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EXPLORATORY ANALYSIS OF THE ASSOCIATION BETWEEN TOTAL T2 LESION VOLUME ON BRAIN MRI AND RESILIENCE IN YOUNG PATIENTS WITH MULTIPLE SCLEROSIS

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Abstract

INTRODUCTION: Multiple Sclerosis is a neurological disorder that affects mostly young adults potentially causing disability due to involvement of motor, sensory, visual and cognitive functions. Frequently patients with multiple sclerosis presents psychological symptoms such as depression and anxiety.
Receiving a diagnosis of multiple sclerosis, especially when it happens during young age, represent a challenge for which each individual must face relevant emotional distress.
The way in which each person copes to disease seems to be strongly related with resilience.
Determinants of resilience include a host of biological, psychological, social, and cultural factors that interact with one another to determine how one respond to stressful experiences.
The links between disease-specific variables at diagnosis, resilience, and psychological adjustment of multiple sclerosis patients remain largely unexplored, especially in young adults.

AIM OF THE STUDY: to explore the hypothesis that psychological adaptation to multiple sclerosis might be driven not only from personal, social and cognitive factors but also from mechanisms that are intrinsic to the disease process.
The primary endpoint of the study was to analyze the correlation between psychological resilience and total T2 lesion volume on brain MRI – i.e. a reliable biomarker of disease severity – in a cohort of young patients newly diagnosed with multiple sclerosis.

MATERIALS AND METHODS: we identified eligible patients from an ongoing observational study at University of Verona in which several clinical, psychological, MRI and laboratory measures are collected cross - sectionally in patients with multiple sclerosis aged 18-45 years at enrolment, which occurs in the first two years after diagnosis according to inclusion criteria.
For MRI segmentation and lesion volume calculation we used the brain MRI scans obtained from routine investigation for diagnosis or clinical assessment (1.5 or 3 T depending on the machine available at the Center where diagnosis was formulated) within 6 months prior and one month after enrolment. The analysis of total T2 lesion volume

(TLV) was made using software open-source ITK-SNAP with semiautomatic segmentation.
In order to measure resilience, the Connor-Davidson Resilience Scale (CD – RISC25) was used.
The statistical analysis included a descriptive analysis of demographical, psychological and clinical characteristics of participants. A non-parametric approach was applied to compare groups, by using the Kruskal-Wallis test. An explorative correlation analysis was conducted to check possible relationship among variables.

RESULTS: our sample consists of 51 consecutive patients, 33 females and 18 males with a mean age of 33.3 years. 88,23% of patients have relapsing-remitting multiple sclerosis and 74,5% a low level of disability (EDSS $\leq$ 2).
The mean T2 lesion volume found was 4.32 cm^3 (range 0,21 – 24,79). For resilience (the maximum score on the CD-RISC is 100), the mean value in our sample resulted 65,13 (CI 60,65 – 69,61).
Considering data about Quality of Life using the MSQoL- 54 scale, the mean score for physical health resulted 61,48 (CI 58.87 – 64.08) while the mean score for mental health resulted 51,13 (CI 48,22 – 54,03). Other two single scores were calculated; the mean for change in health was 50,19 (CI 45,24 – 55,14); for sexual satisfaction it was 76,73 (CI 70,71 – 82,75).
Correlation analysis did not show a significant correlation between T2 total lesion volume and resilience. Despite none of the performed correlation analyses showed statistically significant results, a moderate correlation between resilience and age and between resilience and time from onset of symptoms was numerically observed; a weak inverse correlation was found between EDSS score and resilience.
In addition, there was a numerical correlation between resilience and the physical health subscore of MSQoL-54, particularly in the relapsing-remitting multiple sclerosis patients subgroup.

CONCLUSION: with reference to the primary outcome, the exploratory analysis we performed in our study showed that total T2 lesion volume on brain MRI of young patients with multiple sclerosis is not significantly associated with resilience. Overall, no significant findings were observed for any of analyzed variables, however some of association examined are worthy of attention. The time that took place between onset of disease and

enrollment seems to have a potential moderate correlation with resilience. Among socio-demographic data we have found a possible moderate correlation between resilience and age and also with physical health score in the MSQoL. Also the score regarding physical health on MSQoL numerically shows a moderate correlation with resilience.

Our findings show that resilience of young patients with multiple sclerosis, although not statistically associated with disease burden assessed as T2 lesion load on brain MRI, is possibly connected to demographic variables, physical wellbeing, disease duration and possibly disability accumulation in the early stages of the disease. Therefore, all these features deserve to be furtherly examined as possible determinants of resilience, with the ultimate goal of improving quality of life of people with multiple sclerosis.

1. INTRODUCTION

1.1 GENERAL FEATURES OF MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) with a presumed autoimmune pathogenesis, likely determined by a complex combination of environmental and genetic factors. The effect of this interaction leads to activation of inflammatory mechanisms, which cause damage to myelin, glial, and neuronal structures of the brain, brainstem, cerebellum, optic nerve and spinal cord. Demyelinating lesions commonly named "plaques" interest both the white and grey matter; besides inflammation and demyelination, oligodendrocyte and neuronal loss occur since the earliest stages of the disease, which are associated with irreversible CNS injury. The characteristic symptoms of multiple sclerosis are motor, sensory or visual defects that depend on localisation of lesions and tissue damage within the CNS [(1)].

The disease shows two major forms of clinical presentation: relapsing (RMS) that represents 85% of cases and primary progressive (PPMS) that affects about 10-15% of patients.

The relapsing course is characterised by the subacute appearance of neurological symptoms, defined relapse or attack, which resolve more or less completely, often bringing the patient back to the preceding functional status. The initial event without evidence of spatial and temporal dissemination of demyelinating lesions is recognised as clinically isolated syndrome (CIS). The recurrence over time of relapses – with demonstration of dissemination in space and time without substantial accumulation of disability independent of attacks – characterize the so-called relapsing-remitting course of multiple sclerosis (RRMS). A conspicuous proportion of RRMS cases (up to 75% according to studies) evolve after a variable number of years to a secondary progressive course. Conversely, PPMS is defined by the demonstration of clinical progression from onset.

The progressive forms are characterised by a slow worsening of neurological symptoms over time with irreversible accumulation of disability. In some cases

with progressive MS, clinical relapses can appear [2]. Different degrees of inflammation and neurodegeneration contribute to determine the clinical findings and the course of disease.

The typical clinical features that characterise the onset of the disease are either acute/subacute – for RMS – or chronic – for progressive MS – appearance of motor deficits that may involve one or more limbs, sensitive disorders that can locate in all the areas of the body, coordination or balance disorders or visual defects. In rare cases – particularly with progressive MS – less suggestive symptoms and signs with insidious course, such as cognitive impairment, can be observed at the onset.

With the increased use of brain and spine MRI for diagnostic purposes, focal abnormalities suggestive of MS-like demyelinating lesions are occasionally observed in absence of related symptoms and signs; these findings define the radiological isolated syndrome (RIS) [3].

Multiple sclerosis represents the second cause of disability in young people after accidental trauma. According to available data in the Atlas of Multiple Sclerosis published in 2013 [4] the prevalence of disease is 100-190 person per 100.000 in regions at high risk (North Europe, United States, Canada, New Zealand) and about 2-25 per 100.000 in low risk areas, such as Asia, Africa and South America. In Italy, a region considered at high risk of disease the estimated prevalence is 113 cases per 100000. In 2020 the Atlas of MS estimated that the number of people with multiple sclerosis worldwide has increased to 2.8 million [5].

Epidemiological data have always confirmed that MS affect women more than men with more recent studies reporting a ratio up to 3:1. The age of onset of disease is strongly related to the clinical course; patients with relapsing-remitting forms present first neurological symptoms at a younger age compared to patients with primary progressive MS. The age at which the incidence of multiple sclerosis is higher is between 20 – 40 years. [6]. In 10% of cases MS patients present the first neurological symptoms before 18 years [7].

Essential for a multiple sclerosis diagnosis are clinical symptoms, neuroradiological findings on brain and/or spinal cord MRI and cerebrospinal fluid examination

with the presence of oligolclonal bands that represent marker of immune activation within the CNS.

In 2017 Thompson et al developed the most recent revision of the diagnostic criteria for MS with the aim of simplifying the previous McDonald Criteria to permit an earlier diagnosis [8; 9].

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5. ¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Fig1. Mc Donald 2017 diagnostic criteria (Thompson AJ et al, Lancet Neurol 2018)

Differently from the previous, the new criteria allow diagnosis in a shorter time after clinical onset. The diagnosis of multiple sclerosis may be made if space and time dissemination criteria are satisfied, clinically or radiologically by MRI. Clinical demonstration requires objective evidence of involvement of at least two separate CNS sites at different times.

For dissemination in space on MRI, it is necessary the presence of one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in two or more of four typical areas of the CNS (periventricular, cortical or juxtacortical, infratentorial, or spinal cord). Dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI, or by the presence of oligoclonal bands in the CSF. Objective evidence of at least

one lesion on neurological examination and exclusion of a better explanation of the clinical picture are always required.

Treatment of MS is complex and interdisciplinary, encompassing pharmacological therapies and non-pharmacological interventions, such as rehabilitation and psychological support.

In the last three decades several treatments for multiple sclerosis have been approved and are currently used in different forms and stages of disease. Medications for multiple sclerosis can be differentiated in disease-modifying (DMDs) and symptomatic drugs.

Unfortunately, to date, there are no therapy that can cure the disease. Disease-modifying drugs are treatments that act on the immune system through mechanisms of immunomodulation or immunosuppression with the aim to reduce the risk of clinical relapses and to slow down the accrual of neurological disability, ultimately leading to quality of life improvement. Currently the target of treatment is to reach a state in which there is no evidence of disease activity (NEDA) [10] – i.e. no evidence of relapse, disability progression, and MRI activity. To obtain this goal two different approaches can be used. In the first of this, named escalation therapy, the treatment start with first line DMDs (interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, and azathioprine) and continue until disease activity reappearance; if it appears treatment should be switched to a more effective second line therapy (fingolimod, natalizumab, cladribine, alemtuzumab, ocrelizumab, or ozanimod) depending on the course of MS.

Instead, the strategy called induction or immune reconstitution therapy begins with a strong immunosuppressive action drug (alemtuzumab, cladribine, mitoxantrone, or hematopoietic stem cell transplantation) with the aim of "resetting" the immune system. After the first cycle of treatment patient will be kept under clinical and radiological follow-up and, if necessary, will undergo a new cycle of therapy.

The choice of the strategy to adopt is based on the clinical characteristics of each single patient and particularly on how aggressive multiple sclerosis appears in terms of inflammatory activity.

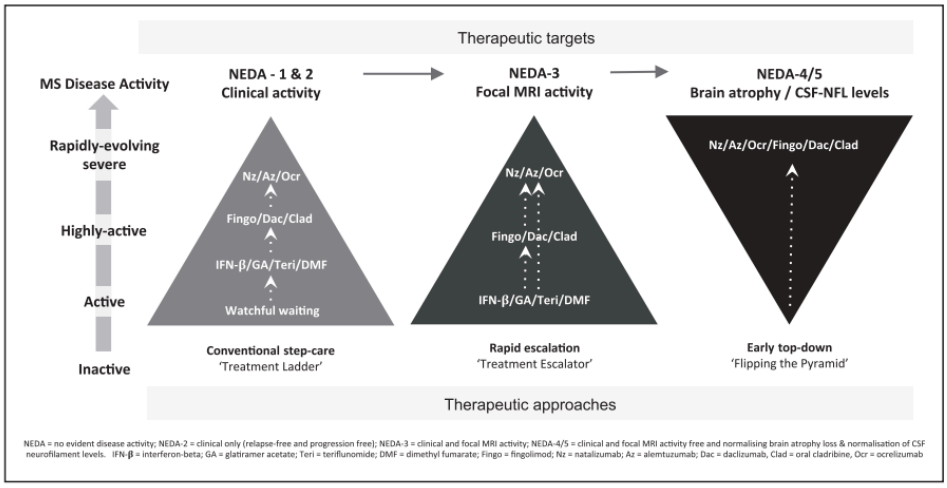

Fig 2: MS therapeutic strategies (from. Giovannoni G., Curr Opin Neurol, 2018)

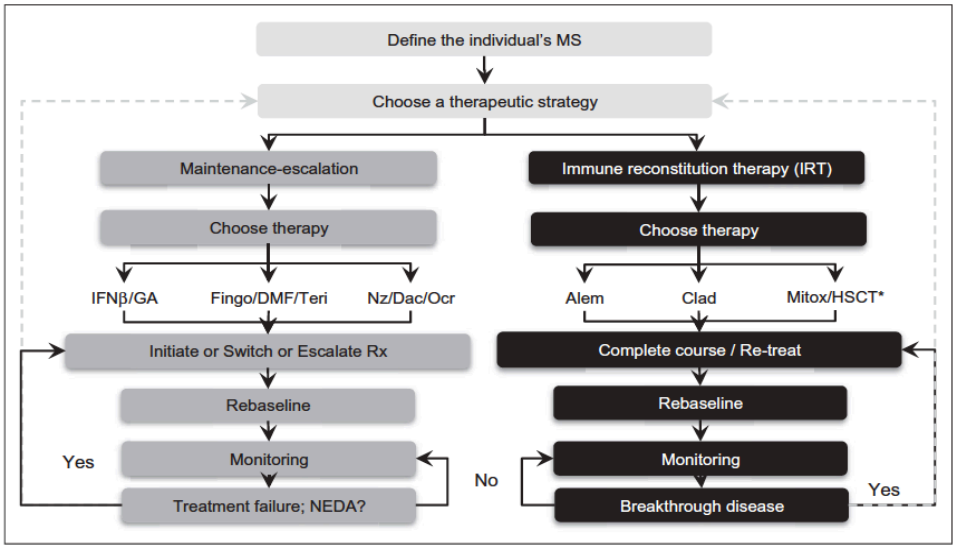

Fig 3: treatment alghoritm (from Giovannoni G., Curr Opin Neurol, 2018)

Several patients have chronic symptoms typical of multiple sclerosis that are at least in part independent of the course and stages of MS. Among these the most frequent are spasticity, fatigue, bladder and bowel or sexual disturbances, difficulty in memory or concentration, and pain; these disorders very frequently influence the quality of life much more than clinical relapses.

For these symptoms symptomatic drugs are widely used: for example amantadine, fampridine or modafinil are widely used for fatigue and gait difficulty. For spasticity baclofen, nabiximols, and tizanidine are commonly used as well as gabapentin, pregabalin, amitriptyline, and duloxetine for neuropathic pain.

It's well know that different symptoms may appear in multiple sclerosis that may cause more or less severe deficits in motor function, balance and coordination. If pharmacological treatment serve to prevent relapses or slow down the progression of disability, rehabilitation becomes necessary in order to improve actual deficit and to preserve residual function.

