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Allostatic overload in the medically ill patients: Results from an observational study

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Abstract

The present study aimed at evaluating the prevalence of allostatic overload (AO) among subjects with different medical diseases and explore whether medically ill patients with or without AO differ for specific clinical features (*i.e.*, co-occurring mental or psychosomatic disorders). An observational cross-sectional study was carried out. Outpatients with a diagnosis of blood cancer, systemic sclerosis, or migraine received a clinical assessment which included the Mini International Neuropsychiatric Interview or the Structured Clinical Interview for DSM-5 and the Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview (DCPR-R SSI). Four hundred and thirty-nine outpatients were enrolled. Among them, 39 (8.9%) had a diagnosis of blood cancer, 200 (45.5%) had a diagnosis of systemic sclerosis, and 200 (45.5%) had a diagnosis of migraine. A total of 104 (23.7%) patients had a DCPR-R diagnosis of AO. Patients with a diagnosis of blood cancer, migraine, or systemic sclerosis did not differ for DCPR-R AO prevalence (P = 0.082). Based on multiple regression analysis, medically ill patients with DCPR-R AO were more likely to satisfy the diagnosis of DCPR-R illness denial (odds ratio [OR] = 2.99, 95% confidence interval [CI] = 1.04 – 8.58), conversion symptoms (OR = 5.32, 95% CI = 1.16 – 24.38), or demoralization (OR = 2.57, 95% CI = 1.08 – 6.11) and a DSM-5 diagnosis of major depressive episode/disorder (OR = 1.90, 95% CI = 1.03 – 3.50), if compared to those without DCPR-R AO. DCPR-R AO is a clinically useful transdiagnostic feature potentially associated with other psychosomatic syndromes and mental disorders that may contribute to the disease burden and the poor global health conditions of medically ill patients.

Keywords: Stress; Medical disease; Cancer; Migraine; Systemic sclerosis

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1. Introduction

Physiological response to stress is activated by stressor at the level of the endocrine, nervous, and immune systems and is sustained for a given interval before being turned

off.[1,2] If the response to stress fails to disengage or shut off at the right moment, allostatic load may ensue.[1,2] If subjects also perceive that environmental challenges exceed their abilities to cope with the situation, allostatic overload (AO) arises.[3] AO implies an overuse of stress systems in a dysregulated manner,[4] which leads to systemic inflammations[5,6] and worsening of physical and mental health.[3,5,6] AO has specific biological[7,8] and clinical signatures.[9] The first were analyzed via biological markers (*e.g.*, resting systolic and diastolic blood pressure, body mass index, plasma C-reactive protein, and cortisol).[8] The latter were incorporated in the Diagnostic Criteria for Psychosomatic Research-Revised (DCPR-R),[10] which refer to AO when an identifiable source of distress in the form of life events and/or chronic stress exceeds individual coping skills and when clinical manifestations of distress and/or impairment in social or occupational functioning and/in environmental mastery occur.[3,9,10]

The relationship between stress and medical disease is rather complex and passes through AO.[4,10] Medically ill patients are more likely to report AO compared to those without a medical disease.[6,11,12] DCPR-R AO has been observed with a relative high rate among outpatients with hypertension (32.50%),[13] congestive heart failure (32.9%),[14] essential hypertension and coronary heart disease (11.2%),[15] migraine (29%),[16] fibromyalgia (25%),[17] and in primary care (15%).[18] Medically ill patients with DCPR-R AO showed significantly higher rates of mental disorders[15] and psychosomatic syndromes,[13,15] compared to those without AO as well as higher levels of psychological distress[14] and lower levels of well-being and quality of life.[13]

The present study aimed at examining DCPR-R AO among subjects with different chronic or life-threatening medical diseases (*i.e.*, blood cancer, systemic sclerosis, and migraine) to verify whether (i) the three clinical populations differ in terms of DCPR-R AO prevalence and (ii) medically ill patients with or without DCPR-R AO differ in terms of specific clinical features (*i.e.*, co-occurring mental disorders or psychosomatic syndromes).

