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NUTRITION AND FRAILTY: HOW TO CAPTURE THE COMPLEXITY OF OLDER PEOPLE

MED/09

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Abstract

The older population is characterized by a high clinical complexity. Poor nutritional status is highly prevalent in older people and has been repeatedly evoked as a major contributor to several health-related negative outcomes. The aim of this thesis was to evaluate the contribution of nutrition in some age-related conditions, taking into account the older people's complexity.

Study I. We explored the association between lack of energy and malnutrition in nursing home residents. Lack of energy was highly prevalent in our sample (i.e., 43.2%). We found a significant association between malnutrition and lack of energy, independent of potential confounders. Decrease in food intake, reduced mobility, and psychological stress or acute disease in the past 3 months were identified as the items of the Mini Nutritional Assessment contributing the most to the association between malnutrition and lack of energy.

Study II. We investigated the association between unintentional weight loss and mortality in a population of older patients undergoing hemodialysis. Older patients experiencing unintentional weight loss during the follow-up period had a 3.4-fold risk of death independently of comorbidities and other risk factors.

Study III. We explored the prevalence of frailty and its association with hospitalization and mortality in a population of older patients undergoing haemodialysis. Study III outlined a high prevalence of frailty (i.e., 55.2%) among older patients undergoing haemodialysis. Frailty was significantly associated with a higher risk of hospitalization and all-cause mortality in our sample.

Conclusions. Nutritional status is an aspect frequently overlooked, despite it has been repeatedly evoked as a major determinant of health status in all stages of life. Our findings clearly show the role of nutritional status as a mediator of several health-related conditions in older people. Indeed, given the burden it poses in terms of adverse health outcomes, increased (research) efforts should be paid to nutritional status. A multidimensional and multidisciplinary approach is pivotal for the early

identification of people presenting nutritional issues in order to prevent the onset of serious complications.

CONTENTS

1. Introduction

1.1. Demographic transition

In the last decade, life expectancy has increased worldwide with a significant number of old and very old individuals. By 2050, people aged 60 and older will double (i.e., about 2 billion) compared to 2015 (i.e., nearly 900 million) [1]. This ageing phenomenon is driven by several factors [2]. First, fertility rate has declined throughout the world, especially in developed countries. Second, infant and child mortality declined since public health conditions have generally improved. Finally, a steady increase in life expectancy at birth and at older age (i.e., at age of 60), contributing to the absolute number of older people, is also observed. This projected growth will represent a challenge for healthcare systems, which were originally based and remain centered on a single disease approach. Older population is characterized by a high clinical complexity, with most older people presenting at least two or more chronic conditions (i.e., multimorbidity). Indeed, there is a need of remodeling the delivery of health and social care in order to bridge a steadily increasing gap.

1.2. Nutrition, frailty and sarcopenia

Aging is characterized by several changes (i.e., physiological, physiological, psycho-social and pathological changes) in many functions (Table 1).

Table 1. Major changes occurring with aging. Reproduced from Azzolino et al. [3] under the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

Physiological	**Pathological**	**Psychosocial**
Digestive system	Diseases	Depression
Hormonal	Medications	Financial status
↓ taste and smell	Neurological disorders	Anxiety
↓ energy expenditure	Swallowing problems	Sleep disorders
Early satiety	Poor dentition	↓ Ability to shop or prepare meals
Cytokines	Poor mobility	Loneliness
Xerostomia		

All these changes lead to poor appetite and negatively impact the quantity and/or quality of food consumed, a condition known as "anorexia of ageing" that may result in overt malnutrition (i.e., undernutrition), sarcopenia, frailty and negative health-related outcomes (including disability and mortality) [4–6].

Hence, poor nutritional status has been repeatedly evoked as a major contributor in the etiopathogenesis of both frailty and sarcopenia. Undernutrition, frailty and sarcopenia share some common determinants and pathophysiological mechanisms [7]. They frequently interact and coexist in older people [8] and include in some way low muscle mass within their definitions [9]. In fact, all these changes seen with aging may negatively impact nutritional status eventually contributing to alterations in body composition which seeem to be the common thread among malnutrition, frailty and sarcopenia [10].

In other words, certain criteria to determine malnutrition, frailty and sarcopenia frequently show a remarkable overlap especially in the physical function domain [11]. To date, a low-grade inflammatory state, the so-called "inflamm-aging", which is characterized by increased circulating levels of cytokines (i.e., IL-1, IL-6, and TNF-α]) [6], seems to be a common pathophysiological mechanisms in the etiology of both malnutrition, frailty and sarcopenia. In fact, inflamm-aging may results in a reduction of food intake, altered metabolism, and increased muscle catabolism, potentially leading to malnutrition, sarcopenia, and frailty [12].

The three conditions (i.e., malnutrition, frailty and sarcopenia) are not confined solely to older persons but can occur earlier in life in presence of several pathological conditions (i.e. end stage renal disease [13–15], end stage liver disease[16,17], HIV [18–20]). In fact, in recent years there has been an increasing interest in assessing these three conditions in several patient's populations [21].

1.1.1. Malnutrition. Synonym: undernutrition

Malnutrition (i.e., undernutrition) is defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) as "a state resulting from lack of uptake or intake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass, leading to diminished physical and mental function as well as an impaired clinical outcome" [22]. The exact prevalence of malnutrition widely varies across populations and settings. A study recruiting older persons in 12 countries reported that the overall prevalence of malnutrition was approximately estimated around 23% [23]. The highest prevalence was observed in rehabilitation settings (50.5%), followed by hospitals (38.7%), nursing homes (13.8%), and communities (5.8%). At the same time, besides these epidemiological data on prevalence, it is well established that older people are at risk of developing malnutrition, independently of the setting where they live [23]. Malnutrition can results from several adverse health outcomes, which are also associated with an increased risk of morbidity and mortality [24]. Consequences of malnutrition include falls, hospitalizations and prolonged hospital stay, vulnerability to infections, electrolyte imbalances, anemia, muscle wasting, and fatigue. All these endpoints obviously lead to consequent functional limitations and severely impact on the individual's quality of life [25–28].

Poor nutritional status has been also invoked as a contributor of fatigue, an often-neglected but frequently reported symptom of by older people [29]. Malnutrition can in fact be responsible of a loss of body weight and nutritional deficiencies which can lead to fatigue by means of "lack of energy" [27,30–32]. When the dietary intake of energy and proteins is not sufficient to meet individual demand, body fat and muscle are catabolized to provide energy [33,34] along with resulting symptoms like as fatigue or tiredness [27,31].

Malnutrition has also been associated with reduced physical performance leading to fatigue [27]. Here too, the muscle is regarded as a key component in the association between malnutrition and poor physical performance [35].

Recently, the Global Leadership Initiative on Malnutrition (GLIM) [12] released a consensus definition establishing the diagnostic criteria for malnutrition. They included three phenotypic criteria (i.e., unintentional weight loss, low body mass index, and reduced muscle mass) and two etiologic criteria (i.e., reduced food intake or assimilation, and inflammation and disease burden). According to GLIM, to diagnose malnutrition at least one phenotypic and one etiologic criterion should be present. It is interesting to note the inclusion in the GLIM criteria of unintentional weight loss as a phenotypic criterion. Unintentional weight loss is, in fact, included in several screening tools to assess malnutrition in older people (i.e., Subjective Global Assessment [36], Malnutrition Inflammation Score [37], Mini Nutritional Assessment [38], Nutritional Risk Screening

2002 [39], Malnutrition Universal Screening Tool [40]) and has been repeatedly associated with higher mortality rates [41]. Unintentional weight loss is also widely recognized as an important contributor of frailty. In fact, in the physical frailty phenotype model developed by Fried et al. [42], unintentional weight loss is listed as one out of five criteria to screen for frailty.

1.1.2. Sarcopenia

With aging both muscle mass and strength progressively decline. In particular, after the fourth decade of life muscle mass declines at a rate of nearly 1–2% per year, while muscle strength at a rate of nearly 1.5% per year. However, muscle strength can decrease even up to 3% per year after the sixth decade of life [43]. The term sarcopenia, was firstly introduced by Irwin Rosenberg in 1988 in a meeting in Albuquerque (New Mexico, USA) [44] and refers to the loss of muscle mass and strength leading to a poor functionality [45]. Sarcopenia is associated with several health-related negative outcomes including falls, fractures, physical disability and mortality [45]. There are multiple pathophysiological mechanisms underlying sarcopenia including malnutrition, physical inactivity, inflammation, mitochondrial dysfunction, hormonal changes, increased catabolism and anabolic resistance, insulin resistance myocyte's loss, reduced satellite cell number and function, and loss of α-motor neurons [46–48]. Nutrition is a mainstay in counteracting sarcopenia. Older people show a reduced anabolic response along with an increased catabolism. Indeed, older adults need more protein (i.e., at least 1.0 g/kg body weight/day) to counteract muscle decline compared to young and adult individuals [47,49]. Energy provision is also pivotal since if caloric intake is not sufficient to meet demands, body fat and muscle are catabolized to provide energy [50].

As mentioned above, the GLIM criteria for malnutrition included reduced muscle mass as one of the three phenotypic diagnostic criteria. Indeed, it has been suggested that the finding of low muscle mass with normal muscle function may be indicative of the presence of malnutrition (i.e., malnutrition-related sarcopenia) [9].

Sarcopenia and frailty frequently overlap, especially when the focus is shifted on the physical function domain. In this context, sarcopenia may represent the entry door for the development of physical frailty and/or for the adverse health outcomes of frailty [51].

1.1.3. Frailty

Frailty is defined as "a clinical state in which there is an increase in an individual's vulnerability for developing an increased dependency and/or mortality when exposed to a stressor" [52]. Frailty is major contributor of several negative health outcomes including falls, fractures, hospitalization, disability, nursing home admission, and mortality [53–55].

There are several operational definitions of frailty. The two main ways to conceptualize frailty are the phenotype model proposed by Fried et al. [42] and the cumulative deficit model proposed by Rockwood and Mitniski [56]. The Fried operational definition of frailty is based on a set of five criteria which are:

1) unintentional weight loss;
2) muscle weakness;
3) slow walking speed;
4) low physical activity;
5) exhaustion.

It should be noted that the frailty model proposed by Fried includes muscle weakness defined by a low grip strength and reduced physical performance (slow walking speed), which are both part of the definition of sarcopenia. As above mentioned, sarcopenia is a main contributing factor in the pathogenesis of frailty when a syndromic approach is applied. Additionally, both entities share several physiological and pathologial determinants (i.e., inflammation, physical inactivity, endocrine factors, and poor nutritional status) [57].

On the other hand, the frailty index developed by Rockwood et al. [58] is based on a multidimensional concept of deficit accumulation including psychological and social components, multi-morbidity and disability in addition to the physical components. The frailty index is simply calculated from the deficits who a person presents divided by the total number of deficits considered. Indeed, this model provides a continuous measure of frailty ranging from 0 (absence of frailty) to 1 (completely frail). However, it should be noted that a score of about 0.7 or higher is rarely reached since might become incompatible with life [59]. The original model of the frailty index comprised 70 items. However, this set of variables are not fixed. In fact, a minimum of 50 items have been generally considered to provide robust estimates of risk. Nevertheless, shorter versions (i.e., from 20 items) can be also found in literature. The suggested cut-off for frailty assessed with the frailty index is >0.25 [60]. The frailty index may be retrospectively computed from medical records or available databases. Indeed, this approach does not require de novo assessments [61].