As defined by Kesselring and Beer [(11)] rehabilitation is "an active process of education and enablement, which is focused on the appropriate management of disability and minimizing limitation of handicap, with the goal of achieving full recovery". In most cases, the target of rehabilitation is to improve a motor deficit like weakness, imbalance, incoordination or spasticity, which could be the result of a clinical relapse or disease progression.

Many studies have underlined beneficial determinants of rehabilitation treatments and exercise in patients with multiple sclerosis [(12)].

Since disability in multiple sclerosis is not caused only by motor symptoms but is also associated with non – motor symptoms, rehabilitation treatment must also be addressed to fatigue, cognitive impairment, emotional problem, bladder and bowel dysfunction with the goal to maintain social functioning and improve quality of life.

Special attention must be paid to the involvement of upper cortical functions (memory, attention, executive functions, language, and visuospatial abilities) because cognitive disorders are less suggestive symptoms of multiple sclerosis and frequently underestimated. In these patients cognitive rehabilitation is also very important to improve cognitive performance and well – being also to prevent the risk of social disfunction.

In multiple sclerosis psychological aspects have always been the subject of numerous studies (see Section 1.2); symptoms such as depression, anxiety, and emotional distress are well described in literature and encountered in clinical practice and they seem to be prevalent in the first two years after diagnosis [(13)]. These

symptoms are likely the result of different factors, in part linked to intrinsic disease features, to the psychological impact of MS (e.g. chronicity and unpredictability of the course, fear of disability) and to the individual's personal characteristics, such as personality trait, personal resources, social and affective functioning. Psychological coping is fundamental in response to distress related to multiple sclerosis diagnosis and it is an important predictor of QoL. Also cognitive impairment has been demonstrated to have a role in coping approach, particularly deficits in sustained attention and executive functioning seem to be related to a worse coping strategy [(14).]

Psychological interventions tailored to improve coping strategies and managing emotional stress are an important element aimed at improving psychological symptoms such as anxiety and depression and therefore they play a role in improving quality of life.

There is also evidence that psychological interventions have a positive impact not only on psychological symptoms but also on physical domains such as fatigue, pain, quality of sleep and physical vitality with an overall improvement of well – being [(15).]

1.1.2 IMMUNOPATHOGENESIS OF MULTIPLE SCLEROSIS

Multiple sclerosis is considered a disorder with an autoimmune pathogenesis; this means that there is a dysfunction of the immune system that reacts against some constitutional elements of the central nervous system. Besides inflammatory damage, neurodegenerative alterations are also associated; these two aspects are related each other in determining the prominent clinical phenotype of the disease (relapsing or progressive), although it has become increasingly evident in recent years that inflammatory and neurodegenerative processes ar deeply intertwined. The aethiology that underlies the dysregulation of the immune system in multiple sclerosis remains unknown; a combination of genetic and environmental factors is assumed.

As for genetic factors, it is well known that multiple sclerosis is not a mendelian hereditary disease but there is an increased risk of recurrence in families of patients with multiple sclerosis, which is independent of environmental factors sharing.

It has been observed that multiple sclerosis is related with major histocompatibility complex (MHC) encoding region variants; particularly, HLA-DRB1*15:01 allele is associated with greater risk of disease [16].

In association with genetic susceptibility also environmental factors contribute to the etiopathogenesis of multiple sclerosis. Epidemiological studies based on the different distributions of the disease in the different world areas have allowed to assume a role for several risk factors: for example, the evidence that in regions where sun exposition is lower – such as high latitude areas – incidence of multiple sclerosis is higher compared to other areas, has suggested a protective effect of vitamin D.

Also infectious agents have long been considered cause of the disease, in particular a role of Epstein-Barr virus has been assumed because – among other evidences – high level of EBV – antibodies are found in MS patients. Cigarette smoking and obesity have been also considered [17].

For many years, as for other autoimmune disorders, also in multiple sclerosis the cause of immune dysregulation has been attributed to T – lymphocytes function

disruption leading to an impaired balance between regulatory and effector T-cells.

The effect of this is the preferential activation of effector cells that, by the release of specific cytokines, determines a pro-inflammatory shift of the immune system. The most involved cells are CD4+ lymphocytes.

Among other mechanisms, T – cells act by stimulating humoral immune response; B- cells react to this cytokine-mediated stimulation with antibody production that determine the damage to localized cellular targets. The role of B cells has long been considered secondary in multiple sclerosis immunopathogenesis, due to the presumed prominence of cellular immunity driven by T lymphocytes [18].

Bar-Or et al in 2007 [19] first published a study in which this theory was questioned; in fact they demonstrated that B cells, both naive and memory cells, have a role that is independent of cellular immunity in determining inflammatory response and exerting it through the production of interleukin 10 (IL-10).

Histological studies performed on brain parenchyma samples of affected subjects have shown the presence of plasma cell infiltrates in peri-lesional areas both in active and chronic plaques. Together with the evidence of a persistent antibody production within CSF (i.e. oligoclonal bands), these findings confirm the theory of a direct and independent B cell pro-inflammatory action mechanism in multiple sclerosis, the final effect of which, together with the production of autoantibodies, is responsible for damage to the structures of the central nervous system.

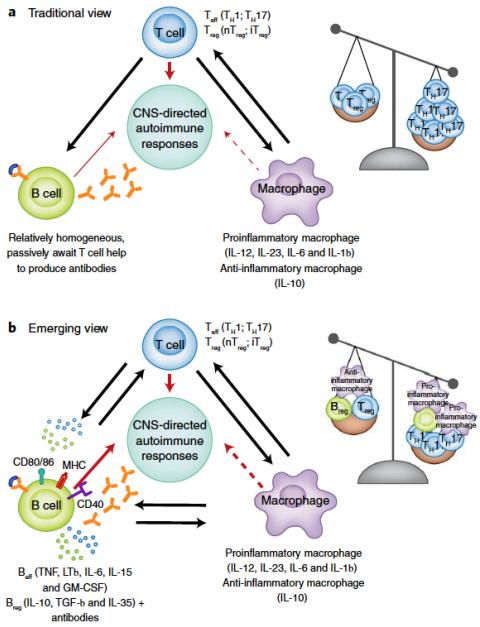

Figure 4 Disanto G., et al The evidence for a role of B cells in multiple. sclerosis. 2012, Neurology

The role of B lymphocyte in multiple sclerosis is also supported by the recent evidence of effectiveness of anti - CD20 monoclonal antibodies therapies.

Considering the description that Charcot did regarding plaques of multiple sclerosis – i.e. areas of tissue damage characterized by loss of myelin with relative spare of axonal structures – multiple sclerosis has long been considered a disease of the white matter.

Based on clinical observations and studies subsequently conducted on MS subjects this observation was gradually questioned. Around the '900, in fact, the first studies on the distribution of lesions of the grey matter at the spinal cord level began to appear; Brownell and Hughes in 1962 described, based on autoptic studies, the localization of plaques at the brain level documenting its presence even close to cortical structures [(20)].

TABLE I

DISTRIBUTION OF 1,594 CEREBRAL PLAQUES IN 22 CASES OF MULTIPLE SCLEROSIS

Anatomical Localization	*Number of Plaques*
Frontal lobe	348 (22%)
Parietal lobe	233 (15%)
Temporal lobe	193 (12%)
Occipital lobe	14 (1%)
Insula	24 (1%)
Corpus callosum	60 (4%)
Internal capsule	19 (1%)
Lateral ventricular system (periventricular)	637 (40%)
Internal nuclei	61 (4%)
Miscellaneous (Hypothalamus, red nucleus, subthalamic nucleus, amygdaloid nucleus, habenulopeduncular tract)	(Less than 5 (1%)

TABLE II

DISTRIBUTION OF 1,594 CEREBRAL PLAQUES IN 22 CASES OF MULTIPLE SCLEROSIS

Position in Grey or White Matter	*Number of Plaques*
Cortex	80 (5%)
Central grey matter	65 (4%)
Junction of cortex and white matter	265 (17%)
White matter	1,184 (74%)

Fig 5: Brownell B, Hughes JT. The distribution of plaques in the cerebrum in multiple sclerosis

Subsequently, in 1998 Trapp et al. undertook a study in which they analyzed the brain of 11 multiple sclerosis subjects and 4 neurologically healthy subjects; the immunohistochemical and microscopic analysis of active and chronic plaques and normal appearing brain showed that in all plaques there are dissected axons debris. Moreover, in addition to the mere pathological description, Trapp documented that axonal damage is a substantial element of the disease, which is correlated with progressive disease course [21].

To date, it is widely documented that MS lesions involve both white and grey matter.

Recent studies documented that lesions in gray matter could also be mediated by an immunopathogenic mechanism. Immunohistochemical analysis conducted on post-mortem brain tissue showed that B-cell follicles were detected in the meninges of secondary progressive multiple sclerosis cases, suggesting that humoral immunity play a role also in cortical damage [22].

It is clear therefore that the fundamental neuropathological hallmark of multiple sclerosis remains the presence of demyelinating lesions that affect in different locations and with different timing the central nervous system, predominantly

within the white matter. However, grey matter is significantly and consistently involved by demyelination. In addition, axonal injury and neuronal loss are present both in the white and grey matter. The localization and the burden of lesions, the degree of inflammation and neurodegeneration likely determine the clinical expression of the disease.

1.1.3 MAGNETIC RESONANCE IMAGING IN MULTIPLE SCLEROSIS

Magnetic resonance imaging (MRI) of the brain and spinal cord has revolutionized the diagnostic approach to multiple sclerosis providing the opportunity to detect in vivo the presence of demyelinating lesions visualized as hyperintense white matter foci on T2-weighted scans. The incorporation of MRI in diagnostic criteria for MS has dramatically increased their sensitivity and specificity and reduced the diagnostic delay compared to the pre-MRI era. Over time it has become clear that presence and accumulation of T2 lesions on MRI have not only a diagnostic value but also prognostic, predictive and treatment monitoring relevance.

Additional MRI measures other than T2 lesions have emerged from several studies as promising prognostic markers in MS, including hypointense lesions on T1-weighted scans, global and regional brain and spinal cord volume, cortical lesions, MR spectroscopy, magnetization transfer ratio, and functional MRI. However, a detailed description of these tools is beyond the scope of the present thesis.

From the beginning of the application of MRI in multiple sclerosis, researchers who have dedicated themselves to deepening their knowledge of the disease have recognized the importance of T2 lesion load in predicting the evolution of the disease.

Filippi et al. [23] published a study in which the importance of carefully studying T2 lesion load on MRI of patients with a first event suggestive of multiple sclerosis (i.e. CIS) was underlined in order to correlate it with the evolution of the disease. The authors focused their attention on the limitations of studies conducted at that time and especially on the difficulties arising from the use of sequences that were not optimal for the purpose, suggesting to use T2 – weighted images.

The Authors also explained how MRI T2 lesion load could be related to clinical variables and other MRI parameters. They found a direct correlation between lesion load at presentation and the increase of lesion volume and disability over the next 5 years while they observed an indirect correlation with time to development of multiple sclerosis. It is necessary to remember that at that time diagnostic criteria were based on clinical demonstration of spatial and temporal dissemination (Poser criteria).

The study showed that patients with a lesion load ≥1.23 cm^3 showed a 90% risk of developing multiple sclerosis, an 86% risk of increasing total load by 1 cm^3 during follow-up (5 years) and a risk of disability accumulation (EDSS ≥ 3) in 52% of cases.

A correlation with neuropsychological status was also found: T2 lesion load was more predictive of cognitive deficits including recent memory, abstract reasoning, problem solving and language compared to the ratio between brain and ventricular volume and corpus callosum size, particularly in those patients who presented with total lesion area ≥ 30 cm^2.

In 1998 Filippi published guidelines for the use of quantitative measures of brain MRI in monitoring treatment efficacy suggesting to use T2-weighted sequences [(24)]

Subsequently, in 1999 the same research group published a work showing how the use of fluid attenuated inversion recovery (FLAIR) sequences in the study of lesion volume allowed to acquire larger lesion volumes in less time compared to previously used images (GRASE: gradient spin - echo), suggesting the use of FLAIR images [(25)].

Di Perri et al [(26)] in 2009 identified a significant difference in T2 and T1 lesion volume in patients with relapsing – remitting compared to primary progressive MS (10.6 cm^3 vs 6.6 cm^3 for T2 lesion load, 2.1 cm^3 vs 2.8 cm^3 for T1 lesion load).

Also more recent studies evaluated total lesion volume as hypothetical predictor of different clinical characteristics of disease. Bodini et al [(27)] in 2010 studied with a follow-up of 10 years patients with PPMS with the aim to investigate lesion load and the location of lesions in T1- and T2- weighed sequences as disability predictors. They found that the localization of T2 lesions in motor and associative tracts of the brain is related with progression of disability in PPMS.

Amato et al. [(28)] in 2012 investigated the role of some MRI metrics with cognitive impairment in subjects with radiologically isolated syndrome. They measured total T2 lesion volume and brain volume in subject with RIS, patient with RMS and healthy subjects finding that lesion volume was comparable in RMS and RIS group when the same cognitive impairment profile was present.

1.2 PSYCHOLOGICAL ASPECTS OF PATIENTS WITH MULTIPLE SCLEROSIS

It's very important to recognise that beyond neurological symptoms, patients affected by multiple sclerosis present a strong psychological involvement related to several elements of disease. There are three characteristic elements of MS that could cause major psychological distress:

- *chronicity*: which means lifetime acceptance of the disease and its consequence;
- unpredictable *course*: characterised by the possibility of clinical relapses and/or disability worsening over time that are not predictable at the individual level;
- *treatment*: the need to continue specific pharmacological therapy for an indefinite time, frequently for many years.

Patients with multiple sclerosis, such as those with other chronic diseases, present often depression, anxiety, fatigue, cognitive impairment that significantly influence quality of life [(13)].

Quality of life (QoL) is not only defined by absence of disease; it's a multidimensional construct based on physical, social and mental well- being (International Health Conference, 2012). When the spectre of illness appears, this vision must be reshaped; with the concept of health related quality of life (HRQoL) the impact of disease and related treatment on patient's health, social functioning, subjective wellbeing and satisfaction is globally defined and this is crucial in the clinical practice when the sharing of therapeutic choices is necessary [(29)].

In 2019 Rintala et al. [(30)] published a review where they found that patients with diagnosis of multiple sclerosis or CIS were affected by mild or moderate symptoms of depression and anxiety, which were not only related to diagnosis and awareness of disease and were associated with a negative influence on quality of life. Silveria et al [(31)], in a cross-sectional study examined quality of life in patients with MS in relation with the co-occurence of different symptoms (fatigue, anxiety, sleep disturbance, depression) concluding that these symptoms negatively impact quality of life. There is also evidence that 18- to 30- years old patients

with multiple sclerosis suffer of psychological distress more than general population of the same age [32].