2. Methods

2.1. Participants and procedure

This was an observational, cross-sectional study involving outpatients with a diagnosis of blood cancer consecutively recruited from July 2021 to August 2023 at the Hematological Unit of the S. Chiara Hospital (Pisa, Italy); outpatients with a diagnosis of systemic sclerosis consecutively recruited from June 2020 to October 2022 at the Rheumatology Unit of the Academic Hospital Careggi (Florence, Italy); and outpatients with a diagnosis of migraine recruited from September 2016 to May 2018 at the Headache and Clinical Pharmacology Center of the Academic Hospital Careggi (Florence, Italy) and described in details elsewhere.[16]

The inclusion criteria for this study were (i) age ≥18 years and (ii) a diagnosis of blood cancer (*i.e.*, lymphocytic or myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and myeloproliferative neoplasm diagnosed by hematologists based on blood tests, bone marrow examination, and imaging tests) or systemic sclerosis (according to the 2013 ACR/EULAR classification criteria)[19] or migraine (according to the International Classification of Headache Disorders).[20,21] The only exclusion criterion was the evidence of cognitive deficits or problems affecting the ability of reading, understanding, and following the study assessment process.

Patients gave written informed consent and were, thereafter, evaluated by trained clinical psychologists who collected sociodemographic information, data on pharmacological and nonpharmacological treatments, and on the clinical history of organic diseases via an *ad hoc* set of questions already used in the past.[16] The following assessment instruments were administered: the Mini International Neuropsychiatric Interview (MINI)[22] or the Structured Clinical Interview for DSM-5 Disorders, Clinical Version (SCID-5-CV)[23] and the Semi-Structured Interview for the DCPR-R (DCPR-R-SSI).[10]

Data collection from patients recruited at S. Chiara Hospital (Pisa, Italy) was approved by the Ethical Committee of the Tuscany Region (Area Vasta Nord Ovest – CEAVNO, protocol number: 20097), and data collection from patients recruited at the University Hospital Careggi (Florence, Italy) was approved by the Ethical Committee of the Tuscan region (Area Vasta Centro – CEAV, protocol numbers: 11633_spe; 16425_spe). All procedures contributing to this work were conducted in compliance with the ethical standards of the relevant national and institutional committees on human experimentation and with the 2013 revision of the Helsinki Declaration of 1975.

2.2. Instruments

The Mini International Neuropsychiatric Interview[22] was used among subjects with a diagnosis of blood cancer or systemic sclerosis. The MINI is a short, widely used structured interview allowing to formulate diagnoses of most common mental disorders and suicidality in Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases. It was designed to meet the need for a short-structured psychiatric interview for multicenter clinical trials and epidemiological studies and to be used as a first step in outcome tracking in non-research clinical settings. It has 11 modules

which allow to formulate the diagnosis of current mental disorders (*i.e.*, major depressive episode/disorder, suicidal behavioral disorder, bipolar disorder, panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, alcohol/substance use disorder, psychotic disorder, anorexia/bulimia nervosa, eating disorder, and antisocial personality disorder) and past/lifetime mental disorders (*i.e.*, past/recurrent major depressive episode/disorder, past bipolar disorder, lifetime suicidal behavioral disorder, panic disorder, and psychotic disorder). Each module has a diagnostic box at the end in which the interviewer can flag whether the mental disorder investigated in the module can be diagnosed; thus, at the end of the interview, the interviewer will have a list of mental disorder diagnosed. The MINI showed a moderate-almost perfect concordance with experts' diagnoses and other diagnostic tools and substantial almost-perfect inter-rater agreement.[22,24] For the present study, the MINI 7.0, which allows to formulate diagnoses according to the DSM-5,[25] was used.

The Structured Clinical Interview for DSM-5 Disorders, Clinical Version (SCID-5-CV),[23] was used among subjects with migraine. The SCID-5-CV is a semi-structured interview guiding the clinician step-by-step through the DSM-5 diagnostic process. Interview questions are provided conveniently along each corresponding DSM-5 criterion, which aids in rating each as either present or absent. The SCID-5-CV is an abridged and reformatted version of the Research Version of the SCID, the structured diagnostic interview most widely used by researchers for making DSM diagnoses for the past 30 years. The SCID-5-CV covers the DSM-5 diagnoses most commonly seen in clinical settings: depressive and bipolar disorders; schizophrenia spectrum and other psychotic disorders; substance use disorders; anxiety disorders (panic disorder, agoraphobia, social anxiety disorder, and generalized anxiety disorder); obsessive-compulsive disorder; posttraumatic stress disorder; attention-deficit/hyperactivity disorder; and adjustment disorder. It also screens for 17 additional DSM-5 disorders. Each module follows the DSM diagnostic algorithm and end with a diagnostic box in which the interviewer can flag whether the mental disorder investigated in the module can be diagnosed. Once again, at the end of the interview, the interviewer will have a list of mental disorder diagnosed. The SCID-5 has shown high reliability, good test–retest validity,[26] good sensitivity,[27] excellent reliability, and high specificity.[28]

