UNIVERSITÀ DEGLI STUDI DI PALERMO
PhD School of Biomedicine and Neuroscience
Department of Biomedicine, Neuroscience and Advanced Diagnostics (BI.N.D)
SSD MED/45

Relationship between clinical variables and Patient-Reported Outcomes in patients with psoriatic disease

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CYCLE XXXIII
YEAR OF DOCTOR TITLE ATTAINMENT 2021

TITLE

Relationship between clinical variables and Patient-Reported Outcomes in patients with psoriatic disease

by CANDIDATE

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Dissertation

Presented for the requirements toward the completion
for the Degree of

Doctor of Philosophy

" "Whatever decision you have made for your future, you are authorized, and I would say encouraged, to submit it to a continuous exam, ready to change it, if it no longer responds to your wishes" Rita Levi Montalcini.

“Qualunque decisione tu abbia preso per il tuo futuro, sei autorizzato, e direi incoraggiato, a sottoporla ad un continuo esame, pronto a cambiarla, se non risponde più ai tuoi desideri” Rita Levi Montalcini.

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Acknowledgements

I would like to thank my doctorate tutor and mentor, Prof. Salvatore Corrao. It was so important for me to start my research career under his guidance. Without his expertise and assistance, this research project would not be possible. I thank him also for supporting and encouraging me both professionally and personally through all these years. A particular thanks to Prof. Francesco Cappello and Prof. Fabio Bucchieri from the Department of Biomedicine, Neuroscience and Advanced Diagnostics (BI.N.D) and from the Euro-Mediterranean Institute of Science and Technology (IEMEST) for the opportunity they gave me to realize my research project. I would like to thank my lovely colleagues and friends Raffaella Mallaci Bocchio and Giuseppe Natoli for their scientific and emotional support throughout these years, thanks to Prof. Salvatore Corrao, we have the best clinical research group we could have asked for. It was a great pleasure to meet my PhD colleagues Simona Terzo and Pietro Salvago for all the support they gave me during this PhD period, we shared moments I will never forget. I hope to have found good friends for my lifetime. I would like to thank my lovely family who always encouraged me to continue studying and be the best person that I could be, hoping that they are proud of me. Last, but certainly not least, I would like to thank all my friends, the nurses and all the students I met during these years who have always believed in me.

ABSTRACT

Background

Psoriatic Arthritis (PsA) is a chronic inflammatory form of Arthritis associated with enthesitis, dactylitis, nail dystrophy, uveitis, and osteitis. PsA is strongly associated with comorbidities such as obesity, metabolic syndrome, and cardiovascular disease. As usual PsA patients are assessed either by rheumatologist or dermatologist but a multiprofessional assessment for those subjects is important to improve their disease control and their quality-of-life. The multidimensional assessment is a new model of care for PsA patients in which a multiprofessional team (rheumatologist, dermatologist, internal medicine physician, nutritionist and a phycologist) with a nurse as case manager, assess patients in the main domains of PsA from the admission to the follow-up. Different validated tools are used by the team to assess different patients' dimension as patient-reported-outcomes. This study aimed to evaluate the association between and among clinical variables and Patient-Reported Outcomes in a real-world sample of PsA patients evaluated according the Multidimensional Assessment.

Methods

A cross-sectional study was conducted. Patients with PsA who signed the informed consent were enrolled at the PsA clinic at the ARNAS Civico in Palermo (Italy) from March 2018 to October 2020. Clinical, pharmacological, anthropometric, laboratory variables, and patient-reported outcomes were evaluated, including:

- Health Assessment Questionnaire (HAQ);
- Facit-Fatigue (FACIT-F);
- Psoriatic Arthritis Impact of Disease Questionnaire (PsAID);
- Patient Health Questionnaire-9 (PHQ-9);
- Disease Activity in PSoriatic Arthritis score (Dapsa);
- Patient global assessment (PGA)

STATA 14.1 was used to perform logistic analysis.

Results

According to CASPAR Criteria, 158 patients aged 55.2 (53.3 – 57.1) affected by Psoriatic Arthritis were included in the study. All the collected variables were evaluated ad a strong association was observed between functional disability measured by HAQ >2 and central

obesity [OR (95% CI) 16.94 (2.22 - 129.48); p < 0.004]. Moreover, data analysis showed an association between high impact of disease on life (PsAID >4) and central obesity [OR (95% CI) 3.33 (1.56 - 7.13); p<0,002]. Models were adjusted for age, sex, years of illness, and biological treatment.

Conclusion

This study demonstrated a high association between functional disability studied subjectively using the HAQ, the impact of the disease on patients' quality-of-life using the PsAID, and central obesity in patients affected by PsA. Data suggest that a multiprofessional evaluation for these patients is important to evaluate different aspect of the disease as the comorbidities. In particular, therapeutic goals should not be focused only on treatment but also on waist circumference reduction to reduce inflammation and improve patients' functional ability and quality-of-life.

Introduction

Psoriatic Arthritis (PsA) is a chronic, immune-mediated, inflammatory spondyloarthropathy pathogenetically associated with Psoriasis. Patients affected by PsA commonly suffer from sleep disorders, fatigue, low-level stress, depression, mood changes, and anxiety that contribute to high rates of absenteeism from work, productivity loss, and unemployment, especially in the first 2-5 years of disease. With this combination of pain, disability, skin disease, fatigue, and poor quality of life, PsA confers considerable psychosocial and functional burden on patients [1-6].

The global epidemiology of PsA differs depending on the population and the criteria utilized. In the general population, PsA has a prevalence of 0.05% to 0.25%, affecting up to 30% of patients with Psoriasis [7-8]. The prevalence is similar among women and men between 30 and 40 years [9], and there are a higher prevalence and incidence rate in Europe and North America than in Asia [10-12]. PsA presents with a varied disease course whose type of tissue involvement can change over time as inflammation of the joints and entheses, including those of the axial skeleton and it is associated with increased mortality from cardiovascular disease [13]. PsA contributes to deformities and joint damage in most patients, with bone erosion often developing in the first two years of the disease. For many years it was classified as a variant of Rheumatoid Arthritis (RA) but radiological, clinical, and laboratory data have established PsA as a distinct, progressive articular entity with the potential to impair function, reduce the quality of life and increase mortality [14]. In the past, PsA was usually underdiagnosed and undertreated, particularly in the primary care environment, in fact many clinicians in primary care and dermatology settings were unaware of the risk for musculoskeletal disease in patients with Psoriasis. The need for regular screening for PsA was underestimated, but early recognition and diagnosis are the key to effective treatment in this patient population [15].

Chapter 1: Psoriatic Arthritis

1.1 Pathogenesis, genetic and environmental triggers

Various genetic, immunological and environmental triggers predispose patients to develop Psoriatic Arthritis and Psoriasis. PsA is a highly heritable disease with a prevalence of 19.7% (95% CI, 18.5%-20.9%) in patients with Psoriasis [16]. A range of genetic factors may contribute to this strong familial component, including frequencies of major histocompatibility complex (MCH) class II alleles such as human leukocyte antigens (HLA)-B*08, B*27, and B*38. Nearly 25% of patients with PsA are positive for human leukocyte antigen (HLA)-B 27. Different PsA manifestations are associated with specific HLA alleles, including symmetric sacroiliitis (HLA-B 27:05), enthesitis (HLA-B 27:05 and HLA-C 01:02), asymmetric sacroiliitis (HLA-B 08:01 and HLA- C 07:01), dactylitis (HLA-B 27:05 and HLA-B 08:01), and synovitis (HLA-B 08:01) [17].

Several environmental factors have been implicated in Psoriatic Arthritis' triggering, with the production of IL-23, by putting stress on joints in genetically susceptible subjects. Some of these factors include (Table 1):

- **Obesity:** obesity may be a predisposing factor for PsA in people affected by Psoriasis, and PsA might also predispose to obesity by reducing physical activity because of functional and or psychological limitations [18]. Visceral adipose Tissue was considered to be a storage organ for fatty acids without other functions, but nowadays, in particular, the visceral one is considered a metabolically active endocrine organ [19-21]. It represents a source of inflammatory mediators, known as adipokines including leptin and adiponectin, plasminogen activator inhibitor-1 (PAI-1), TNF-α, macrophage chemoattractant protein-1, IL-6, leading to a pro-inflammatory status in obese subjects. Adiponectin is an anti-inflammatory cytokine and could exert protective effects in obesity-related metabolic and vascular diseases, presumably due to its anti-inflammatory action. In subjects with inflammatory diseases, high levels of cytokines such as TNFα or IL-6 may further reduce adiponectin synthesis by adipose tissue, in fact low serum levels of adiponectin are frequently reported in patients with obesity or Psoriasis. [22] For all these reasons, obesity is considered a low-grade inflammatory disease. In particular, central obesity may also determine an increased risk of not achieving and maintaining minimal disease activity (MDA) in PsA patients [23],

highlighting the role of central fat accumulation as a negative predictor of good clinical response to treatment, especially the response to TNFα- blockers [24];

- **Nail Involvement:** nail involvement as onycholysis and psoriatic nail pitting; were associated with an increased risk for PsA [25];
- **Smoking:** smoking appears to increase the risk of developing Psoriatic Arthritis in healthy controls but not in patients with Psoriasis. Smoking has been suggested to be protective in Psoriasis (the so-called smoking paradox) an effect related to polymorphisms in the IL13 gene. However, methodological limitations might explain this observation [26];
- **Alcohol:** Excessive ethanol consumption contributes to the increased levels of tumor necrosis factor (TNF)-α-converting enzyme (TACE) and transforming growth factor (TGF)-α receptor 1, which are involved in systemic immunodysregulation in Psoriasis. Epidemiologic evidence suggests that alcohol intake is associated with a risk of incident PsA in women [27];
- **Bacterial and viral infections:** The role for infection as a gene–environment interaction was analyzed by observing and increasing the prevalence of streptococcal antibodies in patients with Psoriatic Arthritis. The increased incidence of Psoriatic Arthritis in HIV-endemic populations of Sub-Saharan Africa suggests roles for both infection and T cells. HIV-associated depletion of CD4-positive T cells has been shown to induce remission of Rheumatoid Arthritis, but induced acute onset or exacerbation of Psoriatic Arthritis. It is unclear whether psoriatic disease is directly triggered by viral infection; or by the depletion of CD4-positive T and CD8-positive T cells' predominance;
- **Trauma:** Trauma (known as the Koebner phenomenon) is a known factor in psoriatic skin lesions. Heinrich Koebner (1838–1904) reported the emergence of new psoriatic lesions in the healthy skin region (non-involved by Psoriasis) following an injury/trauma to the healthy skin areas of psoriatic patients [28];
- **Microbiome**: new evidence suggests that the microbiome may play a pathogenic role in psoriatic disease. The possible role of the microbiome in the gene–environment interaction in Psoriasis and PsA was showed in different studies. As for by studying the faecal bacteria in patients with Psoriatic Arthritis compared with healthy controls, there were significant reductions in Firmicutes, Bacteroidetes and Actinobacteria in psoriatic individuals [29]. The composition of the psoriatic microbiome is unknown. The skin microbiome was analyzed in different studies showing a decreased relative abundance of Propionibacterium in psoriatic lesional skin [30-33]. Loss of Propionibacterium,

which is one of the major components of normal skin microflora, can lead to decreased immune tolerance and an increased propensity for psoriatic inflammation.

Tab.1 Risk factors for the development of PsA.

