



# Prevalence, characteristics, and treatment of fatigue in oncological cancer patients in Italy: a cross-sectional study of the Italian Network for Supportive Care in Cancer (NICSO)

Fausto Roila<sup>1</sup> · Guglielmo Fumi<sup>1</sup> · Benedetta Ruggeri<sup>2</sup> · Andrea Antonuzzo<sup>3</sup> · Carla Ripamonti<sup>4</sup> · Sonia Fatigoni<sup>1</sup> · Luigi Cavanna<sup>5</sup> · Stefania Gori<sup>6</sup> · Alessandra Fabi<sup>7</sup> · Nicola Marzano<sup>8</sup> · Claudio Graiff<sup>9</sup> · Vitaliana De Sanctis<sup>10</sup> · Aurora Mirabile<sup>11</sup> · Samantha Serpentini<sup>12</sup> · Chiara Bocci<sup>13</sup> · Maria Simona Pino<sup>14</sup> · Giuseppina Cilenti<sup>15</sup> · Claudio Verusio<sup>16</sup> · Enzo Ballatori<sup>17</sup> · on behalf of NICSO (Network Italiano per le Cure di Supporto in Oncologia)

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## Abstract

**Background** Fatigue is one of the most distressing symptoms of cancer patients. Its characteristics and impact on quality of life have not been fully explored and treatment of cancer-related fatigue in Italian oncological centers has not been codified.

**Methods** A cross-sectional study was carried out on all patients attending for any reason the 24 participating centers in two non-consecutive days. Patients with fatigue filled out the Brief Fatigue Inventory (BFI) questionnaire and reported any pharmacological or non-pharmacological treatment for fatigue.

**Results** From October 2014 to May 2015, 1394 cancer patients agreed to participate in the study. Fatigue was referred by 866 (62.1%) of patients; its duration was > 4 months in 441 patients (50.9%). In the investigators' opinion, the most important (probable or almost sure) determinants of fatigue were reduced physical activity (271 patients), anxiety (149), pain (131), insomnia (125), anemia (123), and depression (123). Fatigue of moderate/severe intensity was reported by 43%/29.2% of patients, while usual fatigue in the last 24 h by 45%/33.1%, and the worst fatigue in the last 24 h by 33%/54.8%, respectively. Concerning the impact on quality of life, fatigue interfered moderately/severely with general activity in 30.8%/38.6% of patients, with mood in 26.1%/32.8%, with the ability to work in 27.9%/35.6%, with normal work in 26.7%/38.9%, with relationships with others in 21%/23.4% and with the ability to amuse themselves in 22.2%/33.1%. Only 117/866 patients (13.5%) received a pharmacological treatment represented by a corticosteroid in 101 patients (86.3%) while 188 patients (21.7%) received a non-pharmacological treatment such as physical exercise (120 patients, 63.8%) and various alimentary supplements (52 patients, 27.6%).

**Conclusions** Cancer-related fatigue is frequently reported by oncological patients; its intensity and impact on quality of life is relevant.

**Keywords** Cancer-related fatigue · Characteristics of fatigue · Pharmacological treatment · Non-pharmacological treatment

✉ Fausto Roila  
roila.fausto@libero.it

<sup>1</sup> Azienda Ospedaliera S. Maria S.C. Oncologia, Terni, Italy

<sup>2</sup> Clinical Governance, ASUR Marche, AV5, Ascoli Piceno, Italy

<sup>3</sup> University Hospital of Pisa, Pisa, Italy

<sup>4</sup> Oncology Unit 2, Istituto Nazionale dei Tumori, Milan, Italy

<sup>5</sup> Oncologia-Ematologia-AUSL PIACENZA, Piacenza, Italy

<sup>6</sup> Oncology Unit, Ospedale Sacro Cuore Don Calabria, Negrar, Verona, Italy

<sup>7</sup> Division of Medical Oncology, "Regina Elena" National Cancer Institute, Rome, Italy