The DCPR-R-SSI[10] is a tool used for facilitating diagnosis of psychosomatic syndromes according to the DCPR-R.[10] It focuses on signs and symptoms occurring in the 6- to 12-month period leading up to the interview and contains 79 items with a yes/no answer format. This tool assesses 14 psychosomatic syndromes (*i.e.*, AO, health anxiety, disease phobia, hypochondriasis, thanatophobia, illness denial, persistent somatization, conversion symptoms, anniversary reaction, somatic symptoms secondary to a psychiatric disorder, demoralization, irritable mood, type A behavior, and alexithymia) through four diagnostic modules (*i.e.*, stress, illness behavior, psychological manifestation, and personality). The DCPR-R-SSI has shown good incremental validity over DSM-5.[29]

2.3. Statistical analyses

The Kolmogorov–Smirnov test and the Levene's test were used to evaluate normality and heterogeneity of continuous variables, respectively.[30] Comparisons of normally distributed variables between subjects with or without DCPR-R AO were conducted using the *t*-test for independent samples. Comparisons between subjects with or without DCPR-R AO regarding categorical variables were run via the Chi-square test or Fisher's test when more than 20% of cells had expected frequencies of <5 and Z statistic.[30] Cramer's V was calculated to estimate the magnitude of association between categorical variables for a contingency table larger than 2 × 2.[31,32] Phi coefficient and odds ratios were calculated to estimate the magnitude of association between categorical variables in 2 × 2 contingency tables.[31,32] Age was treated as covariate variable.

DSM-5 and DCPR-R diagnoses were grouped not to have frequencies <5% in contingency tables. DSM-5 social anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder now belong to "other DSM-5 diagnoses," whereas DCPR-R health anxiety, disease phobia, hypochondriasis, thanatophobia, illness denial, persistent somatization, conversion symptoms, and anniversary reaction are now under "DCPR-Rillness behavior".[10] DCPR-R secondary somatic symptoms and irritable mood belong to "DCPR-R psychological manifestations".[10] DCPR-R demoralization with hopelessness was subsumed under "DCPR-R demoralization," with hopelessness being the only specifier of the diagnosis.[10] Due to the high number of comparisons, Bonferroni *post hoc* correction was applied.[33]

Binary regression analyses were performed to define the model of the multiple logistic regression. Subjects' status (*i.e.*, with vs. without DCPR-R AO) was used as reference variable. Sociodemographic variables and DSM-5 or DCPR-R diagnoses were used as independent variables (data not shown). Only variables surviving the Bonferroni correction were included in the binary regression analyses as independent variables. Thereafter, a multiple logistic regression analysis was conducted. In this analysis, subjects' status was set as the reference,

while sociodemographic variables, DSM-5 and DCPR-R diagnoses, were included in the model if they reached the statistically significance threshold in the binary regressions. Sex and age were entered in the model as covariates. The coefficient of determination R-squared was calculated as a goodness-of-fit measure.[31,30] Multicollinearity was deemed not to be problematic for the dataset since the tolerance index ranged from 0.93 to 0.96 and variable inflation factors ranged from 1.01 to 1.07.[30]

The two-sided significance level was set at $p < 0.05$. The Statistical Package for the Social Sciences (Version 20.0) was used in the analyses.

