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Challenges of Chronic Kidney Disease on frail patients: two projects addressing the impact of aging and cancer

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Abbreviations

ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine

ADAMTS-13: ADAM Metallopeptidase with ThromboSpondin type 1 motif 13

ADL: Activities of Daily Living

AIRTUM: Associazione Italiana Registro Tumori

AKI: Acute Kidney Injury

ATI: Acute Tubular Injury

ATIN: Acute Tubulointerstitial Nephritis

AUSL: Azienda Unità Sanitaria Locale

BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone

BRCA: Breast Related Cancer Antigen

CAR: Chimeric Antigen Receptor

CARHES: Cardiovascular risk in Renal patients of the Health Examination Survey

CEA: Carcinoembryonic antigen

CCI: Charlson Comorbidity Index

CHOP: Cyclophosphamide, Doxorubicine, Vincristine, Prednisone

CI: Confidence Interval

CKD: Chronic Kidney Disease

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

CRS: Cytokine Release Syndrome

CT: Computed Tomography

eGFR: estimated Glomerular Filtration Rate

EGFR: Epidermoidal Growth Factor Receptor

ER: Estrogen Receptor

ESKD: End-stage Kidney Disease

HER2: Human Epidermal Growth Factor Receptor 2

HL: Hodgkin's Lymphomas

HPC1: Hereditary Prostate Cancer-1

HUS: Haemolytic Uremic Syndrome

IACR: International Association of Cancer Registries

IARC: International Agency for Research on Cancer).

ICDO3M: International Classification of Disease for Oncology, third revision

ICD10: International Classification of Disease, tenth revision

ICIPs: Immune Checkpoint Inhibitors

IRC: Insufficienza Renale Cronica

IRMA: Insuffisance Rénale et Médicaments Anticancéreux - Renal failure and anticancer drugs

KDIGO: Kidney Disease Improving Global Outcomes

KPS: Karnofsky Performance Score

LH-RH: Luteinizing Hormone Releasing Hormone

M: male

MCT: Maximum Conservative Therapy

MDRD: Modification of Diet in Renal Disease

MRI: Magnetic Resonance Imaging

NHANES: National Health And Nutrition Examination Survey

NHL: Non-Hodgkin's Lymphomas

OR: Odds Ratio

PASE: Physical Activity Scale for the Elderly

PD-1: Programmed Death protein 1

PD-L1: Programmed Death-Ligand 1

PET: Positron Emission Tomography

R-CHOP: Rituximab, Cyclophosphamide, Doxorubicine, Vincristine, Prednisone

RT: Radiotherapy

sCr: serum Creatinine

SD: Standard Deviation

SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion

TLS: Tumor Lysis Syndrome

TMA: Thrombotic Microangiopathy

TNM: Tumor, Node, Metastasis

TTP: Thrombotic Thrombocytopenic Purpura

VEGF: Vascular Endothelium Growth Factor

^{18}F-FDG PET: 18-Fluorodeoxyglucose Positron Emission Tomography

1. Abstract

BACKGROUND and OBJECTIVES: There are more and more patients who, in addition to being affected by chronic diseases in an advanced/terminal stage and other comorbidities, have a certain degree of frailty; this makes them susceptible to a greater risk of disability and non-self-sufficiency, a worse quality of life and increased mortality. This thesis focuses on the frailty in two different settings: the outpatient advanced chronic kidney disease clinic and the Onco-Nephrology consultation service.

STUDY DESIGN and SETTING: We conducted two retrospective observational studies; in Project 1, we compared the outcomes of frail patients with chronic kidney disease (CKD) maintained on dialysis or on a conservative kidney management program. In Project 2, we provided new original data on the prevalence and incidence of chronic kidney disease in cancer population.

RESULTS: In Project 1, the use of dialysis has shown a marginal, even though significant, effect on the average survival of frail nephropathic patients; however, they present a higher hospitalization rate with consequent impact on quality of life. In Project 2, we calculated the prevalence of CKD in cancer patients and the incidence of new-onset CKD in the following 24 months since cancer diagnosis; we also performed a descriptive analysis of both groups of patients (pre-existing and new-onset CKD).

CONCLUSIONS: Frailty is a common feature in CKD patients, representing an independent risk factor for death. Therefore, identifying and managing the frail patient is a very complex challenge for our National Health System. Continuous researches are needed to recognize the condition of frailty as an aggravating factor in chronic disease and to define the most appropriate prevention and management models.

Abstract *(Italian version)*

Le sfide dell'insufficienza renale cronica nei pazienti fragili: due progetti sull'impatto dell'invecchiamento e del cancro

BACKGROUND E OBIETTIVI: Sono sempre più numerosi i pazienti che, oltre ad essere affetti da malattie croniche in fase avanzata/terminale ed altre comorbidità, presentano un certo grado di fragilità; ciò li rende suscettibili ad un maggior rischio di disabilità e non autosufficienza, peggiore qualità di vita ed aumento della mortalità. Questa tesi si focalizza sulla fragilità in due diversi contesti: l'Ambulatorio dell'Insufficienza Renale Cronica (IRC) ed il servizio di consulenza Onco-Nefrologica.

DISEGNO DELLO STUDIO e SETTING: Sono stati condotti due studi osservazionali retrospettivi; nel Progetto 1, sono stati confrontati gli outcomes dei pazienti nefropatici fragili affetti da IRC terminale in dialisi ed in terapia conservativa massimale. Con il Progetto 2 sono stati ottenuti dati originali sulla prevalenza e l'incidenza della malattia renale cronica nella popolazione affetta da cancro.

RISULTATI: Nel Progetto 1, l'uso della dialisi ha mostrato un effetto marginale, anche se significativo, sulla sopravvivenza media dei pazienti nefropatici fragili; i pazienti dializzati presentavano tuttavia un tasso di ospedalizzazione più elevato con conseguente impatto sulla qualità della vita. Nel Progetto 2, sono state calcolate la prevalenza di IRC nei pazienti affetti da cancro e l'incidenza di IRC di nuova insorgenza nei 24 mesi successivi alla diagnosi di cancro; è stata inoltre condotta un'analisi descrittiva di entrambi i gruppi di pazienti (IRC pre-esistenti e di nuova insorgenza).

CONCLUSIONI: La fragilità è un aspetto comune nei pazienti con IRC e rappresenta un fattore di rischio indipendente di mortalità. Pertanto, l'identificazione e la gestione clinica dei pazienti fragili rappresentano una sfida molto complessa per il nostro Sistema Sanitario Nazionale. Sono auspicabili

ulteriori studi per riconoscere la fragilità come fattore aggravante nell'IRC e per definire i modelli di prevenzione e gestione più appropriati.

2. Introduction

Among several challenges our health care systems have to deal with, frailty is the greatest one, since it represents the most problematic expression of population ageing. Older adults, especially frail older adults, form the main users of medical and social care services. Nevertheless, current health care systems are not well prepared to deal with the chronic and complex medical needs of frail older patients. Not surprisingly, over the last two decades, frailty has received increasing scientific attention. In almost all medical subspecialties, it is now clear that early detection of the frailty is essential in order to tend to compress morbidity, reducing the adverse outcomes as well as the public costs.

For the special perspective of the clinical nephrologist, frailty in patients with advanced kidney failure represents more than a medical problem, since it is in many instances, above all, an ethical dilemma. The decision to start or not a frail older patient on dialysis is certainly a matter of controversy, and unfortunately not an uncommon one in everyday nephrology practice.

After an attempt for operational definition of frailty and a full review of methodological, semantic and logistical pitfalls of screening for it (presented in Introduction), this thesis focuses on the frailty in two different settings: the outpatient advanced chronic kidney disease clinic and the Onco-Nephrology consultation service.

In the first scenario, described in Project 1, we compare the outcomes of frail patients with end-stage kidney failure maintained on dialysis or on a conservative kidney management program.

At the frontier of nephrology and oncology, in the emerging field of Onco-Nephrology, the frailty is even a more relevant challenge. Clearly, considering the current definitions, cancer patients with concomitant kidney disease are at a very high risk of frailty. Nevertheless, so far, the dearth of data on the prevalence and incidence of chronic kidney disease among these patients has significantly limited any public effort to improve their outcomes. For such a reason, the aim of the second part (reported in Project 2) of our research on frailty was to provide new original data on the prevalence

and incidence of chronic kidney disease in cancer population, in the hope that this new information could be fully translated into clinical practice and health care policy making.

3. Background

3.1 Definition of frailty

In recent years, the concept of "frailty" has raised a lot of interest and debate; despite the large space dedicated in scientific literature, there are no shared criteria to identify frail patients.

Frailty is often underestimated, in part due to lack of a uniform definition and diagnostic criteria [1]. Several Authors [2] have defined frailty as a physiological syndrome-characterized by the reduction of functional reserves, decreased resistance to stressors, sarcopenia, protein malnutrition and atherosclerosis.

Pathogenically, frailty can be seen as the precursor of a progressive functional deterioration which ultimately leads to functional disability (limitations in mobility in activities of daily living- ADL and/or instrumental ADL, e.g., housework, preparing meals, taking drugs, managing money, using telephone or other form of communication, etc.), causing recurrent hospitalizations, institutionalization and death in elderly patients regardless of its initial cause [3, 4]. Not surprisingly, it is also associated with an increase in inflammatory biomarkers [4, 5].

The severity of frailty is also aggravated by other factors such as easy fatigue with self-reported exhaustion of strength, low education, economic and social distress [3].

Fried [3] proposes a definition of frailty, configuring a "fragile phenotype" characterized by five points:

- Weight loss (greater than 4.5 Kg in the last year);
- Fatigue (fatigue in at least 3 days/week);
- Reduction of muscle strength (hand-grip, < 5.85 Kg for males and 3.37 Kg for females);
- Reduced physical activities, assessable with the PASE scale (Physical Activity Scale for the Elderly);
- Reduction in walking speed (> 7 seconds to travel 5 meters on a known route)

There is frailty if 3 or more of these criteria are present.

To evaluate the impact of comorbidities on a frail patient, one of the most used indices is the Charlson Comorbidity Index (CCI) [6]. A CCI > 8 is considered predictive of high mortality at 12 months.

In Table 1 are listed comorbidities examined and the score considered for each of them.

Table 1. Charlson Comorbidities Index for the evaluation of comorbidities (from SICP-SIN shared document: Palliative care in people with advanced CKD)

Score	Comorbidities
1	Ischemic heart disease, chronic heart failure, peripheral and cerebro-vascular disease, dementia, chronic lung disease, connective tissue disease, peptic ulcer, mild liver disease, diabetes mellitus
2	Hemiplegia, moderate or severe CKD, diabetes mellitus with organ damage, cancer, leukemias
3	Moderate or severe liver disease
6	Solid cancer with metastasis

Age: 1 point for each decade beyond that of 40 years

Another important patient evaluation model is the Karnovsky Performance Scale (KPS) which takes into account the patient's quality of life through the evaluation of three parameters: limitation of activity, take care of yourself and self-determination.

Many other features can contribute to frailty such as depression and nutritional status.

Regarding depression, several studies have shown that depressive symptoms are associated with frailty [7- 9]. Depression tends to increase with the intensity of care, with a prevalence of depressive symptoms that ranged from 20% in primary care to over 40% in chronic or long-term care [10]. Depression in the elderly is often associated with a reduced quality of life, an increase in mortality and need for assistance. The causes of depression in older people are multifactorial and they can be divided into 3 broad categories:

2 Physical illness;

3 Social factors (social isolation, loneliness, stress, events such as care of a relative);

4 Mental illness, which may include a family history of depression, cognitive impairment and dementia.

Malnutrition is common in elderly patients and appears to worsen with age, as well as being associated with reduced quality of life and increased mortality.

It is well known that body composition tends to change with age, with an increase in fat body mass and reduction in lean mass potentially leading to sarcopenia [11].

At what point does frailty become advanced or irreversible?

A Canadian study [1] defined as moderately frail patients who need help with activities of daily living (e.g., washing, dressing, using services, continence, feeding) and severely frail patients who are completely dependent on others or who present a terminal illness. Alternatively, recurrent falls, an increase in disability, exacerbation of chronic disease with incomplete recovery, could suggest the presence of advanced frailty.

3.2 Nephropathic frail patients: epidemiology and identification

Chronic kidney disease (CKD) is an important cause of morbidity in the general population and is a public health problem.

It is a progressive disease often linked to some risk factors, that are largely common to those for cardiovascular diseases (diabetes mellitus, hypertension, obesity, advanced age, etc.); an early diagnosis of CKD can allow adequate management of the disease in order to slow down its evolution towards the most advanced stages. Advanced CKD represents the final stage of many nephropathies and is characterized by marked functional insufficiency and clinical symptoms up to the need for replacement treatment with dialysis or kidney transplant.

The CARHES Study provided the data of prevalence of CKD in the Italian population: CKD has a prevalence of 7.5% in men and 6.5% in women [12- 13].

The current socio-demographic changes with the progressive ageing of the population are responsible for the increasing number of people suffering from CKD.

The characteristics common to this age group are: frequent condition of non-self-sufficiency, a high number of associated comorbidities, often an important clinical symptomatology not different from that of cancer patients. In addition, life expectancy is much lower than that of subjects of the same age without CKD and the prognosis may be worse than that of many types of cancer.

There are more and more patients who, in addition to CKD, are affected by other comorbidities having a certain degree of frailty. These patients are more susceptible to a greater risk of disability, a worse quality of life and increased mortality.

Frailty is a common feature in CKD and dialysis population, appearing early and representing an independent risk factor for death and hospitalization [14-16].

One cross-sectional study [17] verified the association between frailty and CKD: the survey highlighted a strong association especially with eGFR < 45 mL/min/1.73m^2; this association was

weaker, but always present, in early CKD stages. The risk of frailty increased approximately 2 times in mild CKD and 6 times in moderate-severe CKD.

Prognostic evaluation models for nephropathic frail patients are now available (Figure 1): the use of these, as part of clinical evaluation, can help decision-making process, favoring the explication of possible therapeutic alternatives with the patients, family and caring team [18-19].

Figure 1. Unfavorable prognostic factors in patients with advanced CKD

Advanced age
Type and severity of associated comorbidities
Severe malnutrition
Severe cognitive impairment
Reduced functional autonomy
Appearance of sentinel events (e.g., frequent hospitalizations)

from Shared SICP-SIN document: Palliative care in people with advanced CKD

Among the prognostic models developed to identify the subjects at highest risk of mortality, both among incident patients on dialysis and those already undergoing chronic dialysis treatment, the one developed by REIN Registry is particularly interesting. The original cohort provided data on patients older than 75 years with a mean age of 81 [18].

