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ORIGINAL ARTICLE

Radiation dose from medical imaging in end stage renal disease patients: a Nationwide Italian Survey

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Abstract

Background and objectives End stage renal disease (ESRD) patients are exposed to the risk of ionizing radiation during repeated imaging studies. The variability in diagnostic imaging policies and the accompanying radiation doses across various renal units is still unknown. We studied this variability at the centre level and quantified the associated radiation doses at the patient level.

Methods Fourteen Italian nephrology departments enrolled 739 patients on haemodialysis and 486 kidney transplant patients. The details of the radiological procedures performed over one year were recorded. The effective doses and organ doses of radiation were estimated for each patient using standardized methods to convert exposure parameters into effective and organ doses

Results Computed tomography (CT) was the major contributor (> 77%) to ionizing radiation exposure. Among the haemodialysis and kidney transplant patients, 15% and 6% were in the high (≥ 20 mSv per year) radiation dose groups, respectively. In haemodialysis patients, the most exposed organs were the liver (16 mSv), the kidney (15 mSv) and the stomach (14 mSv), while the uterus (6.2 mSv), the lung (5.7 mSv) and the liver (5.5 mSv) were the most exposed in kidney transplant patients. The average cumulative effective dose (CED) of ionizing radiation among centres in this study was highly variable both in haemodialysis (from 6.4 to 18.8 mSv per patient-year; $p = 0.018$) and even more so in kidney transplant (from 0.6 to 13.7 mSv per patient-year; $p = 0.002$) patients.

Conclusions Radiation exposure attributable to medical imaging is high in distinct subgroups of haemodialysis and transplant patients. Furthermore, there is high inter-centre variability in radiation exposure, suggesting that nephrology units have substantially different clinical policies for the application of diagnostic imaging studies.

Keywords Cancer · Haemodialysis · Kidney transplantation · Radiation dosimetry

Introduction

End stage renal disease (ESRD) patients make up a population (of the almost) unique risk profile for adverse clinical outcomes spanning from cardiovascular disease to infectious disease and cancer. The death rate for cardiovascular and non-cardiovascular complications in this population is about ten times higher than in the coeval general population [1]. The risk for various types of cancers in ESRD patients younger than 35 years of age is at least three times higher than in age- and sex-matched individuals in the general population [2]. According to the United States Renal Data System (USRDS), ESRD patients on average are hospitalized twice a year and stay in the hospital for 13 days. Due to their high burden of co-morbidities, these patients are repeatedly

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exposed to imaging studies and ionizing radiation both for diagnostic and therapeutic purposes. In the same vein, ESRD patients who receive a kidney transplant frequently undergo diagnostic studies to evaluate early and late graft complications, acute rejection, drug toxicity, ischaemic damage and other renal and extra-renal complications. Because of the cumulative, long-term effects of radiation exposure, this scenario is of concern, particularly for the risk of cancer. The radiation burden of medical imaging in these patients can be high, with an estimated effective dose of more than 100 mSv in just a few years [3–6]. Some ESRD patients, e.g. haemodialysis patients on waiting lists for transplantation, might have sufficiently high exposure to ionizing radiation which may materially contribute to their increased risk of cancer. However, to date, only relatively small single-centre studies have been carried out. These studies are inherently limited because the use of radiation-related procedures is highly variable depending on the (local) availability of technologies, hospital size and output, and local clinical policies. Furthermore, in all these studies radiation exposures were measured by the estimated effective dose (ED), which is a sex- and age- averaged metric and as such is an inherently imperfect estimator of the risk of radiation at the individual level. Studies focusing on patient-specific assessment of cumulated equivalent organ doses (H_T) [7] are (held as) a necessary step to improve the estimate of the risk of ionizing radiation exposure in the ESRD population.

In this survey involving fourteen Italian nephrology units, representative of the diagnostic and monitoring practices in ESRD and transplant patients in Italy, we aimed at quantifying exposure to ionizing radiation on an individual basis by estimating both the cumulated ED and H_T.

The secondary aim was to investigate the presence of differences in average patient radiation exposure among centres.

Materials and methods

Data collection

The Institutional Review Board approved the study of each participating centre.

Given the fact that our study deals with data extracted from electronic medical records for which patients already provided informed consent, no further "informed consent" was requested.

We selected Italian Nephrology and Transplantation units with sizeable dialysis units (i.e. with at least 50 patients) and with follow up clinics dedicated to renal transplant patients. These units had to be located in Hospitals with a well-established Radiological Information System and a Picture Archiving and Management System. A complete list of participating centres can be found in the legend of Tables 2 and 3.