2. Aims

2.1. General aim

The general aim of this thesis was to assess the contribution of nutrition in some age-related conditions, taking into account the older people complexity.

2.2. Specific aims

The specific aims addressed in the three studies were:

1. To investigate whether lack of energy was associated with malnutrition and to determine whether specific aspects of malnutrition would increase the risk of experiencing fatigue in a population of nursing home residents.
2. To investigate associations between unintentional weight loss and mortality in a population of older people undergoing haemodialysis.
3. To investigate the association of frailty with hospitalization and mortality in a population of CKD older patients undergoing haemodialysis.

3. Methods

3.1. Study design and population

3.1.1. Study I.

Data were retrieved from the database of the Incidence of pNeumonia and related ConseqUences in nursing home Residents (INCUR) study cohort [62]. The INCUR was a longitudinal observational study recruiting 800 people aged 60 and older living in 13 randomly selected nursing homes in the Midi-Pyrenees region of France. All the data were directly retrieved from the clinical charts of the nursing home residents. When an information was missing, the study staff could ask to the nursing home professional in order to obtain the most complete set of data. The collection of data was conducted at three time-points, at the baseline and after 6 and 12 months. Information about clinical status, nutrition, physical function, cognition, depression, quality of life, and healthcare costs were recorded. The primary outcome of the INCUR study was the monitoring of incident pneumonia and its clinical and economic consequences. The INCUR study was approved by the Ethical Committee of the Toulouse University Hospital. Since the collected data were all part of the clinical routine, no written informed consent was required according to local regulations. Nevertheless, all participants were adequately informed about the study protocol and were free to decline their participation. After exclusion of 230 individuals who had missing data for the main variables of interest, a total of 570 NH residents were included in the analysis.

3.1.2. Study II and study III

Data were retrieved from the clinical charts of 107 older patients with CKD receiving hemodialysis at the Nephrology Unit of a tertiary hospital in Milan (Italy). The main exclusion criterion consisted in a short-term hemodialysis treatment (i.e., less than three months) for avoiding the inclusion of individuals with terminal illness. Information about clinical status, nutrition, and physical function were recorded.

The study was approved by the Ethical Committee of the Fondazione IRCCS Ca' Granda – Policlinic Hospital of Milan. Since the collected data were all part of the clinical routine, no written informed consent was required according to local regulations. However, all participants were adequately informed about the study procedures and were free to decline their participation.

3.2. Health assessment

3.2.1. Lack of energy (Study I)

Lack of energy was measured at baseline in response to the question "Did you feel full of energy during the past week?", asked as part of the 10-item Geriatric Depression Scale (GDS) [63,64]. Participants who answered "no" were categorized as fatigued.

3.2.2. Nutritional status (Study I)

Nutritional status was assessed through the Mini Nutritional Assessment Short-Form (MNA-SF) [65]. The MNA-SF consists of six items: reduced food intake, non-volitional weight loss in the past three months, mobility, psychological stress or acute disease during the past three months, neuropsychological problems, and body mass index (BMI). If not available, BMI was replaced with calf circumference. The total MNA-SF score ranges from 0 to 14. In particular, a score of 12-14 is indicative of a normal nutritional status, a score of 8-11 is indicative of the risk of malnutrition and a score of 0-7 reflects malnutrition.

3.2.3. Unintentional weight loss (Study II)

Body weight was measured at each clinical visit as part of the routine care. Unintentional weight loss was defined as a loss of body weight higher than 5% occurred over the previous 6 months, or higher than 10% over more than 6 months.

3.2.4. Frailty (Study I, Study II and Study III)

A frailty index was retrospectively computed according to the procedure drawn up by Searle and colleagues [66]. The FI included anamnestic diseases, biochemical and nutritional parameters. Each item constituting the FI was a health deficit and was categorized as 0 (if the deficit was absent) or 1 (if the deficit was present). FI was calculated as the number of deficits presented by each individual divided by the total number of considered deficits (i.e., 36 in study I, 21 in study II and 24 in study III). The item defining unintentional weight loss (independent variable of the study II) was excluded from the computation of the total score used in the analyses.

3.2.5. Other measurements

Sociodemographic data (i.e., age, sex, education) and presence of comorbidities were collected (study II, study II and study III). Depression was measured according to the 10-items GDS [63,64] (study I). The item defining lack of energy (dependent variable of the study 1) was excluded from the computation of the total score used in the analyses. In study I, functional status was assessed through the activities of daily living (ADL) scale (ranging from 0 [dependent] to 6 [independent]) [67] and a modified instrumental activities of daily living (IADL) scale (ranging from 0 [dependent] to 4 [independent]) [68].

3.3. Statistical analyses

Data are presented as mean and standard deviation (SD) or absolute numbers and percentages for continuous and categorical variables, respectively.

In study I, Chi-square and *t*-tests were used to describe the population according to the study outcome. Logistic regression models were performed to test the association of lack of energy (dependent variable) with nutritional status (independent variable). Unadjusted and adjusted (for age, sex, and FI) models were performed. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were reported.

In study II, unintentional weight loss was used as categorical variable in the analyses. Unadjusted and adjusted (considering age, sex, and Frailty Index as covariates) Cox regression models were performed to test the association of unintentional weight loss (independent variable of interest) with death (dependent variable of interest). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were reported. The time to event was defined from the date of the baseline (i.e., three months after the initiation of the hemodialysis program) to the date of death (for those who died) or the date of the last visit (for those who did not).

In study III, unadjusted and adjusted (considering age and sex) Cox proportional hazard models were performed to test the association of frailty (independent variable of interest) with death and hospitalization (dependent variables of interest). Hazard ratios (HRs) and their 95% confidence intervals were calculated.

For all the three studies, statistical significance was set at p value <0.05.

Analyses were performed with IBM SPSS Statistics version 26 (IBM Corp, Armonk, NY) in study I, while with JAMOVI version 1.6 in study II and III.

4. Results

4.1. Relationship between malnutrition and lack of energy (Study I)

The baseline characteristics of the study sample according to the dependent variable of interest are presented in Table 2.

Table 2. Baseline Characteristics of the Study Sample (N=570) according to the presence of Lack of Energy.

Variable	Overall N=570	Lack of energy		P^*
		No (N = 324)	Yes (N = 246)	
Age, y	86.5 (7.5)	85.8 (7.6)	87.3 (7.2)	0.02
Sex (Women)	72.1%	55.2%	44.8%	0.21
BMI, Kg/m^2	25.8 (5.4)	25.9 (5.4)	25.7 (5.4)	0.74
Education, y	8.4 (3.3)	8.4 (3.1)	8.4 (3.5)	0.93
MNA score (0-14)	10.1 (2.3)	10.6 (2.1)	9.7 (2.4)	<0.001
ADL score (0-6)	2.8 (1.8)	3.0 (1.8)	2.4 (1.7)	<0.001
IADL score (0-4)	0.8 (0.7)	0.9 (0.7)	0.8 (0.7)	0.30
GDS* score (0-9)	2.5 (2.2)	1.8 (1.9)	3.4 (2.6)	<0.001
Frailty index	0.37 (0.10)	0.36 (0.11)	0.39 (0.10)	<0.001
Diabetes	15.9 %	15.0 %	17.1 %	0.51
Dementia	34.7 %	35.2 %	34.0 %	0.77
COPD	7.5 %	6.7 %	8.5 %	0.42
Hypertension	61.1 %	60.9 %	61.5 %	0.87
Cancer	15.5 %	14.7 %	16.6 %	0.53
Cerebrovascular disease	11.8 %	12.5 %	10.9 %	0.56
Coronary artery disease	6.6 %	8.0 %	4.9 %	0.14
Congestive heart failure	29.8 %	27.5 %	32.8 %	0.17

Values are presented as mean (SD) or percentage. BMI=Body Mass Index; MNA=Mini Nutritional Assessment; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; GDS=Geriatric depression Scale; COPD=Chronic obstructive pulmonary disease.

*computed excluding “lack of energy”

The results of the logistic regression analyses are presented in Table 3. At univariate logistic regression analysis, MNA score was inversely associated with lack of energy. At multivariate logistic regression analysis, adjusted for age, sex nursing home years and FI, we found that MNA was independently inversely associated with lack of energy.

Malnutrition status was independently associated to the lack of energy in both the unadjusted model as well as after adjustment for age, sex, and Frailty Index.

Table 3. Relationship of the Mini Nutritional Assessment (MNA) Score with lack of energy in nursing home residents

	Unadjusted OR (95% CI)	***P***	**Model 1 OR (95% CI)**	***P***
MNA score continuous	0.84 (0.78-0.90)	<0.001	0.87 (0.80-0.95)	0.002
MNA score categories				
Normal nutritional status (12-14 points, n=180)	Reference group		Reference group	
At risk of malnutrition (8-11 points, n=323)	1.39 (0.95-2.02)	0.09	1.14 (0.77-1.71)	0.51
Malnourished (0-7 points, n=71)	3.42 (1.92-6.08)	<0.001	2.41 (1.29-4.52)	0.006

OR= odds ratio; CI= confidence interval

Model 1: Adjusted for age, sex, frailty index

Adjusted models individually testing each single item of the MNA-SF in the association with the lack of energy were conducted (Table 4). It was found that item A (i.e., decrease in food intake), item C (i.e., reduced mobility), and item D (i.e., acute disease or psychological stress over the past 3 months) were positively associated with the study outcome. Then, a single exploratory model simultaneously including all the MNA-SF items was performed (Model 2). Results were confirmed and did not substantially differ from the previous findings, confirming the associations of the items A, C, and D.

Table 4. Relationship of single items of the Mini Nutritional Assessment (MNA) score with lack of energy in nursing home residents

Single Items of the MNA	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*
A. Decrease in food intake	2.19 (1.50-3.20)	<0.001	1.85 (1.24-2.77)	0.003
B. Involuntary weight loss during the past 3 mo	1.09 (0.75-1.58)	0.67	1.16 (0.78-1.73)	0.46
C. Mobility	1.47 (1.14-1.89)	0.003	1.43 (1.10-1.86)	0.008
D. Acute disease or psychological stress over the past 3 mo	1.55 (1.26-1.91)	<0.001	1.48 (1.19-1.84)	<0.001
E. Neuropsychological problems	0.86 (0.69-1.09)	0.22	0.86 (0.67-1.09)	0.21
F. BMI or CC, cm	1.09 (0.93-1.29)	0.28	1.07 (0.90-1.27)	0.43

N= number of nursing home residents with the item; n= number of patients with the item and lack of energy

BMI=body mass index; CC= calf circumference; OR= odds ratio; CI= confidence interval

Model 1= Adjusted for age, sex, frailty index

Model 2= Adjusted for age, sex, frailty index, lack of energy and all the MNA items

4.2. Relationship between unintentional weight loss and mortality in dialyzed older persons (Study II)

The characteristics of the study sample are presented in Table 5. Median follow-up was 21 (interquartile range 8-32) months.

