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"Analysis of psychopathological dimensions in a cohort of Systemic Lupus Erythematosus patients"

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ABSTRACT

Introduction. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect virtually any organ or tissue. The neuropsychiatric involvement of SLE encompasses a wide spectrum of neurological and psychiatric manifestations, posing a significant challenge for clinicians in terms of both diagnosis and treatment.

Methods. We investigated prevalence of different psychopathological dimensions in a cohort of SLE patients and analysed their potential association with clinical and laboratory features of the disease. Sixty-eight SLE patients were enrolled in the study and underwent comprehensive clinical and laboratory evaluations, including screening for fibromyalgia. Additionally, psychiatric assessments were conducted using the following scales: TAS-20 for alexithymia, BDI-2 for depression, BHS for hopelessness, BIS-11 for impulsiveness, and COPE-60 for coping styles.

Results. In our cohort, prevalence of alexithymia was 23.5%, showing a higher frequency (OR 5.64, p=0.016) and severity (p=0.043) in patients with antiphospholipid antibodies syndrome (APS). The prevalence of depression and hopelessness was 32.4% and 26.5%, respectively. A higher level of depression was found in patients with chronic damage (p=0.046), fibromyalgia (p=0.003) or active arthritis (p=0.02).

Conclusion. Our study clearly indicates the presence of several psychopathological dimensions in patients affected by SLE. A heightened focus by clinicians on these frequently neglected psychopathological facets could significantly improve the quality of life of SLE patients.

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1. INTRODUCTION

1.0 SYSTEMIC LUPUS ERITHEMATOSUS

The word “lupus” was used for the first time by Herbernus of Tours in 916 AD to describe a cutaneous disease and, after him, the term was applied to an exclusively dermatological disease for centuries.[1] Indeed, the first description of the lupus erythematosus (LE), under the term of “erythema centrifugum”, was described by Biett in 1833 and reported by his student Cazenave in 1851 with a totally dermatological optic, even though he mentioned the occurrence of “fever and even pain”.[2,1] In the meanwhile, it was not missing the hypothesis that LE wan an infectious disease, in particular it was associated to lupus vulgaris, a cutaneous infection of M. Tuberculosis, and Hutchinson in 1888 worked on the principal distinctions between these entities. Nevertheless, he was firmly convinced that “it’s only a question of time” that the tubercle bacillus will be detected in LE cases.[3] In 1872, Kaposi described other symptoms than skin lesions, noting that some patients had swelling of lymph nodes as well as joint pain and swelling. Furthermore he stated that LE was associated with severe constitutional symptoms that can lead to death.[4] However, the current expression of “systemic lupus erythematosus” (SLE) was coined by Sir W. Osler[5] when, in 1904 in the last of three papers, he summarized 29 cases of LE with extracutaneous symptoms, more frequently of which presented arthralgia and nephrites.[6] Later, it seems that only 2 cases were truly LE while the others seem to be an immune complex mediated small vessel disease and often a glomerular disease, such as Henoch-Scholein purpura.[7]

1.1 EPIDEMIOLOGY

Systemic lupus erythematosus is a chronic autoimmune disease which can involve many different organs, such as skin, joints, kidney and both central and peripheral nervous system.[8,9] Women are consistently more affected than men with a female-to male incidence and prevalence ratio respectively of 12:1 and 8:1.[10] This difference is probably due to the diverse hormonal setting of these groups, hence its interactions with the immune system. Especially oestrogens seem to prolong the life of lymphocyte and epidemiologic researches suggest that exogenous hormone use (like oral contraceptives) is associated with an increased risk of SLE.[11] Furthermore, an incidence difference in ethnic minorities has been found to be highest in black women, followed by Hispanic, Asian and Caucasian women, with a worse outcome associated. Although the socioeconomic factor is difficult to disentangle, it plays an important role in both course and outcome in these populations.[10,12]

It is not under discussion that SLE develops in individuals that have a genetic predisposition on which environmental factor works, indeed, the heritability of SLE is estimated to be 43.9%.[13] In rare cases, SLE is associated to a single gene mutation with an highly penetrance, chiefly in early-onset juvenile SLE. These are the cases of C1Q, C2 and C4 mutations, that causes a complete deficiency of the classical complement pathways, or non-sense mutation in DNASE1.[14,15] However, in most cases of SLE different genes can be found implicated in the pathogenesis of SLE, but they are not sufficiently, alone, to cause the disease, therefore the genetic backgrounds play a role in related clinical phenotypes under different environmental conditions.[16] Through genome-wide association studies (GWAS) in SLE patients, more insights have helped to clear the genetical predisposition and pathogenesis of the disease, in particular it is highlighted the role of the innate immune system. Mutations that have the consequence to increase type I interferon (INF-I), such as TREX1, type I INFR, toll-like-receptors-7 (TLR-7), IRF5 and others, confer a risk factor for developing SLE and, in support of this, SLE patients have a significantly elevated INF-I serum level compared to controls.[17,18] Lastly, also other genetical mechanisms are implicated in the development of SLE including epigenetic and miRNA.

To the other side, the environment sustains a key role in the epidemiology and pathogenesis of SLE. The most striking aspect is given by the drugs-induced SLE, first described in 1940s, defined as "a lupus-like syndrome that develops because of exposure to a drug and resolves after its cessation". Procainamide and hydralazine have been strongly associated with this syndrome, probably acting through epigenetic mechanism preventing the replication of DNA methylation patterns during mitosis, resulting in hypomethylation of the DNA and lupus-like autoimmunity.[19,20] Severe infections that require hospitalization are associated to the development of autoimmune disease, regardless to the type of the infection, and the risk is higher if the diagnosis of autoimmune disease is as near as the time of the infection. In this setting, serious infections could be the final trigger to the development of clinical autoimmune disease or

might accelerate a preexisting autoimmune condition to progress clinically.[21] Specifically to SLE, EBV seropositivity has been found to be higher in individuals with SLE.[11] Furthermore, EBV DNA and anti-EBV-early antigen IgG have been associated to the activation of INF I pathway and the development of SLE might be due to the SLE genomic risk loci being occupied and rewired by EBV nuclear antigen 2 (EBNA2).[22] On the same way, the stimulation of the immune system through vaccinations has been proposed as a cause of the onset of SLE, though this association has not been confirmed and does not subsist. Particulate air pollution, cigarette smoking, pesticide exposure and polycyclic aromatic hydrocarbons are all associated with increased SLE risk, while an inverse association with moderate alcohol intake has been found.[11] Exposure to respirable silica dust is associated with the development of SLE and other autoimmune diseases, indeed, it has been supposed, following repeated short term airway exposures, that the lung serves as a platform for the early triggering and exacerbation of systemic autoimmunity and glomerulonephritis.[23] If it is well known that sun exposure in SLE patients can exacerbate mainly the cutaneous disease, but also various systemic symptoms,[24] it is largely unclear if UV exposure has a role in the pathogenesis of SLE itself.[25] Finally, pregnancy is associated with and increased activity of SLE, perhaps due to the elevated oestrogens that occur during this period and flares can be seen at any time during pregnancy, as well as in several months after birth.[26] Hence, pregnancy and puerperium may play a role as SLE triggers in predisposed women.

1.2 CLINICAL ASPECTS

Systemic lupus erythematosus is an extremely heterogeneous autoimmune disease, clinically and serologically. Almost any organ can be affected with a broad spectrum of manifestations.[27] Arthritis is between the most common features, followed by cutaneous lesions, renal, neurologic, pulmonary, serous membrane and muscular involvement. The prevalence difference between the various manifestations can be explained through ethnical, genetical and epigenetics, environmental factors, socioeconomic status and access to the health care system.[12,22] Also the accrued damages can be affected by these factors and studies supported that some ethnicity, like African Americans compared to Caucasians, have a worse progress and higher cumulative damage.[28] Regardless of ethnicity, most manifestations occur within the first 5 years of disease.[29] Frequent clinical manifestations that are common at disease early onset and can act as mimickers in SLE patients are also fever, fatigue, weight loss and lymphadenopathy.[30] Before starting clinical aspects description, it should be noted the existence of two subgroups of patients. The first one consists of patients that do not fulfil the SLE diagnostic criteria despite having antinuclear antibodies (ANA) seropositivity, polyarthritis, immunological or haematological disorders. This condition is called incomplete lupus erythematosus (ILE) and it can evolve in proper SLE. In spite of the name, the clinical manifestations can be severe.[31] The second one consists in patients that develop SLE at age of onset ≥50 years, called late-onset SLE, which is an uncommon condition. It is important to remember that this specific population has a different epidemiology (for example female to male ratio is lower) and course of disease, with different frequencies of manifestations than the early-onset SLE.[32]

1.2.1 Cutaneous disease

Skin is prominently affected in lupus erythematosus. Cutaneous lesions occur about 50% of the time in the absence of systemic disease.[33] Cutaneous lupus erythematosus (CLE) has a similar incidence of SLE, but males are 3 fold more interested than those with SLE, hence CLE has a lower female to male ratio than SLE, assessed around 3:1.[34] Ultraviolet light can be a strong trigger of CLE and it can induce lesions after exposition.[35] Sometimes it can cause also systemic symptoms. Gilliam and Sontheimer developed a classification system based on the histopathology of skin lesions and these have been divided into 2 groups: LE-specific lesions and LE-nonspecific lesions. LE-specific lesions include acute, subacute and chronic CLE (ACLE, SCLE and CCLE). The latter includes discoid LE (DLE), LE profundus or panniculitis (LEP), chilblain LE (CHLE) and LE tumidus (LET). LE-nonspecific lesions are not characteristics, but are frequently seen in SLE, such as livedo reticularis, non-scarring alopecia, Raynaud's phenomenon and leukocytoclastic vasculitis.[36,37]

1.2.1.1 Acute cutaneous lupus Erythematosus

Acute cutaneous lupus erythematosus is associated with active SLE. It can be distinguished in a localized or generalized form.[37] The most frequent one is the localized form (i.e., malar or butterfly rash) which refers to erythema

that occurs over both cheeks, extends over the nasal bridge and spares the nasolabial folds. The morphology of the lesions ranges from mild erythema accompanied or not by an intense edema. Malar rash is typically transient, it resolves without scarring lesions, although depigmentation might occur. Poikiloderma, which consist of telangiectasias, dyspigmentation and epidermal atrophy may help to distinguish between malar erythema and other facial eruptions. The generalized form consists in lesions above and below the neck (i.e., photosensitive lupus dermatitis) and consist in a symmetric maculopapular rash that specially involves the photo-exposed skin with sparing of the knuckles, when hands are interested. Moreover, erythema multiforme-like lesions have been described in ACLE or SCLE, called Rowell's syndrome.[38] Indeed, ACLE is associated with an high incidence of anti-dsDNA and anti-Sm antibodies in parallel with active SLE.[39]

1.2.1.2 Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus is the most photosensitive form compared to others CLE after LET,[35] young to middle aged women are the most involved and it accounts for 10-15% of all CLE forms.[40] Lesions typically spare the middle face while involve more commonly the V region of the trunk, lateral portion of the face and extensor superficies of the upper arms. SCLE can present as annular configuration, with raised red borders and blenched centre, or as papulosquamous pattern, which can resemble eczematous or psoriasiform appearance.[37] Papulosquamous lesions look more frequent than annular lesions, but both lesions can be present in the same patient. Another rare variant presentation of SCLE is the poikilodermatousus form.[40] Furthermore, a portion of SCLE patients will develop over time Sjogren's syndrome overlap, indeed, 70% of SCLE patients are anti-Ro/SSA antibodies positive. Interestingly, SCLE can be developed from some drug-intake, such as thiazides diuretics, calcium channel blockers and proton pump inhibitors. It is clinically identical to the others forms of SCLE, with the lesions disappearing when medication is interrupted.[41]

1.2.1.3 Chronic cutaneous lupus erythematosus

Discoid lupus erythematosus. Between the various forms of chronic cutaneous lupus erythematosus, discoid lupus erythematosus has the higher incidence present in 5-10% of SLE patients, making it the most common, with a generally more benign disease.[33,42] Women in their fourth and fifth decade of life are more interested and sun exposure or trauma can exacerbate the disease. As ACLE is divided in localized form, which involves the face, and generalized form, in which lesions appear above and below the neck, DLE has the same differentiation.[37] Localized DLE occurs preferentially on the scalp and ears surface, instead generalized DLE usually appears on the extensor forearms and rarely on mucosal surfaces, moreover it is associated with a higher likelihood of evolution in SLE. Early lesions are a well demarcated, scaly, erythematosus macules or papules that will evolve in an indurated coin-shaped ("discoid") plaques, which is covered by an adherent scale that infiltrates the hair follicles, painful to remove, resulting in a scarring alopecia.

If removed, the under surface of the scale presents a series of keratotic spikes, shaped by the follicles, named the carpet-tack sign.[43] Longstanding lesions are typically dyspigmented, with an atrophic and depigmented central area and hyperpigmentation in the periphery. An unusual variant of DLE is hypertrophic/verrucous DLE, characterized by a very thick scale, resulting in a difficult differential diagnosis with squamous cell carcinoma, which may occur in DLE lesions.

Lupus erythematosus profundus, chilblain lupus and lupus erythematosus tumidus. LE profundus or panniculitis is an intense inflammation of the subcutaneous fat, which involves preferentially face, breast, thighs and upper arms. The painful, firm subcutaneous nodules, that can be present under DLE lesions, can evolve into disfiguring depressed area. Feature is the chronic remission and flare-up course. Chilblain lupus is a rare form of CCLE consisting in dusky purple papules and plaques on the toes, exacerbated by cold. Lesions tend to persist also in warmer weather, differently to idiopathic chilblain. Lupus tumidus is an extremely photosensitive lesion and it is characterized by erythematous papules and plaques, with induration without scale.[35,37]

1.2.1.4 Lupus-nonspecific skin lesions

Unlike the previously described lupus-specific lesions, lupus-nonspecific lesions lack the histologic feature to be distinguished as a type of lupus disease, indeed these can occur also in other diseases. Nevertheless, some manifestations are highly present in LE, some of which are photosensitivity reactions, alopecia, vasculitis, Reynaud's phenomenon, livedo reticularis and others.[37]

Study has found that 93% of LE patients had an abnormal reaction to UV light, making *photosensitivity* the most common skin-related finding in those population.[35] Both UVA and UVB light are involved in eliciting symptoms such as burning, itching and erythema, furthermore in some patients also systemic symptoms can be triggered. Hair loss affects over 85% of SLE patients lifetime and at least three different patterns can be recognised: diffuse or patchy *non scarring alopecia* (NSA) and *lupus hair*.[44] Short hairs alongside the periphery of the scalp are characteristics of lupus hair, along with dryness and fragility. Alopecia is strongly associated with SLE disease activity. Blood vessels involvement in SLE has been recognized with a prevalence that fluctuates between 11-35.9% and skin is the organ most affected by *vasculitis*, founded in 8% of patients.[45] LE vasculitis interests small blood vessels and does not clinically differ from others autoimmune diseases, appearing as a palpable purpura, ulcers and urticaria-vasculitis, while, pathologically, resembles leukocytoclastic vasculitis. *Livedo reticularis* is another possible manifestation of vasculitis, causing also by the presence of antiphospholipid antibodies. *Raynaud's phenomenon* underling an ischemic process that occurs in 18-46% of SLE patients.[46] Typically, it is triggered by cold exposure and consists in a vasospasm that interests mostly the fingers. A recognised sequence has been descripted: first fingers appear white-blenched, followed by cyanosis and then erythematosus, sign that blood starts flowing again.

