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Psycho-cognitive individual resources of Liver Pre-Transplant Candidates pave the way for identifying an adherence core: A Retrospective Pilot Study

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Abstract

Background: Patients' adherence to medical prescription during pre- and post- liver transplant phases is crucial to prevent treatment inefficacy. Literature has highlighted the urge of performing a psychological characterization to prevent post-intervention relapses and to impede treatment non-adherence behavior. The aim of this study is to define an "adherence core" by investigating personality traits, cognitive functions, and affective symptoms of patients waiting for liver transplant to enhance treatment effectiveness. We hypothesize a negative correlation between depressive and anxious symptoms and cognitive abilities and a positive association between some personality traits (Open-mindedness, Conscientiousness and Extraversion) and cognitive functions.

Materials and methods: Forty-six candidates (23 females, mean age: 56.02 ± 7.81 years, range: 39-76) for liver transplantation were assessed utilizing the following psychometric tools: State-Trait Anxiety Inventory Form Y1 and Form Y2, Big Five Questionnaire and Beck Depression Inventory 2. Cognitive assessment included: Coloured Progressive Matrices, Rey's 15-word list, Semantic Incidental Memory Test for Adults, Attentional Matrices Test and Corsi Block-tapping Test.

Results: The findings showed that education level negatively correlated with trait anxiety and positively correlated with Open-mindedness and Emotional Stability. Coloured Progressive Matrices negatively correlated with trait anxiety and depressive symptoms and positively correlated with Emotional Stability and Open-mindedness. Significant correlations were also shown between cognitive tests. Rey Immediate Recall scores showed positive correlation with: Rey Delayed Recall, Semantic Incidental Memory, and Attentional Matrices. Moreover, the findings demonstrated a positive correlation between trait anxiety and depressive symptoms, as well as a negative correlation between trait anxiety and Emotional Stability. Additionally, state anxiety was found to be positively correlated with depressive symptoms and negatively correlated with Energy and Open-mindedness.

Discussion: Higher fluid abilities, with lower degree of depression state, less pronounced anxious trait, and more open-minded personality can potentially aid patients in managing the distress associated with pre- and post-transplantation, ultimately resulting in optimal adherence. Furthermore, the positive association observed between the attention and memory domains might suggest their significant involvement in predicting adherence trajectories. In line with literature highlighting the paramount role of psychological factors in recovering from organ transplant, this study paves the road for the potentiation of individual resources and weaknesses identification to reduce relapses and healthcare costs. However, small sample size and lack of causality direction of results prevent robust conclusions.

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1. Introduction

Liver transplantation (LT) is the elective intervention for a broad range of diseases, but is mainly directed towards patients with hepatic cancers at the early stage, cirrhosis secondary to chronic viral hepatitis, liver-based metabolic conditions, and alcohol abuse (Siciliano et al., 2012). Since the first LT performed by the physician Starzl in the 60s, the number of liver transplants have constantly been growing (Fricker, 2017). In the above-mentioned population, transplantation can substantially increase survival rates, and is growingly used in liver condition management (Howard et al. 1994). Based on 17.044 adult patients obtained from the United Network for Organ Sharing (UNOS), Freischlag and colleagues (2019) reported that the overall post-transplant survival exceeded 85% in the first year and exceeded 75% at 5 years in adults who received a LT between 2006 and 2016. From this perspective, LT constitutes a significant lifesaving surgical procedure that is associated with improved longevity and quality of life. In recent years, machine learning (ML) has been recently proposed in the field of liver transplantation with the aim of increasing diagnostic and prognostic accuracy; in this context, ML models have been developed to predict pretransplant survival in cirrhotic patients, to determine the best donor-to-recipient match during allocation processes, and to predict postoperative complications and outcomes (Ferrarese et al., 2021).

LT is performed by a team of specialists who play a significant role in all the phases of the procedure (pre-, during and post- surgery). However, the management of patients requires a person-centered approach going beyond the mere medical procedure, given the paramount impact of medical conditions, such as organ transplant, on life quality (Åberg, 2020), including body image concerns, depression and anxiety symptoms (Zimbrea et al., 2019; Demir et al., 2021), and higher sense of guilt felt especially by liver and kidney recipients towards organ donors (Tarabeih et al., 2020), who are reported to often develop depression symptoms after intervention (Ng et al., 2021; Ong et al., 2021). Over the years, psychiatrists, psychologists, and other mental health professionals have been involved in the mentioned phases for different

reasons such as i) mental health problems; ii) medication nonadherence; iii) general behavioral issues. In this context, patients' adherence, defined as an extent to which a patient's behavior coincides with medical or prescribed health advice, plays a pivotal role in patients' treatment and recovery (Julius et al., 2009; Iasevoli et al., 2012).