<sup>8</sup> UOSD Oncologia Medica Ospedale S. Paolo, ASL, Bari, Italy

<sup>9</sup> Ospedale Centrale di Bolzano, Bolzano, Italy

<sup>10</sup> Radiotherapy, St. Andrea Hospital, Sapienza University, Rome, Italy

<sup>11</sup> Azienda Ospedaliera S. Antonio, Gallarate, Italy

<sup>12</sup> Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy

<sup>13</sup> Fondazione Salvatore Maugeri, I.R.C.C.S., Pavia, Italy

<sup>14</sup> SOC Oncologia Medica Ospedale S. Maria Annunziata, Florence, Italy

<sup>15</sup> Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

<sup>16</sup> ASST della Valle Olona, Hospital of Saronno, Saronno, Italy

<sup>17</sup> Spinetoli, Ascoli Piceno, Italy

## Introduction

Cancer-related fatigue (CRF) is defined by the NCCN (National Cancer Comprehensive Network) and ASCO (American Society of Clinical Oncology) as a “distressing, persistent subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [1]. Differently from what happens in healthy people, CRF is not completely relieved by sleep and rest.”

Among the symptoms referred by cancer patients, CRF is one of the most frequent: almost 65% of patients experienced CRF, often not only during cancer treatment. CRF is reported by 40% of patients at diagnosis, by 70–100% of patients submitted to active oncological treatments and by 20–50% of patients after the end of therapy [1, 2].

CRF is a very disabling and distressing symptom with a relevant impact on quality of life. Over two thirds of patients report CRF as severe for at least 6 months and one third report CRF as persistent even post-treatment [3, 4]. CRF, involving physical, psychological, and cognitive aspects, is a multi-dimensional symptom often with multiple determinants: the cancer itself and its complications (i.e., anemia, renal, hepatic, and cardiac failure), cancer’s physical symptoms, and/or its treatment (pain, dyspnea), comorbidities (diabetes mellitus, heart failure), psychological and behavioral symptoms (anxiety, depression), iatrogenic factors (chemotherapy, targeted therapies, radiotherapy), and adverse events of other drugs (opioids, psychiatric drugs) [1, 5].

In conclusion, CRF is a very complex symptom; moreover, fatigue is not specific for cancer and can be associated with many diseases. The diagnosis of CRF therefore requires well-defined diagnostic criteria [6].

According to the NCCN and ASCO guidelines [1, 2], all cancer patients should be screened for the presence of CRF at their first oncological visit and subsequently re-evaluated during and at the end of therapy.

An objective evaluation and measurement of CRF is very important but also potentially complicated due to many methodological problems concerning measurement CRF [7–9].

Several scales are available: linear numeric scales, uni-dimensional scales, uni-dimensional multi-item scales (i.e., the Brief Fatigue Inventory [BFI], the Visual Analogue Fatigue Scale [VAFS], the EORTC QLQ-C30 Fatigue Scale, the Functional Assessment of Cancer Therapy-Fatigue Scale [FACT-F]), and multi-dimensional scales (i.e., the Multidimensional Fatigue Inventory [MFI] and the Piper Fatigue Scale [PFS]). One of the most used is the BFI because it is complete and simple and thus easily used in daily clinical practice.

If patients report fatigue, the determinants should be removed or treated if possible. Fatigue which persists despite treatment should be investigated.

The treatment of CRF is not standardized and the efficacy of several therapies has been evaluated: complementary therapies (yoga, acupuncture, ginseng), behavioral therapies (physical exercise), psychosocial interventions, and/or pharmacological therapies (methylphenidate, dexamethasone) [10–14].

In recent years, knowledge of CRF has rapidly increased and four international guidelines are now available [1, 2, 15, 16] together with many published studies regarding treatment.

CRF characteristics in Italian patients have not yet been well defined. Moreover, the attitude of medical oncologists to assess and treat CRF in hospitals and in the National Cancer Institutes is little or completely unknown.

Therefore, the NCSO (Italian Network for Supportive Care in Cancer) promoted an observational cross-sectional study to evaluate the presence and intensity of CRF in Italian cancer patients who are attending each participating cancer center for any reason.