1.1.3 Musculoskeletal disease

Musculoskeletal involvements are widespread among SLE patients concerning joints, muscle and bone. *Arthritis* is the dominant manifestation of active lupus and in 57.6% of cases is present at disease onset.[30] It is a typically symmetric polyarthritis that involves preferentially small joints, indeed hands are more interested with the metacarpal phalangeal, proximal interphalangeal and distal interphalangeal joints. Patients complain pain and morning stiffness and, at physical examination, tenderness with or without joints swelling can be seen because the presence of joint fluid or synovial proliferation. Differently to rheumatoid arthritis (RA), SLE arthritis, in most cases, is not erosive, nevertheless RA-like deformities (e.g., ulnar drift) can be observed, due to ligament laxity and joint subluxation. These deformities are reducible to physical examination and resemble the Jaccoud's arthropathy, which can be seen also in other conditions. Occasionally, erosions can be observed to X-ray and these patients are called "rhupus". In this situation, anti-CCP antibodies are usually found, making think to SLE/RA overlap. Finally, tendonitis and tendosynovitis have been described in SLE. [47] Chronic invalidating *fatigue* is widespread among SLE patients, arriving to be present in a 40-50% of patients, resembling fibromyalgia. However only 10% of patients meet the criteria of this syndrome in one study.[48] Along with fatigue, muscle pain and weakness are not unusual manifestations of SLE and more reasons may explain them, first of all, corticosteroid therapy can be a common cause. *Myositis*, with muscle enzymes elevation (e.g., CPK), has been described with a prevalence of 5-10% of patients.[49] This is indistinguishable from idiopathic inflammatory myopathy and, similarly, proximal muscles are more commonly involved. Another musculoskeletal manifestation, which is more frequent in SLE than other diseases, is *avascular necrosis of bone*. A series of conditions have been associated to it, such as trauma, drugs, cigarette smoking, connective tissue disease, but the glucocorticoid (GC) use is the most consistent risk factor for the development of avascular necrosis.[50] Lastly, *osteoporosis* concerns a wide part of SLE patients and GC therapy is the most implied.[51]

1.1.4 Cardiopulmonary disease

Libman and Sacks were the first to report a cardiac manifestation of SLE in 1924 describing a verrucous valvular lesion,[52] while the pulmonary involvement was recognised when lupus erythematosus was recognised as a systemic disease in 19h century. [7]

1.1.4.1 Cardiac disease

Serositis are frequently observed in SLE patients, including both pleuritis and pericarditis. *Pericarditis* is a presenting symptom in 18.8% of newly diagnosed cases of SLE and its incidence is between 11-54%.[30,53] This wide range is probably due to the fact that pericarditis can be asymptomatic, noticed to echocardiogram accomplished for another motive or follow up. Lupus pericarditis has the same presentation of classic pericarditis with precordial pleuritic pain, alleviated to the sitting upright position and exacerbated by breathing. Moreover, dyspnoea, fever and tachycardia can occur. Pericarditis can be accompanied to pericardial effusion and very

rarely it can cause cardiac tamponade. Anti-Sm and anti-dsDNA antibodies have been associated to pericarditis. *Myocarditis* is another cardiac manifestation of SLE, a life-threatening condition with a mortality that reach 20%. Incidence was drastically decreased after 1950s with glucocorticoids advent and a recent study has found a prevalence of less than 5.7% in SLE patients.[54] Lupus myocarditis presentation is not specifical, chest pain and dyspnoea are typical symptoms and other signs of heart failure can be present. Elevation of cardiac enzymes is always found and depressed ventricular function with left ventricular ejection fraction reduced is commonly observed to the echocardiogram. Anti-Ro/SSA, anti-RNP and antiphospholipid antibodies have been associated to SLE myocarditis. Relapses are rare. Probably, the most known and characteristic cardiac SLE manifestation is the *endocarditis*, called also Libman-Sacks endocarditis (LSE). Its prevalence is not well defined and depending on the study ranged between 2.5-11%. LSE is characterized by a sterile vegetations of valves and, even if all four valves can be involved, mitral and aortic valves are the most interested.[52] Also leaflet thickening has been associated to LS endocarditis. An important risk factor is the presence of secondary antiphospholipid antibodies syndrome (APS), indeed SLE patients without APS show a minor prevalence. Most patients with LB endocarditis are asymptomatic, though complications can be observed, such as valvular insufficiency, infective LS endocarditis and thrombotic events, which may present with stroke or transitory ischemic attack. Others cardiac involvements are recognised in neonatal lupus syndrome, which is the severest manifestation of the syndrome that can lead from a first to a third-degree *congenital heart block (CHB)*.[55] Anti-Ro/SSA (notably Ro52) and anti-La/SSB's mother antibodies are pathogenetic, crossing the placenta and, nevertheless the mechanism of injury is unclear, promoting the fibrosis of the atrio-ventricular node. Among the population with these antibodies, the risk of having a child with CHB is 2%, but the risk increases considerably if mothers have had a previously child affected. Lastly, SLE patients have an important increased risk of *atherosclerotic cardiovascular disease* compared to normal population and, in addition to traditional risk factors, SLE-specific factors have been recognised, such as chronic inflammation and cytokines.[56]

1.1.4.2 Pulmonary disease

Pericarditis along with pleuritis comprise most of the lupus serositis. *Pleuritis* is estimated to involve SLE patients in 30-50% of cases in the course of their disease and it is an onset SLE manifestation in 22.4% of cases.[30,57] Pleural effusion can be also observed and symptoms are the same of the typical pleuritis, punctual chest pain, dyspnoea and cough. Pleural rub can be heard on physical examination. A rare lung SLE manifestation is *acute lupus pneumonitis*, which has an incidence of 1-4% of patients. The presentation is with dyspnoea, cough, haemoptysis and pleuritic chest pain. Although lower than other rheumatic disease, *interstitial lung disease* (ILD) has also been descripted in SLE, with different patterns such as non-specific interstitial pneumonia. Anti-U1-RNP antibodies are considered a risk factor for the development

of ILD. Lung appears with a restrictive pattern on functional tests and diffusing capacity of carbon monoxide (DLCO) is decreased. A life-threatening condition with a high mortality rate is the *diffuse alveolar haemorrhage*, a rare SLE manifestation that usually can occur at disease onset and is commonly seen in occurrence of active lupus nephritis. Moreover, lung vasculature can be interested in SLE, e.g. *pulmonary artery hypertension* (PAH) has been observed. This is included in group 1 of PAH (i.e., pre-capillary hypertension) described as a pulmonary arterial pressure ≥20mmHg and pulmonary arterial wedge pressure ≤15mmHg, measured with right heart catheterization. Current investigations into pathogenesis have focused on venous *thromboembolic disease* in APS setting, systemic sclerosis-pattern vasculopathy and obliterating endothelial cell lesions.[57,58] Lastly, SLE patients can develop a rare syndrome called *shrinking lung syndrome*, which refers to the development of restrictive lung disease. It is characterized by an hemidiaphragms elevation, reduction of total lung capacity and progressive dyspnoea. Pathogenesis is unknown and female are very more interested than male.[59]

1.1.5 Kidney disease

Lupus nephritis (LN) is an important involvement of SLE that can lead to end stage renal disease in 10% of cases and kidney transplantation, resulting in the most weighted manifestation impacting mortality. The prevalence of 29% biopsy proven LN in SLE patients and 50% of renal involvement in epidemiologic studies various considerably between different populations, with higher frequency, fast progression and worse outcome in black and Hispanic people. Only 13.5% of cases have kidney involvement at SLE onset, but kidneys can be interested at each disease flare and should be investigated.[30,60,61] LN is often silent to both symptoms and physical examination and the involvement can be suspected with some alterations of routine exams, such us urine exam and an increasing in creatinine. When suspected, kidney biopsy is necessary for the certainty diagnosis and is used to guide the treatment. Kidney biopsy is suggested when proteinuria ≥ 0.5 g/day and haematuria or cellular casts are found in the sediment examination. The most frequently implicated pathogenesis is the immune-complex-mediated glomerulonephritis (GN), although other mechanisms have been descripted, e.g., thrombotic microangiopathy and lupus podocytopathy, which require a different therapy. Through biopsy, LN has been classified in 6 classes: class I minimal-lesions mesangial GN, class II proliferative mesangial GN, class III focal and segmental proliferative GN, class IV diffuse and global proliferative GN, class V membranous GN and class VI advanced sclerosis GN.[62] Proliferative GN (i.e., classes III/IV) has been also divided into acute and chronic phenotypes. Moreover, the subendothelial immune deposits of classes III/IV and the subepithelial immune deposits of class V suggest a different pathologic mechanism of these classes. Another classification of renal pathology is silent lupus nephritis (SLN), a condition that occur when clinical and pathological finding are discordant because of kidney involvement can be present without any clinical sign. C3

consumption has been associated to SLN and may be a predictor of its progression, which verified in 25.8% of cases.

1.1.6 Haematological disease

Haematological manifestations are common in systemic lupus erythematosus, however the differentiation between disease activity and iatrogenic consequences are not always easy.[63] Anaemia has been found in more than 50% of patients and it has different explanations, such as chronic disease, iron deficiency, autoimmune haemolytic anaemia and thrombotic microangiopathic haemolytic anaemia. Leukopenia is defined as <4000/dL in the ACR/EULAR diagnostic criteria[64] and can be observed either absolute neutropenia and lymphopenia. Lymphopenia is present in 75% of patients with active disease and IgG anti-lymphocytes antibodies seem to be part of the pathogenesis, among other causes. On the opposite, also leucocytosis can be found in SLE patients and is more commonly associated to neutrocytosis, explained by the corticosteroids use. Another haematological manifestation is thrombocytopenia that is commonly caused by antiplatelets antibodies and, rarely, by thrombocytopenic thrombotic purpura (i.e., Moskowitz syndrome). Every red bone marrow line can be affected in SLE, individually or together and pancytopenia can occur. Noteworthy is the possible life-threatening hemophagocytic syndrome where fever, cytopenia and hepatosplenomegaly are caused by an uncontrolled benign macrophages and T cells proliferation and activation, with an increased production of inflammatory cytokines. The occurrence of both autoimmune haemolytic anaemia and autoimmune thrombocytopenia is rare, more often observed at disease onset, and is called Fisher-Evans' syndrome. Lastly, thrombosis in SLE patients is frequently observed and has been associated in some cases to secondary antiphospholipid syndrome and anticardiolipin antibodies may also contribute to haemolytic anaemia.

1.1.7 Other aspects

Systemic lupus erythematosus can virtually affect every organ, including *gastrointestinal system*, although is less common.[65] Many gastrointestinal involvement have been described, such as lupus enteritis, a vasculitis or inflammation of the small bowel, which include the commonest oral ulcers. Lupus mesenteric vasculitis, intestinal pseudo-obstruction and protein losing enteropathy are all a spectrum of lupus enteritis. Moreover, an association between SLE and inflammatory bowel disease and SLE and celiac disease have been hypothesized. More rarely, pancreatitis and hepatobiliary involvement have been observed, for example the primary sclerosing cholangitis. Noteworthy, drugs can damage these organs, hence should be monitored.

SLE may impact considerably the *pregnancy* in women. Although, SLE flairs may occur in every time of pregnancy period, they are more frequent in women who had an active disease during the six month before pregnancy.[26] SLE can be responsible of pregnancy loss, preterm birth, low birth weight and preeclampsia. Furthermore, child at birth can be involved by mother's SLE (i.e., *neonatal lupus syndrome*) and different clinical features may develop.[66] Among these,

cutaneous, haematological and hepatic manifestations are reversible, while cardiac heart block can be permanent.

SLE patients can develop also other autoimmune disease, in this contest called secondary, such as *antiphospholipid* (APS) and *Sjogren's syndromes* (SS).[67,68] The former are characterized by the production of antiphospholipid antibodies (i.e., anticardiolipin and anti-beta2glicoprotein1) and positive lupus anticoagulant (a coagulation test), which are an important thrombosis risk factor. Clinically, APS can cause deep vein thrombosis, venous thromboembolism, stroke, TIA, livedo reticularis and its evolution livedo racemosa, foetal losses, eclampsia, pulmonary hypertension and other. Sjogren's syndrome, instead, is characterized by an autoimmune xerophthalmia and xerostomia and is the most common ocular involvement in SLE. Anti-Ro/SSA and anti-La/SSB antibodies have been associated to SS and may help to the diagnosis.

1.3 NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

Neuropsychiatric manifestations of systemic lupus erythematosus (NPSLE) are a challenge for clinicians, these can vary from mild to severe and the diagnosis is difficult. The ACR in 1999 proposed 19 NPSLE syndromes to facilitate their recognition and create a common terminology.[69] (**table 1.1**) These syndromes were divided depending of the central nervous system (CNS), ulteriorly divided in diffuse and focal, or peripheral nervous system (PNS) involvements. During their development there was a general consensus on some syndromes, especially the focal forms, and many doubts about the diffuse and psychiatric forms. Indeed, the prevalence of NPSLE is very wide, 37-95%, and depends on the criteria used to select patients in the studies, making think their reliability is low. If minor manifestations are excluded, such as anxiety and headache, the prevalence drops down, depend on the studies, reaching 20% or less of SLE patients, while specificity increase. Most NP events occur within the first year after SLE onset and, in general, when disease is mostly active. [70–72] Due to the lack of pathognomonic serological, cerebrospinal fluid (CSF) and imaging signs to identify NPSLE, the ACR established that NP manifestations are ascribable to SLE when all other causes have been excluded and suggested the execution of CSF examination to avoid CNS infection, EEG to relieve underlying seizure disorder and MRI after most common infections, metabolic or endocrine alterations and adverse drugs reactions have been inspected.

Neuropsychiatric syndromes observed in SLE	
Central nervous system	Aseptic meningitis
	Cerebrovascular disease
	Demyelinating syndrome
	Headache (including migraine and benign intracranial hypertension)
	Movement disorder
	Myelopathy
	Seizure disorders
	Acute confusional state
	Anxiety disorder
	Cognitive disfunction
	Mood disorder
	Psychosis
Peripheral nervous system	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
	Autonomic disorder
	Simple/multiple mononeuritis
	Myasthenia gravis
	Cranial neuropathy
	Plexopathy
	Polyneuropathy

Table 1.1. Neuropsychiatric SLE syndromes described in 1999 ACR nomenclature and case definitions.[69]

To facilitate the attribution of NP events to SLE many investigators have tried to develop new algorithms with the support of imaging technics and CSF analysis over the years, nevertheless recognising minor diffuse and focal NP events still remain a challenge. To help clinicians detect neurodegenerative conditions, cognitive disfunction and mood disorders, several screening tools have been developed and some of these can be use in SLE patients, although the best method remain the NP interview conducted by an expert. To identify NPSLE, investigators are trying to find a reliable biomarker, although some of those have potential, none of them can be use in clinical practise because of the insufficiency of accuracy. For example, lipocalin 2 (LCN2) and osteopontin (OPN) are elevated in CSF of NPSLE patients compared to non-NPSLE patients and the latter also decreases after treatment. Furthermore, any imaging has a specific sign to identify NPSLE and about 50% of NPSLE patients have not any abnormalities on MRI, however increased cortical atrophy is more common in NPSLE and there is an association between white matter volume and cognitive impairment.

Several autoantibodies have been assessed for NPSLE, some of these may have a role in the pathogenesis and in the identification of SLE patients with high risk for develop NP events, such as antiphospholipid antibodies, anti-ribosomal P and anti-neuronal antibodies. These can pass the blood-brain barrier (BBB), that is frequently damaged, or can be directly intrathecally produced. In a meta-analysis, anti-ribosomal P antibodies are significantly higher in NPSLE and support their potential diagnostic role.[73] This antibody, as well as anti-NMDAR antibody, is capable of causing apoptotic neuron death through excitotoxicity, which can result in psychosis and depression. Moreover, anti-ribosomal P antibodies are related to a worse prognosis and their structure share clonotypic determinants with anti-Sm antibodies, supposing a common B-cell origin that may have a pathogenic role. Antiphospholipid antibodies are primarily associated with strokes, but also with seizures and myelopathy. Anti-neuromyelitis optica (NMO) IgG antibodies, directed versus aquaporin 4, have been related to transverse myelitis and optical neuromyelitis. Anti-NR2 antibodies (a subunit of NMDAR) can damage the BBB and seem associated to the diffuse central NP involvements. Finally, studies on mouses suggest microglial activation in the brains and increased production of inflammatory cytokines that can lead to NP manifestations.[73]

1.3.1 Neuropsychiatric syndromes

Most NPSLE syndromes are rare (incidence <1%) if excluding the mild manifestations. The most common manifestations (5-15% of cases) include the cerebrovascular disease and seizures, while the uncommon ones (1-5% of cases) include severe cognitive dysfunction, acute confusional state, psychosis and polyneuropathy.[69,70,72] *Headache* is a very common manifestation, reaching a prevalence of 58% to patients in follow-up, but it is a widespread condition among people without SLE and lack of a recognizable typical pattern to be named “lupus headache”. *Cerebral venous sinus thrombosis* can have only headache as symptom, although nausea, vomiting, seizures and diplopia

can occur. The transverse sinus is the most affected. *Cerebrovascular events* are a common manifestation of NPSLE and are characterized by a considerable mortality. Strokes can be due to multiple causes, primary to antiphospholipid syndrome; indeed, the prevalence of cerebrovascular disease is significantly higher in those with APS than in SLE patients without APS. Libman-Sacks endocarditis is another major cause of strokes through a thromboembolic mechanism. Lastly, the CNS vasculitis, although very rare, can cause ischemic strokes. All these syndromes can be as well the aetiology of *seizure*, which is another NPSLE syndrome, along with direct toxicity of some autoantibodies. Seizures are more common in young patients and relapse are associated to higher disease activity and usually they have isolated episodes, with a rare development of epilepsy. Seizures may be an initial manifestation of SLE in 2.8% of cases.[30] Both generalized tonic-clonic (most frequent) and focal crisis have been described. An association with seizures and both antiphospholipid and anti-ribosomal P antibodies in serum have been observed.

Mild to moderate cognitive impairment are frequent in NPSLE, but only 3-5% of SLE patients are affected. Deficit of attention, memory and of the executive functions are the most common findings. The ACR proposed a neuropsychological battery to diagnose cognitive dysfunction in SLE. In those patients with cognitive impairment, *acute confusional state*, i.e. delirium, is more likely to occur. It is characterized by deficit of attention, acute onset and fluctuating state of consciousness. It has been associated to anti-NR2 and anti-Sm antibodies in CSF. Through MRI white matter involvement has been observed, associated to anti-Sm antibodies and elevated mortality in these patients. *Movement disorders* in NPSLE include chorea, ballism, parkinsonism, ataxia and other. The former is the most common and it is seen in paediatric and juvenile patients. Chorea is characterized by involuntary and irregular movements that can interest any part of the body. It usually manifests itself in the early stage of disease and may precede it of years. Antiphospholipid antibodies have been associated to the development of chorea through their capacity to induce neuronal depolarization and sometimes direct injury. However, this disorder is indistinguishable from other causes of chorea, e.g. Sydenham's chorea, that must be ruled out before diagnosing.

