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THE BIOPSYCHOSOCIAL APPROACH IN LIVER AND MULTI-ORGAN TRANSPLANTATION: ASSESSMENT OF THE OUTCOME PREDICTORS

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ABSTRACT

Introduction: During all phases of Liver Transplant (LT) process patients tend to develop psychological distress. Aims of the present study were to evaluate psychological variables at the time of evaluation for listing for LT (T0) and enter in the waitlist for LT (T1). **Methods**: We prospectively enrolled patients admitted at the Bologna Transplant Center between 2017 and 2018. Patients were compared with an age- and gender- matched control group. Significant differences between variables were estimated with non-parametric tests. $\chi 2$ or Fisher's exact test was used for categorical variables while Mann-Whitney for continuous ones. Changes between T0 and T1 were analyzed with Wilcoxon Test. A p value less than 0.05 was pondered as noteworthy for all tests. **Results**: We enrolled 50 patients mainly males (68%) with mean age of 57±7 years. A DSM 5 diagnosis was present in one fifth of patients and DCPR syndrome in 44%. Enrolled subjects at T0 showed anxiety, depression and somatic symptoms. In comparison with control group, experimental one displayed lower scores in PCS and MCS of SF-12 (p=0.000, p=0.000, respectively), BC positive refraining, venting, instrumental support, humor, behavioural disengagement, emotional support, self-blame (all $p<0.05$) and in ISEL and PTG Scale (all p=0.000).

Experimental group reported higher scores in the scale of SQ about anxiey, depression, somatic symptom and BC substance use score (all $p<0.05$).

Twenty-five patients were admitted in the waitlist (T1). From T0 to T1, there was an increase of DSM-5 and DCPR diagnosis. At T1 in comparison with T0, we registered higher scores in SQ Hostility subscale (p=0.084) and BC Self distraction (p=0.079). **Conclusions**: Patients in screening for LT show many psychological disorders, often more pronounced than general population. From screening to enter into waitlist, many psychological patterns tend to worsen.

Psychological support and multidisciplinary view might be useful during the transplant process.

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INTRODUCTION

Organ transplantation represents a consolidated therapeutic tool for many diseases. However, transplant recipients often develop psychological distresses such as re-experiencing, avoidance, excitement and sense of responsibility towards donor, clinicians and family members.

Liver transplantation (LT) comprises an articulated clinical process. Candidates waiting for LT display, by definition, life-threatening disorder needing donor organ for surviving. In this context, risk of death waiting transplant is high (4-5% in Italy). When the organ (from living or dead donor) becomes available, candidates must undergo to major and harmful surgery, followed by short or long intensive care unit hospitalization. After LT, recipients should adapt themselves to personalized immunosuppressive protocols and restrictive life-style instructions. Additionally, potentially life-threatening complications such as graft rejection of, cardiovascular disorders and *de novo* extra-hepatic cancer might occur (in major percentages in comparison with general population). As expected, the quality of life (QoL) of subjects in both pre and post-LT period can be negatively modified. Consequently, candidates to LT and recipients are at high risk of both somatization and mood disorders. All these phenomena generally tend to be reduced during the first year after LT worsening later again. Interestingly, both QoL and psychological distress can be reinforced by the continuous medicalization embodied by the life-long immunosuppressant therapy.

It is widely accepted that many social, psychological and psychiatric factors can alter the overall outcome of patients during transplant process. In particular, considering heart and bone marrow transplant recipients, pre-transplant psychiatric and psychological conditions

such as treatment adherence, social supports, coping, seem to influence the post-transplant morbidity and mortality.

Regarding LT, the predictive capacity of pre-transplant psychiatric and psychological factors is nowadays discussed. Seeing the impact of psychological variables on the entire transplant process, major scientific attention should be deserved to this complex topic.

Seeing these premises, with the present study, we tried to focus the chief psychological patterns of the main steps of the transplant process. We started from pre-LT screening and we analyzed the psychological status at the time of enter into the wainting list. Moreover, we projected to analyze the phases after LT (early after surgery and at 3, 6, 12, 24 months).

1. PSYCHOSOMATIC APPROACH AND MEDICAL ILLNESS

1.1 History and evolution of psychosomatic approach

From the beginning of the 19th century, a holistic thought tradition starts, improving the growth of the age known as "romantic medicine". In this period, for the first time, Heinroth introduced the word "psychosomatics" (1). The main idea of this thought was the introduction of a speculative and mystical view with a focus on the unity of body and mind. This period was characterized by a new attentions toward both unconscious and dreams and was reinforced by philosophers like Schopenhauer (1). In particular, in the middle of the century, W. Griesinger and R. Virchow proposed a toughly scientific medicine with remarkable interest for the social aspects (1). From the end of the 19th and the beginning of the 20th century, the scientific debate focused on the relationship between body and mind has begun to spread (2). In this important period, the evolution of philosophy and psychology (W. Wundt, 1896) to medicine was close. Remarkably, philosophical schools of phenomenology (E. Husserl), existence philosophy, hermeneutics (M. Heidegger), psychiatrist (K. Jaspers) and internist (V.v. Weizsäcker), all strongly influenced the development of psychosomatic medicine. The natural consequence was that interdisciplinary scientific method represented one of the principal scientific base of this psychological approach (3). The consequence of the cited work was that in 1907, L.v. Krehl stated: "We do not treat diseases, but sick people" (1). Psychosomatics continued to develop in 30s thanks to the convergence of the two following concepts: psychogenesis and holism (4,5). This confluence represented the very first step of psychosomatics medicine (1930-1960) bringing to the concept of "Psychosomatic disease". This latter ultimately embodies a somatic disorder that takes origin by psychological factors (6).

In the 60s, the contributions of Kissen (7), Engel (8) and Lipowski (9) marked the overcoming of concept of psychogenesis. According to Kissen (7), it is conceivable that a disease previously considered "psychosomatic" might be "non-psychosomatic" and vice-versa. The relative weight of psychosocial actors in the disease's development can easely change even within the same disorder. Therefore, it is not legitimate to consider a disease as a homogeneous entity. Kissen undoubted had the merit of having shifted the question from "what are psychosocial actors in the development of a disease?" to "who are the patient, within a given population with a certain disorders, for which the psychosocial variables are of primary importance?" (10).

In 1977, Engel (11) definitively marked the overcoming of the dualism between psychogenic, psychosomatic and organic diseases proposing the "biopsychosocial"approach. According to this multi-path model, each disorder is the result of multiple biomedical, psychological, social and environmental causes. Disorders are not the result of the simple combination of distinct etiological factors, but of the complex interaction between them. Later, Lipowsky (5) specified the incompatibility of the concept of psychogenesis with the notion of Engel's multicausality and this became the principal postulate of the modern psychosomatic approach (12).

In this renewed cultural context, psychosocial factors can modulate patients' vulnerability and every phases of a disease, from onset to the rehabilitation process. However, their weight may vary according to the type of disease, its phases and the single subject (13).

In general, the personalized and holistic approach should include integration of medical and psychological therapies in all phases of illness.

Interestingly, the growth of subspecialties such as psychooncology and psychodermatology, drives towards the multidisciplinary organization of Health System to overcome artificial borders.

1.2 Main patterns of Psychosomatic Medicine

Psychosomatic Medicine is a wide interdisciplinary field in which biological, psychological, and social factors influence the balance between health and disease (14,11,15,16) .

Psychosomatic approch provides a conceptual framework for the following major issues:

1. to improve scientific investigations on the role of psychosocial factors affecting individual vulnerability, course, and outcome of disease;
2. to enhance personalized and holistic approach with the chief role of psychosocial assessment;
3. to develop the integration of psychological and psychiatric therapies in the prevention, treatment, and rehabilitation of medical disease;
4. to enrich multidisciplinary organization of health care that can overcome the artificial boundaries of traditional medical specialties.

In the past decades, psychosomatic research resulted in an impressive body of knowledge, with scientific contributions published in all major medical journals. The application of this amount of studies has generated several subdisciplines such as psychooncology, psychonephrology, psychoneuroendocrinology, psychoneurogastroenterology, behavioral cardiology, psychoimmunology, psychodermatology, and others (e.g. transplant psychology). Clinical services, scientific societies, and medical journals grow as natural consequence (17)

The Diagnostic Criteria for Psychosomatic Research (DCPR) can help to translate the psychosocial variables that came from psychosomatic research, into working tools. The

DCPR, introduced in 1995 (18) can be useful in many clinical settings. Their value in the psychosomatic assessment, regardless of the 'organic' or 'functional' nature of the illness, has been widely documented (19-21).

Many factors seem to modulate the individual vulnerability to disease. In particular, the role of early developmental factors in the disorders' susceptibility has been a frequent subject of psychological reseach (22). In fact, the stressfull life events may be followed by many health issues. The introduction of structured methods of data collection and control groups, has allowed to confirm the strong association between life events and medical disorders such as endocrine, cardiovascular, respiratory, gastrointestinal, autoimmune, skin, and neoplastic disease (23,24) .

McEwen (25) proposed a formulation of the relationship between stress and the processes leading to disease based on the concept of allostasis that is the ability of the organism to achieve stability through change. According to this view, allostatic load reflects the cumulative effects of stressful experiences in daily life.

In particular, behaviors that can more often impact the health, concern physical activity, diet, sleep, smoking, drinking, and drug consumption. These behavioral factors are interrelated and can have a synergistic effect on both morbidity and mortality (26,27). It must be underlined that to achieve a wide change of an unhealthy behavior is particuarly difficult. For instance, about 75% of patients with cardiovascular diseases were unable to change their bad habits despite the fact that they were informed about the risk factors (28). Indeed, knowledge about the risks associated with health-damaging behaviors is not necessarily associated with their avoidance.

Social relationships such as social network composition, social support, frequency of social interactions, and the experience of loneliness and isolation have been clearly associated to

both physical and mental health (29). In this way, prospective studies substantiated the role of social support in relation to mortality, psychiatric and physical morbidity, recovery, and adjustment to chronic disease (30). Interventions designed to improve the social environment and interpersonal relationships, are effective in facilitating psychosocial adjustment to medical disorders (30).

Religiosity and spirituality (broadly defined as any feelings, thoughts, experiences, and behaviors that arise from the search for the 'sacred') have been a matter of growing interest in epidemiological research (31). Remarkably, religiosity displays positive effect on survival independently from behavioral factors, negative affect, and degree of social support (31,32).

Assessment of psychosocial factors potentially influencing individual vulnerability to illness is often omitted by the primary care physician or the medical specialist (16). This is the result of a reductionist approach that has deeply influenced medicine (16,33,34,23,11,35).

Psychosocial variables affecting illness vulnerability may encompass a temporal relationship between life events and symptom onset or relapse; the presence of grief reactions, including the loss of a body part or bodily function; the perception by a person of environment as exceeding his/her resources (i.e. allostatic load/overload). Patients often deny a relationship between their allostatic load and symptomatology. In fact, they are unaware of the latency between stress accumulation and symptom onset ("I had bowel symptoms yesterday, which was an easy day at work, and not the previous days, which were awful"). Interestingly, symptom worsening during week-ends and vacation time is a common manifestation of this latency (36); interpersonal relationships providing a buffering role for stress; psychological assets and well-being.

The modality of information may be crucial in managing patients with unexplained somatic symptoms (37) to avoid difficult patient-doctor relationships (38).

Psychosomatic medicine pioneered the self-rated evaluation of psychological status in medical conditions (39).

Rating scales such as the Symptom Check List 90 (40), the Hospital Anxiety and Depression Scale (41), and the Symptom Questionnaire (42), were extensively used in medical settings (43). Evaluations of distress and wellbeing anticipated interest in quality of life assessments and patient-reported outcomes. Notably, there are poor data about definition of quality of life. Indeed, research in this area seeks essentially two kinds of information: the functional status of the individual and the patient's appraisal of his/her own health. Indeed, the subjective perception of health status (e.g. lack of well-being, demoralization, difficulties fulfilling personal and family responsibilities) represents a relevant element that can influence the patients' outcome (44-46). Psychosomatic and clinimetric approach emphatize the relevance of patient-reported outcomes (47). In this way, any report coming directly from patients about how they function or feel in relation to a health condition or its therapy is important (48,49).

Psychiatric illness appears to be strongly associated with physical diseases. Mental disorders increase the risk for communicable and noncommunicable diseases and many health conditions increase the risk for mental disturbances. Notably, comorbidity can complicate recognition and treatment of medical disorders (50). Furthermore, psychiatric disturbances can worsen the course of medical disease in terms of response to treatment and prognosis (50,51).

The main levels of psychosomatic intervention are the following:

1. prevention strategies and health behavior modifications: switching the general population to healthy lifestyles would be a major source of prevention for the most prevalent conditions such as diabetes, obesity, and cardiovascular illness (52-55);

2. type of approach to patient care;

3. specific psychotherapeutic and psychopharmacological management in the setting of medical disease (fava1).

Finally, there have been major transformations in health care needs (56-58). The traditional medical specialties, based mostly on organ systems (e.g. cardiology, gastroenterology), appear to be more and more inadequate in dealing with symptoms and problems that cut across organ system subdivisions and require a comprehensive approach.

Multidisciplinary services have been developed within specialties and subspecialties such as oncology, cardiology, dermatology, gynecology, nephrology, gastroenterology, organ transplantation, and endocrinology (59-62). Such services may be operated by various specialists (group approaches) or by a single specialist with a multidisciplinary background. These services are addressed complaints that fall between disciplines and require a psychosomatic approach.

2. LIVER AND MULTI-ORGAN TRANSPLANTATION PROCESS

2.1 Evolution of liver transplantation

Transplant process includes selection of candidates, long waiting, major surgical act, fine immunological balance between transplanted tissue or organ and recipient. Seen the complexity of this process, it is not surprising that transplantation needed decades to develop and to become a consolidated life-saving surgical act. History of transplantation began in 1968, when Sir Roy Calne completed the first human orthotopic liver transplant (LT) in Europe (Cambridge) (63). Few months later, in North-America, Thomas Starzl made the first effective human LT (64). Then, LT quickly advanced becoming the leading therapy for both acute and chronic liver failure, with more than 100,000 procedures performed (data from European registry: http://www.eltr.org).

According to the conventional or ‘‘Standard” LT technique (whole liver graft), the liver graft is implanted in the right upper quadrant, in the place previously occupied by the diseased liver. The surgical technique differs according to whether or not the recipient’s inferior vena cava (IVC) is conserved. In most European countries, the piggy-back technique is employed, which involves the preservation of the native IVC (65). Anastomosis of the donor’s suprahepatic IVC to the recipient’s three hepatic veins is made (Figure 1), as well as rebuilding of the portal vein, hepatic artery and biliary tree, using duct-to-duct anastomosis between the donor’s main biliary tract and the recipient’s one (66). When the recipients IVC cannot be well-preserved, this surgical procedure includes vascular reconstruction with end-to-end anastomoses.

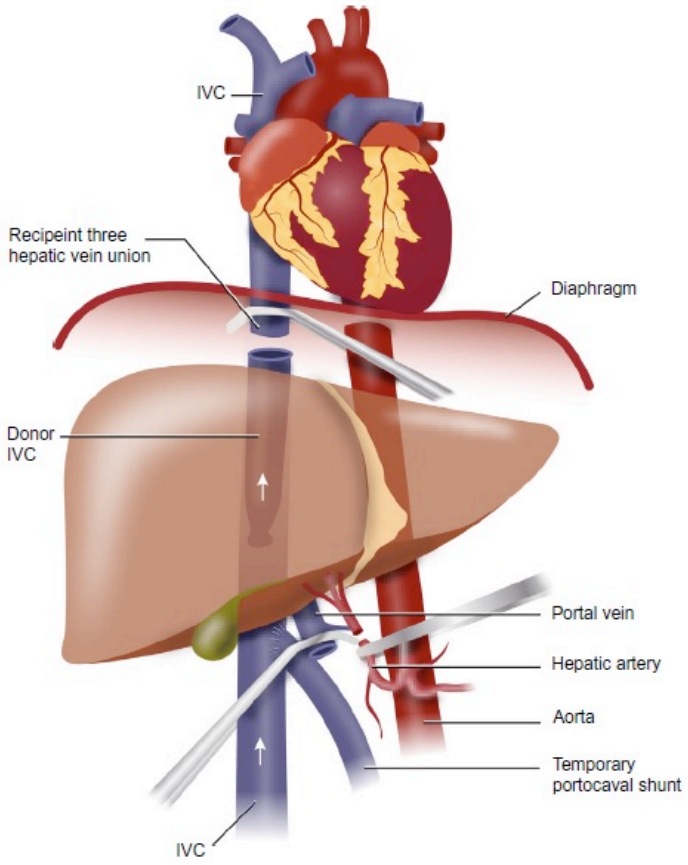

Figure 1. Liver Transplantation with piggy-back technique. Anastomosis of the recipient three hepatic vein union with the donor inferior vena cava (IVC).