3. Results

Four hundred and thirty-nine patients were enrolled. At the time of the study, the subjects were aged 51.26 ± 15.07 years (Levene's test for age: 0.16, $P = 0.682$). Most of the subjects were females ($n = 361$, 82.23%), married ($n = 287$, 65.37%), employed ($n = 260$, 59.22%), and had high school education ($n = 211$, 48.06%). A total of 39 subjects (8.88%) had a diagnosis of blood cancer, 200 (45.55%) had a diagnosis of systemic sclerosis, and 200 (45.55%) had a diagnosis of migraine. Among them, a total of 104 (23.69%) subjects had a diagnosis of DCPR-R AO, which was distributed among the three clinical populations without statistically significant difference (Table 1). Comparing subjects with or without DCPR-R AO, no difference was found for age (49.12 ± 14.55 versus 51.93 ± 15.18 years, $t_{(df)} = 1.66_{(437)}$, $P = 0.096$, $d = -0.188$). Females were distributed almost equally in the two AO categories. However, males not suffering from AO were twice as many as those who did suffer from it. Being married was more represented among those without AO than among those with AO. Subjects with DCPR-R AO were more likely to receive psychotherapy, at least once in life (Table 2), and had significantly higher rates of at least one DSM-5 diagnosis, with reference to major depressive episode or major depressive disorder and panic disorder. Similarly, DCPR-R diagnoses were more represented among subjects with AO, with particular reference to DCPR-R illness behavior diagnoses (which include: a. health anxiety: with AO $n = 9$, 2.68% vs. without AO $n = 9$, 8.65%; b. disease phobia: with AO $n = 3$, 0.89% vs. $n = 3$, 2.88%; c. hypochondriasis: with AO $n = 3$, 0.89% vs. without AO $n = 4$, 3.84%; d. thanatophobia: with AO $n = 3$, 0.89% vs. without AO $n = 1$, 0.96%; e. illness denial: with AO $n = 9$, 2.68% vs. without AO $n = 8$, 7.69%; f. persistent somatization: with AO $n = 15$, 4.47% vs. without AO $n = 8$, 7.69%; g. conversion symptoms: with AO $n = 3$, 0.89% vs. without AO $n = 5$, 4.80%; h. anniversary reaction: with AO $n = 7$, 2.08% vs. without AO $n = 8$, 7.69%), DCPR-R psychological manifestations (which include: a. secondary somatic symptoms: with AO $n = 2$, 0.59% vs. without AO $n = 0$; b. irritable mood: with AO $n = 17$, 2.07% vs. without AO $n = 15$, 14.42%), DCPR-R demoralization, and DCPR-R Type A behavior (Table 3).

Based on the multiple logistic regression analysis, females and unmarried subjects were more likely to face DCPR-R AO. They were also at higher risk of satisfying a DSM-5 diagnosis of major depressive episode or major depressive disorder and at higher risk of presenting DCPR-R diagnoses in the cluster of illness behavior and demoralization ($x^2_{(df)} = 43.43_{(5)}$, $R^2 = 0.142$, $P < 0.001$) (Table 4).

4. Discussion

The present study showed that patients with a diagnosis of cancer, migraine, or systemic sclerosis did not differ for

Table 1. Comparison between subjects without DCPR-R allostatic overload and subjects with DCPR-R allostatic overload concerning medical diseases

Medical diseases	Subjects without DCPR-R allostatic overload	Subjects with DCPR-R allostatic overload	Statistics				
	n (%)	*n* (%)	Chi-square$_{(df)}$	*P*	Z	Phi	OR (95% CI)[a]
	(*n*=190)	(*n*=49)					
Blood cancer	31 (16.31)	8 (16.32)	$0.00_{(1)}$	0.999	-0.086	0.000	1.01 (0.43 – 2.39)
Systemic sclerosis	159 (83.68)	41 (83.67)					
	(*n*=176)	(*n*=63)					
Blood cancer	31 (17.61)	8 (12.69)	$0.82_{(1)}$	0.365	0.829	0.059	1.13 (0.84 – 1.54)
Migraine	145 (82.38)	55 (87.30)					
	(*n*=304)	(*n*=96)					
Systemic sclerosis	159 (52.30)	41 (42.71)	$2.68_{(1)}$	0.101	1.627	0.082	1.10 (0.84 – 1.45)
Migraine	145 (47.69)	55 (57.29)					

Note: Bonferroni *post hoc* correction ($P \leq 0.05/6$ that is $P \leq 0.0083$). [a]Adjusted for age.
Abbreviations: 95% CI: 95% confidence interval; OR: Odds ratio.

