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LOW ADHERENCE TO THERAPY AND CO-MORBID DEPRESSIVE EPISODES ARE INDEPENDENT DETERMINANTS OF EARLY DEATH IN PEOPLE WITH CANCER

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ABSTRACT – *Objective:* The demanding nature of oncological therapies may affect treatment motivation and adherence, leading to an increased risk of premature death. Exploring the interaction between depressive episodes and treatment adherence is essential, considering how depression may influence patients' willingness to continue treatment. This study aims to investigate the association between depressive episodes, low treatment adherence, and premature death in individuals with cancer. The study also assessed whether low adherence to therapy acted as a mediator in the relationship between depression and the risk of early death.

Participants and Methods: This is a 9-month cohort study in which participants were enrolled in two Italian Oncology hospital units. The Patient Health Questionnaire (PHQ-9) was used for depression screening. Stratified analyses were conducted to explore the relationship between depression, low adherence, and premature death.

Results: Out of 263 subjects, depressive episode frequency was 48.2% and low adherence was 9.9%. After 9 months, 13.7% had died. There was a significative association between experiencing a depressive episode (RR=2.14, 95% CI: 1.08-4.39) and low adherence (RR=2.2, 95% CI: 1.01-4.48) upon cohort entry and being deceased at month 9 of observation. The risk associated with depression was found to persist even after accounting for the level of adherence to therapy through standardization (MH-OR=3.11; 95% CI: 1.52-6.34).

Conclusions: Individuals with cancer who experience a depressive episode or demonstrate low adherence to therapy are at risk for premature death. Early intervention targeting depressive symptoms and treatment adherence may improve oncological-related outcomes.

KEYWORDS: Adherence, Depression, Cancer, Psycho-oncology, Death risk.

INTRODUCTION

In a recent cohort study involving people with different kinds of cancer, the presence of a depressive episode during the observation period was found to be associated with an increased risk of premature death [1]. However, this previous research on the same cohort did not explore the link between depressive episodes at the beginning of the evaluations and premature death at the end of the observation period [1]. Moreover, this investigation did not examine the potential connection between depression, low adherence to therapy, and the heightened risk of early death.

Many previous studies have established a relationship between depression and low adherence to therapy [2-4]. Thus, it could be hypothesized that low adherence to therapy might act as a mediator in the association between depression and the risk of early death in people with cancer.

The risk of low adherence to therapy is of utmost importance in cancer treatment [5]. While the treatments for oncological diseases have achieved remarkable advancements in recent decades, they can be demanding and induce significant stress on the patient [6,7]. Consequently, motivation and adherence to treatment may be affected, and it is not surprising that low treatment compliance has been linked to premature death in people with cancer [8]. However, there is a limited number of studies on this subject.

It appears intuitive that two of the most extensively studied risk factors for premature death in cancer (low adherence to therapy and presence of a depressive episode) may interact, wherein the occurrence of a depressive episode can influence treatment adherence. Indeed, depressive symptomatology is often characterized by a loss of hope, which could potentially lead some individuals to no longer wish to continue taking medications or undergoing supportive therapies.

Regarding individuals with cancer specifically, the objectives of this study are as follows:

1) To investigate whether the presence of depressive episodes at the beginning of the cohort is associated with premature death at the end of the observation study (after 9 months).
2) To examine whether adherence to therapy at the beginning of the cohort is a determinant of premature death at the end of the observation study.
3) To assess whether adherence to therapy could act as a mediator in the potential risk of premature death associated with a depressive episode in people with cancer.

PARTICIPANTS AND METHODS

Study Design

This cohort study lasted for 9 months. The entire cohort comprised individuals undergoing cancer treatment and was divided into two sub-cohorts based on their level of treatment compliance. We calculated the risk of premature death associated with the presence of a depressive episode and low compliance to treatment at the entry of the cohort by analyzing the premature death rate in the two sub-cohorts after 9 months. Additionally, we assessed the potential mediating effect of low treatment compliance at the beginning of the cohort on the association between premature death and the presence of a depressive episode.

Study Sample

Participants were enrolled between 2018 and 2020 from the Oncology Clinics at the University Hospital of Cagliari, Italy, and the Hematology and Stem Cell Transplantation Center at “Ospedale Busico” of the Azienda Ospedaliera Brotzu, Cagliari, Italy. The inclusion criteria comprised individuals aged ≥ 18 years, of any gender, with a histologically confirmed malignant cancer undergoing active treatment.