LT is indicated in patients with end-stage liver disease, in patients with hepatocellular carcinoma (HCC) and in subjects with acute liver failure. In particular, cirrhosis represents the most common indication for LT worldwide (in adults). The main indications for LT in Europe are reported in Figure 2 (67).

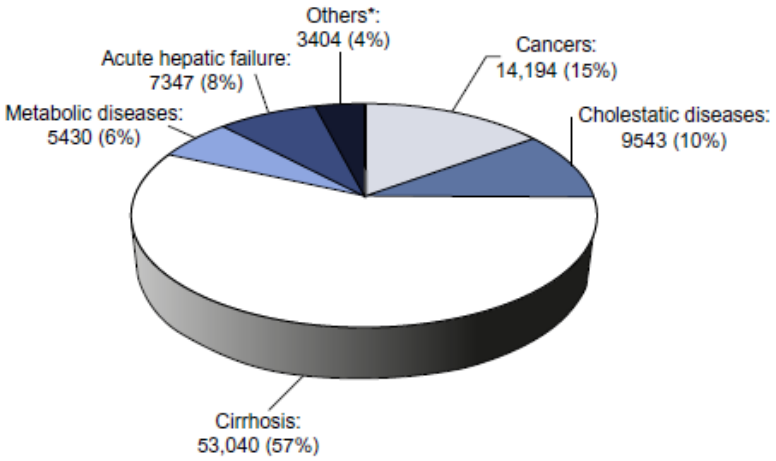

Figure 2. Primary diseases leading to liver transplantation in Europe (time period: year 1988-2011) (data from European registry: http://www.eltr.org). *Others: Budd-Chiari: 792. Benign Liver Tumours or polycystic disease: 1228. Parasic diseases: 80. Other liver disease: 1304.

In particular, in the last 25 years survival percentages considerably increased. Today, we can register an overall 1-year survival of 96% and a 10-year survival of 71% with some differences according to the etiology of liver disease (Figure 3) (68).

Primary indication of liver transplantation	Number of patients	Percentage within the group	5-year survival (%)	10-year survival (%)
Chronic liver diseases	66,808		74	64
Alcoholic related cirrhosis		27.6	74	60
Virus C related cirrhosis		18.9	65	53
Virus B related cirrhosis		7.2	75	69
Virus D related cirrhosis		2.3	89	85
Primary biliary cirrhosis		7.5	80	72
Malignant tumours	15,197		60	47
Hepatocellular carcinoma		86.5	63	49
Cholangiocarcinoma		2.8	31	23
Metastases		3.9	49	31
Acute liver diseases	7585		64	59
Metabolic diseases	5699		79	71
Benign tumours	1317		83	76

Figure 3. Overall result in liver transplantation by indication (data from European registry: http://www.eltr.org).

These great achievements represent consequences of continues surgical, clinical and pharmacological advances (69). In these last years, indications for LT have been expanded considering the efficacy of this therapeutic approach but organ shortage and the consequent high waitlist mortality are actually the true challenges of the transplant community.

2.2 Clinical issues of liver transplant process

Main aim of LT should be to lengthen life expectancy beyond the natural history of underlying liver disease (with achievement of so called "transplant benefit") but also to improve patients' quality of life (QoL). Patients should be designated if estimated survival in the absence of LT is 1 year or less, or if the patient had an unacceptable QoL because of liver disease. A detailed medical evaluation is performed to ensure the feasibility of LT (pre-LT screening).

The ideal moment for referring patients to Transplant Center is the first decompensation of liver disease (variceal bleeding, ascites, hepatorenal syndrome and encephalopathy). On the other hand, acute liver failure is an urgent indication to LT (70).

The timing of LT is a main clinical point. In fact, patients with end-stage liver disease should be transplanted before some life-threatening systemic complications occur. At the same time, candidates should not be transplanted too early (for the risk of not substantial transplant benefit).

In the past years, priority on the waiting list was based mainly on the waiting time. This not objective criterion, since 2002, was replaced by the model of end-stage liver disease (MELD) score (based on objective measures such as creatinine, bilirubin and international normalized ratio) (71). The MELD represents a very good index of three-month mortality. Indeed,

according to this system actually used in the vast part of Transplant Center, patients' priority depends only by disease severity (72). Remarkably, in subjects with MELD <14, 1-year survival was lower with LT than without it (73). Consequently, a MELD score >15 is indicated to list patients with cirrhosis. On the other hand, very sick patients (MELD >30) both morbidity and mortality are very high making indication to LT at least doubtful.

MELD score influences the allocation of grafts in many European countries including Italy. Nevertheless, the definitive decision for allocation has to be based on many further parameters besides MELD including liver-donor match and local-regional allocation systems.

Hepatitis C virus (HCV)-related liver disease represents the main indication for LT worldwide. Today, with development of new direct-acting antivirals, anti-HCV therapy is highly effective and safe. Indeed, at least in developed countries, in the next years HCV will tend to decrease as indication for LT (74). In particular, the HCV replication at the time of LT, does not represent a contraindication, but antiviral treatment will be indicated as soon as possible after surgery.

Alcoholic liver disease represents the other most common indications of LT in Western countries (75). LT for alcoholic cirrhosis has a favourable outcome, similar or better than other aetiologies (76). Several centres developed an evaluation process based on medical and psychiatric criteria to better determine patients that would mostly benefit from the LT. Alcohol abstinence of at least 6 months in order to evaluate the need and timing of LT and to obtain a better control of alcoholism, is usually required (the so called "6-month rule"). This interval is neither a consensus nor an absolute requirement. The risk of alcohol use recidivism is estimated between 15 to 40% depending on the series and how recurrence of alcoholism is defined. If the risk of recurrence might be related to the length of abstinence is debated (77). The interest of the 6-month abstinence rule is double: a) abstinence can lead to significant

improvement of liver function avoiding the need for transplantation; and b) this period of abstinence is an opportunity to assess the patient compliance and to build a whole psyco-social process of support. However, there are strong limitations to this rule: a) the duration of abstinence before LT was not found to be related to the risk of recidivism in many studies; b) the improvement in liver function occurred mainly during the first three months of abstinence; c) during this period some patients with no risk of recidivism will die; d) several authors and today the main scientific associations guidelines, consider that the risk of recidivism is more related to psychosocial factors than to the duration of abstinence itself. Therefore, the most of scientific community has advocated breaking the 6-month rule for selection of canidates (78).

Acute alcoholic hepatitis (AAH) has been considered an absolute contraindication to LT on the grounds that patients with this disorder have been drinking recently and that period of abstinence will allow many to recover. Unfortunately, many patients die during this time interval. Patients who do not recover within the first three month abstinence are unlikely to survive (79). If the AAH is severe (Maddrey's score >32), treatment with steroids can improve the outcome (80). The Lille score allows an evaluation at day 7 after therapy introduction, if it is over 0.45, the expected survival is below 30% at 6 months (81).

In a recent multicentre French study, patients with first episode of severe AAH resistant to steroids, favourable psychosocial environment and good addiction disease consultation, have been transplanted resulting with a dramatic improvement in survival in comparison to their spontaneous expected survival. Moreover, at 2 years from the LT, a low rate of recidivism has been registered (82). This study needs confirmation before achieving a consensus on the indication of LT in relation with abstinence duration. However, it emphasises the significance of psychosocial management of these patients to ensure long-term success of LT.

In the setting of the metabolic or insulin resistance syndrome, NAFLD (Non-Alcoholic liver desease) and NASH (Non-alcoholic steatohepatitis) are becoming increasingly common medical problems in the developed world. Therefore, NASH-related cirrhosis is today a new strong indication for LT (83).

2.3 Psychological and psychiatric aspects

Transplantation must be intended as a complex process made up of different phases which include communication with the patient (and family); the permanence on the waiting list (of varying length); the post-operative hospitalization period and the short-, medium- and long-term post-discharge day care check-up.

Transplanted population shows changes in their relationships with family members and medical staff since they tend to experience the ritual of death and the rebirth to a new life (84). In particular, regaining physical integrity is often complex because patients show difficulties in accepting the new organ as part of the own body and not as a separate identity. Returning to physical activity, social relationships and work after transplant may be associated with psychopathological distress (85,86).

Indeed, the goal of transplantation should not be only to enhance patients' survival, but also to offer the same state of health that they enjoyed before the onset of liver disease. This complex achievement can be reach through a balance between the functional efficiency of the graft and the patient's psychological and physical integrity (87,88).

Organ transplantation is no longer a novel event in many societies. Indeed, social constructions in relation to transplantation itself have emerged in both the medical world and the wider community. It would be important to conceive the transplant as an exchange and a sort of gift. In this way, we can reinforce the idea of donated organ as "gift of life" (89). Fox

and Swazey argued that this concept has become so pervasive that it can be considered the basis for the foundation of all transplantation discourses rest (i.e., medical, organ procurement agencies, and the general public). Many authors reported that the concept of transplant as a gift fails to encompass the myriad psychosocial complexities involved in the transfer of an organ from one person to another (90,91). Shaw (92) suggested that gift-of-life rhetoric might lead recipients to develop a sort of material estimation of transplant experience instead of a true elaboration of the transplant itself.

Some authors suggested that donor organs might be better thought of in a different light, perhaps as donations rather than gifts (93). Both understandings are found in social discourses around organ transplantation. Even though this distinction might seem purely semantic, we contend that it has relevant implications. O'Brein (94) developed an interview analysis of 13 heart transplant patients with the main aim of exploring how the lived experiences of organ transplantation can be grounded in social discourses about organ donation, gift of life, and gratitude. Authors reported that there are relevant differences between organ-as-gift and organ-as-donation. In particular, the concept of organ-as-donation can favor the post-transplant gratitude and, ultimately, the development of meaning(s) gleaned from the transplant experience.

2.3.1 Pre-transplant psychosocial status

LT recipients can develop many psychological distresses such as re-experiencing, avoidance, excitement and sense of responsibility toward donor, clinicians and family members (95-99). In particular, LT includes a complex and articulated clinical process (98). Candidates waiting for LT by definition present life-threatening disease needing donor organ for surviving

(100,101). When the organ becomes available, patients undergo major surgery and then they have to bear short or long intensive care unit hospitalization. After LT, recipients should adapt to immunosuppressive drugs and restrictive life-style rules. Furthermore, potentially life-threatening disorders such as graft rejection, cardiovascular diseases and *de novo* extra-hepatic malignancies might occur. As expected, the QoL of patients in both pre and post-LT period can be negatively altered (102). In this regard, we reported in Figure 4 the main factors altering the QoL of patients in both pre- and post-LT period.

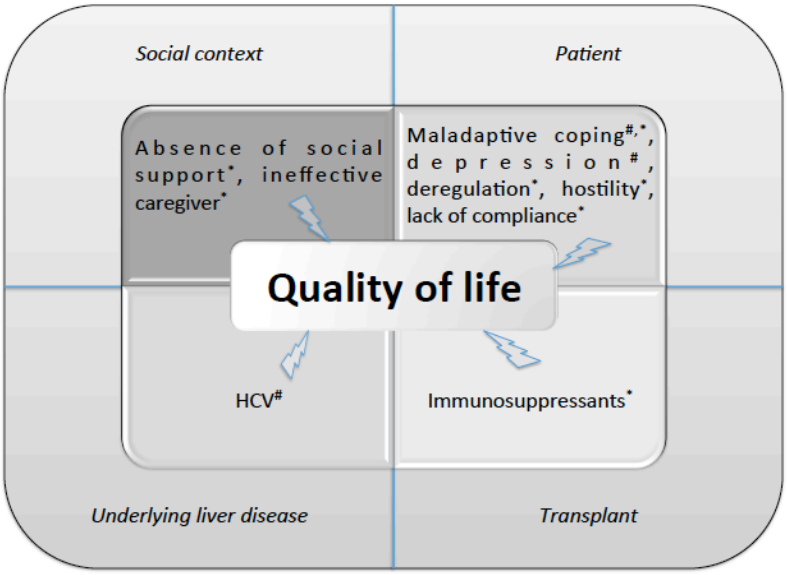

Figure 4. Main factors influencing the quality of life of patients during the transplant process. We detected the following main macro-categories: social context, patient psychological patterns, underlying liver disease and features correlated to transplant. Hashtag indicates the effect on pre-transplant quality of life; asterisk, on post transplant quality of life. HCV, hepatitis C virus.

Figure from: Golfieri L, Gitto S, Vukotic R, Andreone P, Marra F, Morelli MC, Cescon M, Grandi S. Impact of psychosocial status on liver transplant process. Annals of Hepatology 2019.

Becouse of the same considerations, candidates to LT and recipients are at high risk of both somatization and mood disorders. All these conditions tend to be attenuated during the first year after LT worsening later again. Interestingly, both QoL and psychopathology can be reinforced by the continuous medicalization well embodied by the immunosuppressive drugs (103). In particular, social, psychological and psychiatric factors might impact the overall prognosis of transplant recipients (104,105,85). Considering the LT setting, the predictive capacity of pre-transplant psychiatric and psychological factors is actually debated.

During the pre-LT screening process, social, psychological and psychiatric assessments are usually conducted. The aim is to exclude major psychiatric illness (such as schizophrenia) and to analyze the possible lack of adherence associated to active illicit drugs use, active alcohol consumption and deficiency of social support (106,107).

The etiology of liver disease is a relevant risk factor for impairment QoL and mental disorder. It is well known that HCV can alter the QoL showing deleterious impact on mental health and physical well-being (108,109). HCV positive patients tend to develop fatigue, irritability, general disconfort, abdominal pain, joint pain and headache that may impact psychological status and particularly QoL (110,111). HCV negatively modifies the post-LT condition since HCV positive recipients can show higher rates of depression symptoms in comparison with other etiologies (112). Also subjects with alcohol-related liver disease deserve specific selection. In fact, alcohol use disorder (AUD) is associated in about 30% of cases with a mood disorder (113,114). In particular, the presence of negative and passive coping behavior such as anacceptance-resignation strategy is a main reason of mental health weakening leading to an altered insight of physical functioning and a drop of global QoL (115).

2.3.2 Impact of psychological distress on post-transplant outcome

In the immediate post-transplant period, many psychiatric problems can arise which may necessitate the involvement of the psychiatrist/mental health professional. Delirium (also referred to as encephalopathy) is reported to be the most common neuropsychiatric problem after the transplant surgery (116-118). It is characterized by confusion, disorientation, fluctuation in consciousness and agitation, and poses as a management difficulty in the intensive care unit. Development of encephalopathy has been associated with higher rates of mortality (118). The causes of delirium can be varied in a patient of LT and may include concurrent brain pathological processes, e.g. infection or bleed; effects of vasoconstriction secondary to immunosuppressive medications (especially cyclosporine and Tacrolimus); and central nervous system pharmacodynamic effects of the immunosuppressive medications (119). Evaluation of delirium during this period of time must include careful medical examination of the patient and review of the medications and laboratory studies. Neuroimaging, EEG recording, and lumbar puncture can also provide valuable information in evaluating the cause of delirium (120).

In the context of organ transplantation, depression is surely the most studied mental disease. Considering the general population, depression represents not only a significant determinant of QoL (121) but also a relevant predictor of increased clinical burden and poor treatment adherence (122). Few studies are accessible about pre-transplant psychological predictors of post-LT outcome and particularly on the possible role of pre-LT depression. However, depression is present in 15% of candidates waiting for LT (123).