Table 2. Comparison of demographic and clinical variables between subjects without DCPR-R allostatic overload and subjects with DCPR-R allostatic overload

	Subjects without DCPR-R allostatic overload (*n*=335)	Subjects with DCPR-R allostatic overload (*n*=104)	Statistics				
	n (%)	*n* (%)	Chi-square$_{(df)}$	*P*	Z	Phi/ Cramer's V	OR (95% CI)[a]
Demographic variables							
Sex							
Male	67 (20)	11 (10.58)	4.82$_{(1)}$	0.028	−2.09	−0.105	0.45 (0.22 – 0.89)
Female	268 (80)	93 (89.42)					
Education							
Primary school	14 (4.18)	6 (5.77)	2.19$_{(3)}$	0.534	0.071	0.534	-
Secondary school	89 (26.57)	21 (20.19)					
High school	160 (47.76)	51 (49.04)					
University degree and post-university degree	72 (21.49)	26 (25)					
Marital status							
Unmarried	107 (31.94)	45 (43.27)	4.50$_{(1)}$	0.034	−2.12	−0.101	0.65 (0.41 – 1.04)
Married	228 (68.06)	59 (56.73)					
Working activity							
Employed	148 (44.18)	51 (49.04)	0.78$_{(2)}$	0.676	−0.738	0.676	-
Freelance	48 (14.33)	13 (12.50)					
Unemployed	139 (41.49)	40 (38.46)					
Clinical variables							
Alcohol use	73 (21.79)	21 (20.19)	0.12$_{(1)}$	0.728	−0.304	−0.017	0.81 (0.46 – 1.42)
Substance or tobacco use	56 (16.71)	22 (21.15)	1.07$_{(1)}$	0.301	1.073	0.049	1.25 (0.71 – 2.18)
Coffee use	270 (80.59)	75 (72.11)	3.39$_{(1)}$	0.065	−1.861	−0.088	0.62 (0.37 – 1.03)
Currently under medications	285 (85.07)	84 (80.76)	1.09$_{(1)}$	0.295	−1.091	−0.050	0.84 (0.46 – 1.55)
Past psychotherapy	53 (15.82)	37 (35.57)	19.05$_{(1)}$	<0.001	4.264	0.208	2.81 (1.70 – 4.66)
Currently under psychotherapy	11 (3.28)	11 (10.57)	8.86$_{(1)}$	0.003	2.872	0.142	3.24 (1.35 – 7.77)

Note: Bonferroni *post hoc* correction ($P \leq 0.05/17$ that is $P \leq 0.0029$). [a]Adjusted for age.
Abbreviations: 95% CI: 95% confidence interval; OR: Odds ratio.

DCPR-R AO prevalence, and that medically ill patients with DCPR-R AO were more likely to have a diagnosis in the cluster of DCPR-R illness behavior, a diagnosis of DCPR-R demoralization, and a DSM-5 diagnosis of major depressive episode or major depressive disorder than those without DCPR-R AO.

The evidence that the three clinical populations did not differ for DCPR-R AO prevalence suggests that DCPR-R AO is a transdiagnostic feature. Having a chronic or life-threatening medical disease, such as cancer, migraine, or systemic sclerosis, is a source of stress itself which requires adaptation[34] and which might exceed the overall individual capacities of coping. Of course, the adaptation to the stressful experience of disease has interindividual modulations which should be taken into account.[5,35,36]

Consistent with previous findings,[13] subjects with a medical illness and DCPR-R AO, compared to those without DCPR-R AO, showed to be more likely to have a diagnosis in the cluster of DCPR-R illness behavior. For instance, illness denial may help patients to cope with the different stages of the disease and with the treatment path by diluting the distress.[37] On the other hand, it may also be unhelpful delaying treatment seeking, decreasing treatment compliance, and triggering treatment refusal.[37] In addition, patients who are denial of illness may not seek medical help instantly and timely, ending up with more severe illness and exacerbated stress, which predispose them to much worsened AO.