Risk Factor	How Risk Factors May Affect the Development of PsA
Obesity	• Systemic inflammation caused by adipose tissue • Increased mechanical loading on joints • Dyslipidemia
Nail Disease	• Associated with enthesitis • Precedes joint disease • Marker of immunoreactivity
Smoking	• Oxidative stress that stimulates inflammation • Nicotinic receptor activation that inhibits intracellular proinflammatory pathways
Alcohol	• Complex, undetermined
Trauma, Infection, and Stress	• Inflammation triggered by trauma in a genetically susceptible host - Biomechanical sheer stress, microtrauma - Streptococcal infection - Injury, heavy lifting
Microbiome	• Gut microbiota profile in PsA similar to that of inflammatory bowel disease • Dysbiosis may contribute to altered immune response by triggering IL-23 release and type 17 cells

Some PsA patients have more than one comorbid condition in addition to the skin and joint diseases. PsA is strongly associated with different comorbidities including cardiovascular disease, metabolic syndrome, obesity, diabetes mellitus, dyslipidemia, inflammatory bowel disease, fibromyalgia, fatty liver disease, uveitis, kidney disease, infections, osteoporosis, depression, central sensitization syndrome, and gout [34]. In particular, cardiovascular disease is one of the most important causes of death in PsA patients due to the fact that inflammatory state, with high serum levels of circulating interleukin (IL)-17, interferon-alpha and TNF, promotes vasoconstriction and endothelial dysfunction which may lead to plaque formation accelerating the progression of atherosclerosis. TNF is also overexpressed in the adipose tissue that links obesity, diabetes and the chronic inflammation that drives also metabolic syndrome. Serum cytokines are the main actors of the chronic ‘low-grade’ inflammatory state of psoriatic disease which lead to the most important comorbidities.

1.2 The Role of the Cytokines

Psoriatic Arthritis (PsA) is a complex heterogeneous disease with a complex pathophysiology. Also, if the molecular and cellular interactions between skin and joint disease have not been well characterized, novel therapeutics targeting different cytokines (IL-12, IL-23, IL-17, IL-17 receptor, TNF) are effective in treating both the skin and joint manifestations in PsA. In fact, in patients affected by PsA innate and adaptive cells and some pro-inflammatory cytokines are involved, in particular the interleukin 23/17 axis [35].

Serum cytokines play an important role in Psoriatic Arthritis' pathogenesis by initiating and perpetuating various cellular and humoral autoimmune processes. Interleukins are involved in the mechanism of inflammation in PsA, but the pathogenic link between the inflammatory T cell responses of Psoriasis and the joint inflammation of PsA is unclear.

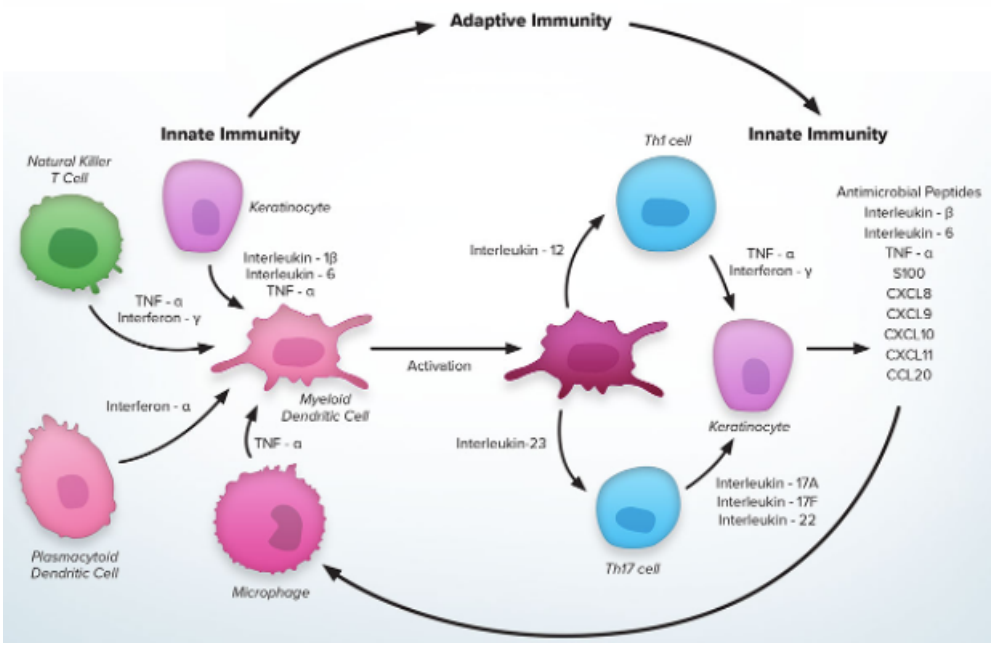
It has been hypothesized that PsA is triggered by autoinflammatory cytokine networks that respond to some environmental stressors.

There are several complex interactions between activated CD4+ T-cells, CD8+ T-cells, lymphocytes, and macrophages in the IL-23/IL-17 immune axis that result in osteoclastogenesis, bone resorption, and cartilage destruction in patients affected by PsA. Moreover, the Janus-Kinase (JAK) family of receptor-associated tyrosine kinases are implicated in the pathogenesis of PsA. JAKs activate signal transducer and activator of transcription (STATs) depending on the cytokine signal they receive and inhibit several pro-inflammatory cytokines, including IL-6, IL-12, and IL-23.

TNF was one of the earliest cytokines to be identified in the pathogenesis of PsA; it is produced by several types of immune cells and activates key effector cells involved in tissue inflammation.

Increased circulating T helper 17 (Th17) cytokines have been detected in patients' peripheral blood with PsA. Th17 pathways may stimulate the release of inflammatory substances such as interleukin (IL)-12, IL-17, IL-22, IL-23, and TNF and, in particular, IL-17 has been found in the skin, synovial tissue, and synovial fluid of patients with PsA. (Figure 1).

Fig 1 Mechanisms of inflammation in Psoriasis and PsA



Generally, in case of tissue damage or autoimmune stimuli the body protects itself with an inflammation response consisting of a cascade of chemicals and cytokines in the affected area. T-cell subpopulations Th1, Th2, Th17, Th9, Th22, and Treg cells secrete pro-inflammatory or anti-inflammatory cytokines. Dendritic cells, macrophages, ILCs, MAIT cells, NK cells and mast cells produce mostly pro-inflammatory cytokines. These pro-inflammatory mediators activate resident cells, including synovial fibroblasts, chondrocytes, osteoblasts, and osteoclasts, which in turn secrete more pro-inflammatory mediators that can further recruit immune cells into the joints, creating a self-perpetuating inflammatory response. Additionally, synovial fibroblasts secrete matrix-degrading enzymes and receptor activator of nuclear factor-kappa-B ligand (RANKL), resulting in cartilage degradation and bone resorption. The inflamed synovial microenvironment leads to the formation of the synovial pannus, entheseal inflammation, and joint destruction (Fig2, Fig3).

Fig 2: Key cell types and secretion of key inflammatory mediators in Psoriatic Arthritis

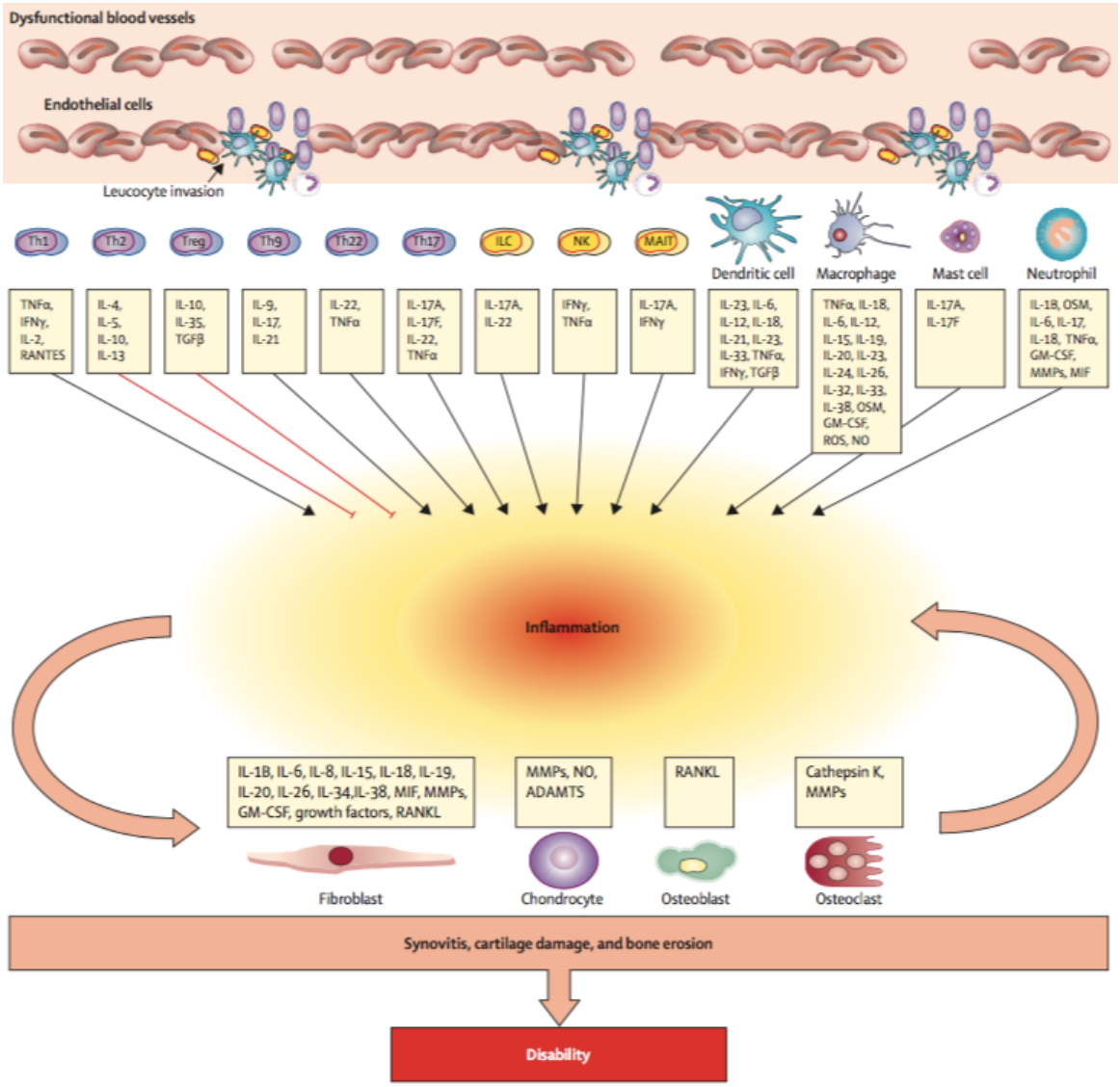


Fig 3 Key cytokines in Psoriatic Arthritis

	Site of expression	Source	Key functions
Tumour necrosis factor	Increased in synovial tissue and synovial fluid	Macrophages, T cells, fibroblast-like synoviocytes, B cells	Activation of circulating and resident cells to induce production of cytokines, adhesion molecules, chemokines, and matrix metalloproteinases; activation of osteoclasts to enhance cartilage and bone resorption
Interleukin 23a	Increased in synovial tissue, synovial fluid, and enthesis	Macrophages, dendritic cells	Promotion of T-helper-17 cell differentiation and granulocyte-macrophage colony-stimulating factor production
Interleukin 17A/F	Increased in synovial tissue, synovial fluid, and enthesis	T cells, mast cells, natural killer cells	Activation of fibroblast-like synoviocytes, chondrocytes, and osteoclasts; stimulation of proinflammatory cytokine and matrix metalloproteinase production, and neutrophil recruitment
Interleukin 22	Increased in synovial tissue, synovial fluid, and enthesis	T cells, innate lymphoid cells	Activation of fibroblast-like synoviocytes; induction of osteoclastogenesis and bone resorption via RANKL
Interleukin 9	Increased in synovial tissue	T cells	Activation of peripheral blood mononuclear cells; stimulation of proliferation of pathogenic T cells
Interleukin 6	Increased in synovial tissue and serum	Macrophages, activated fibroblast-like synoviocytes, B cells	Activation of STAT3 signalling to enhance proinflammatory cytokine production
Interleukin 15	Increased in synovial tissue	Macrophages	Promotion and maintenance of T-cell and natural killer cell activation
Interleukin 12	Increased in synovial tissue and synovial fluid	Macrophages, dendritic cells	Promotion of T-helper-1 cell differentiation through STAT4
Interleukin 1	Increased in synovial tissue	Macrophages, neutrophils, B cells	Proinflammatory signalling
Granulocyte-macrophage colony-stimulating factor	Increased in synovial tissue	T cells, macrophages, fibroblast-like synoviocytes	Recruitment and activation of immune cells
Interferon γ	Increased in synovial tissue	T cells	Promotion of macrophage phagocytosis, T-cell activation, and RANKL secretion
Interleukin 10	Decreased in synovial tissue	T cells, macrophages, fibroblast-like synoviocytes	Anti-inflammatory signalling

RANKL=TNF superfamily member 11. STAT=signal transducer and activator of transcription.