In this study, patients presenting any grade of fatigue were submitted to a fatigue measurement instrument (Brief Fatigue Inventory, BFI) to measure its impact on quality of life; they were then evaluated to assess and possibly remove its potential determinants. Finally, treatment for CRF was registered.

## Patients and methods

### Patients

All cancer patients in any phase of the disease and its treatment, > 18 years old, who attended the participating cancer centers for any reason (i.e., chemotherapy, radiotherapy, adverse events, follow-up control, supportive care, inpatients) in two non-consecutive days previously defined, were accrued to the study after giving informed consent. Patients with cognitive alterations who were unable to adequately comply with the study were excluded.

### Methods

Initially, all patients were asked about the presence of fatigue (yes–no) during the previous week. If the answer to this question was no, the second question was: “Did you receive any treatment for fatigue during the previous week?”

If the patient’s answer was negative for both questions, the study was concluded and patients were invited to respond to a questionnaire (yes–no) regarding the presence of possible determinants of fatigue (anemia, electrolyte abnormalities, dehydration, anorexia/cachexia, hepatic, renal, heart failure and adrenal insufficiencies, hypoxia, fever, pain, dyspnea, dysphagia, anxiety, depression, insomnia, neurological deficits, and reduced physical activity).

If the answer was positive to at least one of the two questions, the intensity as well as the duration of fatigue was evaluated with the BFI (Italian validated version). The questionnaire was filled out by the patient himself, sometimes with the help of a relative or an oncological operator if necessary (nurse, data manager, or psychologist). The BFI evaluated fatigue features and their impact on quality of life using numeric rating scales. The oncologist then reported his own opinion of each patient regarding the most important (probable or almost sure) determinants of fatigue.

For all enrolled patients, demographic characteristics (age, sex) and clinical history (ECOG Performance Status, type of neoplasm, time to diagnosis); state of disease (no evidence of disease, localized cancer, locally advanced cancer, metastatic cancer); reason for going to the oncological center; all surgical, medical, and radiotherapy treatments received; and drugs different from oncological treatment were registered.

Any intervention, pharmacological or other, used to control the CRF was registered. Lastly, each patient was asked to indicate what, in his/her opinion, could be the cause of his/her CRF.

## Statistical analysis

The usual descriptive statistics were used to analyze the study population. Chi-square tests were calculated for comparing two proportions as well as to test the null hypothesis of independence. Sample size was not calculated because the study design was concerned with patients attending for any reason each center in two pre-specified non-consecutive days.

## Results

From October, 2014, to May, 2015, a total of 1394 patients, attending for any reason the 24 participating centers, were enrolled in the study.

Patient characteristics are reported in Table 1.

Median time from the diagnosis of cancer was 1.3 years; median time from the last cancer treatment was 1.3 months from surgery, 1.0 months from radiotherapy, and 0.5 months from last chemotherapy.

CRF was referred by 866 patients (62.1%); its duration was > 4 months in 441 patients (50.9%), and ≤ 4 months in 425 patients (49.1%). Based on answers to BFI, fatigue intensity was reported as moderate (score 4–6)/severe (score 7–10) by 43%/29.2% of patients while usual fatigue during the last 24 h was reported by 45%/33.1% of patients, and the worst fatigue in the last 24 h was reported by 33%/54.8% of patients, respectively.

Table 2 shows the presence of each possible determinant of CRF in all patients, as well as the percentages of patients with fatigue with respect to the presence/absence of its different

