardized clinical examination and musculoskeletal ultrasound improves mechanistic interpretation beyond either modality alone.
4. **Phenotype-oriented framework:**
   The thesis moves beyond binary “pain vs no pain” models, proposing a phase-specific, phenotype-based interpretation of HSP.
5. **Clinical relevance:**
   Identifying early predictors and dominant mechanisms may inform timing and targeting of preventive and therapeutic interventions.

CHAPTER 8 — GENERAL METHODS

This chapter describes the general methodological framework underpinning the two studies included in this doctoral thesis. Although the studies differ in sample size, duration of follow-up, and analytical depth, they share the same core observational longitudinal design, clinical and ultrasound assessment protocols, and conceptual framework. Study 2 represents an extension and refinement of Study 1, rather than a methodologically independent investigation.

8.1 Overall Study Design

Both studies were designed as prospective, observational longitudinal cohort studies, aimed at characterizing the clinical and ultrasonographic evolution of the hemiplegic shoulder following stroke.

The observational design was chosen to:

1. describe the natural history of post-stroke shoulder changes,
2. explore associations between clinical features, ultrasound findings, and pain,
3. avoid interference with standard clinical care.

No experimental interventions were applied as part of the study protocols. All patients received usual stroke-unit and rehabilitation care according to local clinical pathways.

The longitudinal structure allowed repeated within-subject measurements, enhancing sensitivity to temporal changes and reducing inter-individual confounding—an approach repeatedly advocated in the HSP literature but rarely implemented starting from the acute phase (Dyer et al., 2016; Zhang et al., 2021).

8.2 Setting and Population: Inclusion/Exclusion Criteria and Timing

Participants were consecutively recruited from the Stroke Unit of San Martino Policlinic Hospital-IRCCS for acute stroke, with subsequent follow-up during inpatient rehabilitation and after discharge.

Patients were eligible if they:

- had a first-ever ischemic or hemorrhagic stroke, confirmed by neuroimaging;
- presented with unilateral upper-limb motor impairment;
- were assessed within 72 hours of stroke onset;
- were ≥18 years of age;
- were able to provide informed consent directly or via a legal representative.

Exclusion criteria included:

- pre-existing severe shoulder pathology on the paretic side (e.g., prior fracture, surgery, inflammatory arthropathy);
- history of severe shoulder pain or disability prior to stroke;
- bilateral stroke or bilateral upper-limb involvement;
- medical instability precluding clinical or ultrasound assessment.

These criteria were chosen to minimize confounding by pre-existing musculoskeletal disease while preserving ecological validity.

Timing of assessments

- Study 1: assessments at ≤72 hours, 1 month, and 3 months post-stroke.
- Study 2: same early assessments, with extended follow-up at 6 and 12 months**.**

Thus, both studies share the same early time points, with Study 2 expanding the observation window into the chronic phase.

8.3 Clinical Assessment: Tools and Operational Definitions

Clinical assessment followed a standardized protocol identical in both studies.

Pain

Shoulder pain was assessed using the Numeric Rating Scale (NRS, 0–10) at rest and during standardized passive shoulder flexion, abduction, and external rotation movements as described in Chapter 5. Pain presence was operationally defined as NRS ≥1.

Range of Motion

Passive and active ROM were measured using manual goniometry, with particular attention to:

- external rotation, (0–80°)
- abduction, (0–180°)
- flexion. (0–180°)

The limiting factor (pain, mechanical end-feel, or velocity-dependent resistance) was recorded at each assessment.

Strength

Upper-limb strength was evaluated using the MRC scale a six-point system ranging from 0 (complete paralysis) to 5 (normal strength), applied systematically to proximal and distal muscle groups, with particular emphasis on shoulder abductors, flexors and external rotators.

Muscle Tone

Muscle tone in the shoulder extensors, adductors, and internal rotators was assessed using the Modified Ashworth Scale (MAS), a six-point scale ranging from 0 (no increase in tone) to 4 (limb rigid in flexion or extension). For numerical analysis, grade 1 was recorded as 1 and grade 1+ was recorded as 1.5

Subluxation

Clinical screening for glenohumeral subluxation was performed by palpation, while quantitative assessment was obtained via ultrasound (see §8.4).

Functional scales

Upper extremity disability was assessed using the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire, which consists of 38 items rated on a scale of 1 (no difficulty) to 5 (unable to perform). The total score ranges from 0% (no disability) to 100% (total disability)

8.4 Ultrasound Assessment: Equipment, Operators, and Diagnostic Criteria

Ultrasound examinations were performed using a portable ultrasound machine (Minisono Alpinion, Seoul, Republic of Korea) equipped with a linear probe (frequency range 3–12 MHz) connected to a Microsoft Surface Pro 7 tablet. The same ultrasound system was used throughout each study period to ensure consistency.

All ultrasound examinations were performed by two experienced physiatrists, who conducted the assessments jointly to ensure real-time agreement on image acquisition and interpretation. Any uncertainties or discrepant findings were discussed immediately and resolved by consensus at the time of examination

The two studies included in this thesis employed a shared, standardized musculoskeletal ultrasound protocol, with methodological refinements introduced in the second study to enhance longitudinal robustness and analytical depth (Martinoli et al., 2007; Sconfienza et al., 2018; Jacobson, 2018).

The general principles of scanning technique, patient positioning, anatomical landmarks, and physiological reference values have been described in detail in Chapter 6 and are therefore not repeated here.

Assessment of tendon pathology

In both studies, the rotator cuff tendons (supraspinatus, infraspinatus, subscapularis, teres minor) and the long head of the biceps tendon (LHBT) were systematically evaluated.

Tendon pathology was defined using standard sonographic criteria:

- Tendinopathy: focal or diffuse tendon thickening with heterogeneous or reduced echogenicity and preserved fibrillar continuity.
- Partial-thickness tear: focal hypo-anechoic defect within the tendon matrix visible in both longitudinal and transverse planes.
- Full-thickness tear: complete loss or non-visualization of the fibrillar structure.

In Study 1, tendon involvement was summarized using a Total Tendon Score (TTS), grading each of the five tendons from 0 (normal) to 3 (complete tear), yielding a composite score (range 0–15).

In Study 2, tendon abnormalities were instead operationalized by counting:

- the number of tendons affected by tendinopathy,
- the number of tendons affected by tears.

This change reflects a methodological evolution from a severity-weighted composite score to a burden-based representation, allowing more flexible modeling in multivariable longitudinal analyses.

Inflammatory and periarticular findings

Subacromial–subdeltoid (SASD) bursitis was defined in both studies as an anechoic or hypoechoic bursal distension exceeding physiological limits (>2 mm), visible in orthogonal planes (Lee et al., 2009).

LHBT tenosynovitis was identified by anechoic or hypoechoic fluid surrounding the tendon within its sheath, often accompanied by synovial hypertrophy.

Intra-articular glenohumeral effusion was defined as a hypoechoic or anechoic fluid collection within the joint recesses, typically assessed posteriorly. When both LHBT sheath effusion and joint effusion were present, only intra-articular effusion was retained for analysis, to avoid redundancy.
Except for tendon pathology, these findings were classified dichotomously (present/absent) in both studies.

Capsular pathology (adhesive capsulitis)
In both studies, adhesive capsulitis was diagnosed based on inferior capsular thickening at the axillary pouch, defined as:

- capsule thickness > 4 mm, or
- 60% thickening compared with the contralateral side.

As detailed in Chapter 6, inferior capsular thickening was considered diagnostic, while other findings—including coracohumeral ligament thickening**,** rotator interval changes, and biceps sheath effusion—were recorded as supportive but non-mandatory criteria (Stella et al., 2022; Picasso et al., 2023).

Glenohumeral subluxation
Inferior glenohumeral subluxation was quantified using the acromion–greater tuberosity (AGT) distance, measured bilaterally in a standardized coronal plane.
An inter-side difference > 0.4 cm (or >4 mm) in the paretic shoulder was considered indicative of subluxation, in line with previous validation studies (Idowu et al., 2017).

Temporal structure of ultrasound assessments

- **Study 1**: ultrasound assessments at three time points (acute ≤72 h, 1 month, 3 months).
- **Study 2**: same early time points, with extension to five total assessments (T0–T4), covering acute, subacute, and chronic phases up to 12 months.

All ultrasound variables were assessed at each scheduled time point, allowing both cross-sectional and longitudinal analyses.

Conceptual coherence between the two studies
Although minor differences exist in scoring strategy and follow-up duration, both studies share:

- identical diagnostic thresholds,
- identical anatomical targets,
- identical dichotomization of non-tendinous findings,
- and the same conceptual framework linking ultrasound findings to clinical phenotyping.

Study 2 should therefore be interpreted as a methodological and analytical extension of Study 1, designed to overcome limitations of sample size and short follow-up while preserving full comparability of ultrasound measures.

8.5 Primary and Secondary Outcomes

The overarching objectives of this doctoral research program were to systematically investigate the development and evolution of HSP across the continuum of stroke recovery, through the integration of early and longitudinal clinical and ultrasonographic assessment.

Specifically, the research aimed to:

1. Describe the early clinical and ultrasonographic profile of the hemiplegic shoulder in the acute phase after stroke, capturing musculoskeletal and biomechanical alterations occurring within the first 72 hours, prior to the establishment of prolonged immobilization and secondary adaptations.
2. Characterize the longitudinal trajectory of HSP and associated ultrasound findings from the acute phase to the chronic stage, extending observation up to 12 months after stroke, to delineate temporal patterns of pain onset, persistence, or resolution.
3. Identify clinical and ultrasonographic factors associated with the presence and severity of shoulder pain at different stages of recovery, exploring how their relative contribution may change over time.
4. Determine the independent predictive value of early and evolving clinical–ultrasound variables through multivariable analyses, with the aim of distinguishing primary contributors from secondary or incidental findings.
5. Integrate early and long-term findings into a unified pathophysiological framework of HSP, capable of accounting for the dynamic interaction between neurological impairment, biomechanical alterations, and structural musculoskeletal changes.

By adopting this integrated, longitudinal approach, the thesis seeks to move beyond static descriptions of shoulder pathology after stroke and to contribute to the development of

mechanism-oriented models that may support earlier risk stratification, targeted monitoring, and informed preventive strategies in post-stroke shoulder management.

8.6 Statistical Analysis Plan

Study 1

Patients were divided into different groups according to the PNRS, pROM, aROM, MRC, and MAS scores measured for each of the three movements studied (shoulder flexion, abduction, and external rotation). A PNRS score of 0 was defined as no pain, a score between 1 and 3 as mild pain, and a score between 4 and 10 as moderate to severe pain. Based on previous prospective research showing that most stroke patients with HSP experience moderate to severe pain (PNRS > 3), individuals reporting this level of shoulder pain on the hemiplegic side were classified as having HSP [8,37].

For pROM, patients were divided into two groups for flexion and abduction movements: pROM > 90° and pROM ≤ 90°. For external rotation, the categories were pROM > 40° and pROM ≤ 40°. The same categorization was used for aROM.

For muscle strength, patients were divided into two groups: MRC < 3 (no movement against gravity) and MRC ≥ 3 (movement against gravity). For muscle tone, patients were categorized as MAS < 2 (no or mild hypertonia) and MAS ≥ 2 (moderate or severe hypertonia). Finally, patients were classified into two categories based on TTS scores: TTS 0-1 (no tendon lesions or mild tendon lesions) and TTS > 1 (moderate or severe tendon lesions).

Results were reported as median (interquartile range, IQR) or number (N) (percentage, %) by PNRS group (patients with HSP and patients without HSP), and groups were compared using the chi-squared test, Fisher's exact test, or Mann–Whitney test, depending on the nature of the variables. Univariable and multivariable logistic regression models were performed to examine associations between baseline characteristics and HSP. Variables with $p < 0.10$ in the univariable analysis were included in the multivariable models.

