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ORIGINAL RESEARCH

Cancer-related fatigue and depression: a monocentric, prospective, cross-sectional study in advanced solid tumors

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Available online 31 March 2022

Background: Cancer-related fatigue (CRF) is common in patients with advanced solid tumors and several risk factors are described. The possible role of depression is reported by clinicians despite the association with CRF being unclear.

Material and methods: In this monocentric, cross-sectional, prospective study we recruited patients with advanced solid tumors who were hospitalized at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan. The primary objective was to assess the correlation between CRF and depression. Secondary objectives were the estimation of CRF and depression prevalence and the identification of associated clinical risk factors. CRF and depression were evaluated through the Functional Assessment of Cancer Therapy-Fatigue subscale and the Zung Self Depression Scale (ZSDS) questionnaires. The Cochran-Armitage trend test was used to demonstrate the primary hypothesis. Univariate and multivariate logistic regression models were used to investigate the impact of clinical variables.

Results: A total of 136 patients were enrolled. The primary analysis found a linear correlation ($P < 0.0001$) between CRF and depression. The prevalence of CRF and of moderate to severe depressive symptoms was 43.5% and 29.2%, respectively. In univariate analysis, patients with poor Eastern Cooperative Oncology Group performance status (ECOG PS), anemia, distress, pain, and receiving oncological treatment were at a significantly higher risk for CRF, whereas poor ECOG PS, pain, and distress were risk factors for depression. In multivariate analysis, high levels of ZSDS were confirmed to be correlated to CRF: odds ratio of 3.86 [95% confidence interval (CI) 0.98-15.20) and 11.20 (95% CI 2.35-53.36) for ZSDS of 50-59 and 60-100, respectively (P value for trend 0.002). Moreover, the ECOG PS score was confirmed to be significantly associated with CRF (OR 7.20; 95% CI 1.73-29.96; $P = 0.007$).

Conclusions: Our data suggest a strong correlation between CRF and depression in patients with advanced solid tumors. Further investigations are needed to better understand this relationship and if depressive disorder therapeutic strategies could also impact on CRF.

Key words: cancer-related fatigue, depression, patient-reported outcome measures, advanced solid tumor

INTRODUCTION

Cancer-related fatigue (CRF) is the one of the most common symptoms experienced by cancer patients, defined as a 'distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is totally disproportionate to the grade/quantity of physical fatigue physiologically accumulated during the day'.[1] CRF differs from other types of tiredness, mostly for the absence of an improvement with rest, the involvement of different aspects of the patient's life including working ability, and the tendency to get worse especially during oncological treatments and sometimes also to persist after the end of therapies.[2-8] Moreover, affected patients may be less adherent to therapies resulting in increased mortality rate.[9] Although not based on formal diagnostic criteria, CRF prevalence ranges from 40% to 100% and from 14% to 40% during and after oncological treatments, respectively, secondary not only to chemotherapy, but also to endocrine, targeted, and immune therapies.[10-15] Despite the fact that the exact etiopathogenesis still remains not well

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defined, proposed mechanisms include various exogenous and endogenous factors such as anemia, the increase of pro-inflammatory cytokines, neuroendocrine-immune alterations (e.g. hypothalamic-pituitary-adrenal axis and thyroid dysregulations), and sleep disorders.[16-18] Poorly controlled pain could also perpetuate the presence of fatigue in cancer patients.[6,19,20] Different diagnostic criteria have been proposed for CRF diagnosis and, according to European Society for Medical Oncology guidelines, all cancer patients must be not only screened, but also regularly monitored for CRF during their care.[1,21] The use of patient-reported outcome measure (PROM) instruments has been proposed for the screening of CRF [e.g. Functional Assessment of Cancer Therapy-Fatigue (FACT-F), European Organisation for Research and Treatment of Cancer Quality of Life questionnaire-C30 (EORTC C30), and Profile of Moods States Fatigue (POMS-F) scale].[22-25] A PROM is a tool defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'.[26] Among PROMs, FACT-F is a validated tool already used in different clinical trials for the assessment of fatigue in cancer patients.[27] Similarly to CRF, depressive symptoms are also common in cancer patients, with a prevalence between 13% and 40% not including patients with subclinical symptoms that might not meet the depression diagnostic criteria.[28,29] PROMs are also useful to screen patients with depressive symptoms, although a structured clinical interview remains more accurate, but takes longer and is more expensive.[30] A validated and norm-referenced tool used to screen patients' depression in many areas of clinical medicine, from oncology to infectiology, is the Zung Self Depression Scale (ZSDS); this tool evaluates depression focusing on a psychological and cognitive level rather than a psychophysical one.[31-33] Previous studies documented that CRF and depression could coexist in cancer patients, however their possible association and interconnection remain not well established.[15,34-44] Results of these studies have, in fact, demonstrated that when CRF was considered as a one-dimensional construct, it could be a simple symptom of depression; on the contrary, considering CRF in a multidimensional way, it resulted in a syndrome with complex relationships with depressive disorders. In particular, emotional aspects and the inner tension of patients with fatigue present similarities with anhedonia and psychomotor agitation, typical of depressive syndromes.[45,46] Other similarities can be found in etiology. For example, in both syndromes systemic inflammation with high cytokine levels (e.g. interleukin-1, interleukin-6, tumor necrosis factor-α) and endocrine disorders could be involved.[47-52] Finally, overlaps are present even in the pharmacological therapy.[6] On these grounds we decided to design a cross-sectional study aimed at studying the association, through the use of PROMs, between CRF and depression in patients with advanced solid tumors and to investigate the possible clinical risk factors that could impact on their development.

MATERIALS AND METHODS

Study setting and inclusion criteria

This is a prospective, cross-sectional study that enrolled patients affected by advanced solid tumors hospitalized in the Medical Oncology Department of Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy). Patients were enrolled at admission. Eligibility criteria were: (i) age $\geq$18 years; (ii) histologically proven diagnosis of solid malignancy [stage IV according to the 8th edition of the International Union Against Cancer/American Joint Committee on Cancer TNM (tumour-node-metastasis) staging system]; (iii) hospitalization for treatment administration [i.e. chemotherapy, immunotherapy, tyrosine kinase inhibitor (TKI), endocrine therapy, and radiotherapy] or diagnostic procedure. Excluding criteria were: (i) inability to complete PROMs questionnaires; (ii) hospitalization for medical complications/emergency. Previous diagnosis of psychiatric disorders and psychotropic drugs exposure were not considered as excluding criteria.