Anxiety, depression and psychosis are common in SLE patients, but it is very difficult to attribute them to SLE itself. Depression has a prevalence over 25% among SLE patients, while psychosis is rarer and probably more related to glucocorticoid therapy, although anti-ribosomal P and anti-neuronal antibodies have been associated to its development. Psychosis occurs more frequently in the first years or before the onset of disease. *Aseptic meningitis* is a rare manifestation of NPSLE and can be due to SLE itself or medications, such as immunosuppressants. Fever, headache and lymphocytic pleocytosis of CSF are characteristics. *Demyelinating disease* of the CNS is another rare NPSLE manifestation and usually occurs as first symptom of SLE. There is not a characteristic that could distinguish it from multiple sclerosis (MS) and diagnosis can be very

hard, especially for the possibility of these pathologies to overlap. On MRI small multifocal demyelinating lesions can be observed in SLE, APS and MS and differential diagnosis is possible watching the whole picture of the situation, for example autoantibodies and other clinical aspects associated. A particular subtype of demyelinating disease is neuromyelitis optica, although is currently considerate an independent entity, and anti-NMO IgG antibodies have been associated. Neuromyelitis optic can be present in a rare association with myelitis, named Devic's syndrome. *Transverse myelitis* is rare and has been associated to antiphospholipid antibodies. Both grey and white matter can be involved. The letter is more frequent, its presentation can include hyperreflexia and spasticity. MS must be ruled out. Secondary aetiologies are thrombotic and ischemic lesions. *Posterior reversible encephalopathy syndrome* (PRES) was not described in 1999 ACR NPSLE syndromes, but it has been observed, although rarely, in SLE patients. PRES has been associated to renal disease and active lupus and is probably due to the dysregulation in circulatory flow with vasodilatation, hyper-perfusion, breakdown of BBB and vasogenic oedema, mainly in the posterior part of the brain, visible on MRI. It is characterized by headache, seizures, visual disturbance and focal deficit. *Isolated optic neuritis and progressive multifocal leukoencephalopathy* have been also observed, even though rarely, in SLE patients, nevertheless SLE is one of the autoimmune diseases which these occurs more frequently.

About the involving of the peripheral nervous system, *peripheral polyneuropathy* is common in SLE and usually attributable to SLE itself. It can be axonal, demyelinating or mixed and the sensory involvement is most frequent. Patients reports numbness, burning and pain in the affected areas. *Cranial nerves* can be affected too, but less frequently. Another syndrome described in a few cases is the *inflammatory demyelinising polyradiculoneuropathy*, which can be acute (as Guillan-Barré's syndrome) or, most commonly in SLE, chronic (>8 weeks). *Autonomic disorders* have been observed, with wide range of prevalence depending on the assisted method, and it is not related to peripheral neuropathy. *Simple and multiple neuritis* are reported in SLE patients and are characterized by the degeneration of one or more nerve roots. They are due to the vasa nervorum vasculitis, as autopsy studies demonstrated, but also to thrombosis. It manifests with sensory-motor deficit of the extremities. An entire plexus can be affected, although is very rare. Another rare peripheral manifestation is *myasthenia gravis*, usually diagnosed before SLE onset. Notably, 7.7% of female myasthenia gravis patients meet SLE diagnostic criteria and it has been supposed that thymectomy can be a trigger of SLE.

1.4 DIAGNOSIS AND CLASSIFICATION CRITERIA

Systemic lupus erythematosus is a complex autoimmune disease which have a wide range of different presentations, yielding diagnosis not always easy. The lack of a unique diagnostic test to unequivocally recognise SLE has led to the development of different classification criteria over the years, in order to homogenise the patients who could be enrolled in the trials. Notably, these criteria should not be used for diagnosis, which remain clinician's responsibility, and patients with some disease characteristics who do not fulfil the criteria should be treated as well. Hence, many classification criteria were published, but the most used were 1997 ACR criteria and 2012 SLICC criteria, till the last one 2019 ACR/EULAR classification criteria.[64,74–76] The former required to be satisfied 4 criterions of 11 in at least one occasion, also separately, thus the sensitivity in the early stage of disease drops to 66%, although specificity was high (93%), because these items need time to accumulate. Therefore, SLICC criteria were developed to increase sensitivity (97%) but have a lower specificity (84%). Four criterions must be met, at least one clinical and one immunological. In the SLICC classification criteria, however, an important innovation was introduced, that is patient could be classified as SLE if had had a biopsy-proven nephritis compatible with SLE along with ANA or anti-dsDNA antibodies. Finally, the 2019 ACR/EULAR classification criteria were built to have both sensitivity and specificity higher than the previous ones, respectively of 96% and 93%. Another important change was that patient can be classified as SLE if reaches ≥ 10 points. Indeed, each criterion have a different weight which must be summed to obtain the total score. Moreover, ANA antibodies ≥1:80 became an entry criterion, due to its high sensitivity, and is necessary for a patient to be classified as SLE. As SLICC criteria, in the 2019 ACR/EULAR criteria renal biopsy has a great weight and class III or IV lupus nephritis in presence of ANA are sufficient to classify a patient as SLE (**table 1.2**). Notably, these criteria stress the factor that SLE can be diagnosed when other most common causes have been excluded, each criterion can be counted only when there is not a better explanation by another condition.

When SLE is suspected, a series of exams should be asked, such as autoantibodies and others, in base of the patient presentation.[76] ANA (anti-nuclear antibodies) has high sensitivity in SLE, ranging from 95% to 97%, explaining the entry criterion of 2019 ACR/EULAR classification criteria. If positive, it does not confirm SLE diagnosis, however if negative it yields the diagnosis less likely. ANA is usually tested through indirect-immunofluorescent assay (IIFA) on Hep-2 cells and this has been recognised as method of choice for ANA screening.[77] It provides a semiquantitative titre, which is considerate negative less or equal than 1:40. The test should also report the nuclear or cytoplasmatic pattern because some patterns are associated to some specific diseases and may address to request specific autoantibodies. If ANA is positive, it should be followed by ENA (extractable nuclear antigens) panel. Anti-dsDNA antibodies are a characteristic marker for diagnosis and the follow-up of patients with SLE.

Entry criterion			
Antinuclear antibodies (ANA) at a titre of ≥1:80 on Hep-2 cells or an equivalent positive test (ever)			
If absent, do not classify as SLE If present, apply additive criteria			
Additive criteria Do not count a criterion if there is a more likely explanation than SLE Occurrence of a criterion on at least one occasion is sufficient SLE classification requires at least on clinical criterion and ≥10 points Criteria need not occur simultaneously Within each domain, only the highest weighted criterion is counted toward the total score.			
Clinical domains and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional		Antiphospholipid antibodies	
Fever	2	Anti-cardiolipin antibodies OR	
Haematologic		Anti b2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	**Complement proteins**	
Autoimmune haemolysis	4	Low C3 OR low C3	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	**SLE-specific antibodies**	
Psychosis	3	Anti-dsDNA antibody OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria>0.5g/24h	4		
Renal biopsy class II or V lupus nephritis	8		
Renal biopsy class III o IV lupus nephritis	10		
Classify as Systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled			

Table 1.2. The 2019 EULAR/ACR classification criteria of SLE[64]

Their presence can be suggested by homogeneous ANA pattern. There are different methods of measuring anti-dsDNA antibodies, Farr assay and CLIFT offer high specificity while other new methods provide high sensitivity. For this reason, anti-dsDNA dosed with those sensitive methods should be confirmed by CLIFT or Farr assay in new patients. Notably, anti-dsDNA is considered with great weight in the immunological domain by the 2019 ACR/EULAR criteria. The dsDNA-antibody titre can fluctuate during time and is associated to disease activity and kidney involvement. So, these antibodies can be undetectable during

remissions and can increase during flares. Also, anti-Sm antibodies are specific of SLE and present in the 2019 criteria. Anti-Sm antibodies are associated to disease activity and lupus nephritis, moreover they have been associated as a predictor of silent LN and high disease activity. Anti-Ro/SSA and anti-La/SSB are antibodies that can be observed in SLE patients. They are clinically correlated to Sjogren's syndrome, SCLE, photosensitivity and neonatal lupus. Anti-histone antibodies can be seen in a particular situation, which should be suspected by their presence, that is typically the drug-induced SLE.[19] Another antibody that is possible to find in SLE is the anti-C1q antibodies. They have been strongly associated to LN and, as biomarker of its occurrence, seem even superior to anti-dsDNA and C3-C4 consumption. They tend to disappear with low disease activity and have a negative predictive value next to 100% when are negative to the likely of development LN. Thus, it has been supposed anti-C1q antibodies could be necessary, although not sufficient, for the development of proliferative LN.[78] Others antibodies, such as anti-ribosomal P and anti-NR2 antibodies can help to diagnosis NPSLE.[71] Indeed, some antibodies can be found in SLE patients, but they are more typically associated to others diseases.

Beyond autoantibodies, other exams are used to monitor SLE activity. Erythrocyte sedimentation rate (ESR) is frequently used for this purpose, its elevation has been noted in up to 90% of patients and has been associated with disease activity and damage accrual.[79] C-reactive protein (CRP) is commonly used as a marker of inflammation and it can be elevated in SLE patients, although is generally lower compared to other diseases, such as rheumatoid arthritis.[80] An usefulness biomarker used in routine clinical practise of SLE patients is the complement level, included in the 2019 ACR/EULAR classification criteria. The presence of both ANA positive and low levels of C3 and/or C4 are highly indicative of SLE. C3 and C4 reduction have been associated to disease activity and organ involvement, in particular LN, haematological disorders (e.g. haemolytic anaemia and thrombocytopenia), skin rash and arthritis. Moreover, in some studies complement reduction seems to have a prognostic value. Low serum C3 and C4 levels are a predictor of flares, in particular renal and neuropsychiatric flares, although is not universally accepted.[81] Finally, many urinary biomarkers have been recognised in SLE, but none have been approved for clinical practice, except urine proteins and protein/creatinine ratio.

1.5 PRINCIPLES OF THERAPY

For years, systemic lupus erythematosus management has remained a challenge for clinicians, due to the different organs which can be involved, hence the therapeutic strategy must be personalized. In general, the aims of treatment are to induce remission of the flares-up, promote remission maintenance and prevent relapses, with an improvement of the quality of life.[76] The remission state can be assessed with the lupus low disease activity state (LLDAS) instrument, which its attainment is associated with an outcome improvement in SLE.[82] This should be obtained with as less as possible side effects of the drugs used. The treatment is chosen in base of the clinical presentations and the disease activity, measured with different scoring system. The most widely used is the Systemic lupus erythematosus disease activity index-2000 (SLEDAI-2K).[83] These scoring systems are not only used to choose treatment, but also to assess their efficacy. During the last years, there have been many developments in SLE, which have led to the necessity of an update of the 2019 EULAR recommendation for the management of SLE.[84] Indeed, in 2023 the EULAR published the new guidelines for SLE management, in considerations of the new drugs approved for this disease.[85]

An antimalarial, quinine, was the first drug used to treat, initially, cutaneous lupus lesions in 1894 and this class is the mainstay of SLE treatment still today.[85,86] *Hydroxychloroquine* (HCQ) is the principal drug of antimalarial class used and is recommended in all patients. HCQ has demonstrated to decrease SLE activity, to prevent disease flare and to lower the long-term glucocorticoid need. The dose recommended is 5mg/kg real body weight/day. It is important to not exceed this dosage because of the increased risk of retinal toxicity, nevertheless the dosage should be adequate cases per cases, for example decreasing in 50% of the dose is required in patients with renal impairment and <30ml/min of filtration rate. Its mechanism of action is complex and not fully understood. HCQ passes cell membrane and tends to accumulate in the lysosomes where it inhibits the toll-like receptors and the cyclic GMP-AMP synthase-stimulator of interferon genes pathways, resulting in multiple effects like the inhibition of cytokines release. Most recently, it has been supposed HCQ may suppress early mediators like B cell activation factor (BAFF) and interferon (INF) influencing the disease progression. HCQ has shown to be more beneficial in cutaneous lupus and musculoskeletal involvement, while is an adjuvant drug to the immunosuppressive regimens in LN. Moreover, it can be used in pregnancy for its safety and has shown to decrease activity and flares-up during this period. Finally, HCQ seems to be capable in reducing the thrombotic risk in SLE patients with APS.

In the 2023 EULAR recommendations, an important change has been made on the glucocorticoids use, in spite of 2019 guidelines.[84,85] The use of *glucocorticoids* (GC) remain dose based on the type of severity of the organ involvement, but the maintenance acceptable dose passed from 7.5mg/day of prednisone or equivalent to 5mg/day, with the aim of total withdrawal. This change finds foundation in numerous studies that associated the glucocorticoids side effects from the

threshold of 5mg/day of prednisone. Intravenous pulse of methylprednisolone, with doses that depend on the severity of the disease, can be useful to accelerate the GC per os tapering. Furthermore, in patients with sustained remission and therapy tapering, GCs are the first drugs that should be withdrawn.

Immunomodulating/immunosuppressive agents should be considered in the treatment of SLE patients not responding to HCQ or are GC dependent at doses greater of those acceptable. These drugs include conventional and more recent biological immunosuppressive agents. Differently from the 2019 EULAR recommendations, the 2023 recommendation does not impose the use of conventional immunosuppressive agents before the use of biological drugs, despite the higher cost, because biological drugs have proved their efficacy in randomized controlled trials in SLE, while these lacks for the conventional agents (i.e., *methotrexate, azathioprine and mycophenolate*).[84,85] *Belimumab* has been the first biological drug approved for SLE, an IgG directed versus the B-cell-activating-factor (BAFF). BAFF is an element of the immune system relatively specific for certain maturation stages of B cells, dendritic cells and tissue macrophages, supporting their maturation, differentiation and B-cells survival. Through a series of studies, belimumab has demonstrated a high safety profile in both adult and paediatric SLE patients, with no evidence of overall infections increased risk. Patients treated with belimumab experienced a reduction in IgG, IgM and IgA levels below the lower limit of normal, nevertheless there was not seen infections increasing. *Anifrolumab* is the second biological agent approved for the treatment of SLE, it is an IgG directed versus anti-interferon activating factor 1 receptor (INFAR1). The type 1 INF is implicated in the viral infection response and in triggered the initiation and persistence of adaptive immunity. Despite of BAFF, INFAR1 is expressed in most immune and non-immune cells for an immediate activation of innate and adaptive host defence mechanisms. Thus, Anifrolumab is less selective than belimumab. Different studies highlighted an increased risk of upper respiratory tract infections, nasopharyngeal, bronchitis and herpes zoster in patients treated with Anifrolumab, compared to placebo. BAFF and INFAR1 play an important role in the pathogenesis of SLE, indeed Belimumab and Anifrolumab have demonstrated their efficacy in SLE through randomized controlled trials. Both are approved for the treatment of moderate-severe SLE, while the former also for the treatment of active LN.[87]

Some patients may have an organ or life-threatening disease, in these cases, *cyclophosphamide* (CYC) can be used, while in refractory cases also *rituximab* can be considered, nevertheless it is off label.[85] The kidney is the most common organ involved and an important life-threatening condition is the LN and patients with active proliferative LN are generally treated with CYC or mycophenolate and high dose of glucocorticoids for rapid earlier control of inflammation. Moreover, belimumab or calcineurin inhibitors (CNIs, i.e., *cyclosporine, tacrolimus or voclosporin*) can be added, in a combination therapy, helping to control autoimmunity and preventing relapses. The 2023

EULAR suggests the use of low dose intravenous CYC, with a regimen called EuroLupus. This recommendation concerns all class types of LN that need treatment, although further studies are needed for class V LN. Of note, belimumab seems to be more efficacious when the baseline proteinuria is <3g/day, while voclosporin may be preferred in those cases with greater proteinuria because of its capacity to rapidly reduce it. Two CYC regimens have been approved to treat LN, the first and more aggressive was the National Institute of Health regimen (NIH, intravenous bolus of CYC monthly for 6 months, repeatable maximum 2 times) and the second was EuroLupus regimen (500mg pulse of CYC intravenously every 2 weeks for 12 weeks, repeatable maximum 2 times), both followed by azathioprine or mycophenolate to maintain remission.[60] The EuroLupus regimen has demonstrated to be equal to the NIH regimen at 5 and 10 years, but with less toxicity. Calcineurin inhibitors can be used in LN and tacrolimus plus GC induce a complete renal response more frequently than cyclosporine plus GC, and an even higher remission rate could be obtained when tacrolimus and GC are in therapy combination with mycophenolate. Regardless these good results, CNIs have different side effects that can need doses reduction: chronic nephrotoxicity, hypertension, electrolyte disturbance as hyperkalaemia and hypomagnesemia, gingival hypertrophy, dyslipidaemia especially for cyclosporine and hyperglycaemia for tacrolimus. Voclosporin is a novel CNI, developed from cyclosporine, with higher potency and favourable metabolic and safety profile. It binds cyclophilin A which binds and inhibits the calcineurin, a calcium dependent phosphatase involved in cytokine production and T-cells activation. Although voclosporin has not yet been compared to the others CNIs, it has been tested in addition of mycophenolate versus mycophenolate alone in a multiethnic study resulting that the first group was associated with a significantly higher complete renal response. Moreover, in another study voclosporin has been associated, significantly, to a rapid reduction in proteinuria, which is a known risk factor of kidney injury and chronic kidney disease progression.[88] In conclusion, the 2023 EULAR recommends that the immunosuppressive therapy after a LN should be continued for at least 3-5 years and withdrawal can be attempt after remission has been obtained for at least 2 years.