T1-T0 and T2-T0 changes in clinical and ultrasound characteristics were compared using the Wilcoxon or McNemar test, depending on the nature of the variables. T0-T2 changes in clinical and ultrasound assessments were also compared between patients with and without glenohumeral subluxation or adhesive capsulitis at T2 using the Wilcoxon test. All statistical analyses were performed using Stata statistical software (v.18; StataCorp, College Station, TX, USA), and p-values < 0.05 were considered statistically significant.

The sample size was calculated based on the primary outcome, considering the comparison between T0 and T2. The effect size was set at 0.6, corresponding to a moderate-to-large effect. The variability of the effect size was assumed with a standard deviation of the difference equal to 1, an assumption that should be evaluated for its appropriateness in this context. Using a significance level of 0.05 and a statistical power of 80%, the calculation indicated that at least 24 participants were needed to detect this effect. Since our study included 28 participants, it meets the statistical requirements for a preliminary analysis. The sample size calculation was performed using Stata software (v.18; StataCorp, College Station, TX, USA).

Study 2

All statistical analyses were performed using Jamovi (version 2.3.28). The significance level was set at $p < 0.05$ (two-tailed).

To identify HSP predictors, both univariable and multivariable linear regression analyses were conducted, with NRS pain intensity treated as a continuous dependent variable. This approach was chosen to preserve information on pain severity and maximize statistical power. Clinical and ultrasound variables were selected a priori based on clinical relevance or physiological plausibility. At each point, NRS scores were analyzed in relation to the clinical and ultrasound variables measured at the corresponding time point. The only exception was the NIHSS score, recorded only at baseline (T0), which was tested as a predictor of pain intensity at all subsequent time points to assess whether initial stroke severity predicted later pain levels.

In multivariable models, the same variables were entered simultaneously to estimate their independent contribution to pain intensity. For each model, unstandardized coefficients (β), standard errors (SE), standardized coefficients, t-values, and p-values were reported. Model fit was expressed as the coefficient of determination (R^2).

Only for the estimation of HSP prevalence, and to ensure comparability with previous studies (Lindgren et al., 2007; Kim et al., 2014), HSP was defined using an NRS cut-off ≥ 4. In contrast, all univariable and multivariable analyses treated NRS pain intensity as a continuous variable.

PART II: CHAPTER 9 — STUDY 1: EARLY CLINICAL AND ULTRASOUND ASSESSMENT (≤72 H) AND 3-MONTH FOLLOW-UP

9.1 Main Results

Participants

Patients were recruited consecutively among those admitted to the San Martino Policlinic Hospital-IRCCS for acute stroke. Inclusion criteria were: first occurrence of ischemic or hemorrhagic stroke, resulting in contralateral hemiparesis, and age over 18 years. Exclusion criteria were severe consciousness impairment, significant cognitive or behavioral deficits, and pre-existing shoulder pain before the stroke.

According to these criteria, 33 patients were initially enrolled. However, 5 patients dropped out, leaving 28 participants who completed all evaluations at T0, T1, and T2. The mean age of the participants was 65.71 years (SD: 9.80), with 16 males (57.14%). Twelve participants (42.86%) had a hemorrhagic stroke, while the remaining sixteen (57.14%) had an ischemic stroke. The hemorrhages were typically located in the capsular nucleus, while the ischemic strokes occurred in the territory of the middle cerebral artery. Baseline demographic and clinical characteristics collected at T0 are detailed in Table 1

Table 1. Patients' demographic and clinical features. Abbreviations: M: Male; F: Female; R: Right; L: Left; NIHSS: National Institutes of Health Stroke Scale.

Subject	Age	Gender	Type of Stroke	Affected Side	NIHSS
1	61	M	haemorragic	R	11
2	66	M	ischemic	L	4
3	66	F	ischemic	L	8
4	71	F	ischemic	L	16
5	75	F	ischemic	R	6
6	69	M	ischemic	L	4
7	77	F	ischemic	R	3
8	73	M	ischemic	R	5
9	53	M	ischemic	L	5
10	82	F	ischemic	R	15
11	61	M	haemorragic	R	6
12	65	F	haemorragic	R	3
13	87	M	haemorragic	L	10
14	45	M	haemorragic	L	23
15	73	F	ischemic	L	16
16	46	M	haemorragic	L	12
17	73	F	ischemic	L	19
18	64	M	haemorragic	R	6
19	67	F	ischemic	R	11
20	57	F	ischemic	R	16
21	57	M	haemorragic	L	8
22	77	M	haemorragic	L	9
23	61	M	ischemic	L	14
24	56	M	ischemic	R	19
25	61	F	haemorragic	L	10
26	64	M	haemorragic	L	17
27	69	F	ischemic	L	14
28	64	M	haemorragic	L	15

Time Course of Pain

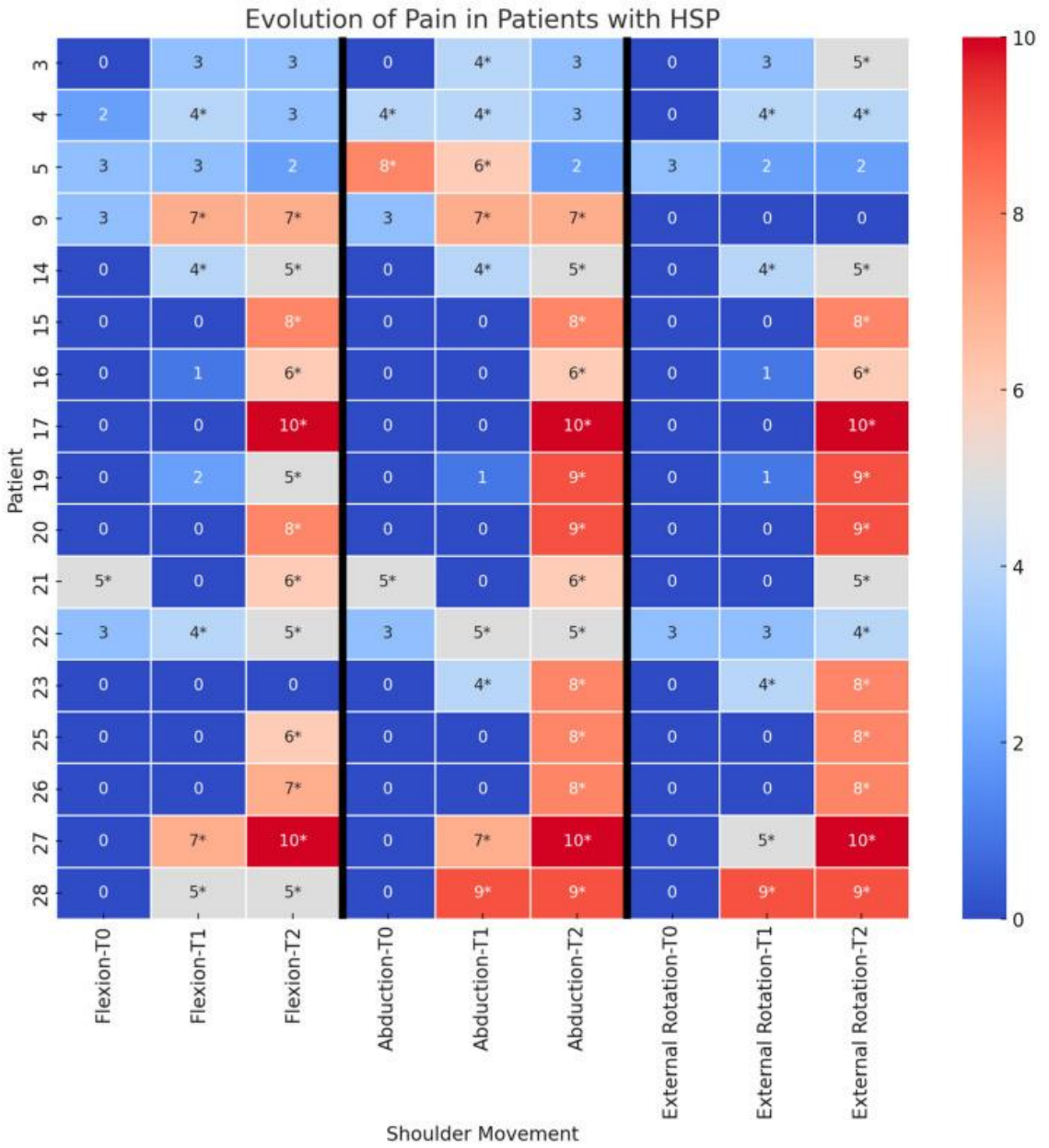
At T0, only three patients (11%) reported HSP (PNRS > 3). Among them, two patients (7%) experienced HSP in a single movement axis, while one patient (4%) reported HSP in two movement axes.

At T1, the number of patients with HSP increased to nine (32%): two (7%) had HSP in a single axis, three (11%) in two axes, and four (14%) in all three movement axes.

At T2, 16 patients (57%) reported HSP. Among them, two (7%) experienced HSP in a single axis, two (7%) in two axes, and twelve patients (43%) in all three movement axes.

Statistical analysis revealed a significant increase in PNRS scores at T1 compared to T0 across all three movement axes (flexion: $p = 0.009$; abduction: $p = 0.035$; external rotation: $p = 0.016$). Similarly, PNRS score increased at T2 compared to T0, again across all movement axes (flexion: $p = 0.002$; abduction: $p = 0.002$; external rotation: $p = 0.001$) (Figure 1).

Figure 1. The heat map illustrates the evolution of shoulder pain in 17 patients diagnosed with HSP. Pain intensity, measured using the Numerical Rating Scale (PNRS), is reported for three shoulder movements—flexion, abduction, and external rotation—at three assessment time points (T0, T1, and T2). Only pain scores greater than 3 (PNRS > 3) have been considered and marked with an asterisk, as this represents the diagnostic threshold for HSP. Warmer colors indicate higher pain levels, while cooler colors represent lower pain intensity



Risk Factors for HSP Development

Univariate and multivariate analyses identified higher NIHSS scores at T0 as a significant risk factor for the development of HSP in all three axes of motion: flexion (OR 1.19, p = 0.040), abduction (OR 1.22, p = 0.026), and external rotation (OR 1.33, p = 0.009). This association remained significant in multivariable analysis for abduction (p = 0.038) and external rotation (p = 0.009). In contrast, other T0 variables showed only non-significant associations with HSP (Table 2).

Table 2. Univariable and multivariable logistic regression models for no HSP patients (PNRS ≤ 3) or HSP patients (PNRS > 3) at T2 during the three assessed passive movements (Flexion, Abduction and External Rotation). Variables with $p < 0.10$ in the univariable analysis were included in the multivariable models. Abbreviation: NIHSS: National Institutes of Health Stroke Scale.