Kanwal (124) showed that cirrhotic patients with low QoL display worse survival respect to the others, even after adjusting for solid clinical factors such as MELD score. Authors

demonstrated that different levels of Short Form Liver Disease Quality of Life independently predicted overall patients' mortality. Interestingly, patients with pre-LT depression-like symptoms show high risk of post-LT overt depression (125). Young age, lack of spouse and unemployment were predictors of post-transplant depression (126). Also other psychological alterations can negatively impact the post-LT mental health. Pre-LT anxiety and neuroticism were associated with worse psychosocial outcome at 1 year from the transplant (127). Pre-transplant vulnerability can forecast the onset of mental status distress after transplantation (128). Additionally, pre-LT maladaptive coping mechanism, disregulation, hostility, lack of effective social support, were associated with worse QoL and mood at 1 year after transplant (129). Corruble (130) demonstrated that depressive symptoms on waitlist were associated to 3- to 4-fold increase risk of graft failure and mortality, independently from all the other main drivers of post-LT outcome such as age, gender or primary liver disease diagnosis. Interestingly, as possible clarification, the authors suggested that transplant recipients with depressive symptoms might be better competent to face psychological distress that commonly arises after transplant. On the other hand, Rogal et al. (131) reported that pre-LT depression did not directly influence theclinical outcome in terms of graft rejection and mortality. However, patients with depression needed more often psychiatric support in the post-LT period (37% vs. 18%). Moreover, patients on effective antidepressant therapy at the time of transplant displayed lower rate of acute cellular rejection in comparison with untreated patients (13% vs. 40%). Indeed, authors suggested that underestimated or untreated depression could harmfully impact the post-LT clinical outcome. The same authors (132) reinforced the message analyzing the long-term transplant outcome proving that the efficient treatment of psychiatric condition might influence patient survival more than the consolidated predictors such as HCV clearance, low MELD score and young donor age. Telles-Correia

(133) showed that pre-transplant solid social support was a significant predictor of 1-year post-LT survival while presence of pre-LT neuroticism was associated with higher post-LT mortality.

2.3.3 Transplantation as opportunity: the post-traumatic growth

After transplantation, according to some authors patients felt a new life and believed that the new organ gave them a new opportunity. According to other studies, patients passed through various phases after surgery the so-called "phases of toleration to the disease." Facing the disease and reformation occurred after transplantation (134). However, according to the study by Kaba, patients can accept the new organ with relevant difficulties (135).

It was found that transplanted patients had more time to spend with their family members and children in the in comparison with the past. After transplantation, they happily spend their time to meet their family members' needs (136).

The patients experienced a fruitful period of life after transplantation, returned to work, increased the level of their activities and enjoyed their life. In particular, patients' abilities to return to normal life and recover from the disease improve spiritual well-being and enjoy life after transplantation (137).

Under these circumstances, the concept of post-traumatic growth, which is the idea that stressful life events may create the opportunity to activate one's resources, leading to a higher level of functioning than before, is highly relevant. This concept, developed by Tedeschi and Calhoun (138) is associated with the positive psychology movement. Basically, post-traumatic growth can be a protective factor (138,139) that enables patients to reframe threats into challenges, thereby strengthening their psychological wellbeing (140,135). Previous studies found high levels of post-traumatic growth after lung transplantation (141) that was even higher than those observed in patients suffering from chronic heart disease, cancer or

HIV. High levels of post-traumatic growth have also been found after haematopoietic stem cell transplantation (HSCT) (142). However, lung transplantation and HSCT have markedly lower survival rates than LT (136) that may have important implications regarding traumatisation as well as post-traumatic growth. To the best of our knowledge, there are only two previous studies dealing with post-traumatic growth in LT recipients (140,135).

Anand-Kumar et al. (143) reported that transplanted patients perceived "advantages" from the transplantation experience accordingly with PTG. In particular, the transplantation experience underlies a change in life philosophy, self-perception and relationships with others (143,144). Within the field of post-traumatic growth, changes in life philosophy might reflect a modification in the perception of life itself (increased appreciation of life, family and friends, increased spirituality) (145). According with the PTG Theory, overcoming a stressful life-event, such as undergoing an organ transplant, can give the opportunity to improve the ability to relate with others and improves the sense of gratitude (146).

Scientific literature reported that some patients attribute an improvement in the perception of their own physical and mental health, along with a greater awareness in the management of these topics, to the transplantation experience. These elements represent a core component of the PTG: augmentation of personal strength and improvement of the capability of overcoming the specific challenges posed by the trauma. Surviving such traumatic experiences may promote planning abilities and the development of strategies for handling life-threatening negative events in the future, such as rejections, recurring infections, immunosuppressant therapy side-effects, re-transplant (145).

Speaking about the relationship between PTG and transplant, Tallman (147) observed a group of marrow transplant patients reporting high levels of physical, spiritual and psychological well-being as well as PTG, connected with factors like female gender, older age, levels of optimism and the presence of social support.

In a longitudinal study, Scrignaro et al (148) used a sample of 100 LT patients from the outpatient population. Participants filled in the Posttraumatic Growth Inventory (PTGI) and group identification scales at two different times 24 months apart. The results showed that post-traumatic growth positively predicted identification with the family group and the transplantee group over time. Zięba (149) examined 48 LT recipients about 10 weeks after surgery. Recipients told two stories about freely chosen important events in their lives. The measurement of post-traumatic growth 10–12 months later showed that the affective tone of the narratives was associated with the level of post-traumatic growth, and that positive affective tone was related to greater post-traumatic growth.

Both studies unveiled potentially important mechanisms by which post-traumatic growth may positively affect well-being. However, the association of post-traumatic growth and QoL which is of central importance in the present study, was not dealt with in those papers.

Post-traumatic growth is also highly relevant for close relatives, particularly caregivers of the LT recipient, who is dependent lifelong on medical care and intensive social support. In this setting, the caregiver is confronted with the profound impact of LT on his or her personal life and its challenging implications (150,151). There is growing evidence regarding the great amount of stress in caregivers before and after LT, which may even result in symptoms of post-traumatic stress (152,153). The close mutual relationship between transplant recipient and caregiver makes it understandable that caregiver stress may also negatively affect the patient's AoL and therapy adherence.

Pérez-san-Gregorio MA (154) demonstrated that regardless of the time elapsed since LT, recipients showed more post-traumatic growth than their caregivers. A high level of post-traumatic growth was associated with high levels of specific aspects of QoL such as vitality, whereas a longer time span since transplantation was related to more pain. Compared with the general population, recipients generally showed lower quality of life, except in patients with high levels of post-traumatic growth. In these cases specific dimensions of quality of life, such as bodily pain, vitality, mental health and general health, equalled or even surpassed scores in the general population. Facilitation of post-traumatic growth after LT may be crucial to ensure long-term quality of life in recipients.

2.3.4 Immunosuppressive drug adherence

The lack of compliance can negatively alter both QoL and clinical outcome of transplant recipients. In fact, it is the most important driver of graft rejection (155). Correct selection of candidates to organ transplant estimates the compliant behavior before surgery (155). In particular, a psychotherapeutic support program for candidates to LT might increase the compliance to medical issues thanks to more efficient adaption to the transplant process (156). However, data about the predictive ability of pre-LT psychosocial condition regarding the immunosuppressive therapy adherence are discordant. Rodrigue (157) reported that pre-LT both mood disorder and social support instability amplified the risk of non-adherence. More recently, Lieber (158) reported high rates of inadequate compliance (50%). However, none of the pre-LT psychosocial patterns were able to predict neither non-adherence nor rejection.

2.3.5 Role of psychologist in the transplant process

The pre-LT psychological evalutation might be significant for the evaluation of LT candidacy and for the enhancement of post-LT clinical outcome (106). Candidates on waitlist often develop fears related to surgery and depression symptoms that can negatively affect functional capacity, social context, economic situation, global mental health status and post-LT outcome (159). The presence of pre-LT mood disorder, the lack of social support, the substance misuse and the alcohol habit, can predict a worsening of post-transplant mental and physical morbidity (160). In this context, targeted psychological intervention can help to support the recovery process improving QoL and observance to clinical indications (159). Moreover, psychosocial interventions can help patients to reduce illness-related fear but also symptoms of anxiety and depression (161). Outstandingly, the psychological intervention has to be fully integrated in a multidisciplinary clinical approach with the participation of all the main professional figures of the LT process (surgeons, hepatologists and psychologists) who should collaborate, interchange information and face together the chief clinical events of the transplant process. In particular, in the context of LT, only a total intervention results to be effective as diagnostic and therapeutic tool (155). The psychological support and care can be instruments for early diagnosis and fast treatment but also elements of empathy toward the entire clinical transplant team. In this way, the medical approach alone might favor the development of negative psychological reactions such as somatization (159). One of the main aims of the transplant psychologist should be the achievement of active coping strategy. As just reported, coping can be defined as all capacities used to face stressful circumstances. The assessment of coping strategies should be studied during the transplant process encouraging patients to use of action-oriented methods and discourage the passive reactions that negatively alter the prognosis (162,163). Telles-Correia (133) demonstrated that active coping is a

significant predictor of short hospitalization after LT. Active coping, social support and multidisciplinary approach might help patients to acquire psychological positive change after LT (164). The relevance of social support has been confirmed in many transplant settings including LT (147). LT candidates with anxious family members tend touse to a lesser extent effective coping strategies such as active fight-ing, self-control/emotional control and seeking for social support (165). Caregivers of LT candidates often show psychological problems and stressors such as doubts about emergency situations (42.6%), mood swings (29.5%), food and medications (27.9%). In general, a quarter of the caregivers feel themselves inadequate/insufficient for their role. Seeing the relevance of the social support, sustenance measures and caregiver-dedicated training should be applied in all transplant centers (166). Multidisciplinary team should help patients to develop positive attitude toward transplant process. In particular, transplant recipients should get a post-traumatic growth that is a positive psychological modification consequent to an adverselife experience. Pérez-San-Gregorio (162) analyzed the predictors of post-traumatic growth (assessed with Posttraumatic Growth Inventory) in LT recipients demonstrating that active coping, instrumental support, emotional support and acceptance, were associated to a major growth. Transplant surely is a stressful event but it can lead to major confidence in own capacities particularly regarding the management of difficulties. Organ transplantation can favor the aptitude to organize and plan the everyday activities and facilitate new adaptive strategies (167). Again Pérez-San-Gregorio (168) studied the post-traumatic growth of caregivers of LT recipients. The authors demonstrated that, also in the caregivers, positive coping strategy correlated with a better post-traumatic growth.

3. THE BIOPSYCHOSOCIAL APPROACH IN LIVER AND MULTI-ORGAN TRANSPLANT : ASSESSMENT OF THE OUTCOME PREDICTORS

3.1 Introduction

LT represents the treatment option for patients with acute liver failure, end-stage liver disease, and HCC (169). Today, thanks to the effective use of immunosuppressant drugs, the growing surgical techniques, and the continuous improvement of post-surgery management, satisfactory 5- and 10-year survival rates after LT can be reached (f.e. for alcohol-related cirrhosis, 74% and 60%, respectively) (170-173).

Notably, LT process can often lead to psychological distress (174-176). In the last years, the scientific and clinical attention toward the mental health status of patients into the Transplant Program is increasing (177). In patients waiting for LT, commonly encountered mental disorders include substance abuse and anxiety (178). After LT, psychological diseases such as depression and stress disorder can affect both drug adherence and QoL (179). Ultimately, LT-related mental diseases can affect the clinical outcome of patients receiving LT (132).

Psychosomatics research highlighted how psychosocial factors may have a predictive value regarding to clinical outcome of LT recipients (180).

Clinical studies reported that pre-transplant psychological and clinical variables (such as compliance, life-style, social support, coping, presence of anxious-depressive suffering) might predict the psychosocial prognosis and influence both post-LT morbidity and mortality (181-182).

Some authors claimed that the pre-LT psychological distress and psychiatric condition may be predictors of insufficient psychosocial adaptation (181-183), organ rejection (184) and mortality (184-186,112).

In a clinical context where the life-long immunosuppressant therapy represents the backbone of the medical therapy, compliance represents a noteworthy clinical challange. Moreover, inter-specialist cooperation is an essential therapeutic element in the transplantation surgery framework (155).

3.2 General study Design

The study should have included several steps. The first time point was the screening evaluation for the LT (T0). Subsequently, enrolled patients should be re-evaluated during the following phases: at the signing of the Informed Consent for the active insertion in the waiting list (T1), soon after the LT (T2), and at 3 (T3), 6 (T4), 12 (T5), 24 months (T6) form the LT. In addition, the test sample was compared (at T0) with a group of subjects selected from the general population to assess the psychological impact of pre-LT screening.

The identification of psychosocial variables that can impact the long-term clinical outcome may represent a starting point for the design and implementation of psychological-clinical support strategies for patients into the tranplant process.

We speculated that pre-LT psychological distress and psychiatric disorder might decrease compliance to therapeutic protocols (pharmacotherapy, life-styles) with consequent negative impact on both morbidity and mortality.

Furthermore, we hypothesized that positive psychological indices, such as post-traumatic growth and gratitude, can be connected to a better psychological-clinical adaptation toward the LT.

3.3 Study 1

3.3.1 Objective

The objective of the study 1 was to evaluate psychological and psychosomatic distress, coping, social support, QoL, post-traumatic growth and sense of gratitude at the time of evaluation for listing for LT (T0 time point). Moreover, to compare enrolled patients at T0 and subjects selected from the general population (control group).

3.3.2 Methods

- *Study population*

The study was conducted on 2 samples of subjects:

- consecutive patients admitted at the Liver Transplantation and Multiorgan Organ Transplants Unit (Prof. M. Cescon) and Medicine for the Treatment of Severe Organ Failures (Dr MC. Morelli) - S. Orsola Hospital (Bologna, Italy) for screening to enter in LT waiting list between June 2017 and June 2018;
- control group coming from general population (matched for gender, age and sociodemographic variables).

Patients are consecutively enrolled after signing the informed consent.

We established the following exclusion criteria (conditions that make the psychological evalutations unfeasible):

- hepatic encephalopathy (degree ≥2 according to the "West Haven criteria" (173);
- Mini Mental State Examination (MMSE) <24 (187);

- Schizophrenic spectrum disorders and other psychotic disorders in active phase according to the Diagnostic and Statistical Manual of Mental Disorder fifth edition (DSM-5) diagnosis performed by a psychiatrist as required by the evaluation protocol for inclusion in the waiting list.

- *Psychometric assessments*

All subjects have been informed about the purpose of the research before giving their informed consent. All participants received a battery of psychometric tests consisting of a heteroevaluation amd self-evaluation.

The heteroevaluation consist of:

1. The structured clinical interview from DSM 5 (SCID 5). The SCID-5 is organized into diagnostic modules, and it assesses mood disorders, psychotic disorders, substance use disorders, anxiety disorders, obsessive–compulsive and related disorders, eating disorders, somatic symptom disorders, some sleep disorders (i.e., insomnia and hypersomnolence disorders), "externalizing disorders" (i.e., intermittent explosive disorder, gambling disorder, and adult attention deficit hyperactivity disorder), and trauma- and stressor-related disorders. It was used a version for clinicians (SCID-CV). (188).
2. The structured interview according to the Diagnostic Criteria for Psychosomatic Research (DCPR). The DCPR are a set of 12 psychosomatic syndromes whose prognostic role in the development, course and outcome of physical diseases, regardless of their 'organic' or 'functional' nature, was documented by a large body of literature. Eight of them refer to the concept of abnormal illness behaviour: persistent somatization, functional somatic symptoms secondary to a psychiatric disorder,

conversion symptoms, anniversary reaction, disease phobia, thanatophobia, health anxiety and illness denial. The four syndromes of alexithymia, type A behaviour, demoralization and irritable mood are mostly related to the field of psychological factors affecting medical conditions (189). The DCPR were intended as screening diagnoses which may supplement Axes I and II of the DSM and they may be integrated by dimensional tools (190). Since their introduction, the DCPR have been widely used in both medical (191,192) and psychiatric (193,194) settings. Furthermore, the DCPR syndromes were proposed to be included among the clinical manifestations of allostatic load (195,196). A structured interview was developed for the assessment of the 12 syndromes. It consists of 58 items with a dichotomous 'yes/no' response format (192). Excellent inter-rater reliability, construct validity and predictive validity for psychosocial impairment and treatment outcome were proven (197,192).