Study Tools

A schedule was implemented to collect sociodemographic and clinical-oncological records. Treatment adherence was evaluated using a dichotomous scale, based on the judgment of the responsible clinician.

To screen for depressive episodes, the Italian version [9] of the “Patient Health Questionnaire” (PHQ-9) [10] was utilized. The PHQ-9 is a self-questionnaire commonly employed in community surveys and clinical settings as a case-finder. It consists of a 9-item scale that assesses the nine DSM-IV-TR criteria for Major

Depressive Disorder (MDD). Each item is scored from 0 (complete absence) to 3 (almost every day). A cut-off of a total score ≥7 is reasonably accurate for screening a mild/moderate MDD [9].

Statistical Analysis

Descriptive statistics were used to report frequencies (percentages) and mean ± standard deviation for sociodemographic and clinical-oncological variables. Chi-square tests were employed to study the association between depressive episodes, low adherence, and premature death.

Stratified analyses were conducted to investigate the relationship between the exposure (depressive episode) and the outcome (premature death) after stratifying by low adherence.

Homogeneity between the stratified odds ratios was assessed using a chi-square test of homogeneity. As the odds ratios did not exhibit significant differences, they were pooled to calculate the Mantel-Haenszel adjusted odds ratio. The significance of the adjusted odds ratio was determined using the Cochran-Mantel-Haenszel method [11]. A *p*-value less than 0.05 was considered significant. The analyses were performed using the online statistical program Statulator [12].

RESULTS

Table 1 presents the main demographic and clinical characteristics of the enrolled subjects in the study. The occurrence rate of depressive episodes ranged from mild/moderate to severe, accounting for 48.2%, while the rate of low adherence was 9.9%. By the conclusion of the observation period (month 9), 36 individuals were found to be deceased, constituting 13.7% of the total cohort.

Table 2 displays the association between experiencing a depressive episode and low adherence upon cohort entry and being deceased at month 9 of observation. The Relative Risk for experiencing a depressive episode was 2.14 (95% CI: 1.08-4.39), while the Relative Risk for low adherence was 2.2 (95% CI: 1.01-4.48).

Table 3 presents the analysis of the association between PHQ-9 positivity (PHQ-9≥7) at the cohort entry and premature death, stratified by low adherence at the cohort entry. As shown in the previous table, the exposure to both variables (low adherence and PHQ-9 positivity) demonstrated a significant association with the outcome (premature death). In stratum 1 (low adherence), the association was measured as an odds ratio of 2.64 (95% CI: 1.02-6.83); *p*-value: 0.039. In stratum 2 (PHQ-9 positivity), the odds ratio was 3.83 (95% CI: 1.28-11.45); *p*-value: 0.012. The test of homogeneity indicated no significant difference (p-value = 0.616). Consequently, the stratified odds ratios were combined to calculate the Mantel-Haenszel adjusted odds ratio, resulting in MH-OR = 3.11; 95% CI: 1.52-6.34. The association between the exposure and the outcome remained significant after adjusting for the stratifying variable (*p*-value = 0.001, refer to Table 3 and Table 4).

DISCUSSION

The results of this study indicate that in individuals with cancer, the occurrence of a depressive episode and exhibiting low adherence to treatment both represent risk factors for early mortality within a 9-month observation period. However, suffering from depressive episodes is independent of adherence to therapy as a determinant. In other words, the risk associated with depression was found to persist even after accounting for the level of adherence to therapy through standardization.

The prevalence of Major Depressive Disorder is notably high among cancer patients, with frequencies reaching up to four times higher than rates observed in community surveys [13]. Depressive disorders, in individuals with cancer, are well-established to be associated with adverse outcomes [13], significant deterioration in health-related quality of life [14], treatment non-adherence [15], and increased mortality [1]. However, the results of this study suggest that low adherence may not be the primary mechanism through which the presence of depression leads to premature death in cancer patients, and possibly not even the most significant one.

The current comprehension of the pathophysiology of mood disorders may propose alternative neurobiological foundations and brain-behavioral mechanisms that could play a role in cancer progression in conjunction with the co-occurrence of a depressive episode.

Table 1. Study Sample.