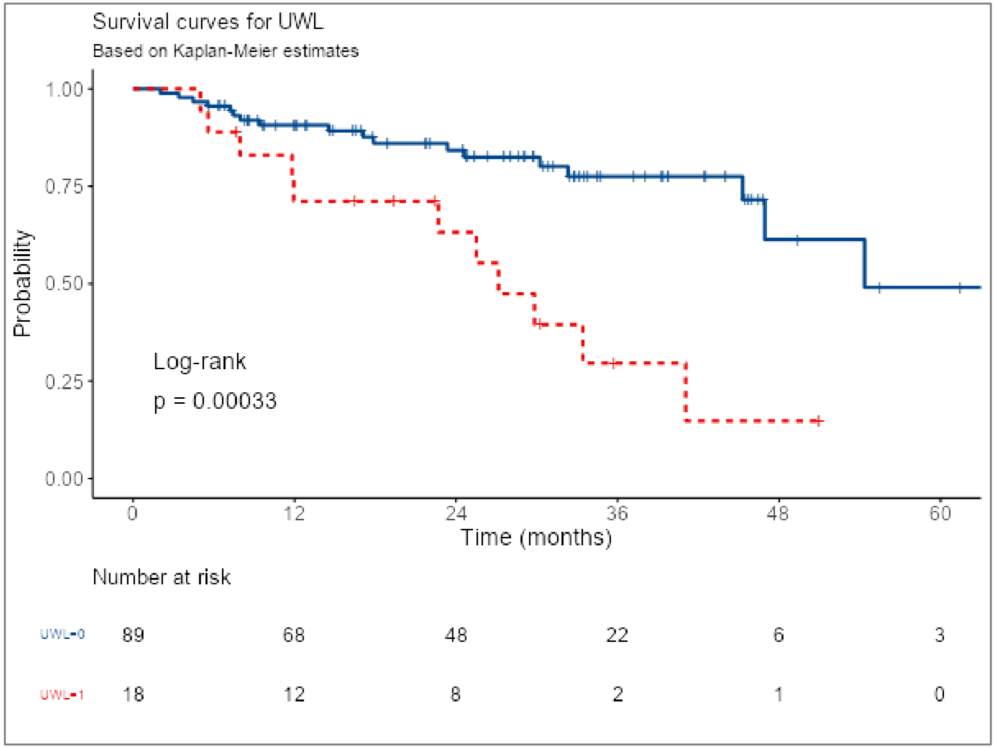
Table 5. Participant characteristics

Variable	N (%), or mean (SD) n=107
Age, y	79.1 (7.7)
Women	38 (35.5)
Diabetes	40 (37.4)
Depression	28 (26.2)
Hypertension	85 (79.4)
CHF	32 (29.9)
CHD	37 (34.6)
Dementia	23 (21.5)
Cancer	17 (15.9)
Thyroid disorders	23 (21.5)
COPD	25 (23.4)
Albumin, g/dL	3.72 (0.5)
Transferrin, mg/dL	183 (41.7)
Weight loss	18 (16.8)
Hospitalization	81 (75.7)
Death	31 (29)
Frailty index	0.23 (0.10)

SD: standard deviation; CHF: Chronic Heart Failure; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease

The results of the Kaplan-Meyer curves are presented in Figure 1.

Figure 1. Survival Curves for UWL



^ UWL=Unintentional weight loss

Results of the multivariate Cox regression analyses are reported in Table 6. In both unadjusted and adjusted models, unintentional weight loss was positively associated with death.

Albumin levels below 3.5 g/dL were significantly associated with death in both the unadjusted and partially adjusted model. However, the association disappeared when the other two variables of interest (i.e., transferrin and unintentional weight loss) were added in the model. On the other hand, transferrin levels below 200 mg/dl were not significantly associated with death in both the unadjusted and adjusted models.

Table 6. Relationship of unintentional weight loss with death in dialyzed older patients

	Unadjusted	***P***	**Model 1**	***P***	**Model 2**	***P***
	HR (95% CI)		**HR (95% CI)**		**HR (95% CI)**	
UWL	3.49 (1.63-7.46)	0.001	3.55 (1.61-7.84)	0.002	3.43 (1.51-7.78)	0.003
Albumin< 3.5 g/dL	2.20 (1.10-4.40)	0.03	2.19 (1.09-4.41)	0.03	1.38 (0.60-3.17)	0.45
Transferrin< 200 mg/dl	1.82 (0.87-3.84)	0.11	1.64 (0.78-3.45)	0.19	1.64 (0.71-3.81)	0.25

HR= hazard ratio; CI= confidence interval; UWL= unintentional weight loss

Model 1: Adjusted for age, sex, frailty index

Model 2: Adjusted for age, sex, frailty index, and the three independent variables of interest

4.3. Association of frailty with death and hospitalization in dialyzed older persons (Study III)

Participant characteristics are presented in Table 7. Median follow-up was 21 (interquartile range [IQR] 8-32) months.

Table 7. Participant characteristics

Variable	N (%), or mean (SD) n=105
Age, y	79.1 (7.6)
Women	37 (35.2)
Diabetes	38 (36.4)
Depression	28 (26.2)
Psychiatric disorders	8 (7.5)
Hypertension	84 (80)
CHF	32 (30.5)
CHD	36 (34.3)
Atrial fibrillation	32 (30.5)
Dementia	23 (21.9)
Cancer	17 (16.2)
COPD	25 (23.4)
PCR	1.23 (2.09)
Albumin, g/dL	3.72 (0.5)
Weight loss	18 (17.1)
Hospitalization	79 (75.2)
Death	29 (27.6)
24-item Frailty index	0.23 (0.10)
FI≥0.25	58 (55.2)

SD: standard deviation ; CHF: congestive Heart Failure; CHD: coronary heart disease

The results of the multivariate Cox regression analysis testing the association between frailty and hospitalization are reported in Table 8. Frailty was positively associated with hospitalization in both unadjusted and adjusted models.

Table 8. Relationship of frailty with hospitalization in dialyzed older patients

	Unadjusted HR (95% CI)	***P***	**Model 1 HR (95% CI)**	***P***
Frailty	1.70 (1.07-2.71)	0.025	1.60 (1.00-2.57)	0.051

HR= hazard ratio; CI= confidence interval

Model 1: Adjusted for age and sex

Also, frailty was significantly associated with all-cause mortality (Table 9). After adjustment for age and sex, these associations remained significant.

Table 9. Relationship of frailty with death in dialyzed older patients

	Unadjusted HR (95% CI)	***P***	**Model 1 HR (95% CI)**	***P***
Frailty	2.48 (1.09-5.63)	0.03	2.52 (1.10-5.80)	0.03

HR= hazard ratio; CI= confidence interval

Model 1: Adjusted for age and sex

5. Discussion

5.1. Main findings

5.1.1. Lack of energy and its association with malnutrition

In study I we demonstrated an extremely high prevalence (i.e., 43.2%) of anergia in the frail population living in nursing homes. In a cohort of NH residents, we found that a poor nutritional status is significantly associated with the lack of energy, independently of potential confounders. In particular, malnourished residents had a 2.4-fold increased risk of being fatigued. Among the MNA-SF items most contributing to this association, the decrease in food intake, the reduced mobility, and the psychological stress or acute disease in the past 3 months were those most relevant. Interestingly, both BMI and unintentional weight loss, were not significantly associated with lack of energy. Therefore, it can be assumed that lack of energy is only partially related to anthropometric measures, providing a more comprehensive measure of malnutrition.

Malnutrition (i.e., undernutrition) is widespread in older people, especially in those who live in nursing homes [69–71]. At once, fatigue, which is frequently manifested as a lack of energy, also constitutes a highly prevalent and particularly burdensome condition among the frailest individuals [72].

Nevertheless, as far as we know, only a few studies investigated the association between malnutrition and fatigue among older people. Singh et al. [27] reported a significant association between self-reported mobility tiredness and body mass index among older adults with undernourishment living in NHs. Recently, Kushkestani et al. [73] described a positive association between malnutrition (assessed through the

MNA) and fatigue (defined according to the Functional Assessment of Chronic Illness Therapy Fatigue questionnaire) in this setting. Another recent study [74] found a positive association between severe weight loss and moderate-to-severe fatigue in older patients at hospital discharge. Finally, Tsutsumimoto et al. [75] reported that anorexia of aging was an independent predictor of exhaustion.

Our findings contribute to the increase of knowledge on lack of energy as a symptom which is frequently reported by older people. It seems that the self-reported lack of energy may potentially serve as a surrogate for estimating the exhaustion of metabolic reserves of the individuals [76]. In fact, besides of being frequently complained by older people, fatigue is strongly associated with the inability to continue functioning at the normal level of activity [72], poor physical performance [77] and represents a powerful predictor of multiple adverse outcomes (i.e., hospitalizations, increased use of healthcare services, incident disability, mortality) [78–80]. Unfortunately, the lack of a gold standard for its assessment as well as the subjectivity of the symptom make lack of energy an unmet clinical need.

Fatigue is a complex and multidimensional symptom, which frequently remains unexplained in older people. Most of the evidence for an association between nutritional status and fatigue comes from cancer patients and chronic fatigue syndrome [3,74]. However, most of the nutritional problems of these patient’s populations are also frequently observed in older people. Fatigue may be looked at as a disorder of energy balance [81], mimicking the exhaustion of the metabolic reserves of the individual [82–85]. In this context, an adequate intake especially in energy and protein may represent a strategy not only in counteracting muscle decline, but also aimed at addressing the symptom of fatigue.

Surprisingly, the univariate analyses, testing the prevalence of single diseases according to the presence of anergia, did not show significant differences. On contrary, NH residents complaining of a lack of energy presented a higher Frailty Index compared to the control group. This may reflect the clinical complexity of the NH population, which is not defined by a single condition but by the interaction of multiple signs, symptoms, diseases, and disabilities. As such, a monodimensional approach to capture the syndromic nature of geriatric conditions (including malnutrition, frailty, and lack of energy) might be inadequate. Indeed, the self-reported lack of energy could reflect the exhaustion of the homeostatic reserves of the individual. In other words, lack of energy may represents a sort of clinical alert launched by the organism challenged in its limited reserves by a disproportionate stressor [81].

5.1.2. Unintentional weight loss as a predictor of mortality

Study II demonstrated a positive association of unintentional weight loss with death in a population of CKD older patients undergoing haemodialysis, independently of potential confounders. Patients experiencing weight loss during the follow-up period had a 3.4-fold risk of death.

Unintentional weight loss is frequently assessed in older people and has been repeatedly associated with higher mortality rates. CKD patients usually present anorexia because of circulating uremic toxins. Low levels of testosterone resulting in augmented leptin levels have been reported in male CKD older patients and can further exacerbate anorexia. Additionally, gastrointestinal symptoms (i.e., nausea, vomiting, and diarrhea) can contribute to weight loss in this population [86]. Dialysis treatment results in increased protein catabolism and has been associated with physical inactivity, consequently increasing the risk of malnutrition and sarcopenia independently of the aging process [87–89].

Our findings are consistent with those of Cabezas- Rodriguez et al. [90] that outlined an association between weight loss and higher rates of mortality in hemodialysis patients over a 6-months period. Additionally, they also reported a higher risk of death in those CKD patients aged 65 and older experiencing weight loss compared to their younger counterparts. Another study [91] evidenced a rapid weight loss, with a nadir at 5 months, in CKD patients surviving to the first year of hemodyalisis. The authors also showed an increased mortality risk in those patients experiencing incrementally larger weight loss during the first 12 months of dialysis.

