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MULTICENTRIC, OBSERVATIONAL, LONGITUDINAL STUDY FOR THE EVALUATION OF NUTRITIONAL MANAGEMENT IMPLICATIONS IN NEWLY DIAGNOSED ITALIAN CANCER PATIENTS: THE ITALIAN REGISTRY OF MALNUTRITION IN ONCOLOGY (IRMO)

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ABSTRACT

Introduction

Malnutrition is a frequent problem in oncology and is associated with reduced response to cancer treatments, increased drug-related toxicity, higher rates of clinical complications, reduced quality of life (QoL), and worse prognosis. Guidelines on clinical nutrition in oncology emphasize the usefulness of early assessment of nutritional status for a prompt identification of malnutrition and the implementation of effective interventions, but no real-world clinical data are available on the adequate management of nutritional support in cancer patients in Italy.

Methods and Analysis

This is an observational, longitudinal, multicenter registry of patients with a new diagnosis of cancer or metastatic disease, candidates for active treatment. They will be identified in at least 15 Italian oncologic centers, members of the Alliance Against Cancer Working Group "Survivorship Care and Nutritional Support". At least 1500 cancer patients are expected to be enrolled each year. Detailed clinical and nutritional data will be collected by oncologists and clinical nutritionists during the visits foreseen in the clinical practice, through an *ad hoc* developed digital platform (e-Nutracare®). The effects of malnutrition and nutritional support – at diagnosis and during follow-up – on overall survival and progression-free survival, as well as on patients' symptoms and QoL, will be investigated.

Ethics and Dissemination

The study protocol was approved by Ethics Committee of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy and from the Ethics Committees of all other participating centers. An informed consent will be obtained from each patient enrolled in the study. Study findings will be disseminated through peer-reviewed journals, conferences, and cancer patients or professional associations. The registry will allow a better monitoring of the nutritional status

of cancer patients, promoting adequate and sustainable nutritional support, with the ultimate goal of improving the care and prognosis of these patients.

Keywords: cancer-related malnutrition, nutritional management, prospective study, quality of life, real-world data, registry, survival.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study will allow the implementation of the first Italian, real-world register for detecting and monitoring malnutrition in cancer patients.
- The study will make use of an *ad hoc* developed digital platform for data collection, which could be proposed and extended in the near future to other oncologic centers within the national territory.
- The study will allow a more appropriate evaluation and monitoring of cancer patients' nutritional status, promoting adequate and sustainable nutritional support, with the ultimate goal of improving the quality of care and prognosis.
- Study limitations consist in the observational design, which will not allow to compare the efficacy of personalized nutritional support interventions in specific oncologic diseases.

INTRODUCTION

Malnutrition is a frequent problem in oncology and is associated with a reduced response to cancer treatment, an increase in treatment-related toxicity, higher occurrence of clinical symptoms and complications, impaired quality of life (QoL), and worse overall prognosis [1-6]. Different causes are linked to this condition, including factors such as cancer site and metastatic localizations, and the deregulation of systemic inflammation pathways [5]. Medical treatments and surgery could also be responsible for nutritional derangements, through the increase of basal caloric requirements and the occurrence of symptoms that negatively impact on food intake and nutrient absorption (e.g., anorexia, mucositis, dysphagia, smell alterations, taste alterations, xerostomia, vomiting, nausea, diarrhea, etc.). Taken together, these factors impair the maintenance of functional body composition [3-5,7].

Sarcopenia (i.e., the loss of skeletal muscle and strength) is the main issue which contributes to functional deterioration in cancer patients [8]. In particular, it has been observed that handgrip strength assessment is a reliable survival predictor associated with body composition variations, being also a good indicator of functional capacities in chronic diseases [9]. In oncology, low handgrip strength levels are associated with fatigue, impaired QoL, treatment-related toxicity, and higher mortality [10,11].

National and international guidelines on clinical nutrition in oncology – including those issued by the Italian Ministry of Health in 2017 [12] – underline the utility of early evaluation of nutritional status in cancer patients and of a prompt and appropriate nutritional support, whenever indicated, in order to prevent or treat malnutrition, improve patients' clinical outcomes and QoL, and increase the efficacy and tolerability of cancer treatments [3-5,12]. Only an early and adequate nutritional support can effectively prevent or treat malnutrition and support cancer patients during their entire illness trajectory.