Variables	Overall (N=263)
HEALTH AGENCY	
Hematology and Stem Cell Transplantation Center "Ospedale Busico"	62 (23.6%)
Oncology Clinics University Hospital Cagliari	201 (76.4%)
SEX	
F	132 (50.2%)
AGE	
Mean (±SD)	61.2 (±13.6)
ACCESS TO CARE	
Out-patient (Day Hospital)	217 (82.5%)
In-patient (Hospital Ward)	46 (17.5%)
TIME SINCE THE BEGINNING OF CARE	
<6 months	111 (42.2.%)
≥6 months	152 (57.8%)
CANCER SITE (blood)	
non-Hodgkin lymphoma	13 (4.9%)
Hodgkin lymphoma	14 (5.3%)
chronic lymphocytic leukemia	10 (3.8%)
immune thrombocytopenic purpura	2 (0.8%)
Langerhans cell histiocytosis	1 (0.4%)
acute myeloid leukemia	1 (0.4%)
multiple myeloma	7 (2.7%)
myelofibrosis	2 (0.8%)
chronic myeloid leukemia	3 (1.1%)
polycythemia vera	1 (0.4%)
myelodysplastic syndrome	3 (1.1%)
unknow	5 (1.9%)
CANCER SITE (solid)	
gastroenteric	92 (35%)
gynecological	32 (12.2%)
breast	32 (12.2%)
lung	18 (6.9%)
uro-genital	17 (6.5%)
head and neck	1 (0.4%)
rare	9 (3.4%)
CANCER TYPE	
blood	62 (23.6%)
solid	201 (76.4%)
CANCER STAGE*	
1 or 2	29 (11.0%)
3 or 4	234 (89.0%)
INTENT OF TREATMENT	
palliative	149 (56.6%)
Curative, adjuvant, support or maintenance	134 (43.4%)
ADHERENCE TO CANCER TREATMENT (at the entry of the cohort)	
yes	237 (87.5%)
no	26 (9.9%)
DEPRESSIVE EPISODES (PHQ-9≥7) (at the entry of the cohort)	
yes	127 (48.2%)
no	136 (51.8%)

*1= unique localization in one nodal station or extra-nodal; 2= two or more localizations from the same side of the diaphragm, 3= localizations from both sides of the diaphragm; 4= diffuse disease.

Table 2. Association between low adherence and depressive episodes (PHQ-9 "positive") at entry of the cohort and deceased at 9 months (N=36, 13.7%).

	Deceased at 9 months	Survivals	Total	Chi-square	Relative Risk
Low Adherence	7	19	26		
High Adherence	29	208	237	4.285, *p*=0.039	2.2 (1.01-4.48)
Total	36	227	263		
PHQ-9 "positive"	24	103	127		
PHQ-9 "negative"	12	124	136	5.641, *p*=0.018	2.14 (1.08-4.39)
Total	36	227	263		

Table 3. Association between low adherence and depressive episodes (PHQ-9 "positive") at entry of the cohort and deceased at 9 months (N=36, 13.7%).

	Deceased at 9 months (PHQ-9 +)	Survivals at 9 months (PHQ-9 +)	Total (PHQ-9 +)
Low Adherence	7 (7)	19 (10)	26 (17)
High Adherence	29 (17)	208 (93)	237 (110)
Total	36 (24)	227 (103)	263 (127)

Table 4. Results of Mantel-Haenszel analyses.

	Odds ratio (95% CI)	Chi-square	df	P
Stratum 1 - Low Adherence	2.64 (1.02, 6.83)	4.28	1	0.039
Stratum 2 – Depressive episode (PHQ-9 +)	3.83 (1.28, 11.45)	6.36	1	0.012
Test of homogeneity		0.25	1	0.616
Mantel-Haenszel analyses	3.11 (1.52, 6.34)	10.34	1	0.001