In PsA some of the most important cytokines are:

- **IL-17:** IL-17 family consists of six proteins of the adaptive and innate immunity (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F). IL-17 is produced by T (17) cells, γδ T cells, natural killer T (NKT) cells, NK cells, and type 3 innate lymphoid cells and plays a significant role in the development of both Psoriasis and PsA. IL-17 can induce the production of pro-inflammatory cytokines, such as IL-6, IL-1, GM-CSF, G-CSF.
- **IL-17A:** is a member of the IL-17 cytokine family. IL-17A producing T cells can be protective for the organism as for skin infections or cause tissue damage. It is implicated in the pathogenesis of inflammatory autoimmune diseases like Psoriasis. Psoriatic skin is characterized by high expression of IL-17A and IL-17F, which act on immune and non-immune cell types and strongly contribute to tissue inflammation. As confirmed in many studies, psoriatic skin is characterized by high expression of IL-17A, IL-17F and Il-17E. For instance, they are involved in neutrophil recruitment. In the skin of psoriatic lesions, neutrophil accumulation is followed by the formation of epidermal micro abscesses. IL-17A and other Th17 cytokines upregulate the production of several chemokines implicated in Psoriasis pathogenesis. Psoriasis skin manifestations, cardiovascular, and metabolic disease in Psoriasis appear to share pathogenic mechanisms evolving around IL-17A and its pro-inflammatory role [36].

- **IL-23:** IL-23 has been implicated in the proliferation and maintenance of IL-17. It regulates the secretion of IL-17, IL-21 and IL-22 by Th17 cells which mediate the epidermal hyperplasia, the keratinocyte differentiation in Psoriasis.
- **The IL-23/IL-17 axis:** is critical in regulating cytokine network and inflammatory mediators contributing in the pathogenesis of Psoriasis. The interleukin (IL)-23– IL-17 axis plays a critical role in osteoclastogenesis.
- **Serum cartilage oligomeric matrix protein (COMP):** is a biomarker for cartilage degradation. COMP has been identified in cartilage, ligaments, meniscus, tendons, synovium, osteoblasts and vascular smooth muscle. COMP has potential as a diagnostic and prognostic indicator and it is a valuable tool to the identification of patients at high risk for rapid joint destruction and monitoring treatment efficacy [37].
- **IL-2:** IL-2 is a member of a cytokine family that includes IL-4, IL-7, IL-9, IL-15, IL 21. L-2 has essential roles in the immune system's key functions, tolerance and immunity, primarily via its direct effects on T cells. In the thymus, where T cells mature, it prevents autoimmune diseases by promoting the differentiation of certain immature T cells into regulatory T cells, which suppress other T cells otherwise primed to attack normal healthy cells in the body. Some evidence indicates that IL-2 is involved in itchy Psoriasis [38].
- **IL-4:** It has an anti-inflammatory action, in fact IL-4 can inhibit the production of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6. Moreover, it has inhibitory action of the synoviocytes proliferation, reducing collagenase synthesis.
- **IL-6:** also called B-cell stimulatory factor-2 (BSF-2) causes increased body temperature in acute inflammatory phase. Serum IL-6 has been found in patients with PsA versus skin disease alone, correlating with the number of joints affected. However, this cytokine is not a specific screening tool.

- **IL-12:** In PsA pathophysiology, IL-12 promotes the differentiation of naïve $CD4^+$ T cells into mature IFNγ-producing T-helper type 1 (Th1) effector cells. It is also a potent stimulus of natural killer cells and induces CD8+ T cells to produce IFNγ. IL-12 has been shown to play a protective role against the development of PsA [39-40]. IL-12 has an anti-inflammatory effect on joints. Therefore, IL-12 is significant to PsA development through its inactivation, or its association with the p40 subunit.
- **IL-8:** Like IL-6, IL-8 can be secreted by cells with Toll-like receptors in response to pathogens' stimulation. IL-8 recruits neutrophils and other target cells through chemotaxis.
- **IL-10:** it has a role in immunoregulation and inflammation. It downregulates the expression of Th1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production.
- **Macrophage colony-stimulating factor** (**M-CSF**)**:** circulating M-CSF concentrations are elevated in the patients with erosive PsA and are correlate with severity of the peripheral erosive disease [41].
- **RANK/RANKL** Receptor activator of nuclear factor κB (RANK) is associated with bone metabolism and promotes osteoclastogenesis. RANKL receptor has been founded on epidermal dendritic cells and can causes increased proliferation of $CD4^+CD25^+$ T cells.
- **TNF alpha:** is a key pleiotropic inflammatory cytokine. It has both growth promotion and inhibition effect to some cells. TNF-α initiates a cascade of cytokines in the local inflammatory immune response and increases vascular permeability recruiting macrophage and neutrophils to a site of infection.

1.3 Diagnosis and clinical features

Clinicians in dermatology, rheumatology and primary care clinics play an important role in screening psoriatic patients for PsA on time to improve patients' quality of life. Patients with Psoriasis typically present first to a dermatologist because arthritis is rarely noted initially, and PsA is often unrecognized until patients consult with a rheumatologist. The reasons why Psoriatic Arthritis sometimes remains unidentified are not clear but might include insufficient musculoskeletal expertise among primary care physicians and dermatologists. Early diagnosis in rheumatology in people with Psoriasis can enable earlier treatment of this disabling disease and prevent unnecessary suffering but can be challenging when arthritis is present without skin lesions. Patients with PsA often have a family history of psoriasis or PsA, but in patients with classic clinical features of PsA but no history of Psoriasis, it is important to examine the patient's scalp, skin, and nails. The diagnosis of PsA is clinical and based on patient history and physical examination and supported by imaging and laboratory evaluation.

PsA can manifest in up to six different clinical domains:

- **Peripheral arthritis:** peripheral arthritis can classify as oligoarticular, polyarticular, and isolated distal interphalangeal joint (DIP) inflammation. Polyarticular PsA symmetrically involves ≥5 joints, instead oligoarthritis, involves <5 joints in an asymmetrical distribution.

- **Axial disease:** is characterized by back pain persisting for >3 months before age 40 years, alternating buttock pain (caused by sacroiliitis), pain causing waking from sleep during the second half of the night and prolonged morning stiffness or stiffness upon immobility;

- **Dactylitis:** inflammation of an entire digit that may be red, hot, and tender or swollen. Dactylitis can occur in isolation or as one of several digits affected. On examination, palpation of distal joints typically reveals soft swelling and tenderness due to inflammation;

- **Enthesitis:** inflammation of the connective tissue between tendon or ligament and bone;

- **Skin and nail disease:** skin can be affected psoriasis; nails matrix can be characterized by nails' pitting, Beau's lines, onychomadesis, trachyonychia, nail dystrophy and leukonychia. Nail bed leads to onycholysis, oil drop patches, subungual hyperkeratosis and splinter hemorrhages [42-43].

At the time, there are no widely accepted diagnostic criteria for PsA. The first classification criteria for PsA were the Moll and Wright criteria, which defined Psoriatic Arthritis as inflammatory arthritis occurring in the presence of Psoriasis but with an absence of rheumatoid factor on serological tests. In 2006 The Classification of Psoriatic Arthritis (CASPAR) criteria was developed and included the presence of inflammatory articular disease (joint, spine, or entheseal), with typical features such as Psoriasis (current, or personal or family history), psoriatic nail dystrophy, absence of rheumatoid factor, dactylitis (current or personal history), and radiological evidence of new juxta-articular bone formation providing additional points to yield a definitive classification [44]. To meet the CASPAR criteria, patients must have signs of inflammatory articular disease (joint, spine, or enthesial) with at least 3 points from the five categories (Table 3). To date, radiographic imaging with power doppler ultrasound is the gold standard for establishing joint damage in PsA, and it is used to find erosive changes in peripheral joints. For the diagnosis of PsA there are no specific serologic tests, but the elevation of acute phase reactants (ESR, CRP) may be found in ~40% of PsA patients. PsA is also associated with systemic diseases such as hypertension, type 2 diabetes, obesity, metabolic syndrome, fatty liver disease, autoimmune disease, malignancies, and cardiovascular disease.

Table 2 CASPAR Criteria. Psoriatic Arthritis is considered to be present in patients with inflammatory articular disease (joint, spine or esthesia) who have a score of at least 3 points from the five categories below.

CASPAR Criteron	Points
1. Evidence of psoriasis (one of the following):	
a. Current psoriasis	2
b. Personal history of psoriasis	1
c. Family history of psoriasis	1
2. Psoriatic nail dystrophy (including onycholysis, pitting, hyperkeratosis)	1
3. Rheumatoid Factor negative	1
4. Dactylitis (one of the following):	
a. Swelling of entire digit	1
b. History of dactylitis	1
5. Radiographic evidence of juxtaarticular new bone formation	1

1.3 Treatment

Therapy in PsA aims to limit skin and joint symptoms and signs, prevent or slow structural damage and complications, maintain health-related quality of life and achieve the lowest possible disease activity level in all domains of the disease. Different drugs are used to treat patients affected by PsA including: non-steroidal anti-inflammatory drugs (NSAIDs), synthetic disease-modifying anti-rheumatic drugs (DMARDs), biologic therapies, biosimilar or the novel small molecules [45]:

- **Non-steroidal anti-inflammatory drugs** (**NSAIDs)** are used in patients with mild symptoms or limited joint involvement and, in the case of inflamed joints, intraarticular corticosteroid injections may be recommended. The EULAR guidelines recommend that systemic glucocorticoids may be used with caution at the lowest effective dose for the shortest possible period.
- **DMARDs**: i.e., methotrexate (MTX), sulphasalazine, cyclosporine, leflunomide, are systemic therapy recommended for patients with three or more inflamed joints or in patients with persistent axial, entheseal, or dactylic disease:

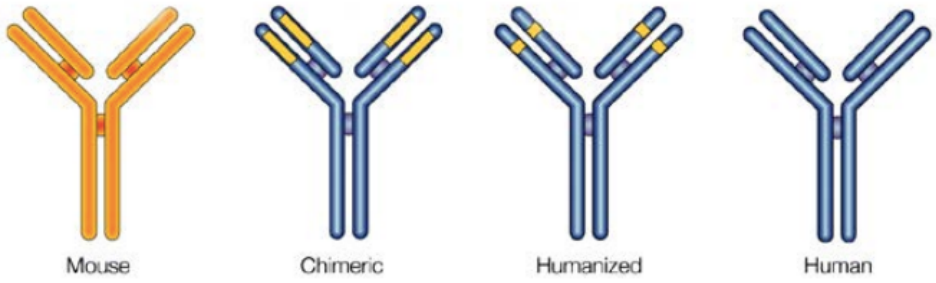
    - **Methotrexate (MTX)** is a folic acid analogue with anti-inflammatory effects mediated primarily through neutrophils, T cells, and monocytes/macrophages. MTX has been commonly prescribed as first-line therapy to reduce joint tenderness and swelling by increasing adenosine release (an anti-inflammatory agent) at the sites of inflammation and by releasing pro-inflammatory cytokines responsible for inflammation in PsA. Early treatment with MTX is associated with mild inhibition of joint damage progression and improved health-related quality of life. Methotrexate is effective in treating cutaneous Psoriasis but not in improving psoriatic nail disease or enthesitis, dactylitis or axial arthritis. Not all patients respond to MTX, in fact patients affected by entheseal disease and spinal inflammation are more responsive to anti-TNF agents than to DMARDs;
    - **Sulfasalazine** is effective in treating peripheral arthritis and axial involvement in PsA, but it is not effective in arresting the progression of clinical and radiologic damage;
    - **Leflunomide** is an oral disease-modifying agent that reduces synovitis by inhibiting dihydroorotate dehydrogenase, an enzyme necessary for the production of DNA and RNA. There are few studies on the efficacy of this drug in enthesitis and axial PsA;

- **Cyclosporine:** this drug has modest efficacy for nail Psoriasis. Data on its efficacy in enthesitis, dactylitis or axial disease are insufficients, and there is no evidence that cyclosporine reduces radiographic progression in patients with PsA.
- **Other csDAMRDs** as azathioprine, gold and hydroxychloroquine are less used in patients affected by PsA.