This model is based on 9 risk factors assessed at the time of starting dialysis treatment and provides an estimate of the risk of death in a short-time period; for each of the 9 factors is assigned a score from 1 to 3 with a total variable from 0 to 16 (Table 2). In the REIN Registry, the 6-month mortality rate was 19% and ranged from a minimum of 8% in patients at lower risk (score 0) to a maximum of 70% in patients at higher risk (score ≥ 9).

Table 2. 6-months mortality risk factors in incident dialysis patients (from SICP-SIN shared document: Palliative care in people with advanced CKD)

Risk factors	**Score**
Diabetes mellitus	1
Arhythmia	1
Cancer	1
Malnutrition (BMI <18.5)	2
Heart failure (stage 3-4)	2
Peripheral vascular disease (stage 3-4)	2
Severe changes in behavior	2
Unscheduled start of dialysis	2
Total dependence for movement	3
Total score	**0-16**

Alongside these prognostic factors and indices, the so-called “surprise question” was developed: “Would I be surprised if the patient were to die in the next 12 months?”. If the answer is “no”, priority should be given to the patient’s concerns, control of his symptoms, help for the family, continuity of care and spiritual support.

The “surprise question”, initially considered effective in identifying fragile nephropathic patients undergoing dialysis and at high risk of early mortality, was also successfully used in patients with chronic diseases in advanced stage [20]. However, according to the study conducted by Javier et al [21], it demonstrates moderate reliability in patients with CKD in stage 4-5 according to KDIGO guidelines [22]. Further studies are therefore needed to examine how best to use the “surprise question” in patients with advanced CKD but not yet dialysis-dependent [21].

3.3 Frailty in dialysis patients

In recent years, also in relation to the increase in the elderly population, there has been a progressive increase in the need for dialysis treatment in patients over 70 years old, who now account for about 53% of new entries on dialysis every year [23].

There are more and more frail nephropathic patients who are at risk of premature mortality, increased hospitalizations and significant worsening of quality of life, despite having absolute contraindications to renal replacement therapy. Indeed, there are no absolute contraindications to starting dialysis, although the condition of severe dementia and advanced cancer with metastasis are coded as indicators of non-initiation of dialysis by the guidelines of the Renal Physician Association [24].

Regarding dialysis options, in most industrialized countries, frail patients with end-stage kidney disease (ESKD) are mostly treated with hemodialysis, despite the costs associated with transportation and frequent difficulties with vascular access (with a high failure rate of arterio-venous fistulas for hemodialysis) [25]. In fact, in these patients it is often forced to use central venous catheters for hemodialysis as vascular access, with an increase in serious complications such as malfunction (which could lead to the use of anticoagulant therapy with consequent haemorrhagic risk) and, above all, infection with severe, life-threatening sepsis [26].

The mean mortality during the first year of dialysis in patients with a mean age of 80 years can approach 46% [27]. Although peritoneal dialysis may be preferable in frail nephropathic patients, it is often not feasible due to lack of assistance.

In Literature, it is now well known that patients aged > 75 years undergoing dialysis with associated comorbidities, in particular ischemic heart disease, have a very reduced survival [28].

In patients over 75 years old (or even in those younger, but in particularly compromised clinical conditions), the non-initiation or discontinuation of dialysis should be evaluated in the presence of at least 2 of the following criteria, known to be significantly associated to a poor diagnosis:

- Negative answer to the “surprise question”;
- Charlson Comorbidity Index > 8;
- Karnofsky Performance Score < 40;
- Serum albumin < 2.5 g/dl.

In the subject with CKD stage G4 or G5, especially if in presence of advanced age and multiple comorbidities, it is important to establish not only the choice of the most suitable treatment, but also the therapeutic perspectives to be pursued through a discussion with the patient and his family.

Frail elderly people with CKD are the most vulnerable patients to the risks associated with dialysis rather than its benefits. Therefore, in frail elderly population, dialysis should be carefully considered: the ethical debate on treatment options should be an integral part of the management of ESKD.

There is now proven evidence that the outcomes of frail nephropathic patients is comparable to that of neoplastic patients.

PROJECT 1

4. Maximum Conservative Therapy vs Dialysis in frail nephropathic patients. Results of a retrospective study

4.1 Abstract

BACKGROUND and OBJECTIVES: Chronic dialysis in frail nephropathic patients can worsen the load of symptoms and functional autonomy, increasing the risk of early mortality. It is important to evaluate if dialysis treatment represents a real advantage for these patients. Maximum Conservative Therapy (MCT), associated with palliative care, could improve their residual quality of life, avoiding the use of dialysis. The aim of this work is to describe the application and the relative terms of MCT in a complete series of cases followed in our Nephrological Clinic.

STUDY DESIGN and SETTING: Retrospective observational study of a cohort of 48 frail nephropathic patients in MCT and 58 on dialysis in the period between January 2013 and December 2019. Place of death, Incidence Rate (IR) and Incidence Rate Ratio (IRR) related to survival and hospitalization rates were studied.

RESULTS: The average duration of MCT was 9.7 months vs 13.5 months of dialysis treatment. One-year probability of survival of dialysis patient was 0.52 [CI 0.38-0.64] vs 0.48 [CI 0.33-0.62] in MCT patients; however, dialysis patients had higher rates of hospitalization (IR 2.780 vs 1.269 in MCT patients), IRR 2.19 [CI 1.66-2.89]. 67% of dialysis patients died in hospital versus 35% of MCT patients. 34% of MCT patients are still alive at the time of data analysis (January 31, 2020); no dialysis patients are still alive on the same date.

CONCLUSIONS: The use of dialysis has shown a marginal, even though significant, effect on the average survival of frail nephropathic patients; however, they present a higher hospitalization rate with consequent impact on quality of life.

4.2 Background

Chronic kidney disease (CKD) is a significant public health problem not only as a cause of morbidity in the general population, but also because it represents an independent risk factor for impairment, functional decline and frailty associated with negative outcomes such as excess of mortality and hospitalization [29].

CKD has a prevalence in Italy of around 7.5% in men and 6.5% in women [12, 13].

Data of the Italian Dialysis and Transplant Registry report an incidence of CKD of about 154 patients per million population, about 9600 new dialysis entries every year and 48,000 prevalent dialysis patients [30].

In Emilia-Romagna, about 40% of patients who start renal replacement therapy (RRT) are over 75 years and, in most of these patients, the onset of dialysis is accompanied by a progressive mentally decline and reduced functional autonomy, with a rapid deterioration in quality of life: 22% of these patients die within 12 months of starting treatment [31].

According to the Renal Association Guidelines, the absolute contraindications to starting dialysis are severe dementia and advanced cancer with metastasis [32]. However, other factors should be taken into account for an overall health balance and for an accurate assessment of the best treatment options for each patient. In particular, the classification of the patient as a frail one should include a multidimensional assessment of the person (cognitive function, frailty, comorbidity, functional and psychosocial factors), through specific clinical and prognostic criteria [Table 2].

In fact, dialysis, while improving many uremic symptoms, could not often guarantee an acceptable quality of life for frail nephropathic patient. Maximum Conservative Therapy (MCT), associated with palliative care, has the aim to improve their residual quality of life avoiding the use of dialysis [33-35].

According to the Guidelines on nutritional therapy in CKD not yet on dialysis [36], the rationale for the use of this therapy must be the prevention and/or control of metabolic alterations and clinical complications [36] becoming an integral part of the MCT in CKD.

It is well known that the alterations of the different metabolic products (urea, organic and inorganic acids, etc.) and of the micronutrients introduced with the diet (phosphorus, sodium, potassium, etc.) are conditioned by nutrition, which must be taken into account in the overall therapeutic strategy; indeed, these alterations are due to the reduction of the glomerular filtrate and they're already evident in early CKD stage [37].

Nutritional therapy plays a fundamental role in the MCT in CKD patients, allowing a better control of metabolic acidosis and level of urea, potassium, sodium, phosphorus and parathyroid hormone, reducing uremic symptoms. Furthermore, well-conducted nutritional therapy is able to avoid malnutrition and maintain residual kidney function for longer [28-38-39].

The aim of this study is to describe the application and the related outcomes of the MCT in a complete series of consecutive cases followed in our Nephrological Clinic, AUSL-IRCCS Reggio Emilia, Italy.

4.3 Methods

4.3.1 Study design and population

This is a single-center, observational, retrospective study. We identified 48 patients with severe CKD (stage G4-G5 according to KDIGO classification with eGFR < 30 ml/min/1.73m^2 calculated with CKD-EPI formula) from January 1st, 2013 to December 31st, 2019, for which it was started MCT in consideration of severe comorbidities, age and prognosis.

Prognosis assessment of frail patients was established through traditional risk factors associated with the presence of comorbidities [Table 2].

Charlson Comorbidity Index (CCI) was used to evaluate the impact of comorbidities on these patients. A CCI > 8 is considered predictive of high mortality at 12 months [6]. All patients were followed up at our Nephrological Clinic at the AUSL-IRCCS of Reggio Emilia, Italy.

Data patients were obtained from several sources:

- Electronic Outpatient Medical Record: this program was used to evaluate patient's medical history, presence of comorbidities and to identify any erythropoietin therapy used for the treatment of anemia secondary to CKD

- Provincial Biochemical Laboratory Database: includes laboratory tests carried out in the provincial public health network, coded with internal classification. Kidney function tests (serum creatinine), estimated glomerular filtration rates (eGFR), hemoglobin, potassium and bicarbonate performed since 2013 were selected.

- Mortality Registry (ReM): contains all patients' deaths in the province of Reggio Emilia by year of death. Causes of death is codified according to the International Classification of Diseases, 10th revision, ICD10.

Control group included a cohort of 58 frail nephropathic patients undergoing dialysis in the same period, with demographic and clinical characteristics superimposed on the MCT group. Data relating to dialysis patients were obtained from the same MCT patients' data sources.

Several variables were considered for the two groups: patient's age and sex, creatinine value and related eGFR, serum albumin, hemoglobin value and the consequent possible use of erythropoietin; main associated comorbidities (diabetes mellitus, hypertensive/ischemic heart disease, atrial fibrillation, peripheral or cerebral vascular diseases, viral or exotoxic/dysmetabolic liver disease, presence and variable degrees of cognitive impairment, malignancies). Settings for death (home/hospital/hospice) and activation of palliative care were considered for both groups.

4.3.2 Endpoints

The following endpoints have been evaluated:

- Duration of MCT from the time of its activation until patient's death;
- Place of patient's death: hospital, hospice or home;
- Causes of death (obtained from Mortality Registry);
- Number of hospital admissions since the activation of MCT or start of dialysis

In 3 dialysis patients, extracorporeal treatment was stopped due to worsening of general clinical conditions and/or of the underlying disease.

MCT was activated for frail nephropathic patients already known to our Nephrological Clinic with stage G4-G5 CKD, severe comorbidities and advanced age (> 75 years), severe malnutrition (albumin value < 2.5 g/dl), moderate-severe cognitive impairment, reduced functional autonomy; moreover, in presence of sentinel events (e.g., frequent hospitalizations) and NO answer to the "surprise question" ("Would I be surprise if the patient died in the next 12 months?") [40, 41].

MCT provides sharing the therapeutic choice to not start dialysis with the patient and family members/care-givers as well as General Practitioner; possible activation of a hypoprotein diet; if indicated; palliative assessment for taking care of pain therapy; patient domiciliation: limiting unnecessary access to Emergency Room.

All MCT patients were treated with a low protein diet as indicated by the Italian Society of Nephrology [42], in one patient supplementation of keto analogues was added; if necessary, a hypokaliemic diet was associated for better control of potassium. Arterial hypertension was treated with prevalent use of calcium channel blockers, beta blockers, diuretics and possible use of ACE inhibitors or angiotensin receptor blockers. Hydro-saline overload was treated with the use of loop diuretic in association with potassium-sparing diuretic if possible, and/or metolazone. Alteration of calcium-phosphorus metabolism and hyperparathyroidism were treated with calcium-base phosphorus binders, active vitamin D and analogous.

4.4 Data analysis

Population characteristics were described using proportions for the categorical and mean variables with relative standard deviation and range for quantitative variables. The proportion of MCT patients' death at home or in hospice was compared with that observed in control group.

Annual hospitalization rate, 12-month survival and the median survival were calculated, estimated as the product limit by Kaplan-Meier survival function [Figure 2] and related 95% confidence intervals calculated with the exact binomial distribution for proportions and rates. The survival median and its confidence interval were linked to the basis of the survival function using STATA 13 stci command.

To compare the prognosis between MCT and dialysis patients, the survival and hospitalization rate of the two cohorts were compared. We presented incidence rate ratio (IRR) and hazard ratio (HR) with relative confidence intervals. Significant level considered is $p < 0.05$.

4.5 Results

We identified 48 frail nephropathic patients in MCT and 58 dialysis patients between January, 2013 and December, 2019. The number of MCT patients has progressively increased from 3 in 2013 to 8 in 2019, with a maximum number of 13 in 2017 (Table 3).

Table 3. Sample size of the two groups (MCT and dialysis) per year

Sample size per year	**Total**		**MCT**		**Dialysis**		
	N	**%**	**N**	**%**	**N**	**%**	***P****
	106		48		58		
Year							*0.000*
2013	13	12%	2	4%	11	19%	
2014	17	16%	6	13%	11	19%	
2015	18	17%	3	6%	15	26%	
2016	17	16%	7	15%	10	17%	
2017	18	17%	13	27%	5	9%	
2018	15	14%	10	21%	5	9%	
2019	8	8%	7	15%	1	2%	

* Fisher's exact test and p-value, for the hypothesis of independence in the two-way table. The p value is referred to the comparison of two group (MCT and dialysis patients)

Of the 58 dialysis patients, only 2 aged less than 75 (average age 83 years); MCT patients were older (87 years). In MCT group, 50% of MTC patients were female, 38% in dialysis group. At the time of initiation of the two different therapy (MCT and dialysis), mean creatinine value in MCT patients was 4.6 mg/dl (SD, ± 1.2) with an average eGFR of 10 ml/min/1.73m^2 (SD, ± 3.63). In control group, mean creatinine value was 6.8 mg/dl (SD, ± 1.88) with an average eGFR of 8 ml/min/1.73m^2 (SD, ± 2.35). Control group was more anemic than MCT patients (9.7 g/dl vs 10.9 g/dl); indeed 77.6% (45 patients) have been treated with erythropoietin (vs 68.8% in MCT, 33 patients) [Table 4].