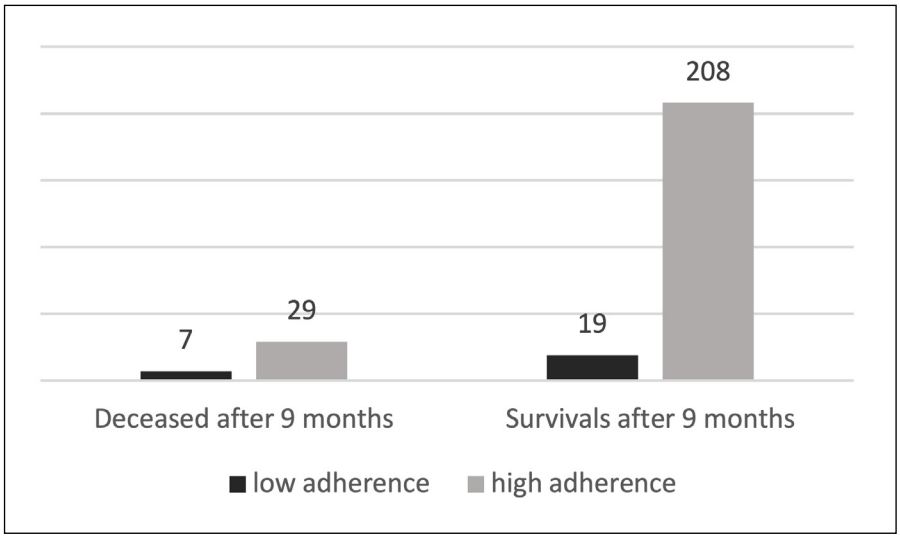

Figure 1. Survival difference between low-adherence patients versus high-adherence patients (frequencies).

Primarily, it is crucial to recognize that the existence of an oncological disease can trigger psychosocial stress mechanisms, setting in motion a cascade of neurobiological phenomena that interface with mood disorders and may potentially exert a synergistic influence on cancer. Specifically, these mechanisms[13,16] include:

1) Decreased efficiency of immune response and immunosurveillance.
2) Increased stress on oxidative/nitrosative processes.
3) Disruption of biological rhythms, with implications for the autonomic nervous system and the hypothalamic-pituitary-adrenal axis.

Mood disorders also encompass unhealthy lifestyles and disrupted social rhythms [17], often characterized by unhealthy dietary habits and inadequate hydration [18], physical inactivity [19], and sleep disturbances [20]. These factors can significantly impact the progression and outcome of the oncological disease. Based on the data from our study and the preceding considerations, it becomes evident that the early identification and management of depressive disorders in individuals with cancer represent both a clinical and public health imperative. Patients experiencing the co-occurrence of cancer and depression may derive substantial benefits from treatment strategies targeting depressive symptoms, fatigue syndrome, and disruptions in social and behavioral rhythms, including sleep disturbances, as well as addressing unhealthy diet and physical inactivity. These therapeutic and rehabilitative interventions could have far-reaching implications not only for alleviating depressive symptoms but also for enhancing oncological-related outcomes [21,22].

Nevertheless, even early intervention on depressive disorders does not fully mitigate the risk associated with low adherence to therapy, which, based on our findings, appears to play a role independent of the potential co-occurrence of ongoing depressive disorders.

Our study has a significant limitation in that the identification of depressive disorders was carried out using a screening tool rather than a semi-structured clinical diagnosis. While screening tools such as PHQ-9 can reasonably assess ongoing depressive episodes, they may not provide a completely accurate diagnosis of Major Depressive Disorder, which is a diagnosis that spans a lifetime. A person may have experienced a depressive episode in the past, but if it has resolved, they may not exhibit enough symptoms to register as positive on the screener at the time of questionnaire administration[23]. This issue can result in significantly lower ratios than those actually reported. Nevertheless, it is reasonable to consider that for such a critical and negative outcome as premature death after nine months of observation, the detected depressive episodes in progress are likely to be the most valid. Additionally, it is possible that a person currently experiencing a depressive episode may have had past episodes of mania or hypomania. In such cases, despite screening positive for a depressive episode, the diagnosis would be Bipolar Disorder rather than Major Depressive Disorder. The matter of diagnostic errors in differentiating depressive episodes in Bipolar Disorder or individuals with a hyperthymic temperament has been extensively addressed in the literature [24-27]. This issue could potentially lead to an overestimation of associations between Major Depressive Disorder and premature death. However, the frequency of Bipolar Disorder is considerably lower than that of Major Depressive Disorder (approximately 1/6 in terms of lifetime prevalence), and thus this bias does not significantly impact the relevance of the results.

CONCLUSIONS

This study demonstrates that individuals with cancer who experience a depressive episode or display low adherence to therapy are at risk for premature death. However, the risk of experiencing depressive episodes is independent of the risk of low adherence to therapy.

