Design and methodology of the chronic kidney disease as a dysmetabolic determinant of disability among older people (CKD-3D) study: a multicenter cohort observational study

Andrea Corsonello¹,⁴ · Francesco Mattace-Raso² · Lisanne Tap² · Marcello Maggio³ · Luna Zerbinati³ · Francesco Guarasci⁴* · Annalisa Cozza⁴ · Sonia D’Alia⁴ · Luca Soraci¹,⁵ · Valentina Corigliano¹,⁵ · Mirko Di Rosa⁴ · Paolo Fabbietti⁴ · Fabrizia Lattanzio⁶

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Abstract

Background Chronic kidney disease (CKD) is a common condition in older people and represents a global health issue since it increases the risk of associated comorbidities and all-cause mortality. Furthermore, older people with reduced renal function might be at higher risk for developing functional limitation and disability. Moreover, the current creatinine-based measures of renal function are influenced by several factors in older population. The aims of the CKD-3D project are to perform an observational study to expand the knowledge about CKD-disability relationship and to investigate the use of novel biomarkers of kidney function.

Methods An observational, multicenter, prospective cohort study will be conducted in 75+ old patients consecutively admitted to acute care wards of geriatric medicine at participating hospitals. The study planned to enroll 440 patients undergoing clinical and laboratory evaluations at baseline and after 12 months. Face-to-face follow-up at 6 months and telephone follow-up at 3 and 9 months will be carried out. Comprehensive Geriatric Assessment (CGA) and the measurement of Cystatin C, Beta-Trace Protein and Beta2-Microglobulin levels will be included.

Discussion This study will provide useful information to prevent CKD-related disability by collecting real-life data over 1-year period. The combined approach of CGA and the investigation of innovative existing biomarkers will make it possible to develop new recommendations and guidelines for a patient-centered approach. It is believed that such a study may lead to an improvement of knowledge on CKD in elderly patients and may also have implications in daily clinical practice and in decision-making process.

Keywords Chronic kidney disease · Disability · Older patients · Physical performance

Background

Chronic kidney disease (CKD) is highly prevalent affecting about 12% of the general population [1] and up to 20% of people in the age group of 60–69 years [2]; it becomes even more common in subjects over 80 years old, with estimated rates of ten times greater than those of younger adults (18–50 years old) [3]. A recent report of the Global Burden of Disease 1990–2017 showed that CKD significantly contributes to the global disease burden, and its impact on prognosis is not declining to the same extent as other highly prevalent non-communicable diseases [4].

As a consequence of the ageing of the general population, CKD is becoming a major global public health problem, imposing a substantial economic burden on health
care systems worldwide [5]. Nowadays, CKD is considered a disease multiplier, because it increases the risk of other common associated comorbidities [6] including acute kidney injury [7], cognitive decline [8], mineral and bone disorders [9], chronic obstructive pulmonary disease (COPD) [10], anemia [11], and all-cause and cardiovascular mortality [12–14].

Early recognition of CKD through the implementation of an adequate screening and intervention strategy has shown to slow the progression of the disease and improve clinical outcomes especially among vulnerable older patients [15]. However, it may not be easy to distinguish ageing kidney from CKD, because they share many functional features, such as glomerular filtration rate (GFR) decline and impairment in tubular salt and water reabsorption [16]. Moreover, even in the absence of a clinically evident nephropathy, normal age-related changes in kidney function might be clinically relevant in the older patients [17]. In addition, it is worth considering that currently available creatinine-based measures of kidney function are plagued by some degree of inaccuracy in elderly populations due to individual anthropometric changes and to the influence of non-GFR determinants of circulating creatinine [18–21]. Indeed, several studies showed the existence of a U-shaped relationship between creatinine-based eGFR and mortality in frail and older people [22–25]. In particular, patients with high GFR values were found to be characterized by low hand grip strength and high prevalence of disability, suggesting that serum creatinine may be low due to sarcopenia rather than normal kidney function [26].

Other filtration markers which are not affected by muscle mass may better predict negative outcomes and are worth of testing [27–29]. Moreover, since CKD is often asymptomatic in older people, the assessment of kidney function is recommended especially in age group with known risk factors for CKD [30].