Despite these indications, there are several are critical issues related to the quality of nutritional care in oncology, and no reliable data are available on the current implementation of adequate nutritional support in cancer patients in Italy. Nowadays, only real-world data collected by administrative databases are available in the context of nutrition in oncology, but these have various inherent weaknesses, which somehow limit the possibility to interpret their evidence from a clinical point of view [13,14]. Therefore, it is of foremost importance to start collecting real-world clinical data on malnutrition in oncology, in order to strengthen the evidence and concretely improve nutritional care practices.

Based on these premises, the study "Italian Registry of Malnutrition in Oncology (IRMO)" has been elaborated in collaboration with the oncologic centers that joined the Working Group (WG) "Survivorship Care and Nutritional Support" of Alliance Against Cancer (Alleanza Contro il Cancro, ACC). This study aims to set up a digital register of newly diagnosed cancer patients, in order to monitor their nutritional status and explore the implications of their nutritional support. This will represent the first national, real-world register for detecting and monitoring malnutrition in cancer patients and will allow the creation of a multicentric, longitudinal cohort of oncologic patients to be used for specific analyses.

METHODS AND ANALYSIS

Study design

This is a multicentric, longitudinal, observational registry of newly diagnosed cancer patients, candidate for active treatment. Detailed clinical and nutritional data will be collected by oncologists and clinical nutritionists during the visits foreseen in the clinical practice, through the *ad hoc* developed digital platform, e-Nutracare®. The initial duration of the study is of three years. Patients' enrolment and follow-up will last for all the duration of the study.

However, for the primary and secondary endpoints of the study only patients enrolled during the first year and followed-up for another year will be analyzed.

Study subjects

Individuals enrolled in the study will be all consecutive newly diagnosed or treated cancer patients, candidate for active treatment identified in a least 15 Italian IRCCS members of the ACC WG "Survivorship Care and Nutritional Support" (**Figure 1**). They should be aged 18 years or more, had a new diagnosis of selected cancer sites (i.e., head and neck, esophagus/stomach, colorectal, hepato-biliary, pancreatic, lung, prostate, other urogenital, breast, gynecological, soft tissue sarcomas, and melanoma), or a new diagnosis of metastatic disease, be eligible for active treatment, and provide informed consent to participate in the registry. Individuals with impossibility to undertake the expected measurements or to guarantee the attendance of the follow-up visits will be excluded.

The digital platform e-Nutracare®

The registry data will be collected through e-Nutracare® (OPT S.r.l., Milan, Italy), a digital, web-based platform specifically designed to provide the participating centers with the necessary resources for data collection. The platform is accessible via an internet browser, without the installation of application modules. It will enable both real-time data collection during routine clinical practice visits and transmission of information to various health professionals who participate in the study, thus facilitating their work, involvement, and collaboration.

Data will be entered in single data-entry. In the electronic database, patients will be identified through a unique identification code to preserve their anonymity. Separately, a list of codes and corresponding identification of patients' data will be kept. Data completeness and

plausibility will be remotely assessed. Once the corrections have been completed ("cleaned" database), the database will be frozen ("closed" database). Access to the application by users will take place only in HTTPS, therefore the information will be always transmitted through an encrypted channel. Data correction after the database closure will have to be jointly agreed by the Research Manager, the Statistician and the Data Manager and appropriately documented. The number of screened patients, of eligible patients and the reason for non-enrollment will also be documented.

Assessments

Medical oncologists will collect baseline data at the first patient's visit and will carry out subsequent assessments during the oncologic scheduled visits, according to treatment and follow-up protocols envisaged for these patients in the clinical practice. All collected variables, resumed in **Table 1**, will include:

i) demographic, anamnestic, and clinical data (such as age, sex, cancer type, tumor stage and comorbidities);

ii) oncologic treatments and related severe (grade ≥3) adverse effects or complications, according to Common Terminology Criteria for Adverse Events (CTCAE v5.0) [15];

iii) anthropometric measurements (actual body weight, height, body mass index, weight and weight trend in the previous six months);

iv) performance status according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale [16];

v) patients' symptoms by the Edmonton Symptom Assessment Scale [17];

vi) QoL assessed using the Short Form 12 questionnaire [18];

vii) disease outcomes (as progression or death).