As already said, multiple sclerosis is a disorder that affects mainly young people; the mean age of onset is between 20 and 40 years. This represents a period of life for each individual that is crucial for building affective, working and social security [33] [34] [35].

It's clear that acceptance of diagnosis can represent a crucial challenge that requires an important

psychological adjustment. This adaptation becomes essential specially in the first year after diagnosis when uncertainty towards developments of disease and the effectiveness of treatment becomes a prevalent feeling [36; 37].

Different Authors highlight that HRQoL is deeply dependent on disease characteristics, psychological aspects and social factors. The ability with which each individual reacts to the disease and its consequence by trying to improve their HRQoL appears strictly related to the level of resilience [38].

Resilience is the ability to react to an emotionally stressful event and to significant adversity, such as the diagnosis of chronic disease, by adapting to the consequent disruption of working, social and relationship life.

A study conducted by Nery-Hurwit [39] with the aim to investigate health-related quality of life in MS patients compared to the general population demonstrated that patients' resilience was positively connected to HRQoL. Tan-Kristanto et al identified a possible relationship between resilience, self-efficacy, coping, anxiety and depression in patient newly diagnosed with multiple sclerosis considering the opportunity to target a psychological intervention on management of depression and anxiety [40].

In their study the Authors included young patients with MS diagnosis (about 97% of participants with RMS) with mean disease duration of 53 months and low level of disability. Patients were given scales to assess resilience, self-efficacy and coping, level of anxiety and depression. With this study they found that depressive and anxiety symptoms were significantly associated with lower use of problem-focused strategies and higher use of emotional-focused and avoidance coping

strategies. In addition, low resilience and particularly low levels of personal competence, significantly predicted depressive and anxiety symptoms.

Southwick et al. (2014) reported that "determinants of resilience including a host of biological, psychological, social, and cultural factors interact one another to determine how one responds to stressful experiences".

In 2015, Black and Dorstyn [41] proposed a bio-psycho-social model of resilience in patients with multiple sclerosis, suggesting that biological, psychological, and social disease-related factors may interact in determining the individual level of resilience.

They recalled the definition of Kumpfer (1999) and defined resilience as a result of risk and protective factors. In MS they consider as protective factors social support, affective relationships, and self efficacy, while disability and fatigue are considered as risk factor. Their results showed that resilience is influenced by disability specific variables in an indirect way and by psychological variables with more strength and reliability.

Rainone at al [42] in 2017 investigated resilience in adolescent and young adults with multiple sclerosis with the evidence that resilience has an important moderating role in the link between affective disorders and HRQoL in adolescents with MS.

The possible link between resilience and intrinsic features of disease activity and severity in patients with MS – such as MRI measures – remains largely unexplored. Available literature is mainly focused on the association between structural characteristics of demyelinating lesions and psychological variables. An interesting review by Solaro et al [43] observed that in addition to genetic, immunological, and psychological factors also the presence of brain damage could be cause of MS-related depression. The Authors reported that T2- weighted lesion load on brain MRI of depressed patients with multiple sclerosis is higher than lesion load found in patients without depressive symptoms [44].

1.3 AIM OF THE STUDY

Starting from the hypothesis of a bio-psycho-social model explaining the interaction between chronic disease and psychological adaptation, the present study aims at investigating the association between the level of resilience and a validated biomarker of disease severity in patients with MS, which is T2 lesion load on brain MRI.

To do so we identified eligible patients from an ongoing observational study at University of Verona in which several clinical, psychological, MRI and laboratory measures are collected cross - sectionally in young patients with MS early after diagnosis.

Given the exploratory and preliminary nature of the study, we focused on an individual biomarker of MS severity for the association with resilience to explore the hypothesis that psychological adaptation to MS might be driven not only from personal, social and cognitive factors but also from mechanisms that are intrinsic to the disease process.

2. MATERIALS AND METHODS

2.1 STUDY DESIGN

In 2018 a group of researchers from the Department of Neuroscience of Verona University started a study with the aim to create a biopsychosocial model of resilience in young adults with a recent diagnosis of multiple sclerosis (BPS-ARMS) [45].

The BPS-ARMS project has an observational cross-sectional design; it started in February 2019 and is currently ongoing. The study is following two main consequential phases. In the first phase, biopsychosocial factors are collected and resilience strategies and QoL assessed. In the second one, the relationship between biopsychosocial factors and resilience will be explored and consequently a biopsychosocial model of resilience in young adults newly diagnosed with MS will be analyzed. Eleven specific work packages (WP) will be accomplished during these two phases (figure 3).

For each WP, different actions will be performed according to the flowchart (figure 4).

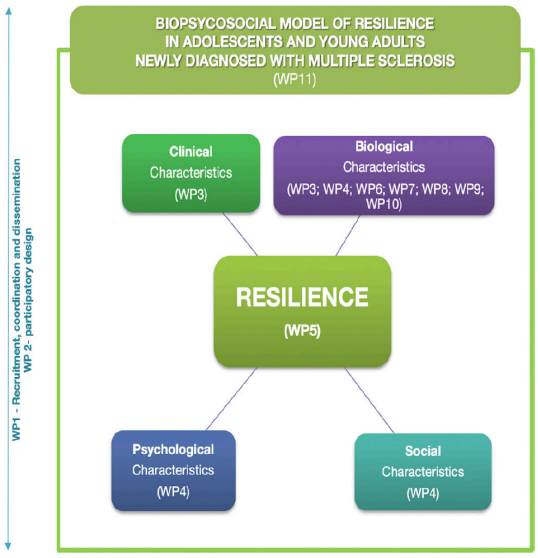

Fig 6: overview of the BPS – ARMS work packages

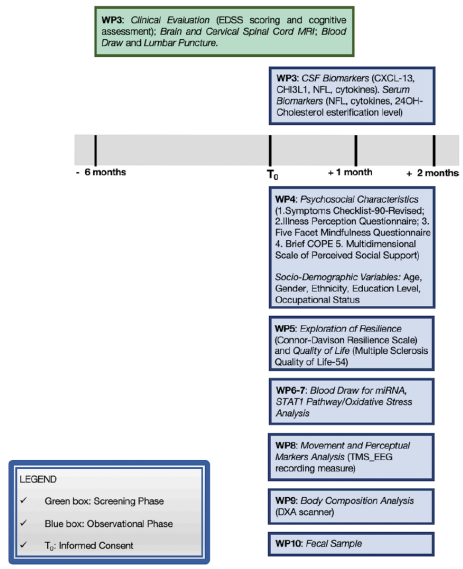

Fig 7: Flowchart of WP activities

WP1 actions include recruitment, coordination and dissemination of the results. WP2 aims to achieve an effective, constant collaboration between researchers, patients and healthcare providers (participatory design). WP3 and WP 6-10 are dedicated to the screening phase for the eligibility of patients and collection of clinical and MRI characteristics and biomarkers of patients. WP4 aims to collect the psychosocial characteristics of young patients. Exploration of resilience and QoL will be performed in WP5 and, considering the results of the previous WPs, WP11 procedures will allow developing the biopsychosocial model of resilience.
Eligible patients are being consecutively enrolled by the neurologists and residents working at the MS Center of Borgo Roma Hospital, Verona. During the first visit at the MS Center, the neurologists/residents explain the study to eligible patients, and the consent form is signed. During this visit, sociodemographic and clinical information are collected, according to routine clinical practice. Within 1 month from consent, patients start a screening phase, which is part of the typical diagnostic work-up of patients with suspected MS (WP3). After screening completion, fulfilment of inclusion criteria and absence of exclusion criteria, patients are enrolled or excluded from the study accordingly. Within 1 month from screen-

ing completion, patients included in the study undergo a blood draw from a peripheral vein at the MS Center, and a faecal sample is collected for gut microbiota analysis (WP 3, 6, 7 and 10). During the same visit, a psychological battery of tests will be administered (questionnaires for both WP4 and WP5). Within 1 month from screening completion, patients can decide to be involved in additional study procedures, regarding the analysis of movement and perceptual markers as well as body composition as measured by dual-energy X-ray absorptiometry (WP8 and WP9) at the dedicated laboratories of the University of Verona.
All procedures must be completed within 2 months of signing consent in order not to cause delays in starting pharmacological treatment.
In Appendix-1 and appendix-2 CRF and psychological questionnaires

2.2 SAMPLE

Candidate Patients for study were identified by neurologists working in the MS Center of Borgo Roma Hospital (Verona) or in the Hub and Spoke network of the province of Verona. The clinical history of eligible patients was therefore analyzed by neurologists and residents working at the MS Center of Borgo Roma Hospital (Verona).

The inclusion criteria are the following:

- age range 18-45 years;
- MS diagnosis in the 2 years prior to study inclusion, according to the revised McDonald Criteria (Thompson et al., 2018);
- MRI of the brain in the 6 months prior to or within one month after screening visit, according to the protocol described below;
- Italian speakers.

Patients are excluded if present with one or more of the following:

- clinically relevant cognitive deficits as evaluated by the treating neurologist;
- treatment with any disease-modifying therapy (DMT) for MS at inclusion and by completion of study procedures (maximum two months from consent);
- steroids administration up to 30 days prior to inclusion is allowed.

BPS-ARMS has been approved by the Ethical Committee of Verona and Rovigo Province (Azienda Ospedaliera Universitaria Integrata di Verona) – study registration number Prog. 2029CESC.

2.3 MRI SEGMENTATION AND TOTAL T2 LESION VOLUME CALCULATION

Study patients underwent 1.5 or 3 Tesla brain MRI depending on the MR machine available at the facility where the scan was acquired, according to the protocol reported below.

The images were displayed using the "HOROS" software (https://horosproject.org). The analysis of total T2 lesion volume (TLV) was made using the open-source software ITK-SNAP with semiautomatic segmentation [46].

Sequences used for different analysis were:

- T1-weighted post gadolinium for assessment of active lesions;
- FLAIR 2D (TR 8500 ms, TE 86 ms, thickness 4.00 mm, array 280 x 320, 25 slices) or 3D (TR 4800 ms, TI 1660 ms, TE 306 ms, thickness 0.57 mm, array 256 x 256, 321 slices) for identification of lesions;

3D FLAIR sequences were preferentially used for segmentation; if not available, FLAIR 2D sequences were used.

2.4 PSYCHOLOGICAL VARIABLES

Resilience was measured using the Connor-Davidson Resilience Scale (CD-RISC; Connor & Davidson, 2003); this evaluation tool is specifically designed to assess resilience features in adolescents and adult. This scale is composed of 25 items and evaluated on a 5-point Likert scale (ranging from 0 "not true at all" to 4 "true nearly all of the time"). Higher scores are linked to higher level of resilience.

This questionnaire has already been used with MS patients (Battalio et al., 2017; Black & Dorstyn, 2015; Koelmel et al., 2017; Senders et al., 2014) and translated in Italian.

Quality of life (QoL) was assessed using the Italian version of the Multiple Sclerosis Quality of Life-54 (MSQoL-54; Solari et al., 1999) [47]. This is a multidimensional HRQoL measure that combines both generic and MS-specific items, such as fatigue and cognitive function. The instrument generates 12 scores (physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall QoL, and sexual function); there are also two summary scores: physical health and mental health that derived from a weighted combination of scale scores.

Socio-demographic variables (age, gender, ethnicity, education level and occupational status) were also collected at the recruitment for each patient through a specific Case Report Form.

2.5 STATISTICAL ANALYSIS

The demographical, psychological and clinical characteristics of participants were described in terms of mean and standard deviation for quantitative variables; in terms of occurrence (*n*) and percentage frequency (%) for qualitative ones.

Since the sample size was small, and some subgroups seemed scarcely represented, where possible 95% interval confidence were shown to account for the variability. The non-parametric approach was applied to compare groups, by using the Kruskal-Wallis test.

A set of preliminary explorations, focused to check possible relationships between MS severity marker (i.e. total T2 lesion volume) and demographical patient characteristics, was performed to exclude concurrent/complementary effects.

The main aim of the study, exploring the effect of total T2 lesion volume on resilience (primary outcome) and quality of life (co-primary outcome), was carried out with the Pearson's correlation coefficients. The degree of correlation was interpreted by using the Cohen's (1988) guideline – i.e., 0.10 (small), 0.30 (moderate), 0.50 (large).

The statistical analysis was conducted using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

3. RESULTS

3.1 SAMPLE

From February 2019 to April 2022 51 multiple sclerosis patients who fulfilled the requirements for enrollment in the study were consecutively identified at the participating centers; among them 3 refuse to participate in the study. After screening at the coordinating center, all patients resulted eligible according to the protocol inclusion and exclusion criteria. Therefore, currently our sample consists of 51 patients, 33 females and 18 males.

Mean age in our sample is 33.35 years. Socio-demographic characteristics of our sample are the following:

46 (90,2%) patients were born in Italy, 5 (9.8 %) were born in other countries, i.e. Morocco, Romania, Serbia and India.

32 subjects (62.7% %) are single, while 19 (37,3%) are married or in a stable relationship. Subjects who are living with spouse or partner are 16 (31,4 %) and also with one child or more 13 (25,5%), 15 with parents (29,4 %), 4 are living alone (7.8%) and 3 only with one child or more (5,9%).

As regards the degree of education and work status, subjects with high school diploma are 18 (35,3 %), 16 are graduated (31,4%), 10 are with professional diploma (19,6 %); 4 with middle school diploma (7,8%), and 3 (5,9%) have reached a post-graduate degree.

40 patients have a stable job (78,4%), 5 are unemployed (9.8 %), 5 are students (9,8 %) and 1 is a housewife.

SOCIODEMOGRAPHIC DATA			
		FREQUENCY	PERCENT
MARITAL STATUS			
	Unmarried	32	62,8
	Married/stable relation	18	35,3
	Partner	1	1,9
FAMILY STATUS			
	Spouse/livemate	16	31,4
	Spouse/livemate/children	13	25,5
	Parents	15	29,4
	Alone	4	7,8
	Children	3	5,9
EDUCATIONAL LEVEL			
	High school diploma	18	35,3
	Degree	16	31,4
	Professional diploma	10	19,6
	Middle school diploma	4	7,8
	Post-graduate	3	5,9
EMPLOYMENT STATUS			
	Stable job	40	78,4
	Unemployed	5	9,8
	Student	5	9,8
	Housewife	1	1,9

Tab 1: sociodemographic data

3.2 CLINICAL DATA

A diagnosis of relapsing – remitting multiple sclerosis was made in 45 patients (88,2%) while 6 patients (11,8 %) had primary progressive MS.