On the other hand, weight gain and higher BMI have been associated to better survival in hemodialysis patients, a phenomenon known as the “obesity paradox” [90–92]. Nevertheless, it is important to note that BMI has several limitations. In fact, its numerator (i.e., body weight) includes both lean and fat mass. Older people are characterized by a decreased lean mass with a concomitant increased adipose tissue even with a normal/overweight BMI. Therefore, BMI categories to determine obesity do not apply to older people, considering also that these cut-off points were derived from young and middle-aged cohorts [93]. Also, the BMI cut-points to define underweight have been considered inadequate for older people, with the majority of instruments to screen for malnutrition adopting higher cut-points [12]. In CKD patients, it has been recommended a BMI cut-off of 23 Kg/m^2 to define malnutrition, regardless of age [87,94,95]. In patients undergoing hemodialysis, fluid retention is frequently observed, thus other measurements like bioelectrical impedance analysis may be inaccurate.

Albumin and transferrin are two negative acute-phase proteins that are sometimes used for nutritional assessment [96]. In particular, low albumin levels have been repeatedly associated with higher mortality rates both in older people and in CKD patients, but not in those patients undergoing hemodialysis [87]. The marginal prognostic value of low albumin and transferrin levels seems to be confirmed in our study. The measurement of unintentional weight loss may provide more accurate information compared to biomarkers given its multidimensional nature. It might therefore better capture the individual's complexity. Additionally, it should be noted that the identification of unintentional weight loss implies the drawing of a longitudinal trajectory, describing the dynamical evolution of the system. In other words, capturing time-related clinical modifications can surely be more informative than the cross-sectional measurement of a biological variable.

5.1.3. Frailty as a predictor of hospitalization and mortality

Our study showed a high prevalence of frailty (i.e., 55.2%) among older patients undergoing haemodialysis. A FI $\geq$ 0.25 was associated with a higher risk of hospitalization and all-cause mortality in hemodialysis older persons. In particular, frail patients had a 1.7-fold and a 2.5-fold risk of hospitalization and mortality, respectively.

The vast majority of studies involving hemodialysis patients generally used the Fried Frailty Phenotype model to measure frailty [97]. To our knowledge, this is the first study applying the FI model in a population of haemodialysis patients. The purpose of the FI is to measure the contribution of accumulating deficits of the individual. The quantitative nature of the FI gives the opportunity to compute the variable independently of the items composing it, mirroring the individual's biological age. The FI, given its comprehensive and multidimensional nature, may better capture the vulnerability of the person. Interestingly, its generation does not require de-novo measurements but can be retrieved by every clinical assessment without substantial deviations from the routine clinical practice. Frailty index has a strong biological validity given that usually have a tendency at increasing with chronological age and rarely reaches a value of 0.7 (i.e., an accumulation of health deficits higher than 70%) which might become incompatible with life [66,98].

Studies have found a large variability (i.e., ranging from 6 to 82%) in the prevalence of frailty in patients undergoing haemodialysis [99,100], Such heterogeneity may be the result of the use of different (and modified) instruments to measure the condition of frailty as well as to the inclusion of young adult patients.

Frailty has long been recognized as a predictor of adverse outcomes, including hospitalization and mortality, in several populations and settings [101]. Johansen et al. [102] found an independent association of frailty with death (adjusted HR 2.24, 95% CI 1.60–3.15) and with a combined outcome of death and hospitalization (adjusted HR 1.63, 95% CI 1.41–1.87) in patients on dialysis. In 2012, Bao et al. [103] reported an independent association of frailty with mortality (HR 1.57, 95% CI 1.25–1.97) and time to first hospitalization (HR 1.26, 95% CI 1.09–1.45). Another study [104], found that frail patients on dialysis had a 2.6-fold risk of death (95% CI 1.04–6.49). Finally, a recent meta-analysis [99] reported that patients with frailty had a greater risk of all-cause mortality compared with those who were not frail (HR 2.02, 95% CI 1.65−2.48). Our results are in line with all these studies, despite none of these used the FI to characterize frailty. Therefore, it should be noted that the use of the FI in our sample has allowed us to capture the multicomponent dimension of frailty.

Given the burden of haemodialytic treatment and the overall mortality, it is important to consider the prognostic value of the FI in this population of patients. The early assessment of frailty through a multidimensional process in patients undergoing hemodialysis may provide useful information about the risk of mortality and hospitalizations and support clinical choices.

Indeed, the frailty index may be used as a guide to implement an adapted care plan in order to identify targets of intervention and support the clinician at distinguishing patients who can undertake dialysis.

5.2. Methodological considerations

All the studies included in the present thesis collected data that were retrospectively analyzed. The main strength of study I is based on the large sample size. In particular, the study is conducted in nursing homes, a setting that has been often neglected by traditional research. At the same time, the analyzed data were all directly retrieved from the clinical charts of the patients, thus providing a real-life description of the studied association. Some limitations of our studies should be considered. Study I was cross-sectional and therefore it could not be determined any causal relationship among the analyzed conditions of interest (i.e., lack of energy and nutritional status). The definition of lack of energy was derived from the GDS, a validated scale to measure depression in older people. Indeed, our operationalization may have well captured the more psychological dimension of the symptom but potentially underestimated the physical one.

Limitations of study II and study III may be represented by the small sample size and by the retrospective design. However, given that we excluded those patients who did not survive the first three months of dialysis treatment, our sample optimally captured a population of older people in the chronic need of hemodyalisis. Indeed, we had the possibility to properly assess the clinical aspect of the variables of interest in the absence of the acute/terminal phase of kidney disease. Another limitation may reside in the single-site experience, which does not allow to exclude that specific peculiarities of our setting might explain our findings.

6. Conclusions

1. Study I highlighted a high prevalence of lack of energy in a population of nursing home residents. Our study outlined a positive association between malnutrition and lack of energy. Therefore, our findings suggest that anergia could represent the clinical manifestation of a poor nutritional status, a sort of alert launched by the organism facing a reduction of the metabolic reserves of the older person. It is thus important to develop research on lack of energy and nutritional status to better clarify the biological and clinical determinants of the symptom, keeping in mind that one may feed the other and vice versa. Information about the influencing factors of fatigue as well as the identification of potential targets of intervention can be used to encourage health providers to assess and intervene in this context.
2. In study II, we demonstrated a significant association between unintentional weight loss and mortality in a cohort of dialyzed older persons. Unintentional weight loss may be looked like a simple, easy to obtain/implement in the routine clinical practice and affordable measure to help clinicians in assessing the nutritional status of CKD patients on dialysis in order to prevent and/or delay poor outcomes.
3. Finally, study III outlined a high prevalence of frailty among older patients undergoing haemodialysis. Our study demonstrated the capacity of the FI to be predictive of negative outcomes (in this case death and hospitalization). The FI may represent a useful tool for measuring the vulnerability of those older people characterized by a high clinical complexity like patients undergoing dialysis. The FI may support a more efficient identification of patients in the

need of adapted and personalized care. Comprehensive efforts aimed at developing interventions to prevent or attenuate frailty in the dialysis population should also be considered.

7. Relevance and implications

Older people represent a growing proportion but also an invaluable resource of our societies. Unfortunately, an attitude to ageism in terms of negative stereotypes, prejudice, and discrimination toward older people is increasingly seen in our societies, with negative consequences on health, well-being, and quality of health care received. With aging, people may experience a decline both in the physical and functional domains. The aim of geriatric medicine is to prevent such decline, preserving individual’s autonomy and functional ability. To adequately manage the high clinical complexity of our ageing societies, health-care models need to be reshaped with the implementation of adapted care based on key prognostic factors (i.e., frailty, functional status, comorbidities) rather than age and single diseases.

In this context, nutritional status is an aspect frequently overlooked, despite it has been repeatedly evoked as a major determinant of health status in all stages of life. Our findings clearly show the role of nutritional status as a mediator of several health conditions in older people. It should not be forgotten that nutrition is a mainstay of treatment in some age-related conditions (i.e., dysphagia, sarcopenia). Indeed, given the burden that a poor nutritional status poses both in terms of adverse health outcomes (i.e., falls, hospitalizations and prolonged hospital stay, vulnerability to infections, mortality) and of healthcare costs, increased (research) efforts should be paid to nutritional status. A multidimensional and multidisciplinary approach is pivotal for the early identification of people presenting nutritional issues in order to prevent the onset of serious complications.

8. Future directions

During the Ph.D. course, I had the possibility of working in several areas of geriatric research. In particular, I have been involved in several research projects funded by both public (i.e., European Commission) as well as private (i.e., Cariplo, Fondazione Penta, Sanofi, Alexion) institutions. In this context, I had the chance to participate in several meetings, symposia and congresses in Italy and Europe, sometimes as a speaker, interacting with researchers internationally renowned. Despite the COVID-19 pandemic has hampered and reshaped several activities (i.e., on-site congresses, recruitment of participants to research projects), my research activities have gone ahead even if redesigned and on occasion focused on COVID-19. My research interests have been focused (but not limited) on the contribution of nutrition in several age-related conditions (i.e., dysphagia, sarcopenia, frailty, end-stage renal disease). In particular, I focused my attention on the assessment of body composition changes occurring with aging on health status and physical function. Indeed, in addition to the presented works, my research activities have led to the publication of other articles in international, peer-reviewed, scientific journals. In the near future, I would first like to study the role of nutrition and body composition in relation to the biological complexity in older people. In particular, I would focus on the study of centenarians, which are an example of extreme longevity and biological complexity. The model of centenarians is considered the most valuable to interpret the biological meaning of the aging process itself and of some age-related conditions. In this context, environmental factors, like as nutrition which is considered one of the main factors of niche construction, can be determinant of those genes that promotes longevity. In other words, it is well recognized that phenotypic variation associated with extreme longevity is attributable in part to genetic factors but also by the influence of epigenetic and environmental factors. Therefore, the study of centenarians may be an example of making the central focus of research on the biology of the person rather than on diseases.

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BRIEF REPORT

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Lack of energy is associated with malnutrition in nursing home residents: Results from the INCUR study

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Abstract

Background: Lack of energy is a symptom frequently complained by older people, leading to the inability to continue functioning at the expected level of activity. This study aimed to investigate whether nutritional status was associated with lack of energy in nursing home (NH) residents.

Methods: This was a cross-sectional study. A total of 570 NH residents (72.1% women) in 13 French NHs from the Incidence of pNeumonia and related ConseqUences in nursing home Residents study cohort were included in the study. Lack of energy was measured by the question "Did you feel full of energy during the past week?" from the geriatric depression scale. Nutritional status was evaluated according to Mini Nutritional Assessment Short-Form (MNA-SF). Unadjusted and adjusted logistic regression models were performed to test the association of nutritional status with lack of energy.

Results: The mean age of participants was 86.5 (SD 7.5) years. A total of 246 NH residents (43.2%) reported a lack of energy. Overall, 71 (12.5%) residents were malnourished and 323 (56.7%) residents were at risk of malnutrition. Malnutrition was significantly associated with lack of energy (OR = 3.42, 95% CI = 1.92–6.08, $P < 0.001$), even after adjustment for potential confounders (OR = 2.41, 95% CI = 1.29–4.52, $P = 0.006$). Among the single items of the MNA-SF, decrease in food intake, low mobility, and psychological stress or acute disease were individually associated with lack of energy, independently of potential confounders (OR = 1.85, 95% CI = 1.24–2.77, $P = 0.003$; OR = 1.43, 95% CI = 1.10–1.86, $P = 0.008$; OR = 1.48, 95% CI = 1.19–1.84, $P < 0.001$; for each point respectively).