1.6 PSYCHIATRIC INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS

Since the beginning of the 20th century, the everyday life anxiety and stressing factors have been suggested to have a role in the pathogenesis of some rheumatic diseases.[89] Neuropsychiatric systemic lupus erythematosus, as told previously, includes a wide range of possible manifestations, from mild, as lupus headache, to more severe, as epilepsy and aseptic meningitis, with a great differences in the prevalence measures (37-95%), depending on the attribution of a syndrome to SLE or not.[70] Of the 19 recognised NPSLE syndromes by the ACR in 1999[69], five in particular are extremely of psychiatric interest. These are the acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder and psychosis, which are among the hardest to ascribe to SLE. Even though the prevalence of developing NPSLE is very high in the course of the disease and patients rarely seek and receive detailed psychiatric assessment, hence, adequate treatment. This is also complicated by the fact that patients rarely notice their cognitive impairment and seek help to physicians, to the other side, overlooking psychiatric symptoms may have consequences in quality of life, disability, loss of employment and of supportive relationships, stigma and shame, closing the circle with the worsening of the psychiatric syndrome.[90] Some studies have reported that half of SLE patients with psychiatric symptoms presented them already before the diagnosis. Rarely psychiatric symptoms are present alone for more than 18 months when they are associated to SLE, therefore when they precede SLE diagnosis of more than 2 years they should be considered primitive and independent from SLE. Depression is the most common psychiatric manifestation in SLE patients presenting a wide range of prevalence about 11-39%, because of the different assessment and diagnostic methods used. Nevertheless, it has been reported that the prevalence of depression in SLE is 4-fold higher compared to a matched non-SLE population. Depression due to the medical condition, in which symptoms are secondary to the disease clinical context, should be differentiated from major depressive disorder, which is primitive. Moreover, it has been noted that the risk of suicide in SLE patients is approximately 9.5%, greater than the suicide risk of the general population, and mania is present in about 3% of patients, which can be due to the disease activity or to glucocorticoid therapy. Mania has been observed also as a first manifestation of SLE. Cognitive impairment, concerning attention, memory and executive functions, has a prevalence 2-fold higher in SLE patients compared to the general population and brain MRI may highlight some changes, although they do not correlate with deficit severity. Anxiety disorder has been noted to be 2-fold higher in SLE than the general population, maybe this can be explained because of the unpredictable flares of the disease. Psychosis, another NPSLE syndrome described in ACR classification, has been described in 2-3% of SLE patients and it may be higher in patients treated with a high dose of glucocorticoids. Furthermore, in a study that compared psychosis in SLE versus rheumatoid arthritis patients has noted that the second group did not show psychosis at all, while it was observed in 10% of patients of the SLE group,

conferring to this syndrome a certain specificity of SLE. Finally, attention deficit with hyperreactivity disorder (ADHD) symptoms are frequent in SLE and in one study they have been associated to disease activity. As well as SLE itself, psychiatric symptoms pathogenesis certainly has both genetic and environmental causes, because neither of them is sufficient alone. However, it seems that only 40% of neuropsychiatric events can be directly attributed to SLE. Inflammation and thrombosis may have a role in the pathogenesis of NPSLE and antiphospholipid syndrome has been associated with different NPSLE syndromes.[70]

The role of psychological stress affecting the immune response has been widely hypothesized, if it is obvious that rheumatic diseases influence the psychological and the social functions of the afflicted individuals, perhaps it is true also that stress can influence the course of these diseases. This is extremely difficult to demonstrate, nevertheless, many studies have tried to investigate on it. The word "stress" was defined by Selye as a "real or perceived threat to homeostasis, to which organism has to react with an adaptive response".[91] If in juvenile chronic arthritis major life events and chronic minor stresses have been significantly associated to the onset and course of the disease, this has not been significantly demonstrated in SLE. Different retrospective studies have reported that many patients proved an unusual emotional stress before the onset of an autoimmune disease, others consider that emotional stress acts as a precipitating factor in SLE or to be one cause of flares, although this statement has not been verified for the failure to provide adequate data. An important study to support this hypothesis has found that stressful events were responsible of more than 50% of the times with an increasing in disease activity. However, another study has found that not all SLE patients are susceptible to stress and have divided stress-responder and not stress-responder patients. Finally, another study has found an association between daily stress and anti-dsDNA antibodies, hence with the SLE disease activity.[89] Moreover, other studies have noted that gastrointestinal tract and immune system are particularly responsive to stress. In the first case, stress seems to induce dysbiosis and hyperpermeability, acting indirectly on the immune system, while in the second case stress seems able to modify directly the systemic immune response and systemic inflammation.[91] Evidence show that microbiota can affect the incidence and severity of immune mediated disease. Also, intestinal hyperpermeability has been associated with the development and flares-up of autoimmune diseases through an increased entry of luminal antigens from the mucosa.

Hence, persisting of stress and an inadequate response to it can lead to harmful maladaptive reactions: both stress itself and stress-induced intestinal barrier defect can contribute to the development and/or exacerbations of an autoimmune disease, such as SLE. Ulterior evidences of the stress role that has a pathogenesis in NPSLE, in particular delirium, psychosis and depression, have been provided by a study on mice, where stress can activate the microglia which upregulate the inflammation related genes, including Il-12b, and cause neuronal dysfunction and neuroinflammation.[92] The researchers hypothesized that psychosis and

ACS may due to the overactivation of the prefrontal-cortex, which dysfunction is critical to their development, in relation to microglial stress activation. Furthermore, blood brain barrier dysfunction, autoantibodies, cytokines and chemokines have been supposed to have a role in the pathogenesis of psychiatric symptoms in SLE.[90] Blood brain barrier dysfunction leads to an increased leukocyte trafficking across the damaged endothelium. Autoantibodies may cross the blood brain barrier or be synthetized intrathecally, found in the cerebrospinal fluid. Indeed, over 20 antibodies have been associated to NPSLE, specifically anti-NR2A and anti-NR2B antibodies, a subgroup of anti-dsDNA antibodies, that can bind neurons and induce apoptosis through excitotoxicity. Anti-dsDNA antibodies are more common in patients with LN, hence, patients with renal involvement are more likely to develop psychiatric symptoms. Finally, anti-NR2 antibodies have been associated to depression, psychosis and hypomania. More controversial is the role of anti-ribosomal P antibodies, there are some doubts if it is related or not to the pathogenesis of NPSLE. Many investigators are working to find a biomarker of psychiatric symptoms in SLE, but now, there is not a specific and sensitive biomarker for helping to SLE diagnosis, although serum BDNF and Il-6 levels seem to be promising. To the other side, immune dysregulation has been observed in some psychiatric disorders, especially in schizophrenia, in which different autoantibodies may be found, including anti-dsDNA antibodies.

Finally, the emergence of a new discipline, the psychoneuroimmunology, has permitted to find new insights between psyche and body integration.[93] It has been accepted that the immune system can be influenced by stress factors, anxiety and mood disorders, and vice versa. Indeed, the immune system receives signals from brain and neuroendocrine system through the autonomic nervous system and hormones. Conversely, the immune system communicates with the brain secreting cytokines and through sensory nerves. This seems to be a long loop of regulatory feedback system able to coordinate psyche to body inflammation and autoimmune response. In this optic, psychological factors may contribute to the onset of immunological diseases acting in different ways, for example interacting and exacerbating the intolerance to native antigens or interfering in some point of the cascade that conduct to the development of an autoimmune disease.[89]

1.7 FIBROMYALGIA IN SYSTEMIC LUPUS EYTHEMATOSUS

Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain and tenderness, with somatic and cognitive symptoms and fatigue.[94] This complex syndrome usually results in an increased prevalence of depression, anxiety and cognitive disfunction, making FM an important predictor of poorer quality of life. The pathogenesis of fibromyalgia still remains unknown, but recent hypothesises suggest a central sensitization and disordered pain regulation, involving changes in neural networking and neurotransmitter functions, especially of the autonomic nervous system and the hypothalamic pituitary axis. These changes result in pain amplification due to a central excitability and/or reduced inhibition in somatosensory nervous system. Fibromyalgia can overlap with similar conditions, indeed in other settings fibromyalgia has received many different names, such as somatoform disorder or functional somatic syndrome, because of the connection with psyche. Fibromyalgia has been investigated among SLE patients and some authors have reported a prevalence of about 20%, without a correlation of the disease activity.[95] However, other authors have noted a very wide range of FM prevalence in SLE patients, from 8% to 61%, and a study conducted on 3591 SLE patients have shown that the prevalence was 6.2%, with a significative difference between patients with a history of SLE disease greater than 5 years and those with a shorter, respectively 6.9% vs. 4%. As expected, SLE patients with FM showed a greater prevalence of depression, compared with those without FM syndrome.[96] Indeed, fibromyalgia can influence the quality of life of SLE patients and their ability to cope adequately in challenge situations. Fibromyalgia and depression have been associated to cognitive symptoms (e.g., subjective sense of memory loss, language problems, deficit of attention and executive functions). Fatigue is another symptom very common in SLE patients and it has been investigated in a study that have shown that 50% of SLE patients complaining chronic fatigue, but only 10% of them met the criteria for fibromyalgia syndrome.[47,94,95]

The American college of rheumatology (ACR) in 2016 published the revised classification criteria for fibromyalgia syndrome.[98] The new criteria has high sensitivity and specificity and the changes made from the 2010/2011 criteria have permitted to use them also as diagnostic criteria. Following these new criteria, fibromyalgia can be diagnosed when all items are met: generalized pain, defined as pain in at least 4 of 5 region (excluding jaw, chest and abdominal pain); symptoms have been present at a similar level for at least 3 months; widespread pain index (WPI) ≥7 and symptoms severity scale (SSS) score ≥5, or WPI of 4-6 and SSS score ≥9; a diagnosis of fibromyalgia is valid irrespective of other diagnosis, and it diagnosis does not exclude the presence of other clinically important illnesses (**table 1.3**). The tender points criteria used in the past decades do not find place in the diagnosis for fibromyalgia due to their low accuracy, but they can still help clinicians to suspect fibromyalgia syndrome and detect generalized pain. The WPI ranges from 0 to 19 areas where patient can complain to have pain divided in 5 body regions: the left and right upper regions, the left and right

lower regions and the axial region. The SSS score ranges from 0 to 12 and 3 items are scored from 0 to 3, which are fatigue, weaking unrefreshing and cognitive symptoms, and 3 score 0 or 1 if absent or present, which are headache, pain or cramps in lower abdomen and depression. Patients should be bothered about these symptoms and they should be occurred during the previous 6 months. Moreover, the total score, given by the sum of WPI and SSS scores, can be used also for determining the severity of the fibromyalgia syndrome.

Criteria

A patient satisfies modified 2016 fibromyalgia criteria if the following 3 conditions are met:
(1) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9.
(2) Generalized pain, defined as pain in at least 4 of 5 regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.
(3) Symptoms have been generally present for at least 3 months.
(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

Ascertainment

(1) WPI: note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19

Left upper region (Region 1)	*Right upper region (Region 2)*	*Axial region (Region 5)*
Jaw, left[a]	Jaw, right[a]	Neck
Shoulder girdle, left	Shoulder girdle, right	Upper back
Upper arm, left	Upper arm, right	Lower back
Lower arm, left	Lower arm, right	Chest[a]
		Abdomen[a]
Left lower region (region 3)	*Right lower region (Region 4)*	
Hip (buttock, trochanter), left	Hip (buttock, trochanter), right	
Upper leg, left	Upper leg, right	
Lower leg, left	Lower leg, right	

(2) Symptom severity scale (SSS) score
Fatigue
Waking unrefreshed
Cognitive symptoms
For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
0 = No problem
1 = Slight or mild problems, generally mild or intermittent
2 = Moderate, considerable problems, often present and/or at a moderate level
3 = Severe: pervasive, continuous, life-disturbing problems
The symptom severity scale (SSS) score: is the sum of the severity scores of the 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0–9) plus the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:
(1) Headaches (0–1)
(2) Pain or cramps in lower abdomen (0–1)
(3) And depression (0–1)

The final symptom severity score is between 0 and 12
The fibromyalgia severity (FS) scale is the sum of the WPI and SSS

Table 1.3. 2016 revised fibromyalgia classification and diagnosis criteria[98]

1.8 PSYCHONEUROIMMUNOLOGY

The psychoneuroimmunology is a recent research branch that aim to study how brain and immune system communicate and interact with each other. In the last decades, much evidence has been accumulated demonstrating that psychological stress interferes with the immune functions, but also peripheral inflammation clearly interferes with brain functions, being able to lead to overt psychiatric illness. The reciprocal influence occurs with four major identified hormonal and neuronal pathways, the hypothalamic-pituitary-adrenal axis (the first one discovered), the sympathetic nervous system, other non-adrenal hormones and the parasympathetic nervous system. Through these pathways, a short (local in the same organ) or long (between different organs) feedback loop circuits have been described. Additionally, recently it has been demonstrated that these circuits show signs of dysfunction in patients with chronic inflammatory disease, leading to incomplete stress responses and favouriting the inflammatory state itself. Both chronic psychological stress and chronic peripheral inflammation have a highly unfavourable influence among them. On the other hand, acute psychological stress or peripheral inflammation can be useful to face challenges, while a chronic state loses this meaning (as for pain). On this way, through various studies have been emerged that psychological stress can influence pathogenesis and exacerbation of chronic autoinflammatory diseases, such as systemic lupus erythematosus. This influence can occur years before the onset of the disease or during it. In this view, psychological stress or depression act as a risk factor for disorders in immune function through the neuroendocrine-immune system due to the overproduction of neuropeptides and cytokines, influencing the host defences, response to vaccines, infectious or malignancy susceptibility and the onset, progression and severity of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Thanks to different studies it has been possible to hypothesize that stress is able to induce an acute phase response, which can become a chronic inflammation.[89,93,99]

Different stress theories have been proposed to explain the influence of stress on health. As told previously, Hans Seyle was the first who spoke of stress and hypothesized that acute stress is a physiological adaptative response to a challenge. When it is perpetuated over time, becoming chronic, it can cause a maladaptive response. Another theory is the allostatic load model. Allostasis is the capability of an organism to keep the stability of the physiological systems through a change. When stress response allostatic load accumulate it induces an overexposure of the body to neural, endocrine and immune mediators to stress that can result in adverse effects and diseases, due to the exhaustion of the allostatic systems. Finally, a coping-based cognitive activation theory of stress supposes that the absence of coping can conduce to stress-related diseases. In conclusion, chronic stress is disease permissive and has been studied in several different conditions and it seems to act through the activation of proinflammatory pathways.[89,93]

2. METHODS

2.1 AIMS OF THE STUDY

A total of 68 patients with systemic lupus erythematosus were enrolled in this study with the purpose to investigate some psychopathological aspects and their role or influence on the course of the disease. The main aims were assessing the prevalence of some psychopathological disorders (alexithymia, depression, hopelessness and impulsiveness, along with coping strategies); investigating possible associations between psychiatric symptoms and SLE disease activity and clinical or laboratory manifestations; finally identifying clinical and laboratory risk factors for the development of psychopathological disorders.