Primary and secondary objectives

The primary objective of this study was to investigate the correlation between CRF and depression. Secondary objectives were the estimation of CRF and depression prevalence, along with the identification and estimation of their protective and risk clinical factors. In order to assess CRF, the Italian version of the FACT-F subscale questionnaire was administered to patients; the FACT-F subscale is composed of 13 items using a five-point Likert-type scale ranging from 0 ('not at all') to 4 ('very much so') with a global score between 0 and 52 (low scores indicating higher risk for fatigue). Based on previous evidence that showed how patients with values $<$34 were at higher risk for fatigue, a score of 34/52 was established as the cut-off point for diagnosis.[23,27] Depression was assessed using the Italian version of the ZSDS, a self-reported Likert-type rating questionnaire where each of the 20-item scores ranged from 1 to 4 resulting in a global ZSDS raw score of between 20 and 80, with higher scores indicating greater depression.[31,53] The raw score was then converted to an index score by multiplying the raw score by 1.25, and the results were then classified as normal ($<$50), mild depression (50-59), moderate to marked major depression (60-69), and severe to extreme major depression ($>$70) based on a ZSDS index score that ranged from 25 to 100. A ZSDS index score $\geq$60 (i.e. with moderate to extreme major depression symptoms) was considered as the cut-off point for depression prevalence detection. Both FACT-F and ZSDS questionnaires were electronically captured using a touchscreen tablet.[54] A full analysis of the potential demographic, clinical, and biological protective or risk factors for CRF and depression was assessed. These variables included: sex (male versus female), age, Eastern Cooperative Oncology Group performance status (ECOG PS), active infection (yes versus no), presence of caregiver (yes versus no), Charlson Comorbidity Index (8-10 and $>$10 versus 0-7),

Child-Pugh score (7-9 and 10-15 versus 5-6), Glasgow prognostic score (1 and 2 versus 0), primary tumor histology, number of metastatic sites (>1 versus 1), active oncological treatment during the past 28 days (yes versus no), line of treatment in the advanced stage (>1 versus 1), hypothyroidism (yes versus no), adrenal insufficiency (yes versus no), anemia [lower limit of normal - 10, 8-10, and <8 (g/dl) versus absent], hyponatremia [125-129 and <125 versus 130-135 (mEq/l)], corticosteroid exposure (yes versus no), and psychopharmacological treatment (yes versus no). Perceived distress, presence of pain (mild, moderate, moderate to severe, and severe versus absent), along with physical, social/family, emotional and functional well-being domains were also evaluated using a visual analogue scale test (0-10-point distress thermometer indicating the level of the stress experienced) and the FACT-F questionnaire, and were considered as other outcomes reflecting patients' psychophysical conditions.[55] Clinical data, blood samples, and PROMs were collected at admission in the department. All patients provided written informed consent for enrollment in the study and for the use of their personal data for research purposes. The study was approved by the Internal Review Board and the Local Ethics Committee of the Fondazione IRCCS Istituto Nazionale dei Tumori (INT 88/20). Patient data were collected according to the ethical principles for medical research involving human subjects adopted in the Declaration of Helsinki.

Statistical analyses

The sample size of the study was calculated assuming that 60%, 15%, 15%, and 10% of enrolled patients could be classified with normal, mild, moderate to severe, and severe depression, respectively, according to the ZSDS, and that 15% of patients with a normal ZSDS score are interested by CRF.[56] A total of 120 patients were necessary to detect increments of 1.8 on the odds of fatigue (i.e. 15%, 24%, 36%, and 50% of patients with fatigue in the normal, mild, moderate to severe, and severe depression categories, respectively) with power of 84% and two-sided alpha of 5%. The 'power trend' command of the Stata software (StataCorp. 2017. Stata statistical software: Release 15, College Station, TX: StataCorp LLC) was used to compute sample size. The Cochran-Armitage trend test was used to test the primary hypothesis. Binomial exact (Clopper-Pearson) methods were used to estimate the prevalence of CRF and depression. Consecutive enrollment of patients was stopped when at least 127 patients were included in order to account for a 5% missing data rate. In univariate and multivariate analyses, the binary logistic regression and the ordered logistic regression models were used to detect and estimate the association between predictors (e.g. age, sex, treatment) and outcomes (i.e. CRF and depression). Predictors significantly associated with outcomes at univariate analysis were included in the multivariable logistic regression model for CRF and depression. In multivariate cluster analysis, an orthoblique principal components-based clustering method was used to cluster predictors.[57] The eigenvalue one criterion was used for solving the number-of-components problem. Multiple correspondence analysis (MCA) was then used to explore geometrically the pattern of relationships between CRF and ZSDS levels within each cluster of predictors. Cluster scores were tested for association with outcomes (i.e. CRF and depression) in a logistic regression framework. Confidence interval (CI) and *P* value of the Pearson correlation coefficient were based on Fisher's *z* transformation. A threshold significance of 0.05 was set for all statistical evaluations. Statistical analysis was carried out using the SAS software for Windows, version 9.4 (Copyright© 2016 by SAS Institute Inc., Cary, NC). The VARCLUS procedure in SAS was used to identify clusters of predictors. The SCORE procedure in SAS was used to compute cluster scores. Rstatistical software version 4.1.1 (R Core Team, 2021) was used for specific tasks. The *rpart* package in R was used to identify the best thresholds for clusters of predictors.[58] The *FactoMineR* package in R was used for computing MCA.[59]

RESULTS

Patient population

Between 23 June 2020 and 25 April 2021, a total of 219 consecutive patients were screened for enrollment in the study (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100457). One hundred and thirty-six patients were enrolled in the study, of whom three (2.2%) were excluded from statistical analysis due to missing data on both outcomes (i.e. CRF and depression). Clinical, tumor, and treatment-related baseline characteristics of patients are shown in Table 1. The median age of the patients was 63.8 years, 64 (48.1%) were females, and 69 (51.9%) were males. Most patients had an ECOG PS of 1 ($n = 61$, 45.9%) or 0 ($n = 44$, 33.1%), whereas 28 (21.0%) were poor (>1) PS patients. As expected, the most representative tumor primary sites were lung ($n = 37$, 27.8%), gastrointestinal tract [$n = 29$ (21.8%) colorectal/anus and 21 (15.8%) gastroesophageal], and breast ($n = 12$, 9.0%). In addition, most patients had two or more metastatic sites ($n = 102$, 76.7%) and 54.9% of the recruited population did not receive any oncological treatment during the previous 28 days before hospitalization, whereas among other patients more than half received chemotherapy ($n = 31$, 51.7%). Considering the line of systemic treatment of advanced disease that patients were receiving, 32 (24.1%) were at the first, 22 (16.5%) at the second, and 18 (13.5%) at the third, whereas 51 patients (38.3%) had not yet started any first-line systemic therapy. We also analyzed corticosteroid and psychotropic drug exposure, treatments that could influence fatigue and depression levels, and we found that 41 patients (32.5%) were exposed to corticosteroids at the time of enrollment and 29 patients (21.8%) were receiving antidepressants, anti-anxiety drugs, stimulants, antipsychotics, or mood stabilizer medications.