Conclusions: Lack of energy and malnutrition were closely associated. The reporting of lack of energy should lead to a comprehensive assessment of the aging individual (as happening for malnutrition) in order to preventively/promptly act on potentially reversible causes.

KEYWORDS
aging, exhaustion, fatigue, frailty, malnutrition

INTRODUCTION

Fatigue or lack of energy is often experienced by older people with frailty. Although pervasive and associated with adverse health events, this symptom is often neglected by healthcare professionals. Indeed, fatigue is strongly associated with inability to continue functioning at a normal level[1] and is a powerful predictor of multiple negative outcomes (e.g., hospitalizations, increased use of healthcare services, mortality).[2–4] The pathophysiology of age-related fatigue is yet to be deciphered; however, malnutrition may represent one pathway to consider. Both nutritional deficiencies[5] and obesity[6] have been reported to influence fatigue levels. Older people have increased requirements of some nutrients, especially in the presence of highly catabolic conditions. When the intake of dietary protein and energy is inadequate to meet demands, body fat and muscle are catabolized to provide energy,[7,8] leading to overt symptoms like fatigue or tiredness.[9,10] Fatigue may therefore be envisioned as a disorder of energy balance,[11] mimicking the exhaustion of the metabolic reserves of the older individual.[7–10] An adequate intake especially in energy and protein may thus represent a strategy to counteract muscle decline and address the symptom of fatigue.

Undernutrition has been associated with poor physical performance with the consequent onset of fatigue.[10] Low-grade systemic inflammation, a hallmark of aging, is responsible for a reduction of food intake, altered metabolism, and increased muscle catabolism.[12] Nevertheless, the association between nutritional status and fatigue has been poorly investigated. In particular, little data are available for the most vulnerable populations, such as nursing home (NH) residents, in whom the prevalence of fatigue and malnutrition is especially high.

To address this gap, we investigated whether lack of energy was associated with nutritional status in a population of NH residents. In addition, we sought to determine whether specific aspects of malnutrition would increase the risk of experiencing fatigue.

Key Points

- Lack of energy is a symptom frequently complained by older people, leading to the inability to continue functioning at the expected level of activity.
- Lack of energy is highly prevalent in nursing home residents (43.2% in our sample).
- Lack of energy and malnutrition are closely associated.
- The presence of lack of energy and/or malnutrition should lead to the comprehensive assessment of the individual.

Why does this Paper Matter?

We found a high prevalence of lack of energy and a significant association between malnutrition and lack of energy. A simple question exploring the possible lack of energy may provide useful information about functional status of older individuals, thus providing the entry door to adapted clinical approach.

METHODS

Study design

We performed a cross-sectional analysis of the Incidence of pNeumonia and related ConseqUences in nursing home Residents (INCUR) study. The design of the INCUR study has been previously described.[13] In short, the INCUR was a longitudinal observational study for which 800 people aged 60 and older living in 13 randomly selected NHs in the Midi-Pyrenees region of France were recruited. The primary objective of the INCUR study was to monitor the incidence of pneumonia and its clinical and economic consequences. All data were collected from the medical charts of NH residents. Information about clinical status, nutrition, physical function, cognition, depression, quality of life, and healthcare costs was recorded. The project was approved by the Ethical Committee of the Toulouse University Hospital. Since the collected data were all part of the clinical routine, no written informed consent was required according to local regulations. However, all participants were informed about the study procedures and free to decline their participation. A total of 570 NH residents were included in the present analysis, after excluding 230 individuals with missing data for the main variables of interest (i.e., malnutrition and lack of energy).

Outcome measure

Lack of energy was measured at baseline as a binary variable in response to the question "Did you feel full of energy during the past week?", included in the 10-item geriatric depression scale (GDS).[14] Participants who answered "no" were categorized as fatigued.

Nutritional status

Nutritional status was evaluated using the Mini Nutritional Assessment Short-Form (MNA-SF).[15] The MNA-SF includes six items: reduced food intake, non-volitional weight loss in the past 3 months, mobility, psychological stress or acute disease during the past 3 months, neuropsychological problems, and low body mass index (BMI). In 135 participants, BMI was not available and was replaced with low calf circumference, as recommended in the MNA-SF guidance[15] being this parameter (1) a marker of poor nutrition, and (2) highly predictive of adverse outcomes in older persons. The total MNA-SF score ranges from 0 (most severe malnutrition) to 14 (no sign of malnutrition). Specifically, a score of 12–14 is indicative of a normal nutritional status, while a score of 8–11 and 0–7 identifies the risk of malnutrition and malnutrition, respectively.

Other measurements

Sociodemographic data and presence of comorbidities were collected. Depression was measured according to the 10-items GDS.[14] The item defining lack of energy (dependent variable of the present study) was excluded from the computation of the total score used in the analyses. Functional status was measured through the activities of daily living (ADL) scale (ranging from 0 [dependent] to 6 [independent])[16] and a modified instrumental ADL (IADL) scale (ranging from 0 [dependent] to 4 [independent]).[17] A 36-item Frailty Index (FI) was computed according to the model proposed by Rockwood and Mitnitski.[18]

Statistical analysis

Chi-square and *t*-tests were used to describe the population according to the study outcome. Logistic regression models were performed to test the association of lack of

TABLE 1 Baseline characteristics of the study sample ($N = 570$) according to the presence of lack of energy

		Lack of energy		
Variable	Overall $N = 570$	No ($N = 324$)	Yes ($N = 246$)	P^a
Age, years	86.5 (7.5)	85.8 (7.6)	87.3 (7.2)	0.02
Sex (women)	72.1%	55.2%	44.8%	0.21
BMI, Kg/m^2	25.8 (5.4)	25.9 (5.4)	25.7 (5.4)	0.74
Education, years	8.4 (3.3)	8.4 (3.1)	8.4 (3.5)	0.93
MNA score (0–14)	10.1 (2.3)	10.6 (2.1)	9.7 (2.4)	<0.001
ADL score (0–6)	2.8 (1.8)	3.0 (1.8)	2.4 (1.7)	<0.001
IADL score (0–4)	0.8 (0.7)	0.9 (0.7)	0.8 (0.7)	0.30
GDS[a] score (0–9)	2.5 (2.2)	1.8 (1.9)	3.4 (2.6)	<0.001
Frailty index (score)	0.37 (0.10)	0.36 (0.11)	0.39 (0.10)	<0.001
Diabetes	15.9%	15.0%	17.1%	0.51
Dementia	34.7%	35.2%	34.0%	0.77
COPD	7.5%	6.7%	8.5%	0.42
Hypertension	61.1%	60.9%	61.5%	0.87
Cancer	15.5%	14.7%	16.6%	0.53
Cerebrovascular disease	11.8%	12.5%	10.9%	0.56
Coronary artery disease	6.6%	8.0%	4.9%	0.14
Congestive heart failure	29.8%	27.5%	32.8%	0.17

Note: Values are presented as mean (SD) or percentage.
Abbreviations: ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GDS, geriatric depression scale; IADL, instrumental activities of daily living; MNA, mini nutritional assessment.
[a]Computed excluding "lack of energy".

energy (dependent variable) with nutritional status (independent variable). Unadjusted and adjusted (for age, sex, and FI) models were performed. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were reported. Statistical significance was set at $P < 0.05$. All analyses were performed with IBM SPSS Statistics version 26 (IBM Corp, Armonk, NY).

RESULTS

The baseline characteristics of the study sample according to the presence of fatigue are presented in Table 1. The study sample consisted of a total of 570 NH residents (mean age 86.5, SD = 7.5 years; women $n = 411$, 72.1%). At baseline, the mean MNA-SF score was 10.1 (SD = 2.3) points, with 71 (12.5%) residents resulting malnourished, and 323 (56.7%) at risk of malnutrition. A total of 246 participants (43.2%) reported a lack of energy. Participants reporting lack of energy were older, more dependent in the ADLs, showed more depressive symptoms according to the GDS, and were frailer.

Results of the logistic regression analyses are reported in Table 2. In both unadjusted and adjusted models, the MNA-SF score was inversely associated with lack of energy. Being malnourished was independently related to lack of energy in the unadjusted model (OR = 3.42, 95% CI = 1.92–6.08, $P < 0.001$) as well as after adjustment for age, sex, and FI (OR = 2.41, 95% CI = 1.29–4.52, $P = 0.006$).

Secondary analyses were conducted to explore which items of the MNA-SF were contributed the most to the reported association. First, adjusted models individually testing each single MNA-SF item in the association with the lack of energy (Table 3, Model 1) were conducted. Item A (i.e., decrease in food intake), item C (i.e., reduced mobility), and item D (i.e., acute disease or psychological stress over the past 3 months) were positively associated with fatigue (OR = 2.19, 95% CI = 1.50–3.20, $P < 0.001$; OR = 1.47, 95% CI = 1.14–1.89, $P = 0.003$; OR = 1.55 95% CI = 1.26–1.91, $P < 0.001$; for each point, respectively). Then, a single exploratory model simultaneously including all MNA-SF items was performed (Model 2). Results were consistent, confirming the association of items A, C, and D with lack of energy.

It could be argued that adjusting for a multidimensional measure as the FI might bring in the models some instability/risk of collinearity. For this reason, additional analyses

TABLE 2 Relationship of the Mini Nutritional Assessment (MNA) Score with lack of energy in nursing home residents

	Unadjusted OR (95% CI)	*P*	Model 1 OR (95% CI)	*P*
MNA score continuous	0.84 (0.78–0.90)	<0.001	0.87 (0.80–0.95)	0.002
MNA score categories				
Normal nutritional status (12–14 points, $n = 180$)	Reference group		Reference group	
At risk of malnutrition (8–11 points, $n = 323$)	1.39 (0.95–2.02)	0.09	1.14 (0.77–1.71)	0.51
Malnourished (0–7 points, $n = 71$)	3.42 (1.92–6.08)	<0.001	2.41 (1.29–4.52)	0.006

Note: Model 1: Adjusted for age, sex, Frailty Index.
Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 3 Relationship of single items of the Mini Nutritional Assessment (MNA) score with lack of energy in nursing home residents

Single items of the MNA	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*
A. Decrease in food intake	2.19 (1.50–3.20)	<0.001	1.85 (1.24–2.77)	0.003
B. Involuntary weight loss during the past 3 months	1.09 (0.75–1.58)	0.67	1.16 (0.78–1.73)	0.46
C. Mobility	1.47 (1.14–1.89)	0.003	1.43 (1.10–1.86)	0.008
D. Acute disease or psychological stress over the past 3 months	1.55 (1.26–1.91)	<0.001	1.48 (1.19–1.84)	<0.001
E. Neuropsychological problems	0.86 (0.69–1.09)	0.22	0.86 (0.67–1.09)	0.21
F. BMI or CC, cm	1.09 (0.93–1.29)	0.28	1.07 (0.90–1.27)	0.43

Abbreviations: BMI, body mass index; CC, calf circumference; CI, confidence interval; OR, odds ratio; Model 1, Adjusted for age, sex, Frailty Index. Model 2, Adjusted for age, sex, Frailty Index, lack of energy and all the MNA items; *N*, number of nursing home residents with the item; *n*, number of patients with the item and lack of energy.

were reperformed using a modified FI computed after the exclusion of items potentially capturing signs of malnutrition and depressive symptoms. However, results did not substantially change.