- **Biologics** (Fig 4) are monoclonal antibodies that target interleukin pathways, modulate T cells, and inhibit JAK pathways. Biologics are named according to a specific nomenclature in fact:

- "-cept" refers to the fusion of a receptor to the Fc part of human immunoglobulin G1 (IgG1)
- "-mab" indicates a monoclonal antibody (mAb)
- "-ximab" indicates a chimeric mAb
- "-zumab" indicates a humanized mAb

Fig 4 Monoclonal antibodies



According to EULAR guidelines, patients with active disease (i.e., a high number of active joints, high inflammatory markers, and ongoing joint damage) should be treated with biologics after the failure of one DMARD. TNF inhibitors have demonstrated efficacy in treating skin and joint involvement as well as in preventing radiographic damage. However, they are associated with a broad spectrum of hematologic and metabolic adverse events (e.g., opportunistic infections such as tuberculosis, cytopenia, lymphoma, heart failure, and hepatotoxicity) so patients should be assessed before to start this kind of therapies. Biologics are:

- **Infliximab:** is a mouse/human chimeric **anti-TNF** that improves Psoriasis severity, enthesitis, dactylitis, nail Psoriasis, axial disease and peripheral joint radiographic progression;
- **Adalimumab:** is a fully human **anti-TNF** monoclonal antibody. It improves Psoriasis severity, symptoms of axial disease and nail Psoriasis and can treat patients affected by bowel diseases;
- **Golimumab:** as Adalimumab it is also a fully human inhibitor of **tumor necrosis factor alpha**. It improves enthesitis, dactylitis, Psoriasis and nail disease;
- **Certolizumab pegol:** is a PEGylated Fab fragment **anti-tumor necrosis factor alpha** antibody approved for the treatment of PsA;
- **Etanercept:** is a human **anti-TNF.** It improves physical function in patients with Psoriatic Arthritis, and reduces the progression of peripheral joint damage as measured by X-ray.

Various biologics as secukinumab, ixekizumab, and brodalumab target either IL-17 or IL-17R and are recommended for patients affected by PsA:

- **Secukinumab**: is a fully human, high-affinity **anti-IL-17A** monoclonal antibody. It reduces radiographic progression of the disease and improves Psoriasis, nail disease, enthesitis and dactylitis;
- **Ixekizumab** is a humanized IgG4 monoclonal antibody that neutralizes **interleukin-17A**. It improves Psoriasis, nail disease, enthesitis, dactylitis and reduces reduced radiographic progression of joint damage;
- **Brodalumab**: a fully human **anti-IL17R** monoclonal antibody. It improves dactylitis, Psoriasis and nail disease.

Research on the IL-23/IL-17 axis has provided drugs as the IL-23 blocker Ustekinumab and Guselkumab:

- **Ustekinumab**: is a monoclonal antibody that inhibits interleukin **IL-12** and **IL-23** important cytokines in the pathogenesis of psoriatic disease. Ustekinumab can be administered as monotherapy or in combination with MTX. It improves Psoriasis, enthesitis, dactylitis and nail disease and physical functioning and decreases radiographic progression in the hands/feet of patients affected by PsA;
- **Guselkumab:** is an interleukin-23 inhibitor approved in Psoriatic Arthritis that also reduces patients' fatigue;

- **Clazakizumab:** it is an **IL-6** monoclonal antibody with high affinity and specificity for IL-6. It may be effective on the musculoskeletal manifestations of PsA, but further studies need to be undertaken;
- **Abatacept:** it is a **selective T-cell co-stimulatory modulator**. It improves skin Psoriasis.

- **Biosimilars:**

Biosimilars are biologic drugs designed to have similar active properties to ones that have been already licensed. The EMA approved biosimilars to date are Benepali (etanercept), Erelzi (etanercept), Amgevita (adalimumab), Inflectra (infliximab), Remsima (infliximab) and some others. The lower cost of these drugs may make them more accessible, especially in resource-poor settings in terms of access may be addressed.

- **JAK inhibitors:**

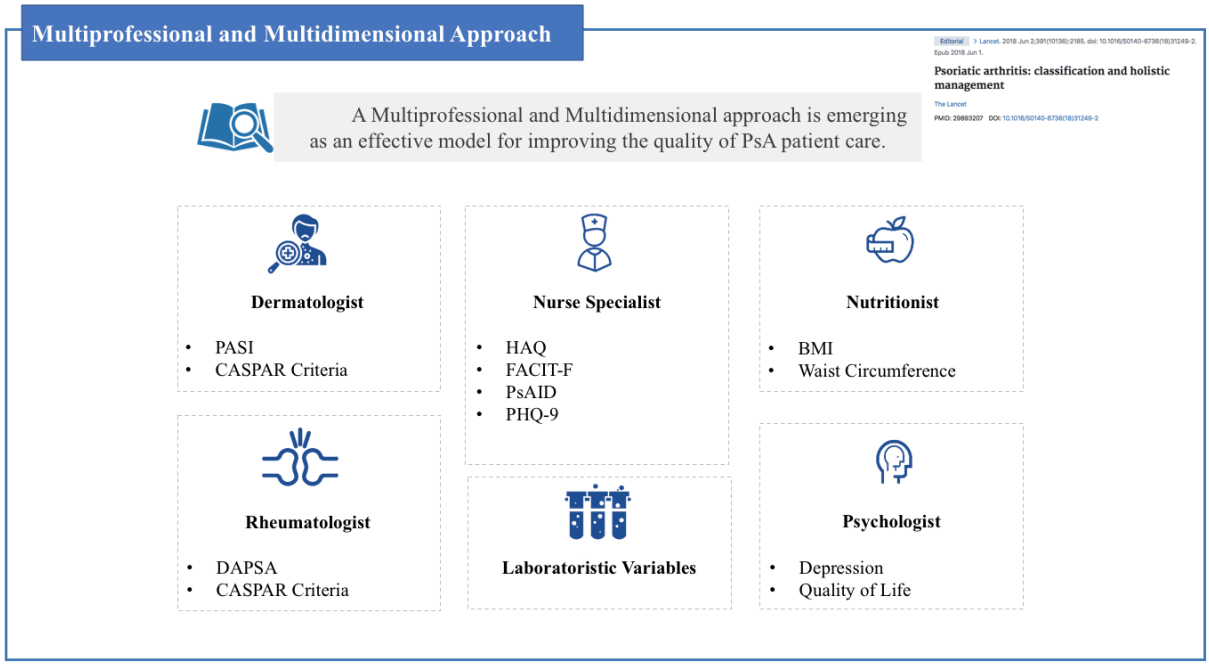
- **Tofacitinib:** it is an oral **JAK inhibitor**. Activated JAKs are pro-inflammatory and recruit and activate signal transducer and activator of transcription (STATs), which drives gene transcription. It inhibits JAK1 and JAK 3a and was approved in 2017 for adults with active PsA who do not respond to DMARDs.
- **Small molecule:** Phosphodiesterase 4 inhibitor (PDE 4-I) Apremilast (Otezla) is an oral phosphodiesterase 4 (PDE 4) inhibitor that has demonstrated clinical benefit for patients with PsA and is now FDA-approved for patients with active PsA. Apremilast is a well-tolerated drug with a safety profile. Apremilast improves enthesitis and nail Psoriasis, but an improvement in dactylitis could not be demonstrated.

Chapter 2. A New Model of PsA Care: The Multidimensional assessment of PsA patients

The early recognition and diagnosis of PsA is significant to ensure that patients with PsA have successful access to the treatment options. However, clinicians in primary care do not always screen the patients with Psoriasis for PsA and do not always refer patients for evaluation by a rheumatologist. Patients affected by Psoriatic Arthritis should be assessed both from rheumatologists and dermatologists with other healthcare professionals' support to improve patients' disease control and their quality of life. Health professionals should provide integrated and multidisciplinary care in which nurses are fundamental. The role of the nurses in rheumatology is changing. More and more specialized rheumatology nurses in the world have an important role of case managers for patients affected by rheumatic diseases. While at time in Italy rheumatology as a nursing specialty does not exist, specialized nurses in other countries act as the interface between patients and the other multidisciplinary team members helping to reduce their workload significantly. Nurses assess patients from the evaluating the symptoms to the diagnosis and the follow-up and have important roles for rheumatic patients. The work of a specifically trained nurse in rheumatology includes self- management support, the monitoring of disease consequences on life and patient education and counselling [46]. In particular, nursing education is important because PsA has consequences on daily activities and participation in society including productivity and employment [47] and evidence suggests that patients who are given educational advises on their condition by the nurses are better able to cope with the physical and psychological challenges of this rheumatic disease [48]. A multidisciplinary and multidimensional assessment made by different healthcare professionals in a dedicated setting is the best model for assessing patients who meet CASPAR Criteria. A nurse specialist coordinates the process to allow patients to have a more comprehensive assessments in a short period and the same setting. The multidimensional assessment includes a standardized evaluation of disease severity, patient-reported outcomes and treatment in both rheumatology and dermatology practice. The multidisciplinary team is made by a nurse specialist, an internal medicine physician, a dermatologist, a rheumatologist, a nutritionist and, in case of depression, a psychologist who assess patients from the first evaluation to the follow-up. Each actor of the process is important to evaluate the patient multidimensionally. The first clinical assessment is done by an internal medicine physician who assesses medical history, lifestyle and patient's health status investigating comorbidities and polytherapy using the Cumulative illness Rating Scale and the Polytherapy record. According to the Group for Research and Assessment of Psoriasis and PsA (GRAPPA), in the multidimensional evaluation

patients are assessed by physicians in the six main domains: peripheral arthritis, skin and nail disease, axial arthritis, enthesitis and dactylitis for the appropriate management of disease activity [49]. After the first evaluation, disease activity is evaluated by physicians to assess the effectiveness of therapy [50]. Due to this, the rheumatologist assesses the six main domains together with the dermatologist. The rheumatologist uses the 68/66 tender and swollen joint count for the Disease Activity in PSoriatic Arthritis (DAPSA) score to evaluate peripheral arthritis while the axial arthritis is evaluated by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The rheumatologist also evaluates patients' enthesitis (defined as the inflammation at the areas of insertion of the tendons, ligaments and joint capsules to the bone) and dactylitis (inflammatory swelling of the entire digit including bone, tendon sheaths, articular and peri-articular tissues). The dermatologist evaluates skin with the Psoriasis area and severity index (PASI). The PASI is a quasi-objective measure that scores the average redness, thickness, and scaling of the lesions (0–4 scale), weighted by the area of involvement. PASI scores range from 0 to 72, where higher scores indicate severe disease. Nails are evaluated by the nail Psoriasis severe index (NAPSI). The nutritionist evaluates, with the Bio-Electrical Impedance Analysis, the skeletal muscle index, the body mass index, the waist circumference and gives nutritional advice to reduce weight and inflammation [51]. According to this care model the nurse specialist assesses vital signs and collects blood sample to evaluate traditional acute phase reactants, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and cytokine levels. Moreover, the nurse helps clinicians evaluating tender and swollen joints and evaluates different aspects of patients' health through patient-reported outcomes (PRO) measures to assess also patients' physical function, fatigue and the impact of the disease on their quality-of-life [52]. According to this new model of care patients affected by Psoriatic Arthritis and their caregivers receive also educational advice by the nurse specialist to improve coping and empowerment (Tab4).