Using anthropometric and nutritional data collected, the Nutritional Risk Screening 2002 (NRS 2002) will be calculated [5,19]. The NRS 2002 is a tool developed by the European Society of Clinical Nutrition and Metabolism, which is currently used to identify patients at risk of surgical complications and mortality and has been recently proposed as a useful tool for indicating the need of an early nutritional intervention in cancer patients [20-22].

Patients at risk of malnutrition (NRS 2002 score ≥3) will be referred for a nutritional examination. Clinical nutritionists will collect the following information:

i) detailed patient' nutritional requirements, nutritional support provided and adherence to the Mediterranean Diet using a validated food frequency questionnaire [23];

ii) body composition parameters obtained throughout scans of computed tomography (CT) at third level of lumbar (L3) or cervical (C3) vertebra as skeletal muscle (SM) and bioelectrical impedance vector analysis (BIVA), as phase angle (PhA), standardized phase angle (SPhA) and fat-free mass (FFM). The measurements will be based on the availability of instrumentation at the different participating centers.

Every effort will be made to ensure the accuracy of patients monitoring and to avoid patients' loss at follow-up.

Table 1. Collected variables.

Age, sex, cancer diagnosis, tumor stage, comorbidities.
Actual body weight, height, BMI, weight loss in the previous 6 months, NRS 2002 score.
Body composition parameters using BIVA (PhA, SPhA, FFM) and CT (SM).
Oncologic treatment, severe adverse effects (grade ≥3 CTCAE).
Performance status (ECOG Scale).
Symptoms (ESAS Scale), QoL (Short Form 12).
Disease outcome (progression or death).

Abbreviations: BIVA, bioelectrical impedance vector analysis; BMI, body mass index; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ESAS, Edmonton Symptom Assessment Scale; FFM, fat free mass; NRS 2002, Nutritional Risk Screening 2002; PhA, phase angle; QoL, quality of life; SM, skeletal muscle; SPhA, standardized phase angle.

Study endpoints

Study endpoints are descripted in **Table 2**. The primary endpoint will be 1-year Overall Survival (OS) and Progression Free Survival (PFS) according to patients' risk of malnutrition (defined as NRS 2002 score ≥3) upon diagnosis.

Secondary endpoints will be 1-year OS and PFS according to malnutrition risk upon diagnosis in relation to cancer type, disease stage, nutritional risk changes and body weight changes during follow-up (at 3, 6, 9, 12 months).

As explorative endpoints, we will investigate 1-year OS and PFS according to the type and timing of nutritional support provided and body composition as well as the rate of severe toxicities (grade III/IV) and discontinuation or delay of treatment according to NRS 2002 score and body composition. Furthermore, we will explore the correlations between NRS 2002 score, body composition parameters, type and timing of nutritional support, QoL, symptoms, and toxicities during follow-up.

Table 2. Study endpoints.

Primary endpoint
• To assess 1-year OS and PFS according to the NRS 2002 cut-off score ≥3 upon diagnosis.
Secondary endpoints
• To assess 1-year OS and PFS according to the NRS 2002 cut-off score ≥3 upon diagnosis of metastatic disease. • To assess 1-year OS and PFS according to the NRS 2002 cut-off score ≥3 upon diagnosis

in the different selected cancer types. • To assess 1-year OS and PFS according to the changes of NRS 2002 score and body weight during the follow-up.
Explorative endpoints
• To assess 1-year OS and PFS according to the type and timing of nutritional support provided. • To assess 1-year OS and PFS according to the body composition measured with CT scan and BIVA methods at diagnosis and during follow up. • To assess the percentage of patients with severe toxicities oncologic and discontinuations or delays of treatment according to the NRS 2002 cut-off scores and body composition evaluated at diagnosis and during follow up. • To explore the correlations between NRS 2002 scores, body composition parameters, type and timing of nutritional support, QoL, symptoms during follow-up.

Abbreviations: BIVA, bioelectrical impedance vector analysis; CT, computed tomography; NRS 2002, Nutritional Risk Screening 2002; OS, overall survival; PFS, progression free survival.

Statistical methods and sample size

The main characteristics of the enrolled patients at baseline will be summarized with appropriate descriptive statistics, such as absolute and relative frequencies for categorical variables, and mean or medians with corresponding precision indices (standard deviation or interquartile range) for continuous variables.