In 19 patients (37,2 %) the first symptoms were consistent with spinal cord involvement, in 14 patients (27,4 %) with optic nerve location, in 11 patients (21,6 %) with a brainstem/cerebellar syndrome, and in 7 (13,7 %) with cerebral hemisphere involvement.

Clinical activity status has been evaluated by the number of clinical relapses reported in history in the period between onset and enrolment: 4 patients (7.8%) reported 2 relapses, 13 patients (25,5 %) one relapse; most of the patients in the sample (34, 66,7%) presented a single clinical event, i.e. no additional relapses from onset to study inclusion.

Radiological activity was also assessed through the presence of gadolinium enhancing lesions on brain MRI. 18 patients (36,7 %) presented with at least one gadolinium enhancing lesion on T1-weighted sequences of the brain MRI performed in the 6 months before or 1 month after enrolment; 31 patients (63,3 %) did not present radiological activity as defined above. This data is not available for 2 patients who did not perform MRI with gadolinium.

The mean time between symptom onset and brain MRI was 822,5 days (range: 5 – 9400); most patients in the sample underwent the brain MRI analyzed for the study before enrollment; the mean time between MRI scan and enrollment was – 72 days (range: from – 183 to + 28).

Clinical severity of the disease has been assessed in accordance with the scale of neurological disability commonly used for multiple sclerosis: the EDSS score (48). The overall degree of disability of study patients is low, indeed EDSS score ranges from 0 to 4.

11 patients (21,6 %) presents with EDSS=0, 11 patients (21,6 %) with EDSS=1, 6 patients (11,8 %) with EDSS=1.5; 10 patients (19.6%) with EDSS=2; 3 patients (5,8 %) with EDSS = 2.5; 7 patients (13,7 %) with EDSS=3, 2 patients (3,9 %) with EDSS=3.5 and 1 patient (1.9 %) with EDSS=4.

In accordance with inclusion criteria all patients have been enrolled within two

years from multiple sclerosis diagnosis; the mean time between onset and enrollment is 29,1 months and it varies from 1 to 234 months. The mean time between symptom onset and diagnosis is 25,3 months and it varies from 0.5 to 235 months. In the study design exclusion criteria have been defined; one of this was the presence of clinically relevant cognitive deficits as judged by treating neurologist. In our sample all patients underwent the symbol digit modality test (SDMT) for cognitive screening and 2 subjects reported a corrected oral score below the normative cut-off; despite this, because during clinical assessment no relevant deficits were observed and assuming that reduced performance was related to emotional factors, the patients were included.

We also considered the presence of other concomitant pathological conditions with particular interest for those requiring chronic treatment. 9 patients reported to suffer from migraine but none of them were taking chronic therapy or prophylaxis. One patients took acetylsalicylic acid for a platelet disorder, another one was treated with a monoclonal antibody for chronic urticarial [appendix-1 for CRF for clinical variables].

CLINICAL DATA			
		FREQUENCY	PERCENT
sex			
	male	18	35,3%
	female	33	64,7%
course			
	RR- MS	45	88,2%
	PP - MS	6	11,8%
CNS region of symptom onset			
	optic nerve	14	27,4%
	brain and brainstem	18	35,3%
	spinal cord	19	37,3%
Active lesion			
	yes	18	35,3%
	no	31	60,8%
	unknow	2	3,9%
Number of relapse			
	0	34	66,7%
	1	13	25,5%
	2	4	7,8%

Tab 2: clinical data

3.3 T2 LESION VOLUME ANALYSIS

Segmentation analysis was applied to FLAIR 3D sequences or, if not available, to 2D FLAIR sequences.

A single neurologist analyzed brain MRI of all subjects at first to identify the lesions and to locate their anatomical site. Subsequently, the images were segmented using ITK - SNAP software and total lesion volume was obtained.

The mean volume found was 4.32 cm^3 (range 0,21 – 24,79). Assuming a difference in the lesion load between patients with RR-MS and PP-MS we calculated also the mean lesion volume in these two different subgroups. In the relapsing form the mean lesion volume was significantly lower than in the progressive form: 3.48 cm^3 (0.21 – 14.34) vs 10.5 cm^3 (2.63 – 24.79) p=0.038.

3.4 PSYCHOLOGICAL VARIABLES

According to the protocol of BPS-ARMS project all patients underwent a battery of questionnaires with the aim to investigate psychosocial characteristics including resilience, QoL, and psychological well-being. Referring to the primary outcome of the study (i.e. resilience), the Connor-Davidson Resilience Scale (CD-RISC) was used, while quality of life (QoL) was assessed by the Italian version of the Multiple Sclerosis Quality of Life-54 (MSQoL-54).

The CD-RISC is composed of 25 items and evaluated on a 5-point Likert scale (ranging from 0 ‘not true at all’ to 4 ‘true nearly all of the time’), with higher scores reflecting higher levels of resilience; the final score is the total sum of each single item.

CONNOR DAVIDSON RESILIENCE SCALE			
ITEM	**MEAN**	**SD**	**IC**
1. Sono in grado di adattarmi ad ogni cambiamento	2,94	1,12	2,62 – 3,25
2. Esiste qualcuno nella mia vita in grado di aiutarmi in caso di bisogno	3,49	0,78	3,26 – 3,71
3. Quando non vedo soluzioni chiare per i miei problemi, spesso solo il fato o Dio mi possono aiutare	1,18	1,32	0,80 – 1,55
4. Sono in grado di affrontare ogni ostacolo nella vita	2,62	0,99	2,34 – 2,90
5. I successi del passato mi hanno dato la sicurezza per affrontare future difficoltà	2,43	1,18	2,09 – 2,76
6. Quando devo risolvere i problemi cerco di vedere il lato divertente delle cose	2,45	1,20	2,11 – 2,78
7. Dover affrontare degli stress mi ha reso più forte	2,86	0,91	2,60 – 3,12
8. Dopo una malattia, incidente o altro grave problema recupero in fretta	2,64	1,00	2,35 – 2,92
9. Nel bene o nel male credo che tutte le cose accadano per un motivo ben preciso	1,96	1,46	1,54 – 2,37
10. Do sempre il meglio di me stesso/a a prescindere dal risultato	3,31	0,92	3,05 – 3,57
11. Penso di poter raggiungere gli obiettivi che mi sono prefissato/a nonostante tutti gli ostacoli	2,92	0,93	2,65 – 3,18
12. Io non mi arrendo mai, nemmeno quando la situazione risulta essere senza speranza	2,78	1,05	2,48 – 3,07
13. Nei momenti di crisi so a chi rivolgermi per ottenere aiuto	3,11	1,12	2,80 – 3,43
14. Quando sono sotto pressione riesco a mantenermi concentrato/a	2,60	1,07	2,30 – 2,91
15 Preferisco prendere l'iniziativa quando si tratta di risolvere dei problemi	2,80	1,13	2,48 – 3,12
16 Non i scoraggio facilmente davanti ad un fallimento	2,50	1,17	2,18 – 2,83
17 Nell'affrontare le difficoltà e le sfide della vita mi ritengo una persona combattiva	3,24	0,93	2,9 – 3,5
18 Se necessario sono in grado di prendere decisioni che gli altri non riescono ad accettare	2,68	1,19	2,35 – 3,02
19 Sono in grado di gestire emozioni come tristezza, paura, rabbia	2,35	0,99	2,07 – 2,63
20 Nell'affrontare problemi quotidiani spesso bisogna agire d'istinto, senza pensare troppo	1,78	1,17	1,45 – 2,11
21 Ho obiettivi ben chiari per la mia vita	2,62	1,05	2,33 – 2,92
22 Mi sento in controllo nella mia vita	2,21	1,02	1,92 – 2,50

23 Amo le sfide	2,11	1,32	1,74 – 2,48
24 Lavoro per raggiungere degli obiettivi definiti a prescindere dagli ostacoli che trovo sulla via	2,94	1,10	2,63 – 3,25
25 Sono orgoglioso/a dei risultati da me raggiunti.	2,72	1,16	2,39 – 3,05
Risultato finale	**65,13**	**15,92**	**60,65 – 69,71**

Tab 3: results for CD – RISC 25

MSQoL-54 is a multidimensional health-related QoL measure that combines generic and MS-specific items, such as fatigue and cognitive function. The instrument generates 12 scores, two summary scores – physical health and mental health –and two additional single-item measures: satisfaction with sexual function and change in health.

For both scales there are no reference values since they are descriptive; for CD – RISC and also for MSQoL – 54 a higher score is related to a better status in resilience and QoL respectively.

For resilience (the maximum score on the CD-RISC is 100), the mean value in our sample resulted 65,13 (CI 60,65 – 69,61).

Considering data about QoL using the MSQoL- 54 scale, the mean score for physical health resulted 61. 48 (CI 58,87 – 64,08) instead the mean score for mental health resulted 51,13 (CI 48,22 – 54,03). Other two single scores were calculated; the mean for change in health was 50,19 (CI 45,24 – 55,14); for sexual satisfaction it was 76,73 (CI 70,71 – 82,75) [see appendix 2 for psychological questionnaire].

MS QUALITY OF LIFE – 54 (MSQOL- 54)			
ITEM	**MEAN**	**SD**	**IC**
1. PHYSICAL FUNCTION	86,86	14,55	82,76 – 90,95
2. HEALTH PERCEPTION	46,71	12,29	42,25 – 50,17
3. ENERGY/FATIGUE	48,70	12,74	45,12 – 52,28
4. ROLE LIMITATION - PHYSICAL	6,12	4,10	4,97 – 7,28
5. PAIN	77,25	22,97	70,79 – 83,71
6. SEXUAL FUNCTION	84,88	24,7	77,86 – 91,91
7. SOCIAL FUNCTION	78,43	15,56	74,05 – 82,80
8. HEALTH DISTRESS	67,74	19,83	62,16 – 73,32
PHYSICAL HEALTH COMPOSITE	**61,48**	**9,16**	**58,87 – 64,08**
1. HEALTH DISTRESS	67,74	19,83	62,16 – 73,32
2. OVERALL QUALITY OF LIFE	44,49	7,64	42,34 – 46,64
3. EMOTIONAL WELL - BEING	38,03	18,30	32,89 – 43,18
4. ROLE LIMITATION - EMOTIONAL	48,36	41,80	36,60 – 60,12
5. COGNITIVE FUNCTION	73,33	17,82	68,32- 78,34
MENTAL HEALTH COMPOSITE	**51,13**	**10,33**	**48,22 – 54,03**

Tab 4: results for MSQoL

3.5 CORRELATION ANALYSIS

The purpose of this study was to explore the possible association between the total volume of brain MRI T2 lesions and biopsychosocial factors, particularly resilience (primary outcome), in patients with multiple sclerosis.

As shown in table 7, an exploratory analysis was made for the association between T2 total lesion volume (TLV) and demographic characteristics of study patients such as sex, marital status, family status, education level and employment. No significant association was found between socio-demographic variables and lesion volume.

explorative analysis between TOTAL LESION VOLUME and	MEAN	SD	IC	Kruskal - Wallis
SEX				
Male	4,89	4,27	2,76 – 7,01	539,50
Female	4,00	5,93	1,86 – 6,14	735,50
				chi2=2,647 p=0,10
MARITAL STATUS				
Unmarried	3,82	3,61	2,47 – 5,17	777.00
Married/stable relation	5,52	7,58	1,75 – 9,29	433,00
Partner	1,58	0	--	15,00
				chi2=0,687 p=0,70
FAMILIAL STATUS				
Spouse/livemate	2,55	2,34	1,25 – 3,85	301,50
Spouse/livemate/sons	6,66	8,51	1,51 – 11,81	347,00
Parents	5,31	4,67	2,61 – 8,01	419,50
Alone	2,50	0,88	1,09 – 3,91	95,00
Sons	2,06	1,12	- 0,80 – 4,93	62,00
				chi2=3,943 p=0,41

explorative analysis between TOTAL LESION VOLUME and	MEAN	SD	IC	Kruskal - Wallis
STATE OF BIRTH				
Italy	4,44	5,49	2,77 – 6,11	1107,00
India	12,78	0	--	45,00
Morocco	2,45	0	--	24,00
Serbia	1,23	0	--	13,00
Romania	1,79	1,61	- 12,75 – 16,34	36,00
				chi2=3,155 p=0,53
EDUCATION LEVEL				
High School diploma	5,11	6,29	1,75 – 8, 46	408,50
Degree	2,51	2,14	- 0,16 – 10,20	334,50
Professional diploma	5,02	7,24	1,37 – 3,66	254,00
Middle school diploma	8,21	6,43	- 2, 03 – 18,45	144,00
Post-graduate	3,47	1,95	- 1,37 – 8,33	84,00
				chi2=3,846 p=0,42
EMPLOYMENT STATUS				
Stable job	2,78	2,13	2,08 – 3,48	850,50
Unemployed	13,89	10,64	0,67 – 27,10	202,00
Student	5,49	6,11	- 2, 09 – 13,09	127,50
Housewife	12,78	0	--	45,00
				chi2=9,050 p=0,02

Tab 5: exploratory analysis between total lesion volume and sociodemographic data

The same analysis was also applied to clinical and psychological characteristics of our patients.

Clinical characteristics of disease considered were: course of disease (RRMS and PPMS); active lesion on brain MRI (the one performed in the period between 6 months before and the month after enrollment); the localization within the CNS of the onset symptom and the number of relapses (table 6).

explorative analysis between TOTAL LESION VOLUME and	MEAN	SD	IC	Kruskal - Wallis
DISEASE COURSE				
SM - RR	3,48	3,63	2,37 – 4,58	1051,00
SM - PP	10,49	10,77	-0,81 – 21,81	224,00
				chi2=4,493 p=0,03
ACTIVE LESION ON BRAIN MRI				
Yes	4,30	4,11	2,31 – 6,28	515,00
No	3,67	5,04	1,75 – 5,59	661,00
Unknow	13,91	--	-112,19 - 140,02	--
				chi2=1,089 p=0,29
CNS REGION OF SYMPTOM ONSET				
Optic nerve	4,77	6,27	1,15 – 8,39	366,00
Brain and brainstem	5,45	6,40	2,16 – 8,75	480,00
Spinal cord	2,97	3,18	1,15 – 8,39	429,00
				chi2=1,389 p=0,49
NUMBER OF RELAPSE				
0	4,68	6,26	2,46 – 6,90	831,5
1	3,16	2,95	1,38 – 4,95	305,5
2	5,1	2,97	0,36 – 9,83	138,00
				chi2=1,784 p=0,40

Tab 6: exploratory analysis between total lesion volume and clinical data

In consideration of the initial hypothesis that specific measures of multiple sclerosis severity can influence resilience, the exploratory correlation analysis was conducted including – in addition to total lesion volume and resilience – other psychological and clinical variables (table 7 a-b-c).