Table 1. Univariate analysis of clinical, tumor, and treatment-related baseline characteristics of patients for CRF and depression

	Overall	FACT-F subscale (CRF)[a]			ZSDS (depression)[a]				
		≥34	<34	OR (95% CI)[b] *P* value	25-49	50-59	60-69	70-100	OR (95% CI)[c] *P* value
Age (years)	133	74	57	0.88[d] (0.65-1.20)	35	57	29	9	0.81[d] (0.61-1.08)
Median (range), years	63.8 (23-84)	64.8 (41-83)	62.7 (23-84)	*P* for trend = 0.41	60.6 (41-80)	63.1 (38-83)	67.3 (42-84)	62.7 (23-70)	*P* for trend = 0.15
Sex									
F	64 (48.1)	31 (41.9)	32 (56.1)	0.56 (0.28-1.13)	13 (37.1)	32 (56.1)	11 (37.9)	6 (66.7)	0.78 (0.41-1.47)
M	69 (51.9)	43 (58.1)	25 (43.9)	*P* = 0.11	22 (62.9)	25 (43.9)	18 (62.1)	3 (33.3)	*P* = 0.45
ECOG PS									
0	44 (33.1)	34 (45.9)	8 (14)	3.68 (2.09-6.48)	23 (65.7)	13 (22.8)	7 (24.1)	0 (0.0)	2.50 (1.67-3.76)
1	61 (45.9)	34 (45.9)	27 (47.4)	*P* for trend <0.0001	11 (31.4)	30 (52.6)	14 (48.3)	4 (44.4)	*P* for trend <0.0001
2	22 (16.5)	6 (8.1)	16 (28.1)		1 (2.9)	11 (19.3)	6 (20.7)	4 (44.4)	
3	5 (3.8)	0 (0.0)	5 (8.8)		0 (0.0)	2 (3.5)	2 (6.9)	1 (11.1)	
4	1 (0.8)	0 (0.0)	1 (1.8)		0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	
Presence of caregiver									
No	3 (2.3)	1 (1.4)	2 (3.5)	0.38 (0.03-4.26)	1 (2.9)	1 (1.8)	0 (0.0)	1 (11.1)	0.76 (0.09-6.23)
Yes	130 (97.7)	73 (98.6)	55 (96.5)	*P* = 0.43	34 (97.1)	56 (98.2)	29 (100.0)	8 (88.9)	*P* = 0.80
Tumor primary site									
Breast	12 (9)	7 (9.5)	5 (8.8)	1	4 (11.4)	5 (8.8)	1 (3.4)	2 (22.2)	1
Melanoma	3 (2.3)	1 (1.4)	2 (3.5)	2.80 (0.20-40.06)	1 (2.9)	1 (1.8)	1 (3.4)	0 (0.0)	1.05 (0.10-11.10)
Urinary tract	9 (6.8)	7 (9.5)	2 (3.5)	0.40 (0.06-2.80)	3 (8.6)	3 (5.3)	3 (10.3)	0 (0.0)	1.05 (0.21-5.27)
Lung	37 (27.8)	19 (25.7)	18 (31.6)	1.33 (0.36-4.95)	4 (11.4)	19 (33.3)	11 (37.9)	2 (22.2)	1.99 (0.59-6.73)
Esophagus and stomach	21 (15.8)	8 (10.8)	12 (21.1)	2.10 (0.49-9.00)	6 (17.1)	9 (15.8)	3 (10.3)	3 (33.3)	1.22 (0.33-4.58)
Colorectal and anus	29 (21.8)	21 (28.4)	8 (14)	0.53 (0.13-2.18)	14 (40)	10 (17.5)	4 (13.8)	0 (0)	0.42 (0.12-1.52)
Biliopancreatic tract	14 (10.5)	6 (8.1)	7 (12.3)	1.63 (0.34-7.95)	2 (5.7)	7 (12.3)	3 (10.3)	1 (11.1)	1.65 (0.38-7.10)
Others (e.g. Merkel)	8 (6.0)	5 (5.8)	3 (5.3)	0.84 (0.13-5.26) *P* = 0.31	1 (2.9)	3 (5.3)	3 (10.3)	1 (11.1)	2.98 (0.57-15.68) *P* = 0.31
Metastatic sites									
1	31 (23.3)	21 (28.4)	10 (17.5)	1.86 (0.80-4.35)	9 (25.7)	13 (22.8)	7 (24.1)	1 (11.1)	1.24 (0.58-2.63)
>1	102 (76.7)	53 (71.6)	47 (82.5)	*P* = 0.15	26 (74.3)	44 (77.2)	22 (75.9)	8 (88.9)	*P* = 0.58
Active infection									
No	123 (92.5)	71 (95.9)	50 (87.7)	3.31 (0.82-13.43)	34 (97.1)	53 (93.0)	26 (89.7)	7 (77.8)	3.06 (0.93-10.07)
Yes	10 (7.5)	3 (4.1)	7 (12.3)	*P* = 0.094	1 (2.9)	4 (7.0)	3 (10.3)	2 (22.2)	*P* = 0.066
Glasgow Prognostic Score									
0	58 (46.8)	39 (57.4	19 (35.2)	1	15 (44.1)	24 (46.2)	14 (51.9)	3 (37.5)	1
1	43 (34.7)	21 (30.9)	20 (37.0)	1.95 (0.86-4.45)	15 (44.1)	17 (32.7)	9 (33.3)	2 (25.0)	0.73 (0.35-1.52)
2	21 (18.5)	8 (11.8)	15 (27.8)	3.85 (1.30-10.65) *P* for trend = 0.007	4 (11.8)	11 (21.2)	4 (14.8)	3 (37.5)	1.37 (0.56-3.40) *P* for trend = 0.73
Missing data	6 (8.1)	3 (5.3)				2(6.9)	1 (11.1)		
Charlson comorbidity index									
0-7	39 (29.3)	25 (33.8)	14 (24.6)	1	16 (45.7)	17 (29.8)	4 (13.8)	2 (22.2)	1
8-10	91 (68.4)	47 (63.5)	42 (73.7)	1.60 (0.73-3.47)	18 (51.4)	39 (68.4)	24 (82.8)	7 (77.8)	2.74 (1.33-5.64)
>10	3 (2.3)	2 (2.7)	1(1.8)	0.89 (0.07-10.75) *P* = 0.047	1 (2.9)	1 (1.8)	1 (3.4)	0 (0.0)	1.76 (0.20-15.62) *P* = 0.024
Child Pugh score									
A: 5-6	99 (85.3)	58 (92.1)	39 (76.5)	3.57 (1.16-10.93)	27 (93.1)	42 (84.0)	20 (80.0)	8 (88.9)	1.65 (0.62-4.37)
B: 7-9	16 (13.8)	5 (7.9)	11 (21.6)	*P* = 0.026	2 (6.9)	7 (14.0)	5 (20.0)	1 (11.1)	*P* = 0.31
C: 10-15	1 (0.9)	0 (0.0)	1 (2.0)		0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	