For the associations of NRS 2022 score and other nutritional factors with OS or PFS, we will use survival analysis methods, such as rate calculation, Kaplan Meier curves, and logrank test. In addition, Cox models will be used to calculate the hazard ratio, and corresponding 95%

confidence interval, for patients at high risk of malnutrition versus low risk patients and other nutritional factors. Hazard ratios will be computed adjusting for potential confounding factors, including age, sex, tumor characteristics, stage, comorbidities. and cancer treatment. For explorative endpoints, we will use logistic regression models to calculate the (crude and adjusted) odds ratio and corresponding 95% confidence interval of severe toxicity and interruption/delay in cancer treatments, and multiple regression methods for the calculation of crude and adjusted associations.

All analyses will be conducted using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Considering that each center will be able to enroll between 30-300 patients/year (depending on their patients' load), we expect to enroll at least 1500 cancer patients/year. Considering an average 1-year survival rate of approximately 75% in the two sexes combined [24] and that the ratio between the number of patients not at risk and those at risk of malnutrition (NRS 2002 score ≥3) is approximately 2.3 [20], with this number we will be able to estimate a 12-month survival hazard ratio of at least 1.36 (corresponding to a 12-month survival of 0.66% in the high-risk group), with a power of 80% and an alpha error of 5%.

Patient and public involvement

The registry has been developed in collaboration with Italian Federation of Volunteer-based Cancer Organizations (FAVO) in order to delineate the better way to improve cancer patients' involvement into the registry.

Ethics and dissemination

The study will be conducted in accordance with the good clinical practice rules, the Declaration of Helsinki, and current national and European laws and regulations. The study

protocol was approved by Ethics Committee of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (05/07/2022; prot. N. 0035571/22) and from the Ethics Committees of all other participating centers. An informed consent will be obtained from each patient enrolled in the study. At any time, patients will have the right to withdraw their consent without modifying their current or future care. The progresses of the study will be shared with the patients' general practitioners.

The results of the study will be presented at local, national, and international medical conferences. The findings will be published in peer-reviewed medical/scientific journals and made open-access on acceptance. Information may also be disseminated to cancer patients and professional associations and the general population via public engagement and community outreach programs.

Discussion

Malnutrition in oncology still represents an overlooked problem, which negatively affects clinical outcomes [4,6,13,25]. An altered nutritional status brings more frequently to drug-related toxicities and requires to suspend or delay anticancer therapies, resulting in reduced response rates and worse prognosis [2]. Therefore, an early nutritional support since treatment beginning is crucial. The target is not only to maintain or improve the nutritional status by providing energy and proteins and fully satisfy nutritional requirements, but also effectively impact on clinical outcomes by enhancing the adherence to anticancer treatment.

The global trend of research in the field of nutrition in cancer is gradually increasing [26]. To date, there is evidence that an individualized nutritional support reduces the risk of mortality and improves QoL in cancer patients at malnutritional risk [27]. Moreover, nutritional support for oncology patients is a low-cost intervention compared to other cares [28] and it does not

require additional costs for the healthcare system [29]. However, the impact on survival still requires confirmation as reliable real-world data are lacking.

This study will allow to collect real-world clinical data on malnutrition in Italy. So, it will be possible to improve the strength of evidence on the impact of malnutrition and nutritional support, and to develop quality improvement programs, which help both healthcare professionals to ameliorate nutritional care practices and institutions to allocate adequate resources to this issue [30]. Moreover, the creation of data registry allows to study the cost-effectiveness of nutritional support on a broader scale [31].

The innovative aspect of this study is the implementation of the first Italian real-world register for detecting malnutrition and monitoring nutritional status in cancer patients. This will allow the creation of a multicentric, longitudinal cohort of oncologic patients for further research in the field of nutrition in oncology. Furthermore, it will permit a better monitoring of the nutritional status of cancer patients, fostering an appropriate and sustainable nutritional support, with the goal to improve their care, in agreement with the most recent evidence-based guidelines and recommendations [3-5,12]. The idea is to build a model for a standardized digital platform to monitor the nutritional status of cancer patients. In the near future, the registry could be extended to all the other oncologic centers within the national territory.

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Authors' contributions

Conceptualization: CB, RC. Methodology: CB, RC. Software: CB. Data Curation: all authors. Writing - Original Draft: CB, AC, EC, RC. Writing - Review & Editing: all authors. Supervision: CB, PP, RC. Project administration: CB, PP, RC.

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Competing interests

All authors declare that they have no competing interests.