DISCUSSION

Our study showed a high prevalence (43.2%) of lack of energy in older adults living in NH. A poor nutritional status was significantly associated with lack of energy, independent of potential confounders. Decrease in food intake, reduced mobility, and psychological stress or acute disease in the past 3 months were identified as the MNA-SF items contributing the most to the association between malnutrition and fatigue. Surprisingly, unintentional weight loss in the past 3 months and BMI, both of which are often used to capture the wasting component of the frailty phenotype, were not significantly associated with lack of energy. This might suggest that lack of energy is only partially related to anthropometry, and provide a more multidimensional measure of the malnutrition status. On the other hand, it is also possible that the MNA represents an assessment instrument capturing something more than malnutrition per se, and more comprehensively capturing the more general complexity of the individual.

Malnutrition (i.e., undernutrition) is highly prevalent in older people, especially among those who live in NHs.[19–21] At the same time, fatigue, frequently manifested as a lack of energy, also represents a highly prevalent and burdening condition in frail older adults.[1] However, to our knowledge, only a few studies have explored the association between poor nutritional status and fatigue in older adults. In 2014, Singh et al.[10] found a negative correlation between self-reported mobility tiredness and BMI ($r = -0.364$, $P = 0.01$) in a population of NH residents with undernourishment. More recently, Kushkestani et al.[22] reported a positive association ($r = 0.410$, $P < 0.001$) between malnutrition, defined according to the MNA, and fatigue (assessed using the Functional Assessment of Chronic Illness Therapy Fatigue questionnaire) in NH residents. Another recent study[23] documented that severe weight loss was an independent predictor of moderate (OR = 1.17, 95% CI = 1.03–1.34, $P = 0.019$) to severe fatigue (OR = 1.21, 95% CI = 1.05–1.39, $P = 0.01$) in older patients at hospital discharge. Tsutsumimoto et al.[24] reported that anorexia of aging was independently associated with exhaustion (OR = 1.39, 95% CI = 1.11–1.74, $P = 0.004$). Recently, Davis et al.[25] explored how perceived fatigability explains the association between poor diet quality and low physical function. They found an inverse association between the Healthy Eating Index and the Pittsburgh Fatigability Scale Physical score.

Interestingly, malnutrition has often and increasingly been associated with the concept of physical frailty. It has even been suggested that the multidimensional nature of malnutrition may somehow mirror the heterogeneous condition of frailty. The MNA itself instrument has been indicated as a possible tool for measuring the frailty status in older persons.[26,27] Among the symptoms most characterizing the frail individual, exhaustion is one of the most representative.[28] Geriatric syndromes have been described as conditions characterized by symptoms that can result not only from diseases but also from the accumulation of deficits in multiple systems determining a decreased compensatory ability.[29] Indeed, given its frequency and etiology in older persons, it becomes clear as fatigue may be looked as a geriatric syndrome.

Interestingly, the univariate analyses testing the prevalence of single diseases according to the presence of lack of energy did not show significant differences. On the other hand, persons reporting lack of energy showed a higher FI compared with non-fatigued peers. This may be explained by the fact that the clinical complexity of the NH population is not defined by a single condition but by the interaction of multiple signs, symptoms, diseases, and disabilities. It can be assumed that the self-reported lack of energy may reflect the exhaustion of the homeostatic reserves of the individual and a sort of clinical alert launched by the organism challenged in its limited reserves by a disproportionate stressor.[11]

Some limitations of our study are important to consider. Our study was cross-sectional. Therefore, no causal relationship among lack of energy and nutritional status could be established. Furthermore, the definition of lack of energy was derived from the GDS. As such, our operationalization of fatigue may have captured the psychological dimension of the symptom and potentially underestimated the physical domain. The measure of lack energy is crude and the yes/no dichotomous outcome may lack sensitivity. More sensitive instrument could better capture the gradient of association between malnutrition (and its components) with increasing levels of anergia, potentially demonstrating a dose–effect relationship between the two.

In conclusion, the present study showed a high prevalence of lack of energy in a cohort of NH residents. Our study identified a positive association between malnutrition and lack of energy. The lack of energy might represent the clinical manifestation of a poor nutritional status and mimic the exhaustion of the metabolic reserves of the individual. More research is needed to clarify the biological and clinical features of lack of energy in frail older persons, especially given the relationship between the symptom and several adverse outcomes (including functional impairment, hospitalizations, increased use of healthcare services, mortality). The identification of potential targets for tackling fatigue might potentially lead in the future to the development of specific pharmacological and non-pharmacological interventions.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Domenico Azzolino and Matteo Cesari contributed to conceptualizing and writing the manuscript. Emanuele Marzetti, Marco Proietti, Riccardo Calvani, Philipe de Souto Barreto, and Yves Rolland edited and revised manuscript. Domenico Azzolino, Matteo Cesari, Emanuele Marzetti, Marco Proietti, Riccardo Calvani, Philipe de Souto Barreto, and Yves Rolland approved the final version of manuscript.

SPONSOR'S ROLE

None.

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Age And Ageing

Unintentional weight loss is associated with death in a population of dialyzed older persons.

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Subject Section:	Sarcopenia and Frailty Research, Ageing - Other
Keypoints:	Older people undergoing hemodialysis have high prevalence of malnutrition often associated with a rapid loss of body weight., Older patients experiencing unintentional weight loss had a 3.4-fold risk of death., The presence of unintentional weight loss should lead to the prompt and comprehensive assessment of the older person on dialysis

Unintentional weight loss is associated with death in a population of dialyzed older persons.

Abstract

Background: Older patients in hemodialysis have a high prevalence of malnutrition that is often associated with rapid weight loss till cachexia. In this population rapid and unintentional weight loss is associated with mortality. We aimed to investigate whether in these patients the association between unintentional weight loss and mortality may be independent of comorbidities and other nutritional risk factors.

Methods: We conducted a retrospective longitudinal study on data coming from the digital records of 107 prevalent patients undergoing hemodialysis for at least three months. Sociodemographic, clinical, and biological data were recorded. Unintentional weight loss was defined as loss of body weight > 5% in 3 months or > 10% in 6 months. We computed a 21-item Frailty Index (FI) that included clinical conditions associated with malnutrition and mortality in this population. A period of 21.5 (range 0-73) months follow-up was considered. Unadjusted and adjusted Cox proportional hazard models were performed to test the association of unintentional weight loss with death. Survival analyses based on Kaplan-Meier estimates were performed.

Results: Patients' age was 79 (±7.7) years; 38 (35%) were women. Eighteen patients (17%) underwent unintentional weight loss and 31 (29%) died during follow-up. In both unadjusted (HR 3.49; $CI_{95\%}$: 1.63-7.46) and adjusted (HR 3.43; $CI_{95\%}$: 1.51-7.78) models, unintentional weight loss was positively associated with death.

Conclusions: In older patients undergoing chronic hemodialysis unintentional weight loss is associated with mortality independently of comorbidities and other risk factors.

Introduction

Older people are vulnerable to nutritional issues because of physical impairment, psycho-social conditions, comorbidities and mutually interactive syndromes [1]. In the last decades, the prevalence of chronic kidney disease (CKD) is substantially increased in older persons and, today, a relevant proportion of patients undergoing hemodialysis is aged 65 years or older [2]. Physiological changes seen with aging are responsible for a decline in renal function. However, age-related chronic diseases, both as stand-alone and simultaneously occurring (i.e., comorbidities), can exacerbate the decline in renal function [3–5].

In the End-Stage Renal Disease (ESRD) context, dialysis treatment is life-saving replacement therapy. However, dialysis may also lead to several health-related problems (i.e., cardiovascular disease, bleeding, renal osteodystrophy, gonadal dysfunction, insulin resistance, immunodeficiency, anemia, malnutrition, and muscle wasting) [6,7]. In particular, dialysis is accompanied by chronic inflammation and increased protein catabolism [8,9]. It has been associated with physical inactivity, thus augmenting the risk of malnutrition and sarcopenia regardless of the aging process [2,10,11]. Unintentional weight loss experienced by many older people may result from several age-related factors, including anorexia and catabolic diseases [2,12]. Furthermore, CKD patients may often present anorexia because of accumulating uremic toxins, depression, fatigue and physical disabilities [13]. Low levels of testosterone and augmented leptin levels have been reported in male CKD older patients, thus exacerbating anorexia. Finally, gastrointestinal symptoms like nausea and vomiting can further contribute to weight loss [14].

Unintentional weight loss has been included in the Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis of malnutrition as a phenotypic criterion [15]. It is also part of several tools for assessing malnutrition in older people both in the general population (e.g., Subjective Global Assessment [16], Malnutrition Inflammation Score [17], Mini Nutritional Assessment [18], Nutritional Risk Screening 2002 [19], Malnutrition Universal Screening tool [20]) and in hemodialyzed patients [17,21]. Therefore, the present study aimed to evaluate whether in patients undergoing chronic dialysis the association between unintentional weight loss and mortality may be independent of comorbidities and other nutritional risk factors.

Methods

Study design and population

Data were retrieved from digital records of 107 older patients receiving chronic hemodialysis at the Nephrology Unit of a tertiary hospital in Milan (Italy) between 2014 and 2020. The main exclusion criterion consisted in hemodialysis treatment for less than three months, this was applied not to include those patients that did not have a stable dry weight as well as to avoid the inclusion of individuals with end-stage illness and very short life expectancy. Information about clinical status, nutrition, biochemical parameters, dialysis, drug therapy and physical function were recorded.

The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the Fondazione IRCCS Ca' Granda – Policlinic Hospital of Milan. Since the collected data were all part of the clinical routine, no written informed consent was required according to local regulations.

Unintentional weight loss

Body weight was measured at each clinical visit as part of the routine care. Unintentional weight loss was defined as a loss of body weight > 5% in 3 months or > 10% in 6 months

Outcomes

The outcome of interest for the present study was the all-cause mortality. Participants were regularly followed over time by the study center as referent for their hemodialyitic procedures. Fatal events were retrieved from medical charts and administrative data.

Other measurements

Sociodemographic data (i.e., age, sex, education) and presence of comorbidities (i.e., diabetes, COPD, dementia, hypertension, cancer, cerebrovascular disease, coronary artery disease, congestive heart failure) were collected. However, the item defining unintentional weight loss (independent variable of the present study) was excluded from the computation of the total score used in the analyses. A 21-item Frailty Index, designed according to the model proposed by Rockwood and Mitnitski [22] was also computed. The variables included in FI are reported in supplemental materials (Table S1).

Statistical analysis

Data are presented as mean and standard deviation (SD) or absolute numbers and percentages for continuous and categorical variables, respectively. Unintentional weight loss was used as categorical variable in the analyses. Unadjusted and adjusted (considering age, sex, and Frailty Index as covariates) Cox regression models were performed to test the association of unintentional weight loss (independent variable of interest) with death (dependent variable of interest). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were reported. Time to event was defined from baseline (i.e., three months after the initiation of the hemodialysis program) to the date of death (for those who died) or the date of the last visit (for those who did not). Statistical significance was set at p value <0.05. All analyses were performed with JAMOVI version 1.6.

Results

Participant characteristics are presented in Table 1. The study sample consisted of a total of 107 CKD older patients undergoing hemodialysis (mean age 79 ± 7.7 years; women n= 38, 35%). Median follow-up was 21.5 (Range 0-73) months. Unintentional weight loss was found in 18 (17%) patients. Mean frailty index was 0.23 (SD 0.10), with 31 (29%) patients who died during the follow-up period.