Continued

Table 1. Continued

	Overall	FACT-F subscale (CRF)[a]			ZSDS (depression)[a]				
		≥34	<34	OR (95% CI)[b] *P* value	25-49	50-59	60-69	70-100	OR (95% CI)[c] *P* value
Missing data	17 (12.8)	11 (14.9	6 (10.5)		6 (17.1)	7 (12.3)	4 (13.8)	0 (0.0)	
Anemia (g/dl)									
Absent	62 (42.6)	41 (55.4)	19 (33.3)	1	21 (60)	24 (42.1)	12 (41.4)	3 (33.3)	1
10-11.8 F/12.5 M	35 (26.3)	19 (25.7)	16 (28.1)	1.82 (0.77-4.29)	6 (17.1)	13 (22.8)	12 (41.4)	3 (33.3)	2.50 (1.13-5.51)
8-10	32 (24.1)	11 (14.9)	21 (36.8)	4.12 (1.66-10.23)	6 (17.1)	18 (31.6)	5 (17.2)	3 (33.3)	1.56 (0.70-3.47)
<8	4 (3.0)	3 (4.1)	1 (1.8)	0.72 (0.07-7.38)	2 (5.7)	2 (3.5)	0 (0.0)	0 (0.0)	0.40 (0.06-2.84)
				P for trend = 0.014					*P* for trend = 0.52
Hyponatremia (mEq/l)									
>135	107 (81.1)	64 (87.7)	41 (71.9)	2.78 (1.12-6.87)	33 (94.3)	45 (80.4)	21 (72.4)	5 (55.6)	3.33 (1.46-7.59)
130-135	22 (16.7)	7 (9.6)	15 (26.3)	*P* = 0.027	2 (5.7)	10 (17.9)	7 (24.1)	3 (33.3)	*P* = 0.004
125-129	2 (1.5)	2 (2.7)	0 (0.0)		0 (0.0)	1 (1.8)	1 (3.4)	0 (0.0)	
<125	1 (0.8)	0 (0.0)	1 (1.8)		0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	
Missing data	1 (0.8)	1 (1.4)	0 (0.0)		0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	
Cortisol deficit									
No	76 (66.7)	41 (65.1)	33 (67.3)	0.90 (0.41-1.99)	19 (59.4)	31 (64.6)	18 (78.4)	6 (66.7)	0.63 (0.31-1.31)
Yes	38 (33.3)	22 (34.9)	16 (32.7)	*P* = 0.80	13 (40.6)	17 (35.4)	5 (21.7)	3 (33.3)	*P* = 0.22
Missing data	19 (14.3)	11 (14.9)	8 (14.0)		3 (8.6)	9 (15.8)	6 (20.7)	0 (0.0)	
Hypothyroidism									
No	128 (96.2)	73 (98.6)	53 (93.0)	5.51 (0.60-50.71)	35 (100.0)	54 (94.7)	27 (93.1)	9 (100.0)	2.02 (0.39-10.36)
Yes	5 (3.8)	1 (1.4)	4 (7.0)	*P* = 0.13	0 (0.0)	3 (5.3)	2 (6.9)	0 (0.0)	*P* = 0.40
Active oncological treatment during the past 28 days									
No	73 (54.9)	47 (63.5)	25 (43.9)	2.23 (1.10-4.51)	21 (60.0)	30 (52.6)	15 (51.7)	5 (55.6)	1.21 (0.64-2.29)
Yes	60 (45.1)	27 (36.5)	32(56.1)	*P* = 0.026	14 (40.0)	27 (47.4)	14 (48.3)	4 (44.4)	*P* = 0.56
Line of treatment									
0	51 (38.3)	32 (43.2)	19 (33.3)	1	16 (45.7)	18 (31.6)	11 (37.9)	4 (44.4)	1
1	32 (24.1)	19 (25.7)	12 (21.1)	1.06 (0.42-2.67)	9 (25.7)	16 (28.1)	5 (17.2)	1 (11.1)	0.82 (0.36-1.89)
2	22 (16.5)	8 (10.8)	13 (22.8)	2.74 (0.96-7.80)	4 (11.4)	6 (10.5)	9 (31.0)	3 (33.3)	2.78 (1.09-7.10)
3	18 (13.5)	11 (14.9)	7 (12.3)	1.07 (0.36-3.23)	4 (11.4)	12 (21.1)	1 (3.4)	1 (11.1)	0.8 (0.31-2.27)
4-9	10 (7.5)	4 (5.4)	6 (10.5)	2.53 (0.63-10.11)	2 (5.7)	5 (8.8)	3 (10.3)	0 (0.0)	1.24 (0.35-4.35)
				P for trend = 0.23					*P* for trend = 0.53
Corticosteroid exposure									
No	85 (67.5)	51 (75.0)	33 (58.9)	2.09 (0.97-4.49)	27 (81.8)	37 (69.8)	15 (53.6)	3 (33.3)	3.11 (1.52-6.37)
Yes	41 (32.5)	17 (25.0)	23 (41.1)	*P* = 0.059	6 (18.2)	16 (30.2)	13 (46.4)	6 (66.7)	*P* = 0.002
Missing data	7 (5.3)	6 (8.1)	1 (1.8)		2 (5.7)	4 (7.0)	1 (3.4)	0 (0.0)	
Active psycho-pharmacological treatment									
No	104 (78.2)	63 (85.1)	39 (68.4)	2.64 (1.13-6.18)	28 (80.0)	48 (84.2)	19 (65.5)	7 (77.8)	1.60 (0.74-3.45)
Yes	29 (21.8)	11 (14.9)	18 (31.6)	*P* = 0.025	7 (20.0)	9 (15.8)	10 (34.5)	2 (22.2)	*P* = 0.24

CI, confidence interval; CRF, cancer-related fatigue; ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; M, male; OR, odds ratio; ZSDS, Zung Self Depression Scale.

[a]Missing data: two patients for FACT-F and three patients for ZSDS.

[b]The binary logistic regression model was used.

[c]The ordered logistic regression model was used.