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FIGURE' LEGEND

Figure 1. Participating centers.

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MULTICENTRIC, OBSERVATIONAL, LONGITUDINAL STUDY FOR THE EVALUATION OF NUTRITIONAL MANAGEMENT IMPLICATIONS IN NEWLY DIAGNOSED ITALIAN CANCER PATIENTS: THE ITALIAN REGISTRY OF MALNUTRITION IN ONCOLOGY (IRMO)

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ABSTRACT

Background

Malnutrition is a frequent problem in oncology and is associated with reduced response to cancer treatments, increased drug-related toxicity, higher rates of clinical complications, reduced quality of life (QoL), and worse prognosis. Guidelines on clinical nutrition in oncology emphasize the usefulness of early assessment of nutritional status for a prompt identification of malnutrition and the implementation of effective interventions, but no real-world clinical data are available on the adequate management of nutritional support in cancer patients in Italy.

Methods and analysis

This is an observational, longitudinal, multicenter registry of patients with a new diagnosis of cancer or metastatic disease, candidates for active treatment. They will be identified in at least 15 Italian oncologic centers, members of the Alliance Against Cancer Working Group "Survivorship Care and Nutritional Support". At least 1500 cancer patients are expected to be enrolled each year. Detailed clinical and nutritional data will be collected by oncologists and clinical nutritionists during the visits foreseen in the clinical practice, through an *ad hoc* developed digital platform (e-Nutracare®). The effects of malnutrition and nutritional support – at diagnosis and during follow-up – on overall survival and progression-free survival, as well as on patients' symptoms and QoL, will be investigated.

Ethics and dissemination

The study protocol was approved by Ethics Committee of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy and from the Ethics Committees of all other participating centers. An informed consent will be obtained from each patient enrolled in the study. Study findings will be disseminated through peer-reviewed journals, conferences, and cancer patients or professional associations. The registry will allow a better monitoring of the nutritional status

of cancer patients, promoting adequate and sustainable nutritional support, with the ultimate goal of improving the care and prognosis of these patients.

Keywords: cancer-related malnutrition, nutritional management, prospective study, quality of life, real-world data, registry, survival.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study will allow the implementation of the first Italian, real-world register for detecting and monitoring malnutrition in cancer patients.
- The study will make use of an *ad hoc* developed digital platform for data collection, which could be proposed and extended in the near future to other oncologic centers within the national territory.
- The study will allow a more appropriate evaluation and monitoring of cancer patients' nutritional status, promoting adequate and sustainable nutritional support, with the ultimate goal of improving the quality of care and prognosis.
- Study limitations consist in the observational design, which will not allow to compare the efficacy of personalized nutritional support interventions in specific oncologic diseases.

INTRODUCTION

Malnutrition is a frequent problem in oncology and is associated with a reduced response to cancer treatment, an increase in treatment-related toxicity, higher occurrence of clinical symptoms and complications, impaired quality of life (QoL), and worse overall prognosis [1-6]. Different causes are linked to this condition, including factors such as cancer site and metastatic localizations, and the deregulation of systemic inflammation pathways [5]. Medical treatments and surgery could also be responsible for nutritional derangements, through the increase of basal caloric requirements and the occurrence of symptoms that negatively impact on food intake and nutrient absorption (e.g., anorexia, mucositis, dysphagia, smell alterations, taste alterations, xerostomia, vomiting, nausea, diarrhea, etc.). Taken together, these factors impair the maintenance of functional body composition [3-5,7].

Sarcopenia (i.e., the loss of skeletal muscle and strength) is the main issue which contributes to functional deterioration in cancer patients [8]. In particular, it has been observed that handgrip strength assessment is a reliable survival predictor associated with body composition variations, being also a good indicator of functional capacities in chronic diseases [9]. In oncology, low handgrip strength levels are associated with fatigue, impaired QoL, treatment-related toxicity, and higher mortality [10,11].

National and international guidelines on clinical nutrition in oncology – including those issued by the Italian Ministry of Health in 2017 [12] – underline the utility of early evaluation of nutritional status in cancer patients and of a prompt and appropriate nutritional support, whenever indicated, in order to prevent or treat malnutrition, improve patients' clinical outcomes and QoL, and increase the efficacy and tolerability of cancer treatments [3-5,12]. Only an early and adequate nutritional support can effectively prevent or treat malnutrition and support cancer patients during their entire illness trajectory.