Characteristics	***Flexion***		***Abduction***		***External Rotation***	
	Univariate	***Multivariate***	***Univariate***	***Multivariate***	***Univariate***	***Multivariate***
	OR (95% CI) p-Value	***Beta (95% CI) p-Value***	***OR (95% CI) p-Value***	***Beta (95% CI) p-Value***	***OR (95% CI) p-Value***	***Beta (95% CI) p-Value***
Age (10-years increase)	*0.42 (0.16; 1.09) 0.076*	*0.46 (0.15; 1.39) 0.170*	*0.38 (0.14; 1.02) 0.056*	*0.38 (0.12; 1.28) 0.120*	*0.56 (0.24; 1.32) 0.187*	---
Gender	*1.29 (0.29; 5.77) 0.743*	---	*1.00 (0.22; 4.47) 1.000*	---	*2.57 (0.54; 12.17) 0.234*	---
Type of stroke	*0.58 (0.13; 2.69) 0.490*	---	*0.74 (0.16; 3.39) 0.699*	---	*0.94 (0.20; 4.29) 0.934*	---
NIHSS	*1.19 (1.01;*	*1.20 (0.99;*	*1.22 (1.02;*	*1.24 (1.01;*	*1.33 (1.07;*	*1.33 (1.07;*

	1.41) *0.040*	*1.46)* *0.061*	*1.46)* *0.026*	*1.53)* *0.038*	*1.64)* *0.009*	*1.64)* *0.009*
Clinical History (Activities/Diseases)						
Overhead Sports/ Occupation	*0.43* *(0.09;* *1.98)* *0.278*	---	*0.30* *(0.06;* *1.44)* *0.133*	---	*0.39* *(0.08;* *1.84)* *0.234*	---
Cardiological	*0.11* *(0.01;* *1.16)* *0.066*	*0.12* *(0.01;* *1.64)* *0.113*	*0.15* *(0.01;* *2.15)* *0.093*	*0.15* *(0.01;* *2.15)* *0.164*	*0.17* *(0.02;* *1.67)* *0.128*	---
Endocrine	*0.67* *(0.14;* *3.19)* *0.612*	---	*0.53* *(0.11;* *2.56)* *0.433*	---	*0.80* *(0.17;* *3.77)* *0.778*	---
Internal	*2.55* *(0.20;* *31.86)* *0.469*	---	*2.17* *(0.17;* *27.08)* *0.548*	---	*1.85* *(0.15;* *23.07)* *0.634*	---
Onco-haematological	*1.18* *(0.14;* *9.83)* *0.877*	---	*1.00* *(0.12;* *8.31)* *1.000*	---	*0.85* *(0.10;* *7.04)* *0.877*	---
Neuropsychiatric	*0.50* *(0.08;* *3.32)* *0.473*	---	*0.42* *(0.06;* *2.77)* *0.365*	---	*0.35* *(0.05;* *2.31)* *0.273*	---

Time Course of Pain in Patients with and Without Capsular Pathology

In patients with capsular pathology at T2, such as shoulder subluxation or adhesive capsulitis, the median increase in PNRS score from T0 to T2 was 6 (IQR 5–8) for flexion, 8 (IQR 5.5–9) for abduction, and 8 (IQR 5.5–9) for external rotation. In contrast, in patients without capsular involvement at T2, the median increase in PNRS score was 0 (IQR 0–0) for flexion, 0 (IQR 0–0) for abduction, and 0 (IQR 0–2) for external rotation. Statistical analysis confirmed a significantly greater increase in PNRS scores in patients with capsular pathology compared to those without ($p < 0.001$), highlighting the impact of these conditions on pain progression.

Shoulder Function in Patients with and Without HSP at T2

At T2, patients with HSP showed a greater restriction in pROM compared to those without HSP. Specifically, the proportion of patients with pROM ≤ 90° in flexion/abduction or ≤40° in external rotation was markedly higher in the HSP group: 71% vs. 0% for abduction ($p < 0.001$) and 60% vs. 15% for external rotation ($p = 0.016$). The difference in flexion (38% vs. 7%) was notable but did not reach statistical significance ($p = 0.069$).
Similarly, aROM was significantly more impaired in HSP patients. At T2, the proportion of patients with aROM ≤ 90° in flexion/abduction or ≤40° in external rotation was 92% vs. 20% for flexion ($p < 0.001$), 93% vs. 14% for abduction ($p < 0.001$), and 73% vs. 31% for external rotation ($p = 0.024$). Muscle strength, as measured by the MRC scale, was also lower in patients with HSP. The percentage of patients with MRC < 3 was 69% vs. 13% for flexion ($p = 0.003$), 64% vs. 14% for abduction ($p = 0.007$), and 53% vs. 23% for external rotation ($p = 0.102$), although the latter did not reach statistical significance.
Spasticity, defined as MAS ≥ 2, was more common in HSP patients with 36% vs. 0% for abduction ($p = 0.041$) and 47% vs. 8% for external rotation ($p = 0.038$). The difference in flexion (31% vs. 7%) was observed but not statistically significant ($p = 0.153$).
Finally, upper limb disability, as measured by the DASH questionnaire, was significantly higher in patients with HSP for all three movement axes ($p < 0.001$ for flexion and abduction, $p = 0.003$ for external rotation), highlighting the substantial functional impact of HSP on daily activities.

Ultrasound Features in Patients with and Without HSP at T2

At T2, the prevalence of adhesive capsulitis was significantly higher in patients with HSP than in those without HSP in all three axes of motion: 46% vs. 0% for flexion ($p < 0.005$),

43% vs. 0% for abduction ($p = 0.016$), and 40% vs. 0% for external rotation ($p = 0.01$). Similarly, shoulder subluxation was more common in patients with HSP compared to those without HSP in two axes of motion: 46% vs. 0% for flexion ($p < 0.005$) and 43% vs. 0% for abduction ($p = 0.016$). In external rotation, subluxation was observed in 33% of patients with HSP vs. 8% of patients without HSP, but the difference was not statistically significant ($p = 0.173$). The remaining ultrasound parameters did not show significant differences between the two groups (Table 3).

Table 3 Ultrasound diagnoses at T2 in patients without HSP and in patients with HSP in the three axes of motion. Results are expressed as number of patients (N) and percentage (%). *p*-values for group comparisons refer to Chi-square test, Fisher's exact test, or Mann–Whitney test, depending on the nature of the variables. TTS, patients are categorized into those with TTS ≤ 1 (no or mild tendinopathy) and those with TTS > 1 (moderate or severe tendinopathy). Abbreviations: PNRS: Pain Numeric Rating Scale; HSP: hemiplegic shoulder pain; TTS: total tendon score; SASD: Subacromial-Subdeltoid Bursa; LHBT: Long Head of the Biceps Tendon.

	PNRS Flexion			**PNRS Abduction**			**PNRS External Rotation**		
	No HSP	**HSP**	***p***	**No HSP**	**HSP**	***p***	**No HSP**	**HSP**	***p***
	N = 15 (54%)	**N = 13 (46%)**	**Value**	**N = 14 (50%)**	**N = 14 (50%)**	**Value**	**N = 13 (46%)**	**N = 15 (54%)**	**Value**
	Median (IQR)	**Median (IQR)**		**Median (IQR)**	**Median (IQR)**		**Median (IQR)**	**Median (IQR)**	
	0 (0; 0)	**6 (5; 8)**		**0 (0; 0)**	**8 (6; 9)**		**0 (0; 0)**	**8 (5; 9)**	
TTS > 1	5 (33%)	3 (23%)	0.686	5 (36%)	3 (21%)	0.678	4 (31%)	4 (27%)	1.000
SASD bursitis	0 (0%)	3 (23%)	0.087	0 (0%)	3 (21%)	0.222	0 (0%)	3 (20%)	0.226
LHBT teno-synovitis	0 (0%)	1 (8%)	0.464	0 (0%)	1 (7%)	1.000	0 (0%)	1 (7%)	1.000

Glenohumeral joint effusion	0 (0%)	1 (8%)	0.464	0 (0%)	1 (7%)	1.000	0 (0%)	1 (7%)	1.000
Adhesive capsulitis	0 (0%)	6 (46%)	0.005	0 (0%)	6 (43%)	0.016	0 (0%)	6 (40%)	0.018
Shoulder subluxation	0 (0%)	6 (46%)	0.005	0 (0%)	6 (43%)	0.016	1 (8%)	5 (33%)	0.173

Ultrasound Changes over Time

The median TTS score remained stable over time, with a value of 0 (IQR 0–1.5) at T0, 1 (IQR 0–2) at T1, and 1 (IQR 0–2) at T2, with no significant variation ($p = 0.175$ for T0–T1; $p = 0.157$ for T0–T2).

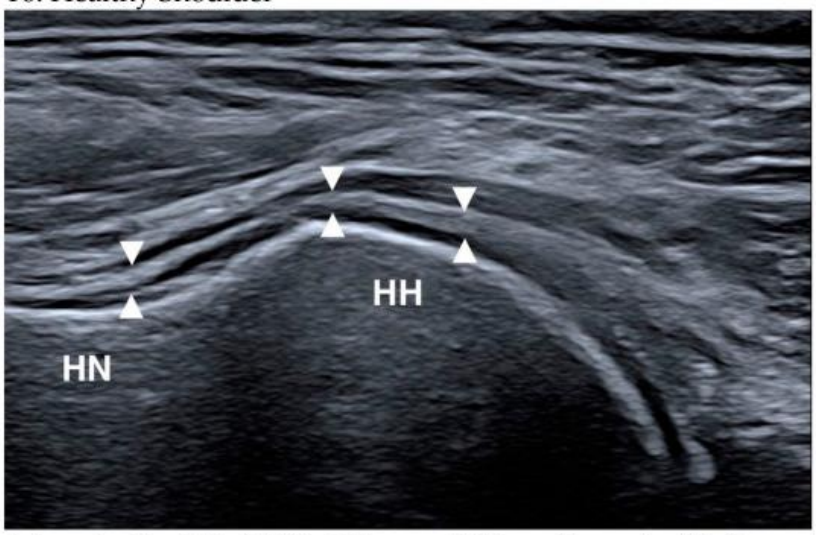
SASD bursitis was seen in 7% of patients at T0, increased to 18% at T1, and then decreased slightly to 11% at T2, with no significant variation ($p = 0.375$ for T0–T1; $p = 1.000$ for T0–T2).

Similarly, LHBT tenosynovitis and glenohumeral effusion were observed in 4% of cases at T0, increased to 7% at T1, and decreased to 4% at T2, with no statistically significant differences over time ($p = 1.000$ for both comparisons).

In contrast, adhesive capsulitis showed a clear upward trend, being absent at T0, appearing in 4% of cases at T1, and increasing to 21% at T2, with a statistically significant change ($p = 1$ for T0–T1; $p = 0.031$ for T0–T2) (Figure 2) illustrates the presence of adhesive capsulitis at T2 versus its absence at T0 in the same patient).

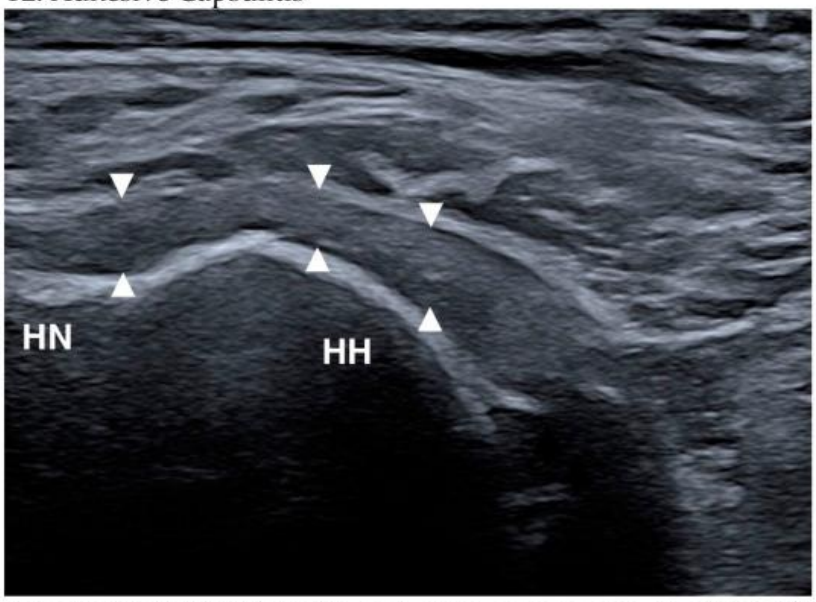
Figure 2. Comparison of a healthy shoulder (T0) and a shoulder affected by adhesive capsulitis (T2) in the same patient. Adhesive capsulitis is characterized by a noticeable thickening of the joint capsule, clearly visible in the T2 scan.