Older individuals with CKD might be at higher risk for developing functional limitation and disability [31]. Data from the InCHIANTI study showed that eGFR, as determined by Modification of Diet in Renal Disease (MDRD)- or CG- equations, could predict decline in activities of daily living score (ADL) over a period of 6 years in community-living older people [32]. Another study using MDRD equation reported similar results in community-dwelling older adults over a 2-years follow-up [33].

Reduced renal function was also found to affect physical performance (e.g. Short Physical Performance Battery-SPPB) [34], frailty [35], cognitive impairment [36, 37], sensory impairment [38, 39], malnutrition [40], and sarcopenia [41]. GFR as determined by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was associated with a lower SPPB total score in older hospitalized patients [32], while highest levels of Cystatin C correlated with a higher risk of self-reported functional limitation over a 1-year follow-up in community dwelling older people [42, 43]. Additionally, impaired kidney function (assessed by mGFR, eGFR or eGFRcys) was found significantly associated with self-reported frailty among participants in the MDRD study [44].

Despite the large amount of epidemiological evidence, there is a need for a comprehensive study aimed at investigating CKD among older patients and taking into account innovative biomarkers, as well as the numerous functional dimensions that CKD is able to impair.

Innovative biomarkers of kidney function, such as Cystatin C, Beta-trace Protein and B2-microglobulin, are low molecular weight proteins which are less or not affected by muscle mass and may better predict negative outcomes compared to serum creatinine among older people [45–47].

At this moment, we have no information on determinants, trajectories, and interacting factors of CKD-related disability. Hence, a prospective observational study in hospitalized patients older than 75 years, including the measure of innovative biomarkers and the systematic use of Comprehensive Geriatric Assessment (CGA) will fill this gap. Moreover, this study will not only assess the technology able to capture the numerous dimensions of health status and their complex interactions in older people, but it will also provide useful data for the development of proactive interventions in the community. It is believed that such a study will lead to an improvement of knowledge about CKD in older patients.

**Methods**

**General objectives**

The main objective of the CKD-3D project is to build an observational study to bridge knowledge gaps about the relationship between CKD and disability. Additionally, the CKD-3D study will investigate the use of innovative biomarkers of kidney function currently not used in routine assessment of CKD, allowing to compare the accuracy of different methods in predicting trajectories of disability over time.

**Study design**

The CKD-3D study is an observational, multicenter, prospective cohort study aimed at identifying the CKD-related disability in patients aged 75 years or older discharged from geriatric acute care wards of participating hospitals. At the baseline, the day before discharge, participants will undergo clinical and laboratory evaluations and then will be followed up at face-to-face visits at months 6 and 12 following enrollment and through intermediate telephone follow-up at 3 and
9 months following recruitment. Figure 1 shows the flow-chart of the observational clinical study.

The study design complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol was approved by ethics committees at all participating institutions. Patients are requested to sign a written informed consent before entering the study.

**Study population**

Patients aged 75 years and older, consecutively admitted to acute care wards of geriatric medicine at participating hospitals, are considered eligible for inclusion. No other inclusion criteria will be considered. The study design aims at minimizing self-selection bias and enrolling real-world patients without stringent inclusion/exclusion criteria. The few exclusion criteria are: age < 75, end-stage renal disease (ESRD) or dialysis, history of solid organ or bone marrow transplantation, active malignancy within 24 months prior to screening, heart failure NYHA IV, life expectancy less than 6 months, severe cognitive impairment (i.e. MMSE < 12), complete dependency in Basic Activity of Daily Living (BADL), patients unwilling to provide consent and those who cannot be followed up, any medical or other reason (e.g. known or suspected inability of the patients to comply with the protocol procedure) in the judgement of the investigators, that the patients is unsuitable for the study. The CKD-3D study aims at finally enrolling 440 participants. The overall design of the study is reported in Fig. 1.

**Study endpoints**

The primary study endpoints of the CKD-3D study are:

- incident disability, defined as the loss of independency in at least 1 BADL [48];
- objectively measured functional decline, defined as the loss of at least 1 point at the assessment of physical performance by the Short Physical Performance Battery (SPPB) [49]; such threshold was formerly recommended as a substantial meaningful change in clinical studies [50].