Despite these indications, there are several critical issues related to the quality of nutritional care in oncology, and no reliable data are available on the current implementation of adequate nutritional support in cancer patients in Italy. Nowadays, only real-world data collected by administrative databases are available in the context of nutrition in oncology, but these have various inherent weaknesses, which somehow limit the possibility to interpret their evidence from a clinical point of view [13,14]. Therefore, it is of foremost importance to start collecting real-world clinical data on malnutrition in oncology, in order to strengthen the evidence and concretely improve nutritional care practices.

Based on these premises, the study "Italian Registry of Malnutrition in Oncology (IRMO)" has been elaborated in collaboration with the oncologic centers that joined the Working Group (WG) "Survivorship Care and Nutritional Support" of Alliance Against Cancer (Alleanza Contro il Cancro, ACC). This study aims to set up a digital register of newly diagnosed cancer patients, in order to monitor their nutritional status and explore the implications of their nutritional support. This will represent the first national, real-world register for detecting and monitoring malnutrition in cancer patients and will allow the creation of a multicentric, longitudinal cohort of oncologic patients to be used for specific analyses.

METHODS AND ANALYSIS

Study design

This is a multicentric, longitudinal, observational registry of newly diagnosed cancer patients, candidate for active treatment. Detailed clinical and nutritional data will be collected by oncologists and clinical nutritionists during the visits foreseen in the clinical practice, through the *ad hoc* developed digital platform, e-Nutracare®. The initial duration of the study is of three years (between October 2022 and September 2025). Patients' enrolment and follow-up will last for all the duration of the study. However, for the primary and secondary endpoints

of the study only patients enrolled during the first year and followed-up for another year will be analyzed.

Study subjects

Individuals enrolled in the study will be all consecutive newly diagnosed or treated cancer patients, candidate for active treatment identified in a least 15 Italian IRCCS members of the ACC WG "Survivorship Care and Nutritional Support" (**Figure 1**). They should be aged 18 years or more, had a new diagnosis of selected cancer sites (i.e., head and neck, esophagus/stomach, colorectal, hepato-biliary, pancreatic, lung, prostate, other urogenital, breast, gynecological, soft tissue sarcomas, and melanoma), or a new diagnosis of metastatic disease, be eligible for active treatment, and provide informed consent to participate in the registry. Individuals with impossibility to undertake the expected measurements or to guarantee the attendance of the follow-up visits will be excluded.

The digital platform e-Nutracare®

The registry data will be collected through e-Nutracare® (OPT S.r.l., Milan, Italy), a digital, web-based platform specifically designed to provide the participating centers with the necessary resources for data collection. The platform is accessible via an internet browser, without the installation of application modules. It will enable both real-time data collection during routine clinical practice visits and transmission of information to various health professionals who participate in the study, thus facilitating their work, involvement, and collaboration.

Data will be entered in single data-entry. In the electronic database, patients will be identified through a unique identification code to preserve their anonymity. Separately, a list of codes and corresponding identification of patients' data will be kept. Data completeness and

plausibility will be remotely assessed. Once the corrections have been completed ("cleaned" database), the database will be frozen ("closed" database). Access to the application by users will take place only in HTTPS, therefore the information will be always transmitted through an encrypted channel. Data correction after the database closure will have to be jointly agreed by the Research Manager, the Statistician and the Data Manager and appropriately documented. The number of screened patients, of eligible patients and the reason for non-enrollment will also be documented.

Assessments

Medical oncologists will collect baseline data at the first patient's visit and will carry out subsequent assessments during the oncologic scheduled visits, according to treatment and follow-up protocols envisaged for these patients in the clinical practice. All collected variables, resumed in **Table 1**, will include:

i) demographic, anamnestic, and clinical data (such as age, sex, cancer type, tumor stage and comorbidities);

ii) oncologic treatments and related severe (grade ≥3) adverse effects or complications, according to Common Terminology Criteria for Adverse Events (CTCAE v5.0) [15];

iii) anthropometric measurements (actual body weight, height, body mass index, weight and weight trend in the previous six months);

iv) performance status according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale [16];

v) patients' symptoms by the Edmonton Symptom Assessment Scale [17];

vi) QoL assessed using the Short Form 12 questionnaire [18];

vii) disease outcomes (as progression or death).

Table 1. Collected variables.