We collected complete demographic and clinical data for each patient and detailed information about examinations involving ionizing radiation exposure, including dosimetric parameters, from all participating units. Physicians at these units were asked to fill in pre-established forms for clinical and dosimetric data and to upload them to an online database. Data were analysed centrally by the coordinating centres of Reggio Calabria and Novara.

Data collection was carried out between 1st January and 31st December, 2011 in 11 Units, and from 1st January to 31st December, 2012 in three Units. We excluded patients who had been diagnosed with cancer within 5 years from the start of the follow-up or during the study period. The exclusion of these patients rested under the assumption that these cancers were unlikely to be related to the exposures being measured for the present analysis. Only patients with a follow-up duration ≥ 1 year were included in the study. Patients who died in the 6 months after the completion of data collection were excluded from the study because their exposure to ionizing radiation risk could be inflated by their poor health status thus ? demanding intensive investigations. Co-morbidities were abstracted by reviewing medical notes, clinical summaries and patient interviews.

Radiology examinations performed during the study period were directly obtained from the Radiology Information System of the participating centres. For conventional radiology examinations, only the number of each specific procedure was recorded. With regard to computed tomography (CT), the number of series, the length of coverage per series, the kV, pitch, average mAs, volumetric CT dose index (mGy), and dose-length product (mGy cm) were registered, while for nuclear medicine procedures, the individual administered activity of a specific radiopharmaceutical was recorded. For interventional radiology procedures, the dose area product (Gy cm^2) was registered.

Data validation

The data set was verified for completeness and consistency by cross-checks of the records in the database. First, missing values and outliers were sought in order to identify potential mistakes. Suspected outliers generated by errors in unit conversion or transcription errors were identified and corrected. Further possible inconsistencies in the data were identified by cross-checking with redundancies in the collected information. All data defined by this process were then analysed in detail. Whenever it was deemed necessary, the participating centres were contacted and asked to integrate incomplete data or correct inconsistent data.

Estimates of radiation doses

Along with current recommendations for conventional diagnostic radiology procedures [8], ED and H_T estimates were derived for each specific examination using the PCXMC 1.5 software (STUK, Radiation and Nuclear Safety Authority, Helsinki, Finland) assuming a fixed set of exposure parameters summarized in Table 1.

For cardiac interventional radiology procedures, radiation doses were measured by the dose area product in Gy cm^2 using inbuilt ionization chambers. The ED and the H_T were derived using conversion factors described elsewhere [9].

The ED and the H_T for CT were estimated using the individual dose reports and the computational software ImPACT CT patient dose calculator v1.03 (ImPACT, London, UK) which uses tissue weighing coefficients, as specified by the International Commission on Radiological Protection publication 103 [10]. Average mAs were used in computations to account for the use of tube current modulation in modern scanners [11].

The ED and the H_T from nuclear medicine procedures were estimated by considering the individual administered activity of specific radiopharmaceuticals. Conversion coefficients relating ED and H_T to administered activity were obtained from the addenda to ICRP Publication 53 [12]. In positron emission tomography/CT studies, the contribution of the CT used for attenuation correction was attributed to nuclear medicine procedures.

Cumulative effective dose (CED) and cumulated H_T were expressed for each patient in mSv per patient-year.

Statistical analysis

Data were described using the mean and standard deviation or median and intra-quartile ranges. One way Analysis of Variance (ANOVA) was used to assess the presence of significant differences among participating centres in terms of CED. The correlation between continuous anagraphic and clinical variables with CED was assessed using Spearman's rank correlation coefficient. The impact of comorbidities on CED was assessed using the Mann–Whitney U test.

CED and cumulated H_T were expressed as least squares means, which are the best linear estimates in the population for the marginal means in the ANOVA design. The standard errors of the means (and thus the 95% confidence intervals) were estimated using the whole data set starting from the error variance [13].

Box and whisker plots were used to provide a graphical representation of the distribution of individual dosimetric indexes among centres.

Statistical analyses were performed using the software STATISTICA 6.0 (StatSoft Inc, Tulsa, OK) using a two-sided type I error rate of 0.05.

Table 1 Parameters of exposure for various diagnostic radiology procedures

Examination	Projection	KV	mAs	FID (cm)	Image size (cm)	ED[a] (mSv)
Skull	AP	65	50	100	24×30	0.1
	Lateral	65	50	100	24×30	
Cervical spine	AP	55	40	180	18×24	0.2
	Lateral	55	40	180	18×24	
	Oblique	60	50	180	18×24	
Thoracic spine	AP	70	80	100	20×40	1.0
	Lateral	60	100	100	20×40	
	Oblique	65	100	100	20×40	
Lumbar spine	AP	75	80	100	20×40	1.5
	Lateral	85	200	100	20×40	
	Oblique	85	200	100	20×40	
Hip	AP	65	100	100	30×40	0.7
Pelvis	AP	90	80	100	24×40	0.6
Abdomen	AP	64	80	100	24×40	0.7
Femur	AP	65	100	100	20×40	0.005
Chest	PA	100	20	180	30×40	0.02
	Lateral	110	25	180	30×40	1.0
Shoulder	AP	65	80	100	24×30	0.01
	Lateral	110	25	180	30×40	
Mammography	Cranio-Caudal	28	55	45	18×24	0.4
	Oblique	28	55	45	18×24	