	TOTAL LESION VOLUME	AGE	SEX
TOTAL LESION VOLUME	1,00		
AGE	0,11	1,00	
SEX	- 0,08	0,13	1,00

	RESILIENCE	AGE	SEX	MSQoL Physical health	MSQoL Mental health	TOTAL LESION VOLUME	EDSS	NUMBER OF RELAPSE
RESILIENCE	1,00							
AGE	0,19	1,00						
SEX	- 0,05	0,13	1,00					
MSQoL Physi-cal health	0,26	0,03	- 0,13	1,00				
MSQoL Mental health	- 0,07	0,01	- 0,22	0,20	1,00			
TOTAL LESION VOLUME	- 0,14	- 0,09	- 0,31	- 0,29	0, 17	1,00		
EDSS	- 0,20	- 0,33	0,03	- 0,48	0,15	0,36	1,00	
NUMBER OF RELAPSE	- 0,002	- 0,26	- 0,02	- 0,07	- 0,13	0,08	0,06	1,00

Tab 7a, 7b: exploratory correlation analysis between psychological variables and clinical data

With the limit of the number of possible observations in our sample, no correlation was found between total lesion volume and the psychological variables analyzed, in particular with resilience values.

Other possible correlations between resilience and clinical variables have been sought without statistical significant results; however, the following findings deserve attention:

- resilience seems to have numerically a moderate correlation with age of patients (0.19)
- a moderate intensity correlation (0.26) was observed between resilience and the values of physical health obtained from MSQoL – 54.
- EDSS score seems to have a weak negative correlation with resilience (-0.19); a weak positive correlation with MSQol mental health (0,15) and a moderate correlation with total lesion volume (0,36)

Observing these results in our sample, assuming a possible difference according to the clinical course of the disease, we tested the same associations in the group of patients with RR-MS, i.e. after excluding patients with PPMS. We found no significant differences compared to the whole sample analysis; only the correlation between resilience and physical health became slightly stronger (0.34 vs 0.26).

4. DISCUSSION

Following the hypothesis of a bio-psycho-social model of resilience in young people with multiple sclerosis, the present study investigated a number of possible associations between clinical and socio – psychological variables, with a particular focus on the correlation between a reliable measure of disease severity – i.e. total T2 lesion volume on brain MRI – and resilience level measured on the Connor-Davidson scale, in a cohort of patients with newly diagnosed multiple sclerosis enrolled at a single academic center. The rationale for this investigation is to identify possible clinical factors that can be related with resilience with the purpose of providing new insights on strategies to improve quality of life of young patients with multiple sclerosis.

Among patients referred to the MS Center of Verona University Hospital and to others MS center in the province of Verona we enrolled subjects with age between 18 and 45 years, with MS diagnosed for less than two years, and not yet treated with specific disease-modifying drugs.

To date, enrolled patients who have completed all the study procedures are 41. As expected according to established epidemiological data of MS, women are more than man in our sample with a ratio 2:1; also the distribution of the frequency of disease course coincides with the one described in literature, with about 85% of our patients having an RRMS form and 15% a primary progressive disease. In our sample patients present a low grade of disability with a maximum score on EDSS scale of 4; 73.2% has an EDSS score ≤ 2.

Considering that according to inclusion criteria enrolled patients should have never been treated with specific disease-modifying therapy, most of study subjects have a moderate disease activity: 29.1% had one or more clinical relapse from onset to enrollment date and 39.0% showed at least one gadolinium-enhancing lesion on brain MRI.

Therefore, despite the limited number of enrolled subjects, our sample, from the clinical point of view, represent well an early untreated multiple sclerosis population according to literature data.

To take in account the potential relevance of social functioning and support on resilience and quality of life, we also collected sociodemographic data and documented that most of the patients in our sample are surrounded by a family network or supporting relationship (87.8%); in addition, they reach a high level of education in most cases (70.7%). With regard to the working status, 80.5% of the subjects in our sample report a stable job.

In our study, considering the characteristics of our sample and the cross-sectional design, we have assumed that total T2 lesion volume on brain MRI may represent a reliable measure of disease severity compared to other possible biomarkers. Patients enrolled in our study are all subjects with an age between 18 and 45 years not yet treated with disease-modifying drugs and in the first two years from diagnosis. Using these inclusion criteria, we have limited the potential variability factors that can affect T2 lesion accumulation in MS to better analyze its possible relationship with psychological variables.

Brain lesions observed on MRI with T2- weighted images series have been used in diagnostic and monitoring protocols of multiple sclerosis since the introduction of MRI in clinical practice; T2 lesion number and location are also relevant prognostic factors. Total T2 lesion load, although not easily assessable in clinical practice, has revealed a reliable prognostic tool for MS in several studies over the last three decades, mainly to predict motor disability.

The importance of structural brain lesions for psychological symptoms in multiple sclerosis is largely unexplored. Solaro et al in 2018 [43] published a review focused on the characteristics of depression in multiple sclerosis, suggesting that this disorder is not only an affective symptom associated with multiple sclerosis, but it could also represent a manifestation of the disease with a biological basis. The authors assumed that genetic, immune and inflammatory factors are involved in the etiology of depression and they also hypothesized that structural changes in the brain of patients with multiple sclerosis might contribute directly to depression development.

Several studies in literature correlate brain atrophy with cognitive impairment and depression in multiple sclerosis; Gobbi et al. [50] described atrophy of frontal, parietal and occipital lobes in patients with depression and fatigue.

Considering that brain atrophy is also a result of normal ageing, more useful elements in understanding the role of demyelinating lesions in neuropsychological disorders in multiple sclerosis, come from studies that analyze T2 lesion load on brain MRI.

Pujol et al. [51] in 1997 supposing a direct effect of demyelination on mood, found that the presence of lesion in left arcuate fasciculus was related with depression. Berg et al. in 2000 [44] found that depressed multiple sclerosis patients had higher lesion load in temporal lobes compared to non – depressed MS patients and this difference was statistically significant for the right temporal lobe. The lesion load in right temporal lobe seemed to be related not only with symptoms but also with severity of depression. Also fatigue and lesion load in right temporal lobe have been documented to have a significant correlation.

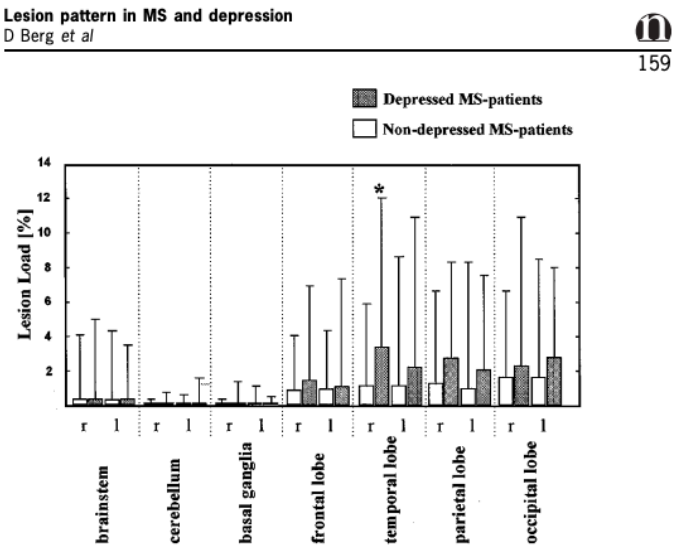

Fig 8: Berg et al. Lesion pattern in MS and depression

Besides anatomical localization of T2 lesion, other studies have analyzed total T2 lesion volume on brain MRI of patients with multiple sclerosis as a quantitative measure to be used as a surrogate biomarker of disease severity and prognostic factor. Overall, in the available published research the characteristics of the sample are often heterogeneous and different across studies making it difficult to compare the results correctly.

According to what is found in literature, the volumetric values of brain T2 lesion load obtained from our sample are quite consistent with data described in some of the studies already published [27] [26]. No previous studies specifically analyzed the association of total T2 lesion load with resilience and quality of life measures.
From the descriptive point of view, quality of life status in our sample was globally in line with that reported in literature, suggesting a negative impact of multiple sclerosis on wellbeing. However, compared with available data the mean value of mental health seems to be lower in our sample compared to other studies. In a study published by Giordano et al in 2019 [53] the mean score for mental health was 66.6 (SD 21.3) in the English-speaking population and 62.9 (SD 20.7) in Italian speakers; the mean in our sample resulted 50.9 (SD 10.2). The results obtained for physical health are similar: 61.5 (SD 8.5) in our population, 61.1 (SD 20.2) in the study of Giordano for Italian speaker and 57.7 (SD 21.5) for English speakers.
With respect to resilience, it is more difficult to compare our results with other studies. The reason is that there is no scale validation on a sample of subjects suffering from multiple sclerosis.
The Connor – Davidson Resilience Scale (CD-RISC) ® manual reports different outcomes of the measurement: for example, the mean values for the general population in different geographical areas, in different groups of ages and in populations suffering from different diseases. Few studies have been applied to patients with multiple sclerosis, sometimes using the abbreviated form CD-RISC10; among them none was conducted in the Italian population. Recently the CD-RISC 25 has been used in patients with multiple sclerosis to investigate the impact of COVID-19 pandemic, but the results are referred to assessment during emergency; no baseline data in this population are available [54].
With reference to the primary outcome, the exploratory analysis we performed in our study showed that total T2 lesion volume in the brain is not significantly associated with resilience.
We therefore sought other possible relationships between the clinical variables and resilience; however, neither clinical course, active lesions nor relapses were significantly associated to resilience level.

Overall, no statistically significant findings were observed for any of the analyzed variables, however some of the correlation coefficients were numerically meaningful and might deserve attention in future research. In particular, the time that took place between onset of disease and enrollment seems to have a moderate correlation with resilience. Considering this result, it can be assumed that for patient this time is necessary to deal with diagnosis and to improve the response to this stressful situation; a time during which the person with MS likely becomes more aware of the disease and also receives adequate responses to the uncertainty that dominates the clinical course.

Among sociodemographic data we found a moderate correlation between resilience and age, and also with physical health score in the MSQoL.

The way in which age influences resilience is unclear, probably greater security and stability in working life and relationships become a solid foundation on which each individual recognizes the tools to adapt their life to a condition of chronic disease.

With respect to the possible correlation between physical health domain on MSQoL and resilience, we assume that the subjective perception of the physical impact of disease (i.e. motor deficits, physical difficulties in performing daily activities, pain and fatigue) is an important factor that influences an individual's ability to react to the disease. This finding was in line with the observation of a weak inverse correlation between EDSS score – which captures mostly physical disability – and resilience, although again the result was not statistically significant.

It therefore appears useful, according to these results, to focus attention, already in the early stages, on symptoms that - maybe more nuanced (e.g. fatigue, pain) - impact on the physical domains of quality of life and therefore, if treated early, could benefit from focused intervention.

Overall, the results of this study suggest that psychosocial wellbeing of young patients recently diagnosed with MS appears largely independent of the intrinsic pathogenetic process, at least as measured by the association between resilience (in addition to other psychological variables) and T2 lesion load on brain MRI.

The first stages after diagnosis are usually those most critical in clinical practice

to focus on therapeutic approach and to identify the most appropriate treatment. In this view, psychological adaptation to multiple sclerosis diagnosis at an early stage appears crucial for patient compliance and adherence to therapies.

We are aware of the limits of our study, including the small number of enrolled patients and the limited range of MS-specific variables considered for analysis. However, our findings show that resilience of young patients with MS, although not statistically associated with disease burden assessed as T2 lesion load on brain MRI, is possibly connected to demographic variables, physical wellbeing, disease duration and possibly disability accumulation in the early stages of the disease. Therefore, all these features deserve to be furtherly examined as possible determinants of resilience, with the ultimate goal of improving quality of life of people with MS.

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APPENDIX -1 : CRF FOR CLINICAL VARIABLES COLLECTION

APPENDIX – 2: PSYCHOLOGICAL QUESTIONNAIRE

ID PAZIENTE

SESSO

☐ M ☐ F

DATA DI NASCITA

☐☐ / ☐☐ / ☐☐☐☐

FIRMA CONSENSO INFORMATO

☐ SI ☐ NO

DATA FIRMA

☐☐ / ☐☐ / ☐☐☐☐

Criteri di inclusione

☐ Età compresa tra 18 – 40 aa

☐ Diagnosi di SM entro I 2 anni dall'inclusione nello studio secondo I criteri McDonald2017

☐ RM encefalo eseguita almeno 6 mesi prima o 1 mese dopo la visita di screening purché eseguita secondo protocollo

☐ lingua italiana

Criteri di esclusione

☐ deficit cognitivi rilevanti valutati alla visita neurologica

☐ trattamento con qualsiasi farmaco disease-modifing per SM al momento dell'inclusione e fino al completamento delle procedure dello studio (max 2 mesi dall'arruolamento); terapia steroidea se eseguita non meno di 30 giorni prima dell'arruolamento

Sociodermo form → vedi WP4

WP3

Data primo evento clinico

☐☐ / ☐☐ / ☐☐☐☐

Dati anamnestici:	**SI**	**NO**
. la Paziente è attualmente in gravidanza o allattamento?	O	O
. il Paziente ha patologie reumatologiche?	O	O
Se si, quali? _____		
. il Paziente ha patologie tiroidee?	O	O
Se si, quali? _____		
. il Paziente ha altre comorbidità?	O	O
Se si, quali? _____		
. il Paziente assume terapia concomitante?	O	O

Sede sintomatologia all'esordio:

- ○ Nervo ottico
- ○ Emisferica
- ○ Tronco encefalico
- ○ Cervelletto
- ○ Midollo spinale
- ○ Altro specificare_____

Sintomatologia all'esordio:

- ○ NORB
- ○ paresi
  - ☐ ASDX
  - ☐ ASSIN
  - ☐ AIDX
  - ☐ AISIN
- ○ deficit nervi cranici
- ○ deficit sensitivo
- ○ disturbo sfinterico
- ○ atassia/dismetria
- ○ fatica
- ○ altro specificare_____

Data diagnosi **Età pz alla diagnosi** ☐☐

☐☐ / ☐☐ / ☐☐☐☐

EDSS ☐

Decorso

☐ SM – RR ☐ SM - P

1. FS visivo	
2. FS tronco encefalico	
3. FS piramidale	
4. FS cerebellare	
5. FS sensitivo	
6. FS funzione sfinteriale	
7. FS cerebrale	
8. Ambulation index	
Distanza massima percorribile con deambulazione autonoma (m)?	
EDSS	

RMN encefalo con mdc ☐☐ / ☐☐ / ☐☐☐☐

- **Lesioni periventricolari** ☐ **SI** ☐ **NO** ☐ **GAD+**
- **Lesioni iuxtacorticali** ☐ **SI** ☐ **NO** ☐ **GAD+**
- **Lesioni sottotentoriali** ☐ **SI** ☐ **NO** ☐ **GAD+**

RMN midollo ☐ **CERV.** ☐ **DORS.** ☐ **LOMB.** ☐ **GAD+**

CUT-OFF NUMERO LESIONI TOTALI:

1-3 ☐

4-8 ☐

>8 ☐

PUNTURA LOMBARE:

BO ☐

Numero di ricadute ☐☐

Sintomatologia ricaduta num1: (ipotizzare per num max di 10 ricadute)

- ○ NORB
- ○ paresi
  - ☐ ASDX
  - ☐ ASSIN
  - ☐ AIDX
  - ☐ AISIN
- ○ deficit nervi cranici
- ○ disturbo sensitivo
- ○ disturbo sfinterico
- ○ atassia/dismetria
- ○ fatica

○ altro specificare_____

Recupero completo dopo la ricaduta ☐ SI ☐ NO

Ulteriori variabili/misure raccolte secondo protocollo di studio.