On the other hand, medication nonadherence is a phenomenon that can reflect the presence of intentional or unintentional psychological barriers to medical prescription pursuit (Lehane & McCarthy, 2007a; 2007b). For example, depressive symptoms are associated with lower perceived autonomy and control, thus preventing their adherence to treatment due to the lack of perceived empowerment (Myles et al., 2020; 2021).

From a pragmatic point of view, lack of adherence towards medical recommendations negatively affects many key aspects including responsibility to take medications (i.e., immunosuppressives), observing medical appointments, undergoing laboratory tests, self-monitoring important vital parameters, maintaining a healthy lifestyle, and avoiding the use of predictable harmful substances (Krahn & DiMartini, 2005). Lack of adherence to treatments lead to serious consequences, such as re-hospitalization, symptoms worsening, low levels of treatment efficacy, increased mortality, and healthcare costs, amongst others (Stephenson, 1999; Willey et al., 2000; Williams et al., 2004; Lehane & McCarthy, 2007a; 2007b).

Adherence to treatment recommendations can be affected by mental health issues, thus jeopardizing the treatment success and the clinical benefits, reducing the overall effectiveness of health systems (Dou et al., 2020).

The rapid identification of mental health issues and related critical aspects play an important role during the pre-operative stage and the subsequent phases, in order to help the medical decision-making process outlining highly individualized care plan management and tailored treatment based on patients' specific psychological, cognitive and behavioral profile (Golfieri et al., 2019; Becker et al., 2021). Therefore, the psychological assessment of candidates under consideration for transplant, including LT, is widely endorsed to optimize future outcomes (Dew et al., 2000; Dobbels et al., 2000; Streisand et al., 1999). In particular, pre-transplant screening should evaluate whether the patients could undergo transplant being aware of the serious consequences of unhealthy lifestyle in post-transplant condition (e.g., drug and alcohol abuse, wrong dietary regimen, neglecting pharmacological prescription), and to discriminate subclinical anxiety and mood-related symptoms limited to the incoming intervention from clinical symptoms that could interfere with patients' adherence and treatment outcomes. As stated by Grover and Sarkar (2012, p. 384), "*the identification and the management of psychiatric problems in the pre-transplant phase is very important because these have a bearing on the post-transplant outcome*".

Since affective states, mental attitude and cognitive abilities concur in determining a lower or higher degree of adherence toward treatments, the assessment of patients' cognitive functions and personality traits is highly recommended to ensure patients' comprehension of the surgical procedure, all transplant-related risks, and to adhere with post-transplant immunosuppressive regimens (Ko et al., 2018; López-Navas et al., 2019; Caputo et al., 2022).

Adherence can be measured by health care workers, with use of patients' self-reports and other instruments such as cognitive tests and structured interviews. The composite nature of the assessment allows a multidimensional evaluation of patients' functioning, which assumes a primary role in high-risk clinical fields such as transplant. A better specification and characterization of mental health difficulties in a reliable way could help clinical interventions to better support people in post-intervention management (Merlo et al., 2022). It is worth to note that an in-depth and systematic characterization of personality traits, affective states and cognitive functions has been conducted in a few chronic diseases, such as osteoporosis (Catalano et al., 2020), hyperthyroidism (Vita et al., 2020), COVID-19 (Orrù et al., 2021; Miniati et al., 2021) and asthma (Silvestro et al., 2023), the latter showing that alexithymia is associated with negative biases (Barchetta et al., 2021); however, psychological and cognitive assessment has not been conducted in liver-transplant patients, yet. Indeed, it has been highlighted the importance of pre-transplant psychological assessment, which is still scarcely investigated, and it does not consider the cognitive domain (Nghiem et al., 2020).

1.1 Aims and hypotheses

Considering the foregoing premises, the aim of the present study is to detect an “adherence core”, that can be defined as a cluster of cognitive and psychological variables, in order to set eligibility criteria permitting liver pre-transplant patients admission to surgical intervention. This will allow us to understand possible relations between cognitive, psychological variables and patients' adherence. We hypothesize a negative correlation between depressive and anxious symptoms and cognitive abilities and a positive association between some personality traits (Open-Mindedness, Conscientiousness, Emotional Stability and Extraversion) and cognitive functions.