3. Mini-mental State Examination (MMSE) - Italian version: evaluation of superior cognitive function. Validation for italian population by Measso et al. (1993) (187). The Mini-Mental State Examination (MMSE) is the most common screening tool to assess global cognitive functioning; As most neuropsychological tools, MMSE scores are influenced by demographic variables, namely age and years of education: subjects with higher education levels perform better than those with lower levels; moreover, elderly people exhibit an age-related condition, characterized by a decline in cognitive performances (198).

The self-evaluation consist of:

1. Kellner's Symptom Questionnaire (SQ) – Italian version. It is a widely used 92-item

instrument for the measurement of the main dimensions of psychological distress: anxiety, depression, somatization, and hostility (199). Each scale consists of two sections, one relating to symptoms and one to wellbeing in the examined area. The SQ contains a list of 92 adjectives to answer yes/no. High scores indicate an increase in psychological distress.

2. Questionnaire on the State of Health (SF12)- Italian version by Apolone G. SF-12 allows to describe the health according to the following scales: physical activity [PF], role and physical health [RP], role and emotional state [RE], mental health [MH], physical pain [BP], general health [GH], vitality [VT] and social activity [SF]. The 12-item Health Survey (SF-12) was developed as a shorter alternative to the SF-36 for use in large-scale studies, and its reliability and validity have been documented (200). Scale scores are estimated for four of the health concepts (PF, RP, RE and MH) using two items each, whereas the remaining four (BP, GH, VT and SF) are represented by a single item. All 12 items are used to calculate the physical and mental component summary scores (PCS-12 and MCS-12) by applying a scoring algorithm empirically derived from the data of a US general population survey (201). Performance of the component summary scores was initially studied in nine languages and it has been recommended that the US-derived summary scores, which yield a mean of 50 and a SD of 10, be used in order to facilitate cross-cultural comparison of results (202).
3. Coping Orientation to Problem Experienced – brief version by Carver et al 1997 – Italian version - is a questionnaire that identifies the coping strategies: the based strategies on the resolution of the problem, it focuses on the emotions, or on the avoidance and denial of the problem. This consists of 14 scales, of two items each: active coping, planning, positive refraining, acceptance, humor, religion, using

emotional support, using instrumental support, self-distraction, denial, venting, substance, behavioural disengagement, self-blame. The items are divided into two macro areas: avoiding coping and active coping (203).

4. Interpersonal Support Evaluation List (ISEL) by Cohen (1983) - Italian translation by Grandi S. and Sirri L. (204). The ISEL measures the perceived availability of social support resources (205,206). The ISEL was developed in the context of the stress buffering model that regards social support as a potential protective factor against psychological and physical distress when people have to face stressful situations (207). It comprises four 10-item subscales reflecting the main functions of social support: appraisal (availability of people one can talk to about personal problems), belonging (availability of someone together with one can do things), tangible (instrumental aid) and self-esteem (perception of a positive comparison when comparing oneself with others) (206). A total score, ranging from 0 to 40, can be also calculated. Each item can be answered 'probably true' or 'probably false'. Higher scores correspond to a better perception of social support availability. Adequate validity and reliability of the ISEL were proven (208,209).

   The short form (ISEL-SF) composed by 15 items each that reflect the principal functions of the social support. (206)

5. Post-traumatic Growth Scale (PTGS) - Italian version by Lawns G, Pietrantoni L. (2014): it is an instrument for assessing positive outcomes reported by persons who have experienced traumatic events. This 21-item scale includes factors of new possibilities, relating to others, personal strength, spiritual change, and appreciation of life. The PTGS is modestly related to optimism and extraversion. The scale appears to have utility in determining how successful individuals, coping with the aftermath of

trauma, are in reconstructing or strengthening their perceptions of self, others, and the meaning of events. (210,211)

6. The Gratitude Questionnaire-Six Item Form (GQ-6) by McCullough, M. E. - Italian version – GQ-6 Items assess experiences and expressions of gratefulness and appreciation in daily life, as well as feelings about receiving from others; reflected the gratitude intensity facet, the gratitude frequency facet, the gratitude span facetand the gratitude density facet. (212)

The psychiatric evaluation was made by the psychiatrist consultant (M.L.R.) of the transplant team and the psychological assessment by the PhD Student (L.G.) and the principal investigator of the study (A.V.).

Statistical analysis

All samples are encoded into a dedicated database (protected by password). Descriptive statistical analyses are developed. Data are expressed as the mean [± standard deviation (sd)], median (with range) as applicable. Confidence interval (CI) is presented where appropriate. Wilcoxon test is utilized to assess tendencies and specific rank test for significance. Significant differences between variables are calculated with non-parametric tests. $\chi 2$ or Fisher's exact test is used for categorical while Mann-Whitney for continuous variables. A p value less than 0.05 is considered significant for all tests. SPSS® software version 20.0 (MJ Norusis, Chicago, US) is used for all statistical analyses.

Ethical approval

The present study was approved by the Independent Ethics Committee of the University Hospital of Bologna, Policlinico Sant'Orsola – Malpighi, with Resolution No. 47/2017 / U

/ Oss of 11/04/2017.

3.3.3 Results

The baseline characteristics of experimental sample are reported in the Table 1, Table 2, Table 3 and Table 4.

Table 1. Socio-demographic patterns of the enrolled patients.

N	**50**
Males n(%)	34(68)
Age (years, mean±sd)	57±7
Marital status n(%)	
unmarried	5(10)
married	29 (58)
separate/divorced	10 (20)
cohabitant	2 (4)
widower	4 (8)
School attendance	
Primary school n (%)	7 (14)
Lower secondary n (%)	22 (44)
High secondary n (%)	15 (30)
graduation n (%)	6 (12)

We enrolled 50 patients at the beginning of the screening process for the LT feasibility (T0). In the vast part of cases, patients were males (34/50, 68%) with mean age of 57±7 years. Patients were married or cohabitant in 31 cases (31/50, 62%), 5 patients were unmarried (5/50, 10%), 10 were separated (10/50, 20%) and 4 were vidower (4/50, 8%). About school attendance 7 patients attended a primary school (7/50 14%), 22 attended lower secondary school (22/50 44%), 15 attended high secondary school (15/50 30), 6 patiets was graduated (6/50 12%).

Table 2. Psychiatric diagnosis of the enrolled patients

DSM - 5 diagnosis n/n patients enrolled	10/50
Alchohol Use Disorder n (%)	7 (14)
Adjustment Disorder n (%)	3 (6)

DSM 5, Diagnostic and Statistical Manual of Mental Disorder - 5

Table 3. Psychological diagnosis of the enrolled patients

DCPR diagnosis n/n patients enrolled	22 /50
Demoralization n (%)	15 (30)
Alexythimia n (%)	6 (12)
Irritable mood n (%)	1 (2)

DCPR, Diagnostic Criteria for Psychosomatic Research

A DSM 5 diagnosis was detected in one fifth of patients, in particular 7 subjects showed an alcohol use disorder and 3 adjustment disorder. A DCPR syndrome was present in 22 subjects (44%): 15 patients displayed demoralization, 6 alexythimia, 1 irritable mood.

Table 4. Psychological and psychiatric diagnosis of the enrolled patients

DCPR + DSM 5 diagnosis n /n patients enrolled	6/50
AUD + Demoralization n (%)	3 (6)
AUD + Alexythimia n (%)	2 (4)
AUD + Irritable mood n (%)	1 (2)

DCPR, Diagnostic Criteria for Psychosomatic Research
DSM 5, Diagnostic and Statistical Manual of Mental Disorder - 5
AUD, Alchohol Use Disorder

Table 4 shows the presence of double diagnosis, DSM-5 e DCPR in 6 enrolled patients: 3 have AUD and demoralization, 2 AUD and alexitimia, 1 AUD and irritable mood.

Table 5. Liver disease of the enrolled patients

Liver disease n/ n patients enrolled (%)	
Virus	24 (48)
Alcohol	9 (18)
Virus+alcohol	3 (6)
Non-alcoholic steatohepatitis	8 (16)
Other	6 (12)
Hepatocellular carcinoma n/n patients enrolled(%)	20 (40)
MELD (mean±sd)	12±4
Waiting list entering	25 (50)
Other medical diagnosis	10(50)
Renal failure n (%)	6 (60)
Cardiovascular disorder n (%)	4 (40)

MELD, model for end-stage liver disease.

The main liver disease aetiology was the viral one (24/50, 48%) while hepatocellular carcinoma was present in 20 subjects (40%).

Among the enrolled patients, 25 entered in to the waiting list for LT.

Median questionnarries' scores at the time of screening (T0) are reported in Table 5.

Table 6. Questionarries' scores at the time of screening for liver transplant (T0).

Survey	Score (median, min-max)
SF12 PCS	43, 21-58
SF12 MCS	46, 24-59
SQ anxiety	5, 0-14
SQ depression	5, 1-18
SQ somatic symptom	9, 0-18
SQ hostility	3, 0-15
BC positive refraining	5, 2-8
BC self distraction	5, 2-8
BC venting	4, 2-6
BC instrumental support	4, 2-8
BC active coping	5, 2-8
BC denial	3, 2-7
BC religion	3, 2-8
BC humor	3, 2-8
BC behavioural disengagement	3, 2-7
BC emotional support	4, 2-8
BC substances use	2, 2-5
BC acceptance	6, 2-8
BC planning	5, 2-8
BC self-blame	4, 2-7
ISEL	23, 14-39
Post traumatic growth	38, 8-85
Gratitude	30, 20-42

SD, standard deviation; SF, 12-item Health Survey (SF-12); PCS, Physical Component Score; MCS, Mental Component Score; SQ, Symptom Questionnaire; BC, Brief Cope; ISEL, Interpersonal Support Evaluation List

The median values of patients were in the mid-range of the regulatory sample for the scale of physical function and the scale of mental functioning. Enrolled subjects showed anxiety, depression, somatic symptoms scores lower than the norm sample value. Furthermore, patients displayed greater values concerning the scale of hostility.

The patients reported al lower score than norm sample related to the gratitude scale.

Then we developed a subanalysis of the questionarries' score according to the main social and clinical registered factors that *a priori* might impact the scores themselves.

Especially, in the Table 6a we subdivided patients according to gender finding that females displayed a score of BC emotional support significantly higher than males ($p=0.001$).

Table 7a. Comparison between enrolled patients (T0) according to gender.

	Males	**Females**	**P value (MW-U)**
Survey score (median, min-max)	**N=34**	**N=16**	**P value**
SF12 PCS	44, 22-58	41, 21-55	0,533
SF12 MCS	47, 24-59	43, 30-57	0,190
SQ anxiety	4, 1-14	5, 0-9	0,983
SQ depression	5, 1-18	7, 1-10	0,483
SQ somatic symptom	9, 0-18	9, 2-14	0,826
SQ hostility	3, 0-15	3, 0-12	0,761
BC positive refraining	5, 2-8	5, 3-8	0,873
BC self distraction	4, 2-8	5, 2-8	0,166
BC venting	4, 2-6	4, 2-6	0,155
BC instrumental support	4, 2-7	5, 3-8	0,175
BC active coping	5, 2-8	6, 3-8	0,220
BC denial	3, 2-6	4, 2-7	0,200
BC religion	2, 2-8	3, 2-8	0,298
BC humor	3, 2-8	3, 2-6	0,684
BC disengagement	3, 2-7	3, 2-6	0,721
BC emotional support	4, 2-8	5, 4-8	0,001
BC substances use	2, 2-5	2, 2-3	0,817
BC acceptance	6, 2-8	6, 2-8	0,584
BC planning	5, 2-8	5, 3-8	0,808
BC self-blame	4, 2-7	4, 2-6	0,472
ISEL	25, 15-39	21, 14-36	0,559
Post traumatic growth	36, 0-85	47, 8-84	0,441
Gratitude	29, 20-42	33, 23-42	0,189

SD, standard deviation; $\chi 2$, Chi-Square test; MW-U, Mann-Whitney U test
SF, 12-item Health Survey (SF-12); PCS, Physical Component Score; MCS, Mental Component Score; SQ, Symptom Questionnaire; BC, Brief Cope; ISEL, Interpersonal Support Evaluation List

In the Table 6b we considered the questionarries subdividing the cohort in patients with or without husband/wife//cohabitant. Subjects of the first subgroup showed an SQ hostility major than the others (p=0.030).

Table 7b. Comparison between enrolled patients (T0) according to marital status.

	Married/Cohabitant	**Unmarried/Separed/Widower**	**P value (MW-U)**
Survey score (median, min-max)	**N=31**	**N=19**	**P value**
SF12 PCS	44, 22-58	38, 21-55	0,678
SF12 MCS	46, 30-59	45, 28-59	0,717
SQ anxiety	5, 1-14	4, 0-14	0,182
SQ depression	5, 1-11	4, 1-10	0,473
SQ somatic symptom	7, 0-18	10, 2-15	0,055
SQ hostility	3, 0-15	1, 0-15	0,030
BC positive refraining	5, 2-8	5, 3-8	0,237
BC self distraction	5, 2-8	5, 2-8	0,616
BC venting	4, 2-6	3, 2-6	0,641
BC instrumental support	4, 2-8	4, 2-8	0,512
BC active coping	5, 2-8	5, 3-8	0,589
BC denial	3, 2-6	3, 2-7	0,904
BC religion	3, 2-8	2, 2-8	0,280
BC humor	3, 2-8	3, 2-6	0,758
BC disengagement	3, 2-6	2, 2-6	0,316
BC emotional support	4, 2-8	4, 2-8	0,840
BC substances use	2, 2-3	2, 2-3	0,530
BC acceptance	6, 2-8	5, 2-8	0,364
BC planning	6, 2-8	5, 4-8	0,616
BC self-blame	4, 2-6	4, 2-6	0,789
ISEL	23, 14-39	23, 15-35	0,846
Post traumatic growth	36, 0-85	53, 3-85	0,143
Gratitude	31, 23-42	31, 25-40	0,696

SD, standard deviation; $\chi 2$, Chi-Square test; MW-U, Mann-Whitney U test
SF, 12-item Health Survey (SF-12); PCS, Physical Component Score; MCS, Mental Component Score; SQ, Symptom Questionnaire; BC, Brief Cope; ISEL, Interpersonal Support Evaluation List

As shown in Table 6c, there are many differences between patients with and without diagnosis of AUD. Subjects with AUD showed higher BC humor, Post traumatic growth and Gratitude score than patients without AUD (p=0.049, p=0003, p=0.013, respectively).

Table 7c. Comparison between enrolled patients (T0) according to diagnosis of alchocol use disorder.

	AUD	**No-AUD**	**P value (MW-U)**
Survey score (median, min-max)	**N= 7**	**N=43**	**P value**
SF12 PCS	48, 36-58	40, 21-56	0,086
SF12 MCS	46, 39-58	47, 24-59	0,989
SQ anxiety	8, 0-14	4, 1-14	0,175
SQ depression	8, 1-10	5, 1-18	0,167
SQ somatic symptom	9, 0-18	8, 1-18	0,330
SQ hostility	4, 0-15	2, 0-15	0,304
BC positive refraining	7, 4-8	5, 2-8	0,175
BC self distraction	5, 4-8	5, 2-8	0,550
BC venting	3, 2-6	4, 2-6	0,604
BC instrumental support	5, 4-6	4, 2-8	0,401
BC active coping	5, 2-8	6, 2-8	0,989
BC denial	4, 2-5	5, 2-7	0,681
BC religion	3, 2-8	2, 2-8	0,304
BC humor	5, 2-6	3, 2-8	0,049
BC disengagement	3, 2-6	3, 2-6	0,586
BC emotional support	4, 2-8	4, 2-8	0,905
BC substances use	2, 2-23	2, 2-5	0,586
BC acceptance	5, 2-28	6, 2-8	0,568
BC planning	5, 4-8	5, 2-8	0,781
BC self-blame	4, 3-7	4, 2-7	0,109
ISEL	25, 17-36	23, 14-39	0,448
Post traumatic growth	70, 33-85	36, 0-85	0,003
Gratitude	34, 29-42	30, 20-42	0,013

SD, standard deviation; $\chi 2$, Chi-Square test; MW-U, Mann-Whitney U test
SF, 12-item Health Survey (SF-12); PCS, Physical Component Score; MCS, Mental Component Score; SQ, Symptom Questionnaire; BC, Brief Cope; ISEL, Interpersonal Support Evaluation List
AUD, alcohol use disorder

Finally, we compared baseline questionarries according to the presence of HCC (Table 6d) demonstrating that patients with cancer had higher SF12 MCS and Post traumatic growth in

comparison to the other patiens (p=0.021, p=0.003, repsetively). Furthermore, patients with HCC displayed lower value in the following questionarries: SQ depression, BC self distraction, BC instrumental support, BC religion, BC behavioural disangagement and Gratitude (p=0.042, p=0.017, p=0.036, p=0.007, p=0.048, p=0.042, respectively).