Age, sex, cancer diagnosis, tumor stage, comorbidities.
Actual body weight, height, BMI, weight loss in the previous 6 months, NRS 2002 score.
Body composition parameters using BIVA (PhA, SPhA, FFM) and CT (SM).
Oncologic treatment, severe adverse effects (grade ≥3 CTCAE).
Performance status (ECOG Scale).
Symptoms (ESAS Scale), QoL (Short Form 12).
Disease outcome (progression or death).

Abbreviations: BIVA, bioelectrical impedance vector analysis; BMI, body mass index; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ESAS, Edmonton Symptom Assessment Scale; FFM, fat free mass; NRS 2002, Nutritional Risk Screening 2002; PhA, phase angle; QoL, quality of life; SM, skeletal muscle; SPhA, standardized phase angle.

Using anthropometric and nutritional data collected, the Nutritional Risk Screening 2002 (NRS 2002) will be calculated [5,19]. The NRS 2002 is a tool developed by the European Society of Clinical Nutrition and Metabolism, which is currently used to identify patients at risk of surgical complications and mortality and has been recently proposed as a useful tool for indicating the need of an early nutritional intervention in cancer patients [20-22].

Patients at risk of malnutrition (NRS 2002 score ≥3) will be referred for a nutritional examination. Clinical nutritionists will collect the following information:

i) detailed patient' nutritional requirements, nutritional support provided and adherence to the Mediterranean Diet using a validated food frequency questionnaire [23];

ii) body composition parameters obtained throughout scans of computed tomography (CT) at third level of lumbar (L3) or cervical (C3) vertebra as skeletal muscle (SM) and bioelectrical impedance vector analysis (BIVA), as phase angle (PhA), standardized phase angle (SPhA) and fat-free mass (FFM). The measurements will be based on the availability of instrumentation at the different participating centers.

Every effort will be made to ensure the accuracy of patients monitoring and to avoid patients' loss at follow-up.

Study endpoints

Study endpoints are descripted in **Table 2**. The primary endpoint will be 1-year Overall Survival (OS) and Progression Free Survival (PFS) according to patients' risk of malnutrition (defined as NRS 2002 score ≥3) upon diagnosis.

Secondary endpoints will be 1-year OS and PFS according to malnutrition risk upon diagnosis in relation to cancer type, disease stage, nutritional risk changes and body weight changes during follow-up (at 3, 6, 9, 12 months).

As explorative endpoints, we will investigate 1-year OS and PFS according to the type and timing of nutritional support provided and body composition as well as the rate of severe toxicities (grade III/IV) and discontinuation or delay of treatment according to NRS 2002 score and body composition. Furthermore, we will explore the correlations between NRS 2002 score, body composition parameters, type and timing of nutritional support, QoL, symptoms, and toxicities during follow-up.

Table 2. Study endpoints.

Primary endpoint
• To assess 1-year OS and PFS according to the NRS 2002 cut-off score ≥3 upon diagnosis.
Secondary endpoints
• To assess 1-year OS and PFS according to the NRS 2002 cut-off score ≥3 upon diagnosis of metastatic disease. • To assess 1-year OS and PFS according to the NRS 2002 cut-off score ≥3 upon diagnosis in the different selected cancer types. • To assess 1-year OS and PFS according to the changes of NRS 2002 score and body weight during the follow-up.
Explorative endpoints
• To assess 1-year OS and PFS according to the type and timing of nutritional support provided. • To assess 1-year OS and PFS according to the body composition measured with CT scan and BIVA methods at diagnosis and during follow up. • To assess the percentage of patients with severe toxicities oncologic and discontinuations or delays of treatment according to the NRS 2002 cut-off scores and body composition evaluated at diagnosis and during follow up. • To explore the correlations between NRS 2002 scores, body composition parameters, type and timing of nutritional support, QoL, symptoms during follow-up.

Abbreviations: BIVA, bioelectrical impedance vector analysis; CT, computed tomography; NRS 2002, Nutritional Risk Screening 2002; OS, overall survival; PFS, progression free survival.

Statistical methods and sample size

The main characteristics of the enrolled patients at baseline will be summarized with appropriate descriptive statistics, such as absolute and relative frequencies for categorical variables, and mean or medians with corresponding precision indices (standard deviation or interquartile range) for continuous variables.