Fig 5 The Multidimensional Assessment of PsA patients



2.1 Patient-reported Outcomes Measures (PROMs) in PsA

To ensure the best possible evaluation of patients affected by PsA, and on the basis of physicians' and patients' perspectives, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) together with the Outcome Measures in Rheumatology (OMERACT) international consensus created a core outcome set (COS) that should be measured at each patients' assessment [53]. Patient-reported outcome measures (PROMs) are used to assess the global and domain-related in patients with PsA [54]. According to the two groups the most important domains to evaluate are: musculoskeletal disease activity, skin disease activity, patient global assessment, physical function, fatigue and the impact of the disease on patients' quality-of-life. PROMs include different tools that nurses can use in their practice. According to this, in the multiprofessional model of care, the nurse specialist evaluates patients' pain with the Visual Analogue Scale (VAS) and patients' function disability using the Health Assessment Questionnaire (HAQ). To assess the impact of the disease on life the nurse uses the Psoriatic Arthritis Impact of Disease Questionnaire (PsAID). The functional assessment of chronic illness therapy-fatigue scale (FACIT-fatigue) was selected to assess patients' fatigue in the multidimensional evaluation. To evaluate patients' mood, the Patient Health Questionnaire-9 (PHQ-9) is used as a screening tool for depression.

Chapter 3: Relationship between clinical variables and Patient - Reported Outcomes in patients with psoriatic disease

2.1 Introduction

Psoriatic arthritis (PsA) is an axial and/or peripheral chronic inflammatory arthritis associated with psoriasis, enclosed in the group of spondylarthritis. It is characterized by distal interphalangeal joint involvement, asymmetric distribution of arthritis, dactylitis, enthesitis, spinal involvement, and a frequent association with HLA-B27. Genetic, environmental, and immunological factors seem to contribute to its development. PsA is strongly associated with obesity, metabolic syndrome, cardiovascular disease and other comorbidities beyond joint and skin manifestations, so, patients need to be assessed both from rheumatologists and dermatologists with other healthcare professionals' support to have a more comprehensive evaluation than the standard assessment. A global assessment is important to improve their disease control and their quality-of-life. A new model of care for PsA patients is the multidimensional assessment that allows to evaluate patients globally paying attention to different aspect of the disease. Differently from the standard practice, in a multidimensional assessment a multidisciplinary team (rheumatologist, dermatologist, internal medicine physician, nutritionist and a phycologist) with a nurse as case manager, assess patients from the admission to the follow-up. According to the GRAPPA and OMERACT groups different validated tools are used by the team to patient-reported-outcomes for fatigue, the impact of disease on quality-of-life, functional disability, disease activity and mood are evaluated by the team. Joint and skin are evaluated with specific tools [54].

2.2 Aim of the study

This study aimed to evaluate the association between and among clinical variables and Patient-Reported Outcomes in a real-world sample of PsA patients.

2.3 Materials and Methods

A new model of care (The Multidimensional Assessment for PsA patients) was developed to globally evaluate patients at the Department of Internal Medicine with Rheumatology and Dermatology of the National Relevance and High Specialization Hospital Trust ARNAS Civico, Di Cristina, Benfratelli in Palermo (Italy). A cross-sectional study was carried out from March 2018 to October 2020. Eligible patients were all the outpatients with Psoriatic Arthritis diagnosis according to CASPAR criteria, aged $\geq$ 18 years, who signed the informed consent to be enrolled in the study. According to the Multidimensional assessment each patient was evaluated in the same setting by a multidisciplinary team made by rheumatologist, dermatologist, nutritionist, psychologist and a specialist nurse with the role of case manager.

2.3.1 Ethics

Patients signed informed consent before their inclusion in the study. The Ethics committee Palermo2 approved the study with protocol number 231 CIVICO 2018. The study was conducted according to the Good Clinical Practice in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Medical practice was performed as stated by the recommendations of the World Medical Assembly. Data privacy was a guarantee by the Personal Data Protection Code (196/2003) and current regulations.

2.3.2 Data collection

A data collection form and a database were created in order to collect different variables from patients. The Core Outcome Set (COS) validated by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) with the Outcome Measures in Rheumatology (OMERACT) international consensus was used as a guide to selecting tools. Data included in this study were:

- Socio-demographic data;
- Data about smoking and alcohol consumption;
- Data about family members and caregivers;
- The Health Assessment Questionnaire (HAQ) to assess functional disability;
- The Facit-Fatigue (FACIT-F) to evaluate fatigue;

- The Psoriatic Arthritis Impact of Disease Questionnaire (PsAID) to investigate about the impact of the disease in patients' quality-of-life;
- The Patient Health Questionnaire-9 (PHQ-9) to evaluate mood and screen depression;
- The Disease Activity in PSoriatic Arthritis score (Dapsa) to assess joint manifestations, pain and disease activity;
- The Patient global assessment (PGA)
- Body Mass Index (BMI)
- Waist circumference
- Complete blood panel (clinical chemistry, lipid and metabolic panel, complete blood count, cytokine levels, liver function, ESR, CRP)

2.3.3 Statistical Analysis

STATA (StataCorp.2016. Stata Statistical Software: Release 14.1, College Station, TX, USA: StataCorp LP) was used for database management and analysis. The statistical analysis was performed using the logistic analysis to study the relationships among all the variables. In particular, a logistic analysis was performed between moderate to severe functional disability (HAQ >2) and central obesity as an independent variable and among the high impact of disease (PsAID >4) as a dependent variable and central obesity as an independent variable. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were computed. A two-tailed $p<0,05$ was considered statistically significant.

2.4 Results

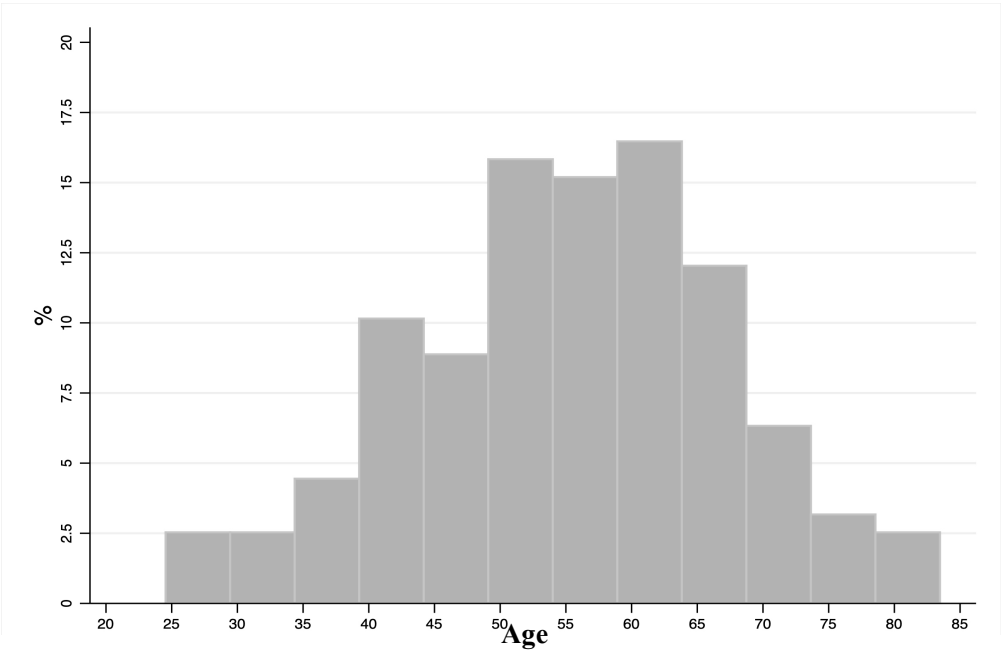
According to CASPAR criteria, 158 patients aged 55.2 (53.3 – 57.1) (Fig 6), affected by Psoriatic Arthritis were consecutively enrolled and evaluated. Both sexes were equally represented. Less than half of the sample do not have a caregiver that is a person who takes care of the patient and only the 31% of included patients attended the high school. Most of them, especially men, attended the elementary or the middle school and this was an important barrier in nursing education during the assessment. Data about the family member were collected to assess the disease burden especially for mothers or fathers who take cares of loved ones despite joint manifestations and the pain. The 24,7% were smokers and only the 5,7% consumed a regular amount of alcohol every day. The average years of illness were 10.6 (9.3-11.9). Characteristics of the participants are reported in Table 3.

Tab 3. Population Characteristics

N	**158**
Men (%)	45,6
Women (%)	54,4
Age*	55.2 (53,3 – 57,1)
Mean age men*	54,8 (52,0 - 57,6)
Mean age women*	55,5 (52,8 - 58,1)
Subjects without caregivers(%)	38,6
Education (%)	
Elementary school	15
Middle school	45
High school	31
Graduation	9
Family members*	3 (1 – 6)
Smokers (%)	24,7
Alcohol consumption (%)	5,7
Years of illness*	10.6 (9.3 - 11.9)
HAQ§	1 (0,25 – 1,75)
Facit Fatigue§	35 (20 - 43)
PSAID§	4 (2 - 6)
PHQ-9§	7 (4 - 13)
PASI§	1 (0 - 2)
Criteri CASPAR§	5 (4 - 6)

* Data are reported as mean (95% Confidence Interval).
§ Data are reported as median (interquartile range).
PSAID Psoriatic Arthritis Impact of Diesease
PHQ-9 Patient Health Questionnaire-9
BMI Body Mass Index

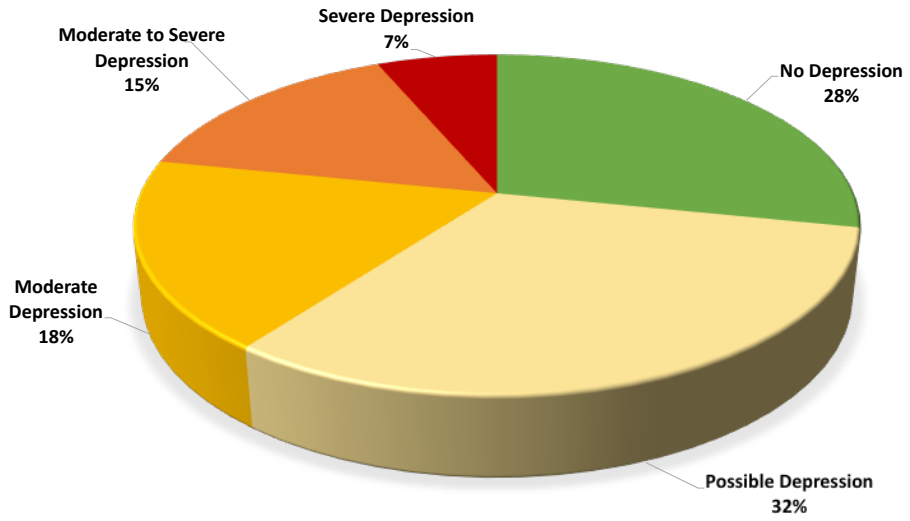
Fig 6 Population distribution for age



The specialist nurse evaluated patients with different PROMs including the Health Assessment Questionnaire (HAQ), the Facit-Fatigue (FACIT-F), the Psoriatic Arthritis Impact of Disease Questionnaire (PsAID) and the Patient Health Questionnaire-9 (PHQ-9).