Table 7d. Comparison between enrolled patients (T0) according to diagnosis of hepatocellular carcinoma.

	HCC	**No-HCC**	**P value (MW U)**
Survey score (median, min-max)	**N=20**	**N=30**	**P value**
SF12 PCS	42, 21-56	43, 24-59	0,560
SF12 MCS	48, 30-59	43, 24-59	0,021
SQ anxiety	4, 1-10	5, 0-14	0,442
SQ depression	4, 1-18	7, 1-11	0,042
SQ somatic symptom	7, 1-18	9, 0-18	0,229
SQ hostility	3, 0-12	3, 0-15	0,705
BC positive refraining	5, 2-8	5, 3-8	0,784
BC self distraction	3, 2-7	5, 2-8	0,017
BC venting	4, 2-6	4, 2-6	0,356
BC instrumental support	4, 2-7	5, 2-8	0,036
BC active coping	4, 2-8	6, 2-8	0,290
BC denial	3, 2-6	4, 2-7	0,798
BC religion	2, 2-7	3, 2-8	0,007
BC humor	3, 2-8	4, 2-6	0,333
BC disengagement	2, 2-6	4, 2-7	0,048
BC emotional support	4, 2-6	4, 2-8	0,234
BC substances use	2, 2-5	2, 2-5	0,081
BC acceptance	5, 2-8	6, 2-8	0,695
BC planning	5, 2-8	5, 3-8	0,506
BC self-blame	4, 2-7	4, 2-7	0,177
ISEL	24, 15-39	22, 14-36	0,789
Post traumatic growth	32, 0-80	22, 3-80	0,003
Gratitude	27, 0-37	33, 20-42	0,043

SD, standard deviation; $\chi 2$, Chi-Square test; MW-U, Mann-Whitney U test
SF, 12-item Health Survey (SF-12); PCS, Physical Component Score; MCS, Mental Component Score; SQ, Symptom Questionnaire; BC, Brief Cope; ISEL, Interpersonal Support Evaluation List
HCC, hepatocellular carcinoma

Enrolled patients were socio-demographic variables, gender- and age-matched with general population (control group). As reported in Table 7, control cohort showed higher scores in both scales (PCS, MCS) of SF-12 (p=0.000, p=0.000, respectively), in BC positive refraining, BC venting, BC instrumental support, BC humor, BC behavioural disengagement, BC emotional support, BC self-blame (p=0.000, p=0.000, p=0.000, p=0.000, p=0.001, p=0.000, p=0.000, individually) and in the ISEL and PTG Scale (p=0.000, p=0.000, respectively).

Experimental group reported higher scores in the scale of SQ about anxiey, depression and somatic symptom (p=0.004, p=0.000, p=0.000, individually). Moreover, higher BC substance use score (p=0.005).

Table 8. Comparison between enrolled patients (T0) and matched general population.

	Experimental	Control	P value (χ2/MW-U)
Characteristic	**N=50**	**N=50**	**P value**
Males n (%)	34 (68)	34 (68)	1,000
Age (years, mean±sd)	57±7	58±8	0,679
Survey score (median, min-max)			
SF12 PCS	43, 21-58	54, 33-59	0,000
SF12 MCS	46, 24-59	54, 31-60	0,000
SQ anxiety	5, 0-14	3, 0-14	0,004
SQ depression	5, 1-18	3, 1-11	0,000
SQ somatic symptom	9, 0-18	4, 0-17	0,000
SQ hostility	3, 0-15	3, 0-10	0,629
BC positive refraining	5, 2-8	7, 2-8	0,000
BC self distraction	5, 2-8	5, 2-7	0,208
BC venting	4, 2-6	5, 4-7	0,000
BC instrumental support	4, 2-8	6, 3-8	0,000
BC active coping	5, 2-8	5, 4-8	0,491
BC denial	3, 2-7	3, 2-7	0,354
BC religion	3, 2-8	3, 2-8	0,201
BC humor	3, 2-8	5, 2-7	0,000
BC disengagement	3, 2-7	5, 2-7	0,001
BC emotional support	4, 2-8	6, 2-8	0,000
BC substances use	3, 2-5	2, 2-4	0,005
BC acceptance	6, 2-8	5, 2-8	0,992
BC planning	5, 2-8	5, 3-8	0,589
BC self-blame	4, 2-7	6, 3-8	0,000
ISEL	23, 14-39	36, 23-40	0,000
Post traumatic growth	38, 8-85	56, 20-88	0,000
Gratitude	30, 20-42	28, 28-42	0,280

SD, standard deviation; χ2, Chi-Square test; MW-U, Mann-Whitney U test
SF, 12-item Health Survey (SF-12); PCS, Physical Component Score; MCS, Mental Component Score; SQ, Symptom Questionnaire; BC, Brief Cope; ISEL, Interpersonal Support Evaluation List

3.4 Study 2

3.4.1 Objective

The aim of the study 2 was to observe the changes of psychological variables from the beginning of pre-LT screening (T0) to the entrance in the waitlist for LT (T1).

3.4.2 Methods

The first psychometric evaluation (T0), which took place during the screening phase for suitability for LT, was followed by a second evaluation carried out at the time of signing the Informed Consent for the active inclusion on the waiting list for LT (T1).

Of the 50 patients enrolled in T0, 25 patients were placed on the waiting list completing the second study time point (T1); 21 patients came out from the study; in particular, 2 patients died before listing, 17 resulted not-transplantable (4 for improvement of illness, 13 for worsening), 2 were transferred to other Transplant Centre; 4 patients was still being screened. The same battery of tests was administered to this group of patients and the same exclusion criteria were considered.

- *Psychometric assessment*

All subjects were given a battery of psychometric tests consisting of heteroevaluatione and self-evaluation.

The heteroevaluation consist of:

1. The structured clinical interview from DSM 5 (SCID5).
2. The structured interview according to the Diagnostic Criteria for Psychosomatic Research (DCPR).
3. Mini-mental State Examination (MMSE).

The self-evaluation concern:

1. Kellner's Symptom Questionnaire (SQ).
2. The 12-item Health Survey (SF-12).
3. Coping Orientation to Problem Experienced (brief version) (Brief –COPE).
4. Interpersonal Support Evaluation List (ISEL).
5. Post-traumatic Growth Scale.
6. The Gratitude Questionnaire-Six Item Form (GQ-6).

Statistical analysis

All samples are encoded into a dedicated database (protected by password). Descriptive statistical analyses are developed. Data are expressed as the mean [± standard deviation (sd)], median (with range) as applicable. Confidence interval (CI) is presented where appropriate. Wilcoxon test is utilized to assess tendencies and specific rank test for significance. Significant differences between variables are calculated with non-parametric tests. $\chi 2$ or Fisher's exact test is used for categorical while Mann-Whitney for continuous variables. A p value less than 0.05 is considered significant for all tests. SPSS® software version 20.0 (MJ Norusis, Chicago, US) is used for all statistical analyses.

Ethical approval

The present study was approved by the Independent Ethics Committee of the University Hospital of Bologna, Policlinico Sant'Orsola – Malpighi, with Resolution No. 47/2017 / U / Oss of 11/04/2017.

3.4.3 Results

Changes of DSM – 5 and DCPR dignosis from screening (T0) to waitlist entrance (T1) were reported in Table 8 and in Table 9.

Table 9. Trends of DSM – 5 diagnosis from screening (T0) to waitlist entrance (T1)

	T0	**T1**
DSM -5 diagnosis n/total patient(%)	10 /50 (20)	13/25 (52)
Alchohol Use disorder n (%)	7 (4)	7 (28)
Adjustment disorder n (%)	3 (6)	4 (16)
Generalized anxiety disorder n(%)	0 (0)	2 (8)

DSM 5, Diagnostic and Statistical Manual of Mental Disorder - 5

Table 10. Trends of DCPR diagnosis from screening (T0) to waitlist entrance (T1)

	T0	**T1**
DCPR diagnosis n/total patient (%)	22/50 (44)	24/25 (96)
Demoralization n (%)	15 (30)	15 (60)
Alexythimia n (%)	6 (12)	6 (24)
Irritable mood n (%)	1 (2)	3 (12)

DCPR, Diagnostic Criteria for Psychosomatic Research

From T0 to T1, there is an increase of DSM-5 and DCPR diagnosis. At T1, 4 patients reported a adjustment disorder, 2 patients generalyzed anxiety disorder, and 3 irritable mood. Trends of questionnaires'scores from T0 to T1 were described in Table 10.

Table 11. Psychological and psychiatric diagnosis at T1

DCPR + DSM 5 diagnosis n /n patients enrolled	7/25
AUD + Demoralization n (%)	3 (12)
AUD + Alexythimia n (%)	1 (4)
AUD + Irritable mood n (%)	2 (8)
Generalized anxiety disorder + Irritable mood n (%)	1 (4)

DCPR, Diagnostic Criteria for Psychosomatic Research
DSM 5, Diagnostic and Statistical Manual of Mental Disorder - 5
AUD, Alchohol Use Disorder

Table 11 shows the presence of double diagnosis, DSM-5 e DCPR in 7 patients at T1: 3 have AUD and demoralization, 1 AUD and alexitimia, 2 AUD and irritable mood, 1 Generalized anxiety disorder and irritable mood.

Table 12. Trends of questionarries' scores from screening (T0) to waitlist entrance (T1).

Survey score (median, min-max)	T0	T1	N patients' modifications			Wilcoxon Test P value
			increase	decrease	equal	
SF12 PCS	43, 22-54	45, 24-56	16	7	1	0,429
SF12 MCS	49, 24-59	45, 23-60	9	15	0	0,199
SQ anxiety	5, 1-14	6, 1-14	14	8	2	0,177
SQ depression	5, 1-18	6, 0-14	13	10	1	0,252
SQ somatic symptom	10, 2-18	10, 0-21	10	11	3	0,917
SQ hostility	2, 0-11	5, 0-13	12	6	6	0,084
BC positive refraining	5, 2-8	5, 3-8	8	13	3	0,669
BC self distraction	4, 2-8	5, 2-8	14	6	4	0,079
BC venting	4, 2-6	4, 2-7	13	7	4	0,389
BC instrumental support	4, 2-7	4, 2-8	11	8	5	0,363
BC active coping	6, 3-8	6, 2-8	10	9	5	0,984
BC denial	4, 2-7	2, 2-8	6	9	9	0,438
BC religion	3, 2-8	2, 2-7	7	9	8	0,772
BC humor	3, 2-8	4, 1-8	10	8	6	0,273
BC disengagement	3, 2-6	3, 2-8	10	8	6	0,790
BC emotional support	4, 2-8	3, 2-8	8	12	4	0,363
BC substances use	2, 2-5	2, 2-5	2	6	15	0,518
BC acceptance	6, 3-8	6, 4-8	14	7	3	0,351
BC planning	5, 3-8	5, 3-8	10	11	3	0,874
BC self-blame	4, 2-7	5, 2-6	12	9	3	0,113
ISEL	26, 15-39	28, 15-51	14	8	2	0,101
Post traumatic growth	39, 8-80	37, 5-84	10	12	2	0,897
Gratitude	30, 20-40	28, 21-39	10	13	1	0,337

SD, standard deviation; $\chi 2$, Chi-Square test; MW-U, Mann-Whitney U test
SF, 12-item Health Survey (SF-12); PCS, Physical Component Score; MCS, Mental Component Score;
SQ,Symptom Questionnaire; BC, Brief Cope; ISEL, Interpersonal Support Evaluation List

There were no statistically significant differences between T0 and T1. However, considering SQ Hostility subscale, 12 of 25 patients report higher scores at T1 in respect to T0 (p=0.084); contemplating BC Self distraction subscale, 14 of 25 subjects showed higher score at T1 in comparison with T0 (p=0.079).

3.5 Discussion

LT is an effective treatment option for patients with acute liver failure, end-stage liver disease and HCC (169). LT has not only a relevant positive impact of patients' survival but also on the QoL (179).

However the post-transplant rehabilitation process requires a psychological adaptation to the new condition of life. Notably, the strong need to follow specific therapeutic regimens (pharmacological and behavioral), the risk of rejection and infections and the clinical complications secondary to immunosoppressive therapy, can determine a lower psychological adaptation of the patient (155).

The presence of psychological distress and psychiatric disorders and the difficulty in coping with the stress of the transplant experience, can compromise the LT outcome mainly reducing the therapeutic adherence (181-182).

On the basis of the scientific evidence, the present research has been divided into two studies. We tried to focus on the complexity of the transplant process. Indeed, we studied the phases of the transplant path to which correspond phases of psychological adaptation.

Concerning the enrolled population, among the 50 patients, only 25 completed the first step (T1). This may indicate that there was a high rate of patients for which the screening process has started too soon or too late.

This study investigated specifically the first step of LT process represented by the pre-LT screenig (T0 of the study). This is a relatively long period (generally form 1 to 3 months) during which patients undergo to an amount of exams that definitely need to exclude contraindications fo the transplant itself. According to the above described concept (necessity of adaptation to the new condition of life), we reported that patients at T0 often showed DCPR diagnosis such as demoralization, alexithymia and irritable mood.

Alexithymia has been the object of a large body of psychosomatic literature and its role is being examined in an ever-increasing number of diseases. Although its prognostic value needs to be further clarified, alexithymia was linked to a worsened outcome of medical conditions, such as cardiovascular diseases, cancer and gastrointestinal disorders. Alexithymia

was also significantly associated with substance abuse and disordered eating and altered immune responses to stress (189).

Demoralization may precede the onset of medical diseases and is triggered by the experience of the disease (189).

The characteristics of demoralization had been descripted by Schmale and Engel's (1967) descripted as the 'giving up– given up complex'. Subjects with the giving up– given up complex experience feelings of helplessness and hopelessness, diminished perception of competence and control, loss of sense of continuity between past and future and impairments in their interpersonal relationships. They are led to relive previous failed or frustrating experiences and feel that personal performance or the environment does not meet their expectations (8).

Demoralization and hopelessness, one of its most relevant features, were significantly associated with both onset and worsened outcome of cancer and car- diovascular diseases (213).

We have divided the sample according to variables that *a priori* can impact the psychological status at the time of screening for LT. In particular, gender does not seem to be a significant element of change. Females showed a statistically higher value in the BC Emotional support scale in comparison with males. Therefore, it is possible that females were able to develop a coping strategy associated with more useful responses to adversity (including adaptive practical adaptation), better results on physical health and a more stable emotional response in comparison with males (129).

In our study, a positive correlation emerges between the marital status and the presence of anger / hostility at the time of screening for LT. It is important to deal with transplantation with a nearby caregiver, but the status of "patient" imposes a restructuring of both social and

emotional relationships. The status of “patient” might be a trigger of a time-consuming adaptation process and could be related to both anger and hostility (95-99).

Hepatitis C virus (HCV) infection may affect the QoL even in absence of advanced cirrhosis showing a harmful impact on both mental health and physical well-being (108-109). HCV positive patients often develop fatigue, irritability, general discomfort, abdominal pain, joint pain and headache that may deteriorate both general psychological status and QoL (213). HCV can negatively modify also the post-LT condition since HCV positive recipients can develop higher rates of depression symptoms in comparison with other etiologies (112).