T0: Healthy Shoulder



A longitudinal 12–3 MHz US scan at T0, performed with the probe oriented parallel to the humerus in the axillary pouch, visualizes the inferior capsule (arrowheads) overlying the humeral head (HH) and folding over the humeral neck (HN).

T2: Adhesive Capsulitis



Longitudinal 12–3 MHz US scan at T2, visualizes a significant thickening of the inferior capsule (arrowheads).

A similar trend was observed for shoulder subluxation, which affected 4% of patients at T0, increased to 11% at T1, and further increased to 21% at T2. This progression approached but did not reach statistical significance ($p = 0.500$ for T0–T1; $p = 0.063$ for T0–T2), suggesting a potential role in the evolving pathophysiology of HSP

9.2 Discussion

This study aimed to identify the causes of HSP through a longitudinal design incorporating early ultrasound assessment. The prevalence of HSP was 11% within 72 h of stroke (T0), increasing to 32% at one month (T1) and 57% at three months (T2). The likelihood of developing HSP was strongly associated with stroke severity as measured by the NIHSS in the acute phase. Consistently, patients with HSP at T2 had a more severe clinical profile than those without HSP.

From an ultrasound perspective, among the various soft tissue changes analyzed, only capsular pathology—specifically adhesive capsulitis and glenohumeral subluxation—was significantly more common in patients with HSP three months after stroke. Notably, adhesive capsulitis was the only change that showed a progressive increase from T0 to T2. Shoulder subluxation followed a similar trend, but did not reach statistical significance. In contrast, all other ultrasound findings remained stable over time and did not correlate with the temporal progression of pain.

Ultrasound Changes over Time

The prevalence of HSP reported in the literature varies widely, ranging from 5% to 84% (Kalichman et al 2011). This wide variability is due to several methodological factors, including the timing of assessment relative to the cerebrovascular event, sample size and characteristics, patient inclusion criteria, and methods used to assess pain. For example, studies with more severely affected populations tend to report higher prevalence rates.

Despite this variability, the literature consistently shows that HSP is rare in the first few days after stroke, but increases progressively over the following weeks, peaking around the fourth month (Adey-Wakeling et al 2015). Our data confirm this trend: the prevalence of HSP at T0 (within 72 h of stroke onset) was found to be 11%, a value consistent with the literature. In fact, the only prospective study reporting early prevalence data (meaning 8.7 days post-stroke) reported a prevalence of 10% (Adey-Wakeling et al 2015).

An interesting aspect highlighted by the study of Adey-Wakeling et al. is that patients who develop HSP in the early phase are not necessarily the same individuals who later experience persistent pain. Our data support this observation: two out of three patients who reported pain at T0 showed a reduction in pain at T2.

At T1 (one-month post-stroke), the prevalence of HSP increased to 32%, a value similar to that reported by Dromerick et al. (Dromerick et al., 2007), who reported a prevalence of 37% in the same period. At T2 (three months post-stroke), the prevalence increased further to 57%, which is like the 55% prevalence reported in the largest epidemiologic study of HSP conducted in Turkey on 1000 patients (Demirci et al., 2007). This value is also consistent with the mean prevalence of 54% calculated in a systematic review of 16 studies (Turner-Stokes et al., 2002)

HSP in the Context of the General Clinical Picture

Several studies have shown that the severity of sensorimotor deficits is a positive predictor of HSP (Gamble et al., 2002; Ratnasabapathy et al., 2003; Pong et al., 2012; Anwer et al., 2020; Li et al., 2023; Kim et al., 2014). It has also been shown that patients with severe hemiparesis tend to have greater soft tissue impairment in the shoulder compared to those with less pronounced strength deficits (Pong et al., 2012; Idowu et al., 2018).

Our study also confirmed the predictive value of the severity of initial neurological impairment, showing that higher NIHSS scores were predictive of HSP. At T2, three months after stroke, patients with HSP remained more impaired than those without HSP, with greater muscle weakness, increased spasticity, and greater reduction in both active and passive range of motion. They also had higher levels of upper limb disability as measured by the DASH scale.

As highlighted in several previous papers, the extent of the neurological deficit plays a critical role in the pathogenesis of pain, both indirectly and directly. Indirectly, severe neurological deficits promote soft tissue changes that contribute to pain. For example, muscle flaccidity—more pronounced in severe stroke—can lead to glenohumeral subluxation (Kalichman et al., 2011; Li et al., 2023), while paralysis-induced immobility can promote adhesive capsulitis (Kalichman et al., 2011). Directly, spasticity of the shoulder muscles can cause pain by exerting excessive traction on the periosteal attachments (Turner-Strokes et al., 2002). However, we must also recognize the bidirectional relationship between neurological damage and shoulder pain: pain itself can exacerbate spasticity, further limit joint range of motion, and lead clinicians to underestimate a patient's true

strength due to protective disuse (antalgic sparing) (Trompetto et al., 2014; Trompetto et al., 2023).

The Relationship Between HSP and Ultrasound Abnormalities

Our ultrasound evaluation focused on the major shoulder pathologies that have been associated with HSP in previous studies (Kalichman et al., 2011; Pong et al., 2012; Doğun et al., 2014; Kim et al., 2014; Tao et al., 2015; Korkmaz et al., 2020; Li et al., 2023).

The present findings indicate that only capsular pathologies—specifically, adhesive capsulitis and glenohumeral subluxation—were significantly more prevalent in patients with HSP compared to those without HSP at three months post-stroke (T2). In contrast, all other ultrasound-detected abnormalities showed no significant differences between the two groups. Longitudinal analysis further revealed a statistically significant worsening of adhesive capsulitis from T0 to T2, while shoulder subluxation followed a similar trend, approaching but not reaching statistical significance. Conversely, no significant changes were observed in other ultrasound-detected soft tissue pathologies. Finally, in patients with capsular pathologies, pain progression was more pronounced than in those without such conditions.

Overall, our results suggest that, within the first three months post-stroke, adhesive capsulitis and glenohumeral subluxation play a pivotal role in the pathogenesis of HSP. These findings align with previous studies on the time course of adhesive capsulitis in stroke patients, where the painful onset phase typically occurs around three months post-stroke (Bruckner et al., 1981). Similarly, glenohumeral subluxation tends to develop in the initial months after stroke. Although the relationship between glenohumeral subluxation and stroke remains debated, multiple studies have highlighted its potential contribution to HSP (Kalichman et al., 2011). Consistent with our findings, Aras et al. reported that, at two months post-stroke, 50% of patients with HSP exhibited subluxation, compared to only 16% of those without HSP, underscoring the importance of proper shoulder positioning in preventing this condition (Aras et al., 2004). Likewise, Kim et al. observed an association between glenohumeral subluxation and HSP within the first three months post-stroke (Kim et al., 2014).

The initial three months post-stroke represent a critical window, as they coincide with heightened neuroplasticity and the greatest potential for functional recovery (Trompetto et al., 2014). Intensive rehabilitation efforts are typically concentrated within this period to maximize spontaneous recovery (Trompetto et al., 2023). However, the presence of

HSP can significantly hinder rehabilitation by restricting movement and exacerbating discomfort, ultimately limiting functional progress. Identifying the primary contributors to HSP during this critical phase is therefore essential for optimizing rehabilitation strategies.

From a clinical standpoint, it is crucial to emphasize that shoulder subluxation can be effectively managed using shoulder braces (Nadler et al., 2017). In contrast, adhesive capsulitis requires a multifaceted approach, with four of the most commonly used treatments being suprascapular nerve block, intra-articular corticosteroid injection, hydrodilatation, and physiotherapy incorporating mobilization techniques and therapeutic exercises (Hill et al., 2024). Early recognition and targeted intervention for these conditions may be instrumental in mitigating pain-related functional limitations and enhancing post-stroke rehabilitation outcomes.

9.3 Study Limitations

Although the number of participants aligns with the sample size calculation, this study should be considered preliminary and requires confirmation in a larger population. A larger sample size would enhance statistical power and allow for a more precise analysis of the predictive factors associated with the onset and progression of HSP.

Another limitation concerns the follow-up duration, currently restricted to three months. Extending the follow-up to at least six months would provide a more comprehensive understanding of the evolution of HSP, allowing for the assessment of potential late-onset symptoms and structural changes in the shoulder. A longer observation period would also help distinguish between transient and persistent pain, offering further insights into the factors contributing to chronicity.

Additionally, as a longitudinal observational study, this research is subject to inherent methodological limitations. Selection bias may be present, as patient recruitment was conducted in a single center with specific inclusion criteria, which could limit the generalizability of the findings. Observer bias is another potential concern, given that clinical and ultrasound assessments rely on evaluators' expertise. To minimize this, all assessments were performed by experienced clinicians using standardized protocols. Moreover, limited control over variables is an intrinsic limitation of non-experimental designs, as potential confounding factors could influence the outcomes. Future research should aim to mitigate these constraints through multicenter recruitment, blinding procedures, and a more comprehensive control of confounders.

Finally, the study was conducted in a single-center setting, which may further restrict its external validity. Including participants from multiple centers would improve the generalizability of the findings and allow for comparisons across different clinical settings.
Despite these limitations, this study provides important preliminary evidence on the clinical and ultrasound characteristics of HSP in the early post-stroke phase. Future studies with a larger sample size, extended follow-up, and refined methodology will be crucial to optimizing prevention and treatment strategies for HSP.

9.4 Conclusions

Our findings point to the involvement of the joint capsule as a key factor in the pathogenesis of HSP in the first three months after stroke, downplaying the contributions of bursitis and tendinopathies. These findings, which require confirmation in a larger sample, may have important practical implications, as both adhesive capsulitis and glenohumeral subluxation can be prevented to some extent and, importantly, treated early with conservative approaches.

CHAPTER 10 — STUDY 2: TRAJECTORY AND PREDICTORS OF HEMIPLEGIC SHOULDER PAIN UP TO 12 MONTHS (T0–T4)

10.1 Main Results

Temporal trajectory of HSP

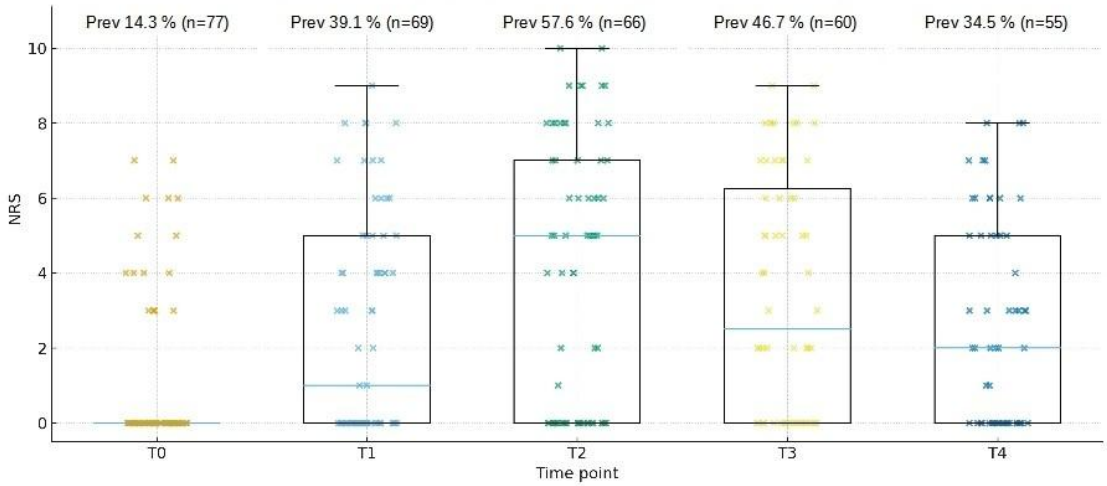
At baseline (T0), HSP was minimal, with a mean NRS of 0.95 and a median value of 0.00.