Secondary end-points will include: CKD complications (anemia, hyperphosphatemia, acidosis, hypoalbuminemia, hyperparathyroidism, hyperkaliemia, hypertension, cardiovascular diseases (CV)); overall and CV mortality; polypharmacy and adverse drug reactions (ADRs) [51]; overall comorbidity [52]; cognitive impairment [53]; depression [54]; malnutrition/undernutrition [55]; vision and hearing impairment [56]; lower urinary tract symptoms (LUTS) [57]; decline in muscle mass assessed by bioimpedance.
analysis [58, 59]; hand grip strength [60]; health-related quality of life [61], healthcare resource consumption (see below); caregiver burden [62]; dependency in instrumental activities of daily living [63]. The CGA domains to be tested during the CKD-3D project are described in Table 1.

**Study visits**

Following enrollment, participants will be seen by the study teams at baseline (i.e. at discharge from participating wards) and at 6 and 12 months at a face-to-face meeting. Demographic data and socioeconomic status (occupation before retiring, economic status, formal and informal care) will be documented and followed up at each visit. Physical examination will be performed by medical doctors according to standardized procedure given in the visit protocol. Medical history and use of medication and adverse drug reactions classified according to the World Health Organization (WHO) definition [64] will be collected in each visit. During all face-to-face visits, a comprehensive geriatric assessment (CGA) will be performed using the instruments described in Table 1.

An ad-hoc resource use questionnaire was developed using a 3-month recall time-frame, to retrieve the following information by interviewing patient and/or caregiver: physician visits (general practitioners, specialists, or physician at the Emergency Room), use of diagnostic tests and specialist clinic procedures, use of care services (e.g. nurse home visit, physiotherapy, home help, social transport, day care center) and hospital admissions (number and duration of hospitalization, type of reimbursement).

During enrollment and 12-month follow-up visits blood and urine samples will be collected for biomarkers assessment (see “Laboratory parameters and biomarkers”). During COVID-19 outbreak, follow-up visits were stopped, and as a consequence, 67 patients were missing at FU. Nevertheless, the number of patients completing the study was 456, which is in keeping with the sample size calculation.

**Telephone follow-up**

At 3 and 9 months, participants and/or caregivers will be interviewed by phone to collect information on vital and functional status and healthcare resource consumption. Changes in medical history and adverse drug reactions will also be collected.

**Laboratory parameters and biomarkers**

Serum creatinine measurement will be assessed by Isotope-Dilution Mass Spectrometry (IDMS)-standardized method. Creatinine-based eGFR will be calculated using the Berlin Initiative Study 1 (BIS1) equation, which has been developed in a population older than 70 years [46]. ESRD will be defined as GFR < 15 mL/min/1.73 m² or dialysis [65].

The panel of laboratory parameters to be measured at baseline, 6 and 12 months by local laboratories will also include: complete blood cells count, lipids profile, electrolytes, nutritional status, serum creatinine, urinary albumin and albumin-to-creatinine ratio and urine analysis. Blood and urine samples will be collected at the time of discharge and at the last follow-up visit, processed and shipped frozen to the INRCA BioGer biobank, where

| Table 1 Comprehensive geriatric assessment domains to be tested during the CKD-3D project |
|-------------------------------------------------------------------------------------------------|
| Basic (ADL) and instrumental activities of daily living (IADL)/self-reported disability [48, 49, 63] |
| Mini-mental state examination (MMSE)/cognitive status [53] |
| 15-items Geriatric Depression Scale (GDS)/mood [54] |
| Cumulative Illness Rating Scale (CIRS)/overall comorbidity [52] |
| History of falls and incident falls |
| Vision and hearing impairment will be coded on a scale from 0 (adequate) to 4 (no vision/hearing present) [56] |
| Lower urinary tract symptoms (LUTS): The presence of LUTS will be ascertained by asking the patient to rate on a 5-point (0–4) Likert scale how big a problem, if any, has each of the following items been during the last 4 weeks: 1. dripping or leaking urine, 2. pain or burning in urination, 3. bleeding with urination, 4. weak urine stream or incomplete emptying, 5. waking up to urinate, 6. need to urinate frequently during the day [57] |
| Nutritional status: anthropometric parameters (calf circumference, arm circumference, body mass index (kg/m²), waist–hip ratio, waist-to-height ratio), mini nutritional assessment (MNA) [55] |
| Short physical performance battery (SPPB) [49] |
| Grip strength [60] measured using JAMAR hydraulic dynamometer |
| Bioelectrical impedance analysis (BIA)a [58]. Muscle mass will be calculated using the Janssen et al. equation, using the instrument Akern BIA101 |
| Health-related quality of life will be rated by the Euro-QoL 5D [61] |

aBIA will not be performed in patients with pacemaker or implantable cardioverter defibrillator

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Cystatin C (CysC) [66], Beta-Trace Protein (BTP) and Beta2-Microglobulin will be measured using standardized methods [27, 28].