All patients enrolled fulfilled the 2019 ACR/EULAR classification criteria for SLE.[64] The patients were enrolled during the periodic follow-up visits, in which anamnesis, physical examination, blood exams and psychological questionnaires were conducted. Specifically, patients were investigated for the presence of disease activity through both physical examination and blood exams, which included haemachrome, plasmatic protein electrophoresis, complement levels of C3 and C4, urine exams, hepatic exams, screening for the presence of anti-dsDNA antibodies, antiphospholipid antibodies (anti-cardiolipin, anti-b2glicoprotein1 and lupus anticoagulant) and ENA antibodies (anti-Sm, anti-Ro/SSA and anti-La/SSB) and 24h-proteinuria exam in patients with a renal involvement. The current therapy at the visit was collected for each patient. The SLEDAI-2K, LLDAS and SDI instruments were used to assess, respectively, the disease activity, the state of lupus low level disease activity and the damage index at the time of the evaluation.[82,83,100] Moreover, a screening for fibromyalgia following the 2016 revised criteria[98] was executed. Finally, patients were submitted to five psychological questionnaires after the clinical evaluation was concluded and were instructed to consider the approximative period of the last month for their completion. These questionnaires have all been validated in Italian and are the Beck depression inventory II (BDI-II), 20-item Toronto alexithymia scale (TAS-20), Beck hopelessness scale, Barratt impulsiveness scale-11 (BIS-11) and Coping orientation to problems experienced-60 (COPE-60).[101–105]

2.2 SYSTEMIC LUPUS EYTHEMATOSUS ASSESSMENT

The 2023 EULAR guidelines for the management of systemic lupus erythematosus suggest that SLE disease activity should be assessed at each clinic visit using validated instrument and, every year an assessment of all irreversible damage accrued should be taken because of its significant prognostic value. Moreover, the treatment target is the disease remission, however, when it is not possible, a state of low disease activity has shown to reduce the risk of damage and adverse outcomes in patients with SLE, hence this goal is accepted too.[85]

Systemic lupus erythematosus disease activity index 2000 (*SLEDAI-2K).* The most common and accepted disease activity instrument used is the Systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K, **attached 6.1**), developed in 2002.[83] It has been validated and compared to the original SLEDAI as a predictor of mortality and in describing changes in disease activity from one visit to another. However, unlike the original SLEDAI, the SLEDAI-2K counts the persistent activity in skin rush, alopecia or mucosal ulcers and proteinuria (>0.5g/day) and not only when they are of new onset. The scoring system is based on items with different weight, ranging from 1-8, which are simply added to obtain the total score. Items consider both clinical specific manifestations in 9 organ systems and laboratory tests, for a total of 24 items, within a period of 10 days preceding assessment. Though, SLEDAI-2K score measured over the last 30 days has been found to be comparable to the SLEDAI-2K score measured over 10 days. A SLEDAI-2K score of 0 indicates absence of disease activity, of 1-5 indicates moderate disease activity, while a score of 6 or greater indicates high disease activity. A change of 3 or more in the SLEDAI-2K score from the last assessment can indicate both a flare-up or a response to the treatment and improvement in the disease activity, respectively when the score increases or decreases.[106]

Systemic lupus international collaborating clinics/American college of rheumatology damage index (*SDI)*.The instrument most used to assess the damage accrued in SLE is the Systemic lupus international collaborating clinics/American college of rheumatology damage index (SLICC/ACR-DI or SDI, **attached 6.2**), developed in 1996.[100] It has been validated to measure changes in damage in both patients with active and inactive disease. The former is susceptible to a greater increase in damage, while patients with a low or stable disease the SDI remains fixed. This instrument records the damage accrual in SLE patients regardless of the cause, including damages derived from either previous disease activities sequelae, from medications adverse effects or concomitant diseases. For definition, SDI is 0 at diagnosis and damage can be considered when it persists for at least 6 months or associated with a pathological scar. SDI covers 12 systems in 41 items, each one recorded as present or absent, some items can be score with 2 for recurrent events in different sites, while the end stage renal disease is scored with 3. Total score is obtained with adding each item, but total score is less relevant in defining prognosis than the single components (e.g., renal

impairment is a predictor of renal failure, while pulmonary involvement of mortality). SDI score tends to increase with time and an higher score at the early stages of disease (2 or more at 5 years from diagnosis) correlates with the risk of mortality.[106] The accumulated disease damage index (SDI ≥1) has been associated with higher disease duration and also glucocorticoids dose, hypertension and exposure to cyclophosphamide.[107]

Low-lupus disease activity state (*LLDAS).* The state of low disease activity was defined in 2016 with the development of the low-level lupus disease activity state instrument (LLDAS, **table 2.1**).[82] This validated instrument has demonstrated that patients followed for almost 4 years who spend more than 50% of the time in LLDAS has significantly reduced organ damage accrual, compared to patients who spend less than 50% of time in LLDAS. The first group is less likely to has an increase in the SDI, finally, the LLDAS has been associated with improved outcomes in SLE. LLDAS is achieved when SLEDAI-2K is ≤4, without activity in major organ systems; no new lupus disease activity compared since the last visit; SELENA-SLEDAI physician global assessment ≤1; a current prednisone dose ≤7.5mg/day; and therapy is well tolerated. However, the most recent 2023 EULAR guidelines suggested that daily prednisone dose should be ≤5mg, looking for the total withdrawn. Hence, the guidelines suggest to adapt the new definition of LLDAS to those level of prednisone.[85]

LLDAS definition
Domain and items
Disease activity
1. SLEDAI-2K≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity
2. No new features of lupus disease activity compared with the previous assessment
3. SELENA-SLEDAI physician global assessment (PGA, scale 0-3) ≤1
Immunosuppressive medications
4. Current prednisolone (or equivalent) dose ≤7.5mg daily
5. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs

Table 2.1. Low level disease activity state criteria[82]

2.3 PSYCHIATRIC ASSESSMENT

Patients with systemic lupus erythematosus usually do not receive adequate psychiatric assessment during their disease, regardless the different psychiatric syndromes that have been described. Some syndromes seem to have an elevated prevalence among SLE patients and if they are not recognised and adequately treated, they can have important consequence on SLE patients life, impairing their quality of life, disability and worsen depression and other psychiatric symptoms.[90] Moreover, some theories have hypothesized the relationship between major and minor daily stress and the worsening of the disease or even acting as a possible trigger for its development.[89]

In this study, five psychometric scales were used to measure some psychological features of the investigated SLE patients: the Beck depression inventory II (BDI-II), the 20-item Toronto alexithymia scale (TAS-20), the Beck hopelessness scale, Barratt impulsiveness scale-11 (BIS-11) and the Coping orientation to problems experienced-60 (COPE-60).

The *Beck depression inventory II* is one of the most self-assessment scale used to detect depression, published in 1996, created following the publication of DSM-IV.[101] The questionnaire includes 21 items concerning different symptoms domains, each one have four possible answers with a score that ranges from 0 to 3 respectively to increasing severity. 13 items address cognitive or affective symptoms (i.e., hopelessness and guilt, depression mood and loss of interest or pleasure in usual activities). The remaining 8 items assess somatic symptoms (insomnia, fatigue and poor appetite). Total score ranges from 0 to 63. This instrument is easy to administer and boasts high reliability and internal consistency, showing a good capacity to discriminate between depressed and non-depressed subjects.[108] While in a screening purpose a cutoff of 10 is widely used for clinically significant depression, a metanalysis has shown that a score of 13 in primary care and healthy people should be used as a cutoff to indicate depression. However, an agree to the cutoff has not yet been reached.[109] A further subdivision is to differentiate mild (10-19), moderate (20-29) and severe depression (30 or higher). The Beck depression inventory has been already used in SLE patients by different studies and a systematic review has conducted a meta-analysis of 59 studies to establish the prevalence of depression in SLE patients. The result has confirmed that depression prevalence in SLE is higher than the general population and inspected through the gold standard clinical interview (DSM or ICD) the prevalence of major depressive disorder found is 24%. However, due to the different methods of evaluation, the prevalence of depression detected ranged widely from 2% to 91.7%, settling at 39% assessed through BDI-2 with a threshold of 14.[110] The questionnaire has been validated in Italian and is comparable to the original edition (**attached 6.3**).[111]

The *20-item Toronto alexithymia scale*, published in 1994, is the most widely used questionnaire to measure the alexithymia construct.[105,112] It is a reliable instrument that reflect the original definition of alexithymia coined by Nemiah et al. as composed of deficit in affect awareness, expression and operational thinking. The term

alexithymia expresses the difficult in identifying and describing emotions. Introspective thinking, fantasy and daydreaming are lack in alexithymic patients, indeed, their thought is extremally concrete, utilitarian and externally focused. Moreover, it has a higher prevalence in patients with chronic disease, such as SLE. The prevalence of alexithymia in the general population has been found to be about 10%, while in SLE patients it ranges from 17.5% to 50.9%, significantly higher in various studies. The TAS-20 has been also correlated with depression.[113] It is composed by 20 items, rated on a 5-point Linkert scale and alexithymia degree is greater the higher is the total score. Three subscales can be obtained by the questionnaire, i.e., factor 1 "difficulty identifying feelings" (which indicates the difficulty to differentiate an affective state from a body sensation or to identify an experience as affective), factor 2 "difficulty describing feelings" (which indicates the incapability to give a name and describe one's own feelings), factor 3 "externally oriented thinking" (which indicates the measure of understanding more the objective events than the psychological processes). Nevertheless, the total score is preferable because each factor contribute to the overall measurement of alexithymia differently. Alexithymia is considered present if the total score is >60, although alexithymia trait can be present with a score between 52-60. The Italian version shows a good internal reliability and test-retest reliability and has been validated in both nonclinical and medical or psychiatric patients (**attached 6.4**).[114]

The *Beck hopelessness scale* was published in 1974 as a method to measure a negative view of the future. It is composed by 20 true or false items.[102] Hopelessness is strictly associated to the risk of suicide and poor quality of life. Score ranges from 0 to 20 and hopelessness is greater the higher is the score obtained. The authors identified 3 factors: factor 1 "feeling about the future", factor 2 "loss of motivation" and factor 3 "Future expectations", although many studies failed to support this distinction. Therefore, a study suggest that the questionnaire should consider a unidimensional measure of hopelessness, with a positive score of ≥ 9.[115] Moreover, the hopelessness, used to detect the suicidal ideation, assessed with the BHS can be considered mild with a score from 4 to 8, moderate from 9 to 14 or severe >14. In another study, the BHS has been submitted to SLE patients and respectively 34%, 14% and 22% of patients have showed mild, moderate and severe level of hopelessness.[116] Moreover, it was higher in the group of SLE patients with major depression. The BHS has been adapted and validated in Italian (**attached 6.5**).[117]

The *Barratt impulsiveness scale* is the most used questionnaire to investigate the presence of impulsivity and impulse control.[103] It is composed by 30 items, from 1-4 each, with a total score ranging from 30 to 120 and it is greater the higher is the impulsivity. Barratt, originally, identified three subdomains (i.e., attention, motor and non-planning), but recent studies do not support this subdivision.[118] The Italian version has been validated in nonclinical subjects and it demonstrated that the total score is consistent in being a homogeneous measure of impulsiveness (**attached 6.6**).[119]

The *Coping orientation to problems experienced* questionnaire has been developed in 1989 with the purpose of differentiate how people respond to stress.[104] It is composed by 60 items, each scored from 1 to 4 depend on the frequency, differentiated in 15 mechanisms of coping, which can be regrouped by a factorial analysis in 5 dimensions. These domains are: 1 social support (seeking of instrumental social support, seeking of emotional social support, focus on and venting of emotions), 2 avoidance strategies (denial, behavioural disengagement, mental disengagement, alcohol or drug use), 3 positive attitude (acceptance, positive reinterpretation and restraint coping), 4 problem orientation (active coping, planning, suppression of competing activities), 5 transcendent orientation (turning to religion and humour). Higher score in one item indicates a preference to use that coping style. The questionnaire has been validated in Italian language (**attached 6.7**).[120,121] This inventory has been already used on SLE patients and it has been observed that acceptance and turning to religion coping strategies are significantly higher in SLE patients than the general population, while planning, suppression of competing activities, restraint coping, focusing on and venting emotions, and strategies focused on problem have significantly a lower scores compared to control. Finally, the study has found that joint pain seems to influence coping strategies.[122]

2.4 STATISTICAL ANALYSIS

The descriptive analysis was adopted to summarize the factors studied, using mean, standard deviation, 95% confidence interval and Shapiro-Wilk test p-value as normal distribution test. These factors included demographic description with age, age onset and SLE illness duration, the prednisone dose, the SLEDAI-2K, SDI and the questionnaires used, BDI-2, TAS-20, BHS, BIS-11 and COPE-60. Frequency analysis was executed to describe drugs in therapy at the evaluation, the SLE disease manifestations occurred and laboratory characteristics, the SLEDAI-2K items noted, the prevalence of LLDAS, fibromyalgia, BDI-2, TAS-20 and BHS. For the inferential analysis, the correlation matrix with the Spearman's Rho test, because the non-normal distributions, was used for all the psychological scales, the SSS, age and the age onset. Student-t test was employed for TAS-20 and Mann-Whitney test for BDI-2 or contingency with Fisher-exact test, cause the small sample, for BDI-2 and TAS-20. Univariate and multivariate logistic regression analysis were used to identify risk factors for the development of psychiatric symptoms. The statistical assessment was conducted with the aid of Jamovi software.[123–126]

3. RESULTS

3.1 DESCRIPTIVE STATISTICAL ANALYSIS

3.1.1 Patient description and clinical assessment

A total of 68 patients with systemic lupus erythematosus were enrolled in this study. As expected, 60 were female while only 8 were male (F/M=7.5/1). The prevalent ethnicities were Caucasic (49 patients) and Hispanic (14 patients), the remaining minority were African and Indian. The mean age was 47.3 years old (SD 13.1); the mean of the disease age onset was 31.5 years old (SD 12.8), while the disease duration mean was 16 years old (SD 10.8, **table 3.1**).

Descriptors	Mean ± SD
Age	47.3±13.1
Age onset	31.5±12.8
Disease duration	16±10.8
M/F	1/7.5

Table 3.1. Demographic description

All patients were in treatment for SLE, 60 patients were in treatment with hydroxychloroquine, 34 with DMARDs, 14 with Belimumab and 29 with glucocorticoids and a total of 73.5% of patients had the dosage below or equal to the threshold suggested by 2023 EULAR guidelines of ≤5mg/day of prednisone or an equivalent.[85] Finally, a total of 17.6% of patients were in treatment with antidepressant drugs (**Table 3.2**).

The most common disease manifestations during the patients' SLE history were arthritis (82,4%), followed in order by haematological, mucocutaneous, renal, serositis and neuropsychiatric (**table 3.3**).

Drugs	N (%)
Hydroxychloroquine	60 (88.2)
Glucocorticoids	29 (42.6)
DMARDs	34 (50)
Belimumab	14 (20.6)
Antidepressant	12 (17.6)

Table 3.2. Patients' treatment description

Disease manifestations	Overall N (%)
Articular	56 (82.4)
Haematologic	45 (66.2)
Leukopenia	33 (48.5)
Thrombocytopenia	23 (33.8)
Haemolytic anaemia	20 (29.4)
Mucocutaneous	39 (57.4)
Malar rash	29 (42.6)
Photosensitivity	20 (29.4)
DLE	10 (14.7)
SCLE	2 (2.9)
Renal	38 (55.9)
Serositis	20 (29.4)
Neuropsychiatric	18 (26.5)

Table 3.3. Overall SLE manifestations

The overall prevalence of anti-dsDNA antibodies in patients was 66.2% and of anti-Sm antibodies was 23.5%, while prevalence of anti-Ro/SSA antibodies was 45.6% and of anti-La/SSB antibodies was 16.2%. The consumption of both C3 and C4 was found in 54.4% of patients, while considering only C3 or C4 alone it reached the 80.9% of patients. The antiphospholipid antibodies were found in 39.7% of patients, however, only 16.2% received the diagnosis of antiphospholipid syndrome. (**Table 3.4**).

The disease activity mean measured through the SLEDAI-2K instrument considering the last 30

days was 2.65 (SD 3.06) and the SLICC/ACR damage index (SDI) mean was 1.22 (SD 1.67). In further detail, SLEDAI-2K was 0 for 24 (41.2%) patients, while SDI is 0 for 31 (45.6%) patients (**table 3.6**).

Laboratory features	Overall
Anti-dsDNA Ab	45 (66.2)
Anti-Ro/SSA Ab	31 (45.6)
Anti-La/SSB Ab	11 (16.2)
Anti-Sm Ab	16 (23.5)
C3 or C4 consumption	55 (80.9)
C3 and C4 consumption	37 (54.4)
APL	27 (39.7)
APS	11 (16.2)

Table 3.4. Overall patients' laboratory features

Complement consumption was the most frequently SLEDAI-2K item observed with a frequency of 44.1%, followed by the presence of anti-dsDNA antibodies (35.3%). The least represented were proteinuria (10.3%), haematologic manifestations (principally leukopenia and thrombocytopenia) and arthritis (**table 3.5**). Finally, only two patients presented fever, one malar rash, one haematuria, one optic neuromyelitis and one pericarditis.

SLEDAI-2K descriptors	N (%)
Complement consumption	30 (44.1)
Anti-dsDNA Ab	24 (35.3)
Proteinuria	7 (10.3)
Haematologic	6 (8.8)
Leukopenia	4 (5.9)
Thrombocytopenia	2 (2.9)
Arthritis	5 (7.4)
Fever	2 (2.9)
Malar rash	1 (1.5)
Pericarditis	2 (1.5)
Haematuria	3 (1.5)
Optic neuromyelitis	4 (1.5)

Table 3.5. Frequency of items noticed and counted in the SLEDAI-2K

Since the low mean of the SLEDAI-2K observed and the low incidence of new features of SLE disease activity, the low level of disease activity state was reached in 69.1% of patients considering the glucocorticoid dosage ≤7.5mg of prednisone, as the original definition of the LLDAS.[82] The accrued damage assessed with the SDI≥1 was present in 54.4% of patients. Fibromyalgia was diagnosed in 5 patients (7.4%, **table 3.6**).

Descriptors	Mean ± SD
SLEDAI-2K	2.65±3.06
SDI	1.22±1.67
Frequency	**N (%)**
LLDAS	47 (69.1)
SDI≥1	37 (54.4)
Fibromyalgia	5 (7.4)

Table 3.6. Mean and frequencies observed of disease activity, accrued damage and fibromyalgia

3.1.2 Psychiatric assessment

The 20-items Toronto alexithymia scale mean was of 51.3 (SD 12.4). The possible presence of alexithymia was identified in 44.1% of patients, considering a threshold of 52, while alexithymia assessed with a score >60 was present in 23.5% of patients. Depression was found in 32.4% of patients through the BDI-II scale using a threshold of 16, and 22.1% of patients presented a mild (10-19), 16.2% a moderate (20-29) and 11.8% a severe depression (≥30). The BDI-II mean was 13.1 (SD 11.5). Hopelessness characterized 26.5% of patients of the cohort, observed, when a threshold of 9 on the BHS scale was considered. Mild level of hopelessness (4-8) was found in 38.2% of patients, moderate (9-14) in 23.5% and severe (>14) in 2.9%. The BHS mean was 5.69 (SD 4.25). The Barratt

impulsiveness scale mean was 63 (SD 13.4) and there was not a threshold to identify the presence of impulsiveness (**table 3.7**).