[d]OR for 10 years increase in age.

https://doi.org/10.1016/j.esmoop.2022.100457

Primary analysis

Out of 133 patients enrolled in this study, 128 were considered for the primary analysis since 8 (6.0%) patients did not complete FACT-F and/or ZSDS questionnaires (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100457). Of them, 56 (43.8%) had a FACT-F subscale score <34, and 57 (44.5%), 28 (21.9%), and 9 (7.0%) patients had a ZSDS of 50-59, 60-69, and 70-100, respectively (Table 2). The primary hypothesis was statistically demonstrated: a linear correlation between CRF, assessed by the FACT-F subscale and Zung levels, was found with a *P* value for trend <0.0001 (Table 2). Moreover, if FACT-F subscale and ZSDS scores were analyzed as continuous outcomes, the linear correlation was confirmed with a Pearson's correlation index (ρ) of −0.72 (95% CI −0.80 to −0.63; *P* value <0.0001) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100457). Thus, considering that lower FACT-F scores corresponded with higher CRF levels, contrary to the ZSDS-depression ones, there was a direct correlation between CRF and depression levels.

Secondary analyses

Focusing on the prevalence of CRF and depressive symptoms according to PROMs results, we found 57 out of 131 patients to have a FACT-F subscale score <34, with a prevalence of 43.5% (95% CI 34.9% to 52.4%), and a total of 38 out of 130 assessable patients to have a ZSDS ≥60 (prevalence of 29.2%; 95% CI 21.6% to 37.8%), indicating moderate to severe levels of depressive symptoms (Table 2).

Univariate analysis for CRF in cancer patients

In univariate analysis for fatigue, we found that patients with poor ECOG PS and higher Glasgow Prognostic Index (intermediate or poor prognosis) were at significantly higher risk of CRF (*P* value for trend < 0.001 and 0.007, respectively) (Table 1). Further, patients with Child-Pugh score levels of B or C, known to be associated with poor prognosis, were at higher risk for CRF with an odds ratio (OR) of 3.57 (95% CI 1.16-10.93; *P* = 0.026). Concerning laboratory examinations of patients, both the severity of anemia and hyponatremia were found to be associated with CRF (*P* value of 0.014 and 0.027, respectively). Analysis of the impact of active treatments on CRF documented that receiving oncological treatment during the 28 days before hospitalization and the assumption of a psychotropic drug could influence CRF levels [OR 2.23 (95% CI 1.10-4.51; *P* = 0.026) and 2.64 (95% CI 1.13-6.18; *P* = 0.025)]. Analysis of other outcomes measured at enrollment also found a positive correlation between higher levels of pain and distress levels with CRF (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100457). In detail, patients experiencing mild pain had an OR of 1.59 (95% CI 0.68-3.74), those with moderate intensity had an OR of 3.83 (95% CI 1.22-11.02), and those with moderate to severe pain had on OR of 22.15 (95% CI 2.54-192.9) to be affected by CRF if compared with patients without pain, with a *P* value for trend of 0.001. Only two patients reported severe pain. Patients with higher levels of distress were at risk for CRF (OR 5.47; 95% CI 1.17-25.54; *P* value for trend 0.031). Also, in our study FACT questionnaires investigated four other domains of cancer patients and higher scores in three of these domains were related with a lower risk of CRF: 'physical well-being score' (OR 0.03; 95% CI 0.01-0.11; *P* value for trend <0.001), 'emotional global score' (OR 0.14; 95% CI 0.04-0.42; *P* value for trend 0.001), and 'global functional score' (OR 0.09; 95% CI 0.04-0.25; *P* value for trend <0.001).

Table 2. Correlation between CRF assessed by FACT-F subscale and depression assessed by ZSDS and respective prevalence

Correlation between CRF and depression					
FACT-F subscale	ZSDS				
	25-49	50-59	60-69	70-100	Total
Total	34	57	28	9	128[a]
≥34	30 (88.2)	33 (57.9)	9 (32.1)	0 (0.0)	72
<34	4 (11.8)	24 (42.1)	19 (67.9)	9 (100.0)	56
Cochran-Armitage test for trend	Two-sided *P* value: <0.0001				
Prevalence of CRF and depression					
	N	%	Cumulative % (95% CI)		
FACT-F subscale					
≥34	74	56.5	100		
<34	57	43.5	43.5 (34.9-52.4)		
ZSDS					
25-49	35	26.9	100		
50-59	57	43.8	73.1 (64.6-80.5)		
60-69	29	22.3	29.2 (21.6-37.8)		
70-100	9	6.9	6.9% (3.2-12.7)		

CI, confidence interval; CRF, cancer-related fatigue; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; ZSDS, Zung Self Depression Scale.
[a]Missing data: five patients for FACT-F subscale and/or ZSDS levels.

Univariate analysis for depression in cancer patients

Similarly to CRF, different parameters were also associated with depression symptoms assessed by ZSDS at univariate analysis: poor ECOG PS (OR 2.50; 95% CI 1.67-3.76; *P* value for trend <0.001) and high Charlson Comorbidity Index OR 2.74 (95% CI 1.33-5.64; *P* value 0.024) for values between 8 and 10 and OR 1.76 (95% CI 0.20-15.62; *P* value = 0.024) for values >10 (Table 1). Equally, presence of hyponatremia was associated with the risk of depressive symptoms, with an OR of 3.33 (95% CI 1.49-7.59; *P* value 0.004). The presence of pain and distress that could affect advanced stage patients could also impact on the risk of depressive symptoms (*P* value for trend <0.001 for pain and <0.0001 for distress), with an OR of 2.39 (95% CI 1.11-5.16) for mild, 4.32 (95% CI 1.62-11.51) for moderate, and 14.48 (95% CI 1.62-11.51) for moderate to severe intensity of pain, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100457). Focusing on the other domains assessed by FACT questionnaires, 'physical well-being score' (OR 0.12; 95% CI 0.05-0.026; *P* value for trend <0.001), 'social and family well-being global score' (OR 0.37; 95% CI 0.19-0.71; *P* value for trend 0.003), 'emotional global score' (OR 0.02; 95%

CI 0.01-0.08; *P* value for trend <0.0001), and 'functional global score' (OR 0.01; 95% CI 0.002-0.03; *P* value for trend <0.001) confirmed their importance and were significantly associated with higher ZSDS levels.

Multivariate analyses for fatigue and depression in cancer patients

In multivariate analysis adjusting the potential association between ZSDS levels and CRF for other clinical-, tumor-, and treatment-related characteristics, the presence of depressive symptoms remained significantly related to fatigue [OR 3.86 (95% CI 0.98-15.20) and OR 11.20 (95% CI 2.35-53.36) for ZSDS scores of 50-59 and 60-100, respectively; *P* value for trend 0.002] (Figure 1). ECOG PS was confirmed as the most important predictor for fatigue in advanced cancer patients (OR 5.57; 95% CI 2.37-13.09; *P* value for trend <0.0001).