Table 4. Clinical-laboratory data of MCT and dialysis patients

Variables	**Total**	**MCT**		**Dialysis**		
		N	**%**	**N**	**%**	***P****
	106	48		58		
GENDER						*0.241*
F	46 (43.4)	24	50	22	37.9	
M	60 (56.6)	24	50	36	62.1	
AGE (years)						
median (range)	84.5 (80-87)	87 (85-90)		83 (79-85)		*0.000*
mean±SD	84.2 (5.01)	86.7 (5.06)		82.0 (3.9)		*0.000*
SERUM CREATININE (mg/dl)						
median (range)	5.7 (4.6-6.9)	4.6 (3.9-5.3)		6.8 (6.1-7.6)		*0.000*
mean±SD	6.0 (1.98)	4.7 (1.20)		7.0 (1.88)		*0.000*
eGFR (ml/min/1.73m²)						
median (range)	9 (7-11)	10 (9-13)		8 (6-9)		*0.000*
mean±SD	9.2 (3.34)	10.8 (3.63)		7.8 (2.35)		*0.000*
HEMOGLOBIN (g/dl)						
median (range)	10.4 (9.4-11.3)	10.9 (10.3-11.5)		9.7 (8.9-10.9)		*0.000*
mean±SD	10.3 (1.51)	10.6 (1.10)		9.9 (1.62)		*0.000*
EPOIETIN						*0.272*
No	27 (26.0)	15	31.3	12	21.4	
Yes	77 (74.0)	33	68.8	44	78.6	
SERUM ALBUMIN (g/dl)						
median (range)	3.6 (3.2-3.7)	3.7 (3.4-3.9)		3.5 (3.2-3.6)		*0.002*
mean±SD	3.5 (.41)	3.6 (.41)		3.4 (.39)		*0.011*
DURATION OF THERAPY (months)						
median (range)	10.2 (4-18)	9.7 (4-12)		13.4 (4-24)		*0.555*
mean±SD	13.4 (11.4)	9.6 (6.0)		15.3 (13.1)		*0.023*

*t tests (mean-comparison tests) and p-value, median tests (nonparametric test on the equality of medians) and p-value

Of the 48 patients in MCT, 18 were diabetics, 29 had heart diseases (whether chronic ischemic or hypertensive), 11 patients had atrial fibrillation in anticoagulant oral therapy. From a prognostic point of view, it should be emphasized that more than half of the MCT patients (57%) had a variable degree of cognitive impairment (in 17 patients was performed a specialistic geriatric evaluation) with reduced functional autonomy and daily life activities. 84% of cases (36 patients) had an anamnestic history and/or instrumental diagnosis of cerebral vasculopathy (previous transient ischemic attack, minor stroke, atheromasia of supra-aortic trunk); 17% patients had a positive history of past or active cancer. In dialysis group, 14 were diabetic, 47 had an ischemic-chronic or hypertensive heart disease (81%) and 34% also had a diagnosis of atrial fibrillation. 4 patients suffered of cognitive impairment

(in one patient data not available), even if about half of the cohort had a cerebral vasculopathy diagnosis. 23 patients had a positive neoplastic history [Table 5].

Table 5. Clinical characteristics of the two groups (MCT and dialysis)

Comorbidities	**Total**	**MCT**		**Dialysis**		
		N	**%**	**N**	**%**	***P****
	106	48		58		
N° of COMORBIDITIES						
0	1 (0.9)	0	0	1	1.7	
1	10 (9.4)	4	8.3	6	10.3	
>1	95 (89.6)	44	91.7	51	87.9	
HEART FAILURE						
No	29 (27.6)	18	38.3	11	19.0	*0.031*
Yes	76 (72.4)	29	61.7	47	81.0	
ATRIAL FIBRILLATION						*0.511*
No	69 (69.0)	31	73.8	38	65.5	
Yes	31 (31.0)	11	26.2	20	34.5	
LIVER DISEASE						*1.000*
No	93 (95.9)	38	95.0	55	96.5	
Yes	4 (4.1)	2	5.0	2	3.5	
COGNITIVE IMPAIRMENT						*0.000*
No	71 (71.7)	18	42.9	53	93.0	
Yes	28 (28.3)	24	57.1	4	7.0	
CEREBRAL VASCULOPATHY						*0.000*
No	36 (36.0)	7	16.3	29	50.9	
Yes	64 (64.0)	36	83.7	28	49.1	
PERIPHERAL VASCULOPATHY						
No	37 (37.6)	12	30.0	25	43.1	*0.210*
Yes	61 (62.2)	28	70.0	33	56.9	
CANCER						*0.517*
No	53 (57.0)	18	51.4	35	60.3	
Yes	40 (43.0)	17	48.6	23	39.7	

*Pearson's chi-squared test or Fisher exact test and p-value for the hypothesis of independence in the two-way table

No significant differences in potassium, hemoglobin and bicarbonate values were highlighted in the two different group, subdivided in eGFR tertile [Table 6].

Table 6. Hemoglobin (Hb), potassium (K) and bicarbonate (HCO3) values in MCT and dialysis patients

	MCT			**Dialysis**			
eGFR (ml/min/1.73m²)	1° tertile (4-9)	2° tertile (10-11)	3° tertile (13-21)	*eGFR (ml/min/1.73m²)*	1° tertile (3-7)	2° tertile (8-9)	3° tertile (10-14)
Hemoglobin (g/dl)	10.7	11	11.4	*Hemoglobin (g/dl)*	9.7	10.2	10.3
K (mmol/L)	4.5	4.5	4.5	*K (mmol/L)*	4.5	4.3	4.8
HCO3 (mmol/L)	23.7	25	23.1	*HCO3 (mmol/L)*	22.2	23.5	22.3

By comparing the number of hospital admissions, regardless of the causes of access, dialysis patients have a greater number of hospitalization than MCT patients (IR 2.780 vs 1.269) [Table 7], in accordance with literature [39].

Dialysis patients have an IRR of hospitalization of 2.19 [CI 1.66-2.89].

Table 7. Number of hospital admissions, hospitalization rate for period and IRR

Hospital admissions	**Total**	**MCT**		**Dialysis**		
		N	%	N	%	***P****
						0.001
0	17 (16.0)	13	27.1	4	6.9	
1	28 (26.4)	16	33.3	12	20.7	
>1	61 (57.6)	19	39.6	42	72.4	

* Fisher exact test and p-value for the hypothesis of independence in the two-way table

Treatment	**n. of subject**	**n. events**	**Time**	**Incidence Rate**	**[95% Interv confid]**
MCT	48	67	52.7830	1.269	0.984 – 1.612
Dialysis	58	206	74.0999	2.780	2.413 – 3.187

Hospital admissions	**IRR**	**[95% Interv confid]**
MCT	1	
Dialysis	2.19	1.66 – 2.89

The mean duration of MCT was 9.7 months vs 13.5 months of dialysis treatment. MCT patients had a one-year survival probability of 0.48 [CI 0.33-0.62] compared with 0.52 of dialysis patients [CI 0.38-0.64]; the probability of 2-years survival was 0.26 in MCT patients [CI 0.13-0.42] and 0.24 for dialysis patients [CI 0.14-0.36] (Table 8).

Table 8. 1 and 2-year survival in MCT and dialysis patients

Time (year)	**Survivor Function**	**[95% Inter confid]**
MCT		
1	0.4835	0.33 - 0.62
2	0.2659	0.13 - 0.42
Dialysis		
1	0.5172	0.38 - 0.64
2	0.2414	0.14 - 0.36

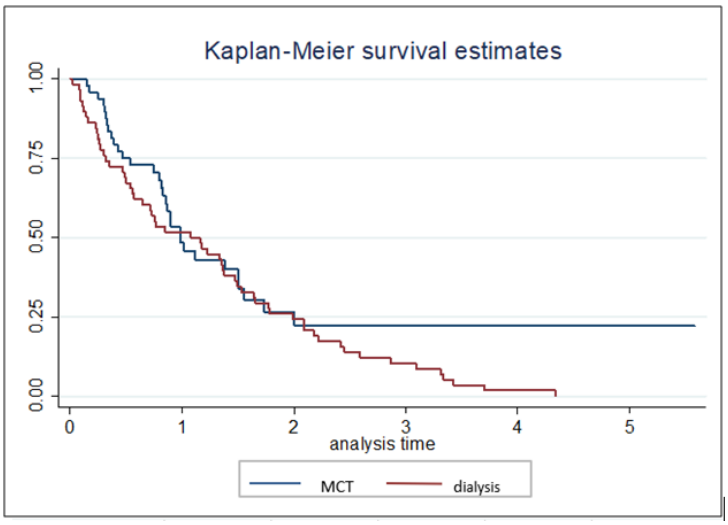
For MCT patients, place of death was home or hospice in 12 cases; in 17 cases death occurred in hospital, data not available for 3 patients. 39 dialysis patients died in hospital (67%), only 18 patients died at home and/or in hospice (31%). At the time of data analysis (January 31st, 2020), none of patients in dialysis were alive; 34% of MCT patients were still alive and in regular nephrological follow-up [Table 9 and Figure 2].

Table 9. Number and place of death of the two groups (MCT and dialysis)

	Total	**MCT**		**Dialysis**		
		N	%	N	%	*p**
Death						*0.000*
NO	17 (16.0)	17	35.4	0	0.0	
YES	89 (84.0)	31	64.6	58	100	
Place of death						*0.000*
Hospice	8 (7.6)	4	8.3	4	6.9	
Home	21 (19.1)	7	14.6	14	24.1	
Home/Hospice	1 (0.9)	1	2.1	0	0.0	
Hospital	56 (52.8)	17	35.4	39	67.2	
NA	20 (18.9)	19	39.6	1	1.7	

* Fisher exact test and p-value for the hypothesis of independence in the two-way table

Figure 2. Graph Kaplan-Meier survivor function, by treatment



Among causes of death obtained from Mortality Registry (ReM), the most frequent causes of death in MCT patients were kidney failure (12 cases), diabetes mellitus (5 cases) and ischemic heart disease (5 cases); also in dialysis group, the main cause of death was kidney failure (19 cases), bacterial infections (6 cases), ischemic heart disease (6 cases) and cerebrovascular diseases (4 cases). All other causes of death have been classified into "other causes" group [Table 10].

Table 10. Causes of death

DEATH CAUSES	**MCT**	**DIALYSIS**
Kidney failure	12	19
Diabetes mellitus	5	3
Ischemic heart diseases and other forms	5	6
Other infections	2	6
Cerebrovascular diseases	0	4
Other causes (lungs/gastrointestinal-cardiovascular diseases)	2	6
Other causes (Multiple Myeloma, solid tumor)	1	8

4.6 Discussion

Although dialysis has become a routine treatment also for elderly patients, today it is not univocally indicated in frail nephropathic patients, overcoming the "automatism" for which, anyone presents a terminal uremia, should starts RRT. In fact, dialysis has an impact on quality of life and frail nephropathic patients have a symptomatic and care burden similar to cancer patients. Indeed, they have a similar or worse prognosis, being more vulnerable to the risks connected to dialysis rather than its benefits [43].

As highlighted by Carson at al. [39], although dialysis prolongs the survival of patients compared with those in MCT, the "earned" time is spent between dialysis, transport to and from the hospital and any hospitalizations.

Therefore, for patients who refused dialysis or for those with advanced age with severe comorbidities who would not benefit from dialysis, MCT must be considered. It provides the adoption of a personalized nutritional program based on low-protein diet and supplementation of keto analogues if necessary [36] protocols shared with the General Practitioner for home management of intercurrent clinical critical issues, pain and/or hydro-saline overload. MCT could therefore reduce hospitalizations and improve access to palliative care; it may also not adversely affect survival or quality of life [44]. MCT represents an optional treatment for frail nephropathic patients with reduced functional autonomy, according to ERBP Guidelines group [45].

Our study has some limitations: it is a retrospective study, conducted in a single Center and on a limited cohort of patients. Clinical characteristics of the two groups of patients are not homogeneous: in our series, although older than those on dialysis, MCT patients had an overall better nutritional status, correction of symptoms of CKD and eGFR. A further limitation of the study is having defined the causes of death on the basis of the ICD10 classification reported by Mortality Registry: it does not allow to identify in detail the complications that actually caused patient's death.

It is difficult to define what factors have determined the start of dialysis or MCT. The retrospective nature of the study could generate doubts about the uniformity of judgment by the various physicians involved; moreover, could imply negative selection bias for the most compromised patients. However, the evaluation of the data confirms that the expected survival and type of comorbidity seems to have had a prevalent impact.

With these limits, our experience is in accordance with what is reported in literature data.

The use of dialysis treatment has shown a marginal, even though, effect on the average survival of frail nephropathic patients (13.5 vs 9.7 months); conversely causes a significant increase in number of hospitalizations with consequent impact on quality of life. In our opinion, it is significant that, despite a substantially overlapping performance status, patients with heart failure were more often in dialysis than in MCT; instead, cognitive impairment was more frequent in MCT group. This confirms the hypothesis that the choice of the treatment for CKD is not only conditioned by the number of comorbidities, but above all by the type of the latter, representing each time an element in favor of the MCT (difficult clinical management, reduced compliance related to cognitive impairment, etc.) or dialysis (volume control). These observations require caution in the quantitative approach to define the best treatment in frail nephropathic patients. It confirms, once again, the common notion of a shared decision that must always be individualized and tailored to each patient.

4.7 Conclusion

Frailty is a common feature in CKD patients, representing an independent risk factor for death and hospitalization.

Frail nephropathic patients are identified by risk scores and prognostic models that are universally recognized as powerful predictors of negative short-term outcomes.

For these patients it is fundamental to investigate whether dialysis represents a real advantage or whether maximum conservative therapy is no longer adequate.

Maximum conservative therapy, which is based on pharmacological and dietary treatments, allows to treat the symptoms and complications related to the uremic syndrome, maintaining a residual kidney function for longer.

Therefore, the goals of care in frail nephropathic patients should be aimed to minimizing symptoms and disability, improving quality of life as much and as long as possible, guaranteeing a global assistance to the patient and his family, especially in the final phase of life.