Sample size and statistics

The CKD-3D project will enroll a total of 440 participants. Considering that 33% of older patients discharged from hospital experience the loss of dependency in at least 1 BADL during a 12-month follow-up period [67], a sample of 368 patients will allow to detect a hazard ratio of 1.3 in time-to-event analyses with 80% power (alpha = 0.05) for the incidence of loss of at least 1 BADL. The same sample will allow to detect a 1-point (SD = 1.48) decline (i.e. substantial meaningful change) at SPPB measurement with 80% power in a between-group analysis [50]. Finally, even a 20% drop out rate will not affect the statistical power of the study.

Statistical analysis will include descriptive analysis, logistic and linear regression, Kaplan–Meier and Cox regression analysis. The accuracy of different measures of kidney function in predicting outcomes will be investigated by calculating the area (AUC) under the receiver operating characteristic (ROC) curve, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and C statistic.

Main predictors of CKD-related health-care resource consumption will be also investigated.

Discussion

The CKD-3D study is a prospective observational cohort study aimed at screening for CKD among older patients discharged from acute care wards, planned to build a prospective observational cohort database of older patients discharged from hospitals. The current paper outlines the study protocol including statistical analysis of data and risk prediction modeling related to CKD during the advanced ageing process. The strength of the protocol outlined in this paper is the real-life setting for recruitment of participants. Considering that such a high-risk population is usually affected by multiple chronic diseases, the CKD-3D study aims at minimizing selection bias by choosing broad and non-restrictive inclusion criteria: all patients with age ≥ 75 years consecutively admitted to participating wards will be requested to participate in the study. Consequently, study results may reasonably be generalized to the whole population of older patients discharged from hospital. This is the primary strength of the CKD-3D study. The collection of real-life data in a longitudinal fashion over a 1-year period of time will allow to test the relationship between CKD and disability in the context of a real-world population, to measure outcomes relevant to older populations by the systematic use of CGA, and to compare the ability of current and innovative biomarkers in predicting trajectories of disability over time.

With these features, CKD-3D study will not only significantly impact current knowledge about CKD in older people, but it will also promote innovation in this area.

The CKD-3D project, in fact, has a high-impact translational relevance. It has been shown that CKD is associated with important changes in body function and structure able to impair physical performance and to increase the risk of disability, as well as other important geriatric outcomes. Consequently, a project based on laboratory parameters and CGA has the potential to improve the approach to CKD in older patients discharged from acute care hospitals, allowing a more patient-centered and individualized approach for screening and advanced care planning for older subjects prone to kidney function decline [68].

Findings from the CKD-3D project will significantly impact the national health system by shedding light on the complex interactions between CKD and disability, and would represent the epidemiological and methodological basis for strategic plans aimed at preventing CKD-related disability. Ultimately, the CKD-3D study will provide important information about the main predictors of costs in CKD, which will be of paramount importance for the national health system.

In conclusion the CKD-3D project, through the use of CGA and the concurrent investigation of existing biomarkers, will be able to build new evidence in the development of recommendations and guidelines for a patient-centered approach in the screening and management of older people at risk for CKD.

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Author contributions AC and FL conceived the study, coordinated study protocol and data collection, participated in manuscript drafting and revising. MDR and PF participated in study protocol design, data analysis, writing of the manuscript. FG taking responsibility for the publication process. FMR, LT, MM, LZ, AC, FG, SD, LS and VC participated in study protocol design, data collection, and manuscript revision and approval. All authors have read and approved the manuscript.

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**Availability of data and materials** The datasets generated and/or analysed during the current study will be locally available for participating researchers.

**Compliance with ethical standards**

**Conflict of interest** The authors declare no competing interests.

**Ethics approval and consent to participate** The study protocol was approved by ethics committees at all participating institutions, and complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients signed a written informed consent to be enrolled. Only baseline data are used in the present study. Ethics approvals have been obtained by Ethics Committees in participating institutions as follows: Italian National Research Center on Aging (INRCA), Italy, #179/65/2016, University of Parma, Parma, Italy, #33968/2017.

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