Scale	Mean ± SD
TAS-20	51.3±12.4
BDI-2	13.1±11.5
BHS	5.69±4.25
BIS-11	63±13.4
Frequency	**N (%)**
TAS-20>60	16 (23.5)
BDI>15	22 (32.4)
Mild	15 (22.1)
Moderate	11 (16.2)
Severe	8 (11.8)
BHS	18 (26.5)
Mild	26 (38.2)
Moderate	16 (23.5)
Severe	2 (2.9)

Table 3.7. Mean and frequencies of the psychiatric assessment

The coping orientation to problems experienced (COPE-60) showed that planning, acceptance, positive reinterpretation and active coping were the coping strategies most employed, while alcohol and drug use was the least (**table 3.8**).

Coping strategies	Mean (SD)
Positive reinterpretation	11.8 (3.02)
Mental disengagement	9.0 (2.45)
Focus on and venting emotions	8.94 (2.57)
Seeking of instrumental social support	10.5 (3.38)
Active coping	11.5 (2.38)
Denial	7.49 (2.79)
Turning to religion	8.47 (4.31)
Humour	8.53 (3.47)
Behavioural disengagement	7.84 (2.32)
Restraint coping	10.1 (2.00)
Seeking of emotional social support	9.53 (3.53)
Alcohol or drug use	4.78 (2.18)
Acceptance	11.8 (5.03)
Suppression of competing activities	10.2 (2.6)
Planning	11 (2.59)

Table 3.8. Mean of coping styles from COPE-60

3.2 INFERENTIAL STATISTICAL ANALYSIS

From an initial observation, the SLEDAI-2K was correlated negatively with the age of the patients (p=0.028) and with the age onset (p=0.048). The SDI was correlated positively with the age (p=0.023). All the psychological scales (TAS-20, BDI-II, BHS and BIS-11) used in this study were correlated very strongly each other (t**able 3.8).**

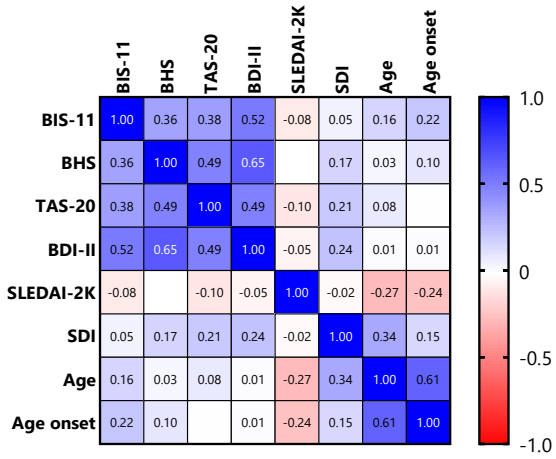


Table 3.8. Correlation matrix

Alexithymia among SLE patients. The prevalence of alexithymia (TAS-20>60) was higher in the group of SLE patients with secondary APS (OR 5.64, p=0.016), six (54.55%) of these were positive to TAS-20, while only 10 (17.54%) of SLE patients without APS resulted alexithymic. The level of alexithymia, assessed with TAS-20 instrument, was found higher in SLE patients with secondary APS (p=0.043) and in those who had neuropsychiatric manifestations (p=0.043, **table 3.9**). Furthermore, higher level of the positive reinterpretation (p<.001) and the focus on and venting of emotions (p=0.013) coping styles were observed in alexithymic patients. The presence of secondary APS in SLE patients as a risk factor for the development of alexithymia

was confirmed by the univariate logistic regression (OR 5.64, p=0.013), along with focus on and venting of emotions coping strategy (OR 1.32, p=0.019), while positive reinterpretation coping style was protective (OR 0.643, p<.001).

Fisher's exact test (TAS-20>60)			
Variable	OR	95% CI	p
APS	OR 5.64	1.55-21.66	0.016
Student's t test (TAS-20)			
Variable	M (Yes)	M (Not)	p
APS	58.18	49.95	0.043
NPSLE	56.33	49.46	0.043

Table 3.9. Significant odds ratio and mean differences of TAS-20 basing on patients features with relative Fisher's exact test and Student's t test

Lastly, a multivariate logistic regression was made using the previous significant findings: presence of the APS (OR 35.77, p=0.002) and of the focus on and venting of emotions (OR 1.68, p=0.009) coping style were significantly associated with an increased risk to develop alexithymia, while the positive reinterpretation coping strategy was protective (OR 0.514, p<.001, **table 3.11**). No significative correlations were found between the presence of alexithymia and either SLEDAI-2K, SDI or LLDAS.

Depression among SLE patients. The prevalence of depression was higher in patients with SDI≥1 (OR 3.18, p=0.042) and in patients with fibromyalgia (OR 10.0 p=0.042). Higher level of depression was observed in patients with SDI≥1 (p=0.046), fibromyalgia (p=0.003), in those with active arthritis (p=0.02) and in those treated with antidepressant drugs (p=0.024, **table 3.10**).

Fisher's exact test (BDI-II>15)			
Variable	OR	95% CI	p
SDI≥1	3.18	1.01-10.2	0.042
Fibromyalgia	10	1.42-124.4	0.042
Mann-Whitney's U test (BDI-II)			
Variable	M (Yes)	M (Not)	p
SDI≥1	13	7	0.047
Fibromyalgia	35	8	<.001
Active arthritis	28	8	0.029

Table 3.10. Significant odds ratio and median differences of BDI-II basing on patients features with relative Fisher's exact test and Mann-Whitney's U test

The presence of SDI≥1 was confirmed by a univariate logistic analysis as a risk factor for developing depression (OR 3.175, p=0.04), along with fibromyalgia (OR 10, p=0.046) and being in therapy with antidepressant drugs (OR 3.83, p=0.042, **table 3.12**).

Univariate (BDI-II>15)			
Variable	OR	95% CI	p
SDI≥1	3.175	1.05-9.57	0.04
Fibromyalgia	10	1.05-95.68	0.046
Active arthritis	3.47	0.54-22.50	0.191
AntiD. Drugs	3.83	1.05-13.92	0.042

Table 3.12. Univariate and multivariate logistic regression for BDI-2

No significant associations were found with the BHS and the BIS-11 scales.

	Univariate			Multivariate		
Variable	OR	95% CI	p	OR	95% CI	p
APS	5.64	1.43-22.18	0.013	35.79	4.66-478.8	0.002
NPSLE	2.9	0.99-9.54	0.08			
Positive reinterpretation	0.643	0.50-0.83	<.001	0.513	0.32-0.71	<0.01
Focus on and venting of emotions	1.32	1.04-1.67	0.019	1.684	1.21-2.58	<0.006

Table 3.11. Univariate analysis and multivariate logistic regression model for TAS-20>60

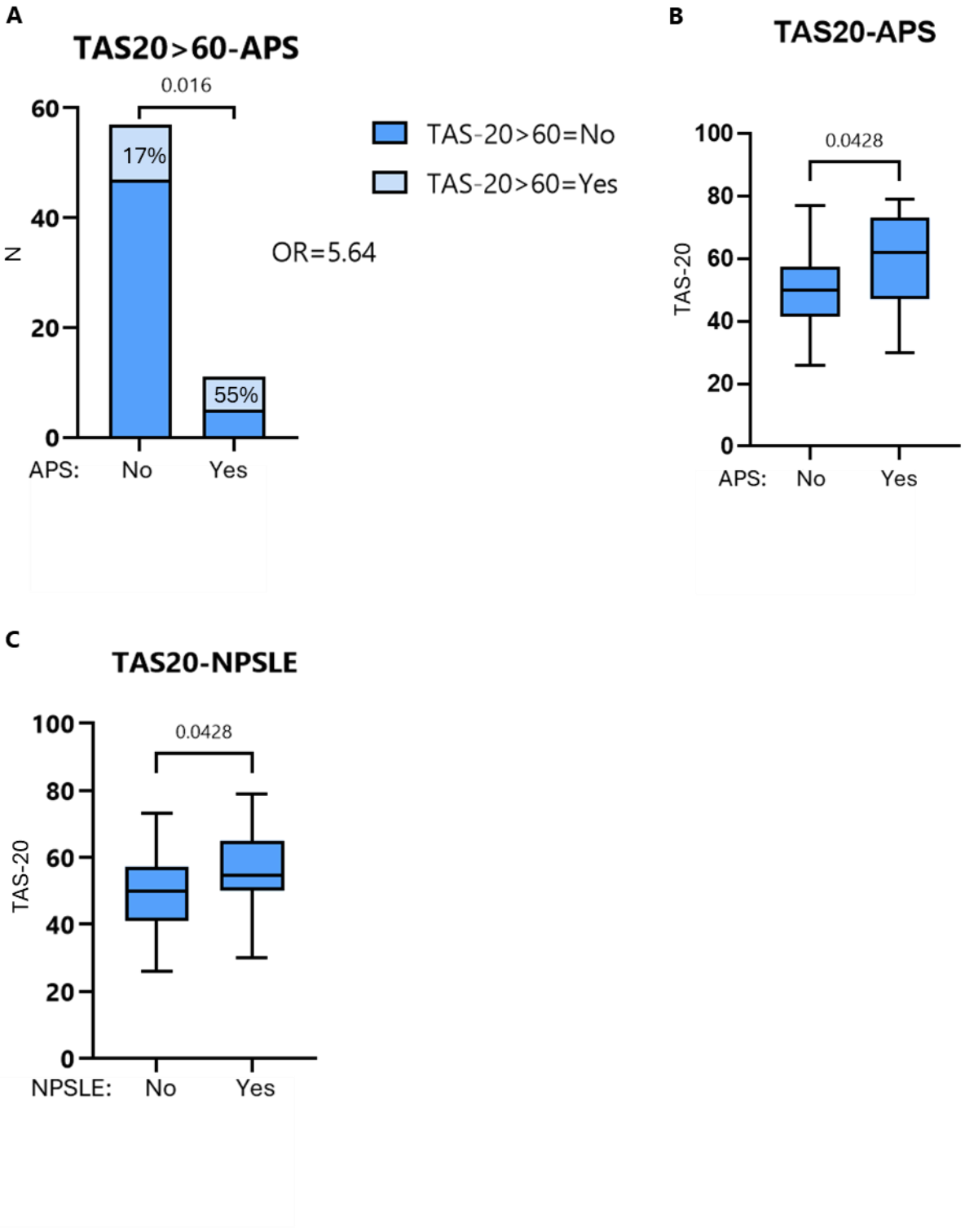


Figure 3.1. A. Prevalence of alexithymia in SLE patients with APS compared with those without. **B.** Level of alexithymia in SLE patients with APS compared with those without. **C.** Level of alexithymia in SLE patients with NPSLE compared with those without.

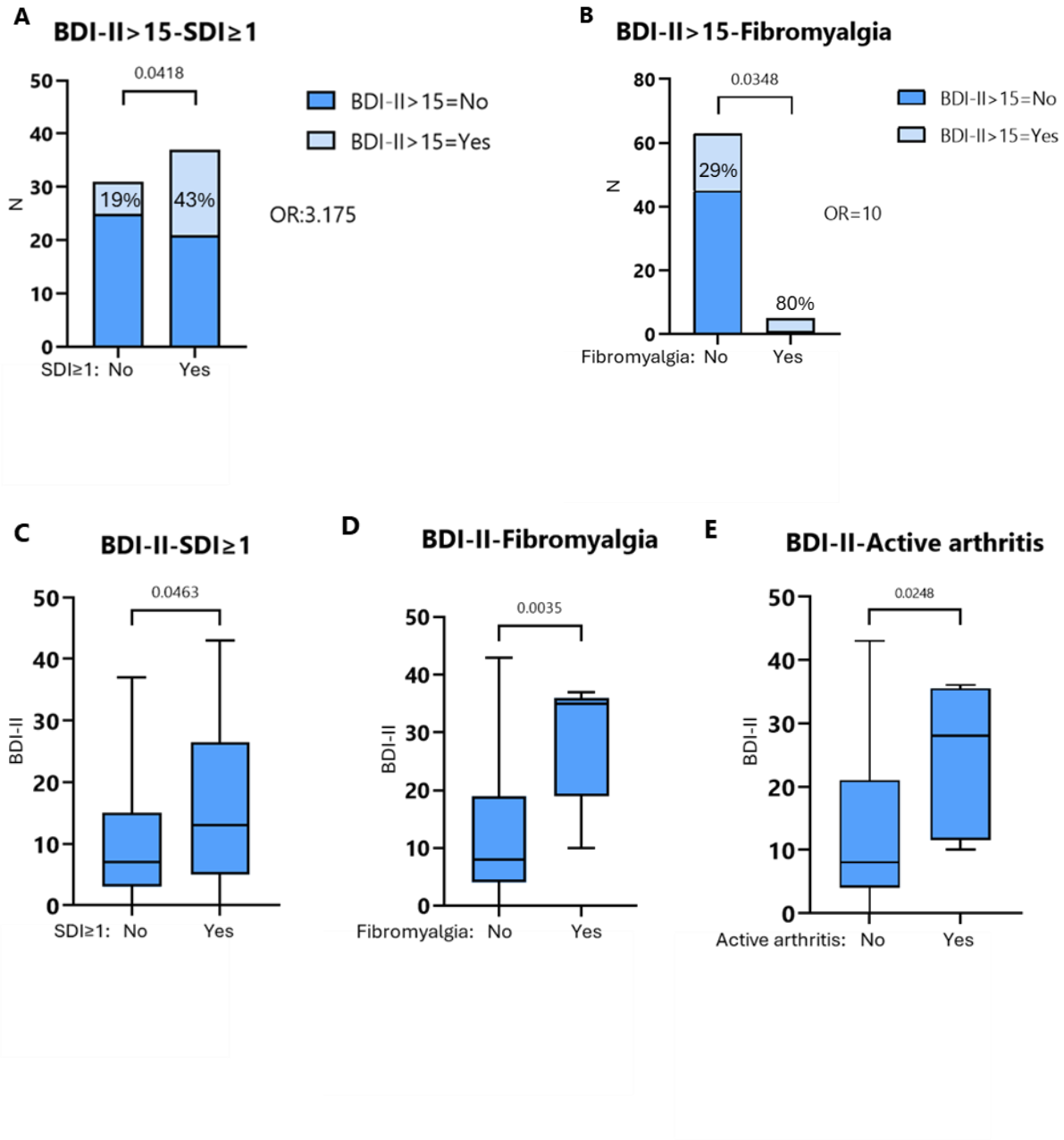
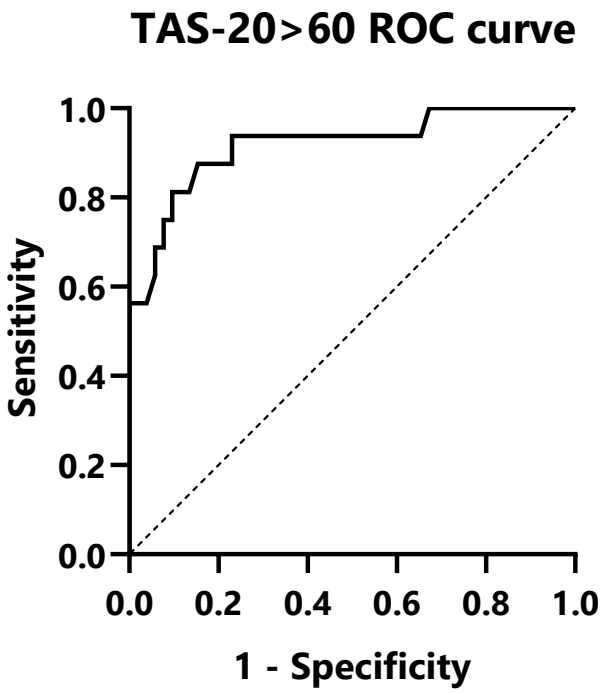


Figure 3.2. A. Prevalence of depression in SLE patients with SDI≥1 compared with those with SDI=0. **B**. Prevalence of depression in SLE patients with fibromyalgia compared with those without. **C.** Level of depression in SLE patients with SDI≥1 compared with those with SDI=0. **D.** Level of depression in SLE patients with fibromyalgia compared with those without. **E.** Level of depression in SLE patients with active arthritis compared with those without.



Prediction (%)	
Accuracy	88.2
Specificity	94.2
Sensitivity	68.8
Negative predictive power	90.7
Positive predictive power	78.6

Multivariate logistic regression model prediction power

Figure 3.3. Multivariate logistic regression model for the prediction of TAS-20>60 in SLE patients. Components of the model: APS (OR 35.77, p=0.002), positive reinterpretation (OR 0.514, p<.001) and focus on and venting of emotions (OR 1.68, p=0.009) coping styles. The model showed high specificity but low sensitivity and good negative predictive power.