Moreover, five different groups of factors were identified by exploratory multivariable cluster analysis (Table 3, Figure 2). This analysis showed that poor ECOG PS, pain, and hyponatremia were predictors closely correlated to each other and that patients with these factors had higher levels of fatigue and depression (*P* value of cluster number 4 for CRF and ZSDS: <0.0001). In the same way, patients with anemia and poor prognosis assessed by Glasgow prognostic score were at higher risk for fatigue (*P* value of cluster number 1 for CRF: 0.001). Concerning the impact of therapies on CRF, patients who received an active oncological treatment for advanced stage tumor experienced fatigue more frequently, especially if the treatment was administered as subsequent (>1) line of therapy (OR 3.00; 95% CI 0.91-9.87; *P* value of cluster number 2 for CRF: 0.015). On the contrary, older patients and those with comorbidity were at higher risk for depression, but not for fatigue (*P* value of cluster number 3 for ZSDS and CRF: 0.035 and 0.911, respectively).

DISCUSSION

Results of our study demonstrated a clear direct correlation between depressive symptoms and CRF levels in patients affected by advanced solid tumors. Previously, numerous studies have been conducted aiming to explore this association, and different hypotheses have been formulated.[34-44] According to Reuter and Härter,[46] CRF could be interpreted as part of a depressive disorder where somatic symptoms play a central role. Conversely, Jacobsen et al.[60] concluded that patients' fatigue cannot be summarized as the 'loss of energy' of the physical exhaustion diagnostic criteria for depression. In addition, Jacobsen et al.[60] emphasized how the association remained even after the elimination of 'somatic symptoms' from the depression diagnostic criteria, supporting the theory that CRF and depression could be interpreted as two distinct entities with a possible common etiopathogenesis. In this study we used standardized and validated questionnaires to investigate the patients'

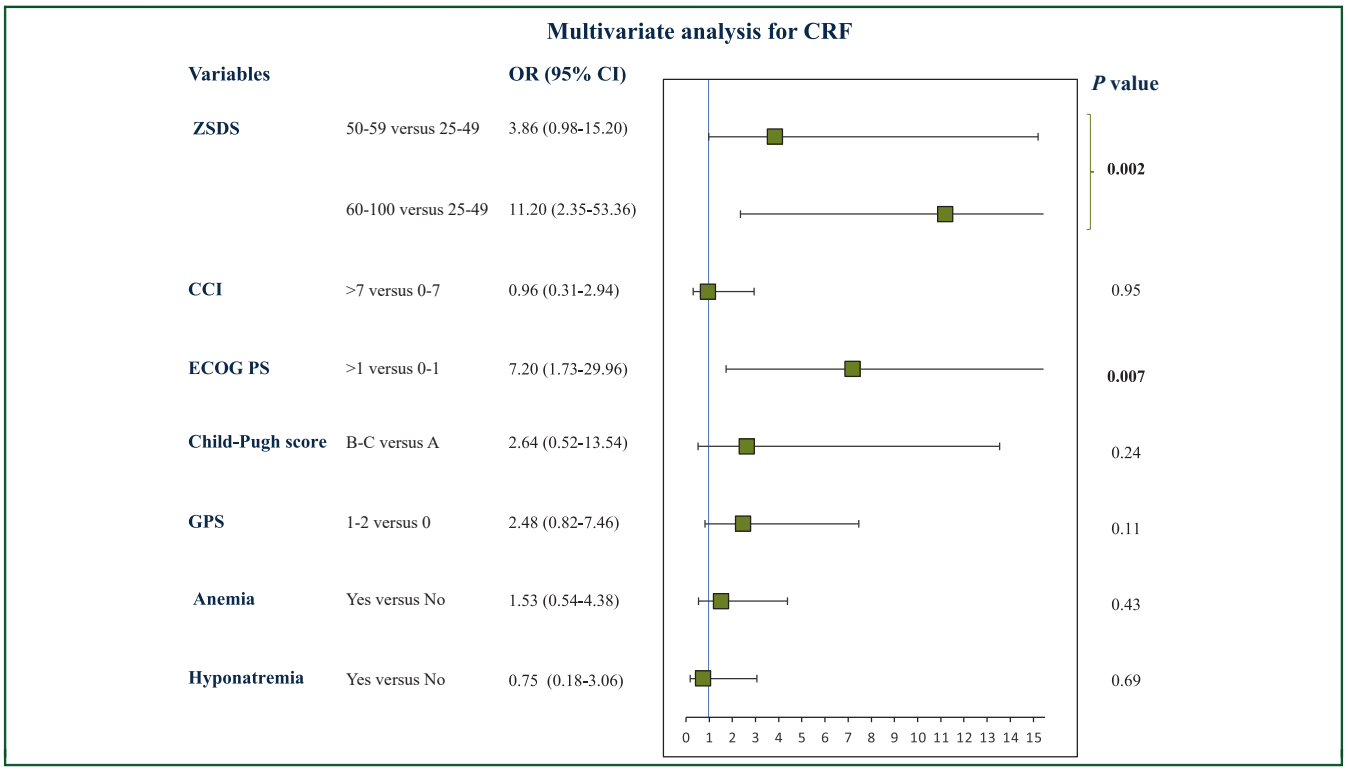

Figure 1. Multivariable logistic regression model adjusting the potential association between CRF and ZSDS levels for other clinical-, tumor- and treatment-related characteristics.

The *P* value is indicated in bold numbers when statistically significant.

CCI, Charlson Comorbidity Index; CI, confidence interval; CRF, cancer-related fatigue; ECOG PS, Eastern Cooperative Oncology Group performance status; GPS, Glasgow prognostic score; OR, odds ratio; ZSDS, Zung Self Depression Scale.