2. Materials and methods

2.1 Participants

Forty-six Italian-Speaking participants were recruited. The sample with a comprehensive evaluation consisted of 46 liver pre-transplant candidates (females = 23; mean age = 56.02 ± 7.81 years, range: 39-76; mean education = 9.01 ± 3.53 , range: 5-18). The participants were recruited

from February 2019 to February 2020. All patients were referred from the Hepatobiliary Surgery and Liver Transplantation Unit (University of Pisa Medical School Hospital) to Santa Chiara's Hospital (AOUP, University of Pisa) with a history of chronic liver dysfunction of exotoxic origin, viral type B (HBV), C (HCV), D (HDV), or E (HEV), and metabolic dysfunction. The exclusion criteria were the following: (i) age ≤ 18 ; (ii) education level below 5 years; (iii) poor knowledge of the Italian Language; (iv) uncorrected vision. Moreover, patients with a history of drug abuse, those affected by neurologic or psychiatric diseases, and those receiving medication having significant effects on the central nervous system were excluded.

The local ethical committee of University of Pisa (Prot. 0036349/2020, 10/04/2020) approved all procedures. All patients gave their consent before participating. All participants performed the experimental session, and no dropouts have been registered.

2.2 Procedure

After a semi-structured comprehensive interview performed by an expert psychiatrist (A.G.) to collect medical and biographical information, patients underwent a psychological and cognitive assessment (detailed described below). Each patient underwent a single session comprising a self-report psychometric and a neuropsychological battery. Patients were required to identify choices, preferences, and strengths of feeling (test of typical performance, psychometric evaluation), and to put their maximum effort in task performance (test of maximum performance, cognitive test). At the end of the interview, they were given the following instructions: "Now you will undergo some questions and tests about your way of thinking and feeling in this moment and in everyday life. Try to stay focused on the task and, should you need further clarification, feel free to ask".

The psychological assessment included the following psychometric inventories: *State-Trait Anxiety Inventory Form Y1 and Form Y2* (STAI-Y1, Y2; Spielberger, 1983), *Big Five Questionnaire* (BFQ, Caprara et al., 1993) and *Beck Depression Inventory 2* (BDI, Beck et al., 1996).

- *State-Trait Anxiety Inventory Form Y1 and Form Y2* (STAI-Y1, Y2; Spielberger, 1983, italian version: Pedrabissi & Santinello, 1989) is a self-report questionnaire to assess state and trait anxiety. The STAI-Y is a self-administered instrument composed of two subscales that may be used independently evaluating state anxiety (STAI-Y1) and trait anxiety (STAI-Y2). Both subscales rely on 20 items, scored on a Likert scale from 1 to 4. The total score of the two subscales ranges from 20 to 80 and identifies three levels of anxiety severity: absent/low (20-39), medium (40-59), high (60-80) (Pedrabissi & Santinello, 1989; Spielberger et al., 1983, 1970). It has been reported a good internal consistency

for both the state and trait anxiety subscales of the STAI, with Cronbach's alpha coefficients ranging from 0.91-0.95 and 0.85-0.90, respectively.

- *Big Five Questionnaire* (BFQ, Caprara et al., 1993) is a 132 items self-report questionnaire to assess personality traits using 5-point ratings (1 = very false for me to 5 = very true for me) The BFQ-C encompasses five dimensions, namely Energy/Extraversion, Agreeableness, Conscientiousness, Emotional Instability, and Intellect/Openness. Energy/Extraversion pertains to attributes like sociability, assertiveness, and enthusiasm. Agreeableness involves qualities reflecting consideration for others. Conscientiousness is associated with reliability and tidiness. Emotional Instability (Neuroticism) is linked to mood variations, such as susceptibility to anger, depression, or anxiety. Intellect/Openness revolves around imagination, creativity, intelligence, and a willingness to embrace new experiences. The questionnaire has a good internal consistency, ranging from 0.74 and 0.83.
- *Beck Depression Inventory-II* (BDI, Beck et al., 1996; italian version: Sica & Ghisi, 2007). The BDI-II is a self-administered instrument for the assessment of the severity of depression in already diagnosed patients and for the detection of the risk of depression in the normal population. It has also proven effective in discriminating between patients with clinical depression from non-depressed psychiatric patients.
- The Italian translation of Sica and Ghisi (2007) has been used for the purpose of this study. The internal consistency was 0.80, the item correlation ranged from 0.30 to 0.46. The test-retest correlation was good: 0.76.

The cognitive assessment included *Coloured Progressive Matrices* (CPM47) (Caltagirone et al., 1995; Carlesimo et al., 1996), *Rey's 15-word list* (Rey-15) (Rey, 1958; italian version: Carlesimo et al., 1996), *Semantic Incidental Memory Test for Adults* (SIM) (Spinnler & Tognoni, 1987), *Attentional Matrices Test* (AM) (Spinnler & Tognoni, 1987) and *Corsi Block-tapping Test* (Spinnler & Tognoni, 1987).