**Table 1** Patient characteristics

		No. (%)
Total		1394 (100)
Gender	Male	581 (41.7)
	Female	813 (58.3)
Age	< 50	263 (18.9)
	50–69	709 (50.9)
	≥ 70	422 (30.2)
	Mean (SD)	62.21 (12.1)
	Median (min–max)	64 (19–93)
ECOG PS	0	878 (63.0)
	1	407 (29.2)
	2–3	109 (7.8)
Diagnosis	Breast	474 (34.0)
	Colorectal	167 (12.0)
	Lung	121 (8.7)
	Prostate	73 (5.2)
	Other	559 (40.1)
Stage	NED	417 (29.9)
	Localized	132 (9.5)
	Locally advanced	170 (12.2)
	Metastatic	674 (48.4)
Reasons for attending the oncological center	Follow-up	314 (22.6)
	Supportive care	154 (11.0)
	Chemotherapy	683 (49.0)
	Target therapy	148 (10.6)
	Radiotherapy	95 (6.8)
Time from cancer diagnosis	> 1 year	615 (44.1)
	≤ 1 year	779 (55.9)
	Mean (SD), years	3.07 (4.2)
	Median (min–max), years	1.29 (0–37.4)
Surgery	Yes	984 (70.7)
	No	410 (29.3)
Radiotherapy	Yes	485 (34.8)
	No	909 (65.2)
Chemotherapy	Yes	1076 (77.2)
	No	318 (22.8)

possible determinants (i.e., 54.3% of patients had fatigue without anemia versus 85.3% of anemic patients). These percentages should be evaluated considering that in the whole study population, 62.1% of patients suffered from fatigue. The differences in the presence of fatigue between patients who had or did not have each possible determinant are all significant at  $p < 0.001$ .

In the investigators' opinion, the most important (probable or almost sure) determinants of fatigue were reduced physical activity (271 patients), anxiety (149), pain (131), insomnia (125), anemia (123), and depression (123).

Concerning concomitant drugs used (another possible determinant of fatigue), opioids, benzodiazepines, and

**Table 2** Association between presence of fatigue and health problems (no. and % of patients suffering from fatigue in each group)

		No. (%)	No. (%) of patients with fatigue <sup>§</sup>
Anemia	No	1041 (74.7)	565 (54.3)
	Yes	353 (25.3)	301 (85.3)
Electrolyte abnormalities	No	1330 (95.4)	805 (60.2)
	Yes	64 (4.6)	61 (95.3)
Dehydration	No	1316 (94.4)	790 (60.0)
	Yes	78 (5.6)	76 (97.4)
Anorexia	No	1243 (89.2)	724 (58.2)
	Yes	151 (10.8)	142 (94.0)
Hepatic failure	No	1350 (96.8)	826 (61.2)
	Yes	44 (3.2)	40 (90.9)
Renal failure	No	1342 (96.3)	822 (61.3)
	Yes	52 (3.73)	44 (84.6)
Heart failure	No	1366 (98.0)	841 (61.6)
	Yes	28 (2.0)	25 (89.3)
Hypoxia	No	1367 (98.1)	839 (61.4)
	Yes	27 (1.9)	27 (100)
Adrenal insufficiencies	No	1382 (99.1)	854 (61.8)
	Yes	12 (0.9)	25 (89.3)
Fever	No	1339 (96.1)	813 (60.7)
	Yes	75 (3.9)	53 (96.4)
Neurologic failure	No	1307 (93.8)	785 (60.0)
	Yes	87 (6.2)	81 (93.1)
Pain	No	1090 (78.2)	603 (55.3)
	Yes	304 (21.8)	263 (86.5)
Dyspnea	No	1244 (89.2)	721 (58.0)
	Yes	150 (10.8)	145 (96.7)
Difficulty swallowing	No	1310 (94.0)	791 (60.4)
	Yes	84 (6.0)	75 (89.3)
Anxiety	No	1005 (72.1)	519 (51.6)
	Yes	389 (27.9)	347 (89.2)
Depression	No	1101 (79.0)	597 (54.2)
	Yes	293 (21.0)	269 (91.8)
Insomnia	No	1042 (74.7)	552 (53.0)
	Yes	352 (25.3)	314 (89.2)
Decreased physical activity	No	845 (60.6)	357 (42.2)
	Yes	549 (39.4)	509 (92.7)

<sup>§</sup> All differences of percentages of patients suffering from fatigue between the two groups of each factor are significant at  $p < 0.001$

psychiatric drugs were associated with fatigue (81.2%, 86.6%, and 83.1% of patients, respectively); these results should be interpreted considering that the overall percentage of patients reporting fatigue was 62.1%. Even patients submitted to corticosteroids reported fatigue more often than the average (72.6%). However, in this case, the patients probably had received corticosteroids just to control CRF.