Table 3. Multivariate analyses using cluster models

Cluster number	Predictors	R^2 own cluster[a]	R^2 other cluster[b]	1-R^2 ratio	Association[c]		Cluster category[d]	Odds ratio	
					CRF	ZSDS		Fatigue	ZSDS
1	Glasgow prognostic score (0, 1, 2)	0.752	0.112	0.279	0.001	0.325	GPS = 0; Anemia = 0	1	1
	Anemia (absent = 0, LLN-10 = 1, 8-10 = 2, <8)	0.467	0.053	0.563			GPS = 0; Anemia = 1, 2	1.01 (0.33-3.06)	1.46 (0.56-3.78)
	Child-Pugh score (5-6, 7-9, 10-15)	0.446	0.135	0.640			GPS = 1; Anemia = 0, 1	1.44 (0.56-3.69)	0.89 (0.39-2.03)
	Active infection (No = 0, Yes = 1)	0.343	0.078	0.712			GPS = 1; Anemia = 2	6.46 (1.50-27.90)	0.86 (0.26-2.80)
							GPS = 2	4.04 (1.37-11.91)	1.30 (0.51-3.33)
2	Line of treatment (0, 1, >1 = 2)	0.769	0.039	0.240	0.015	0.529	LOT = 0; nSite = 1	1	1
	Treatment during the last 28 days (No = 0, Yes = 1)	0.675	0.046	0.340			LOT = 0; nSite > 1	1.30 (0.39-4.33)	0.73 (0.25-2.11)
	Number of metastatic sites (1, >1)	0.264	0.037	0.765			LOT > 0; Treat = 0	1.00 (0.27-3.66)	0.97 (0.31-2.97)
							LOT = 1; Treat = 1	1.54 (0.43-5.54)	0.52 (0.17-1.63)
							LOT = 2; Treat = 1	3.00 (0.91-9.87)	1.12 (0.39-3.17)
3	Charlson comorbidity index (0-7 = 0, 8-10 = 1, >10)	0.814	0.002	0.186	0.911	0.035	CCI = 0	1	1
	Age, years (<60 = 0, ≥60-<75 = 1, >75 = 2)	0.814	0.050	0.196			CCI = 1; Age = 0	3.32 (1.07-10.25)	4.36 (1.57-12.13)
							CCI = 1, Age = 1	1.45 (0.63-3.34)	2.20 (1.02-4.73)
							CCI = 1, Age = 2	0.81 (0.23-2.81)	3.23 (1.08-9.61)
4	ECOG PS (0-1 = 0, >1 = 1)	0.675	0.171	0.392	<0.0001	<0.0001	Na = 0; PS = 0; Pain = 0	1	1
	Hyponatremia (No = 0, Yes = 1)	0.553	0.099	0.496			Na = 0; PS = 0; Pain > 0	5.08 (0.89-28.95)	6.54 (1.94-22.02)
	Presence of pain (absent = 0, mild = 1, moderate = 2, moderate to severe = 3, severe)	0.393	0.035	0.629			Na = 0; PS = 1; Pain = 0	9.62 (1.64-56.37)	6.83 (1.88-24.81)
							Na = 0; PS = 1; Pain = 1	8.94 (1.77-45.25)	7.07 (2.33-21.50)
							Na = 0; PS = 1; Pain = 2, 3	22.00 (3.99-121.4)	14.21 (4.23-47.77)
							Na = 1	19.55 (3.71-103.0)	18.53 (5.69-60.41)
5	Sex (F, M)	0.577	0.020	0.432	0.453	0.988	CD = 1; Sex = F	1	1
	Cortisol deficiency (No = 0, Yes = 1)	0.577	0.025	0.434			CD = 0; Sex = M	0.76 (0.24-2.38)	0.99 (0.35-2.79)
							CD = 0; Sex = F	1.46 (0.54-3.93)	2.04 (0.82-5.07)
							CD = 0; Sex = M	0.74 (0.29-1.88)	1.07 (0.46-2.51)

CCI, Charlson Comorbidity index; CD, cortisol deficiency; CRF, cancer-related fatigue; ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; GPS, Glasgow prognostic score; LLN, lower limit of normal; LOT, line of treatment; M, male; Na, hyponatremia; nSite, number of metastatic sites; Treat, active oncological treatment during the past 28 days; ZSDS, Zung Self Depression Scale.

[a]Squared correlation coefficient between a given predictor and its own cluster.

[b]The next highest squared correlation coefficient between a given predictor and any other cluster.

[c]*P* value from 1 d.f. Wald X2 for association with outcome.

[d]The *r part* and *prune* functions of the 'r part' package in R were used to identify the best thresholds for each cluster. Cluster score was used as outcome of each tree-based model. A minimum number of 10 patients was requested for each final cluster category (the following option of the *r part* function was used: minbucket = 10). Tree size that minimized the cross-validated error was selected.