4. DISCUSSION

Systemic lupus erythematosus is a complex autoimmune disease with unpredictable flares up and higher morbidity and mortality without adequate treatment.[8] SLE can involve different organs with a great number of possible manifestations. The neuropsychiatric involvement is one of the most difficult manifestations to ensure that is caused by SLE, indeed it has a prevalence that ranges from 37% to 95%.[70] NPSLE syndromes were described in 1999 by the ACR and 19 different manifestations were attributed to SLE, involving both central nervous system and peripheral nervous system, neurological and psychiatric syndromes.[69] Nevertheless, some NPSLE manifestations are more likely to be caused by SLE and easily recognised, especially the most neurological forms as vasculitis, cerebrovascular disease and aseptic meningitis, while many NPSLE syndromes remain of difficult attribution to SLE. This is particularly true for the psychiatric manifestations described in SLE patients, which are acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder and psychosis, explaining the NPSLE prevalence variability.

No direct correlation was found between disease activity, as assessed through the SLEDAI-2K, and the psychological scales studied, suggesting that the psychopathological aspects analysed do not influence the disease activity. However, the assessment was carried out in patients during of the follow-up visit, which does not necessarily correspond to a SLE flare up, as can be seen from the low mean of SLEDAI-2K (M 2.65, SD 3.06). This leaves room to the possibility of continuing the study resending the questionnaires when new flares are detected, using these initial results as control.

Alexithymia among SLE patients. Since the beginning of the XX century, the role of psychological stress which may precipitate or exacerbate rheumatic diseases was hypothesized.[89] However, It had to wait till the end of 1970s for the birth of the interdisciplinary psychoneuroimmunology field, in which psychological, neurological, endocrinological and immunological aspects were studied together sought to understand the functional relationship between the brain and the immune system.[127] Indeed, evidence support that psychological stress can influence pathogenesis and exacerbation of chronic autoimmune-inflammatory rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus, mediated by the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, the parasympathetic nervous systems and the endocrine system.[93] Several psychological conditions were associated with increased susceptibility to the development of autoimmune diseases and alexithymia is one of them.[113]

In previous studies, systemic lupus erythematosus patients showed a higher prevalence of alexithymia than general population, indeed, a 23.5% of the enrolled patients in this study were positive to the presence of alexithymia.[113]

Coping strategies were also investigated and we found that planning, acceptance, positive reinterpretation and active coping were the most common, while alcohol and drug use was the

least. The results we obtained were superimposable with those of Rinaldi et al.[122]. In their study, joint pain was the only clinical variable which seems to influence coping styles. However, in our study active arthritis was not associated to a significant difference in coping strategies, probably because of joint pain concerns also other manifestations than arthritis alone.

We noted that the coping style "Focus on and venting of emotions" was significantly higher in patients who results positive for alexithymia than those not. Alexithymia is characterized by a deficit in the awareness, expression, identification and description of one's own feelings and emotions, does not meaning that feeling and emotions are not experienced. Indeed, maybe the difficulty to recognise them make alexithymic patients more susceptible to focus on and trying to vent emotions, looking for a name of what they felt.

Coping strategy of positive reinterpretation was observed to be significantly lower in SLE patients with alexithymia.

Relationship between alexithymia and SLE disease activity (SLEDAI-2K), damage index (SDI) and patients who were in state of low disease activity (LLDAS) were investigate, but none of these associations were significative. This suggests that alexithymia was not influenced by the disease activity, in line with the study of Vadacca et al.[128], or damage accrued.

Patients clinical and laboratory features were collected at time of psychological evaluation. Of these, the patients who had neuropsychiatric SLE manifestations in their history showed a significative greater prevalence of alexithymia than those who had not. Pathogenesis of NPSLE is not fully understood, especially the cognitive and the affective manifestations, and different mechanisms have been considered: autoantibodies, such as anti-NMDAR and anti-ribosomal P protein antibodies might explain diffuse NPSLE presentations, targeting specific brain structures through direct neuronal toxicity or indirect damage to the blood-brain barrier; microglial activation and inflammatory cytokines secretion (e.g. IL-6); vasculitis and thrombosis, involving antiphospholipid antibodies (aPL) and anti-endothelial cell antibodies.[71,129] Some studies suggest that cerebrovascular disease might play a role in causing acquired alexithymia and higher rates were observed on the right brain stroke involvement than the left.[130]

Similarly, patients with secondary antiphospholipid syndrome showed a significative higher prevalence of alexithymia. The association between APS and NPSLE is well known, mainly because of the development of thrombosis in the cerebral arteries due to the antiphospholipid antibodies (aPL), but no significant association was found in this study.[73] Furthermore, the positivity of antiphospholipid antibodies (anti-cardiolipin, anti-beta-2-glicoprotein-1 and lupus anticoagulant test) was not associated with higher presence of alexithymia. This may be explained because positivity to the antiphospholipid antibodies does not implicate necessarily the presence of the aPL disease, which required also clinical criteria (i.e., macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic manifestations).[131] Since alexithymia has been

associated to neurovascular disease, cerebral damage is probably needed and the only presence of antiphospholipid autoantibodies does not implicate it, instead it might be observed in those patients with the APS.

Correlation between either aPL or APS and neuropsychiatric manifestations was already described, mainly about cognitive dysfunction.

Indeed, patients with antiphospholipid antibodies are reported to have a high frequency of cognitive dysfunction (19-40%), which doubles when patients with primary antiphospholipid syndrome are considered (42-80%). Regards to SLE patients, the prevalence of cognitive impairment is significantly higher in those with aPL (21-54%) than in those without (4-7%).[73] Furthermore, the APL titres were correlated to the cognitive impairment in primary and secondary APS patients and this disorder seems to be independent of any history of neurologic involvement. However, a study conducted on 1000 SLE patients showed that aPL were no longer associated to NPSLE when stroke is excluded, suggesting that the thromboembolic role of the aPL, through endothelial dysfunction, platelet activation, and complement and coagulation activation, is the most involved mechanism.[132]

Through magnetic resonance imaging studies, cognitive dysfunction in APS patients was associated to white matter lesions, ischemic lesions and cortical atrophy. An association between brain ischemic involvement, such as multifocal infarcts, white matter demyelination and cerebral atrophy with aPL positivity was reported, although should note that other studies did not find this.[133] Diffusion magnetic resonance imaging was used to investigate white matter in healthy patients, who were administered the TAS-20, to explore possible associations with certain cerebral tracts and alexithymia and emotion regulation. White matter microstructures of motor and somatosensory areas, language areas and limbic areas were significantly associated with TAS-20, supposing the possible role of these areas in emotion regulation.[134] White matter abnormalities, especially infarct and hyperintense white matter foci, were reported in APS patients and it is supposed to be related mainly to attentional and executive cognitive impairment.[135]

Our finding suggests that alexithymia and emotions regulation are associated with antiphospholipid syndrome, but not with the only presence of the antiphospholipid antibodies. The possible mechanism may be the involvement of the white matter lesions, characteristically described in APS patients, in areas associated with emotion regulation, which in turn may lead to the development of alexithymia. Hence, in addition to cognitive dysfunction, alexithymia should be considered as a psychopathological dimension which could interest more frequently SLE patients with the APS.

Depression among SLE patients. Mood disorders, especially major depression disorder, were included in the 19 neuropsychiatric syndromes described by the ACR in 1999.[69] Although, if some of these syndrome (e.g. cerebrovascular disease and seizures) are relatively easy to diagnose and to be attributed to SLE, the same could not be said for others, especially the milder neuropsychiatric syndromes and which ones with high prevalence in the general population (e.g.

anxiety disorder and headache). In general, the EULAR suggests that most NPSLE events occur within the first year after SLE onset, particularly in presence of generalized disease activity, and a series of exams should be conducted in order to excluded other most common causes before attributing them to SLE.[72] Five NPSLE syndromes are typically of psychiatric interest: anxiety and mood disorders, acute confusional state, cognitive dysfunction and psychosis. While anxiety disorder is extremely unspecific, psychosis and depression are the most studied and mechanisms, such as anti-ribosomal-P antibodies, anti-endothelial cell antibodies and cytokine-mediated inflammation, not least glucocorticoid therapy, were implicated.[129]

Depression was widely investigated in systemic lupus erythematosus patients and a prevalence of four-fold higher than general population was found, making it one of the most common neuropsychiatric syndromes.[90] The estimated prevalence in a meta-analysis of major depressive disorder diagnosed by clinical interview was 24%, while greater variability and heterogeneity was observed when self-assessments instruments were used.[110] In our study we found depression frequency of 32.4%, assessed with the Beck depression index-2 (BDI-2).

Depression in SLE patients was hypothesized to be associated to their disease activity, increasing in severity as the disease progresses, though also disease activity was supposed to be related to the level of depression.[136] However, in this study no association between depression and disease activity, assessed with the SLEDAI-2K, was found, neither differences with patients in the state of low lupus disease activity (LLDAS). Another study tried to identify predictive clinical and laboratory risk factors for the development of psychiatric syndromes in SLE.[137] In this study, the antiphospholipid antibodies (aPL), anti-cardiolipin and anti-beta-2-glicoprotein-1, were most commonly observed with significance in patients with mood disorders. However, we did not find this association. The only SLE clinical variable that we observed to be a risk factor for depression was the disease damage accrued, assessed with the SLICC/ACR damage index (SDI≥1), according with the study of D. J. Park et al..[138] The SLICC/ACR damage index was validated to measure changes in damage in both patients with active and inactive disease.[100] The former is susceptible to a greater increase in damage, while patients with a low or stable disease the SDI remains fixed. This instrument records the damage accrual in SLE patients regardless of the cause, including damages derived from either previous disease activities sequelae, from medications adverse effects or concomitant diseases. Indeed, the presence of damage (SDI≥1) was associated with demographic factors (e.g. older age at diagnosis and longer disease duration), clinical (e.g. hypertension and antiphospholipid antibodies) and precedent treatment (e.g. cyclophosphamide exposure).[107] SLE is associated with a lower health-related quality of life (HRQoL) and depression seems to significantly affects it, suggesting that the presence of depression needs to be included in the patient assessment and management routinely.[139] Finally, psychoanalytic psychotherapy showed significant efficacy in improving quality of life and coping skills and reducing depression and anxiety in SLE patients

in a randomized controlled trial, hinting that psychotherapy could be part of SLE medical care.[140]

Since depression is associated to fibromyalgia, we also investigated its presence along SLE patients and its possible role to the development of depression. We found that the prevalence of fibromyalgia was 7.4% and higher level of depression was observed. Our finding is in linear with a study conducted in a large registry of SLE patients, fibromyalgia had a prevalence of 6.2% and patients who was diagnosed fibromyalgia syndrome showed a significant higher frequency of depression than patients without.[96] A possible explanation may be that fibromyalgia and fatigue are known factor of poorer quality of life in SLE patients, regardless the disease activity, and poorer functional outcome rather than to active disease.[141] Furthermore, in this study the only SLE manifestation associated significantly with depression was active arthritis, indeed, in these patients higher level of depression was observed, probably because arthritis is of the one of the most relevant manifestations affecting the daily life. However, both fibromyalgia and active arthritis were not significant to a multivariate regression analysis in which only the presence of damage at the SLICC/ACR damage index was a significant predictive risk factor for the development of depression.

5. CONCLUSION

This study confirms the high prevalence of the psychopathological involvement in SLE patients and identifies associations between clinical or laboratory features of SLE for the development of alexithymia and depression.

This study confirms the high prevalence of alexithymia in SLE patients and identify the APS as important clinical risk factor for its development. The APS is frequently observed in SLE, being able to reach the 35% of patients, and is associated with a worse course of illness and outcome.[142] When considering the higher frequency of alexithymia in SLE patients with secondary APS, it becomes important to investigate its presence. Alexithymia may affect the ability to cope adequately stressful situations and contribute to generate psychological stress in the individual. Evidence about the relationship between psychological and immune system are accumulating during years and new therapies were developed, nevertheless more trials should be conducted.[93] Finally, considering the well-established high prevalence of cognitive impairment in APS patients, further researches on primary and secondary APS along with the alexithymia construct and other psychopathological dimensions should be evaluated, in order to investigate their possible association, physiopathology and prognosis.

Depression is frequently observed in systemic lupus erythematosus patients and many patients are untreated. This study tried to identify patients which can be at risk to develop depression analysing clinical and laboratory features of SLE. We found that the presence of damage accrued, assessed with the SLICC/ACR damage index (SDI≥1), was significant, suggesting that patients with a damage which persist for at least 6 months are more susceptible to develop depression. This may help clinicians to promptly identify and manage depression early in SLE patients, improving HRQoL and illness perception.

Further studies in the psychoneuroimmunology field should be carried out to better understand the relationship between the brain and the immune system, likewise, to improve knowledge of the role of psychopathological stress in the pathogenesis and the exacerbations of chronic autoimmune-autoinflammatory rheumatic diseases.

6. ATTACHED

Weight	SLEDAI SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / x10^9/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / x10^9/L, exclude drug causes.

Attached 6.1. SLEDAI-2K data collection form[83]

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change *or* optic atrophy	1
Neuropsychiatric	
Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) *or* major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 if >1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate <50%	1
Proteinuria ≥3.5 gm/24 hours	1
or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina *or* coronary artery bypass	1
Myocardial infarction ever (score 2 if >1)	1 (2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic, murmur, or systolic murmur >3/6)	1
Pericarditis for 6 months, *or* pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (e.g., loss of digit or limb) (score 2 if >1 site)	1 (2)
Venous thrombosis with swelling, ulceration, *or* venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if >1 site)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture *or* upper gastrointestinal tract surgery ever	1
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if >1)	1 (2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for >6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site)	1 (2)

* Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

Attached 6.2. Systemic lupus international collaborating clinics/ American college of rheumatology damage index[100]

BDI – II

Istruzioni

Il presente questionario consiste di 21 gruppi di affermazioni. Per favore legga attentamente le affermazioni di ciascun gruppo. Per ogni gruppo scelga quella che meglio descrive *come lei si è sentito nelle ultime due settimane* (incluso oggi). Faccia una crocetta sul numero corrispondente all'affermazione da lei scelta. Se più di un'affermazione dello stesso gruppo descrive ugualmente bene come lei si sente, faccia una crocetta sul numero più elevato per quel gruppo. Non scelga più di un'affermazione per ciascun gruppo, inclusa la domanda 16 ("Sonno") e la domanda 18 ("Appetito"). È importante ricordare che non ci sono risposte giuste o sbagliate. Non si soffermi troppo su ogni affermazione. La prima rispsota è spesso la più accurata. Grazie.

1. Tristezza

0. Non mi sento triste.
1. Mi sento triste per la maggior parte del tempo.
2. Mi sento sempre triste.
3. Mi sento così triste o infelice da non poterlo sopportare.

2. Pessimismo

0. Non sono scoraggiato riguardo al mio futuro.
1. Mi sento più scoraggiato riguardo al mio futuro rispetto al solito.
2. Non mi aspetto nulla di buono per me.
3. Sento che il mio futuro è senza speranza e che continuerà a peggiorare.

3. Fallimento

0. Non mi sento un fallito.
1. Ho fallito più di quanto avrei dovuto
2. Se ripenso alla mia vita riesco a vedere solo una serie di fallimenti.
3. Ho la sensazione di essere un fallimento totale come persona.

4. Perdita di piacere

0. Traggo lo stesso piacere di sempre dalla cose che faccio.
1. Non traggo più piacere dalle cose come un tempo.
2. Traggo molto poco piacere dalle cose che solitamente mi divertivano.
3. Non riesco a trarre alcun piacere dalle cose che una volta mi piacevano.

5. Senso di colpa

0. Non mi sento particolarmente in colpa.
1. Mi sento in colpa per molte cose che ho fatto o che avrei dovuto fare.
2. Mi sento molto spesso in colpa.
3. Mi sento sempre in colpa.

6. Sentimenti di punizione

0. Non mi sento come se stessi subendo una punizione.
1. Sento che potrei essere punito.
2. Mi aspetto di essere punito.
3. Mi sento come se stessi subendo una punizione.

7. Autostima

0. Considero me stesso come ho sempre fatto.
1. Credo meno in me stesso.
2. Sono deluso di me stesso.

3. Mi detesto.

8. Autocritica

0. Non mi critico né mi biasimo più del solito.
1. Mi critico più spesso del solito.
2. Mi critico per tutte le mie colpe.
3. Mi biasimo per ogni cosa brutta che mi accade.

9. Suicidio

0. Non ho alcun pensiero suicida.
1. Ho pensieri suicidi ma non li realizzerei.
2. Sento che starei meglio se morissi.
3. Se mi si presentasse l'occasione, non esiterei ad uccidermi.

10. Pianto

0. Non piango più del solito.
1. Piango più del solito.
2. Piango per ogni minima cosa.
3. Ho spesso voglia di piangere ma non ci riesco.

11. Agitazione

0. Non mi sento più agitato o teso del solito.
1. Mi sento più agitato o teso del solito.
2. Sono così nervoso o agitato al punto che mi è difficile rimanere fermo.
3. Sono così nervoso o agitato che devo continuare a muovermi o fare qualcosa.

12. Perdita di interessi

0. Non ho perso interesse verso le altre persone o verso le attività.
1. Sono meno interessato agli altri o alle cose rispetto a prima.
2. Ho perso la maggior parte dell'interesse verso le atre persone o cose.
3. Mi risulta difficile interessarmi a qualsiasi cosa.