Considering the reasons of the visit to the oncological centers, patients in follow-up reported fatigue less

frequently (49.7%), while patients receiving supportive care reported CRF more frequently (81.2%) than those submitted to chemotherapy (62.1%), targeted therapy (66.9%), and radiotherapy (65.3%). Interestingly, the patients receiving an active oncological therapy reported CRF with a similar frequency, regardless of the specific type of treatment.

Table 3 shows that 50.6% of patients without evidence of neoplastic disease reported fatigue, while in patients with

**Table 3** Fatigue and disease extension

Fatigue	Disease extension [no. (%)]			
	No evidence of disease	Localized	Locally advanced	Metastatic
Yes	211 (50.6)	80 (60.6)	124 (72.9)	450 (66.8)
No	206 (49.4)	52 (39.4)	46 (27.1)	224 (33.2)
Total	417 (100)	132 (100)	170 (100)	674 (100)

Chi-square test for the independence is significant at  $p < 0.001$

localized, locally advanced, and metastatic disease the percentage was 67.0% ( $p < 0.001$ ).

Considering the ECOG Performance Status (Table 4), the prevalence of CRF significantly increased from ECOG 0 to ECOG 1 and ECOG 2–3 ( $p < 0.001$ ).

Fatigue was also slightly more referred by female (529/813, 65.1%) than male patients (337/581, 58.0%).

Furthermore, the prevalence of fatigue seems unrelated to patient age (62.7% in those < 50 years old, 61.5% in 50–69 years old, and 62.8% in  $\geq 70$  years old).

Concerning the impact of CRF on quality of life, fatigue interfered moderately/severely with general activity in 30.8%/38.6% of patients, with mood in 26.1%/32.8%, with the ability to work in 27.9%/35.6%, with normal work in 26.7%/38.9%, with relationships with other people in 21%/23.4% and with the ability to amuse oneself in 22.2%/33.1%.

In the patients' opinion, the most important determinant of fatigue was (alone/together with other causes) the following: chemotherapy (33.7%/18.9%, total 52.6%), cancer (15.3%/13.3%; total 28.6%), adverse events of therapy and/or uncontrolled symptoms (8.9%/5.8%; total 14.7%), anxiety and emotional tension (3.8%/3.1%; total 6.9%), surgical intervention (2.5%/2.2%; total 4.7%), other causes (radiotherapy, drugs, age, social difficulties, low physical activity, etc. 13.5%).

Only 117/866 (13.5%) patients suffering from CRF received pharmacological treatment for fatigue that was a corticosteroid in 101 patients (86.3%). Other drugs (megestrol, carnitine, antidepressants, homeopathic drugs) were used in the remaining 13.7% of patients. Moreover, 188 patients (21.7%) received a non-pharmacological treatment such as physical exercise or yoga (122 patients, 65%) and various alimentary supplements in the remaining 27.6% of patients: ginseng (9 patients), food supplements (52 patients), mix (propolis, artemisia, vegan diet, and pollen; 32 patients).

From the patients' point of view, of 305 patients receiving treatment for fatigue (pharmacological 117 or non-pharmacological 188), 159 (52.1%) patients achieved benefit from it.

At the end of the interview, the oncologists suggested other treatments (alone/together with other advice) to 229/673 (34%) of patients referring fatigue: drugs (28%/6.9%; total 34.9%), physical activity (17.9%/14.4%; total 32.3%),

psychological support (6.5%/8.3%; total 14.8%), food supplements (7.8%/7.4%; total 15.2%), ginseng (3.4%/3.9%; total 7.3%), lifestyle changes (3.9%/2.6%; total 6.5%), other (socialization, yoga, diet, and vitamins to 10% of patients).