Figure S1 shows the results of the Kaplan-Meyer curves. Results of the multivariate Cox regression analyses are reported in Table 2. In both unadjusted (HR 3.49; $CI_{95\%}$: 1.63-7.46; *P*=0.001) and adjusted models (HR 3.43; $CI_{95\%}$: 1.51-7.78; p=0.002), unintentional weight loss was positively associated with all-cause mortality. The results were confirmed after potential confounders were progressively included as covariates in the Cox proportional hazard model. Interestingly, the association between unintentional weight loss and all-cause mortality was independent of FI.

Also, albumin levels below 3.5 g/dL were significantly associated with all-cause mortality in both unadjusted (HR 2.20, $CI_{95\%}$ 1.10-4.40, P=0.03) and partially adjusted models (HR 2.19, $CI_{95\%}$ 1.09-4.41, P=0.03). Although, the association disappeared when the other two variables of interest (i.e., transferrin and unintentional weight loss) were added in the model. On the other hand, transferrin levels below 200 mg/dl were not significantly associated with death in both the unadjusted and adjusted models.

Discussion

Our study demonstrated a significant association of unintentional weight loss with all-cause mortality in a population of older patients undergoing chronic hemodialysis. In particular, patients experiencing unintentional weight loss during the follow-up period had a 3.4-fold risk of death. Notably, this association was independent of other potential confounders that may have influenced the overall prognosis and that are summarized by individual FI.

Unintentional weight loss is frequently assessed in older people and has been repeatedly associated with higher mortality rates [24]. This is true also in CKD patients where malnutrition and rapid involuntary weight loss are very commonly observed, particularly in patients undergoing hemodialysis [25,26]. Our results are in line with those of Cabezas- Rodriguez et al. [27] that reported an increased mortality risk in CKD patients experiencing weight loss over 6 months. The authors also showed that those CKD patients aged 65 and older with weight loss, had a higher risk of death compared to their younger counterparts. Chang et al. [26] reported a rapid decline in body weight, with a nadir at 5 months, in those patients who survived the first year of hemodialysis. They also reported an association between rapid weight loss during the first 12 months with a higher risk of mortality.

Of particular note, unintentional weight loss is a well-known contributor of frailty. To date, the frailty phenotype model, proposed by Fried et al. [12], includes weight loss as one of the five criteria to define frailty. Conversely, higher body mass index (BMI), as well as weight gain, have been associated to better survival rates in hemodialysis patients [7], the so-called "obesity paradox" [26]. Albumin levels have been extensively reported to be predictive of mortality in the older population and in CKD patients, but not in hemodialysis older patients [2]. Our study seems to confirm a rather marginal prognostic capacity of serum albumin in patients with chronic renal failure. Similar results were also obtained for transferrin, a negative-phase serum protein that is sometimes used to determine the nutritional status [28]. Differently, the assessment of unintentional weight loss may provide more accurate information than the biomarkers. It might be hypothesized that, thanks to its multidimensional nature, it might better capture the individual's complexity. Furthermore, it is noteworthy that the definition of unintentional weight loss implies the drawing of a longitudinal trajectory, describing the dynamic evolution of the system. The capacity to capture time-related clinical modifications is surely more informative than the cross-sectional measurement of a biological variable.

Limitations of our study may reside in the retrospective design and the small sample size. However, it should be noted that our sample optimally captures a population of older persons in the chronic need of hemodialysis, since we excluded those who did not survive the first three months after initiation of the treatment. In this way, we have been able to well define the clinical relevance of unintentional weight loss in the absence of the acute/terminal phase of the renal disease.

In conclusion, our study showed a significant association between unintentional weight loss and mortality in older patients undergoing hemodialysis. Indeed, unintentional weight loss may be looked as a simple, easy to obtain/implement in the routine clinical practice and affordable measure to help clinicians in assessing nutritional status of CKD patients on dialysis in order to prevent and/or delay poor outcomes.

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Table 1. Participant characteristics

Variable	N (%), or mean (SD) n=107
Age, y	79.1 (7.7)
Women	38 (35.5)
Diabetes	40 (37.4)
Depression	28 (26.2)
Hypertension	85 (79.4)
CHF	32 (29.9)
CHD	37 (34.6)
Dementia	23 (21.5)
Cancer	17 (15.9)
Thyroid disorders	23 (21.5)
COPD	25 (23.4)
Albumin, g/dL	3.72 (0.5)
Transferrin, mg/dL	183 (41.7)
Weight loss	18 (16.8)
Hospitalization	81 (75.7)
Death	31 (29)
Frailty index	0.23 (0.10)

SD: standard deviation; CHF: Chronic Heart Failure; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease

Table 2. Relationship of unintentional weight loss with death in dialyzed older patients

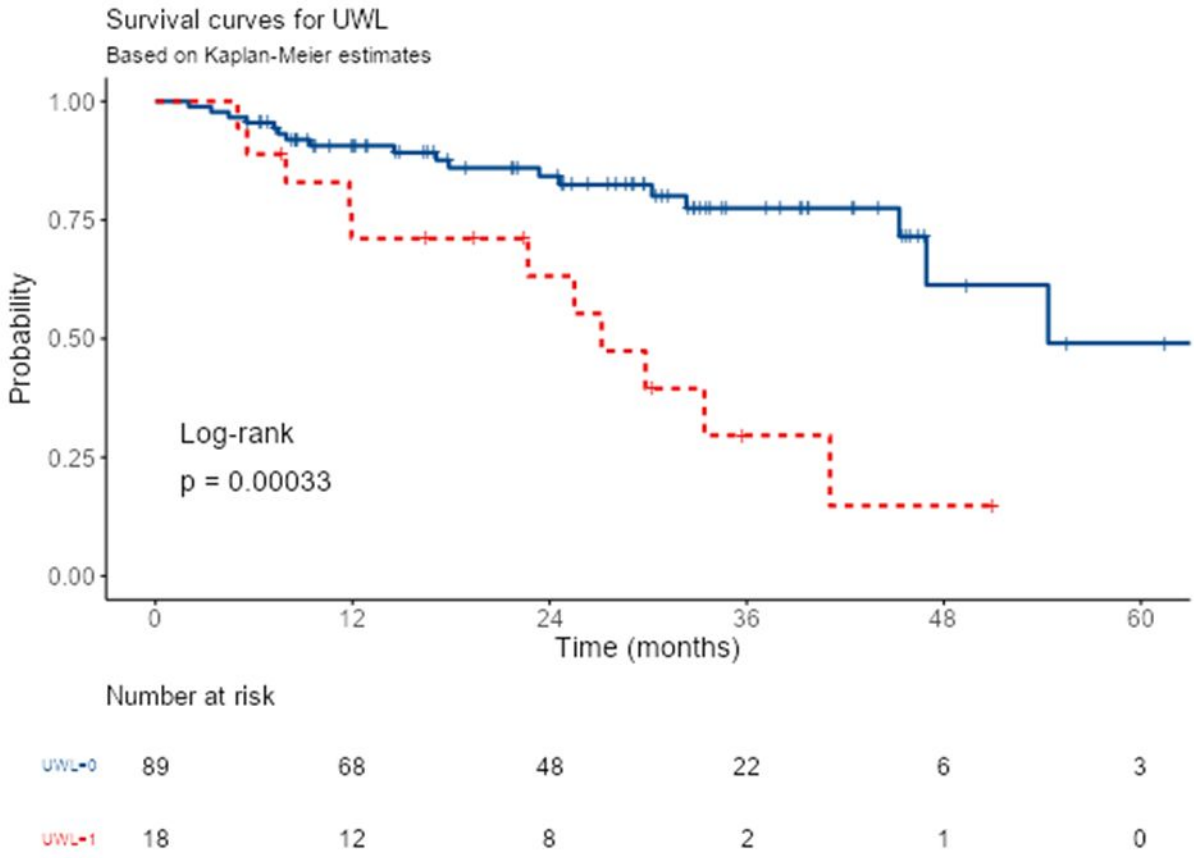
	Unadjusted HR (95% CI)	***P***	**Model 1 HR (95% CI)**	***P***	**Model 2 HR (95% CI)**	***P***
UWL	3.49 (1.63-7.46)	0.001	3.55 (1.61-7.84)	0.002	3.43 (1.51-7.78)	0.003
Albumin< 3.5 g/dL	2.20 (1.10-4.40)	0.03	2.19 (1.09-4.41)	0.03	1.38 (0.60-3.17)	0.45
Transferrin< 200 mg/dl	1.82 (0.87-3.84)	0.11	1.64 (0.78-3.45)	0.19	1.64 (0.71-3.81)	0.25

HR= hazard ratio; CI= confidence interval; UWL= unintentional weight loss

Model 1: Adjusted for age, sex, frailty index

Model 2: Adjusted for age, sex, frailty index, and the three independent variables of interest

Supplementary Figure S1. Survival Curves for UWL



^ UWL=Unintentional weight loss

Supplementary table S1. List of the variables used for the computation of the frailty index

1. Depression
2. Psychiatric disorders
3. Diabetes
4. Hypertension
5. CHF
6. CHD
7. Pacemaker
8. Thyroid disorders
9. Cancer
10. History of cancer
11. COPD
12. Fractures
13. Cerebrovascular disease
14. Dementia
15. Hepatopathy
16. Hepatic insufficiency
17. Gastrointestinal disorders
18. Peripheral artery disease
19. Atrial fibrillation
20. HBV
21. HCV

CHF: Chronic Heart Failure; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease;

HBV: Hepatitis B Virus; HCV: Hepatitis C virus

Aging Clinical and Experimental Research

Frailty index and adverse outcomes in older patients in haemodialysis.

--Manuscript Draft--

Manuscript Number:	
Full Title:	Frailty index and adverse outcomes in older patients in haemodialysis.
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Abstract:	Background In older individuals, the prevalence frailty is inversely proportional to renal function, therefore it is supposed to be the highest in haemodialysis patients. However, frailty and its association with adverse outcomes have been scarcely investigated in this population. Aim The aim of the present study was to characterize the frailty status and explore its association with hospitalization and mortality in a cohort of older CKD patients undergoing chronic haemodialysis. Methods A 24-item frailty index (FI) based on sociodemographic, clinical and biological data was computed. During the follow-up, death and hospitalizations events were recorded. Unadjusted and adjusted Cox proportional hazard models were performed to test the association of frailty with hospitalization and death. Results Frail subjects where at higher risk of hospitalization (HR 1.60, 95% CI 1.00-2.57, p = 0.05) and of all-cause mortality (HR 2.52, 95% CI 1.10-5.80, p=0.03) Conclusions Frailty is highly prevalent among older people undergoing haemodialysis. Frail individuals present higher risk of hospitalizations and mortality. The FI is a reliable tool to study vulnerability in this population.
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Frailty index and adverse outcomes in older patients in haemodialysis.

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Abstract

Background: In older individuals, the prevalence frailty is inversely proportional to renal function, therefore it is supposed to be the highest in haemodialysis patients. However, frailty and its association with adverse outcomes have been scarcely investigated in this population.

Aim: The aim of the present study was to characterize the frailty status and explore its association with hospitalization and mortality in a cohort of older CKD patients undergoing chronic haemodialysis.

Methods: A 24-item frailty index (FI) based on sociodemographic, clinical and biological data was computed. During the follow-up, death and hospitalizations events were recorded. Unadjusted and adjusted Cox proportional hazard models were performed to test the association of frailty with hospitalization and death.