13. Indecisione

0. Prendo decisioni come sempre.
1. Trovo più difficoltà del solito nel prendere decisioni.
2. Ho molte più difficoltà nel prendere decisioni rispetto al solito.
3. Non riesco a prendere nessuna decisione.

14. Senso di inutilità

0. Non mi sento inutile
1. Non mi sento valido e utile come un tempo.
2. Mi sento più inutile delle altre persone.
3. Mi sento completamente inutile.

15. Perdita di energia

0. Ho la stessa energia di sempre.
1. Ho meno energia del solito.
2. Non ho energia sufficiente per fare la maggior parte delle cose.
3. Ho così poca energia che non riesco a fare nulla.

16. Sonno

0. Non ho notato alcun cambiamento nel mio modo di dormire.

1a. Dormo un po' più del solito.
1b. Dormo un po' meno del solito.

2a. Dormo molto più del solito.
2b. Dormo molto meno del solito.

3a. Dormo quasi tutto il giorno.
3b. Mi sveglio 1-2 ore prima e non riesco più ad addormentarmi.

17. Irritabilità

0. Non sono più irritabile del solito.
1. Sono più irritabile del solito.
2. Sono molto più irritabile del solito.
3. Sono sempre irritabile.

18. Appetito

0. Non ho notato alcun cambiamento nel mio appetito.

1a. Il mio appetito è un po' diminuito rispetto al solito.
1b. Il mio appetito è un po' aumentato rispetto al solito.

2a. Il mio appetito è molto diminuito rispetto al solito.
2b. Il mio appetito è molto aumentato rispetto al solito.

3a. Non ho per niente appetito.
3b. Mangerei in qualsiasi momento.

19. Concentrazione

0. Riesco a concentrarmi come sempre.
1. Non riesco a concentrarmi come al solito.
2. Trovo molto difficile concentrarmi per molto tempo su qualsiasi cosa.
3. Non riesco a concentrarmi su nulla.

20. Fatica

0. Non sono più stanco o affaticato del solito.
1. Mi stanco e mi affatico più facilmente del solito.
2. Sono così stanco e affaticato che non riesco a fare molte delle cose che facevo prima.
3. Sono talmente stanco e affaticato che non riesco più a fare nessuna delle cose che facevo prima.

21. Sesso

0. Non ho notato alcun cambiamento recente nel mio interesse verso il sesso.
1. Sono meno interessato al sesso rispetto a prima.
2. Ora sono molto meno interessato al sesso.
3. Ho completamente perso l'interesse verso il sesso.

Attached 6.3. Beck Depression Inventory II (BDI-II) Italian version[111]

Appendice 2.: 20-Toronto Alexithymia Scale (TAS-20) (Bressi e coll., 1996)

Seguendo le istruzioni sotto elencate indichi quanto è d'accordo o meno con ciascuna delle seguenti affermazioni segnando una **X** sopra il numero corrispondente.

Segnare una sola risposta per ciascuna frase.

1= NON SONO PER NIENTE D'ACCORDO
2= NON SONO MOLTO D'ACCORDO
3= NON SONO NE' D'ACCORDO NE' IN DISACCORDO
4= SONO D'ACCORDO IN PARTE
5= SONO COMPLETAMENTE D'ACCORDO

1. Sono spesso confuso/a circa le emozioni che provo	1	2	3	4	5
2. Mi è difficile trovare le parole giuste per esprimere i miei sentimenti	1	2	3	4	5
3. Provo delle sensazioni fisiche che neanche i medici capiscono	1	2	3	4	5
4. Riesco facilmente a descrivere i miei sentimenti	1	2	3	4	5
5. Preferisco approfondire i problemi piuttosto che descriverli semplicemente	1	2	3	4	5
6. Quando sono sconvolto/a non so se sono triste, spaventato/a o arrabbiato/a	1	2	3	4	5
7. Sono spesso disorientato dalle sensazioni che provo nel mio corpo	1	2	3	4	5
8. Preferisco lasciare che le cose seguano il loro corso piuttosto che capire perché sono andate in quel modo	1	2	3	4	5
9. Provo sentimenti che non riesco proprio ad identificare	1	2	3	4	5
10. E' essenziale conoscere le proprie emozioni	1	2	3	4	5
11. Mi è difficile descrivere ciò che provo per gli altri	1	2	3	4	5
12. Gli altri mi chiedono di parlare di più dei miei sentimenti	1	2	3	4	5
13. Non capisco cosa stia accadendo dentro di me	1	2	3	4	5
14. Spesso non so perché mi arrabbio	1	2	3	4	5
15. Con le persone preferisco parlare di cose di tutti i giorni piuttosto che delle loro emozioni	1	2	3	4	5
16. Preferisco vedere spettacoli leggeri, piuttosto che spettacoli a sfondo psicologico	1	2	3	4	5
17. Mi è difficile rivelare i miei sentimenti più profondi anche ad amici più intimi	1	2	3	4	5
18. Riesco a sentirmi vicino ad una persona, anche se ci capita di stare in silenzio	1	2	3	4	5
19. Trovo che l'esame dei miei sentimenti mi serve a risolvere i miei problemi personali	1	2	3	4	5
20. Cercare significati nascosti in films o commedie distoglie dal piacere dello spettacolo	1	2	3	4	5

Attached 6.4. 20-item Toronto Alexithymia Scale (TAS-20) Italian version[114]

Hopelessness Scale, Beck et al.

University of Pennsylvania and Philadelphia General Hospital.
(Novembre 2007)

Istruzioni: Qui sotto vi sono 20 affermazioni. Risponda se per Lei siano vere o false segnando una croce (+ o x) nelle caselle corrispondenti. In caso di dubbio, dia la risposta che ritiene più vicina a quello che Lei crede corrisponda meglio a quello che pensa. Abbia cura di segnare uno **solo** tra Vero e Falso per **tutte** le affermazioni.

Affermazioni:	Vero	Falso
(1) Vedo il futuro con speranza ed entusiasmo.	☐	☐
(2) Potrei arrendermi perché non posso migliorare le cose per me.	☐	☐
(3) Quando le cose vanno male, mi consola sapere che non può durare così in eterno.	☐	☐
(4) Non posso immaginare quello che sarà della mia vita tra 10 anni.	☐	☐
(5) Ho abbastanza tempo per realizzare le cose che desidero fare.	☐	☐
(6) Nel futuro mi aspetto di riuscire in quello che mi interessa di più.	☐	☐
(7) Il mio futuro mi sembra buio.	☐	☐
(8) Mi aspetto di ottenere dalla vita più cose buone rispetto alla persona media.	☐	☐
(9) Semplicemente non riesco ad avere buone occasioni e non c'è motivo per cui ci riesca in futuro.	☐	☐
(10) Le mie esperienze passate mi hanno preparato bene per il futuro.	☐	☐
(11) Se guardo avanti vedo solo situazioni spiacevoli piuttosto che piacevoli.	☐	☐
(12) Non mi aspetto di ottenere ciò che voglio veramente.	☐	☐
(13) Quando guardo al futuro, mi aspetto di essere più felice di adesso.	☐	☐
(14) Semplicemente, le cose non vanno come io desidero che vadano.	☐	☐
(15) Ho una grossa fede nel futuro.	☐	☐
(16) Non ottengo mai ciò che desidero, quindi è sciocco desiderare alcunché.	☐	☐
(17) È molto inverosimile che nel futuro io ottenga una vera soddisfazione.	☐	☐
(18) Il futuro mi sembra vago e incerto.	☐	☐
(19) Posso aspettarmi che arrivino bei tempi, piuttosto che brutti.	☐	☐
(20) E' inutile provare ad ottenere ciò che voglio perché probabilmente non ci riuscirò.	☐	☐

Attached 6.5. Beck Hopelessness Scale (BHS) Italian version[117]

BARRATT IMPULSIVENESS SCALE, Version 11
BIS-11 # 758

Cognome e Nome..... Data di nascita.....

Codice Paziente..... Valutatore..... Data valutazione.....

ISTRUZIONI

Le persone agiscono e pensano in maniera diversa nelle diverse situazione. Questo è un test per valutare alcuni modi in cui lei agisce e pensa. Legga attentamente ciascuna affermazione ed **annerisca il quadratino** che corrisponde alla risposta che più si adatta a lei. Risponda rapidamente e sinceramente.

	Raramente/Mai	Occasionalmente	Spesso	Quasi sempre/ Sempre
1. Io programmo accuratamente le attività	❑	❑	❑	❑
2. Faccio le cose senza pensare	❑	❑	❑	❑
3. Decido con molta rapidità	❑	❑	❑	❑
4. Prendo il mondo come viene	❑	❑	❑	❑
5. Non presto attenzione	❑	❑	❑	❑
6. I miei pensieri "corrono"	❑	❑	❑	❑
7. Programmo i miei viaggi con molto anticipo	❑	❑	❑	❑
8. Sono padrone di me	❑	❑	❑	❑
9. Mi concentro facilmente	❑	❑	❑	❑
10. Io risparmio con regolarità	❑	❑	❑	❑
11. Sto sulle spine al teatro o alle conferenze	❑	❑	❑	❑
12. Sono uno che pensa accuratamente	❑	❑	❑	❑
13. Faccio piani per un investimento per il futuro	❑	❑	❑	❑
14. Dico le cose senza pensare	❑	❑	❑	❑
15. Mi piace pensare a problemi complessi	❑	❑	❑	❑
16. Cambio spesso lavoro	❑	❑	❑	❑
17. Io agisco d'impulso	❑	❑	❑	❑
18. Mi annoio facilmente quando affronto ragionamenti complessi	❑	❑	❑	❑
19. Agisco sotto l'impulso del momento	❑	❑	❑	❑
20. Sono uno che pensa con serietà	❑	❑	❑	❑
21. Cambio spesso abitazione	❑	❑	❑	❑
22. Compro le cose impulsivamente	❑	❑	❑	❑
23. Posso pensare solo ad un problema alla volta	❑	❑	❑	❑

	Raramente/Mai	Occasionalmente	Spesso	Quasi sempre/ Sempre
24. Cambio spesso i miei hobby	❑	❑	❑	❑
25. Spendo o addebito sul mio conto più di quello che guadagno	❑	❑	❑	❑
26. Quando penso ho pensieri estranei, parassitari	❑	❑	❑	❑
27. So più interessato al presente che al futuro	❑	❑	❑	❑
28. Sono irrequieto alle conferenze o ai discorsi	❑	❑	❑	❑
29. Mi piacciono i puzzle	❑	❑	❑	❑
30. Faccio progetti per il futuro	❑	❑	❑	❑

Attached 6.6. Barratt Impulsiveness Scale (BIS-11) Italian version[119]

COPE

Siamo interessati ad indagare come le persone reagiscono quando si imbattono in eventi stressanti, che generano disagio, ansietà e preoccupazione. Ci sono molti modi per affrontare tali situazioni. Pensi a che cosa lei fa di solito quando si trova a dover fronteggiare una situazione difficile, critica o stressante; valuti quindi in quale misura ciascuna delle seguenti affermazioni corrisponde al suo modo di agire.
La ringraziamo per la collaborazione.

Non mi capita mai	**Mi capita Raramente**	**Mi capita abbastanza frequentemente**	**Mi capita molto spesso**
1	**2**	**3**	**4**

AFFERMAZIONI				
1) Cerco comunque di trarre vantaggio dall'esperienza ai fini della mia crescita personale.	**1**	**2**	**3**	**4**
2) Mi rifugio nel lavoro o in altre attività alternative per tenere lontana la mente da quanto potrebbe essere fonte di disturbo o preoccupazione	**1**	**2**	**3**	**4**
3) Mi rattristo e do sfogo alle mie emozioni.	**1**	**2**	**3**	**4**
4) Cerco di consigliarmi con qualcuno su che cosa fare.	**1**	**2**	**3**	**4**
5) Concentro i miei sforzi per trovare un rimedio.	**1**	**2**	**3**	**4**
6) Dico a me stesso che non può essere vero quanto è accaduto.	**1**	**2**	**3**	**4**
7) Ripongo la mia fede in Dio.	**1**	**2**	**3**	**4**
8) Rido della situazione.	**1**	**2**	**3**	**4**
9) Ammetto di non poter controllare la situazione e rinuncio ad insistere.	**1**	**2**	**3**	**4**
10) Evito di fare alcunché troppo rapidamente.	**1**	**2**	**3**	**4**
11) Parlo dei miei sentimenti con qualcuno.	**1**	**2**	**3**	**4**
12) Faccio uso di alcool o droghe per sentirmi meglio.	**1**	**2**	**3**	**4**
13) Mi abituo all'idea di quanto è accaduto.	**1**	**2**	**3**	**4**
14) Parlo con qualcuno per sapere di piu' sulla situazione.	**1**	**2**	**3**	**4**
15) Evito di farmi distrarre da altri pensieri o attività.	**1**	**2**	**3**	**4**
16) Sogno ad occhi aperti altre situazioni diverse da quella che mi è capitata.	**1**	**2**	**3**	**4**
17) Mi scoccio e ne sono pienamente consapevole.	**1**	**2**	**3**	**4**

Non mi capita mai	Mi capita Raramente	Mi capita abbastanza frequentemente	Mi capita molto spesso
1	2	3	4

18) Cerco l'aiuto di Dio.	1	2	3	4
19) Preparo un piano d'azione.	1	2	3	4
20) Scherzo sulla situazione.	1	2	3	4
21) Prendo atto di ciò che è accaduto e accetto l'idea che non può essere cambiato.	1	2	3	4
22) Mi astengo a fare alcunchè, per quanto è possibile.	1	2	3	4
23) Cerco di avere il sostegno emotivo di amici o parenti.	1	2	3	4
24) Sostanzialmente rinuncio a perseguire i miei scopi.	1	2	3	4
25) Provo nuove soluzioni per cercare di liberarmi al piu' presto della situazione problematica.	1	2	3	4
26) Cerco di estraniarmi per un po' bevendo alcool o assumendo droghe.	1	2	3	4
27) Rifiuto di credere a quanto è accaduto.	1	2	3	4
28) Do sfogo ai miei sentimenti.	1	2	3	4
29) Cerco di vedere la situazione sotto una luce diversa così da farla sembrare piu' positiva.	1	2	3	4
30) Parlo con qualcuno che potrebbe fare qualcosa di concreto riguardo al problema.	1	2	3	4
31) Dormo piu' del solito.	1	2	3	4
32) Cerco di mettere a punto una strategia sul da farsi.	1	2	3	4
33) Mi concentro sulla gestione del problema e se necessario metto da parte altre cose.	1	2	3	4
34) Cerco la simpatia e la comprensione di qualcuno.	1	2	3	4
35) Bevo alcool o consumo droghe al fine di pensare meno alla situazione.	1	2	3	4
36) Ironizzo sulla situazione.	1	2	3	4
37) Rinuncio al tentativo di avere ciò che voglio.	1	2	3	4
38) Cerco di trovare qualcosa di buono in quello che sta accadendo.	1	2	3	4
39) Penso a come potrei gestire il problema nel modo migliore.	1	2	3	4
40) Mi convinco che non è accaduto nulla	1	2	3	4
41) Mi assicuro di non peggiorare le cose agendo troppo presto.	1	2	3	4
42) Cerco accuratamente di evitare che altre cose interferiscano con i miei tentativi di venire a capo della situazione.	1	2	3	4
43) Vado al cinema o guardo la TV, per pensarci di meno.	1	2	3	4
1	2	3	4	

44) Accetto la realtà di quanto accaduto.	1	2	3	4
45) Chiedo alle persone che hanno avuto esperienze simili che cosa hanno fatto.	1	2	3	4

46) Provo molto disagio emotivo e mi rendo conto di esprimere ampiamente tale disagio.	**1**	**2**	**3**	**4**
47) Reagisco immediatamente per aggirare il problema.	**1**	**2**	**3**	**4**
48) Cerco di trovare conforto nella mia religione.	**1**	**2**	**3**	**4**
49) Mi sforzo di aspettare sino al momento giusto per fare qualcosa.	**1**	**2**	**3**	**4**
50) Mi prendo gioco della situazione.	**1**	**2**	**3**	**4**
51) Limito la quantità degli sforzi che rivolgo alla soluzione del problema.	**1**	**2**	**3**	**4**
52) Parlo a qualcuno di come mi sento.	**1**	**2**	**3**	**4**
53) Faccio uso di alcool o droghe per aiutarmi a farcela.	**1**	**2**	**3**	**4**
54) Imparo a convivere con la situazione che si è verificata.	**1**	**2**	**3**	**4**
55) Metto da parte altre attività allo scopo di concentrarmi su quanto accaduto.	**1**	**2**	**3**	**4**
56) Rifletto molto su quali passi fare.	**1**	**2**	**3**	**4**
57) Mi comporto come se l'evento non fosse neppure accaduto.	**1**	**2**	**3**	**4**
58) Faccio quello che deve essere fatto, un passo alla volta.	**1**	**2**	**3**	**4**
59) Imparo qualcosa dall'esperienza.	**1**	**2**	**3**	**4**
60) Prego più del solito.	**1**	**2**	**3**	**4**

Attached 6.7. Coping Orientation to Problems Experienced (COPE-60) [120,121]

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