- *Coloured Progressive Matrices* (CPM47, Caltagirone et al., 1995; Carlesimo et al., 1996) is a nonverbal group test used to measure abstract reasoning and is considered a non-verbal estimate of fluid intelligence. This test contains a set of 36 items. The final score is the sum of correct answers provided (range: 0-36) (cut-off: 18.96). The Cronbach alpha coefficient for the whole scale was determined as 0.83.
- *Rey's 15-word list* (Rey-15, Rey, 1958; italian version: Carlesimo et al., 1996) is a verbal memory test. Patients were required to recall a word list of 15 words immediately

following its presentation five times and, again, after a delay interval (15 minutes). At the end of the reading, the patient was asked to repeat as many words as possible. The procedure is used five consecutive times and is used to measure the immediate recall (IR). After an interval of 15 minutes, during which other tests were performed, patients were asked to remember (without the list being re-proposed by the examiner) as many words as possible from the list. This was the second part of the test and is used to measure the deferred recall (DR). For the IR, the final score was the sum of each word recalled correctly (range 0-75) (cut-off: 28.53). Regarding the DR, the final score depended on the number of the words recalled from the list (range 0-15) (cut-off: 4.69). Information regarding test-retest reliability is not available for the standard protocol, but the work of Paul et al., (1992) found a 2-week retest value of .48 which achieves 0.88 under simulation condition.

- *Semantic Incidental Memory Test for Adults* (SIM, Spinnler & Tognoni, 1987) was applied to evaluate the antegrade memory in incidental learning conditions. Patients were provided with a list of animals and were required to associate at least one prototypical color to each animal's name. The final score was based on the number of stimuli provided by the subject (range: 0-20).
- *Attentional Matrices Test* (AM, Spinnler & Tognoni, 1987) was applied to assess the subjects' ability to detect visual targets among distractors. With this purpose, three matrices of numbers were administered with the instruction to cross out, as fast as possible, target numbers containing one, two or three digits. The overall number of correct crossed out targets obtained across the three matrices was the final score. Reliability index was determined as 0.53.
- *Corsi Block-tapping Test* (CBT, Spinnler & Tognoni, 1987) was adopted for measuring spatial learning ability. The subject was required to touch a progressively increasing number of blocks in a specific order shown by the researcher until he was no longer able to perfectly reproduce the sequence seen. The final score derived from the longest sequence correctly remembered. Reliability index was determined as 0.37.

2.3 Statistical analysis

The Shapiro-Wilk test was used to check the normality hypothesis of data distribution. As data did not conform to gaussian distribution ($p < 0.05$), the Spearman's rank-order correlation was employed to examine interrelationships between variables. Statistical significance was set up at $p \leq 0.05$. Since we stated the exploratory nature of the study and given the focus on data exploration and hypothesis generation, the study opted not to perform multiple comparisons.

Sample size was determined based on a priori power analysis using G*Power (alpha=0.05, power= 0.80). Since this work constitutes a pilot study, we enrolled 46 participants by achieving the following parameters: alpha=0.08, power=0.65. However, we based the number of participants by reviewing studies with similar purposes, finding a numerical overlap with our sample size.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

3. Results

A total of 46 liver-transplant candidates (females=23; mean age=56.02±7.81 years, range: 39-76; mean education: 9.01±3.53, range: 5-18) participated in the study. All the variables considered were the following: age, education, psychological (STAI-Y1, STAI-Y2, BDI-II and Big Five) and cognitive measures (CPM47, IR and DR of Rey-15, AM, CBT, SIM). Means, standard deviations (SD), mean standard error for age, education (both quantitative and discrete) and tests scores (quantitative and continuous) are reported in Table 1. Spearman's coefficients are shown in Table 2.

Table 1. Demographic features, cognitive performance, and psychological measures

Sample Size (N=46)	Mean	Std. dev. (SD)	Range
Age	56.02	7.81	39-76
Education	9.91	3.53	5-18
CPM47	27.26	6.21	8-37
IR	30.04	9.54	18-53
DR	8.80	2.99	0-14
CBT	4.67	0.85	2-6
SIM	11.70	3.05	3-17
AM	48.96	8.55	19-60
STAY-Y1	40.96	9.78	26-64
STAY-Y2	37.87	9.46	22-65
BDI-II	9.37	6.64	0-27
Big5E	71.65	7.60	51-87
Big5C	78.54	7.57	65-95
Big5S	74.37	13.45	40-108
Big5M	76.54	13.21	32-104
Big5L	36.83	10.74	23-85