The article emphasizes the importance of early recognition of depressive disorders among people with cancer as a crucial clinical and public health priority. Individuals facing the co-occurrence of cancer and depression could potentially benefit from treatment strategies aimed at addressing depressive symptoms, which may also lead to improvements in oncological-related outcomes. It is important to note that even with early intervention targeting depressive disorders, the risk associated with low adherence to therapy remains, independent of the possible coexistence of ongoing depressive disorders.

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Ethical Committee approval:
The study received approval from the autonomous Ethical Committee of Azienda Ospedaliero-Universitaria di Cagliari, Italy (reference number PG/2018/13269).

Informed consent:

Each participant furnished written informed consent subsequent to being presented with comprehensive explanations regarding the objectives and methodologies of the study, being informed about data security, and being assured of their ability to discontinue their participation at any point. All procedures were executed in compliance with the Helsinki Declaration.

Authors contribution:

FS and MGC: conception and design of the study; OM, CM and EM: acquisition of data, FS and MGC: analysis and interpretation of data; FS: drafting the article; MGC, GLN, GC, FR, VG, GO, MS, AEN: making critical revisions related to the relevant intellectual content of the manuscript; MGC: supervision; all the Authors: validation and final approval of the version of the article to be published.

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Conflict of interest:

The Authors declare that they have no conflict of interest to disclose.

Data availability statement:

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. Sancassiani F, Massa E, Pibia C, Perda G, Boe L, Fantozzi E, Cossu G, Caocci G, Mulas O, Morelli E, Lindert J, Lai E, Nardi AE, Scartozzi M, La Nasa G, Carta MG. The association between Major Depressive Disorder and premature death risk in hematologic and solid cancer: a longitudinal cohort study. J Public Health Res 2021; 10: 2247.
2. Decker VB, Tofthagen C. Depression: Screening, Assessment, and Interventions in Oncology Nursing. Clin J Oncol Nurs 2021; 25: 413-421.
3. Rosenblat JD, Kurdyak P, Cosci F, Berk M, Maes M, Brunoni AR, Li M, Rodin G, McIntyre RS, Carvalho AF. Depression in the medically ill. Aust N Z J Psychiatry 2020; 54: 346-366.
4. Saracino RM, Nelson CJ. Identification and treatment of depressive disorders in older adults with cancer. J Geriatr Oncol 2019; 5: 680-684.
5. Coskun S, Bagcivan G. Associated factors with treatment adherence of patients diagnosed with chronic disease: Relationship with health literacy. Appl Nurs Res 2020; 27: 151368.
6. Harper FWK, Heath AS, Moore TF, Kim S, Heath EI. Using Music as a Tool for Distress Reduction During Cancer Chemotherapy Treatment. JCO Oncol Pract 2023; 11: OP2200814.
7. Müller F, Veen LM, Galenkamp H, Jim HSL, Lok A, Nieuwkerk PT, Suurmond J, van Laarhoven HWM, Knoop H. Emotional distress in cancer survivors from various ethnic backgrounds: Analysis of the multi-ethnic HELIUS study. Psychooncology 2023; 32: 1412-1423.
8. Vergara-Duarte M, Borrell C, Pérez G, Martín-Sánchez JC, Clèries R, Buxó M, Martínez-Solanas È, Yasui Y, Muntaner C, Benach J. Sentinel Amenable Mortality: A New Way to Assess the Quality of Healthcare by Examining Causes of Premature Death for Which Highly Efficacious Medical Interventions Are Available. Biomed Res Int 2018; 2018: 5456074.
9. Carta MG, Atzeni M, D'Oca S, Perra A, D'Aloja E, Brasesco MV, Moro MF, Minerba L, Sancassiani F, Moro D, Mausel G, Bhugra D. Depression in Sardinian immigrants in Argentina and residents in Sardinia at the time of the Argentinian default (2001) and the Great Recession in Italy (2015). BMC Psychiatry 2017; 17: 59.
10. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999; 282: 1737-44.
11. Rothman K, Greenland S (1998). Introduction to stratified analysis. In Rothman K, Greenland S (Eds), Modern Epidemiology (Second ed., pp. 253). Lippincott Williams and Wilkins, Philadelphia.
12. Dhand N K, Khatkar MS. Statulator - An online calculator that conducts statistical analyses and interprets the results: Stratified Analyses. http://statulator.com/stat/stratified-analyses. (accessed July 25, 2023).
13. Bortolato B, Hyphantis TN, Valpione S, Perini G, Maes M, Morris G, Kubera M, Köhler CA, Fernandes BS, Stubbs B, Pavlidis N, Carvalho AF. Depression in cancer: The many biobehavioral pathways driving tumor progression. Cancer Treat Rev 2017; 52: 58-70.
14. La Nasa G, Caocci G, Morelli E, Massa E, Farci A, Deiana L, Pintus E, Scartozzi M, Sancassiani F. Health Related Quality of Life in Patients with Onco-hematological Diseases. Clin Pract Epidemiol Ment Health 2020; 16: 174-179.
15. Mausbach BT, Schwab RB, Irwin SA. Depression as a predictor of adherence to adjuvant endocrine therapy (AET) in women with breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 2015; 152: 239-46.