Some drugs for PsA are associated with an increased risk of psychiatric symptoms, including depression, suicidal thoughts or suicidal behaviours if patients had a history of depression. For this reason, PHQ-9 was used as a screening tool to investigate about patients' mood and to screen depression. According to PHQ-9, the 40% of the enrolled sample had from moderate to very severe depression as shown in figure 7.

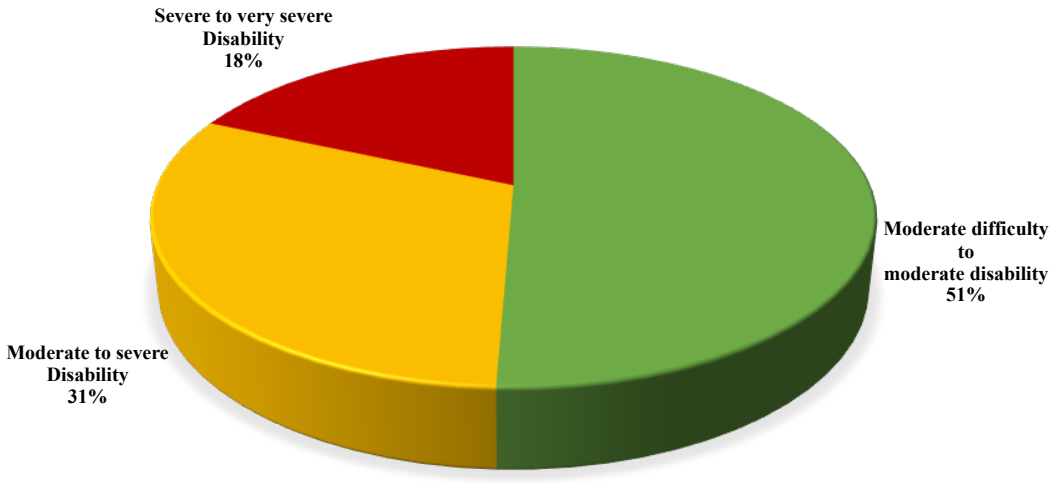
Fig 7 Patient Health Questionnaire -9



The Health Assessment Questionnaire (HAQ) was used to assess if patients had discomfort or were unable to do some daily movement as dressing, arising, eating, walking, hygiene, reach, grip, and activities in which joints are involved.

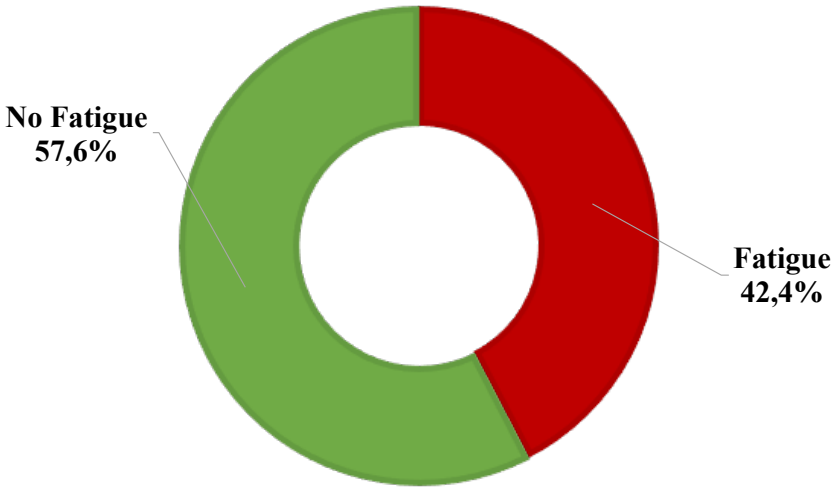
The average HAQ was 1 (0.25 - 1.75), and data analysis showed 51% of patients with normal-mild functional disability, 31% moderate to severe disability, and 18% severe to very severe disability (Fig 8).

Fig. 8 Health Assessment Questionnaire



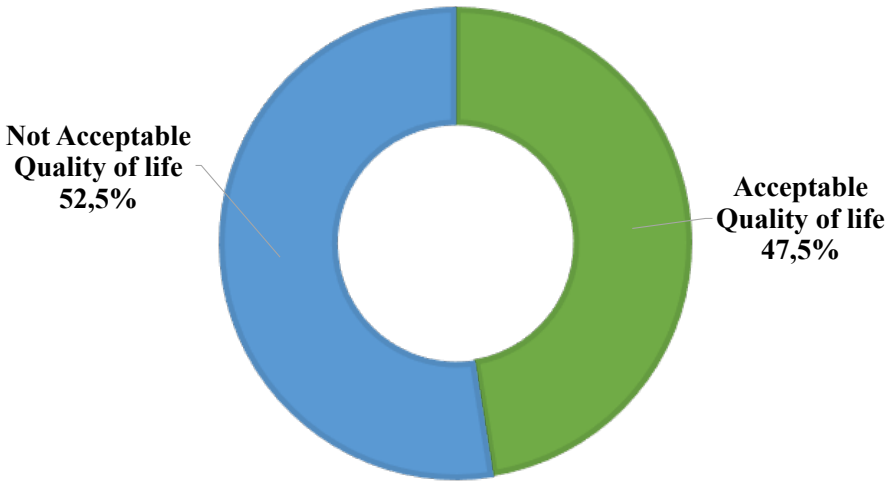
Fatigue in PsA patients is a synonymous of weakness and lack of motivation. It is underestimated and not often included in the standard assessment but it has implication for patients in terms of loss of employment, social isolation and decreased quality-of-life due to disease. In the Multidimensional assessment patients' fatigue was evaluated with the FACIT-F questionnaire that showed the 42,4% of the sample with high fatigue (fig 9).

Fig. 9 Facit–Fatigue



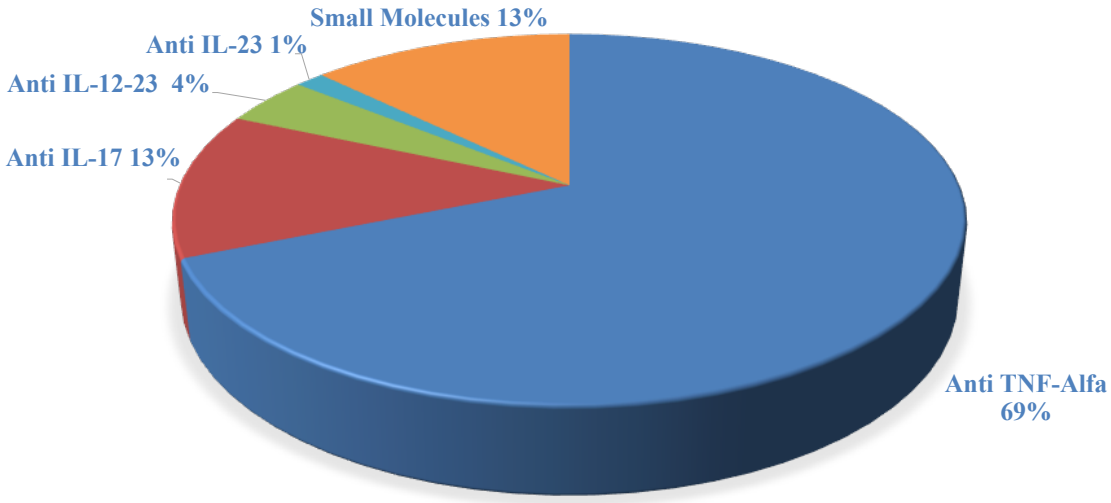
Psoriatic Arthritis negatively impact on patients' quality of life, in fact, 52.5% of the sample had a high impact of the disease on life, according to the PsAID questionnaire (fig 10).

Fig 10 Psoriatic Arthritis Impact of Disease (PsAID)



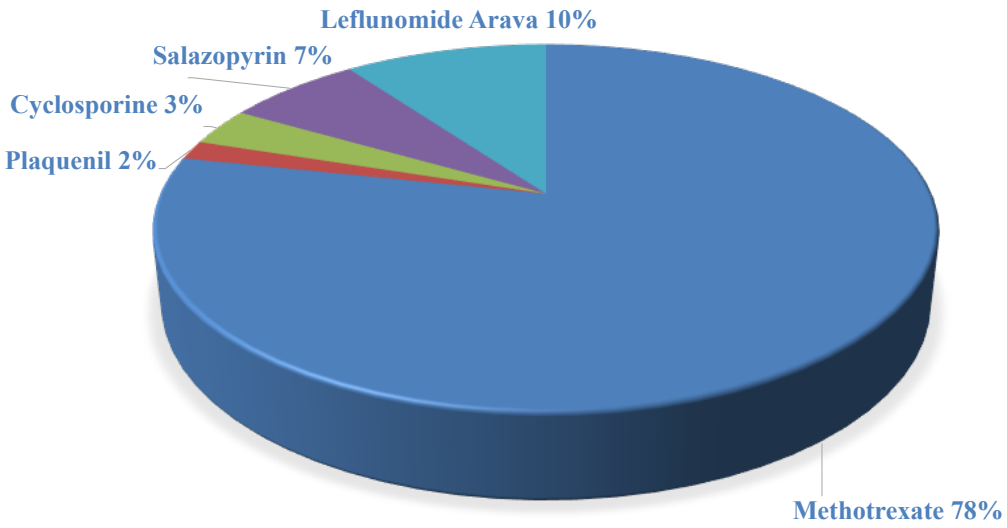
Data analysis showed that the 81.3% of the sample was treated with biological therapy (69% anti TNF- alfa, 1% anti IL-23, 4% anti IL12-23, 13% anti IL 17, and 13% small molecules) (fig 11).

Fig 11 patients treated with biological therapy



41.6% of patients were treated with DMARDS (78% methotrexate, 10% leflunomide, 7% salazopyrin, 5% cyclosporine) (fig 12) while some of them were treated with combinations of both biologics and DMARDs.

Fig 12 patients treated with DMARDS



From all the collected variables important observations came out from the anthropometric assessment. 70.2% of the 158 enrolled patients had central obesity (61.1% men and 77.9% women) with an average waist circumference of 104.3 (101 – 107.5) for women and 105.5 (102.5 -108.5) for men. Central obesity occurs when there is excessive central fat around the stomach and was measured as waist circumference (cm). It is known that increased obesity-related health risks are associated with a waist circumference greater or equal to 94 cm in men and 80 cm in women and the mean waist circumference for both sexes was 104,8 (102,6 – 107,0), so, the enrolled sample was considered at risk (tab 4).