Notes: *AM*, Attentional Matrices Test; *BDI-II*, Beck Depression Inventory-II; *Big5E*, Big Five Questionnaire Energy; *Big5C*, Big Five Questionnaire Conscientiousness; *Big5S*, Big Five Questionnaire Emotional Stability; *Big5M*, Big Five Questionnaire Open-Mindedness; *Big5L*, Big Five Questionnaire Lie; *CBT*, Corsi Block-tapping Test; *CPM47*, Coloured Progressive Matrices; *DR*, Differed Recall of Rey's 15-word list; *IR*, Immediate Recall of Rey's 15-word list; *SIM*, Semantic Incidental Memory Test for Adults; *STAI-Y1*, *Y2*, State-Trait Anxiety Inventory Form Y1 and Form Y2.

We hypothesized that higher socioeconomic status and educational level were positively correlated to Open-mindedness, Emotional Stability and Conscientiousness personality traits and to cognitive functions, too. As regards demographic data, a negative and moderate correlation is shown between education level and trait anxiety (STAI-Y2, $r_s = -0.32$, $p = 0.027$), while a positive and moderate correlation is shown with Open-mindedness personality trait (Big5M, $r_s = 0.43$, $p = 0.003$) and Emotional Stability (Big5S, $r_s = 0.32$; $p = 0.029$). Patients with higher educational levels showed a lower anxiety trait, a higher emotional stability and they are more open-minded.

Concerning association between cognitive test and psychometric data, significant associations are shown. CPM score showed negative and moderate correlation with STAI-Y2 ($r_s = -0.36$, $p = 0.013$) and BDI-II ($r_s = -0.380$, $p = 0.010$) and positive and moderate correlation with Big5S ($r_s = 0.34$, $p = 0.029$) and Big5M ($r_s = 0.30$, $p = 0.003$). Patients who better scored CPM, specifically designed to measure the g factor as the purest measure of fluid intelligence, showed lower degree of trait anxiety, depressive symptoms and higher Emotional Stability and Open-mindedness.

Significant associations are also shown between cognitive tests assessing different functions. Rey IR scores showed positive and strong correlation with Rey DR ($r_s = 0.67$, $p < 0.0001$), positive and moderate correlation with SIM ($r_s = 0.30$, $p = 0.043$) and AM ($r_s = 0.30$, $p = 0.007$). Patients who had better short-term memory performance also displayed better semantic incidental memory and selective attention performances.

We hypothesized that high level of trait anxiety was associated with high level of state anxiety, which, in turn, could be associated with depressive symptoms. We also hypothesized that this anxious-depressive cluster was negatively correlated to Open-mindedness, Energy and Emotional Stability. As regards the associations between psychometric variables, results showed a strong and positive correlations between STAI-Y1 and STAI-Y2 ($r_s = 0.701$, $p < 0.0001$), moderate and positive correlation between STAI-Y1 and BDI-II ($r_s = 0.36$, $p = 0.015$), moderate and negative correlation between STAI-Y1 and Big5S ($r_s = -0.50$, $p = 0$). Patients who experienced more anxiety states are more likely to have a more pronounced anxious trait, as well as to experience more depressive symptoms and to be less emotionally stable. Patients with higher levels of trait anxiety are more susceptible to experiencing depressive symptoms and tend to exhibit less emotional stability, lower energy levels, and reduced openness to new experiences.

The results concerning the STAI-Y2 revealed a moderate and positive correlation with BDI-II ($r_s = 0.62$, $p < 0.0001$), alongside moderate and negative correlation with Big5E ($r_s = -0.42$, $p = 0.004$), Big5S ($r_s = -0.60$; $p < 0.0001$) and Big5M ($r_s = -0.40$, $p = 0.006$). Patients with higher levels of trait anxiety are more susceptible to experiencing depressive symptoms and tend to exhibit less emotional stability, lower energy levels, and reduced level of open-mindedness.

Regarding BDI-II, results showed moderate and negative correlation with Big5E ($r_s=-0.32$, $p=0.029$), Big5S ($r_s=-0.33$, $p=0.025$). Patients that are more likely to experience depressive symptoms showed less emotional stability and energy.

Concerning Big5 scales, results showed a positive and slight correlation between Big5E and Big5C ($r_s=0.29$; $p=0.048$); a positive and moderate correlation between Big5E and Big5M ($r_s=0.54$; $p=0$); Big5E and Big5L ($r_s=0.34$; $p=0.020$). Patients with higher levels of energy are more open-minded, conscientious, and emotionally stable.

Table 2. This table shows Spearman’s coefficients: association between demographics, psychological and cognitive measures. In bold, the values different from zero with a p-value ≤ 0.05 .