Compared with baseline, pain increased significantly at T1 (mean 2.54, median 1) and further rose at T2, where the highest values were observed (mean 3.98, median 5). Subsequently, pain levels decreased at T3 (mean 3.40, median 2.5) and showed a further reduction at T4 (mean 2.73, median 2). Overall, the Friedman test confirmed a significant change in pain over time ($\chi^2 = 29.4$, $p < 0.001$). Post-hoc Wilcoxon tests with Holm correction showed that pain levels at all follow-up time points were significantly higher than baseline (all adjusted $p < 0.001$).

At T0, 11 patients presented with an NRS score ≥ 4 (prevalence 14.3%). The number of newly incident patients with an NRS score ≥ 4 since the previous time point was 17 at T1, 13 at T2, 5 at T3, and 1 at T4. Conversely, the number of patients whose NRS score passed from ≥ 4 to less than 4 was 0 at T1, 2 at T2, 11 at T3, and 6 at T4. This resulted in a steady rise in HSP prevalence at T1 (39.1%) and T2 (57.6%), with a subsequent progressive decline in prevalence at T3 (46.7%) and T4 (34.5%).

The temporal trajectory of pain intensity is shown in Figure 1.

Figure 1. Distribution of NRS scores over time with HSP prevalence annotations.

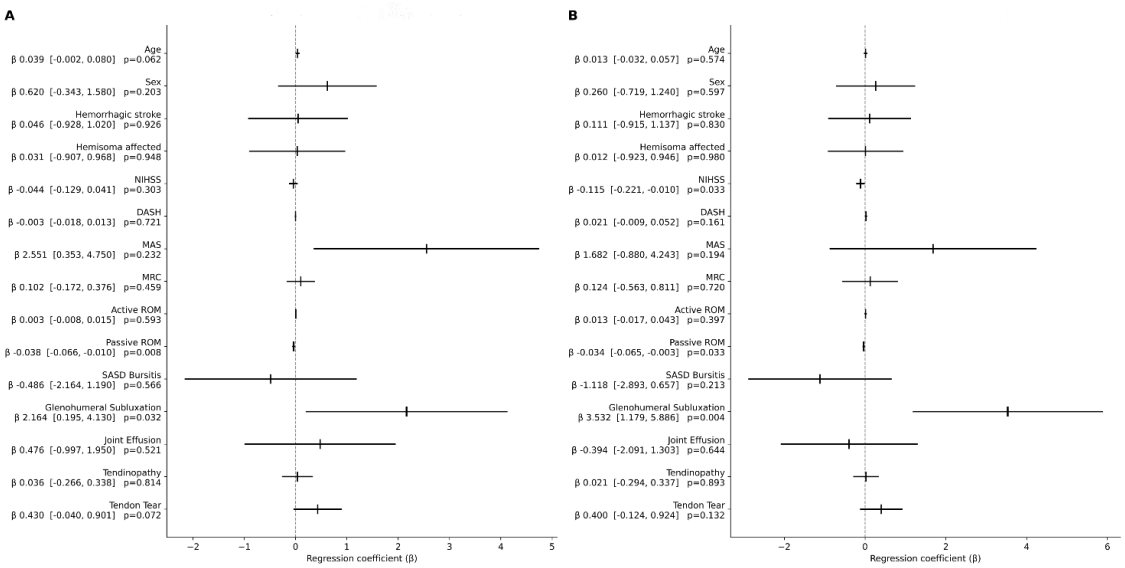


Boxplots summarize NRS at each time point (T0–T4), with individual observations overlaid. Labels above boxes report HSP prevalence (NRS ≥ 4) and the number of valid observations.

Longitudinal predictors of hemiplegic shoulder pain across timepoints

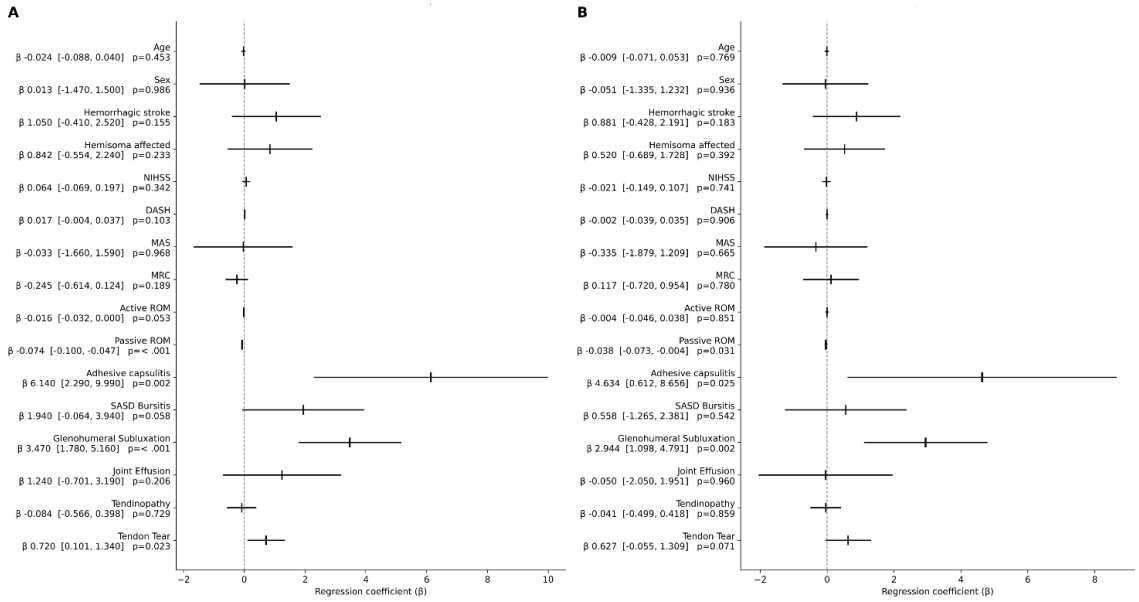
Timepoint T0: in the univariable analysis, HSP was associated with reduced passive ROM and with glenohumeral subluxation. In the multivariable model, reduced passive ROM remained independently associated with pain, with the regression coefficient indicating that each 1% loss of passive ROM corresponded to an average increase of 0.034 points on the NRS pain scale. Glenohumeral subluxation also remained independently associated with higher pain intensity, corresponding to an adjusted increase of 3.53 points on the NRS scale. Baseline neurological severity (NIHSS) emerged as an additional independent predictor of pain after adjustment, with higher NIHSS scores being associated with lower pain intensity (β = −0.1152 per NIHSS point), while no significant association was observed in the univariable analysis (Figure 2).

Figure 2. Forest plot graph of predictive factors for shoulder pain at baseline (T0). Panel A shows the results of the univariate regression analyses and Panel B shows the results of the multivariate regression model. Vertical lines represent regression coefficients (β), horizontal lines indicate 95% confidence intervals, and the vertical dotted line indicates the null effect (β = 0).



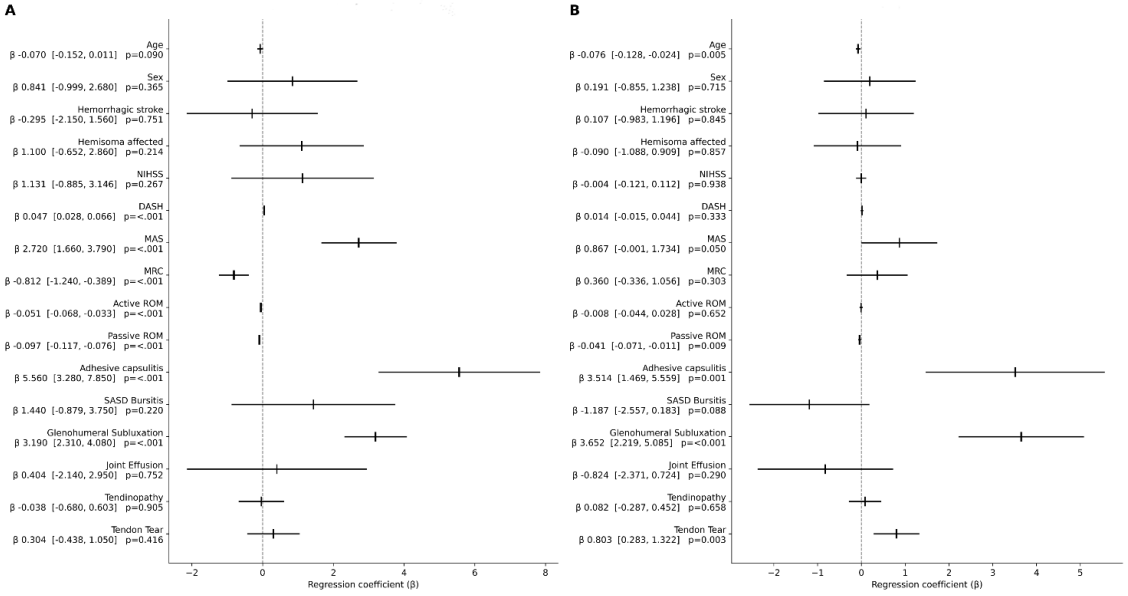
Timepoint T1: in the univariable analysis, HSP was associated with reduced passive ROM, glenohumeral subluxation, adhesive capsulitis, and tendon tears. In the multivariable model, reduced passive ROM remained independently associated with pain, with the regression coefficient indicating that each 1% loss of passive ROM corresponded to an average increase of 0.038 points on the NRS pain scale. Glenohumeral subluxation also remained independently associated with higher pain intensity, corresponding to an adjusted increase of 2.94 points on the NRS scale. Adhesive capsulitis likewise remained independently associated with pain, with an adjusted increase of 4.63 points on the NRS pain scale (Figure 3).

Figure 3. Forest plot graph of predictive factors for shoulder pain at T1. Panel A shows the results of the univariate regression analyses and Panel B shows the results of the multivariate regression model. Vertical lines represent regression coefficients (β), horizontal lines indicate 95% confidence intervals, and the vertical dotted line indicates the null effect (β = 0).