AP anteroposterior, *PA* posteroanterior, *FID* Focus image distance

[a]ED referred to a standard patient (1.7 m tall, weighing 70 kg)

Results

Overall, 739 haemodialysis and 486 kidney transplant patients entered this study over the (fixed) 1-year time window. The demographic and clinical characteristics of these patients listed by centre are reported in Tables 2 and 3, respectively. On average, age was 67 ± 15 years (63% males) for haemodialysis patients and 55 ± 13 years (63% males) for kidney transplant patients. Among haemodialysis patients, 11% were on the renal transplant waiting list, 27% had diabetes, 22% had a history of coronary heart disease, and 14% had had a neoplasia. The corresponding figures for these co-morbidities among kidney transplant patients were 13% (both for diabetes and coronary heart disease) and 8% (neoplasia).

Statistically significant correlations between continuous anagraphic and clinical variables with CED and the impact of comorbidities on CED are reported in Table 4.

The total number of radiology procedures carried out during the 1-year follow-up was 3093 in haemodialysis and 836 in transplant patients. The median number of procedures was 2 (interquartile range 1–6) in the former group and 1 (0–3) in the latter. The frequency distribution of radiological procedures among participating centres is reported in Fig. 1.

The proportion of total radiation exposure attributable to different types of investigations is shown in Table 5, together with mean CED and Total CED. The median CED in haemodialysis patients was 2.4 mSv (interquartile range 0.2–11.7 mSv), which was six times higher than the corresponding value of 0.4 mSv (IQR = 0.0–2.0) in kidney transplant patients. The distribution of CED among centres is reported in Fig. 2.

We calculated population-based rates of CED for the overall study population according to the categories proposed by Fazel et al. [14]. Among haemodialysis patients, 40% were in the negligible (< 1 mSv per year), 45% were in the low-moderate (< 20 mSv per year), 10% were in the high (20 to < 50 mSv per year) and 5% in the very high (≥ 50 mSv per year) radiation dose levels. Among the kidney transplant subjects, 40% were in the negligible, 54% were in the low-moderate, 4% were in the high and 2% in the very high radiation dose levels.

The averages of the estimated CED are reported in Fig. 3 in increasing order of magnitude across different centres. Average CED among participating centres ranged from 6.4 to 18.8 mSv per patient-year among haemodialysis patients

Table 2 Haemodialysis patients' demographic and clinical characteristics

Centre	N° of Patients	Male (%)	Age (y) Mean ± SD	Haemodialysis vintage (y) Mean ± SD	Transplant Waiting List (%)	Ischaemic heart disease or previous MI (%)	Diabetes mellitus (%)	Previous cancer (%)
ANC	–	–	–		–	–	–	–
BOL	46	46	71 ± 13	3.0 ± 4.4	9	30	39	15
BRE	58	59	61 ± 17	4.5 ± 6.5	14	26	33	8
GEN	61	59	68 ± 14	6.5 ± 7.5	13	30	31	25
LEC	63	64	67 ± 14	8.5 ± 9.1	13	29	22	11
MIL	60	65	66 ± 17	3.6 ± 4.9	18	27	8	12
MON	61	56	66 ± 15	8.2 ± 16.0	13	26	26	10
NOV	97	64	65 ± 17	3.1 ± 5.6	10	30	33	8
PIS	60	70	65 ± 14	5.8 ± 7.5	12	23	33	20
TOC	61	66	70 ± 14	5.5 ± 5.8	20	25	16	11
TOM	–	–	–		–	–	–	–
TRI	60	65	70 ± 12	2.4 ± 3.4	MD	28	40	13
UDI	52	71	64 ± 15	4.7 ± 4.5	10	31	20	15
VEN	60	65	70 ± 15	4.2 ± 5.5	5	42	17	27
TOT	739	63	67 ± 15	4.9 ± 7.6	11	22	27	14