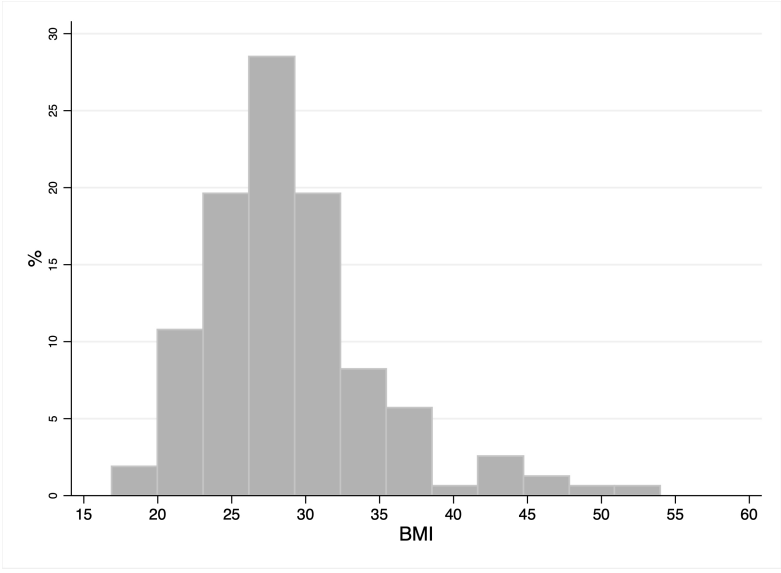
Tab 4. Anthropometric data of the sample

N	**158**
BMI*	28,9 (28,0 – 29,8)
Waist Circumference*	104,8 (102,6 – 107,0)
Waist Circumference men*	105,5 (102,5 – 108,5)
Waist Circumference women*	104,3 (101,0 – 107,5)
Central Obesity (%)	70,2
Central Obesity men (%)	61,1
Central Obesity women (%)	77,9

*** Data are reported as mean (95% Confidence Interval).**
§ Data are reported as median (interquartile range).
BMI Body Mass Index

The Body Mass Index (BMI) is a person's weight in kilograms divided by the square of height in meters, and it is an indicator of body fatness. In the enrolled sample, the mean BMI was 28,9 (28,0 – 29,8) as showed in figure 12. Normal or healthy weight ranges from 18.5 to 24.9, instead, according to the BMI weight status categories, people with a BMI that ranges from 25 to 29.9 would be classified as overweight so the studied population can be classified as overweight.

Fig 12 Body mass index of the study population



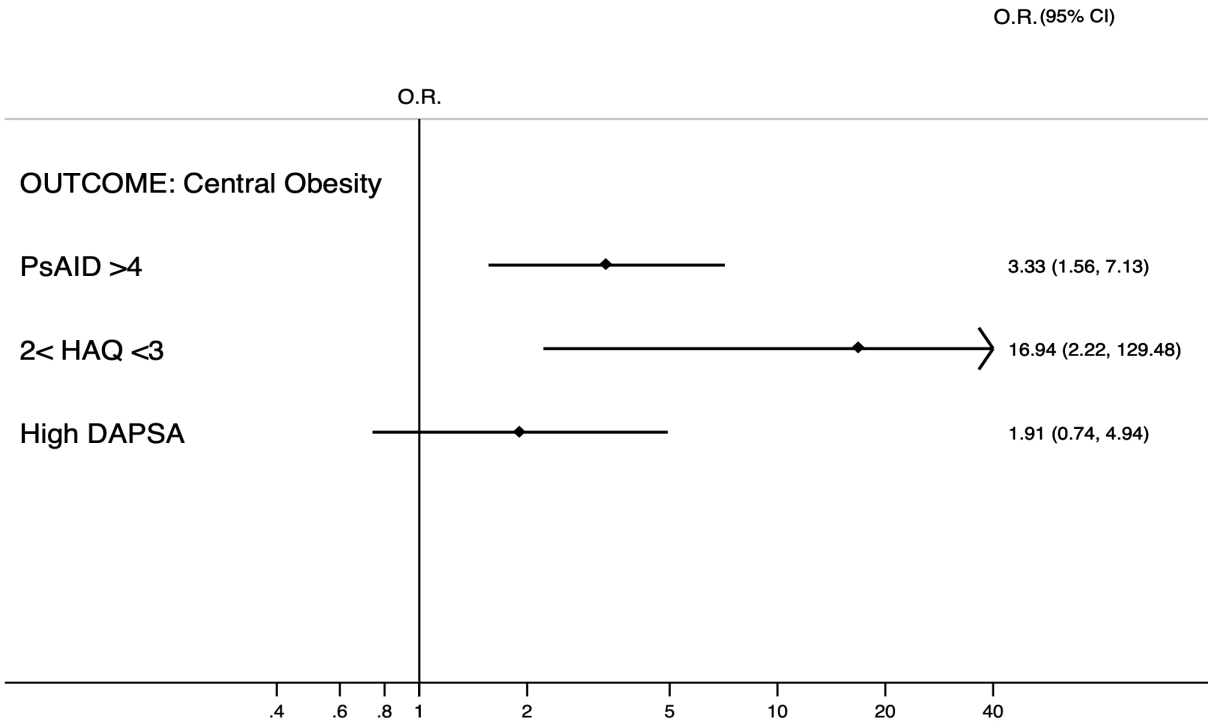
Patients were divided by subgroups as affected by central obesity or without central obesity as shown in table 5.

Tab 5 population with central obesity or without central obesity

	Patients affected by Central Obesity (n=111)	**Patients without Central Obesity (n=47)**	**p**
Men (%)	39,6	59,6	**0.0214**
Age*	57,2 (54,9 – 59,4)	50,4 (47,3 – 53,6)	**0.0011**
Years of illness*	10,8 (9,3 – 12,3)	10,0 (7,5 – 12,5)	0.4623
Smokers(%)	23,4	27,7	0.5724
Alcohol Consumption(%)	7,3	2,1	0.2041

All the collected variables were associated with PROMs with the statistical analysis and a strong association was observed between functional disability measured by HAQ >2 and central obesity [OR (95% CI) 16.94 (2.22 - 129.48); p < 0.004]. Moreover, data analysis showed an association between high impact of disease on life (PsAID >4) and central obesity [OR (95% CI) 3.33 (1.56 - 7.13); p<0,002]. Models were adjusted for age, sex, years of illness, and biological treatment.

Fig 13 association between functional disability (HAQ >2), high impact of disease on life (PsAID >4) and central obesity



2.5 Discussion

Psoriatic Arthritis is a disease treated both from rheumatologists and dermatologists and guidelines on this topic approach the management of the disease from different perspectives. EULAR guidelines [56] are more focused on pharmacological treatments for musculoskeletal manifestations, and only in cases of substantial skin or nail bed manifestations EULAR recommends working closely with a dermatologist. Even if the GRAPPA recommendations [57] were developed by consensus among the two specialists, PsA patients have usually more than one comorbid condition in addition to the skin and joint diseases so, they need to have a more comprehensive assessment. As Visalli et al. said PsA can be optimally treated by a multidisciplinary approach so the multidimensional assessment represents a new model of care that allows patients to receive the best possible quality of care [58]. The multiprofessional team evaluated skin and joint manifestation, pain and disease activity, anthropometric measures, physical function, fatigue and the impact of the disease on patients' quality-of-life. Psoriatic Arthritis is an inflammatory disease, and all the others inflammatory conditions may affect patient outcomes. One of the most important observation during the three years of patients'

examination was about the quality-of-life in patients with high waist circumferences so we aimed to study the association among central obesity and the role of central obesity as a predictor of high impact of disease on quality-of-life and disease activity. Corrao et al. highlighted the role of central obesity in increasing the inflammatory status. According to the authors, central obesity occurs when there is an excessive intra-abdominal visceral fact and has been strongly linked to cardiovascular disease. Visceral adipose Tissue was considered to be a storage organ for fatty acids without other functions, but nowadays in particular the visceral one is considered a metabolically active endocrine organ. In fact, it represents a source of inflammatory mediators, known as adipokines, including leptin and adiponectin, plasminogen activator inhibitor-1 (PAI-1), TNF-α, macrophage chemoattractant protein-1, IL-6, leading to a pro-inflammatory status in obese subjects [59-61]. TNF is overexpressed in the adipose tissue that links obesity, diabetes and chronic inflammation [62]. In addition, obesity promotes expansion of Th17 cells in adipose tissue and peripheral tissues [63]. For all these reasons, obesity is considered as a low-grade inflammatory disease and, in particular, central obesity may also determine an increased risk of not achieving and maintaining minimal disease activity (MDA) in PsA patients [64]. Inflammation affects joints and reduces patients' ability. This study demonstrated that patients with central obesity have functional disability and a high impact of the disease on their quality-of-life. Data suggest that a multiprofessional evaluation for these patients is important to evaluate different aspect of the disease as the comorbidities that may impact negatively on outcomes and helps to improve patients' quality of life.

Conclusion and future prospective

This study demonstrated that this new model of care (The Multidimensional Assessment) for these patients is important to evaluate different aspect of the disease as the comorbidities. In particular, therapeutic goals should not be focused only on treatment but also on waist circumference reduction to reduce inflammation and improve patients' functional ability and quality-of-life. Further research is needed to study the relationship between serum cytokine levels and clinical variables in PsA patients according to their treatment to find the correct drug. Serum samples were collected at the same time of patients' evaluations and stored. The MAGPIX® system will analyze serum cytokine levels. This system will use customized magnetic bead-based multi-analyte panels, as a novel protein array system denoted as multiplex cytokine assay, to simultaneously measure the levels of 10 circulating cytokines of patients with PsA. We will analyze: COMP, IL-2, IL-4, IL-6, IL-10, IL-17A (CTLA-8), IL-23, M-CSF, RANKL, and TNF alpha in order to match results with the collected variables.

List of abbreviations

Classification Criteria for Psoriatic Arthritis = (CASPAR)

Confidence Interval = (CI)

Disease modifying antirheumatic drugs = (DMARDS)

Health Assessment Questionnaire = (HAQ)

Human leukocyte antigen complex = (HLA)

Minimal disease activity =(MDA)

Nonsteroidal anti-inflammatory drugs = (NSAID)

Odd Ratio = (OR)

Plasminogen activator inhibitor-1 = (PAI-1)

Psoriasis Area Severity Index = (PASI)

Psoriatic Arthritis = (PsA)

Psoriatic Arthritis Impact of Disease = (PsAID)

Tumor necrosis factor = TNF α

T-helper cell=Th

Regulatory T cell=Treg

Innate lymphoid cell= ILC

Mucosal-associated invariant T= MAIT

NK=natural killer

TNF superfamily member 11=RANKL

Interferon γ=IFNγ

Interleukin=IL

Transforming growth factor β=TGFβ

C-C motif chemokine ligand 5=RANTES

Oncostatin M= OSM

Granulocyte-macrophage colony-stimulating factor=GM-CSF

Reactive oxygen species=ROS

Nitric oxide=NO

Matrix metalloproteinases=MMPs

Macrophage migration inhibitory factor=MIF

References

[1] Taylor WJ, Mease PJ, Adebajo A, et al. Effect of psoriatic arthritis according to the affected categories of the international classification of functioning, disability and health. J Rheumatol. 2010;3:1885-1891.

[2] Taylor W, Gladman D, Helliwell P, et al. CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.

[3] Haddad A, Chandran V. Arthritis mutilans. Curr Rheumatol Rep. 2013 Apr;15(4):321.

[4] Chandran V, Gladman DD, Helliwell PS, et al. Arthritis mutilans: a report from the GRAPPA 2012 annual meeting. J Rheumatol. 2013 Aug;40(8):1419-22.

[5] Cohen MR, Reda DJ, Clegg DO. Baseline relationships between psoriasis and psoriatic arthritis: analysis of 221 patients with active psoriatic arthritis. J Rheumatol. 1999 Aug;26(8):1752-6.

[6] Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii3-8.

[7] Taylor WJ. Impact of psoriatic arthritis on the patient: through the lens of the WHO International Classification of Functioning, Health, and Disability. Curr Rheumatol Rep 2012;14:369-374.

[8] Singh JA, Strand V. Spondyloarthritis is associated with poor function and physical health-related quality of life. J Rheumatol 2009;36:1012–1020.

[9] Villani AP, Rouzaud M, Sevrain M, et al. Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: Systematic review and meta-analysis. J Am Acad Dermatol. 2015 Aug;73(2):242-8.