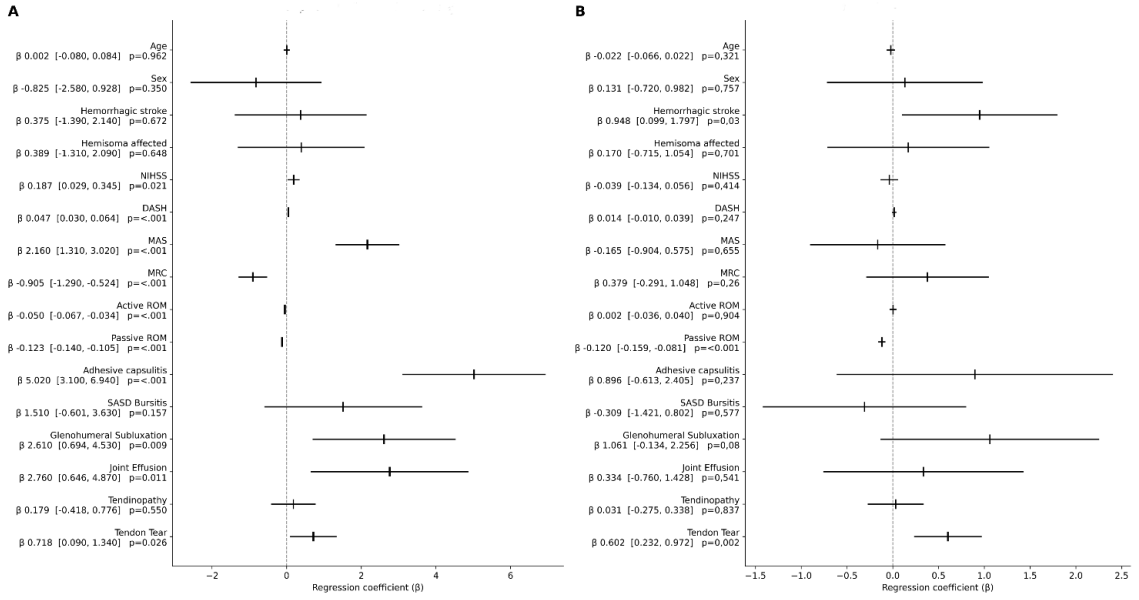
Timepoint T2: in the univariable analysis, HSP was associated with reduced passive and active ROM, increased spasticity, decreased muscle strength, adhesive capsulitis, glenohumeral subluxation, and higher disability scores. In the multivariable model, reduced passive ROM remained independently associated with pain, with the regression coefficient indicating that each 1% loss of passive ROM corresponded to an average increase of 0.041 points on the NRS pain scale. Glenohumeral subluxation also remained independently associated with higher pain intensity, corresponding to an adjusted increase of 3.65 points on the NRS scale, and adhesive capsulitis likewise remained independently associated with pain, with an adjusted increase of 3.51 points on the NRS pain scale. Tendon tears emerged as an additional independent predictor of pain after adjustment, with each additional tendon tear corresponding to an average increase of 0.80 points on the NRS pain scale, while no significant association was observed in the univariable analysis. Younger age also emerged as an independent predictor of higher pain intensity after adjustment (Figure 4).

Figure 4. Forest plot graph of predictive factors for shoulder pain at T2. Panel A shows the results of the univariate regression analyses and Panel B shows the results of the multivariate regression model. Vertical lines represent regression coefficients (β), horizontal lines indicate 95% confidence intervals, and the vertical dotted line indicates the null effect (β = 0).



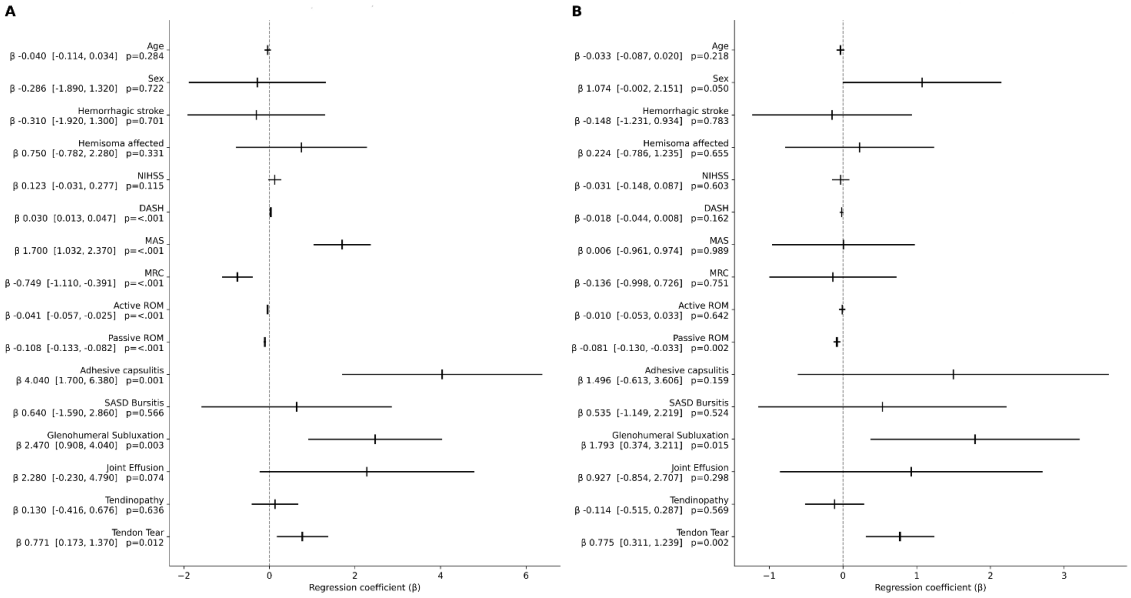
Timepoint T3: In the univariable analysis, HSP was associated with higher disability scores, increased spasticity, reduced passive and active ROM, decreased muscle strength, adhesive capsulitis, glenohumeral subluxation, intra-articular effusion, tendon tears, and greater neurological severity. In the multivariable model, reduced passive ROM remained independently associated with pain, with the regression coefficient indicating that each 1% loss of passive ROM corresponded to an average increase of 0.12 points on the NRS pain scale. The number of tendons affected by tears also remained independently associated with pain, with each additional tendon tear corresponding to an average increase of 0.60 points on the NRS pain scale. Hemorrhagic stroke emerged as an additional independent predictor of pain after adjustment, corresponding to an adjusted increase of 0.95 points on the NRS pain scale (Figure 5).

Figure 5. Forest plot graph of predictive factors for shoulder pain at T3. Panel A shows the results of the univariate regression analyses and Panel B shows the results of the multivariate regression model. Vertical lines represent regression coefficients (β), horizontal lines indicate 95% confidence intervals, and the vertical dotted line indicates the null effect (β = 0).



Timepoint T4: in the univariable analysis, HSP was associated with reduced passive and active ROM, increased spasticity, decreased muscle strength, adhesive capsulitis, glenohumeral subluxation, the presence of tendon tears, and higher disability scores. In the multivariable model, reduced passive ROM remained independently associated with pain, with the regression coefficient indicating that each 1% loss of passive ROM corresponded to an average increase of 0.081 points on the NRS pain scale. Glenohumeral subluxation also remained independently associated with higher pain intensity, corresponding to an adjusted increase of 1.79 points on the NRS scale. The number of tendons affected by tears likewise remained independently associated with pain, with each additional tendon tear corresponding to an average increase of 0.78 points on the NRS pain scale (Figure 6).

Figure 6. Forest plot graph of predictive factors for shoulder pain at T4. Panel A shows the results of the univariate regression analyses and Panel B shows the results of the multivariate regression model. Vertical lines represent regression coefficients (β), horizontal lines indicate 95% confidence intervals, and the vertical dotted line indicates the null effect (β = 0).



10.2 Discussion

Temporal evolution of hemiplegic shoulder pain

In this cohort, evaluated longitudinally from the first 72 hours after stroke (T0), HSP exhibited a characteristic temporal trajectory, with a sharp increase during the first three months (T2), followed by a progressive decrease over time.

This pattern is highly consistent with previous longitudinal studies and meta-analyses, which similarly report an early onset, a peak around the third-fourth month, and a subsequent decrease over time (Lindgren et al., 2007; Adey-Wakeling et al., 2016; Holmes, 2020; Wang et al., 2021). The later decline in prevalence does not necessarily reflect spontaneous remission but may instead result from the cumulative effect of standard rehabilitation and, in selected cases, targeted interventions (Ahmad et al., 2011; De Sire et al., 2021). Overall, these findings confirm that HSP is an early and dynamic complication of stroke, with its key determinants largely consolidating within the first trimester.

Interpretation of passive ROM across timepoints

Among all clinical and ultrasound variables, passive ROM was the only factor consistently associated with shoulder pain across all timepoints (T0–T4). This finding highlights the central role of passive mobility in the pain experience after stroke, while also requiring careful interpretation of its underlying mechanisms.

Because passive ROM was expressed on a 0–100% scale, the regression coefficient reflects the effect of minimal changes in mobility; when applied to clinically realistic ROM losses, the associated increase in pain becomes substantial. Thus, despite the small per-unit effect size, reduced passive mobility consistently translated into meaningful pain amplification throughout the post-stroke course.

In principle, reduced passive ROM may reflect muscle contracture or capsular restriction, conditions known to generate pain when shortened tissues are stretched. Such structural mechanisms could plausibly contribute to pain from T1 onward, when soft-tissue alterations have had sufficient time to develop. However, reduced passive ROM was already associated with pain at T0, within the first 72 hours after stroke, when true muscle shortening or capsular fibrosis is highly unlikely.

This early association strongly suggests a pain-dependent measurement effect; whereby passive mobilization is prematurely interrupted because the examiner must stop the movement when discomfort arises. Importantly, this pain-related mechanism may also persist at later timepoints. Consequently, even beyond the acute phase, reduced passive

ROM cannot be reliably interpreted as a purely causal determinant of pain, as it may still, at least in part, represent a consequence rather than a cause of shoulder pain.

T0 – Mechanical pain

In the acute phase, within the first 72 hours after stroke, HSP was already independently associated with glenohumeral subluxation and neurological severity, as measured by the NIHSS. Acute stroke immediately produces paresis and muscle hypotonia, which represent the negative signs of the upper motor neuron syndrome and precede the later development of positive phenomena such as spasticity, co-contractions, and muscle spasms (Trompetto et al., 2014). This early flaccid paresis markedly reduces muscular support around the shoulder, promoting glenohumeral subluxation (Stolzenberg et al., 2012; Lakra et al., 2023; Tan et al., 2024). The resulting traction and stretching of periarticular soft tissues provide a plausible explanation for the pain observed, in line with previous observations (Paci et al., 2007; Suethanapornkul et al., 2008).

The independent association between pain and stroke severity further supports this interpretation: more severe strokes typically produce more pronounced paresis and hypotonia, increasing susceptibility to glenohumeral subluxation (Stolzenberg et al., 2012).

Although neurological severity was not associated with pain in the univariable analysis, it emerged as an independent predictor after multivariable adjustment, suggesting that its effect is partially masked by biomechanical factors in unadjusted analyses. Importantly, the persistence of an independent association between NIHSS and pain after adjustment indicates that stroke severity contributes to pain beyond mechanical instability alone. This additional contribution may reflect severity-related sensory impairment and reduced protective feedback (Gamble et al., 2002).

T1 – Mechanical and capsular pain

At one month, HSP remains associated with glenohumeral subluxation, and adhesive capsulitis emerges as an additional contributor. At this stage, reduced joint use and prolonged immobilization play a central role in driving capsular involvement. Limited shoulder movement promotes synovial inflammation, collagen deposition, and progressive capsular stiffening, creating the biological substrate for capsular pain (Pompa et al., 2011; Najenson et al., 2011). Ultrasonographic studies further support the link between reduced joint use, altered biomechanics, and early capsular restriction (Lin et al., 2023).

In summary, T1 reflects the coexistence of mechanical pain due to glenohumeral instability and immobility-driven capsular changes.

T2 – Convergence of mechanical, capsular, and tendon-related pain

At three months, HSP reached its peak, consistent with most longitudinal studies (Lindgren et al., 2007; Cotellessa et al., 2024). At this stage, glenohumeral subluxation and adhesive capsulitis remained independently associated with pain, indicating the persistence of both mechanical instability and capsular inflammation as major contributors, in line with previous observations (Shah et al., 2008; Zhu et al., 2013). Furthermore, tendon tears also emerged as independent predictors.

The temporal emergence of tendon-related pain is physiologically plausible. During the first three months after stroke, patients typically undergo substantial motor recovery and progressively increase their level of activity during intensive rehabilitation. In individuals with pre-existing degenerative changes and/or impaired scapulohumeral biomechanics, this sharp rise in activity may increase mechanical load on the rotator cuff and the long head of the bicep's tendon, thereby converting subclinical tendinopathies into symptomatic tears or unmasking previously asymptomatic lesions. This interpretation is supported by several ultrasonographic and MRI studies showing that tendinopathies and tendon tears are frequently observed in patients with shoulder pain during the subacute and chronic phases (Shah et al., 2008; Fatma Zaiton et al., 2011; Lin et al., 2023).