Similarly, the diagnosis of conversion symptoms, which are in the cluster of DCPR-R illness behavior, might have a role in the occurrence of AO. In DCPR-R, conversion

Table 3. Comparison in DSM-5 and DCPR-R diagnoses between subjects without DCPR-R allostatic overload and subjects with DCPR-R allostatic overload

	Subjects without DCPR-R allostatic overload (*n*=335)	Subjects with DCPR-R allostatic overload (*n*=104)	Statistics				
	n (%)	*n* (%)	Chi-square$_{(df)}$	*P*	Z	Phi	OR (95% CI)[a]
DSM-5 diagnoses							
At least one diagnosis	71 (21.25)	39 (37.50)	11.23$_{(1)}$	0.001	4.4042	0.160	2.21 (1.37 – 3.56)
Major depressive episode/disorder	43 (12.83)	30 (28.84)	14.67$_{(1)}$	<0.001	3.758	0.183	2.89 (1.69 – 4.95)
Bipolar disorder	0 (0.00)	0 (0.00)	-	-	-	-	-
Panic disorder	20 (5.97)	14 (13.46)	6.23$_{(1)}$	0.013	2.485	0.119	2.42 (1.17 – 5.01)
Agoraphobia	13 (3.84)	7 (6.73)	1.48$_{(1)}$	0.279	1.295	0.058	1.62 (0.62 – 4.21)
Other DSM-5 diagnoses	13 (3.88)	10 (9.61)	5.25$_{(1)}$	0.022	2.282	0.109	2.51 (1.06 – 5.94)
DCPR-R diagnoses							
At least one diagnosis	131 (39.10)	71 (68.26)	27.17	<0.001	5.223	0.249	3.35 (2.09 – 5.35)
Illness behavior	48 (14.32)	34 (32.69)	17.61$_{(1)}$	<0.001	4.107	0.200	2.77 (1.65 – 4.65)
Demoralization	12 (3.94)	14 (14.58)	13.58$_{(1)}$	<0.001	3.486	0.184	4.22 (2.07 – 8.72)
Psychological manifestations	19 (5.67)	15 (14.42)	8.51$_{(1)}$	0.004	2.865	0.139	2.60 (1.25 – 5.38)
Type A behavior	30 (8.95)	18 (17.30)	5.68$_{(1)}$	0.017	2.389	0.114	2.02 (1.06 – 3.82)
Alexithymia	57 (17.01)	18 (17.30)	0.005$_{(1)}$	0.945	0.120	0.003	1.11 (0.61 – 202)

Note: Bonferroni *post hoc* correction ($P \leq 0.05/15$ that is $P \leq 0.0033$). Fisher's test. [a]Adjusted for age.
Abbreviations: DSM-5: Diagnostic and Statistical Manual of mental disorders, fifth edition; DCPR-R: Diagnostic Criteria for Psychosomatic Research–Revised; 95% CI: 95% confidence interval; OR: Odds ratio.

Table 4. Multiple logistic regression analysis for determining predictors of DCPR-R allostatic overload

Dependent variables	B	*P*	OR	95% CI	TI	VIF
Age	−0.01	1.121	0.98	0.97 – 1.00	0.96	1.03
Sex	−0.82	0.026	0.44	0.21 – 0.90	0.99	1.01
DSM-5 major depressive episode/disorder	0.77	0.009	2.16	1.21 – 3.87	0.92	1.08
DCPR-R illness behavior	0.92	0.001	2.53	1.47 – 4.34	0.96	1.03
DCPR-R demoralization	1.23	0.002	3.42	1.57 – 7.43	0.93	1.07

Note: B: Regression coefficient
Abbreviations: 95% CI: 95% confidence interval; DSM-5: Diagnostic and Statistical Manual of mental disorders, fifth edition; DCPR-R: Diagnostic Criteria for Psychosomatic Research–Revised; OR: Odds ratio; TI: Tolerance index; VIF: Variance inflation factor.

symptoms were formulated according to the Engel's criteria[38] for positive identification and are in line with interoception.[39] Thus, this DCPR-R diagnosis could be justified in medically ill patients by their attention to the body manifestation due to the medical disease as well as by the fact that conversion symptoms can be precipitated by psychological stress (including AO), but the association of which with the patient remains elusive. Medically ill patients with DCPR-R AO could also be more prone to report an enhanced general sensitivity to physical pain and discomfort, which might increase the vulnerability to conversion symptoms.