PROJECT 2

5. ROCK Study: Research study Of Cancer associated Kidney diseases

5.1 Abstract

BACKGROUND AND AIMS: It is now well known that chronic kidney disease (CKD) and cancer are connected in several ways. Nevertheless, although emerging evidence suggests that the risk of renal impairment in cancer patients is high and increasing, the overall incidence and prevalence of CKD in this population are still uncertain. The improvement in the survival rates of cancer patients due to the new oncological and biological agents has led to an increase in those who develop CKD, simultaneously increasing the burden of frailty in this population. The purpose of the study is to provide data on the prevalence and incidence of CKD in cancer patients, hopefully helping both physicians and health providers to address this emerging public health problem.

METHODS: This is a single-center, observational and retrospective study including patients enrolled in the Cancer Registry of the province of Reggio Emilia, Italy, since January, 1st to December, 31st 2016. For all patients, data on sex, age, ethnicity, serum creatinine and related eGFR, type and number of tumors, diagnosis of diabetes mellitus were collected. The main cancer sites considered were breast, colorectal, lung, pancreas, gastric, prostate, lymphomas and leukemias. An eGFR $\geq$ 60 ml/min1.73m^2 was indicative of a normal kidney function, while an eGFR <60 ml/min/1.73m^2 as kidney impairment. All the eGFR data were calculated with both the CKD-EPI formula and the Wright formula.

RESULTS: 4254 patients with a cancer diagnosis were identified; of these, 171 patients were excluded due to lack of data. Of the remaining 4083 patients, 776 (19%) had at least an eGFR value <60 mL/min/1.73m^2 prior to cancer diagnosis and 497 patients (11.7%) were identified as affected by CKD. The incidence of new-onset CKD in the following 24 months since cancer diagnosis was

4.4% (186 patients) [95% CI 3.9-5.3] using CKD-EPI formula; using Wright formula, we identified 140 (3.4%) [95% CI 2.9-4.0] new cases of CKD in the same period. We also performed a descriptive analysis of both groups of patients with pre-existing CKD and new-onset CKD. Referring to the CKD-EPI formula, in patients with pre-existing CKD, the mean age was 81 years (SD ± 8.4), 53.7% were men, 18.3% had a known diagnosis of type 2 diabetes mellitus, 3.6% of these patients had 2 or more cancer diagnosis in the study period. 44.3% were alive at the end of the follow-up (December 31st, 2018). Using Wright formula, patients with pre-existing CKD had an average age of 82 years (SD ± 8.4) and in 55.4% of cases were men; 18.8% had type 2 diabetes mellitus and 3.8% had 2 or more cancer diagnosis.

CONCLUSIONS: The ROCK study is the first large cohort study that allows a clearer estimation of the frequency of CKD in Italian cancer patients. Knowledge of the prevalence of CKD in cancer patients is essential for proper clinical and therapeutic management and implementation of preventive strategies.

5.2 Background

The use of a growing number of innovative antineoplastic drugs and the extension of therapeutic lines to patients with greater comorbidities (e.g., diabetes mellitus, arterial hypertension, cardiovascular disease), as well as the improvement of survival rates of neoplastic patients, has led to an increase in those who develop renal disease due to cancer (e.g., paraneoplastic glomerulonephritis, nephrotoxicity from oncological therapy, etc.…) [46, 47].

Moreover, the impact on kidney function of these novel targeted therapies is increasingly known [48, 49].

The development of Onco-Nephrology, a new sub-specialized area in Nephrology that deals with nephropathic oncological patients, has emphasized the importance of the interaction between cancer and kidney disease.

Even in nephropathic and cancer patients, frailty has a predictive power in term of mortality and increased risk of adverse events. This results in particular attention to the management and definition of a therapeutic plan that take into account the presence of frailty.

Indeed, chemotherapy is also increasingly used in frail elderly patients who represent a subpopulation particularly vulnerable to the nephrotoxicity of some chemotherapeutic agents and of the contrast medium used in radiological staging and follow-up investigations [50, 51].

Furthermore, some peculiar features of anti-cancer therapy, such as stem cell transplantation, tumor lysis syndrome and the use of potentially nephrotoxic drugs (e.g., antibiotics, non-steroidal anti-inflammatory drugs) has increased the risk of acute kidney injury (AKI) in hospitalized cancer patients [52, 53, 54, 55]. Moreover, it is now well known that the survival rates of cancer patients who develop AKI is significantly reduced [56].

However, the overall incidence and prevalence of chronic kidney disease (CKD) in cancer patients are still uncertain, but much evidence suggests that the risk is high and increasing.

The risk for the development of acute and chronic kidney failure depends on the type of cancer and chemotherapy administered, pre-existing clinical conditions (e.g., diabetes mellitus, arterial hypertension, cardiovascular disease, hyponatremia) as well as the procedures or interventions to which the patient has undergone (e.g., contrast medium, nephrotoxic antibiotics, use of non-steroidal anti-inflammatory drugs) [46, 57, 58, 59].

Since many neoplastic patients have pre-existing renal impairment and survival is significantly lower in cancer patients with CKD, the prevention of AKI and its potential evolution into CKD are of fundamental importance.

However, in neoplastic patients, there is a lack of definitive and solid data on the frequency, progression and presentation of CKD.

In Literature, there are few studies that have evaluated the incidence rates and outcomes of cancer patients who have developed AKI [46]. In Salahudeen et al. study, 12% of hospitalized cancer patients developed AKI, 45% of patients had AKI during the first two days of hospitalization, 55% in the following days. Nephrological counseling was requested in 10% of cases and renal replacement treatment was required in 4% of cases.

In the multivariate model, the odds ratio (OR) of developing AKI was significantly higher in patients with diabetes mellitus (OR, 1.89; 95% [CI], 1.51-2.47), undergoing chemotherapy (OR, 1.61; 95 % CI, 1.26-2.05), contrast medium administration (OR, 4.55; 95% CI, 3.51-5.89), hyponatremia (OR, 1.97; 95% CI, 1.57-2.47) and antibiotics (OR, 1.52; 95 % CI, 1.15-2.02). In patients with AKI, length of hospitalization, health care costs and mortality were significantly increased.

The first studies that reported the prevalence of CKD in cancer patients were the "IRMA studies" (Insuffisance Rénale et Médicaments Anticancéreux - Renal failure and anticancer drugs) [60, 61]. The two cohorts (IRMA-1 and IRMA-2) included approximately 10,000 adult patients with solid cancer (mainly breast, colorectal and lung), admitted in a number of French oncology departments. About half of the patients had no metastases at the time of inclusion, and were not on dialysis. In these cohorts, 52.9% and 50.8% of patients in IRMA-1 and IRMA-2 had a low estimated glomerular

filtration rate (eGFR) (less than 90 mL/min/1.73 m²), respectively 12% and 11.8% had a CKD stage G3 or G4.

The relative frequency by type of cancer, interventions, procedures, chemotherapies, age and gender has not been studied in these patients. Furthermore, these studies have the limit of having been carried out before the publication of the 2012 KDIGO guidelines on CKD [62], which redefined the staging by introducing, alongside the traditional classification based on the eGFR, three classes risk based on the presence and extent of albuminuria.

The included population was not representative of the current incident cancer population because these studies have been conducted prior to the introduction of the novel targeted therapies and monoclonal antibodies. Furthermore, the formulas used for the calculation of eGFR were the MDRD and improperly the Cockcroft-Gault equation.

The results of this latter equation generally overestimate the real GFR since they represent an estimate of the serum creatinine clearance, that is an estimate of the real GFR value plus the value of tubular secretion of creatinine, which is variable because it can increase due to nephropathy or reduce due to the effect of some drugs [63].

Moreover, the formula was obtained from the analysis of the relationship between age and urinary excretion of creatinine per kilogram of body weight in male adults without any data on the real GFR having been collected; in this context, therefore, the role in the equation of age, sex and body weight provides an estimate of urine creatinine taking into account the expected differences in muscle mass (i.e. creatinine generation) due to age (progressive decrease with aging), gender (15% lower in women) and weight (used as a simple index of muscle mass).

In addition, the data obtained from the IRMA-2 study showed that the 2-year survival rate was lower in patients with CKD stage G3 or higher (MDRD <60 ml/min/1.73 m2), likely related to cardiovascular complications following non-dose adjustment of chemotherapy drugs.

There is also a lack of data on the correct frequency using the CKD-EPI formula [64], now recognized as the reference formula for estimating eGFR in the general population, or even the Wright formula [65] which seems to provide the best estimate in cancer patients.

The rapid evolution of treatments and the diagnostic anticipation have drastically changed the risk and prognostic factors of kidney disease in cancer patients. Therefore, studies aimed at investigating the risk and prognosis of CKD in this population are desirable.

The Research study Of Cancer associated Kidney disease (ROCK study) is an observational and retrospective study that was conducted to assess data on the prevalence and incidence of CKD in Italian cancer patients. Secondary objective is to compare the prevalence of CKD at cancer diagnosis for the main cancer sites.

ROCK study enrolled a total of 4,254 patients with a cancer diagnosis included in the Cancer Registry of the province of Reggio Emilia, Italy, from January, 1st to December, 31st 2016.

In table 11 are listed the types of cancer included in the study, their clinical characteristics and therapeutics approaches.

Table 11. Epidemiology, risk factors, diagnosis, symptoms, treatment and nephrotoxicity of cancer therapies of the types of cancer included in the study

Type of cancer	Epidemiology	Risk factors	Diagnosis	Symptoms	Treatment	Chemotherapy/Immunotherapy	Nephrotoxicity of cancer therapy
Breast	29% of all cancer that affect women; higher rate in economically advanced countries	Fat intake, body weight, later age at first pregnancy (> 30 years), menarche before age 12, menopause after age 50, familiarity	Abnormal mammogram or breast ultrasound; histologic evaluation	Breast (hard, immovable, single dominant lesion with irregular borders) or axillary mass with or without skin changes (erythema, thickening, or dimpling of the overlying skin; if metastatic breast cancer, they depend on the organs involved (common sites are bone, liver, and lungs).	Surgery, radiation therapy and chemotherapy	Capecitabine, doxorubicin, gemcitabine, taxanes and vinorelbine. Anti-HER2 drugs (e.g., trastuzumab/pertuzumab) for HER2-overexpressing tumors. Tyrosine kinase inhibitors (e.g., lapatinib, neratinib) for HER2 + tumors. Olaparib and talazoparib for advanced breast cancer associated with alterations in BRCA genes.	Gemcitabine: HUS and rare cases of TMA. Doxorubicin: free radical formation and iron-dependent oxidative damage of biological macromolecules; increased glomerular capillary permeability and tubular atrophy (in rats). Trastuzumab: electrolyte disorders
Colorectal	Second largest malignant cancer (after breast in women and lungs and prostate in men)	High animal fats and protein intake, low fiber diet, obesity and sedentary lifestyle; age, smoking, chronic inflammatory bowel diseases	Colonoscopy with biopsies, CT of the abdomen and chest with contrast medium; high levels of CEA in 70% of patients (neither sensitive nor specific)	Variable (site of cancer, extension, presence or absence of obstructions or bleeding); fatigue, anemia, weight loss, persistent constipation alternating with diarrhea	Surgical resection, sometimes in combination with chemotherapy, radiation therapy, or both	Fluoropyrimidines (intravenous 5-fluorouracil, oral capecitabine), oxaliplatin and irinotecan; bevacizumab and aflibercept (anti-VEGF); cetuximab, panitumumab and regorafenib (anti-EGFR)	Oxaliplatin: intravascular hemolysis and hemolytic anemia. Bevacizumab: mild or moderate proteinuria (mainly reversible)/nephritic syndrome (rare cases), AKI, interstitial nephritis and thrombotic microangiopathy. Cetuximab/Panitumumab: hypomagnesemia
Lung	First cause of death from cancer in men and the second in women	Cigarette smoking chemical carcinogens such as asbestos, radon and heavy metals	Chest *x*-rays; CT or PET; microscopic examination of the lung tissue (obtained by bronchoscopy) sputum or malignant pleural effusion cytology	Continuous cough, hoarseness, hemoptysis, shortness of breath, chest pain, weight loss, respiratory infections (bronchitis or pneumonia); bone pain and jaundice, neurological symptoms such as headache or dizziness, and visible nodules on the skin (when metastasis); paraneoplastic symptoms: hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion	Non-small cell lung cancer: surgery; radiotherapy (localized/advanced tumors not suitable for surgery); chemotherapy; Small cell lung cancer: chemotherapy (cisplatin/carboplatin), etoposide, doxorubicin, cyclophosphamide and topotecan; immune checkpoint inhibitors	Cisplatin or carboplatin in combination with gemcitabine, etoposide, pemetrexed, docetaxel, paclitaxel or vinorelbine; gefitinib, erlotinib, afatinib and osimeritinib (if mutation of EGFR genes); immune checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab, durvalumab)	Cisplatin: non-oliguric AKI, glycosuria, aminoaciduria, magnesium depletion, TMA. Pemetrexed: acute tubular necrosis, interstitial edema, tubular acidosis and diabetes insipidus; AKI and proteinuria. Tyrosine kinase inhibitors (e. g. gefitinib): kidney injury (possible allergic events), minimal change disease with nephrotic syndrome (one case). Immune checkpoint inhibitors (ICPIs): ATIN (granulomatous) and immune complex glomerulonephritis, TMA, minimal change disease, immune complex glomerulonephritis, and drug-induced lupus (unusual). Cyclophosphamide: hyponatremia