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1 Age	1	0.16	-0.07	-0.18	-0.16	-0.01	-0.06	-0.04	-0.12	-0.15	-0.27	0.04	0.07	0.25	0.15	0.06
2 Education	0.16	1	0.26	0.00	-0.13	0.14	0.06	0.08	-0.21	-0.32	-0.17	0.09	0.28	0.32	0.43	-0.10
3 CPM47	-0.07	0.26	1	0.11	0.08	0.26	0.17	0.20	-0.13	-0.36	-0.38	0.23	0.18	0.34	0.30	-0.04
4 IR	-0.18	0.00	0.11	1	0.67	0.09	0.30	0.39	-0.09	0.04	-0.03	0.25	0.01	0.03	0.13	0.10
5 DR	-0.16	-0.13	0.08	0.67	1	0.11	0.22	0.19	0.11	0.22	-0.05	0.08	-0.23	-0.00	-0.09	0.13
6 CBT	-0.01	0.14	0.26	0.09	0.11	1	0.12	-0.00	-0.02	-0.02	-0.07	0.09	-0.18	0.23	0.24	0.02
7 SIM	-0.06	0.06	0.17	0.30	0.22	0.12	1	0.14	0.01	-0.02	-0.03	0.15	-0.07	-0.14	0.11	0.08
8 AM	-0.04	0.08	0.20	0.39	0.19	-0.00	0.14	1	0.03	0.00	0.05	-0.07	-0.08	-0.04	0.00	0.00
9 STAY-Y1	-0.12	-0.21	-0.13	-0.09	0.11	-0.02	0.01	0.03	1	0.70	0.36	-0.24	-0.03	-0.50	-0.19	-0.22
10 STAI-Y2	-0.15	-0.32	-0.36	0.04	0.22	-0.02	-0.02	0.00	0.70	1	0.62	-0.42	-0.19	-0.60	-0.40	-0.24
11 BDI-II	-0.27	-0.17	-0.38	-0.03	-0.05	-0.07	-0.03	0.05	0.36	0.62	1	-0.32	-0.23	-0.33	-0.29	-0.11
12 Big5E	0.04	0.09	0.23	0.25	0.09	0.09	0.15	-0.07	-0.24	-0.42	-0.32	1	0.29	0.24	0.54	0.34
13 Big5C	0.07	0.28	0.18	0.01	-0.23	-0.18	-0.07	-0.08	-0.03	-0.19	-0.23	0.29	1	0.07	0.28	-0.10
14 Big5S	0.25	0.32	0.34	0.03	-0.00	0.23	-0.14	-0.04	-0.50	-0.60	-0.33	0.24	0.07	1	0.32	0.09
15 Big5M	0.15	0.43	0.30	0.13	-0.09	0.24	0.11	0.00	-0.19	-0.40	-0.29	0.54	0.28	0.32	1	0.11
16 Big5L	0.06	-0.10	-0.04	0.10	0.13	0.02	0.08	0.00	-0.22	-0.24	-0.11	0.34	-0.10	0.09	0.11	1

Notes: *AM*, Attentional Matrices Test; *BDI-II*, Beck Depression Inventory II; *Big5E*, Big Five Questionnaire Energy; *Big5C*, Big Five Questionnaire Conscientiousness; *Big5S*, Big Five Questionnaire Emotional Stability; *Big5M*, Big Five Questionnaire Open-Mindedness; *Big5L*, Big Five Questionnaire Lie; *CBT*, Corsi Block-tapping Test; *CPM47*, Coloured Progressive Matrices; *DR*, Differed Recall of Rey’s 15-word list; *IR*, Immediate Recall of Rey’s 15-word list; *SIM*, Semantic Incidental Memory Test for Adults; *STAI-Y1, Y2*, State-Trait Anxiety Inventory Form Y1 and Form Y2.

4. Discussion

This pilot study investigated a set of cognitive and psychological variables that might concur to constitute an adherence core in liver pre-transplant candidates. With this in-depth investigation, we identified recurrent psycho-cognitive associations that could play a pivotal role in pre-transplant candidates' adherence; the aim was driven by the necessity of a better comprehension of behavior, feelings, cognitive abilities, and personality traits that could be determinant for clinical outcomes and quality of life in post-transplant phase (Grover & Sarkar, 2012). In a clinical setting, adherence is a multifactorial construct representing a mixture of cognitive abilities (e.g., to comprehend and remember physician's prescriptions) and psychological factors (feeling of anxiety, depression, lack of motivation, lack of problem-solving abilities to cope with the situation). It is worth noting that the pre-transplant phase could represent a distressing situation that requires a set of ability to counteract possible stress-related side effects. Previous studies identified adherence often using a compartmentalized perspective, without taking into consideration the multifactorial nature of this variable (Julius et al., 2009). Among the tools used for adherence assessment, self-report measures are often employed because they are practical and cheap, but to the detriment of sensitivity (Stirratt et al., 2015).