Results: Frail subjects where at higher risk of hospitalization (HR 1.60, 95% CI 1.00-2.57, p = 0.05) and of all-cause mortality (HR 2.52, 95% CI 1.10-5.80, p = 0.03)

Conclusions: Frailty is highly prevalent among older people undergoing haemodialysis. Frail individuals present higher risk of hospitalizations and mortality. The FI is a reliable tool to study vulnerability in this population.

Keywords: Chronic Kidney Disease; End Stage Renal Disease; Aging; Dialysis; Renal Function

Statements and declarations

Competing Interests: MC has received honoraria from Nestlé Health Science for presentations at scientific meetings and being part of expert advisory boards. The other authors declare no conflict of interest.

Introduction

Several changes accompanying the aging process are responsible for a decline in renal function, which can be further exacerbated by the presence of other pathological conditions [1]. Indeed, chronic kidney disease (CKD) is a highly prevalent condition among older people. The estimated prevalence of CKD ranges from 10 to 40% in those people aged 65 and older [2].

Renal replacement therapy is a life-saving therapy in patients with end-stage renal disease (ESRD). In young adults, renal replacement therapy is associated with increased life span and relief of symptoms. However, the high clinical complexity of older people makes them at greater risk of poor outcomes when undergoing haemodialysis [3]. Unfortunately, the number of older people requiring haemodialysis is steadily increasing worldwide.

Frailty is an age-related state of increased vulnerability, characterized by a reduction of functional reserves of the individual [4]. Frailty is a strong predictor of adverse clinical outcomes in all stages of CKD, including increased hospitalization and mortality [5]. Haemodialysis has been associated with a prevalence of frailty which ranges from 21 to 73%, depending on the tool used for its assessment [6]. It is difficult to estimate upfront which older patients will benefit from dialysis initiation and for which vulnerable patients' existence on dialysis will be challenging. In recent years, the interest on the frailty of older patients eligible for dialysis has been increasing. Unfortunately, despite growing evidence showing the predictive value of frailty for adverse outcomes, frailty measures are not routinely incorporated into nephrology care. The assessment of the frailty status of the individual offers the opportunity to consider the contribution of the aging process itself as well as of pathological conditions on the cumulative decline in multiple physiological systems.

Aim of this study was to determine frailty prevalence and its association with hospitalization and mortality in a population of CKD older patients undergoing haemodialysis.

Methods

Study design and population

Data come from the clinical charts of 105 incident older outpatients undergoing chronic renal replacement therapy, after 90 days from dialysis initiation (in order to correct for early mortality). We collected data about clinical status, nutrition, biochemical parameters, dialysis, medications, and physical function. The study protocol was approved by the local ethics committee (Fondazione IRCCS Ca' Granda – Policlinic Hospital of Milan) and conformed to the Declaration of Helsinki. No written informed consent was required according to local regulations, since the recorded data were part of the clinical routine practice. However, all the participants were adequately informed about study procedures and were free to decline their participation.

Frailty

A 24-item FI was retrospectively computed according to the procedure drawn up by Searle and colleagues [7]. FI included anamnestic diseases, biochemical and nutritional parameters (Supplementary Table 1). Each item constituting the FI was a health deficit and was categorized as 0 (if the deficit was absent) or 1 (if the deficit was present). FI was calculated as the number of deficits presented by each individual divided by the total number of considered deficits (i.e., 24). The variables included in FI are reported in supplemental materials (Table S1).

Outcomes

The outcomes of interest for the present study were all-cause mortality and unprogrammed all-cause hospitalization. All patients were routinely followed over time by the study center as referent for their hemodialytic procedures. Hospitalizations and fatal events were retrieved from medical charts and administrative data. Only the first hospitalization was considered for the present analysis.

Statistical analysis

Variables are expressed as mean and standard deviation (SD) for categorical variables or absolute numbers and percentages for categorical variables. Hazard ratios (HRs) and their 95% confidence intervals for all-cause mortality and hospitalization were calculated using unadjusted and adjusted Cox proportional hazard models. Statistical significance was set at $P < 0.05$. All analyses were performed with JAMOVI version 1.6.

Results

The characteristics of the study sample are presented in table 1. A total of 105 individuals (mean age 79.1, SD 7.6 years; women n= 37, 35%) were included in the study. Median follow-up was 21 (interquartile range [IQR] 8-32) months. The most prevalent pathologies were diabetes (n = 38, 36%) and hypertension (n = 84, 84%).

Overall, 58 (55%) patients were frail (i.e., FI $\geq$ 0.25); the mean FI was 0.23 (SD 0.10). No participant had a FI higher than 0.7, in line with the biological assumption of the model [7]. Among participants, 29 (28%) died and 79 (75%) required hospitalization during the follow-up period.

Frailty was associated with all-cause mortality at univariate analysis (HR 2.48, 95% CI 1.09-5.63, $p = 0.03$) and this association remained statistically significant even after adjustment for age and sex (HR 2.52, 95% CI 1.10-5.80, $p = 0.03$; table 2). Frailty was also positively associated with all-cause hospitalization in both unadjusted (HR 1.70, 95% CI 1.07-2.71, $p = 0.025$) and adjusted (HR 1.60, 95% CI 1.00-2.57, $p = 0.051$) models (table 3).

Discussion

This study showed a high prevalence of frailty (i.e., 55%) among older patients undergoing haemodialysis. A FI ≥ 0.25 was associated with a higher risk of hospitalization. Our study also demonstrated that frailty increased the risk of all-cause mortality in older patients undergoing long-term haemodialysis. In particular, frail patients presented a 2.5- and 1.7-fold increased risk of mortality and hospitalization, respectively.

Previous studies have found a large variability (i.e., ranging from 6 to 82%) in the prevalence of frailty in patients undergoing haemodialysis [8,9]. Such heterogeneity may be the result of the use of different (and modified) instruments to measure the condition of frailty as well as the inclusion of young adult patients. Several tools have been developed (Renal Epidemiology and Information Network [REIN] score [10], , and BANSAL score [11]) to estimate the short-term mortality risk associated with the beginning of dialysis. However, the mono-dimensional nature of these tools makes them inadequate to exhaustively capture the clinical complexity of the older person. Besides, those scores applied in the pre-dialysis phase could overrate first-month dialysis's mortality and likewise underestimate the nutritional and rehabilitative benefits of late referral patients. Most studies on frailty involving haemodialysis patients generally used the phenotypic model proposed by Fried and colleagues [4]. To our knowledge, this is the first study applying the FI model in a population of incident haemodialysis patients. The purpose of the FI is to measure the contribution of accumulating deficits on the individual's health and residual life. The quantitative nature of the FI gives the opportunity to compute the variable independently of the items composing it, mirroring the individual's biological age. The FI, given its comprehensive and multidimensional nature, may better capture the vulnerability and complexity of the aging person. Interestingly, its generation does not require *de novo* measurements but can be retrieved by every clinical assessment without substantial deviations from the routine clinical practice as soon as a few standardization criteria are met [7]. The FI has a strong biological validity, demonstrated by its tendency at increasing with chronological age and a “natural” limit of 0.7 (also confirmed in our study) setting the level of incompatibility between the accumulation of deficits and life [7].

Frailty has long been recognized as a predictor of adverse outcomes, including mortality and hospitalization and, in several populations and settings [12]. Johansen et al. [13] found an independent association of frailty with death and with a combined outcome of death and hospitalization in patients on dialysis. In 2012, Bao et al. [14] reported an independent association of frailty with mortality and time to first hospitalization. Another study [15], found that frail patients on dialysis had a 2.6-fold risk of death. Finally, a recent meta-analysis [8] reported that frail patients had a greater risk of all-cause mortality compared with those who were not frail. Our results are in line with all these studies, despite none of them was based on FI to characterize frailty. Therefore, it should be noted that the use of FI in our sample has allowed us to capture the multicomponent dimension of frailty.

Given the negative impact of renal replacement therapy on the burden of comorbidity and on the quality of life of this high risk population, we believe that the prognostic value of FI should be taken into account to better address their overall prognosis and to support individualized clinical indications. Indeed, the FI may be used in these patients as a guide to implement an adapted plan of care and possibly to identify personalized targets of intervention with the final aim to reduce the overall burden of disease consequent to the initiation of renal replacement therapy.

Some limitations of our study should be mentioned. First, the small sample size may have limited the observation and precluded some more in-depth analyses. However, our sample was composed of a population of older persons in chronic need of haemodialysis after exclusion of individuals with very short survival. Secondly, this study reflects a single-center experience, which may limit the generalizability of our results.

In conclusion, we found a high prevalence of frailty in a cohort of older patients undergoing haemodialysis. Moreover, our study demonstrated that the FI is a reliable instrument to predict relevant negative outcomes as mortality and hospitalization. Therefore, our results support the role of the FI in the identification of those patients that may benefit the most from an adapted and personalized plan of care.

Conflict of interest: MC has received honoraria from Nestlé Health Science for presentations at scientific meetings and being part of expert advisory boards. The other authors declare no conflict of interest.

Author contributions: AS and MMP equally contributed to conceptualizing and writing the manuscript. DA, MC and SV edited and revised the manuscript. AS, MMP, DA, SV and MC approved the final version of manuscript.

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Table 1. Participant characteristics

Variable	N (%), or mean (SD) n=105
Age, y	79.1 (7.6)
Women	37 (35)
Diabetes	38 (36)
Depression	28 (26)
Psychiatric disorders	8 (7)
Hypertension	84 (80)
CHF	32 (31)
CHD	36 (34)
Atrial fibrillation	32 (31)
Cognitive impairment	23 (22)
Cancer	17 (16)
COPD	25 (23)
CRP, mg/dl	1.2 (2.1)
Albumin, g/dL	3.72 (0.5)
Involuntary weight loss	18 (17)
Hospitalization	79 (75)
Death	29 (28)
24-item Frailty index	0.23 (0.10)
FI≥0.25	58 (55)

SD: standard deviation ; CHF: congestive Heart Failure; CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, CRP: C-reactive protein, FI: frailty index

Table 2. Relationship of frailty with death in dialyzed older patients

	Unadjusted HR (95% CI)	***P***	**Model 1 HR (95% CI)**	***P***
Frailty	2.48 (1.09-5.63)	0.03	2.52 (1.10-5.80)	0.03

HR= hazard ratio; CI= confidence interval

Model 1: Adjusted for age and sex

Table 3. Relationship of frailty with hospitalization in dialyzed older patients

	Unadjusted HR (95% CI)	***P***	**Model 1 HR (95% CI)**	***P***
Frailty	1.70 (1.07-2.71)	0.025	1.60 (1.00-2.57)	0.051

HR= hazard ratio; CI= confidence interval

Model 1: Adjusted for age and sex

Table S1. List of the variables used for the computation of the frailty index

1. Depression
2. Psychiatric disorders
3. Diabetes
4. Hypertension
5. CHF
6. CHD
7. Pacemaker
8. Thyroid disorders
9. Cancer
10. History of cancer
11. COPD
12. Fractures
13. Cerebrovascular disease
14. Cognitive impairment
15. Hepatopathy
16. Hepatic insufficiency
17. Gastrointestinal disorders
18. Peripheral artery disease
19. Atrial fibrillation
20. HBV
21. HCV
22. Albumin levels < 3.5 g/dL
23. Transferrin levels < 200 mg/dl
24. Unintentional weight loss

CHF: Chronic Heart Failure; CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease;

HBV: Hepatitis B Virus; HCV: Hepatitis C virus