Type of cancer	Epidemiology	Risk factors	Diagnosis	Symptoms	Treatment	Chemotherapy/Immunotherapy	Nephrotoxicity of cancer therapy
Pancreas	4% of all newly diagnosed cancer in males and females (2017)	Type 2 diabetes mellitus, von Hippel-Lindau syndrome, occupational exposure (industrial and agricultural solvents and derivates of processing oil), obesity, cigarette smoking	CT or a special type of MRI, endoscopic ultrasound and endoscopic retrograde cholangiopancreatography.	Vague, no particular signs (pain in the upper abdomen/centrally in the back, weight loss, jaundice	Surgery: duodenocephalopancreasectomy (20% of cases); chemotherapy and radiotherapy	Erlotinib (tyrosine kinase inhibitors)	Hypomagnesemia (rare)
Gastric	Second most common cancer (especially East Asia and Eastern Europe), twice as common in males than females	Diet rich in starches, fats and foods preserved in oil, salted or smoked (which contain nitrites and nitrates, precursors of carcinogens such as nitrosamines) consumption of alcohol; Helicobacter pylori infection; cigarette smoking	Gastroscopy and subsequently of CT of the abdomen and chest with contrast medium endoscopic ultrasound and 18F-FDG PET	Nonspecific (dyspepsia)/ pain, difficulty in digestion, feeling of fullness or swelling after a small meal, nausea or vomiting (including blood), presence of blood in the stool, significant weight loss.	Surgery: submucosal dissection (early gastric cancer), partial/total gastrectomy; chemotherapy	Fluorouracil, doxorubicin, mitomycin, cisplatin or leucovorin; trastuzumab; pembrolizumab	Mitomycin C: TTP and HUS; kidney injury, hypertension, non-cardiogenic pulmonary edema and, rarely, congestive heart failure and neurological changes
Prostate	20% of all cancers diagnosed in males	Age, familiarity, mutations in some genes such as BRCA1, BRCA2 or HPC1, high levels of hormones such as testosterone	Titration of serum levels of prostate specific antigen, rectal examination; histological confirmation (by transrectal ultrasound-guided needle biopsy), CT or MRI; bone scintigraphy	Hematuria and symptoms of bladder obstruction (when advanced disease)	Surgical/RT (cancer located within the prostate); hormonal therapy, RT or chemotherapy (extra prostatic cancer)	Gonadotropin-releasing hormone (LH-RH) agonists (e.g., leuprolide, goserelin, triptorelin, histreline and buserelin) and antagonist (e.g., degarelix); docetaxel	Not known

Type of cancer	Epidemiology	Risk factors	Diagnosis	Symptoms	Treatment	Chemotherapy/Immunotherapy	Nephrotoxicity of cancer therapy
Lymphomas	Hodgkin's lymphoma (HL): quite rare disease (10% of cases), one of the most frequent forms of cancer in population aged between 15 and 35 year; Non-Hodgkin's lymphomas (NHL): 4-5% of new cancer diagnoses in the western population, 5th most common cancer diagnosis in men and 6th in women (in Italy)	Hodgkin's lymphoma (HL): probably exposure to pesticides, toxic chemicals and ionizing radiation; Epstein-Barr virus infection; Non-Hodgkin's lymphomas (NHL): exposure to insecticides, benzene, ionizing radiation, chemotherapy used for previous cancers, immunosuppression, autoimmune disorders or chronic bacterial or viral infections	Hodgkin's lymphoma (HL):excisional lymph node biopsy and histological examination; chest X-ray and a contrast-enhanced CT scan of the neck, the chest and the abdomen; whole-body PET; Hodgkin's lymphomas (NHL): biopsy of an entire lymph node or a sample of the tumor mass; PET-CT	Hodgkin's lymphoma (HL): enlarged lymph nodes in the neck, armpits or groin, not motivated by infections, low-grade or persistent fever, profuse night sweats or irrepressible itching; Non-Hodgkin's lymphomas (NHL): swelling of the lymph nodes in the neck, armpits or groin in the absence of pain, fever, night sweat, weight loss and persistent itching	Hodgkin's lymphoma (HL): chemotherapy followed by RT; Non-Hodgkin's lymphomas (NHL): *indolent lymphomas*: monoclonal antibodies, allogenic transplant; *aggressive lymphomas:* chemotherapy and monoclonal antibodies	Hodgkin's lymphoma (HL): adriamycin, bleomycin, vinblastine and dacarbazine; Non-Hodgkin's lymphomas (NHL): *indolent lymphomas*: Rituximab; *aggressive lymphomas*: CHOP and R-CHOP	Hodgkin's lymphoma (HL): Vinblastine: TMA; SIADH; Non-Hodgkin's lymphomas (NHL): see above
Leukemias	Acute leukemias: over 25% of all cancer in children; chronic leukemias: typical of adulthood, rare in pediatric age	Exposure to massive doses of radiation, chemicals (benzene, formaldehyde) or previous RT and chemotherapy	Complete blood count, complete metabolic panel, liver function test, and coagulation panel; bone marrow biopsy, combined with radiography, ultrasound or CT	Nonspecific: fever, fatigue, weight loss, bone pain, bruising, or bleeding, hepatosplenomegaly, lymphadenopathy and musculoskeletal symptoms (especially in the spine and long bones)	Chemotherapy; radiation therapy, monoclonal antibodies and stem cell transplantation	Imatinib; chimeric antigen receptor (CAR) T-cells therapy	Imatinib: AKI, acute tubular necrosis and vacuolation of tubular cells, Fanconi syndrome with phosphate depletion and hypophosphatemia; case of TMA and end-stage kidney disease (ESKD) have also been described; (CAR) T-cells therapy: Cytokine release syndrome (CRS), prerenal AKI, ischemic acute tubular injury (ATI), tumor lysis syndrome (TLS)

5.3 Methods

5.3.1 Study design and population

This is a single-center, observational, retrospective study. Patients data were gathered from the Reggio Emilia Cancer Registry which includes all cases of cancer diagnosed in the province of Reggio Emilia, Italy, since January, 1st 1996.

The aim of the study was to evaluate the prevalence of CKD at cancer diagnosis and the incidence of CKD during the first 24 months since cancer diagnosis and any differences between kind of cancers. CKD is defined by the presence of kidney function and/or structure's abnormalities, highlighted for more than 3 months, with implications for health (Kidney Disease: Improving Global Outcomes, KDIGO, 2012) [61]. It is classified on the basis of the cause, the eGFR value and the presence of albuminuria.

Serum creatinine (SCr) data were gathered from AUSL (local health authority) laboratory information system for the period 2014-2018.

It is a database containing laboratory results of all tests carried out in the provincial public health network, coded using internal classification. The estimation of kidney function was made with the CKD-EPI formula [64], recognized as the reference formula for estimating eGFR in the general population, and the Wright formula [65], which seems to provide the best estimate in cancer patient. For the full definition, see APPENDIX 1.

The diagnosis of CKD was confirmed by GFR (eGFR < 60 mL/min/1.73 m^2) measured in the same period (2014-2018).

Kidney function, obtained from the use of the two formulas mentioned above, was classified according to the criteria defined by the 2012 KDIGO Guidelines [57].

Inclusion criteria were:

- Patients with a cancer diagnosis occurring from January, 1st to December, 31st 2016 residents in the province of Reggio Emilia, Italy, at the time of diagnosis;
- Patients included in the Cancer Register among the incident cases in 2016;
- Age > 18 years.

Exclusion criteria were:

- Age < 18 years;
- Patients suffering from chronic myeloproliferative diseases, myelodysplastic syndromes and non-melanomatous skin cancer (according to the international rules of cancer registries).

We included 4,254 patients with a cancer diagnosis occurring from January, 1st to December, 31st 2016, residents in the province of Reggio Emilia at the time of diagnosis. The follow-up ended on December 31st, 2018 or by emigration or death.

Data included in the study were obtained from several sources:

- Cancer Registry

The Reggio Emilia Cancer Registry includes all cases of malignant cancers diagnosed in the province of Reggio Emilia since January, 1st 1996. The Reggio Emilia Cancer Registry is accredited by AIRTUM (Associazione Italiana Registro Tumori) and IACR (International Association of Cancer Registries). It regularly submits data, passing all quality and completeness checks, to the AIRTUM and IARC database (International Agency for Research on Cancer).

The tumor site is coded on the basis of the ICDO3M, International Classification of Disease for Oncology, third revision.

- Laboratory results database

  Provincial Biochemical Laboratory Database: includes laboratory tests carried out in the provincial public health network, coded with internal classification. From this archive, kidney function tests (serum creatinine, eGFR) performed from 2013 to 2018 were selected.

- Mortality Registry

  It contains all the deaths of resident patients in the province of Reggio Emilia by year of death. The cause of death is codified according to the International Classification of Disease, tenth revision, ICD10.

- Residents Population Registry

  At the end of the follow-up, a check was carried out to verify any cancellations due to migration of the patients included in the cohort. For this purpose, a link was made with the residents' archive used by the Cancer Registry.

- Diabetes Registry

  A link was made to assess the presence of diabetes mellitus at the diagnosis of cancer and any cases of diabetes developed during the follow up.

Different time intervals were considered:

- “pre-diagnosis” period (at least 3 months before cancer diagnosis);
- "around the diagnosis" (period from 3 months before to 2 weeks after cancer diagnosis);

- "2 weeks to 3 months after" cancer diagnosis;
- "3 to 12 months after" cancer diagnosis;
- "12 to 24 months after" cancer diagnosis.

For all of each patients' eGFR values, we kept the minimum eGFR value in each of these intervals. An eGFR ≥ 60 mL/min1.73m^2 was therefore considered indicative of a condition of normal kidney function, while a diagnosis of kidney impairment was made by two determination of eGFR < 60 mL/min1.73m^2 at least 3 months apart.

Data of kidney function was limited to the eGFR criterion only, as data relating to the other markers of kidney injury, such as proteinuria or microalbuminuria, are not usually included among the routine tests.

Data about kidney function were not available for some patients and it was not possible a certain classification of the presence of CKD so they were excluded from the study.

5.3.2 Endpoints

The following endpoints were evaluated:

- Prevalence of CKD at cancer diagnosis: 2 eGFR values < 60 mL/min/1.73m^2, the first in the pre-diagnosis period and the second around cancer diagnosis;
- Incidence of CKD during the first 24 months after cancer diagnosis: an eGFR values > 60 mL/min/1.73m^2 around cancer diagnosis period and 2 eGFR values < 60 mL/min/1.73m^2 at least 3 months later and in any period after cancer diagnosis;
- Total prevalence of CKD: 2 eGFR values < 60 mL/min/1.73m^2, of which an eGFR value < 60 mL/min/1.73m^2 around the cancer diagnosis;

- Proportional distribution of CKD cases by stage based on eGFR values (stage G3 to G5 according to KDIGO guidelines).
- Total prevalence of CKD at cancer diagnosis for the main cancer sites: breast, colorectal, lung, pancreas, gastric, prostate, lymphomas and leukemias.
- Rate of progression of CKD: reduction of eGFR/year for each patient affected by CKD.

5.3.3 Variable of interest

For all patients included in the study, data on sex, age, ethnicity, serum creatinine and related eGFR, type and number of tumors, diagnosis of diabetes mellitus were collected.

Diagnosis of diabetes mellitus was ascertained through linkage with the local Diabetes Registry [66]. We obtained information on death from Mortality Registry, that contains all the deaths of residents in the province of Reggio Emilia by year of death. The cause of death is codified according to the International Classification of Disease, tenth revision, ICD10. Furthermore, we got information on emigration and ethnicity from Resident Population Registry of the local health authority.

Patients were considered enrolled in the cohort at the time of cancer diagnosis (which was identified with the date of incidence reported in the Cancer Registry, generally coinciding with the date of the histological report).

A link was also made with the Diabetes Registry and with the Laboratory Database to define the conditions at the baseline.

The classification was carried out on serum creatinine values closest to the date of the cancer diagnosis in an interval of 3 months before to 2 weeks after diagnosis. This interval made possible to include almost all the clinical investigations to which the patient underwent during the phase of diagnosis and classification of the pathology, which generally precedes the histological report by some time, but not to include examinations made during chemotherapy treatment. Tests relating to

kidney function around the cancer diagnosis were found in the vast majority of patients; nevertheless, for some patients it was not possible a certain classification of the presence of CKD.

5.3.4 Statistical methods

Outcomes were presented as absolute and relative frequencies. Continuous variables were reported as mean and standard deviation, and categorical variables as proportions. The association between qualitative clinical and demographic variables and outcomes was evaluated through Pearson's chi-squared test or Fisher's exact test. The statistical significance of differences in estimated average eGFR between the cancer sites were assessed using the analysis-of-variance (one-way ANOVA); while the statistical significance of differences in estimated average eGFR between the first and the last time intervals were assessed using the Student's t-test and Mann-Whitney test. P values are reported as continuous measures and no preset significance threshold was used. We used Stata 13.0 SE (Stata Corporation, Texas, TX) software package for the main analysis.

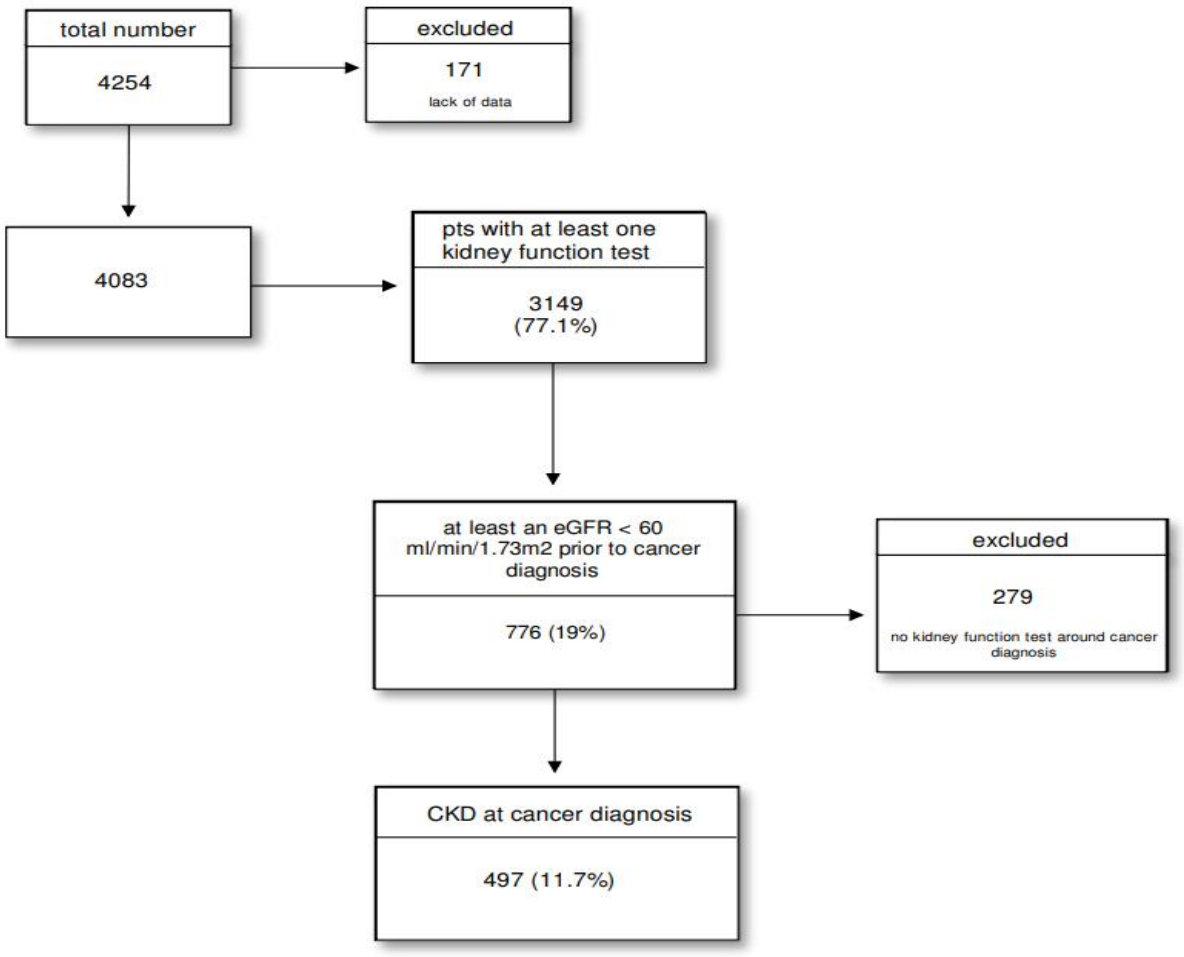
5.4 Results

In an initial phase of data analysis, CKD-EPI formula was used to calculate the eGFR.