Catena leggera Neurofilamenti
Liquor (SIMOA): _____pg/ml
Siero (SIMOA): _____pg/ml

CXCL-13 su Liquor (ELISA): _____pg/ml

CHI3L1 su Liquor (ELISA): _____ng/ml

Esterificazione 24OH-colesterolo su siero (ratio): _____

Symbol digit modality test:

Indicatore per fatica → vd MSQOL54

Firma del Compilatore _____

Firma dello sperimentatore _____

Stato civile:

Celibe/ Nubile ☐

Coniugato/Unione civile ☐

Separato/divorziato ☐

Vedovo/vedova ☐

Nazione di nascita: _____

Titolo di studio più elevato conseguito:

Nessun titolo ☐

Licenza elementare ☐

Licenza media inferiore ☐

Diploma professionale ☐

Diploma media superiore ☐

Diploma universitario o laurea ☐

Titolo post-laurea (specilizzazione, master, dottorato,.....) ☐

Situazione lavorativa-occupazionale attuale:

Occupato ☐

Disoccupato ☐

Studente ☐

Casalinga/o ☐

Pensionato/a ☐

Altro ☐

Con chi vive:

Genitori (padre e/o madre) ☐

Coniuge o convivente ☐

Figli ☐

Altri conviventi familiari ☐

Altri conviventi non familiari ☐

Da solo ☐

MSQOL-54

Id:_____

Data:_____

STUDIO BPS-ARMS (wp4 e wp5)

Istruzioni: Il questionario intende valutare cosa lei pensa della sua salute. Le informazioni raccolte permetteranno di essere aggiornati su come si sente e su come riesce a svolgere le sue attività consuete.

Risponda a ciascuna domanda del questionario indicando la sua risposta come mostrato di volta in volta. Se non si sente certo della risposta, effettui la scelta che comunque le sembra migliore.

1. In generale, direbbe che la sua salute è:

(indichi un numero)

Eccellente……1

Molto buona……..2

Buona……3

Passabile……4

Scadente……5

2. Rispetto ad un anno fa, come giudicherebbe, ora, la sua salute generale?

(indichi un numero)

Decisamente migliore adesso rispetto ad un anno fa……1

Un po' migliore adesso rispetto ad un anno fa……..2

Più o meno uguale rispetto ad un anno fa……3

Un po' peggiore adesso rispetto ad un anno fa……4

Decisamente peggiore rispetto ad un anno fa……5

Istruzioni: le seguenti domande riguardano alcune attività che potrebbe svolgere nel corso di una qualsiasi giornata. La sua salute la limita attualmente nello svolgimento di queste attività?

3. La sua salute la limita attualmente nello svolgimento di **attività fisicamente impegnative**, come correre, sollevare oggetti pesanti, praticare sport faticosi?

(Indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

4. La sua salute la limita attualmente nello svolgimento di **attività di moderato impegno fisico**, come spostare un tavolo, usare l'aspirapolvere, giocare a bocce o fare un giretto in bicicletta?

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

5. La sua salute la limita attualmente nel **sollevare o portare le borse della spesa?**

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

6. La sua salute la limita attualmente nel **salire qualche piano di scale**?

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

7. La sua salute la limita attualmente nel **salire un piano di scale**?

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

8. La sua salute la limita attualmente nel **piegarsi, inginocchiarsi o chinarsi**?

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

9. La sua salute la limita attualmente nel **camminare per un chilometro**?

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

10. La sua salute la limita attualmente nel **camminare per qualche centinaio di metri?**

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

11. La sua salute la limita attualmente nel **camminare per circa cento metri?**

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

12. La sua salute la limita attualmente nel **fare il bagno o vestirsi da solo**?

(indichi un numero)

SI, mi limita parecchio.....1

SI, mi limita parzialmente.....2

NO, non mi limita per nulla.....3

Nelle ultime 4 settimane, ha riscontrato i seguenti problemi sul lavoro o nelle altre attività quotidiane, a causa della sua salute fisica?

Risponda SI o NO a ciascuna domanda.

13. Nelle ultime 4 settimane, a causa della sua salute fisica ha ridotto **il tempo dedicato al lavoro o ad altre attività?**

(Indichi per ogni domanda il numero 1 o 2)

SI.....1

NO.....2

14. Nelle ultime 4 settimane, a causa della sua salute fisica ha reso **meno di quanto avrebbe voluto**?

(indichi per ogni domanda il numero 1 o 2)

SI.....1

NO.....2

15. Nelle ultime 4 settimane, a causa della sua salute fisica ha dovuto **limitare alcuni tipi di lavoro o altre attività**?

(indichi per ogni domanda il numero 1 o 2)

SI.....1

NO.....2

16. Nelle ultime 4 settimane, a causa della sua salute fisica ha avuto **difficoltà nell'eseguire il lavoro o altre attività** (ad esempio, ha fatto più fatica)?

(indichi per ogni domanda il numero 1 o 2)

SI.....1

NO.....2

Nelle ultime 4 settimane, ha riscontrato i seguenti problemi sul lavoro o nelle altre attività quotidiane, a causa del suo stato emotivo (quale il sentirsi depresso o ansioso)?

Risponda SI o NO a ciascuna domanda.

17. Nelle ultime 4 settimane, a causa del suo stato emotivo ha ridotto il **tempo dedicato al lavoro o ad altre attività**?

(indichi per ogni domanda il numero 1 o 2)

SI.....1

NO.....2

18. Nelle ultime 4 settimane, a causa del suo stato emotivo ha **reso meno di quanto avrebbe voluto**?

(indichi per ogni domanda il numero 1 o 2)

SI.....1

NO.....2

19. Nelle ultime 4 settimane, a causa del suo stato emotivo ha avuto **calo di concentrazione** sul lavoro o in altre attività?

(indichi per ogni domanda il numero 1 o 2)

SI.....1

NO.....2

20. Nelle ultime 4 settimane, in che misura la sua salute fisica o il suo stato emotivo hanno **interferito con le normali attività sociali** con la famiglia, gli amici, i vicini di casa, i gruppi di cui fa parte?

(indichi un numero)

Per nulla.....1

Leggermente.....2

Un po'.....3

Molto.....4

Moltissimo.....5

21. Quanto **dolore fisico** ha provato nelle ultime 4 settimane?

(indichi un numero)

Nessuno.....1

Molto lieve.....2

Lieve.....3

Moderato.....4

Forte.....5

Molto forte.....6

22. Nelle ultime 4 settimane, in che misura il **dolore l'ha ostacolata** nel lavoro che svolge abitualmente (sia in casa sia fuori casa)?

(indichi un numero)

Per nulla.....1

Leggermente.....2

Un po'.....3

Molto.....4

Moltissimo.....5

Le seguenti domande si riferiscono a come si è sentito nelle ultime 4 settimane.
Risponda a ciascuna domanda scegliendo la risposta che più si avvicina al suo caso.

23. Per quanto tempo nelle ultime 4 settimane si è sentito **vivace e brillante**?

(indichi un numero)

Sempre.....1
Quasi sempre.....2
Molto tempo.....3
Una parte del tempo.....4
Quasi mai.....5
Mai.....6

24. Per quanto tempo nelle ultime 4 settimane si è sentito **molto agitato**?

(indichi un numero)

Sempre.....1
Quasi sempre.....2
Molto tempo.....3
Una parte del tempo.....4
Quasi mai.....5
Mai.....6

25. Per quanto tempo nelle ultime 4 settimane si è sentito così **giù di morale** che niente avrebbe potuto tirarla su?

(indichi un numero)

Sempre.....1
Quasi sempre.....2
Molto tempo.....3
Una parte del tempo.....4
Quasi mai.....5
Mai.....6

26. Per quanto tempo nelle ultime 4 settimane si è sentito **calmo e sereno**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

27. Per quanto tempo nelle ultime 4 settimane si è sentito **pieno di energia**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

28. Per quanto tempo nelle ultime 4 settimane si è sentito **scoraggiato e triste**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

29. Per quanto tempo nelle ultime 4 settimane si è sentito **sfinito**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

30. Per quanto tempo nelle ultime 4 settimane si è sentito **felice**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

31. Per quanto tempo nelle ultime 4 settimane si è sentito **stanco**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

32. Nelle ultime 4 settimane, per quanto tempo la sua salute fisica o il suo stato emotivo hanno interferito nelle sue **attività sociali**, in famiglia, con gli amici?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

Scelga la risposta che meglio descrive quanto siano **VERE o FALSE** le seguenti affermazioni.

33. Mi pare di ammalarmi un po' più facilmente degli altri.

(indichi un numero)

Certamente vero.....1

In gran parte vero.....2

Non so.....3

In gran parte falso.....4

Certamente falso.....5

34. La mia salute è come quella degli altri.

(indichi un numero)

Certamente vero.....1

In gran parte vero.....2

Non so.....3

In gran parte falso.....4

Certamente falso.....5

35. Mi aspetto che la mia salute andrà **peggiorando**.

(indichi un numero)

Certamente vero.....1

In gran parte vero.....2

Non so.....3

In gran parte falso.....4

Certamente falso.....5

36. Godo di **ottima salute.**

(indichi un numero)

Certamente vero.....1

In gran parte vero.....2

Non so.....3

In gran parte falso.....4

Certamente falso.....5

37. Nelle ultime 4 settimane, per quanto tempo si è sentito **riposato** al suo risveglio al mattino?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

38. Nelle ultime 4 settimane, per quanto tempo si è sentito **scoraggiato** a causa della sua salute?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

39. Nelle ultime 4 settimane, per quanto tempo si è sentito **frustrato** a causa della sua salute?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

40. Nelle ultime 4 settimane, per quanto tempo si è sentito **preoccupato** a causa della sua salute?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

41. Nelle ultime 4 settimane, per quanto tempo si è sentito **oppresso** a causa della sua salute?
(indichi un numero)

Sempre.....1
Quasi sempre.....2
Molto tempo.....3
Una parte del tempo.....4
Quasi mai.....5
Mai.....6

42. Nelle ultime 4 settimane, per quanto tempo ha provato **difficoltà di concentrazione e di ragionamento**?
(indichi un numero)

Sempre.....1
Quasi sempre.....2
Molto tempo.....3
Una parte del tempo.....4
Quasi mai.....5
Mai.....6

43. Nelle ultime 4 settimane, per quanto tempo ha trovato difficile mantenere la sua **attenzione** a lungo durante lo svolgimento di una attività?
(indichi un numero)

Sempre.....1
Quasi sempre.....2
Molto tempo.....3
Una parte del tempo.....4
Quasi mai.....5
Mai.....6

44. Nelle ultime 4 settimane, per quanto tempo ha avuto difficoltà a **ricordare**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

45. Nelle ultime 4 settimane, per quanto tempo altre persone (familiari o amici) le hanno fatto notare che ha difficoltà a **ricordare ed a concentrarsi**?

(indichi un numero)

Sempre.....1

Quasi sempre.....2

Molto tempo.....3

Una parte del tempo.....4

Quasi mai.....5

Mai.....6

Le prossime domande riguardano la sua attività sessuale ed il grado di soddisfazione.
Risponda a ciascuna domanda scegliendo la risposta che più si avvicina al suo caso.
Consideri solo le ultime 4 settimane.

46. Nelle ultime 4 settimane, in che misura la **mancanza di stimoli sessuali** ha rappresentato un problema?

(indichi un numero)

Nessun problema.....1
In piccola parte un problema.....2
In parte un problema.....3
In gran parte un problema.....4

47. Nelle ultime 4 settimane,
in che misura la difficoltà nell'avere o nel mantenere **un'erezione** ha rappresentato un problema per lei? (risposta maschile)
in che misura la difficoltà nell'avere o nel mantenere **la lubrificazione** ha rappresentato un problema per lei? (risposta femminile)

(indichi un numero)

Nessun problema.....1
In piccola parte un problema.....2
In parte un problema.....3
In gran parte un problema.....4

48. Nelle ultime 4 settimane, in che misura la difficoltà nel **raggiungere l'orgasmo** ha rappresentato un problema per lei?

(indichi un numero)

Nessun problema.....1
In piccola parte un problema.....2
In parte un problema.....3
In gran parte un problema.....4

49. Nelle ultime 4 settimane, in che misura la capacità di **soddisfare sessualmente il partner** ha rappresentato un problema per lei?

(indichi un numero)

Nessun problema.....1

In piccola parte un problema.....2

In parte un problema.....3

In gran parte un problema.....4

50. In generale, quale è stato il suo livello di **soddisfazione rispetto alla sua attività sessuale** nelle ultime 4 settimana?

(Indichi un numero)

Molto soddisfatto.....1

Abbastanza soddisfatto.....2

Né soddisfatto né insoddisfatto.....3

Piuttosto insoddisfatto.....4

Molto insoddisfatto.....5

51. Nelle ultime 4 settimane, i **disturbi urinari o intestinali** le hanno impedito di svolgere le normali attività di relazione con i familiari, con gli amici, con i vicini o nei gruppi di cui fa parte?