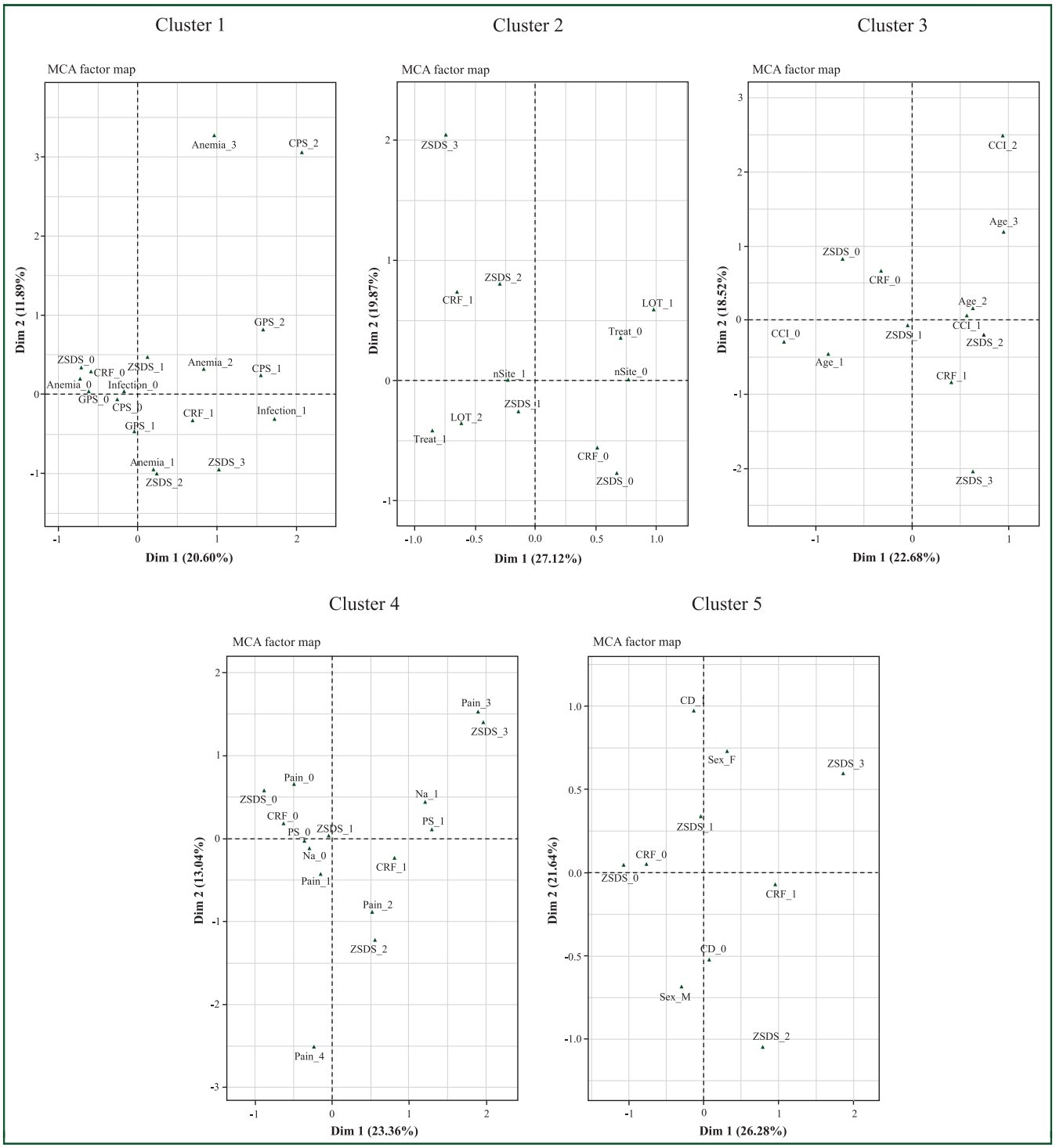

Figure 2. Multiple correspondence analysis (MCA) graphical output exploring the pattern of relationships between CRF and ZSDS levels within each cluster of predictors identified by multivariable cluster analysis.

CCI, Charlson Comorbidity Index; CD, cortisol deficiency; CPS, Child-Pugh score; CRF, cancer-related fatigue; Dim, dimension; GPS, Glasgow prognostic score; LOT, line of treatment; Na, hyponatremia; nSite, number of metastatic sites; PS, performance status; Treat, treatment during the last 28 days; ZSDS, Zung Self Depression Scale.

perspective about CRF and depression, to demonstrate their association, and to explore possible risk factors. This patient-centered approach is rapidly increasing in the oncology community because it could reduce clinicians' interpretation of patients' response, resulting in it being particularly objective and valid.[26,61] Previous published studies showed that the use of PROMs in the clinical setting may increase the connection between patients and clinicians, with consequent improvement of patients' compliance, and may impact on quality of life when their administration is supervised by clinicians.[32,62-64] In our study, the use of the ZSDS, which focuses evaluation of depression on psychological and cognitive aspects using items almost completely different from the FACT-F

subscale, allowed a clear discrimination between somatic symptoms of depression and CRF. The prevalence of fatigue in this study was found to be 43.5%, consistent with literature data in cancer patients.[11-15] Different types of advanced stage neoplasms were included, but melanoma, stomach, and pancreatic tumors seem to be particularly associated with high fatigue levels. These tumors usually present a high tumor burden at diagnosis, with a relative important activation of the immune system, resulting in increased inflammatory cytokine levels and consequent worsening of patients' conditions, as evidenced by the poor ECOG PS score of these patients.[6] Additionally, patients with more advanced disease could have chronic, uncontrolled pain that was demonstrated to be statistically associated with higher CRF levels in our study. Furthermore, patients who received not only chemotherapy, but also other oncological treatments within the last 28 days from the administration of the FACT-F questionnaire, were at higher risk of CRF, according to previous published evidence.[10,12-16,65,66] The possible etiology in these patients is not yet well defined and complex mechanisms have to be considered, such as endocrine autoimmune dysregulation in those treated with immunotherapy, increased levels of pro-inflammatory serum cytokines especially in patients with immune response activation secondary to tumor cell lysis, and the specific toxicity profile of the different oncological agents (e.g. anemia for chemotherapy, arthralgia and depressive symptoms for endocrine treatment, and myalgia for TKI).[6,67] In our study, the role of endocrine alterations was not confirmed, however the presence of anemia was demonstrated to be a possible predictor for CRF in line with results of other cross-sectional studies previously conducted in cancer patients.[27,68-70] Despite all clinical variables investigated and described above, our study confirmed that a patient's general condition was the most important predictor/outcome of CRF in advanced cancer, as shown by the multivariable model. A worsening of the general condition, in fact, could be associated with a high tumor burden and inflammatory activation in cancer patients, factors known to be associated with CRF.[19,20,71-73] Concerning the prevalence of moderate to severe depressive symptoms in advanced cancer patients, our results were consistent with literature, ranging about 29%.[29] A review conducted by Sotelo et al.[50] reported how increased stress levels, with the consequent release of cytokines, could be one of the etiological factors for depression in cancer patients through the activation of the self-sustaining 'central nervous system stress circuit'. Our results confirmed this possible role, since patients with higher thermometer distress values presented lower ZSDS levels with a significant association at univariate analysis. In addition, uncontrolled chronic pain was confirmed as one of the possible etiological and exacerbating factors, despite the exact mechanism behind this close interconnection needing further investigation.[74-76]

To the best of our knowledge this was the first study aimed at assessing the correlation between CRF and depression using PROMs in a heterogeneous cancer population and to perform a full analysis of the most important clinical factors for these patients. Recent studies which analyzed this association in a specific tumor histology, centered their attention on specific risk factors (e.g. anemia) or evaluated this association in the advanced palliative setting.[34,77,78] Moreover, considering the complexity of these syndromes that usually need a comprehensive evaluation, our study represents an important point of view in this field of research. In this way, the use of the FACT questionnaires also allowed the analysis of other domains of these patients, such as emotional, functional, and physical well-being, that significantly impact on CRF and depression in our evaluations. A limitation of this study is mainly represented by the single time point assessment of FACT-F and ZSDS questionnaires during the clinical course of cancer patients. This prevents deeper evaluation of how fatigue and depression levels vary over time and the identification of parameters that could influence these modifications. Other limitations of this study were the relatively small sample size that prevents definitive conclusions, especially regarding the secondary objectives of the study, as well as the monocentric nature that could limit generalization of our observations.

Despite this, our results represent a starting point for further future studies that should include the monitoring over time of fatigue and depression, the investigation of their possible causal relationships, and at the same time, of the possible therapeutic aspects for prevention and treatment of CRF. In this way, cancer patients screened and identified to be affected by CRF and depression may be randomized in future clinical trials to specific interventions targeting fatigue and/or mood disorders. These may include nonpharmacological interventions, such as psychosocial therapies, behavioral or mindfulness-based stress therapies, sleep therapy, physical therapy programs (e.g. exercise, yoga, massage therapy) and acupuncture, or pharmacological interventions (i.e. stimulants, antidepressants, acetylcholinesterase inhibitors, and corticosteroids). In addition, the concomitant evaluation of cytokine level modifications over time, already widely described in literature as possible involved factors for CRF and depression, and of their possible association with PROMs results and patients' symptoms, might also represent another future perspective already poorly investigated.[16,19,20,79,80]

FUNDING

None declared.

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

Raw data generated and analyzed during the current study are available from the corresponding author on reasonable request.

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