4,254 patients with cancer diagnosis were identified between January, 1st and December, 31st 2016; of these, 171 patients were excluded due to lack of data. Of the remaining 4,083 patients, 3,149 (77.1%) had at least one kidney function test prior to cancer diagnosis.

In this patient group, 776 patients (19%) had at least an eGFR value <60 mL/min/1.73m^2 prior to cancer diagnosis; 279 patients were excluded from primary analysis because no data on kidney function around the time of diagnosis were found. Therefore, the remaining 497 patients (11.7%) were identified as affected by CKD at the time of cancer diagnosis (see Figure 3).

Figure 3. Flowchart displaying the chart evaluation process for all cancer patients included in the Cancer Registry of Reggio Emilia



For both cohorts of patients (pre-existing CKD and CKD diagnosed at the time of cancer diagnosis), descriptive analyzes were conducted on demographic and clinical data; in addition, the evaluation of the eGFR was carried out both with the CKD-EPI formula and Wright formula.

Referring to the CKD-EPI formula, in patients with pre-existing CKD (497 patients, 11.7%), the mean age was 81 years (SD ± 8.4), 297 (53.7%) were male, 91 patients (18.3%) had a known diagnosis of type 2 diabetes mellitus, 18 (3.6%) of these patients had 2 or more cancer diagnosis. 220 (44.3%) were alive at December 31st, 2018, end date of the analyzes.

Using Wright formula, 504 patients (11.8%) with CKD already present at the time of cancer diagnosis were identified; these patients had an average age of 82 years (SD ± 8.4) and 279 (55.4%) were male; 94 (18.7%) had type 2 diabetes mellitus and 19 (3.8%) had 2 or more cancer diagnosis.

We also calculated the number of patients who developed CKD in the following 24 months after cancer diagnosis.

Even for this population, data on age, sex, presence of diabetes mellitus and simultaneous presence of 2 or more cancer diagnosis were evaluated.

Using CKD-EPI formula, in the cohort of 4.083 patients, we identified 186 patients who developed CKD in the following 24 months after cancer diagnosis; the incidence of CKD in this period was 4.6% [95% CI 3.9-5.3].

These patients had an average age of 77 years (SD ± 10.7), 115 (61.8%) were male, 15 (8.1%) were diabetic, and 5 (2.6%) patients had 2 or more cancer diagnosis. 75 patients were alive at the end of the follow-up (40.3%).

Using Wright formula, we identified 140 (3.4%) [95% CI 2.9-4.0] new cases of CKD in the following 24 months after cancer diagnosis, with an average age of 79 years (SD ± 9.6), 93 (66.4%) were male, 14 (10%) were diabetic and 4 (2.9%) had 2 or more cancer diagnosis. At the end of the follow-up, 61 patients were alive (43.6%) (see Table 12).

Table 12. Baseline characteristics of cancer patients using CKD-EPI and Wright formula for the estimation of eGFR

Variables	**All patients**	**CKD-EPI formula**		**Wright formula**	
		Pre-existing CKD	*New cases of CKD*	*Pre-existing CKD*	*New cases of CKD*
N. of patients	4254	497	186	504	140
%		11.7	4.4	11.8	3.3
Age,y (SD)	68 (14.7)	81 (8.4)	77 (10.7)	82 (8.4)	79 (9.6)
Sex (M)	2197 (51.6)	267 (53.7)	115 (61.8)	279 (55.4)	93 (66.4)
Alive (at 12/31/2018)	3027 (71.2)	220 (44.3)	75 (40.3)	221 (43.9)	61 (43.6)
Type 2 Diabetes mellitus (%)	470 (11.1)	91 (18.3)	15 (8.1)	94 (18.7)	14 (10)
2 or more cancer diagnosis (%)	103 (2.4)	18 (3.6)	5 (2.6)	19 (3.8)	4 (2.9)

For the main cancer sites considered (breast, colorectal, lung, pancreas, gastric, prostate, lymphomas and leukemias), we highlighted the following data:

- Breast cancer patients (480, 11.3%) were women in 98.8% of cases, had an average age of 63 years (SD, ± 15.2) and 19 (4%) had a CKD; calculating the eGFR in the different time intervals considered, we observed that breast cancer patients had an average eGFR of 42.5 mL/min/1.73m^2 (SD, ± 14.7) at the moment of cancer diagnosis that decreased to 37.1 ml/min/1.73m^2 (SD, ± 11.4) in the period “12 to 24 months after” cancer diagnosis.

- Patients with colorectal cancer (346, 8.1%) had an average age of 72 years (SD, ± 13.2); 181 (52.3%) were male; 75 (21.7%) had CKD; in this group of patients the mean eGFR decreased from 40.5 mL/min/1.73m^2 (SD, ± 11.8) at cancer diagnosis period to 36.4 mL/min1.73m^2 (SD, ± 13.9) in the period "12 to 24 months after" cancer diagnosis.

- 333 (7.8%) patients with lung cancer were identified, with an average age of 73 years (SD, ± 11.3) and 227 (68.2%) were male; a diagnosis of CKD was made in 72 (21.6%) of these patients. In this group, eGFR at cancer diagnosis period and "12 to 24 months after" cancer

diagnosis decreased from 38.5 mL/min/1.73m^2 (SD, ± 13.7) to 29.6 mL/min/1.73m^2 (SD, ± 17.1).

- Regarding pancreas cancer, 150 patients (3.5%) were identified, with an average age of 74 years (SD, ± 12.3); 67 were male (44.7%); in this group of patients, 34 (22.7%) had a CKD diagnosis; moreover, patients had a significant reduction of the mean eGFR values between the time intervals considered: in particular, the mean eGFR decreased from 42.3 mL/min/1.73m^2 (SD, ± 11.1) at cancer diagnosis period to 32 ml/min/1.73m^2 (SD, ± 5.4) in the period "12 to 24 months after" cancer diagnosis.

- Patients with gastric cancer (131, 3.1%), had an average age of 73 years (SD, ± 12.4), 79 (60.3%) were male; 27 patients (20.6%) had a CKD diagnosis; in these patients we observed an eGFR values of 41.7 mL/min/1.73m^2 (SD, ± 11.4) at the moment of cancer diagnosis, which remained unchanged until the end of the follow-up (40 mL/min/1.73m^2; SD, ± 15.9).

- Patients with prostate cancer (292, 6.9%), had a mean age of 71 years (SD ± 8.4), 33 patients (11.3%) had CKD diagnosis with an eGFR at cancer diagnosis period of 40.4 mL/min/1.73m^2 (SD, ± 17.4) and 35.9 mL/min/1.73m^2 (SD, ± 15.2) in the period "12 to 24 months after" cancer diagnosis.

- Patients affected by lymphomas (149, 3.5%), had an average age of 66 years (SD, ± 16.8), 77 (51.7%) were male; 29 patients (19.5%) had CKD with an eGFR reduction from 45.8 mL/min/1.73m^2 (SD, ± 10.7) at the moment of cancer diagnosis to 40.8 mL/min/1.73m^2 (SD, ± 14.8) in the period "12 to 24 months after" cancer diagnosis.

- 65 patients (1.5%) had a leukemia diagnosis with an average age of 70 years (SD, ± 17.3), 34 were male (52.3%) and 22 (33.9 %) had a CKD diagnosis. In these patients the eGFR at the moment of cancer diagnosis was 34.8 mL/min/1.73m^2 (SD, ± 15.1) and 41.3 mL/min/1.73m^2 (SD, ± 16.2) in the period "12 to 24 months after" cancer diagnosis.

Furthermore, for each cancer site, we evaluated the rate of progression of CKD calculating the reduction of eGFR/year in mL/min/year for each patient affected by CKD.

Among cancer sites evaluated, patients with lung cancer were those with the greatest reduction of eGFR in the first year since cancer diagnosis, whereas during the second year of follow-up the greatest reduction in eGFR was seen in patients with pancreas cancer.

At cancer diagnosis and during the subsequent observation period, ANOVA was used to evaluate the difference between the mean eGFR at cancer diagnosis in the main cancer sites.

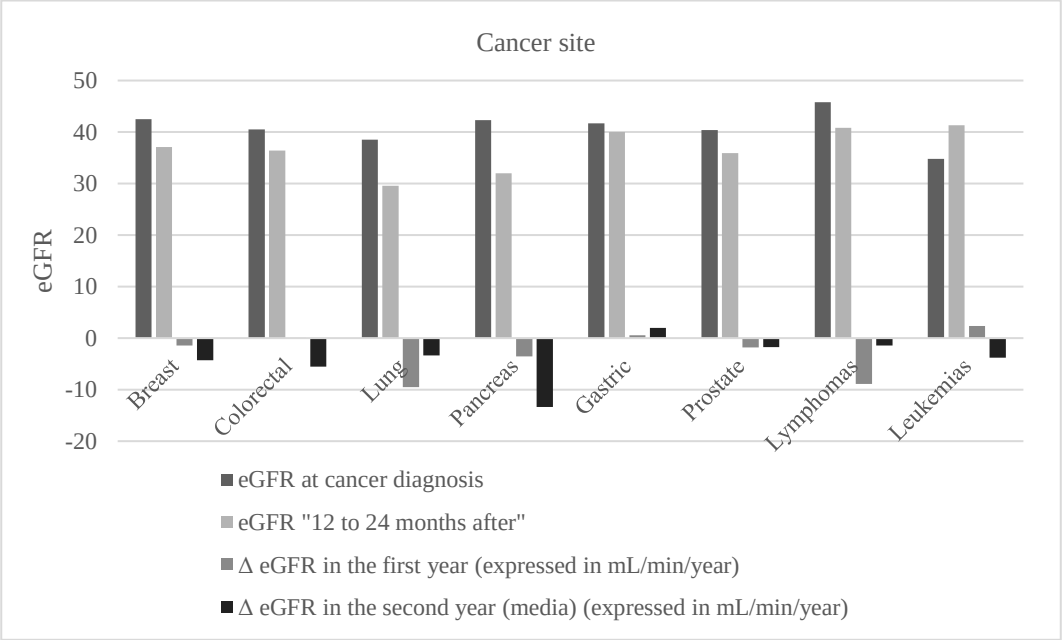
At the time of cancer diagnosis and during the follow-up period, no significant difference was found in the mean eGFR of the 8 cancer sites included in our analysis (one-way ANOVA, $p > 0.05$) (Table 13 and Figure 4).

Table 13. eGFR values in two different periods (at cancer diagnosis and "12 to 24 months after cancer diagnosis")

Site of cancer	All cancer	Breast	Colorectal	Lung	Pancreas	Gastric	Prostate	Lymphomas	Leukemias	*p**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
	4254	480 (11.3)	346 (8.1)	333 (7.8)	150 (3.5)	131 (3.1)	292 (6.9)	149 (3.5)	65 (1.5)	
eGFR at cancer diagnosis (SD)	40.6 (13.4)	42.5 (14.7)	40.5 (11.8)	38.5 (13.7)	42.3 (11.1)	41.7 (11.4)	40.4 (17.4)	45.8 (10.7)	34.8 (15.1)	*0.118*
eGFR "12 to 24 months after" (SD)	36.5 (14.0)	37.1 (11.4)	36.4 (13.9)	29.6 (17.1)	32.0 (5.4)	40.0 (15.9)	35.9 (15.2)	40.8 (14.8)	41.3 (16.2)	*0.511*
Δ eGFR in the first year (expressed in ml/min/year)		-1.46	0.04	-9.48	-3.56	0.57	-1.80	-8.86	2.36	
Δ eGFR in the second year (expressed in ml/min/year)		-4.27	-5.56	-3.38	-13.35	2	-1.76	-1.42	-3.8	

* p-value one-way analysis-of-variance (ANOVA)

Figure 4. Progression rate of CKD based on eGFR reduction in cancer site evaluated



For every cancer site evaluated, we calculated the different CKD's stage distribution.

In particular at cancer diagnosis, in patients with breast cancer (19), 11 (57.8%) had a G3a stage, 3 (15.7%) had a G3b stage, 4 (21%) had a G4 stage and only one patient (5.3%) had a G5 stage.

For colorectal cancer (75), in the same period, 29 (38.7%) had a G3a stage, 34 (45%) had a G3b stage, 10 (13%) had a G4 stage and 2 patients (3%) had a G5 stage.

The same data were collected for lung cancer (72): 30 (41.6%) had a G3a stage, 24 (33%) had a G3b stage, 15 (20.8%) had a G4 stage and 3 (4.2%) had a G5 stage.

For pancreas cancer patients (34), 18 patients (53%) had a G3a stage, 11 (32%) had a G3b stage, 4 (11.7%) had a G4 stage, only one patient (3%) had a G5 stage.

In patients with gastric cancer and CKD (27), the vast majority had a G3a stage (13, 48%), 11 (40.7%) had a G3b stage, 3 (11%) had a G4 stage, no patients had a G5 stage.

Even in prostate cancer, more than half of the patients (19, 57.6%) had a G3a stage, 6 (18.2%) had a G3b stage, 3 (9.1%) had a G4 stage and 5 (15%) had a G5 stage.