Similar concepts exist for patients with alcohol habit although they show great long-term post-LT outcomes (173).

AUD is associated in about 30% of cases with mood disorder (113,114). Nevertheless, it has been suggested that etiology of liver disease is not the main predictor of altered mental status during the staying on waitlist. Remarkably, the presence of negative and passive coping behavior such as an acceptance-resignation strategy represents a leading cause of mental health impairment. In particular, it determines an altered insight of physical functioning and a fall of global QoL (115).

In our study, patients with AUD at T0 point time reported use of humor as a coping strategy more than patients without AUD. Furtermore, patients with AUD showed poor perception of social support. Active coping, social support and interdisciplinary approach might help patients to achieve psychological positive change after LT (164). The importance of social support has been confirmed in many transplant settings including LT (147). In fact, LT candidates with anxious family members tend to use to a lesser extent successful coping strategies such as active fighting, self-control/emotional control and seeking for social support (165). Caregivers of LT candidates often display psychological stress such as doubts about

emergency situations (42.6%), mood swings (29.5%), food and medications (27.9%). In general, about 25% of caregivers feel themselves inadequate for their role. Due to the importance of the social support, caregiver-dedicated training might be applied in all transplant centers (166). In this context, multidisciplinary team should help patients to develop positive attitude toward transplant process.

Among enrolled patients, it has to be underlined that the prevalence of HCC (40%) and viral etiology (48%) is coherent respect to literature (172). The cancer *per se* can negatively influence the psychological status being a relevant independent factor of psychological distress (214). In our study, patients with HCC in respect to the others, displayed lower levels of depression and lower use of self distraction and behavioral disengagement coping and higher sense of gratitude in respect to patients without cancer. These findings might indicate that the presence of HCC could be a trigger to effective coping the illness but this should be confirmed through dedicated studies.

Data from the study 1 showed that control group (general population) had a better perceived state of health and a tendentially active coping than the patients group. This data could be a confirm of the difficult process of adaptation linked to the transplant path, since its early steps (screening and waiting list) (174-176).

According to literature data, patients in pre-LT screening report anxiety, depression and somatic symptoms (177).

In the evaluation of the transplant candidate, the possibility of patient's under-reporting them must be considered. Patients might anticipate that if they report high levels of psychopathology and/or alcohol issues this might prejudice them in terms of getting on the transplant list. Patients have their own theories as to why staff are assessing their mental health and may alter their responses based on these (113,114).

In study 2, the evaluation of trends from T0 to T1, does not reveal statistically significant differences about psychological variables. This can be explained mainly by the relative short time between the two time points and the low sample size. However, an increase in scores can be seen in the hostility symptom and in the self-distraction coping.

For patients in pre-LT screening, inclusion on the waitlist is the beginning of a real path toward the transplantation, which definitely represents a chance of a new life. However, listing is often associated with worsening liver disease, physical and psychological deterioration. Coherently, in our study, we registered an increase of diagnoses of DSM and DCPR from T0 and T1.

From T0 to T1, we did not detect significant differences in positive psychological indices, post traumatic growth and gratitude. These indices seem to be related to the LT rather than enter in the waitlist since LT itself represents a true transformed event.

Our data support the importance of multidisciplinary approach in the management of the patients during the entire transplant process.

Our study shows some limitations. First of all the small sample size. Patients undergo many screening examinations and some are excluded for the emergence of medical comorbidities and, as a result, are no longer included in the waiting list criteria.

So, it could also be useful to increase the sample to think of a multicenter study.

Secondly, the relatively short time period of observation limited to the first two steps of LT process. We suggest the needing of further multicenter studies to confirm our data and to analyze all the LT stages. This appears as the only feasible approach to plan an early diagnosis, an effective therapy and a whole social, psychological and clinical support for patients.

Since research found an increase in psychological distress and psychosomatic factors in a

small number of patients over the time period involved, in the future a useful addition to the research might have to include a qualitative dimension, in particular, to interview those patients who experienced negative changes. This could identified in more detail what actually happened for those individuals.

The present research program could have important practical implications. The identification of psychological, psychiatric and psychosomatic predictors of long-term clinical outcome may lay the basis for the development of psychological strategies aimed at improvement the clinical course of LT through the modulation of psychological risk factors.

The modification of psychological risk factors through specific psychotherapeutic strategies (cognitive-behavioral therapy, life-style modification, stress management, relaxation training, motivational interviewing, acceptance and commitment therapy, compassion focused therapy) may results in the improvement of LT recipients' psychological adjustment (reduction of psychological distress and allostatic load), patients' adherence to medical therapies (pharmacological therapies, healthy life-style), patients' clinical course (less re-hospitalization, relapses, morbidities).

On the other side, the identification of clinical and instrumental predictors of quality of life may lay the basis for the detection of those LT recipients at a higher risk of inadequate psychological adjustment and who deserve specific psychotherapeutic interventions.

Another useful addition to the study could be to to ask at least a subset of participants how they experienced being given such an extensive battery of psychometric tests and screening measures. For example, how acceptable is it for patients to complete numerous psycho-metric measures, did any find it off-putting, impersonal or distressing? Enquiring about this could have informed future routine practice.

CONCLUSION

Main aim of LT should be to lengthen life expectancy beyond the natural history of underlying liver disease (with achievement of so called “transplant benefit”) but also to improve patients’ quality of life (QoL). Patients should be designated if estimated survival in the absence of LT is 1 year or less, or if the patient had an unacceptable QoL because of liver disease. A detailed medical evaluation is performed to ensure the feasibility of LT (pre-LT screening).

The ideal moment for referring patients to Transplant Center is the first decompensation of liver disease (variceal bleeding, ascites, hepatorenal syndrome and encephalopathy). On the other hand, acute liver failure is an urgent indication to LT (70).

The goal of transplantation should not be only to enhance patients’ survival, but also to offer the same state of health that they enjoyed before the onset of liver disease. This complex achievement can be reach through a balance between the functional efficiency of the graft and the patient’s psychological and physical integrity (87,88).

Analysis of literature on psychological, psychosomatic and psychiatric correlates LT highlighted the presence of several publications on the QoL and psychiatric morbidity of patients included in the Transplant Program.

Studies and transplant guidelines (107) suggest the importance of psyhcological and psychiatric evaluation in the setting of LT. In fact, it has been documented that the presence of some psychosocial problems in the pre-transplant period might have negative prognostic impact on the transplant outcome.

LT includes a complex and articulated clinical process (98). Candidates waiting for LT by definition present life-threatening disease needing donor organ for surviving (100,101). When

the organ becomes available, patients undergo major surgery and then they have to bear short or long intensive care unit hospitalization. After LT, recipients should adapt to immunosuppressive drugs and restrictive life-style rules.

Also the etiology of liver disease is a relevant risk factor for impairment QoL and mental disorder. It is well known that HCV can alter the QoL showing deleterious impact on mental health and physical well-being (108,109).

Also subjects with alcohol-related liver disease deserve specific selection (113-114).

So the predictive aptitude of pre-transplant psychiatric and psychological factors is actually debated. However, seeing the impact of psychological variables on the entire transplant process, major scientific attention should be deserved to this complex topic.

Notably, achievement of survival benefit and return to satisfying QoL should represent the main goals of transplantation. In fact, transplant recipients should obtain the health status that they had before the onset of liver disease with a complex steadiness between graft functionality and recipient integrity (215). Psychological support within a multi-disciplinary team is a powerful tool to achieve these aims. Only a multi-disciplinary transplant team can guarantee an effective holistic orientation towards patients (216).

Seeing the relationship between psychosocial patterns and clinical outcome, the multidisciplinary methodology represents the only rational ways to achieve a global benefit (217).

We well know that psychological status of LT candidates might influence post-LT adherence, QoL and clinical outcome. Many psychosocial factors can influence the transplant process.

As we demonstrated, in the early phases of Transplant process, patients already show many patterns of psychosomatic distress needing a prompt psychological support. Notably, Schneekloth et al. (218) suggested the prominence of the pre-LT psychological assessment.

We also demonstrated a worsening of many psychosomatic and psychiatric patterns from the first phase of Transplant Process to the enter in the waiting list. This is a very complex period since it can have a very variable length. Moreover, every step of the pre-LT screening can represent a turning point for the possible detection of a contraindication for transplant itself. Indeed, it is not surprising that deterioration can be registered. However, our data suggest and confirm the relevance of an early intervention.

REFERENCES

1. Deter HC, Kruse J, Zipfel S. History, aims and present structure of psychosomatic medicine in Germany. Biopsychosoc Med. 2018 Jan 2;12:1.
2. Henkelmann T, Hahn P. Historical insights of psychosomatic medicine in Heidelberg. NewYork: Proc 16 EurConf on Psychosomatic Research; 1987. pp. 47–52.
3. Hahn P. Wissenschaftstheoretische Leitlinien. In: Hahn P, editor. Ärztliche Propädeutik (German) Heidelberg: Springer; 1988. pp. 65–148.
4. Halliday JL. Psychosocial medicine. A study of sick society. London: Heinemann, 1948.
5. Lipowsky ZJ. Psychosmatic medicine: past and present. Canadian Journal Of Psychiatry; 1986; 31, 2-21.
6. Fava GA, Sirri L, Fabbri S. Le applicazioni cliniche della medicina psicosomatica. Psichiatria di consultazione. 2005; VIII, 235-241.
7. Kissen DM. The significance of syndrome shift and late syndromeassociation on psychosomatic medicine. Journal of Nervous and Mental Desease; 1963; 136, 34-42.
8. Engel GL. The concept of psychosomatic disorder. Journal of Psychosomatic Research; 1967; 11, 3-9.
9. Lipowsky ZJ. Review of consulting psychiatric and psychosomatic medicine. III. Theoretical issue. Psychosomatic Medicine; 1968; 30: 395-422.
10. Fava GA, Sonino N. Psychosomatic medicine: emerging trends and perspective. Psychoter Psychosom; 2000; 69, 184-197.
11. Engel GL. The need for a new medical model: a challange for biomedicine. Science. 1977; 196: 129-136.
12. Fava GA, Fabbri S, Sirri L, Sonino N. gli ambiti applicative della medicina

psicosomatica. Medicina Psicosomatica. 2005; 50: 7-15.

13. Stemberg EM. Emotional and disease: from balance of humors to balance of molecules. Nature Medicine. 1997; 3: 264-267.
14. Engel GL. A unified concept of health and disease. Perspect Biol Med 1960; 3: 459–485.
15. Fava GA, Sonino N. Psychosomatic assessment. Psychother Psychosom 2009; 78: 333–341.
16. Tinetti ME, Fried T. The end of the disease era. Am J Med 2004; 116: 179–185.
17. Fava GA, Sonino N. Psychosomatic medicine. Int J Clin Pract 2010; 64: 1155–1161.
18. Fava GA, Sonino N, Wise TN, editors. The Psychosomatic Assessment. Basel: Karger, 2012.
19. Panconesi E. Psychosomatic dermatology: past and future. Int J Dermatol 2000; 39: 732–734.
20. Panconesi E. Psychosomatic factors in dermatology: special perspectives for application in clinical practice. Dermatol Clin 2005; 23: 629–633.
21. Lipowski ZJ. Physical illness and psychopathology. Int J Psychiat Med 1974; 5: 483–497.
22. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007; 87: 873–904.
23. Novack DH, Cameron O, Epel E, Ader R, Waldstein SR, Levenstein S, Antoni MH, Wainer AR: Psychosomatic medicine: the scientific foundation of the biopsychosocial model. Acad Psychiatry 2007; 31: 388–401
24. Theorell T: Evaluating life events and chronic stressors in relation to health. Adv Psychosom Med 2012; 32: 58–71.

25. McEwen BS: Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007; 87: 873-904.
26. Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Actual causes of death in the United States, 2000. JAMA 2004; 291: 1238–1245
27. Agirbasli M, Tanrikulu AM, Berenson GS: Metabolic syndrome: bridging the gap from childhood to adulthood. Cardiovasc Ther 2016; 34: 30–36
28. Emmen MJ, Peters E, Elving LD, Bredie SJH, Wollersheim H, Bleijenberg G, Schippers GM: A brief behavioral feedback intervention in hospital outpatients with a high cardiovascular risk. Patient Educ Couns 2006; 60: 32–40.
29. Gianaros PJ, Manuck SB: Neurobiological pathways linking socioeconomic position and health. Psychosom Med 2011; 72: 450–461.
30. Roy R: Social Support, Health and Illness. A Complicated Relationship. Toronto, University of Toronto Press, 2011.
31. Chida Y, Steptoe A, Powell LH: Religiosity/ spirituality and mortality. Psychother Psychosom 2009; 78: 81–90.
32. Morandi A, Narayanan Nambi AN (eds): An Integrated View of Health and Well-being. Dordrecht, Springer, 2013
33. Andrasik F, Goodie JL, Peterson AL: Biopsychosocial Assessment in Clinical Health Psychology. New York, Guilford Press, 2015
34. Gordon JS: Manifesto for a New Medicine. Reading, Addison-Wesley, 1996.
35. Levenstein S: Stress and peptic ulcer: life beyond helicobacter. BMJ 1999; 316: 538–541.
36. Waeldin S, Vogt D, Linden M, Hellhammer DH: Frequency of perceived post-stress symptoms in inpatients, outpatients and healthy controls. Psychother Psychosom

2016; 85: 36–44.

37. Katon WJ, Walker EA: Medically unexplained symptoms in primary care. J Clin Psychiatry 1998; 59: 15–21.
38. Hahn SR, Thompson KS, Wills TA, Stern V, Budner NS: The difficult doctor-patient relationship. J Clin Epidemiol 1994; 47: 647–657
39. Fava GA, Sonino N, Wise TN (eds): The Psychosomatic Assessment. Basel, Karger, 2012.
40. Derogatis LR, Lipman RS, Covi L: SCL-90: an outpatient psychiatric rating scale – preliminary report. Psychopharmacol Bull 1973; 9: 13–28.
41. Snaith RP, Zigmond AS: The hospital anxiety and depression scale. Br Med J (Clin Res Ed) 1986; 292: 344.
42. Kellner R: A symptom questionnaire. J Clin sychiatry 1987; 48: 268–274.
43. Bech P: Clinical Psychometrics. Oxford, Wily- Blackwell, 2012.
44. Bech P: Measurement of psychological distress and well-being. Psychother Psychosom 1990; 54: 77–89.
45. Rodriguez-Urrutia A, Eiroa-Orosa FJ, Accarino A, Malagelada C, Azpiroz F: Incongruence between clinicians' assessments and selfreport functioning is related to psychopathology among patients diagnosed with gastrointestinal disorders. Psychother Psychosom 2016; 85: 244–245.
46. Topp CW, Østergaard SD, Søndergaard S, Bech P: The WHO-5 Well-Being Index: a systematic review of the literature. Psychother Psychosom 2015; 84: 167–176.
47. Concato J, Feinstein AR: Asking patients what they like: overlooked attributes of patient satisfaction with primary care. Am J Med 1997; 102: 399–406.
48. Bottomley A, Jones D, Claassens L: Patientreported outcomes: assessment and current

perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicine Agency. Eur J Cancer 2009; 45: 347–353

49. Clancy C, Collins FS: Patient-Center Outcomes Research Institute: the intersection of science and health care. Sci Transl Med 2010; 3:37
50. Sartorius N, Holt RIG, Maj M (eds): Comorbidity of Mental and Physical Disorders. Basel, Karger, 2015.
51. Cosci F, Fava GA, Sonino N: Mood and anxiety disorders as early manifestations of medical illness. Psychother Psychosom 2015;84:22-29
52. Djoussé L, Driver JA, Graziano JM: Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA 2009; 302: 394–400.
53. Forman JP, Stampfer MJ, Curhan GC: Diet and lifestyle risk factors associated with incident hypertension in women. JAMA 2009; 302: 401–411.
54. Tomba E: Assessment of lifestyle in relation to health. Adv Psychosom Med 2012; 32: 72–96.
55. Stone NJ: Focus on lifestyle change and the metabolic syndrome. Endocrinol Metab Clin North Am 2004; 33: 493–508.
56. Tinetti ME, Fried T: The end of the disease era. Am J Med 2004; 116: 179–185.
57. Tinetti ME, Fried TR, Boyd CM: Designing health care for the most common chronic condition – multimorbidity. JAMA 2012; 307: 2493–2494.
58. Suls J, Green PA, Davidson KW: A biobehavioral framework to address the emerging challenge of multimorbidity. Psychosom Med 2016; 78: 281–289.
59. Sonino N, Peruzzi P: A psychoneuroendocrinology service. Psychother Psychosom 2009; 78: 346–351.
60. The Remission Clinic Task Force: The Remission Clinic approach to halt the

progression of kidney disease. J Nephrol 2011; 24: 274–281

61. Fung-Kee-Fung M, Kennedy EB, Biagi J, Colgan T, D'Souza D, Elit LM, Hunter A, Irish J, McLeod R, Rosen B: The optimal organization of gynecologic oncology services: a systematic review. Curr Oncol 2015; 22:e282–e293.
62. Betteridge N, Boehncke WH, Bundy C, Gossec L, Gratacós J, Augustin M: Promoting patient-centred care in psoriatic arthritis: a multidisciplinary European perspective on improving the patient experience. J Eur Acad Dermatol Venereol 2016; 30: 576–585.
63. Calne RY, Williams R, Dawson JL, Ansell ID, Evans DB, Flute PT, et al. Liver transplantation in man. II. A report of two orthotopic liver transplants in adult recipients. Br Med J 1968;4:541–546
64. Starzl TE, Marchioro TL, Porter KA, Brettschneider L. Homotransplantation of the liver. Transplantation. 1967;5:790–803.
65. Gonzalez FX, Garcia-Valdecasas JC, Grande L, Pacheco JL, Cugat E, Fuster J, et al. Vena cava vascular reconstruction during orthotopic liver transplantation: a comparative study. Liver Transpl Surg 1998;4:133–140.
66. Figueras J, Llado L, Ramos E, Jaurrieta E, Rafecas A, Fabregat J, et al. Temporary portocaval shunt during liver transplantation with vena cava preservation. Results of a prospective randomized study. Liver Transpl 2001;7:904–911.
67. Dutkowski P, Linecker M, DeOliveira ML, Mullhaupt B, Clavien PA. Challenges to liver transplantation and strategies to improve outcomes. Gastroenterology 2015;148:307–323.
68. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol 2012;57:675–688.