(Indichi un numero)

Per nulla.....1

Leggermente.....2

Un po'.....3

Molto.....4

Moltissimo.....5

52. Nelle ultime 4 settimane in che misura la sua vita è stata compromessa dal **dolore fisico**?

(Indichi un numero)

Per nulla.....1

Leggermente.....2

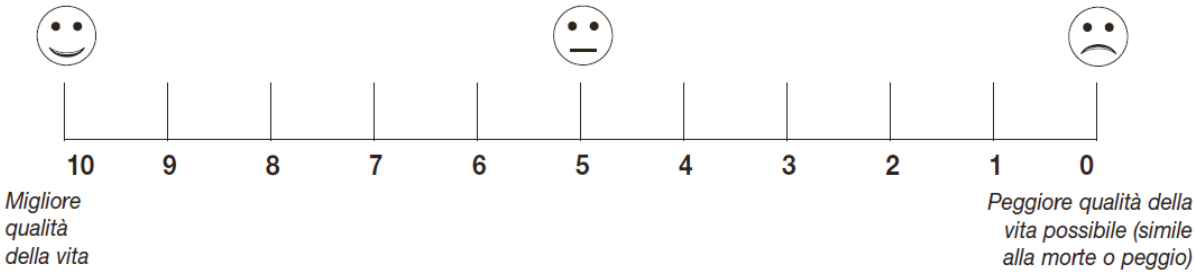
Un po'.....3

Molto.....4

Moltissimo.....5

53. In termini generali, come giudicherebbe la qualità della sua vita?

(Indichi un numero nella scala)



54. Quale dei seguenti termini descrive meglio come si sente se pensa alla sua vita, nel suo insieme?

(Indichi un numero)

Malissimo.....1

Scontento.....2

In gran parte insoddisfatto.....3

Tanto soddisfatto quanto insoddisfatto allo stesso modo.....4

In gran parte soddisfatto.....5

Contento.....6

Benissimo.....7

CD-RISC-25

(Scala di resilienza di Connor e Davidson)

Id:_____

Data:_____

STUDIO BPS-ARMS (wp4 e wp5)

Istruzioni: per favore risponda a ciascuna delle affermazioni riportate qui di seguito segnando il riquadro che corrisponde alla sua risposta. Nel rispondere, si basi sugli eventi dell'**ultimo mese** o, in alternativa, su quelli del passato recente.

0= per nulla vero
1= un po' vero
2= abbastanza vero
3= spesso vero
4=quasi sempre vero

1. Sono in grado di adattarmi al cambiamento.	0	1	2	3	4
2. Esiste qualcuno nella mia vita in grado di aiutarmi in caso di bisogno.	0	1	2	3	4
3. Quando non vedo soluzioni chiare per i miei problemi, spesso solo il fato o Dio mi possono aiutare.	0	1	2	3	4
4. Sono in grado di affrontare ogni ostacolo nella vita.	0	1	2	3	4
5. I successi del passato mi hanno dato la sicurezza necessaria per affrontare future difficoltà.	0	1	2	3	4
6. Quando devo risolvere i problemi cerco di vedere il lato divertente delle cose.	0	1	2	3	4
7. Dover affrontare degli stress mi hanno reso più forte.	0	1	2	3	4
8. Dopo una malattia, incidente o altro grave problema recupero in fretta.	0	1	2	3	4
9. Nel bene o nel male, credo che tutte le cose accadano per un motivo ben preciso.	0	1	2	3	4
10. Do sempre il meglio di me stesso/a, a prescindere dal risultato.	0	1	2	3	4
11. Penso di poter raggiungere gli obiettivi che mi sono prefissato/a nonostante tutti gli ostacoli.	0	1	2	3	4
12. Io non mi arrendo mai, nemmeno quando la situazione risulta essere senza speranza.	0	1	2	3	4
13. Nei momenti di crisi so a chi rivolgermi per ottenere aiuto.	0	1	2	3	4
14. Quando sono sotto pressione riesco a mantenermi concentrato/a.	0	1	2	3	4
15. Preferisco prendere l'iniziativa quando si tratta di risolvere dei problemi.	0	1	2	3	4
16. Non mi scoraggio facilmente davanti al fallimento.	0	1	2	3	4
17. Nell'affrontare le difficoltà e le sfide della vita mi ritengo una persona combattiva.	0	1	2	3	4
18. Se necessario sono in grado di prendere decisioni che gli altri non riescono a accettare.	0	1	2	3	4
19. Sono in grado di gestire emozioni come tristezza, paura, rabbia.	0	1	2	3	4
20. Nell'affrontare problemi quotidiani spesso bisogna agire d'istinto, senza pensare troppo.	0	1	2	3	4
21. Ho obiettivi ben chiari per la mia vita.	0	1	2	3	4
22. Mi sento in controllo nella mia vita.	0	1	2	3	4
23. Amo le sfide.	0	1	2	3	4
24. Lavoro per raggiungere degli obiettivi definiti a prescindere dagli ostacoli che trovo sulla via.	0	1	2	3	4
25. Sono orgoglioso/a dei risultati da me raggiunti.	0	1	2	3	4

B-IPQ

Id:_____

Data:_____

Istruzioni: per le seguenti domande, per favore cerchi il numero che meglio corrisponde al suo punti di vista.

Quanto la sua malattia influenza la sua vita?

1 2 3 4 5 6 7 8 9 10

Non l'influenza per niente — La influenza gravemente

Per quanto tempo pensa la sua malattia continuerà?

1 2 3 4 5 6 7 8 9 10

Per un tempo molto breve — Per sempre

Quanto controllo crede di avere sulla sua malattia?

1 2 3 4 5 6 7 8 9 10

Assolutamente nessun controllo — Un controllo assoluto

Quanto pensa che il suo trattamento (pillole, ecc.) possa aiutare la sua malattia?

1 2 3 4 5 6 7 8 9 10

Per nulla — Estremamente di aiuto

Quanto sente i sintomi della sua malattia?

1 2 3 4 5 6 7 8 9 10

Alcun sintomo — Sintomi molto gravi

Quanto è preoccupato per la sua malattia?

1 2 3 4 5 6 7 8 9 10

Per nulla preoccupato — Estremamente preoccupato

Quanto crede di capire bene la sua malattia?

1 2 3 4 5 6 7 8 9 10

Per nulla — Capita molto chiaramente

Quanto la sua malattia ha cambiato le sue emozioni? (per esempio la fa arrabbiare, spaventare, turbare, deprimere?)

1 2 3 4 5 6 7 8 9 10

Non ha cambiato per nulla le emozioni — Le ha cambiate estremamente

Per favore, elenchi in ordine di importanza i tre fattori principali che hanno causato la sua malattia:

1)
2)
3)

PSYCHOSOCIAL INDEX (PSI)

Id:_____

Data:_____

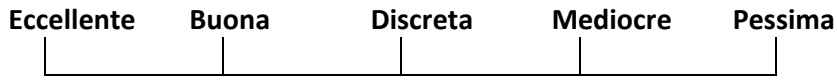
Pensa ora a quello che è avvenuto nell'ultimo anno:		
1 È morto un familiare o un amico stretto?	**SI**	**NO**
2 Ti sei lasciato con tuo marito/moglie o con il partner?	**SI**	**NO**
3 Ci sono stati cambiamenti di scuola o di lavoro?	**SI**	**NO**
4 Ci sono stati problemi economici?	**SI**	**NO**
5 Hai traslocato (nella stessa città)?	**SI**	**NO**
6 Hai cambiato città?	**SI**	**NO**
7 Hai avuto problemi legali?	**SI**	**NO**
8 Hai iniziato una nuova relazione?	**SI**	**NO**
Rispondi alle seguenti domande		
9 Hai un lavoro?	**SI**	**NO**
<u>Se hai un lavoro</u>:		
10 Sei soddisfatto/a dei tuoi studi o del tuo lavoro?	**SI**	**NO**
11 Ti senti sotto pressione a scuola o a lavoro?	**SI**	**NO**
12 Hai dei problemi con i compagni di scuola o con i colleghi di lavoro?	**SI**	**NO**
<u>Se non hai un lavoro</u>:		
13 Sei un pensionato o uno studente?	**SI**	**NO**
14 Ti senti sotto pressione durante il giorno?	**SI**	**NO**
15 Non riesci a trovare un lavoro?	**SI**	**NO**
16 Hai avuto serie discussioni con familiari stretti?	**SI**	**NO**
17 Hai avuto serie discussioni con altre persone?	**SI**	**NO**
18 Hai avuto nell'ultimo anno familiari stretti gravemente malati? Se sì, specificare:_____	**SI**	**NO**
19 In casa c'è tensione?	**SI**	**NO**

20	Vivi da solo?	**SI**	**NO**
21	Ti senti solo, isolato?	**SI**	**NO**
22	Hai qualcuno di cui fidi e con cui puoi confidarti?	**SI**	**NO**
23	Ti trovi bene con la gente?	**SI**	**NO**
24	Quello che la vita ti richiede ti sembra troppo?	**SI**	**NO**
25	Hai spesso la sensazione di non farcela?	**SI**	**NO**
26	Tendi ad essere influenzato dalle persone che hanno opinioni forti?	**SI**	**NO**
27	Tendi a preoccuparti di quello che gli altri pensano di te?	**SI**	**NO**

Recentemente hai accusato qualcuno di questi problemi o difficoltà? Quanto disagio ti hanno procurato?

	No, per niente	Un po'	Molto	Moltissimo non potrebbe andare peggio
28 Molto tempo prima di addormentarsi				
29 Sonno agitato con frequenti risvegli				
30 Svegliarsi troppo presto ed incapacità a riprendere sonno				
31 Svegliarsi già stanco				
32 Disturbi di stomaco, intestino				
33 Cuore che batte forte o veloce senza ragione				
34 Vertigini o sensazione di stare per svenire				
35 Oppressione, pesantezza alla testa e al corpo				
36 Respiro difficile o sentirsi come se non ci fosse abbastanza aria				
37 Stanco, senza energie				
38 Irritabile				
39 Triste o depresso				
40 Teso, tirato, nervoso				
41 Perdita di interesse per la maggior parte delle cose				
42 Attacchi di panico				
43 Pensi di avere una malattia che i medici non hanno ancora diagnosticato?				
44 Quando leggi o senti parlare di una nuova malattia, accusi sintomi simili a quella malattia?				
45 Quando avverti sensazioni nel tuo corpo, ti riesce difficile pensare a qualcos'altro?				

46 Come giudichi la qualità della tua vita?



FFMQ-SF

Id:_____

Data:_____

STUDIO BPS-ARMS (wp4 e wp5)

Istruzioni: di seguito troverà alcune affermazioni sulla sua esperienza quotidiana. Usando la scala da 1 a 5 sotto riportata indichi per favore, nella casella a destra di ogni affermazione, con che frequenza ha avuto ciascuna esperienza NELL'ULTIMO MESE. Per favore risponda in base a ciò che realmente rispecchia la sua esperienza anziché a ciò che pensa che la sua esperienza dovrebbe essere**.**

	Mai o molto raramente	**Spesso non vero**	**A volte vero a volte non vero**	**Spesso vero**	**Molto spesso o sempre vero**
1.Sono bravo/a a trovare le parole che descrivano i miei sentimenti.	**1**	**2**	**3**	**4**	**5**
2.Riesco facilmente a trovare le parole per esprimere le mie convinzioni, le mie opinioni e le mie aspettative.	**1**	**2**	**3**	**4**	**5**
3.Faccio attenzione ai miei sentimenti senza farmi coinvolgere troppo da essi.	**1**	**2**	**3**	**4**	**5**
4.Dico a me stesso/a che non dovrei sentirmi nel modo in cui mi sento.	**1**	**2**	**3**	**4**	**5**
5.Mi è difficile trovare le parole per descrivere ciò che penso.	**1**	**2**	**3**	**4**	**5**
6.Presto attenzione alle esperienze fisiche, come il vento nei capelli o il sole sul viso.	**1**	**2**	**3**	**4**	**5**
7.Tendo a giudicare i miei pensieri come buoni oppure come cattivi	**1**	**2**	**3**	**4**	**5**
8.Mi è difficile rimanere concentrato/a su quello che succede nel presente.	**1**	**2**	**3**	**4**	**5**
9.Quando sono turbato/a da immagini o pensieri, non mi lascio trasportare da essi	**1**	**2**	**3**	**4**	**5**
10.Generalmente, presto attenzione ai rumori, come ad esempio il ticchettio dell'orologio, al cinguettio degli uccelli, o al passaggio delle macchine.	**1**	**2**	**3**	**4**	**5**
11.Quando provo sensazioni fisiche, mi è difficile trovare le parole giuste per descriverle	**1**	**2**	**3**	**4**	**5**
12.Mi sembra di "funzionare in automatico" senza troppa consapevolezza di quello che sto facendo.	**1**	**2**	**3**	**4**	**5**
13.Quando immagini o pensieri mi stressano, riesco a calmarmi in poco tempo.	**1**	**2**	**3**	**4**	**5**
14.Dico a me stesso/a che non dovrei pensare nel modo in cui penso	**1**	**2**	**3**	**4**	**5**
15.Faccio attenzione agli odori e ai profumi delle cose.	**1**	**2**	**3**	**4**	**5**
16.Anche quando sono molto arrabbiato/a riesco a trovare il modo per dirlo a parole.	**1**	**2**	**3**	**4**	**5**
17.Svolgo rapidamente le mie attività senza prestarvi davvero attenzione.	**1**	**2**	**3**	**4**	**5**

	Mai o molto raramente	Spesso non vero	A volte vero a volte non vero	Spesso vero	Molto spesso o sempre vero
18.Quando i miei pensieri o immagini mi turbano sono in grado di accorgermene senza reagire.	**1**	**2**	**3**	**4**	**5**
19.Ritengo che alcune delle mie emozioni siano cattive o inappropriate e che non dovrei sentirle.	**1**	**2**	**3**	**4**	**5**
20.Noto gli aspetti visivi nell'arte o nella natura, come i colori, le forme, o i giochi di luci ed ombre.	**1**	**2**	**3**	**4**	**5**
21.Quando i miei pensieri o immagini mi turbano, me ne accorgo e li lascio andare.	**1**	**2**	**3**	**4**	**5**
22.Faccio lavori o compiti automaticamente senza essere consapevole di quello che sto facendo.	**1**	**2**	**3**	**4**	**5**
23.Mi trovo a fare cose senza prestarvi attenzione.	**1**	**2**	**3**	**4**	**5**
24.Sono fortemente critico con me stesso/a quando mi vengono delle idee poco sensate.	**1**	**2**	**3**	**4**	**5**

SCL-90-r

Id:_____

Data:_____

STUDIO BPS-ARMS (wp4 e wp5)

Istruzioni: nella lista che segue, sono elencati problemi e disturbi che spesso affliggono le persone. Legga attentamente e cerchi di ricordare **se ne ha sofferto nella scorsa settimana, oggi compreso, e con quale intensità.**
Risponda a tutte le domande facendo una crocetta sulla risposta corrispondente all'intensità di ogni disturbo. Se dovesse sbagliare o cambiare idea, corregga in maniera comprensibile, grazie.