Regarding lymphomas (29), 17 patients (58.6%) had a G3a stage, 10 (34.5%) had a G3b stage, 2 (6.8%) had a G4 stage, no patients had a G5 stage.

In patients with leukemias and CKD (22), 8 (36.4%) had G3a stage, 6 (27.3%) had a G3b stage, 7 (31.8%) had a G4 stage, one patient (4.5%) had a G5 stage.

We also calculated the different CKD's stage distribution for cancer sites (Figure 5, 6 and 7).

Figure 5. CKD's stage distribution at cancer diagnosis for every cancer site evaluated

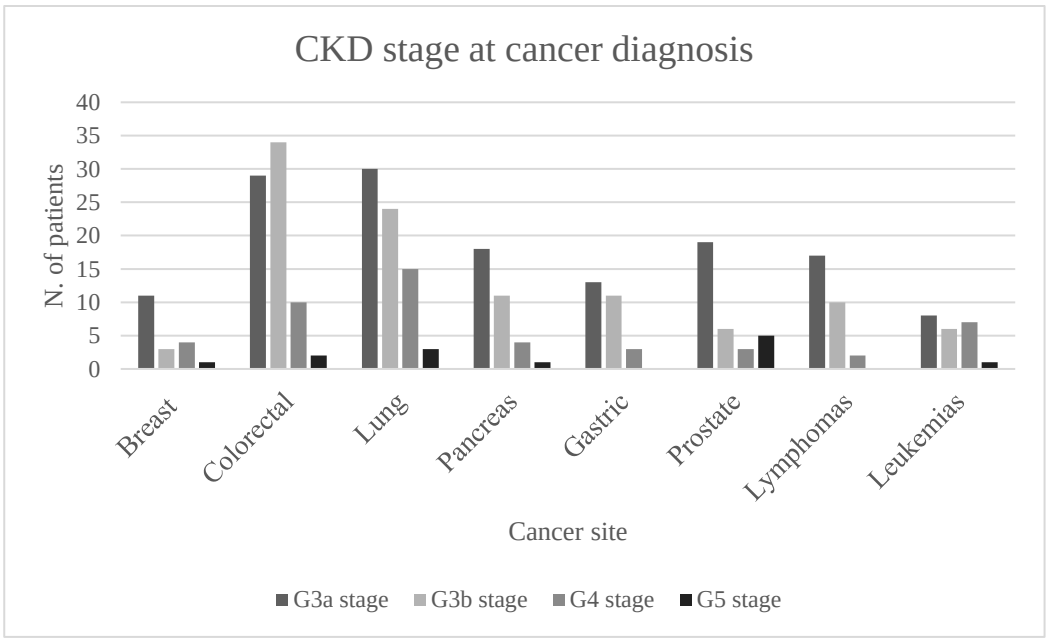


Figure 6. CKD's stage distribution for every cancer site evaluated and different time intervals considered

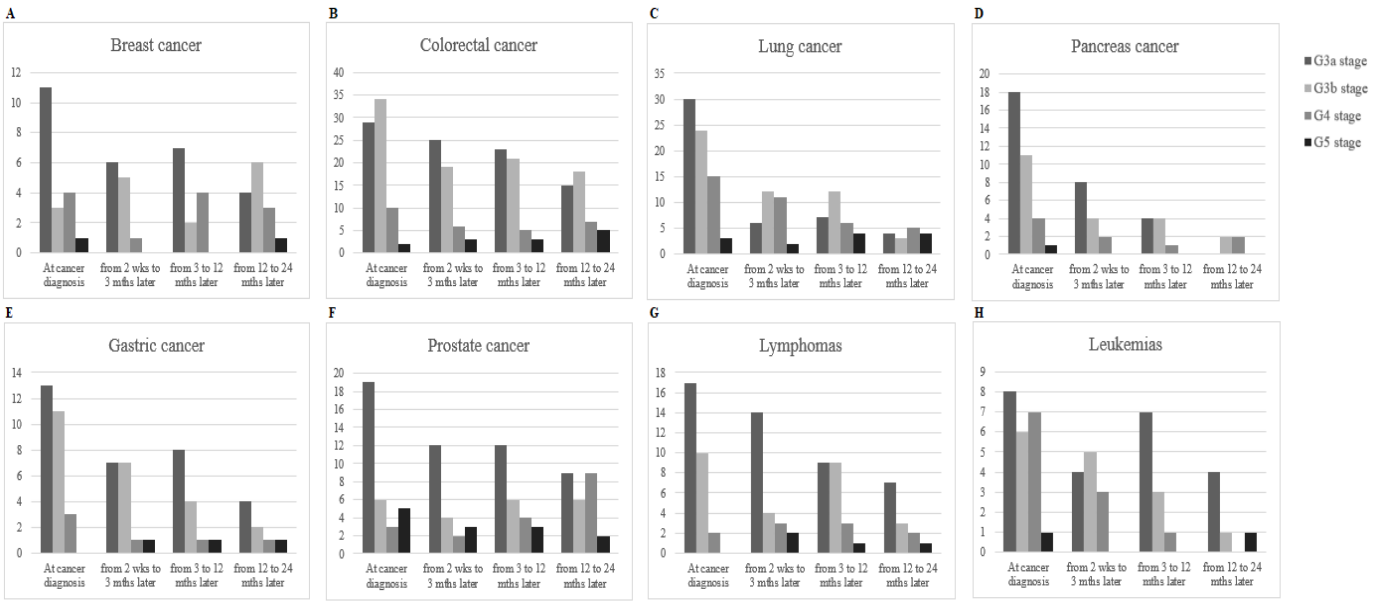
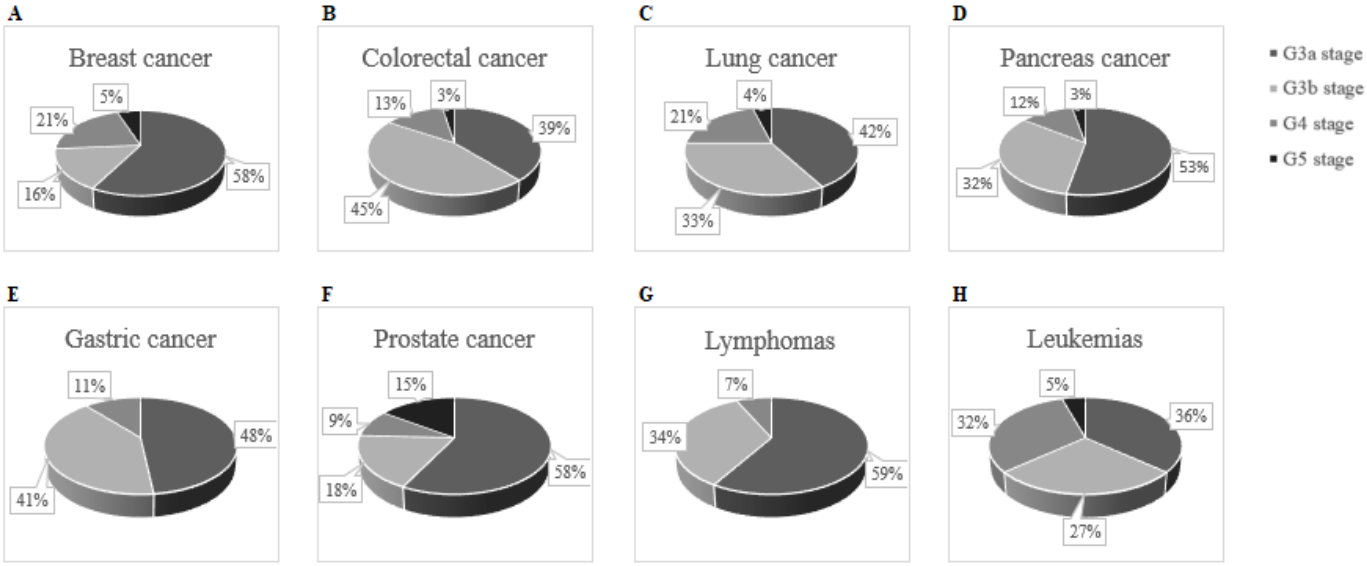


Figure 7. CKD's stage distribution for single cancer site evaluated



- *Breast cancer*

In our study, 19 out of 480 patients with breast cancer had CKD at cancer diagnosis. The vast majority had a CKD G3a stage (11, 58%), only one patient (5%) had a G5 stage already at the time of cancer diagnosis. Compared with other cancer site, the average eGFR value at cancer diagnosis period was slightly higher than other types of cancer (42.5 mL/min/1.73m^2, SD +/- 14.7); with an eGFR reduction in the second follow-up year ("12 to 24 months after" cancer diagnosis) of 4.27 mL/min/year (SD ±14.34).

It is important to highlight that they were younger than other cancer patients (mean age 63 years, SD ± 15.2).

The prevalence of CKD in breast cancer patients using MDRD formula was 50.8% in Launay-Vacher V. et al study [83] referring to all patients with an eGFR values less than 90 mL/min/1.73m^2. In our study, this percentage was significantly lower (4%) because we calculated CKD prevalence referring to breast cancer patients with an eGFR less than 60 mL/min/1.73m^2.

Our results were similar to previously published data: breast cancer showed a relatively lower prevalence of CKD (3.6%) as demonstrated by Sun Young Na et al. [67]. In the study cited, CKD was defined as an eGFR < 60 mL/min/1.73m^2, however it was estimated using MDRD formula.

Since the prevalence and incidence of CKD is significantly increasing in decades [84, 85, 86], this could probably explain why our population with breast cancer had a mild CKD at cancer diagnosis.

- *Colorectal cancer*

In our population, colorectal cancer patients with CKD were 75 (21.7%), the vast majority were male (52.3%); according to Literature data [101, 102], our cancer patients are elderly with an average age of 72 years (SD ±13.2). The mean eGFR at cancer diagnosis was 40.5 mL/min/1.73m^2 (SD ±11.8). Compared to Kozlowski et al. [103], our CKD prevalence was apparently higher (21.7% vs 15%). In the study cited, CKD was defined according to KDIGO guidelines and eGFR was estimated using CKD-EPI formula. In colorectal cancer patients, we observed an average eGFR reduction in follow-up period of 5.56 ml/min/year and more than half of the patients had a cumulative percentage of 61% of G3b, G4 and G5 stage, indicative of a moderate to severe kidney impairment. This condition could be related to both advanced age of the patients and the aggressiveness of neoplastic pathology.

- *Lung cancer*

In ROCK study, we identified 333 patients with lung cancer with an average age of 73 years (DS ± 11.3), the vast majority (68.2%) were male; 72 out of 333 (21.6%) patients had a CKD diagnosis.

In our population, lung cancer patients with CKD presented the higher percentage of G4 stage compared to other cancer sites; 3 patients (4%) had a G5 stage. Moreover, we demonstrated the most relevant eGFR reduction in the first year of follow-up (- 9.48 mL/min/year, SD ± 14.2).

The prevalence of CKD in our lung cancer patients was 21.6%, as demonstrated by Ming-Shian et al. study using CKD-EPI formula [104]. Interestingly, in this study, authors used both CKD-EPI and Cockcroft–Gault formula: using the first one, CKD prevalence was 21.7%, that increased to 38.3% when the second formula was used.

Our data differ from what published in the IRMA study in which CKD prevalence in lung cancer patients was 56%; however, in IRMA study prevalence of CKD was calculated on eGFR values < 90 ml/min/1.73m^2, as noted before.

In other study, the coexistence of lung cancer and CKD is reported at approximately 13% (using CKD-EPI formula) [67].

- *Pancreas cancer*

In our study, we identified 150 patients (3.5%) with pancreas cancer. Among this population, 34 (22.7%) had a coexisting CKD diagnosis with a significant eGFR reduction (13.25 mL/min/1.73m^2, SD ± 6.1) between cancer diagnosis period (42.3 mL/min/1.73m^2, SD ± 11.1) and "12 to 24 months after" cancer diagnosis period (32 mL/min/1.73m^2, SD ± 5.4). The vast majority (18, 53%) of pancreas cancer patients with CKD had a G3a stage, only one patient (3%) had a G5 stage.

CKD prevalence in pancreas cancer in ROCK study was relevant higher compared to what has been identified in Norman et al. study (0.15%) [105]. However, it must be emphasized that in the latter study renal impairment was defined as an increased serum creatinine above 3 mg/dL on laboratory tests within 24 hours prior to surgery: such definition cannot be used to evaluate the frequency of CKD.

To the best of our knowledge, no previous study has been conducted to evaluate the prevalence of CKD in pancreas cancer patients.

- *Gastric cancer*

In ROCK study, CKD prevalence in gastric cancer patients (131) was 20.6% (27 patients) that is higher than what calculated in another study (26 of 2021, 1,28%) [106]. However, it should be noted that patients included in the study cited were classified as affected by end-stage kidney disease (ESKD) but the study didn't provide any classification on CKD stages; our patients were older than the study cited (mean age 73 years, SD ± 12.4 vs 67.9 years, SD ± 9.4). 48% patients had G3a stage, 41% had a G3b stage, no patients had G5 stage of CKD. To the best of our knowledge, there is no data in literature on the prevalence of CKD in patients with gastric cancer.

- *Prostate cancer*

ROCK study identified 33 CKD cases out of 292 patients affected by prostate cancer; CKD prevalence was 11.3%, which is similar to what is described in the study by Sung Han Kim et al. [107]; however, the study didn't provide any classification of CKD stages because all patients were classified as affected by ESKD.

Other study had shown a wide difference in CKD prevalence: from 1.29% (1.766 patients with CKD out of 136.790 US males, aged ≥ 20 years with prostate cancer undergoing prostatectomy; not included 273 patients with ESKD requiring dialysis) [108] to 50.1% (4.374 patients out of 8.612 males receiving radical prostatectomy for prostate cancer) in Schmid et al. study [109]. In the first study cited, mean age of CKD patients was 64.5 ± 0.18 years, so they were younger than our population (average age of 71 years, SD ± 8.4); this could probably explain the higher CKD prevalence in ROCK study as well as the highest G5 stage CKD prevalence (5 patients, 15%) compared to other cancer sites. However, the study didn't provide any CKD classification. In the latter study 12.6, 0.7 and 0.9% were respectively classified into CKD G3-4 and 5 stages.

- *Lymphomas*

We identified 29 patients out of 149 (19.5%) affected by lymphoma and CKD. In Literature, CKD prevalence varies from 34.5% in Ubukata M. et al study [110] to 13%, as evidenced in the study of Ghassan Al-Shbool et al [111].