## Discussion

CRF is frequently reported by oncological patients: 62% in about 1400 patients enrolled in 24 Italian oncological centers in our study. This value is similar to the literature data, with a prevalence of about 65% of CRF in oncological patients (range 15–90%) and the true incidence very difficult to ascertain [17–19].

CRF may arise at any time in oncological patients: in our study by 49.7% of patients survivors, by 81.2% of patients receiving supportive care, and by about 62.1–66.9% of patients in active treatment. Two American surveys [20, 21] showed similar results many years ago: in the first survey, 74% of patients reported fatigue at some point during the course of illness, with 32% reporting daily fatigue; in the second, 76% and 30%, respectively.

Notably, the proportion of patients experiencing fatigue is over 50% among those without evidence of disease as well as among those with 0 ECOG Performance Status.

The intensity of CRF was moderate/severe in 43%/29% of patients, and the duration was more than 4 months in 51% of patients. Moderate/severe intensity of CRF usually may interfere with daily activities. As regards the intensity of CRF, literature data are very heterogeneous because of the interaction of many variables that are also time-dependent. For example, for patients receiving chemotherapy, CRF is commonly cyclic; in contrast, the intensity of CRF in patients submitted to RT typically peaks toward the end of therapy. Concerning CRF duration, the available data suggest that up to one third of patients will have persistent fatigue even for a number of post-treatment years [22, 23].

A relevant impact of CRF on different aspects of quality of life, such as general activity, ability to work, mood, and relationship with other people, was reported: 21–31% of patients referred a moderate impact and 23–39% severe impact. Moreover, the majority of patients presented CRF interfering with quality of life.

At present, there is no standard, specific, useful pharmacological treatment for CRF. Many studies evaluating psychostimulants (such as methylphenidate) or other drugs (steroids), nutraceutical treatments (ginseng), have shown them to be negative, while physical exercise and psycho-behavioral interventions have been demonstrated efficacious [14].

In our study, only 13% of patients received a pharmacological treatment, most often represented by a corticosteroid (86% among those who were treated). Due to the lack of efficacious pharmacological treatment for CRF, many patients received non-pharmacological treatments (physical exercise in about 65% of patients) or various alimentary supplements.

**Table 4** Fatigue and ECOG PS [no. (%)]

Fatigue	ECOG PS		
	0	1	2–3
Yes	467 (53.2)	304 (74.7)	95 (87.2)
No	411 (46.8)	103 (25.3)	14 (12.8)
Total	878 (100)	407 (100)	109 (100)

Chi-square test for the independence is significant at  $p < 0.001$

This observational study presents some limitations. Firstly, it was carried out in 24 Italian medical oncology centers; therefore, the prevalence of CRF could be different in patients receiving palliative care in a hospice or at home. Similarly, CRF intensity, duration, and impact on quality of life could be different. Another limitation is that, despite the high number of patients evaluated, there was a wide heterogeneity of conditions even if our sample presents the characteristics of patients referred to medical oncology departments. For these reasons, our results must be considered an indication of prevalence of fatigue among cancer patients.

Nevertheless, this study is important in order to animate the interest of oncologists regarding the important problem of CRF, often under-reported by our patients, but too often under-evaluated by clinicians. In American surveys [20, 21], only 50% of patients had discussed fatigue with their clinician, and in only one fourth of cases was any intervention proposed. Moreover, patients and oncologists often disagreed on the importance of CRF. The Italian situation in the year 2017 is very similar.

In conclusion, oncologists in the immediate future should start evaluating fatigue and its characteristics in all patients admitted to the oncological center as outpatients. At the same time, the oncologists should make a greater effort to identify new and more effective treatments to improve CRF, through improving the quality of research on this topic.

In the meantime, it is important to know and apply the available guidelines on CRF, despite the important barriers (at the patient, clinician, and system level) to the implementation of these guidelines in clinical practice [24–26].

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## Compliance with ethical standards

**Conflict of interest** Fausto Roila declares no conflict of interest. Fausto Roila declares to have full control of all primary data and he agrees to allow the journal to review the data if requested.

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