4.1 Psycho-cognitive relations: fluid intelligence, affective states, and personality traits

Our results showed that candidates who better performed CPM47, specifically designed to measure the g factor and as the purest measure of fluid intelligence, showed lower degree of trait anxiety, depressive symptoms and higher emotional stability and open-mindedness. Several studies pointed out the power of personality traits in affecting fluid reasoning. Studies on the relationship between intelligence and trait anxiety have yielded contradictory findings (Matarazzo, 1972). Although some studies have reported a negative correlation between trait anxiety and intelligence (Samuel, 1980, Tapasak et al., 1978), others did not find a significant relationship between the two of them (Leith, 1972; Leon & Revelle, 1985). To our knowledge, since fluid intelligence also concerns the ability of problem solving, self confidence in disentangling life issues might result in low levels of dispositional anxiety; on the other hand, a causal role of low anxiety in laying the foundations for better problem-solving abilities cannot be definitely ruled out. Another possible explanation of the inverse relationship between anxiety and intelligence might not necessarily imply that individuals experiencing test anxiety perform poorly on cognitive tests solely due to their anxiety. In fact, individuals with lower intelligence, aware of their potential for below-average performance, may experience heightened anxiety during tests (Mueller, 1992). However, Tobias (1985) argued that the "*deficit hypothesis*" does not

adequately elucidate the negative correlation between test anxiety and performance observed in high-achieving individuals.

Another perspective comes from Oostdam and Meijer (2003), who conducted a study investigating whether the negative correlation between test anxiety and IQ test performance aligns more with the deficit hypothesis or with the occurrence of task-irrelevant processing, referred to as the interfering hypothesis. Their results supported the interfering hypothesis over the deficit hypothesis, suggesting that factors such as task-irrelevant processing may play a more significant role in the observed association between test anxiety and intelligence test performance.

As regards open-minded personality traits and fluid intelligence, several studies have established significant relations. As fluid intelligence had been defined as the ability of “*making meaning out of confusion; developing new insights; going beyond the given to perceive that which is not immediately obvious*” (Raven et al., 1998, p. 64), an open-minded personality trait could fit with this construct. Moreover, it is likely that objective competencies (e.g., high Gf) support intellectual interests such as those represented by the Openness trait (Matthews et al., 2000). Cattell (1943) had already suggested that Gf is a precondition for knowledge acquisition and application. Another explanation could be sustained: in fact, fluid intelligence may influence the development of Openness over time (Moutafi et al., 2006), stating that individuals showing higher Gf have an innate ability to cope more efficiently with novel experiences, and to deal with stimulating tasks which would thus make it rewarding for them to perform such activities. Similarly, individuals with lower on Gf may in time grow to avoid such activities, due to their low ability to handle them, which would thus make them less rewarding

Interestingly, among psychometric tests assessing affective-state symptoms, only mood depressive deflections, assessed with BDI-II, are inversely associated with fluid intelligence. Generally, previous studies have found a positive association between these two variables, with depressive people scoring higher on a measure of fluid intelligence compared to controls or other clinical populations (Schaefer et al., 2017), whereas other studies reported intelligence impairments in depressed populations (Hammar & Årdal 2009; Brevik et al., 2013). In the clinical field, depressive symptoms are associated with high rates of health care utilization and severe limitations in daily functioning (DiMatteo et al., 2000). It seems reasonable to anticipate a certain level of depressive symptoms in candidates undergoing transplantation, considering the distressing nature of the situation. The negative association between depressive symptoms and fluid intelligence may be influenced by patients' clinical history. For instance, it has been reported that candidates for kidney transplant may experience cognitive deficits, particularly in

executive function, attention, processing speed, planning ability, and deductive as well as reproductive abilities (Stoessel et al., 2017). This could sustain the relationship between depressive symptoms and fluid intelligence in our sample. Additionally, it is noteworthy that, given the significance of cognitive and affective variables in adherence, a role of fluid intelligence in “counteracting” depressive symptoms could be also proposed. Higher fluid intelligence has been generally linked to a lower likelihood of depression, suggesting that a decline in mental abilities may be accompanied by symptoms of psychological distress (Gale, 2011).