In the first study cited, the mean age of the study population with CKD was 65.2±15.1 years and 65.2% were male. They calculated the different CKD stage classification: among patients with eGFR < 60 mL/min/1.73m^2, 75 (17.8%) had a G3a stage, 31 (7.2%) had a G3b stage, 5 (1.2%) had a G4 stage and 3 patients (0.6%) had a G5 stage. The mean eGFR value in CKD patients were 55 mL/min/1.73m^2 (SD ± 21.2).

In the latter study [111], CKD was defined as GFR <60 mL/min/1.73m^2 and eGFR was calculated using the CKD-EPI formula; it was not possible to obtain further information on CKD stages classification. Patients were younger than our study (median age 55 y), similarly 54% were male.

In ROCK study, the population were aged 66 (SD ± 16.8 year) and were male in 51.7%; the vast majority had a G3a stage, no patients had a G5 stage CKD. The eGFR at “cancer diagnosis” period was higher than other cancer sites (45.8 mL/min/1.73m^2; SD ± 10.7), probably due to the younger age of patients.

- *Leukemias*

Our study identified 22 patients out of 65 (33.9%) with a diagnosis of CKD and leukemias. The mean age was 70 years (SD ± 17.3), were male in 52.3%. The vast majority (17, 59%) had a G3b stage, 10 (34%) had a G3b stage, 2 patients (7%) had a G4 stage, no patient had a G5 stage.

Referring to Sidelmann Christensen A. et al study [112], which calculated a CKD prevalence of 29% (27% G3 stage and 2% G4 stage), ROCK study highlighted a higher total prevalence (33.9%) and CKD stage distribution: a cumulative percentage of 63.7% had G3a and G3b stage, 31.8% had a G4 stage. In the study cited, the mean age of patients was 63.2 years, 45% were male; in our study, patients were older (mean age 70 years, SD ± 17.3), and 52.3% were male. Moreover, unlike our study, eGFR was calculated using MDRD formula, which is less accurate at eGFR > 60 mL/min/1.73 m^2 [113]. This could probably explain why our CKD prevalence is higher.

In our study, patients affected by leukemias and CKD had shown an eGFR improvement (from 34.8 mL/min/1.73m^2, SD ± 15.1 at cancer diagnosis to 41.3 mL/min/1.73m^2, SD ± 16.2 in "12 to 24 months after" cancer diagnosis period); it probably depends on a selection bias of the patients during follow-up period because very few survived, likely those in better clinical conditions.

In Sidelmann Christensen A. et al study [112], 51% of the patients had an improvement of kidney function during the study, despite a total of 20% of patients had a rapid loss of kidney function (annual decline in eGFR > 3 mL/min/1.73 m^2): patients with leukemias are known to have a high risk of cardiovascular disease, which might partly explain the high proportion of patients with a rapid loss of eGFR.

5.5 Discussion

Comparing data obtained from our study with those of the IRMA study, we can underline how the prevalence of CKD between the two studies are similar: among the whole patients included in IRMA study (4,684), 339 patients (7.2%) had a serum creatine value > 1.25 mg/dl (laboratory value considered as cut off for kidney impairment); however, the vast majority of these population had decreased eGFR: 57.4% and 52.9% of patients had abnormal eGFR values when calculated according to the Cockcroft-Gault and the MDRD formula, respectively. Moreover, this high prevalence of CKD was observed even in 3,903 patients with normal serum creatinine (< 1.25 mg/dl): even in these patients, using Cockcroft-Gault and the MDRD formula, 60.3% and 54.7% of patients had abnormal eGFR.

However, these percentages decreased to 12% when referred only to patients with CKD stage G3 or higher (eGFR <60 ml/min/1.73 m^2), which are similar to what highlighted in ROCK study (11.7% and 11.8% using CKD-EPI and Wright formula respectively). Moreover, our data are similar to what highlighted by Sun Young Na et al study (CKD prevalence 12.8%) [67].

However, it must be emphasized that our study differs from IRMA study for some important features. We referred to the last definition of CKD [62], using CKD-EPI and Wright formula [64, 65].

As already mentioned, Cockcroft-Gault formula has some limitations and the main is that assumes that the GFR increases with increasing of body weight. This is based on the assumption that as body weight increases, muscle mass increases and therefore the production of creatinine.

Thus, the formula, that is not adjusted for body surface as CKD-EPI and MDRD, tends to overestimate GFR in patients with a value < 60 mL/min as well as obese and edematous patients, in whom weight is not affected by muscle mass. Therefore, for a correct evaluation of creatine clearance with this formula, the lean mass should be calculated [68], but this is not normally performed.

Regarding MDRD formula, this equation was developed in a group of patients with CKD. The studies [69, 70, 71] concluded that the MDRD formula had a much better predictivity than Cockcroft-Gault, which should no longer be used.

In extensive meta-analysis, one of the limitations of MDRD formula is that it has shown to underestimate up to 15% [69] the eGFR in subject with normal kidney function. Moreover, it is not validated for elderly patients.

CKD-EPI formula is more accurate than MDRD, particularly in individuals with higher GFR such as those without kidney disease. This formula has been shown to be more precise, more accurate and with less bias in almost any eGFR, especially > 60 mL/min/1.73m^2 and it provides significantly higher GFR than those obtained with MDRD formula (especially in young people, women and white race). Using CKD-EPI formula it is possible to make more precise diagnosis of the degree of kidney failure.

It is known that CKD is a predictor of cardiovascular (CV) risk and it increases linearly with decreasing kidney function, especially in patients with eGFR < 60 mL/min/1.73m^2: patients with CKD and CVD have a higher mortality rate (58-71%) compared with patients with CVD and normal renal function (22-27.5%) [72].

Even in the IRMA-2 study [60], the patients with CKD stage G3 or higher at the time of inclusion had a lower survival rate than the patients with eGFR $\geq$60 mL/min/1.73 m^2.

A formula that calculates GFR is more accurate the more it is able to predict the CV risk associated with GFR. Compared with MDRD formula, the CKD-EPI formula provides more accurate GFR estimation and lower prevalence of CKD, and more accurate risk prediction for adverse outcomes [73]. Therefore, CKD-EPI formula, predicting the CV risk associated with kidney impairment better than MDRD, is more correct to classifying patients with CKD.

For these reasons we collected data on kidney function only for patients with an eGFR less than 60 mL/min/1.73m^2, those with the greatest clinical implications, especially for survival.

However, like MDRD, it must be emphasized that CKD-EPI formula shows some limitations, in particular populations. Similarly, the two formulas are not considered reliable in patients with liver cirrhosis or liver transplants [74].

Referring to CARHES study [75], which provided data on CKD prevalence in Italy on a national scale, the prevalence of CKD (eGFR < 60 mL/min/1.73m^2) in the general Italian population was 7.5% in men and 6.5% in women, with a higher prevalence of CKD G1 and G2 stage (approximately 60%), compared with CKD G3 to G5 stage (about 40%). This latter percentage appears significantly different from our data. However, in CARHES study was enrolled a "random" sample of general population stratified by decades of age and sex; in our study, we analyzed data obtained from cancer patients with known CKD diagnosis, with a higher average age and with at least one major risk for kidney disease such as diabetes mellitus.

Our study has a number of strengths.

In IRMA study, data collection on kidney function was made only on 1 of 2, specific, 15-day periods: in such a short time frame, it is not possible to exclude that some kidney function tests have been interpreted as indicative of CKD, being unable, on the contrary, to exclude cases of AKI.

In our study, data on kidney function were collected over a very long-time interval allowing a correct diagnosis of CKD cases. Notably, our study may give a more accurate measure of the CKD prevalence at cancer diagnosis as it is based on multiple eGFR measurements taken on separate dates.

Furthermore, in IRMA study were included prevalent cancer patients (who were being treated for solid cancer in an Oncology department); on the contrary, in ROCK study were enrolled only patients with a new cancer diagnosis (incident cases in 2016).

In our knowledge, an important strength is that this study is the first Italian population-based study to investigate the prevalence of CKD in cancer patients. It presents very few missing baseline data: using linked data from Cancer Registry, we accurately ascertained all cancer diagnoses.

Moreover, we evaluated the progression of CKD over time and the relationship with cancer because we obtained data of serum creatinine and eGFR not only at baseline, but even in three different follow-

up periods. Indeed, we ascertained longitudinal measures of eGFR based on the recommended CKD-EPI and with Wright formula.

However, we are aware of several limitations of our study. Apart from those investigated, no further cancer sites were evaluated due to the small number of patients, although significant kidney involvement cannot be excluded. Among cancer sites not evaluated, kidney and urinary tract cancers were excluded because those cancers are characterized by a high-risk of kidney function impairment both during the disease itself and to treatment (e.g., obstruction, reduction of nephron mass by nephrectomy). Moreover, multiple myeloma was excluded because it is known to result in CKD and reduced kidney function. Indeed, it is known that kidney failure occurs in approximately 50% of patients with multiple myeloma at some point during the course of their disease [76].

Furthermore, we did not obtained information for all known risk factors for cancer (e.g., tobacco, alcohol use, diet, physical activity), other comorbidities and their severity (e.g., cardiovascular disease, arterial hypertension, ischemic heart disease, concomitant hyponatremia), neither chemotherapy used. No data were also available for the use of non-steroidal-inflammatory drugs or potential nephrotoxic antibiotics.

Regrettably, no data were collected on urinary protein, which may be regarded as a study weakness. Indeed, albuminuria is associated with cancer incidence (as a paraneoplastic phenomenon and as a reflection of an inflammatory process) [77] and it is associated to mortality as well as CKD and organ damage [67, 78, 79, 80, 81].

Finally, since our study sample refers to cancer patients included in the Cancer Registry of the province of Reggio Emilia, results may not fully applicable to other populations and practice settings. Onco-nephrology is a new sub-specialized area in Nephrology and has emerged as a therapeutic perspective for cancer patients. Despite the improvement of survival rates of cancer patients due to conventional and new molecularly targeted therapies, nephrotoxic effects of these drugs have been reported.

Indeed, approximately 50% of all antineoplastic agents are cleared by the kidney. Any impairment in kidney function results in accumulation of potentially toxic metabolites and overdosage of the drug. These aspects can cause neurologic, hematologic, cardiologic, and hepatologic toxicities, besides kidney disease and electrolyte disorders.

Thus, recognition of the adverse consequences due to the use of anticancer drugs, in particular AKI and worsening of CKD, is clearly required.

Furthermore, using potentially nephrotoxic anticancer drugs require specific monitoring: evaluation of kidney function tests is crucial both before and during the treatment to highlight early nephrotoxicity. Impaired kidney function has critical consequences on anticancer drugs handling.

When available, specific prevention methods to help reduce the risk of nephrotoxicity (e.g., appropriate hydration, withdrawal of other potentially nephrotoxic drugs, avoid dehydration due to vomiting), could prevent further issues due to the anticancer therapy, especially in patients who already have abnormal kidney function.

Therefore, the identification of high-risk cancer patients is required to prevent or reduce the development and severity of nephrotoxicity. The presence of a pre-existing impaired kidney function affects the clinical management of cancer patients.

5.6 Conclusion

CKD is a major public health problem with an increasing prevalence in the general population; it also represents a risk factor in people with neoplastic diseases amplifying the risk of adverse events and worsening outcomes. It is now well known that CKD and cancer are connected in several ways: pre-existing CKD might impair the use of a new oncological agents; likewise, a drug could lead kidney failure or worsen pre-existing CKD.

The ROCK study is the first large cohort study that allows a clearer estimation of the frequency of CKD in Italian cancer patients. Our results indicate that, among patients with a newly diagnosed cancer, the prevalence of CKD is much higher than that reported in the general population. Cancer patients have also a clinically significant risk of new-onset CKD in the first 2 years since cancer diagnosis. Moreover, our data provide new and substantial information on the frequency of CKD at the diagnosis, the risk of new-onset kidney impairment, and the slope of eGFR for a number of different types of cancers.

Cancer patients present more and more frequently with multiple comorbidities, which must be taken into account in the overall management of their therapeutic path.

The knowledge of CKD prevalence in cancer patients is essential for proper clinical and therapeutic management and implementation of preventive strategies.

Our data will help in establishing clinical management strategies aimed at early diagnosis and proper therapy, hopefully preventing and/or delaying the progression of kidney disease toward ESKD.

5.7 Appendix

The estimation of kidney function will be carried out by calculating the eGFR using the MDRD [20] and CKD-EPI [21] formulas.

MDRD formula:

GFR (mL / min / 1.73 m2) = 175 × Scr −1.154 × age − 0.203 × 1.212 [if African-American race], × 0.742 [if female]

With Scr measured in mg/dl

CKD-EPI formula:

GFR = 141 × min (Scr / κ, 1) α × max (Scr / κ, 1) -1.209 × 0.993 Age × 1.018 [if female] 1.159 [if African-American race]

Scr indicates serum creatinine calculated in mg/dL, κ equals 0.7 for females and 0.9 for males, α equals -0.329 for females and -0.411 for males, min indicates the minimum of the Scr/κ ratio or 1, and max indicates the maximum of the ratio Scr/κ or 1.

Wright formula

GFR (mg/dL) = {[6550 – (38.8 × Age)] × [1 – (0.168 × Sex)] × BSA}/ (SCr*88.42)

SCr is measured in mg/dl. Age is measured in years and Sex = 0 (male) or 1 (female). BSA is not available for this study, so we use the approximation 1.73 m^2.

CKD is defined as the presence of abnormal kidney structure or function present for > 3 months, with implications for health. It is classified on the basis of the cause, the eGFR value and the presence of albuminuria.

GFR values in CKD

GFR values	**GFR (mL/min/1.73m^2)**	**Description**
G1	≥ 90	normal or elevated
G2	60- 89	slightly reduced
G3a	45- 59	slightly to moderately reduced
G3b	30- 44	moderately to severely reduced
G4	15- 29	severely reduced
G5	< 15	end-stage kidney disease

Albuminuria values in CKD

Class	**AER (mg/24 ore)**	**ACR (mg/g)**	**Description**
A1	< 30	< 30	normal or slightly increased
A2	30- 300	30- 300	moderately increased
A3	> 300	> 300	severely increased *

Abbreviations: AER, albumin excretion rate; ACR, albuminuria / creatininuria ratio
* including nephrotic syndrome (albumin excretion> 2200 mg / 24 hours [ACR> 2200 mg / g])

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