The fact that tendon tears became significant only in the multivariable model suggests a suppression effect. At this stage, tendon pathology strongly covariates with passive ROM limitation and adhesive capsulitis, both of which are closely linked to pain. Once these factors are accounted for, the independent contribution of tendon tears to pain becomes apparent, consistent with the increased mechanical stress imposed on vulnerable tendons by capsular stiffness and painful motion restriction.

Spasticity was associated with shoulder pain in the univariable analysis. However, this association should be interpreted with caution. Previous evidence indicates that spasticity per se is not inherently painful; rather, pain emerges when increased muscle tone is accompanied by muscle shortening and reduced extensibility, reflecting the development of early contracture (Trompetto et al., 2023). This conceptual framework may help explain the loss of significance of spasticity in the multivariable model. At T2, passive ROM likely reflects, at least in part, the presence of soft-tissue shortening and early contracture, as discussed above. Once passive ROM is included in the model, it may capture the structural component responsible for pain, thereby absorbing the effect attributed to spasticity in unadjusted analyses. As a result, spasticity may no longer contribute independently to pain, supporting the interpretation that its role at this stage is largely indirect and mediated

by contracture-related biomechanical changes rather than representing a primary nociceptive mechanism.

Younger age was independently associated with higher pain intensity, despite not being associated with pain in the univariable analysis. This finding is consistent with previous reports (Jönsson et al., 2006) and may reflect greater perceptual sensitivity and more responsive nociceptive afferents in younger individuals. In the presence of structural or biomechanical abnormalities, these factors could contribute to an amplification of pain perception, making age-related differences more apparent only after adjustment for concurrent mechanical and structural drivers.

Overall, T2 represents the time point at which mechanical instability and capsular pathology converge with overt tendon involvement, producing the most complex and symptomatic configuration of HSP along its temporal trajectory.

T3 – Tendon-related pain

At six months, the HSP profile shifts toward a predominantly tendon-driven pattern. In the multivariable model, tendon tears emerged as the main independent determinant of pain, while adhesive capsulitis and glenohumeral subluxation were no longer associated. The disappearance of the association with adhesive capsulitis likely reflects treatment effects rather than spontaneous resolution. In this cohort, most cases identified at three months underwent ultrasound-guided hydrodistension, a procedure associated with improvements in pain and shoulder ROM (Pandey et al., 2021; Dakkak et al., 2024).

Similarly, the lack of association between glenohumeral subluxation and pain should be interpreted considering targeted management strategies, including rehabilitation, shoulder orthoses, and local injection therapies. Supportive devices and injections have been shown to reduce subluxation severity and shoulder pain in selected patients (Ada et al., 2005; Kumar et al., 2019; Snels et al., 2002; Shah et al., 2019).

Hemorrhagic stroke also showed an independent association at T3, a finding restricted to this stage and without a clear mechanistic explanation, warranting cautious interpretation.

Overall, T3 represents the consolidation of a tendon-related pain phenotype.

T4 – Tendon-driven residual pain and the late reappearance of subluxation

In the multivariable analysis at 12 months, tendon tears again emerged as a key independent HSP predictor, consistent with the pattern already observed at T2 and T3. This reinforces the interpretation that tendon pathology represents the most stable and persistent driver of pain in the chronic phase (Shah et al., 2008; Lin et al., 2023).

Glenohumeral subluxation also reappeared as an independent predictor at T4. Its late recurrence, however, cannot be conclusively interpreted based on the present data.
The borderline association with female sex aligns with our earlier findings in upper-limb spasticity, where women reported higher pain intensity (Trompetto et al., 2022).
Overall, the one-year profile indicates that tendon pathology becomes the predominant determinant of residual shoulder pain intensity.

Integrated Perspective and Preventive Approach

HSP develops predominantly within the first three months after stroke, representing a critical window during which newest cases arise. Across this interval, our data reveal a clear temporal sequence of mechanisms: early mechanical pain related to glenohumeral subluxation, capsular pain associated with the onset of adhesive capsulitis, and subsequent tendon-related pain. This temporal profile supports a targeted and phase-specific approach to prevention.
In the acute phase, when the patient is admitted to the stroke unit, prevention should focus on minimizing mechanical traction on the paretic shoulder through careful handling and appropriate support to limit humeral head descent. At the same time, regular passive mobilization should be initiated to reduce the risk of capsular stiffening. These measures should continue into the subacute phase, when patients are transferred to intensive rehabilitation, where systematic shoulder ultrasound becomes essential for detecting early capsular involvement and pre-existing or emerging tendon abnormalities. If capsulitis develops within the first three months, physiotherapeutic mobilization may be complemented by capsular hydrodistension. Because tendon tears correlate with pain from the third month onward and are typically preceded by tendinopathy, early identification and treatment of tendon pathology, potentially including focused shockwave therapy, may help prevent progression to rupture. Moreover, in patients with tendon abnormalities, therapeutic exercise should be carefully supervised to preserve physiological scapulohumeral rhythm and avoid overload.
Compared with current guidelines, which focus mainly on safe handling, correct positioning, and gentle passive mobilization (Bowen et al., 2016; Heran et al., 2022), this framework adds a mechanism-based and temporally structured perspective. By aligning preventive actions with the sequential emergence of mechanical, capsular, and tendon-

related mechanisms, and by integrating early ultrasound screening and targeted interventions, it offers a more proactive and pathophysiologically informed strategy for reducing the onset and chronicity of post-stroke shoulder pain.

10.3 Limitations

This study has several limitations. Its observational design limits causal inference, and the sample size, particularly at later timepoints, may have reduced statistical power for detecting smaller effects. Although ultrasound assessments were standardized, a degree of operator dependency cannot be completely excluded. Finally, as this was a real world observational study, patients received usual care and therapeutic interventions according to clinical indications. While this approach enhances external validity, it also implies that rehabilitative and medical treatments may have influenced the incidence and intensity of shoulder pain over time, and their effects could not be systematically controlled.

10.4 Conclusions

HSP follows a distinct temporal evolution in which early mechanical instability and capsular changes progressively give way to tendon involvement, with tendon tears emerging as the most persistent correlate of pain in the chronic phase. By integrating longitudinal clinical and ultrasound assessments from the acute to the chronic stage, this study provides novel evidence that phase-specific mechanisms underlie HSP and that preventive and therapeutic approaches should be tailored accordingly over time.

CHAPTER 11 — GENERAL DISCUSSION, INTEGRATED MODEL, AND CONCLUSIONS

11.1 Integrated Synthesis of Findings from Study 1 and Study 2

The present doctoral thesis was designed as a longitudinal research program aimed at elucidating the mechanisms underlying HSP across the continuum of stroke recovery. By integrating early and extended follow-up data, the two studies provide complementary insights into the temporal evolution**,** structural correlates, and clinical relevance of shoulder pathology after stroke.

Study 1 demonstrated that shoulder pain may already be present in the acute phase (≤72 hours) after stroke and that, during the first three months, pain was associated primarily with glenohumeral subluxation and adhesive capsulitis, while other ultrasound findings were not significantly related to pain. These results challenged the prevailing assumption that early HSP is mainly driven by tendinous pathology and instead highlighted the role of mechanical instability and early capsular involvement.

Study 2 extended these observations by following patients up to 12 months post-stroke, allowing characterization of the long-term trajectory of HSP and identification of clinical and ultrasound predictors at different stages. The extended follow-up confirmed that early findings retained prognostic relevance and that the relationship between pain and ultrasound abnormalities evolved over time, reinforcing the concept that HSP is a dynamic and multifactorial condition, rather than a static post-stroke complication.

11.2 Neuroscientific Interpretation: Brain–Biomechanics–Structure–Pain

From a neuroscientific perspective, the findings of this thesis support a multi-level model linking central nervous system injury to peripheral musculoskeletal pathology and pain perception.

Stroke-induced damage to motor and sensory networks results in paresis, altered muscle activation, loss of anticipatory postural control, and impaired proprioception, particularly affecting proximal joints such as the shoulder (Turner-Stokes & Jackson, 2002). These central deficits lead to abnormal loading conditions, reduced dynamic stabilization, and altered afferent feedback from the shoulder complex.

The shoulder, as a joint highly dependent on neuromuscular control, becomes particularly vulnerable to micro-instability and capsular stress in the absence of adequate muscle coordination. This vulnerability is already detectable in the acute phase, as demonstrated by early associations between pain, subluxation, and capsular involvement.

Over time, persistent abnormal biomechanics and reduced use of the paretic limb may promote capsular fibrosis, synovial inflammation, and secondary tendon overload, while central mechanisms—such as maladaptive plasticity, altered pain modulation, and nociplastic processes—may further amplify pain perception (Klit et al., 2009; Woolf, 2011).

Thus, HSP emerges as the product of an evolving interaction between central neural impairment, peripheral biomechanical alterations, and structural musculoskeletal changes, rather than as a purely local shoulder disorder.

11.3 Temporal Phenotypes of HSP and Their Implications

A key contribution of this thesis is the conceptualization of temporal phenotypes of HSP. Rather than categorizing patients solely based on the presence or absence of pain, the integrated findings suggest that different mechanisms may predominate at different stages of recovery.

In the early phase, pain appears closely linked to loss of dynamic stabilization and inferior glenohumeral alignment, emphasizing the role of mechanical factors. During the subacute phase, capsular involvement, becomes increasingly relevant, consistent with progressive stiffness, pain and loss of passive movements. In later stages, tendinous pathology and mixed mechanisms, including central pain modulation, may contribute to persistent symptoms.

Importantly, these phenotypes are not mutually exclusive and may overlap within the same individual. However, recognizing their temporal dimension has important implications for diagnostic reasoning, monitoring, and intervention timing.

This phenotype-oriented perspective extends earlier clinical models (Turner-Stokes & Jackson, 2002) by grounding them in prospective clinical and ultrasound data.

11.4 Implications for Clinical Practice

Prevention in the Stroke Unit

The demonstration that shoulder pain and relevant ultrasound abnormalities can be detected within the first 72 hours after stroke underscores the importance of early preventive

strategies in the stroke unit. Proper positioning, handling, early mobilization, and awareness of shoulder vulnerability should be prioritized even before pain becomes clinically evident.

Timing and Role of Ultrasound

These findings support the use of early musculoskeletal ultrasound as a complementary tool to clinical assessment. Early ultrasound may help identify patients at higher risk of developing HSP by detecting subluxation or capsular changes before overt symptoms appear.

Repeated ultrasound assessment during rehabilitation allows monitoring of structural evolution and may guide adjustments in therapeutic strategies.

11.5 General Limitations of the Thesis

Several limitations of this doctoral research should be acknowledged and critically discussed, as they also help to contextualize the scope and interpretation of the findings.

First, although the research program was longitudinal and methodologically rigorous, it was conducted in a single care centre, which may limit the generalizability of the results to other healthcare systems, rehabilitation settings, or patient populations. Stroke care pathways, rehabilitation intensity, and handling practices may vary across centres and countries, potentially influencing the development and trajectory of HSP.

Second, while musculoskeletal ultrasound represents a major strength of this thesis, it remains an operator-dependent technique. Despite the use of standardized scanning protocols, predefined diagnostic criteria, and experienced examiners, some degree of subjectivity cannot be eliminated. This limitation is inherent to ultrasound-based research and underscores the importance of training, consensus procedures, and methodological transparency in future multicentre studies.

Third, the observational nature of both studies precludes definitive causal inference. Although the longitudinal design strengthens temporal interpretation, associations between clinical or ultrasound findings and pain cannot be interpreted as direct causal relationships. Interventional studies will be required to determine whether modifying specific mechanisms (e.g., subluxation prevention or early capsular mobilization) can effectively reduce the incidence or severity of HSP.