16. Grassi L, McFarland D, Riba M. The Risk and The Course of Cancer Among People with Severe Mental Illness. Clin Pract Epidemiol Ment Health 2023; 19: e174501792301032
17. Carta MG, Ouali U, Perra A, Ben Cheikh Ahmed A, Boe L, Aissa A, Lorrai S, Cossu G, Aresti A, Preti A, Nacef F. Living with Bipolar Disorder in the Time of Covid-19: Biorhythms During the Severe Lockdown in Cagliari, Italy, and the Moderate Lockdown in Tunis, Tunisia. Front Psychiatry 2021; 12: 634765.
18. Velluzzi F, Cossu G, Fosci M, Montisci R, Zaccheddu R, Minerba L, Musu M, Pintus E, Fortin D, Romano F, Aviles Gonzalez CI, Melis P, Deledda A, Loviselli A, Carta MG. Effect of a Low-Moderate Exercise Program on Dysmetabolism in Older Adults: Results of a Randomized Controlled Trial. Nutrients 2022; 14: 3337.
19. Carta MG, Aviles Gonzalez CI, Minerba L, Pau M, Musu M, Velluzzi F, Ferreli C, Pintus E, Machado S, Romano F, Vacca V, Preti A, Cossu G, Atzori L. Exercise in Older Adults to Prevent Depressive Symptoms at the Time of Covid-19: Results of a Randomized Controlled Trial with Follow-Up. Clin Pract Epidemiol Ment Health 2022; 18: e174501792112231.
20. Carta MG, Preti A, Akiskal HS. Coping with the New Era: Noise and Light Pollution, Hyperactivity and Steroid Hormones. Towards an Evolutionary View of Bipolar Disorders. Clin Pract Epidemiol Ment Health 2018; 14: 33-36.
21. Zhu C, Ma H, He A, Li Y, He C, Xia Y. Exercise in cancer prevention and anticancer therapy: Efficacy, molecular mechanisms and clinical information. Cancer Lett 2022; 544: 215814.
22. Idorn M, Thor Straten P. Exercise and cancer: from "healthy" to "therapeutic"? Cancer Immunol Immunother 2017; 66: 667-671.
23. Carta MG, Moro MF. Autoimmune Thyroiditis and Depression. JAMA Psychiatry 2018; 75: 1203-1204.
24. Zimmerman M, Galione JN, Ruggero CJ, Chelminski I, Young D, Dalrymple K, McGlinchey JB. Screening for bipolar disorder and finding borderline personality disorder. J Clin Psychiatry 2010; 71: 1212-1217.
25. Zimmerman M, Galione JN, Chelminski I, Young D, Dalrymple K. Psychiatric diagnoses in patients who screen positive on the Mood Disorder Questionnaire: Implications for using the scale as a case-finding instrument for bipolar disorder. Psychiatry Res 2011; 185: 444-9.
26. Kalcev G, Cossu G, Preti A, Littera MT, Frau S, Primavera D, Zaccheddu R, Matza V, Ermellino M, Pintus E, Carta MG. Development and validation of the questionnaire for adaptive hyperactivity and goal achievement (AHGA). Clin Pract Epidemiol Ment Health 2023; 19: e174501792303281.
27. Kalcev G. Scano A, Orrù G, Primavera D, Cossu G, Nardi EA, Carta MG. Is a genetic variant associated with bipolar disorder frequent in people without bipolar disorder but with characteristics of hyperactivity and novelty seeking? Clin Pract Epidemiol Ment Health 2023; 19: e174501792303280.