69. Dutkowski P, De Rougemont O, Mullhaupt B, Clavien PA. Current and future trends in liver transplantation in Europe. Gastroenterology 2010;138:802–809, e1–e4.

70. Lee WM, Squires Jr RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. Hepatology 2008;47:1401–1415.

71. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–96.

72. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.

73. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005; 307–313.

74. Pawlotsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. Gastroenterology 2014;146:1176–1192.

75. <http://www.eltr.org>.

76. Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G, et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010;10:138–148.

77. Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nussler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2007;13:197–205.

78. Yates WR, Martin M, LaBrecque D, Hillebrand D, Voigt M, Pfab D. A model to examine the validity of the 6-month abstinence criterion for livertransplantation. Alcohol Clin Exp Res 1998;22:513–517.

79. Mathurin P, Duchatelle V, Ramond MJ, Degott C, Bedossa P, Erlinger S, et al. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. Gastroenterology 1996;110:1847–1853.
80. Mathurin P, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut 2011;60:255–260.
81. Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, et al. The Lille model: a new tool for therapeutic strategy in patients with sever alcoholic hepatitis treated with steroids. Hepatology 2007;45:1348–1354.
82. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790–1800.
83. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology 2011;141: 1249–1253.
84. Rauch JB, Kneen KK. Accepting the gift of life: heart transplantation recipients' post-operative adaptive tasks. Soc Work Health Care 1989; 14: 47.
85. Dew MA, Myaskovsky L, Switzer GE, DiMartini AF, Schulberg HC, Kormos RL. Profiles and predictors of the course of psychological distress across four years after heart transplantation. Psychol Med 2005; 35: 1215.
86. Muehrer RJ, Becker BN. Life after transplantation: new transitions in quality of life and psychological distress. Semin Dial 2005; 18: 124.
87. Bergner M. Quality of life, health status and clinical research. Med Care 1989; 27(Suppl.): S148.
88. Wilson I, Cleary P. Linking clinical variables with healthrelated quality of life. JAMA

1995; 273: 59.

89. Fox, R. C.,Swazey, J. P. (2002). The courage to fail: A social view of organ transplants and dialysis. New Brunswick,NJ: Transaction.

90. Shaw, R. (2010). Perceptions of the gift relationship in organ and tissue donation: Views of intensivists and donor and recipient coordinators. Social Science & Medicine, 70, 609–615.

91. Shaw, R., Bell, L., Webb, R. (2012). New Zealanders' perceptions of gift and giving back as participants of organ transfer procedures. Kotuitui: New Zealand Journal of Social Sciences Online, 7, 26–36.

92. Shaw, R. (2012). Thanking and reciprocating under the New Zealand organ donation system. Health, 16, 298–313.

93. Siminoff, L. A., & Chillag, K. (1999). The fallacy of the "gift of life." Hastings Center Report, 29(6), 34–41.

94. O'Brien GM, Donaghue N, Walker I, Wood CA . Deservingness and Gratitude in the Context of Heart Transplantation. Qualitative Health Research 2014, Vol. 24(12) 1635-1647

95. Annema C, Drent G, Roodbol PF, Metselaar HJ, Van Hoek B, Porte RJ, Schroevers MJ, et al. A prospective cohort study on posttraumatic stress disorder in liver transplantation recipients before and after transplantation: prevalence, symptom occurrence, and intrusive memories. J Psychosom Res 2017; 95: 88-93.

96. Hackmann A, Ehlers A, Speckens A, Clark DM. Characteristics and content of intrusive memories in PTSD and their changes with treatment. J Trauma Stress 2004; 17: 231-40.

97. Goetzmann L, Sarac N, Ambühl P, Boehler A, Irani S, Muellhaupt B, Noll G, et al.

Psychological response and quality of life after transplantation: a comparison between heart, lung, liver and kidney recipients. Swiss Med Wkly 2008; 23; 138:477-83.

98. Golfieri L, Gitto S, Morelli MC, Pinna AD, Grandi S, Andreone P. Impact of hepatitis C virus infection on health-related quality of life before and after liver transplantation: a multidisciplinary point of view. Expert Review of Anti-infective Therapy 2017; 15: 759-65.

99. Paslakis G, Beckmann M, Beckebaum S, Klein C, Gräf J, Erim Y. Posttraumatic Stress Disorder, Quality of Life, and the Subjective Experience in Liver Transplant Recipients. Prog Transplant 2018; 28: 70-6.

100. Available from: http://www.trapianti.salute.gov.it/imgs/C_17_pubblicazioni_2591_allegato.pdf.

101. Northup PG, Intagliata NM, Shah NL, Pelletier SJ, Berg CL, Argo CK. Excess mortality on the liver transplant waiting list: unintended policy consequences and Model for End-Stage Liver Disease (MELD) inflation. Hepatology 2015; 61: 285-91.

102. Sainz-Barriga M, Baccarani U, Scudeller L, Risaliti A, Toniutto PL, Costa MG. Quality-of-Life Assessment Before and After Liver Transplantation. Transplantation Proceedings 2005; 37: 2601-4.

103. Bona MD, Rupolo G, Ponton P, Iemmolo RM, Boccagni P, Destro C, Ermani M, et al. The effect of recurrence HCV infection of life after liver transplantation. Transpl Int 1998; 11: S475-9.

104. Sirri L, Potena L, Masetti M, Tossani E, Magelli C, Grandi S. Psychological predictors of mortality in heart transplanted patients: A prospective, 6-years follow-up study. Transplantation 2010; 89: 879-86.

105. Tschuschke V, Hertenstein B, Arnold R, Bunjes D, Denzinger R, Kaechele H. Associations between coping and survival time of adult leukemia patients receiving allogeneic bone marrow transplantation Results of a prospective study. J Psychosom Res 2001; 50: 277-85.

106. Fineberg SK, West A, Na PJ, Oldham M, Schilsky M, Hawkins KA, Hochang BL. Utility of pretransplant psychological measures to predict posttransplant outcomes in liver transplant patients: a systematic review. Jen Hosp Psychiatry 2016; 40: 4-11.

107. Liver Transplantation. Recommendations of "Associazione Italiana per Studio lo studio del Fegato (A.I.S.F)" Febbraio 2008.

108. Nelligan JA, Loftis JM, Matthews AM, Zucker BL, Linke AM, Hauser P. Depression comorbidity and antidepressant use in veterans with chronic hepatitis C: results from a retrospective chart review. J Clin Psychiatry 2008; 69: 810-6.

109. Foster GR. Quality of life considerations for patients with chronic hepatitis C. J Viral Hepat 2009; 16: 605-11.

110. Marcellin P. Hepatitis C: the clinical spectrum of the disease. J Hepatol 1999; 31(S1): 9-16.

111. Poynard T, Cacoub P, Ratziu V, Myers RP, Dezailles MH, Mercadier A, Ghillani P, et al. Fatigue in patients with chronic hepatitis C. J Viral Hepat 2002; 9: 295-303.

112. De Bona M, Ponton P, Ermani M, Iemmolo RM, Feltrin A, Boccagni P, Gerunda G, et al. The impact of liver disease and medical complications on quality of life and psychological distress before and after liver transplantation. J Hepatol 2000; 33: 609-15.

113. Gitto S, Golfieri L, Caputo F, Grandi S, Andreone P. Multidisciplinary View of Alcohol Use Disorder: From a Psychiatric Illness to a Major Liver Disease. Biomolecules 2016; 6: 11.

114. Klimkiewicz A, Klimkiewicz J, Jakubczyk A, Kieres-Salomoński I, Wojnar M. Comorbidity of alcohol dependence with other psychiatric disorders. Part I. Epidemiology of dual diagnosis. Psychiatr Pol 2015;49:265-275.

115. Jurado R, Morales I, Taboada D, Denia F, Mingote JC, Jiménez MÁ, Palomo T, et al. Coping strategies and quality of life among liver transplantation candidates. Psicothema 2011; 23: 74-9.

116. Menegaux F, Keeffe EB, Andrews BT, et al. Neurological complications of liver transplantation in adult versus pediatric patients. Transplantation. 1994;58:447–450.

117. Ghaus N, Bohlega S, Rezeig M. Neurological complications in liver transplantation. J Neurol. 2001;248:1042–1048.

118. Guarino M, Stracciari A, Pazzaglia P, et al. Neurological complication of liver transplantation. J Neurol. 1996;243:137–142.

119. Beresford TP. Neuropsychiatric complications of liver and other solid organ transplantation. Liver Transpl. 2001;7(11 suppl. 1):S36–S45.

120. DiMartini A, Crone C, Fireman M, Dew MA. Psychiatric aspects of organ transplantation in critical care. Crit Care Clin. 2008;24: 949–98

121. Pirkola S, Saarni S, Suvisaari J, Elovainio M, Partonen T, Aalto AM, Perälä J, et al. General health and quality of life measures in active, recent, and comorbid mental disorders: a population-based health 2000 study. Compr Psychiatry 2009; 50: 108-14.

122. Lavretsky H, Zheng L, Weiner MW, Mungas D, Reed B, Kramer JH, Jagust W, et al. Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. Am J Psychiatr 2010; 167: 589-97.

123. Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, Kulig CC, et al. Health related quality of life in patients with chronic hepatitis C and advanced fibrosis. J Hepatol 2007; 46: 420-31.

124. Kanwal F, Gralnek IM, Hays RD, Zeringue A, Durazo F, Han SB, Saab S, et al. Health-related quality of life predicts mortality in patients with advanced chronic liver disease. Clin Gastroenterol Hepatol 2009; 7: 793-9.

125. Miller LR, Paulson D, Eshelman A, Bugenski M, Brown KA, Moonka D, Abouljoud M. Mental health affects the quality of life and recovery after liver transplantation. Liver Transpl 2013; 19: 1272-8.

126. Zahn A, Seubert L, Junger J, Schellberg D, Weiss KH, Schemmer P, Stremmel W, et al. Factors influencing long-term quality of life and depression in German liver transplant recipients: a single-centre cross-sectional study. Ann Transplant 2013; 18: 327-35.

127. O'Caroll RE, Couston M, Cossar J, Masterton G, Hayes PC. Psychological outcome and quality of life following liver transplantation: a prospective, national, single-center study. Liver Transpl 2003; 9: 712-20.

128. Goetzman L, Klaghofer R, Wagner-Huber R, Halter J, Boehler A, Muellhaupt B, Schanz U, et al. Psychological vulnerability predict psychological outcome after an organ transplant: results of a prospective study with lung, liver and bone-marrow patients. Journal of Psychosomatic research 2007; 62: 93-100.

129. Stilley CS, Flynn WB, Sereika SM, Stimer ED, DiMartini AF, deVera ME. Pathways of psychosocial factors, stress, and health outcomes after liver transplantation. Clin Transplant 2012; 26: 216-22.

130. Corruble E, Barry C, Varescon I, Durrbach A, Samuel D, Lang P, Castaing D, et al. Report of depressive symptoms on waiting list and mortality after liver and kidney transplantation: a prospective cohort study. BMC Psychiatry 2011; 11: 182.

131. Rogal SS, Landsittel D, Surman O Chung RT, Rutherford A. Pretransplant depression, antidepressant use, and outcomes of orthotopic liver transplantation. Liver Transpl 2011; 17: 251-60.

132. Rogal SS, Dew MA, Fontes P, Di Martini AF. Early treatment of depressive symptoms and long-term survival after liver transplantation. Am J Transplant 2013; 13: 928-35.

133. Telles-Correia D, Barbosa A, Mega I, Barroso E, Monteiro E. Psychiatric and Psychosocial predictors of medical outcome after liver transplantation: a prospective, single-center study. Transpl Proceed 2011; 43: 155-7.

134. Walton J, St Clair K. " A beacon of light". Spirituality in the heart transplant patient. Critical Care Nursing Clinics of North America 2000;**12**:87-101.

135. Kaba E, Thompson DR, Burnard P. Coping after heart transplantation: a descriptive study of heart transplant recipients' methods of coping. J advanc nurs 2000;**32**:930-6.

136. Tayebi Z, Abedi HA. The lived experiences of liver transplant patients. Iran J Nurs Midwifery Res 2009;13.

137. Bean KB. An exploratory investigation of quality of life in adult liver transplant recipients. Progress Transplant 2005;**15**:392-6.

138. Stolf NAG, Sadala MLA. Experiencing heart transplantation: the patients' perspective. Revista Brasileira de Cirurgia Cardiovascular 2006;**21**:314- 23.

139. Del Barrio M, Lacunza M, Armendariz AC, et al. Liver transplant patients: their experience in the intensive care unit. A phenomenological study. J clin nurs 2004;**13**:967-76.

140. Diekelmann N. Narrative pedagogy: Heideggerian hermeneutical analyses of lived experiences of students, teachers, and clinicians. ANS Adv Nurs Sci 2001;**23**:53-71.

141. Heinrich TW, Marcangelo M. Psychiatric issues in solid organ transplantation. Harv rev psychiatry 2009;**17**:398-406.

142. Tong A, Morton R, Howard K, Craig JC. Adolescent experiences following organ transplantation: a systematic review of qualitative studies. J pediatrics 2009;**155**:542-9. e5.

143. Anand-Kumar V, Kung M, Painter L, Broadbent E. Impact of organ transplantation in heart, lung and liver recipients: Assessment of positive life changes. Psychology & Health 2014; 29:6: 687-697

144. Helgenson VS, Reynolds KA, Tomich PL. A meta-analytic review of benefit finding and growth. J Cons And Clinical Psychology 2006; 74: 797-816

145. Janoff-Bulman R. Posttraumatic growth: Three explanatory model. Psychological Inquiry 2004; 15: 30-34

146. Park CL, Lechner SC, Antoni MH, Santon AL. Medical illness and postitive life change: can crisis lead to personal trasformation? Washington DC: American Psychological Association 2009

147. Tallman, B., Shaw, K., Schultz, J., & Altmaier, E. Well-Being and Posttraumatic Growth in Unrelated Donor Marrow Transplant Survivors: A Nine-Year Longitudinal Study. Rehabilitation Psychology 2010; 55: 204–210

148. Scrignaro M, Sani F, Wakefield JR, et al. Post-traumatic growth enhances social identification in liver transplant patients: A longitudinal study. J Psychosom Res 2016;88:28–32.