[10] Gladman DD, Shuckett R, Russell ML, et al. Psoriatic arthritis (PSA)-an analysis of 220 patients. Q J Med. 1987 Feb;62(238):127-4.

[11] Alinaghi F, Calov M, Kristensen LE, *et al.*: Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies. *J Am Acad Dermatol.* 2019; 80(1): 251–265. e19.

[12] Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. Rheum. Dis. Clin. North Am. 2015 Nov;41(4):545-68.

[13] Belasco J., Wei N., Psoriatic Arthritis: What is Happening at the Joint? Rheumatol Ther (2019) 6:305–315 https://doi.org/10.1007/s40744-019-0159-1

[14] Merola JF, espinoza LR, Fleischmann R. Distinguishing rheumatoid arthritis from psoriatic arthritis. RMD Open 2018;**4**: e000656. doi:10.1136/ rmdopen-2018-000656.

[15] Maren C. Karreman Angelique E. et al. Prevalence of Psoriatic Arthritis in Primary Care Patients with Psoriasis Psoriatic Arthritis 04 Dec 2015 https://doi.org/10.1002/art.39530.

[16] Farzad Alinaghi, Monika Calov , Lars Erik Kristensen. Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies. Am Acad Dermatol. 2019 Jan;80(1):251-265.e19.doi: 10.1016/j.jaad.2018.06.027. Epub 2018 Jun 19.

[17] Oliver FitzGerald1, Muhammad Haroon1, Jon T Giles2 et al. Concepts of pathogenesis in psoriatic arthritis: genotype determines clinical phenotype FitzGerald et al. Arthritis Research & Therapy (2015) 17:115 DOI 10.1186/s13075-015-0640-3.

[18] Soltani-Arabshahi R, Wong B, Feng BJ et al (2010). Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol; 146:721 6.

[19] Chiara TD, Argano C, Corrao S et al (2015). Circulating adiponectin: a cardiometabolic marker associated with global cardiovascular risk. Acta Cardiol.;70(1):33-40.

[20] Di Chiara T, Licata A, Argano C, et al. (2014). Plasma adiponectin: a contributing factor for cardiac changes in visceral obesity-associated hypertension.Blood Press.;23(3):147-53. doi: 10.3109/08037051.2013.823767.

[21] Licata G, Scaglione R, Avellone G, et al. Obesity, hypertension and atherosclerosis. Int Angiol. 1993 Dec;12(4):326-30. PMID: 8207307.

[22] Aprahamian TR, Sam F (2011) Adiponectin in cardiovascular inflammation and obesity. Int J Inflam 2011:376909. https://doi.org/ 10.4061/2011/376909.

[23] Di Minno MN, Peluso R, Iervolino S, et al. (2013) Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. Arthritis Care Res (Hoboken) 65:141–147. https://doi.org/10.1002/acr. 21711.

[24] Hojgaard P, Glintborg B, Kristensen LE, et al. (2016) The influence of obesity on response to tumour necrosis factor-alpha inhibitors in psoriatic arthritis: results from the DANBIO and ICEBIO registries. Rheumatology (Oxford) 55: 2191–2199. https://doi.org/10.1093/rheumatology/kew326.

[25] Solmaz D, et al., Update on the epidemiology, risk factors, and disease outcomes of psoriatic arthritis, Best Practice & Research Clinical Rheumatology (2018), https://doi.org/ 10.1016/j.berh.2018.09.006.

[26] Uyen-Sa D. T. Nguyen, Yuqing Zhang, Na Lu et al. The Smoking Paradox in the Development of Psoriatic Arthritis among Psoriasis Patients – A Population-Based Study Ann Rheum Dis. 2018 January ; 77(1): 119–123. doi:10.1136/annrheumdis-2017-211625.

[27] Wu S, Cho E, Li WQ, Han J, Quereshi AA. Alcohol intake and risk of incident psoriatic arthritis in women. J Rheumatol
2015;42:835e40.

[28] Jane Hsieh & Sabeeda Kadavath & Petros Efthimiou Can traumatic injury trigger psoriatic arthritis? A review of the literature Clin Rheumatol 2013 DOI 10.1007/s10067-013-2436-7.

[29] Naiem Issa, Ladan Afifi, Caleb Jeon et al. The Role of the Skin and Gut Microbiome in Psoriatic Disease Curr Dermatol Rep. 2017 June; 6(2): 94–103. doi:10.1007/s13671-017-0178-5.

[30] Gao Z, Tseng CH, Strober BE, et al. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PloS one. 2008; 3(7): e2719.doi: 10.1371/journal.pone.0002719.

[31] Hok Bing Thio. The Microbiome in Psoriasis and Psoriatic Arthritis: The Skin Perspective Rheumatol Suppl 2018 Jun;94:30-31 DOI: 10.3899/jrheum.180133

[32] Fahlen A, Engstrand L, Baker BS, et al. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Archives of dermatological research. 2012; 304(1):15–22. DOI: 10.1007/s00403-011-1189-x.

[33] Drago L, De Grandi R, Altomare G, et al. Skin microbiota of first cousins affected by psoriasis and atopic dermatitis. Clinical and molecular allergy : CMA. 2016; 14:2.doi: 10.1186/ s12948-016-0038-z.

[34] Lourdes M. Perez-Chada, Joseph F. Merola. Comorbidities associated with psoriatic arthritis: Review and update. Clinical Immunology 2020 May;214:108397. doi: 10.1016/j.clim.2020.108397.Epub 2020 Mar 27.

[35] Sakkas, L. I., and Bogdanos, D. P. (2017). Are psoriasis and psoriatic arthritis the same disease? e IL-23/IL-17 axis data. *Autoimmun. Rev.* 16 (1), 10–15. doi: 10.1016/j.autrev.2016.09.015.

[36] Wilson NJ, Boniface K, Chan JR, et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol.* (2007) 8:950–7. doi: 10.1038/ni1497.

[37] Susan Tseng, A. Hari Reddi, and Paul E. Di Cesare Cartilage Oligomeric Matrix Protein (COMP): A Biomarker of Arthritis Biomark Insights. 2009; 4: 33–44. 2009 Feb 17. doi: 10.4137/bmi.s645.

[38] Reich A, Szepietowski JC (2007). "Mediators of pruritus in psoriasis". Mediators of Inflammation. 2007: 1–6. doi:10.1155/2007/64727. PMC 2221678. PMID 18288273.

[39] Liu Y, Helms C, Liao W, Zaba LC, et al. (2008) A Genome-Wide Association Study of Psoriasis and Psoriatic Arthritis Identifies New Disease Loci. PLoS Genetics 4 (4):e1000041. doi:10.1371/journal.pgen.1000041.

[40] Chandran V (2013) The genetics of psoriasis and psoriatic arthritis. Clinic Rev Allerg Immunol 44 (2):149–156.

[41] Dalbeth et al.: Circulating mediators of bone remodeling in psoriatic arthritis: implications for disordered osteoclastogenesis and bone erosion. Arthritis Research & Therapy 2010 12:R164.

[42] Wolska H. Nail psoriasis. Przegl Dermatol. 2010;97:243–253.

[43] Grover C, Reddy BS, Uma Chaturvedi K. Diagnosis of nail psoriasis: importance of biopsy and histopathology. Br J Dermatol. 2005;153:1153–1158.

[44] Taylor W, Gladman D, Helliwell P, et al. Classi cation criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; **54:** 2665–73.

[45] Coates, L. C., & Helliwell, P. S. (2017). Psoriatic arthritis: state of the art review. Clinical Medicine, 17(1), 65–70.doi:10.7861/clinmedicine.17-1-65.

[46] Yvonne van Eijk-Hustings, Astrid van Tubergen, Carina Boström et al. EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis Ann Rheum Dis: first published as 10.1136/annrheumdis-2011-200185 on 28 October 2011.

[47] G. Candelas, V. Villaverde, S. García et al. Benefit of health education by a training nurse in patients with axial and/or peripheral psoriatic arthritis: A systematic literature review Rheumatol Int. DOI 10.1007/s00296-016-3549-5.

[48] V. Chandran & AB Maharaj (2016): Assessing disease activity in psoriasis and psoriatic arthritis: impact on management and therapy, Expert Review of Clinical Immunology, DOI: 10.1586/1744666X.2016.1146133.

[49] Ritchlin CT, Kavanaugh A, Gladman DD, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). treatment recommendations for psoriatic arthritis. Ann Rheum Dis 2009;68:1387-94.

[50] Mease PJ, Antoni CE, Gladman DD, et al. Psoriatic arthritis assessment tools in clinical trials. Ann Rheum Dis 2005;64 Suppl 2: ii49-54.

[51] Anna Russolillo, Salvatore Iervolino, Rosario Peluso Obesity and psoriatic arthritis: from pathogenesis to clinical outcome and management RHEUMATOLOGY September 18, 2012 doi:10.1093/rheumatology/kes242.

[52] Ana-Maria Orbai, Maarten de Wit, Philip J. Mease et al. Updating the Psoriatic Arthritis (PsA) Core Domain Set: A Report from the PsA Workshop at OMERACT 2016. J Rheumatol 2017;44;1522-1528

[53] Gladman DD, Mease PJ, Strand V et al. Consensus on a core set of domains for psoriatic arthritis. J Rheumatol 2007;34:1167-70.

[54] Pil Højgaard , Louise Klokker , Ana-Maria Orbai. A systematic review of measurement properties of patient reported outcome measures in psoriatic arthritis: A GRAPPA-OMERACT initiative. SeminArthritisRheum2018Apr;47(5):654-665.doi:10.1016/j.semarthrit.2017.09.002

[55] Editorial. Psoriatic arthritis: classification and holistic management 2018 Jun 2;391(10136):2185.doi: 10.1016/S0140-6736(18)31249-2.Epub 2018 Jun 1.

[56] Laure Gossec Xenofon Baraliakos, Andreas Kerschbaumer et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies:2019update Annals of the Rheumatic Diseases 2020; 79 680-682 Published Online First: 20 May 2020. doi: 10.1136/annrheumdis-2020-217236

[57] Arthur Kavanaugh, Laura C. Coates, Danielle A. van der Windt, GRAPPA Treatment Recommendations: Updates and Methods. The Journal of Rheumatology Supplement June 2020, 96 41-45; DOI: https://doi.org/10.3899/jrheum.200126

[58] Elisa Visalli , Natascia Crispino , Rosario Foti Multidisciplinary Management of Psoriatic Arthritis: The Benefits of a Comprehensive Approach Adv Ther 2019Apr;36(4):806-816. doi: 10.1007/s12325-019-00901-0.Epub 2019 Feb 25.

[59] Licata G, Scaglione R, Avellone G, Parrinello G, Merlino G, Corrao S. Obesity, hypertension and atherosclerosis. Int Angiol. 1993 Dec;12(4):326-30. PMID: 8207307.

[60] Chiara TD, Argano C, Corrao S et al (2015). Circulating adiponectin: a cardiometabolic marker associated with global cardiovascular risk. Acta Cardiol.;70(1):33-40.

[61] Di Chiara T, Licata A, Argano C, Corrao S (2014). Plasma adiponectin: a contributing factor for cardiac changes in visceral obesity-associated hypertension.Blood Press.;23(3):147-53. doi: 10.3109/08037051.2013.823767.

[62] G.S. Hotamisligil, Inflammation and metabolic disorders, Nature 444 (2006) 860–867.

[63] M. Chehimi, H. Vidal, A. Eljaafari, Pathogenic role of IL-17-producing immune cells in obesity, and related inflammatory diseases, J. Clin. Med. 6 (2017).

[64] Di Minno MN, Peluso R, Iervolino S, et al. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. Arthritis Care Res (Hoboken) (2013) 65:141–147. https://doi.org/10.1002/acr. 21711