For the associations of NRS 2022 score and other nutritional factors with OS or PFS, we will use survival analysis methods, such as rate calculation, Kaplan Meier curves, and logrank test. In addition, Cox models will be used to calculate the hazard ratio, and corresponding 95% confidence interval, for patients at high risk of malnutrition versus low-risk patients and other nutritional factors. Hazard ratios will be computed adjusting for potential confounding factors, including age, sex, tumor characteristics, stage, comorbidities. and cancer treatment. For explorative endpoints, we will use logistic regression models to calculate the (crude and adjusted) odds ratio and corresponding 95% confidence interval of severe toxicity and interruption/delay in cancer treatments, and multiple regression methods for the calculation of crude and adjusted associations.

All analyses will be conducted using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Considering that each center will be able to enroll between 30-300 patients/year (depending on their patients' load), we expect to enroll at least 1500 cancer patients/year.

Since the average 1-year survival rate for the two sexes combined is 75% [24] and about 30% of patients are at risk of malnutrition (NRS 2002 score ≥3) [20], we estimate a hazard ratio of 12-month mortality of at least 1.36 for malnourished patients, with a power of 80% and an alpha error of 5%.

Patient and public involvement

The registry has been developed in collaboration with Italian Federation of Volunteer-based Cancer Organizations (FAVO) in order to delineate the better way to improve cancer patients' involvement into the registry.

Ethics and dissemination

The study will be conducted in accordance with the good clinical practice rules, the Declaration of Helsinki, and current national and European laws and regulations. The study protocol was approved by Ethics Committee of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (05/07/2022; prot. N. 0035571/22) and from the Ethics Committees of all other participating centers. An informed consent will be obtained from each patient enrolled in the study. At any time, patients will have the right to withdraw their consent without modifying their current or future care. The progresses of the study will be shared with the patients' general practitioners.

The results of the study will be presented at local, national, and international medical conferences. The findings will be published in peer-reviewed medical/scientific journals and made open-access on acceptance. Information may also be disseminated to cancer patients and professional associations and the general population via public engagement and community outreach programs.

Discussion

Malnutrition in oncology still represents an overlooked problem, which negatively affects clinical outcomes [4,6,13,25]. An altered nutritional status brings more frequently to drug-related toxicities and requires suspending or delay anticancer therapies, resulting in reduced response rates and worse prognosis [2]. Therefore, an early nutritional support since treatment beginning is crucial. The target is not only to maintain or improve the nutritional status by

providing energy and proteins and fully satisfy nutritional requirements, but also effectively impact on clinical outcomes by enhancing the adherence to anticancer treatment.

The global trend of research in the field of nutrition in cancer is gradually increasing [26]. To date, there is evidence that an individualized nutritional support reduces the risk of mortality and improves QoL in cancer patients at malnutritional risk [27]. Moreover, nutritional support for oncology patients is a low-cost intervention compared to other cares [28] and it does not require additional costs for the healthcare system [29]. However, the impact on survival still requires confirmation as reliable real-world data are lacking.

This study will allow to collect real-world clinical data on malnutrition in Italy. So, it will be possible to improve the strength of evidence on the impact of malnutrition and nutritional support, and to develop quality improvement programs, which help both healthcare professionals to ameliorate nutritional care practices and institutions to allocate adequate resources to this issue [30]. Moreover, the creation of data registry allows to study the cost-effectiveness of nutritional support on a broader scale [31].

The innovative aspect of this study is the implementation of the first Italian real-world register for detecting malnutrition and monitoring nutritional status in cancer patients. This will allow the creation of a multicentric, longitudinal cohort of oncologic patients for further research in the field of nutrition in oncology. Furthermore, it will permit a better monitoring of the nutritional status of cancer patients, fostering an appropriate and sustainable nutritional support, with the goal to improve their care, in agreement with the most recent evidence-based guidelines and recommendations [3-5,12]. The idea is to build a model for a standardized digital platform to monitor the nutritional status of cancer patients. In the near future, the registry could be extended to all the other oncologic centers within the national territory.

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Conceptualization: CB, RC. Methodology: CB, RC. Software: CB. Data Curation: all authors. Writing - Original Draft: CB, AC, EC, RC. Writing - Review & Editing: all authors. Supervision: CB, PP, RC. Project administration: CB, PP, RC.

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Competing interests

All authors declare that they have no competing interests.

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FIGURE' LEGEND

Figure 1. Participating centers.