149. Zięba M, Zatorski M, Boczkowska M, et al. The affective tone of narration and posttraumatic growth in organ transplant recipients. Polish Psychological Bulletin 2015;46:376–83.

150. Rodrigue JR, Dimitri N, Reed A, et al. Quality of life and psychosocial functioning of spouse/partner caregivers before and after liver transplantation. Clin Transplant 2011;25:239–47

151. Meltzer LJ, Rodrigue JR. Psychological distress in caregivers of liver and lung transplant candidates. J Clin Psychol Med Settings 2001;8:173–80.

152. Young GS, Mintzer LL, Seacord D, et al. Symptoms of posttraumatic stress disorder in parents of transplant recipients: incidence, severity, and related factors. Pediatrics 2003;111:e725–e731.

153. Young AL, Rowe IA, Absolom K, et al. The effect of liver transplantation on the quality of life of the recipient's main caregiver -a systematic review. Liver Int 2017;37:794–801

154. Perez-San-Gregorio MA, Martin-Rodr.guez, A, Borda-Mas M, Avargues-Navarro ML, Perez-Bernal J, Conrad R, Gomez-Bravo MA. Post-traumatic growth and its relationship to quality of life up to 9 years after liver transplantation: a cross-sectional study in Spain. BMJ Open 2017;7:e017455.

155. Bunzel B, Laederach-Hofman K. Solid organ transplantation: are the predictors for posttransplant noncompliance? A literature overview. Transplantation 2000; 70: 711-6.

156. Kober B, Kuchler T, Broelsch C, Kremer B, Henne-Bruns D. A psychological support concept and quality of life research in a liver transplantation program: an interdisciplinary multicenter study. Psychother Psychosom 1990; 54: 117-31.

157. Rodrigue JR, Nelson DR, Hanto DW, Reed AI, Curry MP. Patient-reported immunosuppression nonadherence 6 to 24 months after liver transplant: association with pretransplant psychosocial factors and perceptions of health status change. Prog Transplant 2013; 23: 319-28.

158. Lieber SR, Helcer J, Leven E, Knight CS, Wlodarkiewicz C, Shenoy A, Shemesh E, et al. Pretransplant Psychosocial Risk Factors May Not Predict Late Nonadherence and Graft Rejection in Adult Liver Transplant Recipients. Exp Clin Transplant 2017 Sep 30.

159. Santos GG, Gonçalves LC, Buzzo N, Mendes TA, Dias TP, da Silva RC, da Silva RF, et al. Quality of life, depression, and psychosocial characteristics of patients awaiting liver transplants. Transplant Proc 2012; 44: 2413-5.

160. Eftekar M, Pun P. Psychiatric risk factors predicting post-liver transplant physical and psychiatric complications: a literature review. Australas Psychiatry 2016; 24: 385-92

161. Stewart KE, Hart RP, Gibson DP, Fisher RA. Illness apprehension, depression, anxiety, and quality of life in liver transplant candidates: implications for psychosocial interventions. Psychosomatics 2014; 55: 65

162. Pérez-San-Gregorio MÁ, Martín-Rodríguez A, Borda-Mas M, Avargues-

Navarro ML, Pérez-Bernal J, Gómez-Bravo MÁ. Coping Strategies in Liver Transplant Recipients and Caregivers According to Patient Posttraumatic Growth. Front Psychol 2017; 8: 18.

163. Golfieri L, Lauro A, Tossani E, Sirri L, Dazzi A, Zanfi C, Vignudelli A, et al. Coping strategies in intestinal transplantation. Transplant Proc 2007; 39: 1992-4.

164. Andrykowski MA, Bishop M, Hahn EA, Cella DF, Beaumont JL, Brady ML, Horowitz MM, et al. Long-Term Health-Related Quality of Life, Growth, and Spiritual Well-Being After Hematopoietic Stem-Cell Transplantation. Journal of Clinical Oncology 2005; 23: 599-608.

165. Pérez-San-Gregorio MA, Martín-Rodríguez A, Pérez-Bernal J. Influence of the psychological state of relatives on the quality of life of patients at 1 year after transplantation. Transplant Proc 2008; 40: 3109-11.

166. Domínguez-Cabello E, Martín-Rodríguez A, Pérez-San-Gregorio MA, Fernández-Jiménez E, Sousa-Martín JM, Bernardos-Rodríguez A. Coping strategies in liver patients as a function of relatives' anxiety level. Transplant Proc 2012; 44: 2616-8.

167. Miyazaki ET, Dos Santos R, Miyazaki MC, Domingos NM, Felicio HC, Rocha MF, Arroyo PC Jr, et al. Patients on the waiting list for liver transplantation: caregiver burden and stress. Liver Transpl 2010; 16: 1164-8.

168. Pérez-San-Gregorio MÁ, Martín-Rodríguez A, Borda-Mas M, Avargues-Navarro ML, Pérez-Bernal J, Gómez-Bravo MÁ. Family Caregivers of Liver Transplant Recipients: Coping Strategies Associated With Different Levels of Post-traumatic Growth. Transplant Proc 2018; 50: 646-9.

169. Martin P, Di Martini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59:1144-1165

170. Bozorgzadeh A, Orloff M, Abt P, Tsoulfas G, Younan D, Kashyap R et al. Survival outcomes in liver transplantation for hepatocellular carcinoma, comparing impact of hepatitis C versus other etiology of cirrhosis. Liver Transpl 2007;13:807–813

171. Nekrasov, V., Matsuoka, L., Rauf, M., Kaur, N., Cao, S., Groshen, S., & Alexopoulos, S. P. (2016). National outcomes of liver transplantation for model for end-stage liver disease score ≥40: The impact of share 35. American Journal of Transplantation : Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 16(10), 2912-2924.

172. O'Mahony CA, Goss JA. The future of liver transplantation. Tex Heart Inst J 2012;39:874–875

173. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016 Feb;64(2):433-485

174. Schulz, K., & Kroencke, S. (2015). Psychosocial challenges before and after organ transplantation. Transplant Research and Risk Management, 7, 45-58.

175. Zarrinpar, A., & Busuttil, R. W. (2013). Liver transplantation: Past, present and future. Nature Reviews.Gastroenterology & Hepatology, 10(7), 434-440.

176. DiMartini A, Dew MA, Chaiffetz D, Fitzgerald MG, Devera ME, Fontes P. Early trajectories of depressive symptoms after liver transplantation for alcoholic liver disease predicts long-term survival. Am J Transplant 2011;11:1287–1295

177. Naughton MJ, Weaver KE. Physical and mental health among cancer survivors: considerations for long-term care and quality of life. N C Med J 2014;75:283–286

178. Grover S, Sarkar S. Liver transplant—psychiatric and psychosocial aspects. J Clin Exp Hepatol 2012;2:382–392

179. Fukunishi I, Sugawara Y, Takayama T, Makuuchi M, Kawarasaki H, Surman OS. Psychiatric disorders before and after living-related transplantation. Psychosomatics 2001;42:337–343

180. Grandi S, Fabbri S, Tossani E, Mangelli L, Branzi A, Magelli C. Psychosocial evaluation after cardiac transplantation: the integration of different criteria. Psychoterapy and Psychosomatics 2001; 70:176-183

181. Burra, P., & De Bona, M. (2007). Quality of life following organ transplantation. Transplant International, 20(5), 397-409.

182. Tschuschke V, Hertenstein B, Arnold R, Bunjes D, Denzinger R, Kaechele H. Associations between coping and survival time of adult leukemia patients receiving allogeneic bone marrow transplantation Results of a prospective study. J Psychosom Res 2001;50:277–85

183. Walter M, Moyzes D, Rose M, Neuhaus R, Danzer G, Klapp BF. Psychosomatic interrelations following liver transplantation. Clin Transpl 2002;16:301 – 5

184. O'Caroll RE, Couston M, Cossar J, Masterton G, Hayes PC. Psychological outcome and quality of life following liver trans- plantation: a prospective, national, single-center study. Liver Transpl 2003;9:712 – 20

185. Mollasiotis A, Van den Akker OBA, Milligan DW, Goldman JM. Symptom

distress, coping style and biological variables as predictors of survival after bone marrow transplantation. J Psychosom Res 1996;42:275 – 85

186. Rodrigue JR, Pearman TP, Moreb J. Morbidity and mortality following bone marrow transplantation: predictive utility of pre- BMT affective functioning, compliance, and social support stability. Int J Behav Med 1999;6:241–54

187. Giovanni Measso , Fabiano Cavarzeran , Giuseppe Zappalà , Barry D. Lebowitz , Thomas H. Crook , Francis J. Pirozzolo , Luigi A. Amaducci , Danilo Massari & Francesco Grigoletto. The mini-mental state examination: Normative study of an Italian random sample, Developmental Neuropsychology 1993; 9:2, 77-85

188. First M.B., Structured Clinical Interview for the DSM (SCID), Wiley Online Library, Gen 2015

189. Sirri L, Fava GA. Diagnostic criteria for psychosomatic research and somatic symptom disorders. International Review of Psychiatry, February 2013; 25(1):19-30

190. Fava , G.A. , Freyberger , H.J. , Bech , P. , Christodoulou , G. , Sensky , T. , Theorell , T. & Wise , T.N . (1995) Diagnostic criteria for use in psychosomatic research . Psychotherapy and Psychosomatics , 63,1 – 8

191. Porcelli , P. & Rafanelli , C . (2010) . Criteria for psychosomatic research (DCPR) in the medical setting . Current Psychiatry Reports , 12 , 246 – 254 .

192. Porcelli , P. & Sonino , N . (2007) . Psychological Factors Affecting Medical Conditions . A New Classifi cation for DSM-V . Advances in Psychosomatic Medicine, vol. 28 . Basel, Switzerland:Karger.

193. Chaturvedi , S.K. & Goswami , K . (2012) . Feasibility of Diagnostic Criteria for Psychosomatic Research in India: A pilot qualitative evaluation . Psychotherapy and Psychosomatics ,81 , 320 – 321 .

194. Tomba , E. , Rafanelli , C. , Grandi , S. , Guidi , J. & Fava , G.A . (2012) . Clinical confi guration of cyclothymic disturbances . Journal of Affective Disorders , 139 , 244 – 249

195. Fava , G.A. , Guidi , J. , Semprini , F. , Tomba , E. & Sonino , N . (2010a) . Clinical assessment of allostatic load and clinimetric criteria . Psychotherapy and Psychosomatics , 79 ,280 – 284.

196. Tomba , E. & Offi dani , E . (2012) . A clinimetric evaluation of allostatic overload in the general population. Psychotherapy and Psychosomatics , 81 , 378–379 .

197. Galeazzi , G.M. , Ferrari , S. , Mackinnon , A. & Rigatelli , M . (2004) . Interrater reliability, prevalence, and relation to ICD-10 diagnoses of the Diagnostic Criteria for Psychosomatic Research in consultation – liaison psychiatry patients . Psychosomatics , 45 ,386 – 393 .

198. Carpinelli Mazzi M, Iavarone A, Russo G , Musella C Milan G, D'Anna F, Garofalo E, Chieffi S, Sannino M, Illario M, De Luca V, Postiglione A, Abete P. Mini-Mental State Examination: new normative values on subjects in Southern Italy. Aging Clinical and Experimental Research. June 2019.

199. Fava GA, Kellner R. Italian validation of the Symptom Rating scale (SRT) and symptom Questionnaire (SQ). The Canadan Journal of Psychiatry/ LA Revue canadienne de psychiatrie 1983

200. Ware JE, Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996,34: 220–233.

201. Ware JE, Kosinski M, Keller SD: How to score the SF-12 physical and mental

health summary scales. 2nd edition. Boston, MA: The Health Institute; 1995.

202. Gandek B, Ware JE Jr, Aaronson NK, Alonso J, Apolone G, Bjorner J, Brazier J, Bullinger M, Fukuhara S, Kaasa S, Leplege A, Sullivan M: Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998, 51: 1171–1178.

203. Carver CS. You want to measure coping but your protocol' too long: consider the brief cope. International Journal of Behaviour Medicine 1997; 4:92

204. Sirri L, Magelli C, Grandi S. Predictors of perceived social support in long-term survivors of cardiac transplant: The role of psychological distress, quality of life, demographic characteristics and clinical course. Psychology and Health Vol. 26, No. 1, January 2011, 77–94

205. Cohen, S., & Hoberman, H.M. (1983). Positive events and social supports as buffers of life change stress. Journal of Applied Social Psychology, 13(2), 99–125.

206. Cohen, S., Mermelstein, R., Kamarck, T., & Hoberman, H.M. (1985). Measuring the functional components of social support. In I.G. Sarason & B.R. Sarason (Eds.), Social support: Theory, research and applications (pp. 73–94). Boston: Martinus Nijhoff Publishers.

207. Cohen, S., & Wills, T.A. (1985). Stress, social support, and the buffering hypothesis. Psychological Bulletin, 98(2), 310–357.

208. Brookings, J.B., & Bolton, B. (1988). Confirmatory factor analysis of the Interpersonal Support Evaluation List. American Journal of Community Psychology, 16(1), 137–147.

209. Delistamati, E., Samakouri, M.A., Davis, E.A., Vorvolakos, T., Xenitidis, K.,

& Livaditis, M. (2006). Interpersonal Support Evaluation List (ISEL) – college version: Validation and application in a Greek sample. International Journal of Social Psychiatry, 52(6), 552–560.

210. Tedeschi, R. G., & Calhoun, L. G. The Posttraumatic Growth Inventory: Measuring the positive legacy of trauma. Journal of Traumatic Stress 1996; 9: 455–471

211. Prati, G., & Pietrantoni, L. Crescita post-traumatica: un'opportunità dopo il trauma? Psicoterapia Cognitiva e Comportamentale 2006; 12:133-144

212. McCullough, M. E., Kilpatrick, S. D., Emmons, R. A., & Larson, D. B. Is gratitude a moral affect? Psychological Bulletin 2001; 127: 249–266

213. Poynard T, Cacoub P, Ratziu V, Myers RP, Dezailles MH, Mercadier A, Ghillani P, et al. Fatigue in patients with chronic hepatitis C. *J Viral Hepat* 2002; 9: 295-303.

214. Rafanelli, C., Roncuzzi, R., Milaneschi, Y., Tomba, E., Colistro, M.C., Pancaldi, L.G. & Di Pasquale, G. Stressful life events, depression and demoralization as risk fac- tors for acute coronary heart disease. Psychotherapy and Psycho- somatics. 2005; 74, 179–184.

215. Mikkelsen HET1, Vassbakk-Brovold K, Antonsen AJ, Berntsen S, Kersten C, Fegran L. Cancer Patients' Long-term Experiences of Participating in a Comprehensive Lifestyle Intervention Study While Receiving Chemotherapy. Cancer Nurs. 2018 Oct 12.

216. Burra P, De Bona M, Germani G, Canova D, Masier A, Tomat S, Senzolo M. The concept of quality of life in organ transplantation. Transplant Proc 2007; 39: 2285-7.

217. Magistri P, Marzi L, Guerzoni S, Vandelli M, Mereu F, Ascari F, Guidetti C, et al. Impact of a Multidisciplinary Team on Alcohol Recidivism and Survival After Liver Transplant for Alcoholic Disease. Transplant Proc 2019; 51: 187-9.

218. De Geest S, Burkhalter H, Berben L, Bogert LJ, Denhaerynck K, Glass TR, Goetzmann L, et al. The Swiss Transplant Cohort Study's framework for assessing lifelong psychosocial factors in solid-organ transplants. Prog Transplant 2013; 23: 235-46.

219. Schneekloth TD, Hitschfeld MJ, Petterson TM, Narayanan P, Niazi SK, Jowsey-Gregoire SG, Thusius NJ, et al. Psychosocial Risk Impacts Mortality in Women After Liver Transplantation. Psychosomatics 2019; 60: 56-65.