Fourth, central pain mechanisms—including neuropathic and nociplastic components—were inferred based on clinical presentation and existing literature but were not directly measured using neurophysiological, neuroimaging, or quantitative sensory testing meth-

ods. As a result, the contribution of central mechanisms may be underestimated or insufficiently characterized, particularly in patients with persistent pain despite limited structural abnormalities.

Finally, although functional scales were included, the thesis did not incorporate objective kinematic or biomechanical measurements, which could have provided additional insight into movement strategies, compensatory patterns, and load distribution at the shoulder joint.

Despite these limitations, the thesis is strengthened by its early initiation of assessment**,** repeated within-subject measurements, and integration of clinical and imaging data, which together address major gaps identified in previous literature.

11.6 Conclusions: Key Messages

This doctoral thesis demonstrates that HSP should be understood not as a static or inevitable complication of stroke, but as a dynamic, evolving condition arising from the interaction between central neurological impairment**,** biomechanical vulnerability, and peripheral musculoskeletal adaptations.

The key conclusions of this work can be summarized as follows:

1. HSP may already be present in the acute phase after stroke, highlighting that vulnerability of the shoulder begins immediately after central nervous system injury and not only during rehabilitation.
2. Early shoulder pain is primarily associated with biomechanical instability and capsular involvement, rather than with tendinous pathology traditionally emphasized in later-stage assessments.
3. The relationship between pain and structural ultrasound findings evolves over time, supporting the concept that different mechanisms may contribute to pain at different stages of recovery.
4. Longitudinal clinical–ultrasound assessment provides insights that cannot be obtained from cross-sectional studies, allowing identification of early predictors and temporal trajectories of shoulder pathology.
5. Early identification of patients at risk for HSP may enable timely, targeted preventive strategies, shifting clinical focus from reactive treatment to anticipatory management.

Overall, this thesis supports a paradigm shift in the conceptualization of post-stroke shoulder pain—from a late musculoskeletal complication to an early, specific mechanism-driven process that unfolds across the recovery continuum.

11.7 Future Directions

The findings of this thesis open several important avenues for future research and clinical innovation.

Methodological and research perspectives
Future studies should aim to:

- Conduct multicenter longitudinal investigations to validate these findings across different populations and care settings and to improve external validity.
- Combine clinical and ultrasound assessment with objective kinematic and biomechanical analyses, such as motion capture or wearable sensor technologies, to better quantify shoulder movement patterns and loading conditions.
- Integrate advanced imaging techniques and biomarkers to characterize inflammatory, fibrotic, and central pain mechanisms, particularly in patients with persistent or disproportionate pain.
- Explore neurophysiological and neuroimaging correlates of HSP to better understand the interaction between cortical reorganization, sensory processing, and peripheral pathology.

Clinical and translational perspectives

From a translational standpoint, future research should focus on:

- Developing early screening algorithms that combine clinical severity, ultrasound findings, and functional measures to stratify risk for HSP.
- Designing phenotype-driven interventional trials, testing phase-specific preventive and therapeutic strategies (e.g., early stabilization, capsular mobilization, or targeted neuromodulation).
- Evaluating the cost-effectiveness of early ultrasound screening in stroke units as part of comprehensive secondary complication prevention.
- Integrating shoulder assessment into standardized stroke care pathways, emphasizing the shoulder as a critical determinant of upper-limb recovery and quality of life.

Final Perspective

By framing HSP as a time-dependent phenomenon driven by specific mechanisms, this doctoral thesis contributes to a more nuanced understanding of one of the most debilitating complications of stroke. The integration of early and longitudinal clinical and ultrasound assessment provides a basis for more precise, proactive and personalised approaches to shoulder care after stroke, with the ultimate goal of improving functional recovery and patient quality of life.

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CHAPTER 12 — PHD ACTIVITIES

Full Papers

- Trompetto C, Marinelli L, Mori L, Bragazzi N, Maggi G, Cotellessa F, Puce L, Vestito L, Molteni F, Gasperini G, Farina N, Bissolotti L, Sciarrini F, Millevolte M, Balestrieri F, Restivo DA, Chisari C, Santamato A, Del Felice A, Manganotti P, Serrati C, Currà A. Increasing the Passive Range of Joint Motion in Stroke Patients Using Botulinum Toxin: The Role of Pain Relief. Toxins (Basel). 2023 May 13;15(5):335. doi: 10.3390/toxins15050335. PMID: 37235369; PMCID: PMC10223867.

- Cotellessa F, Puce L, Formica M, May MC, Trompetto C, Perrone M, Bertulessi A, Anfossi V, Modenesi R, Marinelli L, Bragazzi NL, Mori L. Effectiveness of a Preventative Program for Groin Pain Syndrome in Elite Youth Soccer Players: A Prospective, Randomized, Controlled, Single-Blind Study. Healthcare (Basel). 2023 Aug 22;11(17):2367. doi: 10.3390/healthcare11172367. PMID: 37685401; PMCID: PMC10486402.

- Mannarelli D, Pauletti C, Missori P, Trompetto C, Cotellessa F, Fattapposta F, Currà A. Cerebellum's Contribution to Attention, Executive Functions and Timing: Psychophysiological Evidence from Event-Related Potentials. Brain Sci. 2023 Dec 7;13(12):1683. doi: 10.3390/brainsci13121683. PMID: 38137131; PMCID: PMC10741792.

- Cotellessa F, Bragazzi NL, Trompetto C, Marinelli L, Mori L, Faelli E, Schenone C, Ceylan Hİ, Biz C, Ruggieri P, Puce L. Improvement of Motor Task Performance: Effects of Verbal Encouragement and Music-Key Results from a Randomized Crossover Study with Electromyographic Data. Sports (Basel). 2024 Jul 30;12(8):210. doi: 10.3390/sports12080210. PMID: 39195586; PMCID: PMC11359751.

- Puce L, Ceylan Hİ, Trompetto C, Cotellessa F, Schenone C, Marinelli L, Zmijewski P, Bragazzi NL, Mori L. Optimizing athletic performance through advanced nutrition

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- Puce L, Marinelli L, Currà A, Mori L, Schenone C, Cotellessa F, Tatarelli A, Pucci D, Bragazzi NL, Trompetto C. EMG-assessed paratonia: A novel approach to investigating motor response inhibition in healthy subjects. PLoS One. 2024 Dec 18;19(12):e0315274. doi: 10.1371/journal.pone.0315274. PMID: 39693365; PMCID: PMC11654976.

- Cecchella E, Bragazzi NL, Cotellessa F, Campanella W, Puce L, Marinelli L, Currà A, Schenone C, Mori L, Trompetto C. Barriers to Long-Term Adherence in Botulinum Toxin Therapy for Post-Stroke Spasticity: Insights and Implications from a Single-Center Study in North Italy. Toxins (Basel). 2025 Feb 22;17(3):102. doi: 10.3390/toxins17030102. PMID: 40137875; PMCID: PMC11946851.

- Cotellessa F, Campanella W, Puce L, May MC, Ponzano M, Picasso R, Mordeglia M, Subbrero D, Cecchella E, Mori L, Sassos D, Del Sette M, Formica M, Trompetto C. Clinical and Ultrasound Evaluation of Hemiplegic Shoulder Pain in Stroke Patients: A Longitudinal Observational Study Starting in the First Hours After Stroke. Medicina (Kaunas). 2025 Mar 11;61(3):484. doi: 10.3390/medicina61030484. PMID: 40142295; PMCID: PMC11944265.

- Cotellessa F, Campanella W, Pedrini R, Trompetto C, Stella SM, Becciolini M. Ultrasound Identification of an Atypical Course of the Deep Branch of the Radial Nerve Passing Through the Proximal Interosseous Space: A Case Report. J Clin Ultrasound. 2025 Jun;53(5):1171-1175. doi: 10.1002/jcu.23969. Epub 2025 Mar 20. PMID: 40109255.

- Stella SM, Saponara A, Gualtierotti R, Vita F, Miccoli M, Becciolini M, Galletti S, Cotellessa F, Trompetto C. Thickening of the Intramuscular Fascia of the Iliacus Muscle as Evidence of Myofascial Pathology: A New Hip Pain Syndrome. Pain Ther. 2025 Dec;14(6):1935-1947. doi: 10.1007/s40122-025-00777-9. Epub 2025 Sep 23. PMID: 40986268; PMCID: PMC12634967

- Becciolini M, Bisogni M, Stella SM, Trompetto C, Mori L, Puce L, Campanella W, Catalano O, Cotellessa F. Ultrasound Evaluation of the Regenerating Tendon of the Semitendinosus After Harvest for Anterior Cruciate Ligament Reconstruction. J Clin Med. 2025 Nov 5;14(21):7862. doi: 10.3390/jcm14217862. PMID: 41227257; PMCID: PMC12610182

- Cotellessa F, Campanella W, Pedrini R, Trompetto C, Puce L, Bisogni M, Stella SM, Catalano O, Becciolini M. Femoral nail impingement with the quadriceps: an ultrasound case report on orthopedic hardware conflict. Med Ultrason. 2025 Nov 18. doi: 10.11152/mu-4561. Epub ahead of print. PMID: 41252615.

Conferences

- **Speaker**, XXII National Congress of S.I.R.N., Riva del Garda, April 16–18, 2023 *"Sport as Medicine in Neurological Disability"*
- **Speaker**, 51st National Congress of SIMFER 2023, October 12–15, 2023 *"Effectiveness of a Preventive Treatment Program for Groin Pain Syndrome in Elite Youth Soccer Players: A Prospective, Randomized, Single-Blind Controlled Study"*
- **Speaker**, "Update in Neurorehabilitation" Meeting, October 27–28, 2023 *"Evolution of Clinical and Ultrasound Shoulder Findings in Post-Stroke Hemiparetic Patients: Identification of Clinical and Ultrasound Predictors of Hemiplegic Shoulder Pain (HSP)"*
- **Speaker**, 51st National Congress of SIMFER 2023, October 12–15, 2023 *"Effectiveness of a Preventive Treatment Program for Groin Pain Syndrome in Elite Youth Soccer Players: A Prospective, Randomized, Single-Blind Controlled Study"*
- **Speaker**, "Update in Neurorehabilitation" Conference, October 27–28, 2023 *"Evolution of Clinical and Ultrasound Shoulder Findings in Post-Stroke Hemiparetic Patients: Identification of Clinical and Ultrasound Predictors of Hemiplegic Shoulder Pain (HSP)"*
- **Speaker**, XXIII National Congress of SIRN, February 15–17, 2024 *"Evolution of Clinical and Ultrasound Shoulder Findings in Post-Stroke Hemiparetic Patients: Identification of Clinical and Ultrasound Predictors of Hemiplegic Shoulder Pain (HSP)"*

- **Speaker,** 11th National Congress on “Cerebral Stroke”, 3–5 April 2025: “*Clinical and Ultrasound Evaluation of Hemiplegic Shoulder Pain in Stroke Patients: A Longitudinal Observational Study Starting in the First Hours After Stroke”*
- **Speaker,** Congress on Integrated Approaches in the Diagnosis and Treatment of Shoulder Disorders, 14 November 2025*: “Conservative Management of Rotator Cuff Pathology”*
- 30th Siumb National Congress 15-18 November 2025

Teaching

- June 2023 – Theoretical-practical course: "Muscular Ultrasound in the Targeted Treatment of Spasticity"
- October 2024 – Theoretical-practical course: "Muscular Ultrasound in the Targeted Treatment of Spasticity”
- October 2025 – Basic Course in Musculoskeletal Ultrasound: “Shoulder, Elbow, and Knee”

Visiting Researcher

- Department of Rehabilitation Sciences, Stroke Rehabilitation Research Team, KU Leuven, Belgium 2024

Awards

- First Prize – Vincenzo Ieracitano Award, November 2025