As mentioned above, both DCPR-R illness denial and DCPR-R conversion symptoms can be subsumed under the DCPR-R diagnostic rubric of illness behavior,[10] *i.e.*, the ways in which subjects experience, perceive, evaluate, and respond to their own health status.[10] DCPR-R AO seems to deeply affect the way medically ill patients view, evaluate, and react to their own disease.[6]

Compared with previous findings,[15] medically ill patients with DCPR-R AO were more likely to satisfy the DCPR-R diagnosis of demoralization and the DSM-5 diagnoses of major depressive episode or major depressive disorder. Demoralization and depression are different and independent clinical phenomena that may coexist.[40] It may be expected that, in medically ill patients with DCPR-R AO, the subjective perception of being overloaded by stressful life experiences related to the medical disease may make them more vulnerable to mood worsening.[12,15]

The evidence that medically ill patients with or without DCPR-R AO differ in terms of specific clinical features *(i.e.*, co-occurring DCPR-R illness behavior, demoralization, DSM-5 major depressive episode or major depressive disorder) suggest that considering medical disease only from the biological point of view is reductionistic.[36,41] Medically ill patients are in need of a comprehensive assessment which include, among others, the appraisal of stressful events as well as their relation to the disease, and of coping strategies used to deal with it.[36,41] This approach allows to clinically distinguish among subjects with otherwise deceptively similar medical disease due to the same medical diagnosis made.[3]

The present study has some limitations. First, female subjects were overrepresented in this study, but such sex unbalance mirrors the clinical realm which is characterized by higher prevalence and incidence of systemic sclerosis and migraine among females than males.[42,43] Second, it was not possible to establish a causal relationship among mental disorders, psychosomatic syndromes, and DCPR-R AO since this study adopted a cross-sectional design; therefore, longitudinal studies unraveling this relationship are warranted. In this study, we measured the DCPR-R AO prevalence across different populations with medical diseases, an achievement that had not been attained by a previous research.

5. Conclusion

DCPR-R AO is a clinically useful transdiagnostic feature potentially associated with other psychosomatic syndromes and mental disorders that contribute to the disease burden and to poor health conditions in medically ill patients. DCPR-R,[10] which allows to diagnose AO and relevant psychosomatic syndromes, should become part of the armamentarium of clinicians together with tools that allow to formulate DSM diagnoses as well as clinimetric instruments for assessing psychosocial aspects of medical diseases.[44] A detailed and comprehensive anamnesis should also be conducted for understanding and managing health-damaging behaviors, such as unhealthy lifestyle, high level of disability, and/or compromised quality of life in relation to what is expected in disease status, illness behavior, and lack of treatment adherence.[44] This means applying a novel global clinimetric assessment which outlines biopsychosocial variables and integrates the interplay among the variables under study.[44] It would contribute to characterizing unique individual profiles for patients. Such approach is a stepping stone to attaining comprehensive care path, which should also include education about healthy lifestyle,[44] psychological interventions aimed at empowering quality of life and increasing individual functioning, and, when appropriate, structured psychotherapies such as cognitive behavior therapy aimed at reshaping dysfunctional automatic thoughts related to stressful events such as medical diseases,[45] and well-being therapy.[46] We have now ushered in an era where it is necessary to transcend the boundaries of organ disease and break the unseen hurdles imposed by the myopic medical practices that fixate only at the dimension of single apparatus or organ system.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Giovanni Mansueto, Fiammetta Cosci
Formal analysis: Giovanni Mansueto
Investigation: Sara Romanazzo, Caterina Romaniello
Methodology: Giovanni Mansueto, Sara Romanazzo, Caterina Romaniello
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Writing – review & editing: Giovanni Mansueto, Serena Guiducci, Sara Galimberti, Fiammetta Cosci

Ethics approval and consent to participate

Data collection on patients recruited at S. Chiara Hospital (Pisa, Italy) was approved by the Ethical Committee of the Tuscany Region (Area Vasta Nord Ovest – CEAVNO, protocol number: 20097); data collection on patients recruited at the University Hospital Careggi (Florence, Italy) was approved by the Ethical Committee of the Tuscan region (Area Vasta Centro – CEAV, protocol numbers: 11633_spe; 16425_spe). All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All patients gave written informed consent.

Consent for publication

Both written and verbal permissions were obtained from each of the subjects to publish their data, and effort has been made by the authors to conceal any identifying information of the participants that appear in the paper.

Availability of data

Data collected can be obtained from the corresponding author following formal request.

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