IN CHE MISURA SOFFRE O HA SOFFERTO DI……..	0	1	2	3	4
1. Mal di testa	Per niente	Un poco	moderatamente	Molto	moltissimo
2. Nervosismo o agitazione interna	Per niente	Un poco	Moderatamente	Molto	Moltissimo
3. Pensieri sgradevoli che si ripetono	Per niente	Un poco	Moderatamente	Molto	Moltissimo
4. Sensazione di svenimento o di vertigine	Per niente	Un poco	Moderatamente	Molto	Moltissimo
5. Perdita dell'interesse o del piacere sessuale	Per niente	Un poco	Moderatamente	Molto	Moltissimo
6. Tendenza a criticare gli altri	Per niente	Un poco	Moderatamente	Molto	Moltissimo
7. Convinzione che qualcun altro possa controllare i suoi pensieri	Per niente	Un poco	Moderatamente	Molto	Moltissimo
8. Sensazione che gli altri siano responsabili della maggior parte dei suoi problemi	Per niente	Un poco	Moderatamente	Molto	Moltissimo
9. Difficoltà a ricordare le cose	Per niente	Un poco	Moderatamente	Molto	Moltissimo
10. Preoccupazioni per la sua negligenza o trascuratezza	Per niente	Un poco	Moderatamente	Molto	Moltissimo
11. Sentirsi facilmente infastidito o irritato	Per niente	Un poco	Moderatamente	Molto	Moltissimo
12. Dolori al cuore o al petto	Per niente	Un poco	Moderatamente	Molto	Moltissimo
13. Paura degli spazi aperti o delle strade	Per niente	Un poco	Moderatamente	Molto	Moltissimo
14. Sentirsi debole o fiacco	Per niente	Un poco	Moderatamente	Molto	Moltissimo
15. Idee di togliersi la vita	Per niente	Un poco	Moderatamente	Molto	Moltissimo
16. Udire voci che altre persone non odono	Per niente	Un poco	Moderatamente	Molto	Moltissimo
17. Tremori	Per niente	Un poco	Moderatamente	Molto	Moltissimo
18. Sensazione di non potersi fidare della maggior parte delle persone	Per niente	Un poco	Moderatamente	Molto	Moltissimo
19. Scarso appetito	Per niente	Un poco	Moderatamente	Molto	Moltissimo
20. Facilità al pianto	Per niente	Un poco	Moderatamente	Molto	Moltissimo
21. Sentirsi intimidito o a disagio con l'altro sesso	Per niente	Un poco	Moderatamente	Molto	Moltissimo
22. Sensazione di essere preso in trappola	Per niente	Un poco	Moderatamente	Molto	Moltissimo
23. Paure improvvise senza ragione	Per niente	Un poco	Moderatamente	Molto	Moltissimo
24. Scatti di ira incontrollabili	Per niente	Un poco	Moderatamente	Molto	Moltissimo
25. Paura di uscire di casa da solo	Per niente	Un poco	Moderatamente	Molto	Moltissimo

26. Attribuirsi la colpa di tutto	Per niente	Un poco	Moderatamente	Molto	Moltissimo
27. Dolori alla bassa schiena	Per niente	Un poco	Moderatamente	Molto	Moltissimo
28. Senso di incapacità a portare a termine le cose	Per niente	Un poco	Moderatamente	Molto	Moltissimo
29. Sentirsi solo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
30. Sentirsi giù di morale	Per niente	Un poco	Moderatamente	Molto	Moltissimo
31. Preoccuparsi eccessivamente per qualsiasi cosa	Per niente	Un poco	Moderatamente	Molto	Moltissimo
32. Mancanza di interesse	Per niente	Un poco	moderatamente	Molto	Moltissimo
33. Senso di paura	Per niente	Un poco	Moderatamente	Molto	Moltissimo
34. Sentirsi facilmente ferito o offeso	Per niente	Un poco	Moderatamente	Molto	Moltissimo
35. Convinzione che gli altri percepiscano i suoi pensieri	Per niente	Un poco	Moderatamente	Molto	Moltissimo
36. Sensazione di non trovare comprensione o simpatia	Per niente	Un poco	Moderatamente	Molto	Moltissimo
37. Sensazione che gli altri le siano ostili o la abbiano in antipatia	Per niente	Un poco	Moderatamente	Molto	Moltissimo
38. Dover fare le cose molto lentamente	Per niente	Un poco	Moderatamente	Molto	Moltissimo
39. Palpitazione o sentirsi il cuore in gola	Per niente	Un poco	Moderatamente	Molto	Moltissimo
40. Senso di nausea o mal di stomaco	Per niente	Un poco	Moderatamente	Molto	Moltissimo
41. Sentirsi inferiore agli altri	Per niente	Un poco	Moderatamente	Molto	Moltissimo
42. Dolori muscolari	Per niente	Un poco	Moderatamente	Molto	Moltissimo
43. Sensazione che gli altri la osservino o parlino di lei	Per niente	Un poco	Moderatamente	Molto	Moltissimo
44. Difficoltà ad addormentarsi	Per niente	Un poco	Moderatamente	Molto	Moltissimo
45. Bisogno di controllare ripetutamente ciò che fa	Per niente	Un poco	Moderatamente	Molto	Moltissimo
46. Difficoltà a prendere decisioni	Per niente	Un poco	Moderatamente	Molto	Moltissimo
47. Paura di viaggiare in autobus, in metropolitana o in treno	Per niente	Un poco	Moderatamente	Molto	Moltissimo
48. Sentirsi senza fiato	Per niente	Un poco	Moderatamente	Molto	Moltissimo
49. Vampate di calore o brividi di freddo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
50. Necessità di evitare certi oggetti, luoghi o attività perché la spaventano	Per niente	Un poco	Moderatamente	Molto	Moltissimo
51. Senso di vuoto mentale	Per niente	Un poco	Moderatamente	Molto	Moltissimo
52. Intorpidimento o formicolio di alcune parti del corpo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
53. Nodo alla gola	Per niente	Un poco	Moderatamente	Molto	Moltissimo
54. Guardare al futuro senza speranza	Per niente	Un poco	Moderatamente	Molto	Moltissimo
55. Difficoltà a concentrarsi	Per niente	Un poco	Moderatamente	Molto	Moltissimo

56. Senso di debolezza in qualche parte del corpo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
57. Sentirsi teso o sulle spine	Per niente	Un poco	Moderatamente	Molto	Moltissimo
58. Senso di pesantezza alle braccia o alle gambe	Per niente	Un poco	Moderatamente	Molto	Moltissimo
59. Idee di morte o di morire	Per niente	Un poco	Moderatamente	Molto	Moltissimo
60. Mangiare troppo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
61. Senso di disagio quando la gente la guarda o parla di lei	Per niente	Un poco	Moderatamente	Molto	Moltissimo
62. Avere dei pensieri che non sono suoi	Per niente	Un poco	Moderatamente	Molto	Moltissimo
63. Sentire l'impulso di colpire, ferire o fare male a qualcuno	Per niente	Un poco	Moderatamente	Molto	Moltissimo
64. Svegliarsi presto al mattino	Per niente	Un poco	Moderatamente	Molto	Moltissimo
65. Avere bisogno di ripetere lo stesso atto come toccare, contare, lavarsi le mani, ecc.	Per niente	Un poco	Moderatamente	Molto	Moltissimo
66. Sonno inquieto o disturbato	Per niente	Un poco	Moderatamente	Molto	Moltissimo
67. Sentire l'impulso di rompere o spaccare gli oggetti	Per niente	Un poco	Moderatamente	Molto	Moltissimo
68. Avere idee o credenze che gli altri non condividono	Per niente	Un poco	Moderatamente	Molto	Moltissimo
69. Sentirsi penosamente imbarazzato in presenza di altri	Per niente	Un poco	Moderatamente	Molto	Moltissimo
70. Sentirsi a disagio tra la folla come nei negozi, al cinema, ecc.	Per niente	Un poco	Moderatamente	Molto	Moltissimo
71. Sensazione che tutto richieda uno sforzo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
72. Momenti di terrore e di panico	Per niente	Un poco	Moderatamente	Molto	Moltissimo
73. Sentirsi a disagio quando mangia o beve in presenza di altri	Per niente	Un poco	Moderatamente	Molto	Moltissimo
74. Ingaggiare frequenti discussioni	Per niente	Un poco	Moderatamente	Molto	Moltissimo
75. Sentirsi a disagio quando è solo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
76. Idea che gli altri non apprezzino nella giusta misura i suoi successi	Per niente	Un poco	Moderatamente	Molto	Moltissimo
77. Sentirsi solo e triste anche in compagnia	Per niente	Un poco	Moderatamente	Molto	Moltissimo
78. Senso di irrequietezza tanto da non poter stare seduto tranquillo	Per niente	Un poco	Moderatamente	Molto	Moltissimo
79. Sentimenti di inutilità	Per niente	Un poco	Moderatamente	Molto	Moltissimo
80. Presentimento che debba accaderle qualcosa di spiacevole	Per niente	Un poco	Moderatamente	Molto	Moltissimo
81. Urlare o scagliare oggetti	Per niente	Un poco	Moderatamente	Molto	Moltissimo
82. Avere paura di svenire davanti agli altri	Per niente	Un poco	Moderatamente	Molto	Moltissimo

83. Impressione che gli altri possano approfittare di lei, se lei glielo permette	Per niente	Un poco	Moderatamente	Molto	Moltissimo
84. Pensieri sul sesso che la affliggono	Per niente	Un poco	Moderatamente	Molto	Moltissimo
85. Idea di dover scontare i propri peccati	Per niente	Un poco	Moderatamente	Molto	Moltissimo
86. Pensieri e immagini di natura spaventosa	Per niente	Un poco	Moderatamente	Molto	Moltissimo
87. Pensiero di avere una grave malattia fisica	Per niente	Un poco	moderatamente	Molto	Moltissimo
88. Non sentirsi mai vicino alle altre persone	Per niente	Un poco	Moderatamente	Molto	Moltissimo
89. Sentirsi in colpa	Per niente	Un poco	Moderatamente	Molto	Moltissimo
90. Idea che qualche cosa non vada bene nella sua mente	Per niente	Un poco	moderatamente	Molto	Moltissimo

MSPSS

Id:_____

Data:_____

STUDIO BPS-ARMS (wp4 e wp5)

Istruzioni: di seguito troverà 12 affermazioni (riguardanti i suoi rapporti con amici e parenti) con le quali può essere d'accordo o non d'accordo. Indichi con un segno il suo grado di accordo considerando la seguente griglia.

1= moltissimo in disaccordo
2= molto in disaccordo
3= un po' in disaccordo
4= né d'accordo né in disaccordo
5= un po' d'accordo
6= molto d'accordo
7= moltissimo d'accordo

	Grado d'accordo						
1. C'è una persona che mi è vicina quando ne ho bisogno.	1	2	3	4	5	6	7
2. C'è una persona particolare con cui posso condividere le mie gioie e i miei dispiaceri.	1	2	3	4	5	6	7
3. La mia famiglia cerca veramente di aiutarmi.	1	2	3	4	5	6	7
4. Ricevo dalla mia famiglia l'aiuto morale e il sostegno di cui ho bisogno.	1	2	3	4	5	6	7
5. Ho una persona particolare che è un'autentica fonte di supporto per me.	1	2	3	4	5	6	7
6. I miei amici cercano veramente di aiutarmi.	1	2	3	4	5	6	7
7. Posso contare sui miei amici quando le cose vanno male.	1	2	3	4	5	6	7
8. Posso parlare dei miei problemi nella mia famiglia.	1	2	3	4	5	6	7
9. Ho amici con i quali posso condividere le mie gioie e i miei dispiaceri?	1	2	3	4	5	6	7
10. C'è una persona particolare nella mia vita che si interessa dei miei sentimenti.	1	2	3	4	5	6	7
11. La mia famiglia è disponibile ad aiutarmi quando devo prendere decisioni.	1	2	3	4	5	6	7
12. Posso parlare dei miei problemi con i miei amici.	1	2	3	4	5	6	7

COPE

(Coping Orientation to Problems Experienced)

Id:_____

Data:_____

STUDIO BPS-ARMS (wp4 e wp5)

Istruzioni: il presente questionario ti chiede di indicare che cosa hai fatto e cosa hai provato di fronte alle difficoltà e alle situazioni sfavorevoli che hai appena riportato. Ti chiediamo di rispondere alle seguenti domande utilizzando la seguente scala di risposta.

Non ho fatto assolutamente questo (1)	**Ho fatto questo poche volte (2)**	**Ho fatto questo in misura moderata (3)**	**Ho fatto spesso così (4)**			
1. Mi sono dedicato al lavoro o ad altre attività sostitutive per distogliere la mia mente dagli eventi			1	2	3	4
2. Ho concentrato i miei sforzi nel fare qualcosa per la situazione in cui mi trovavo			1	2	3	4
3. Mi sono detto "questo non è reale"			1	2	3	4
4. Ho fatto uso di alcol o di stupefacenti per sentirmi meglio			1	2	3	4
5. Ho cercato di ottenere un supporto emotivo dagli altri			1	2	3	4
6. Ho rinunciato a cercare di occuparmene			1	2	3	4
7. Ho messo in atto azioni per cercare di migliorare la situazione			1	2	3	4
8. Ho rifiutato di credere che sia accaduto			1	2	3	4
9. Ho detto cose che hanno lasciato venir fuori i miei sentimenti spiacevoli			1	2	3	4
10. Ho cercato aiuto e consigli da parte degli altri			1	2	3	4
11. Ho fatto uso di alcol o droghe per aiutarmi a superare questo			1	2	3	4
12. Ho cercato di vedere la cosa in una luce diversa per farla apparire più positiva			1	2	3	4
13. Sono stato autocritico			1	2	3	4
14. Ho cercato di trovare una strategia per ciò che si deve fare			1	2	3	4
15. Ho cercato conforto e comprensione dagli altri			1	2	3	4
16. Ho rinunciato a tentare di affrontare la situazione			1	2	3	4
17. Ho cercato di trovare qualcosa di buono in ciò che è accaduto			1	2	3	4
18. Ci ho scherzato sopra			1	2	3	4
19. Ho fatto qualcosa per pensare di meno a questo, come andare al cinema, guardare la televisione, leggere, sognare ad occhi aperti, dormire, fare spese			1	2	3	4
20. Ho accettato la realtà del fatto che ciò era accaduto			1	2	3	4
21. Ho espresso le mie sensazioni negative			1	2	3	4
22. Ho cercato di trovare conforto nella mia religione o nelle mie convinzioni spirituali			1	2	3	4
23. Ho cercato di ottenere dagli altri consigli o aiuti su ciò che era necessario fare			1	2	3	4
24. Ho imparato a conviverci			1	2	3	4
25. Ho pensato seriamente a quali mosse fare			1	2	3	4
26. Ho rimproverato me stesso per quanto è accaduto			1	2	3	4
27. Ho pregato o meditato			1	2	3	4
28. Ho messo in ridicolo la situazione			1	2	3	4