Fluid intelligence might play a pivotal role in adherence since it represents the ability to adapt our thinking to a new cognitive problem or situation. Gf is critical for a wide variety of cognitive tasks, and it is considered one of the most important factors in learning. In this perspective, adherence could be positively influenced by Gf, since patients have to adapt to new cognitive and affective situations requiring solving new problems, changing habits and self-monitoring. Given the results of our study, we can suggest that a particular cluster of characteristics associated with higher fluid ability, that are lower degree of depression state, less pronounced anxious trait, more open-minded personality, could help patients to manage pre and post transplantation distress and pave the road for optimal adherence.

4.2 Positive relation between memory abilities and attentional skills

Significant positive associations are also shown between cognitive tests assessing different functions.

Candidates who scored better at the Rey IR test showed a better performance in Rey DR, SIM test and AM.

It is not surprising that the above-mentioned domains resulted to be positively correlated, since attention lays the foundations for information encoding (Chun & Turk-Browne, 2007; Orrù et al., 2009). Moreover, good performance in verbal working memory tasks is highly associated with good long-term memory, since phonological loop functioning paves the road for optimal information storage (Kim et al., 2019).

Neuroanatomical evidence corroborates the foregoing results, since neural substrates of attention and memory are partly overlapped, especially the prefrontal cortex (Petersen & Posner, 2012). Brain areas that are crucial for memory, such as the hippocampus and medial temporal lobe structures, are recruited in attention tasks, and memory directly affects frontal-parietal networks. Furthermore, same memory networks with different activation are thought to be engaged for both episodic and semantic memory (Chun & Turk-Browne, 2007), supporting the positive correlation between semantic and episodic tasks.

It is important to point out that cognitive skills are involved in everything a human being may possibly do, since they refer to all the processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used (Neisser, 1967).

In the clinical field, research has reported that poorer cognitive function, particularly in memory, is associated with reduced adherence among patients with heart failure (Dolansky et al., 2016). Additionally, poor performance in attention, executive functions, and memory has been correlated with hospital readmissions in elderly patients across various medical conditions (Coin et al., 2009; Anderson & Birge, 2016). However, contrasting findings have been reported in studies assessing adherence in other clinical contexts. For instance, clinical samples with mild to moderate cognitive impairment may possess sufficient insight into the consequences of non-adherence to medication, leading to greater motivation to adhere (Ownby et al., 2006). Moreover, Nöhre et al., (2019) observed that there was no difference in adherence behavior between kidney transplant patients with and without cognitive impairment, suggesting that impaired cognitive functioning can be mitigated by social support and the implementation of practical strategies to enhance adherence (Smith et al., 2017). Conversely, it is worth noting that self-report instruments may not be the ideal means of assessing adherence in patients with cognitive impairment, as they may not accurately recall whether they have taken their medication.

These findings thus highlight the complex nature of medication adherence, which may be sustained by several factors beyond the cognitive domain. Nevertheless, proficient cognitive functioning could serve as a valuable asset in enhancing adherence.

5. Conclusion

Cognitive and psychological assessment carried out among liver transplant candidates allowed the detection of a cluster of associated state and dispositional characteristics that could constitute an adherence core. In particular, high fluid intelligence, emotional stability and open-mindedness, and low levels of trait anxiety and depressive symptoms resulted to be correlated and could be predictive characteristics of optimal adherence. On the other hand, lack of the aforementioned characteristics could represent risk factors for readmission to hospital, symptoms worsening, increased mortality and healthcare costs. In light of the foregoing evidence, cognitive and psychological assessment is strictly recommended in pre- and post-transplant phases, in order to manage patients' conditions from multidisciplinary perspectives and to prevent treatment nonadherence leading to serious outcomes.

6. Limitations

This study faced several limitations that should be addressed in future research endeavors. The modest sample size and its homogeneity with respect to ethnicity and age may have limited the robustness of our conclusions. Regarding statistical analysis, the decision to conduct correlations did not specify the direction of interaction and could have been influenced by latent factors impacting the variables under examination. Another concern is the extensive number of variables we assessed, hindering a concise a parsimonious explanation of adherence within the psycho-cognitive domains (Myles et al., 2023). By overcoming these issues, it will be possible to draw a personalized characterization of an adherence profile, and also establish an optional psychological intervention (such as psychotherapy) to improve patients' adherence, thus enhancing subjective quality of life after transplant. This study has a novelty aspect that could pave the road for better managing the post transplantation path, thus also reducing the biopsychosocial cost for the healthcare system.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

Data Availability Statement

Data are available on reasonable request to the corresponding author.

Ethics Statement

The study was carried out with written informed consent from all subjects, in accordance with the Declaration of Helsinki. All procedures followed the ethical standards and were approved by the Ethics Committee of the University of Pisa (Prot. 0036349/2020, 10/04/2020).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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