ANC: Ospedali Riuniti; Ancona. BOL: Azienda Ospedaliera Policlinico S.Orsola-Malpighi; Bologna. BRE: Spedali Civili di Brescia, Azienda Ospedaliera; Brescia. GEN: Azienda Ospedaliera Universitaria "S. Martino"; Genova. LEC: Azienda Ospedaliera Provincia di Lecco; Lecco. MIL: Ospedale "Niguarda Ca' Granda"; Milano. MON: Azienda Ospedaliera "San Gerardo"; Monza. NOV: Az. Ospedaliero-Universitaria "Maggiore della Carità"; Novara. PIS: Azienda Ospedaliero-Universitaria Pisana; Pisa. TOC: Az. Ospedaliero-Universitaria "Città della salute e della scienza (CTO)"; Torino. TOM: Az. Ospedaliero-Universitaria "Città della salute e della scienza." (Molinette); Torino. TRI: Az. Ospedaliero-Universitaria "Ospedali Riuniti"; Trieste. UDI: Az. Ospedaliero-Universitaria "S. Maria della Misericordia"; Udine. VEN: Ospedale dell'Angelo; Venezia-Mestre

SD standard deviation, *MI* myocardial infarction, *MD* Missing data

Table 3 Kidney Transplant patients' demographic and clinical characteristics

Centre	N° of Patients	Male (%)	Age (y) Mean ± SD	Transplant vintage (y) Mean ± SD	Ischaemic heart disease or previous MI (%)	Diabetes mellitus (%)	Previous cancer (%)
ANC	40	53	52 ± 11	0.9 ± 0.6	12	3	0
BOL	–	–	–		–	–	–
BRE	38	58	54 ± 13	1.8 ± 3.7	8	11	5
GEN	43	61	60 ± 11	9.9 ± 6.2	12	7	7
LEC	38	69	54 ± 11	5.2 ± 3.2	18	13	3
MIL	38	70	54 ± 11	9.5 ± 7.6	13	13	8
MON	21	62	60 ± 11	7.0 ± 6.6	14	15	10
NOV	70	71	54 ± 14	7.4 ± 6.1	19	23	9
PIS	27	52	48 ± 13	1.8 ± 1.3	MD	15	0
TOC	–	–	–		–	–	–
TOM	50	56	61 ± 11	7.0 ± 5.8	18	14	30
TRI	40	70	58 ± 12	8.8 ± 6.0	8	10	5
UDI	40	75	53 ± 13	1.7 ± 1.0	15	10	5
VEN	39	54	50 ± 15	5.4 ± 4.0	5	14	10
TOT	486	63	55 ± 13	5.8 ± 5.8	13	13	8

ANC: Ospedali Riuniti; Ancona. BOL: Azienda Ospedaliera Policlinico S.Orsola-Malpighi; Bologna. BRE: Spedali Civili di Brescia, Azienda Ospedaliera; Brescia. GEN: Azienda Ospedaliera Universitaria "S. Martino"; Genova. LEC: Azienda Ospedaliera Provincia di Lecco; Lecco. MIL: Ospedale "Niguarda Ca' Granda"; Milano. MON: Azienda Ospedaliera "San Gerardo"; Monza. NOV: Az. Ospedaliero-Universitaria "Maggiore della Carità"; Novara. PIS: Azienda Ospedaliero-Universitaria Pisana; Pisa. TOC: Az. Ospedaliero-Universitaria "Città della salute e della scienza (CTO)"; Torino. TOM: Az. Ospedaliero-Universitaria "Città della salute e della scienza." (Molinette); Torino. TRI: Az. Ospedaliero-Universitaria "Ospedali Riuniti"; Trieste. UDI: Az. Ospedaliero-Universitaria "S. Maria della Misericordia"; Udine. VEN: Ospedale dell'Angelo; Venezia-Mestre

SD standard deviation, *MI* myocardial infarction, *MD* Missing data

Table 4 Correlation of anagraphic and clinical variables and impact of comorbidities on CED in haemodialysis and kidney transplant patients

Haemodialysis			
	Yes	No	P value
	CED median (interquartile range) in mSv		
Myocardial infarction	1.70 (0.00075–8.82)	2.62 (0.57–13.03)	0.05
Diabetes	2.00 (0.02–11.51)	4.24 (1.00–13.34)	0.003
Cancer	8.61 (3.51–37.14)	2.31 (0.09–11.73)	0.03
Age	r = − 0.10		0.004
Haemodialysis vintage	r = − 0.15		< 0.001
Kidney transplant			
Males	0.01(0.00–1.71)	1.00 (0.00–2.80)	0.002

and from 0.6 to 13.7 mSv per patient-year among kidney transplant patients. Of note, the variation of average CED among participating centres was highly significant both in haemodialysis (F = 2.10; p = 0.018) and in kidney transplant (F = 2.69; p = 0.002) patients.

The average cumulated H_T are reported in ascending order in Fig. 4. In haemodialysis patients, the most exposed organs were the liver (16 mSv), the kidney (15 mSv) and the stomach (14 mSv), while the uterus (6.2 mSv), the lung (5.7 mSv) and the liver (5.5 mSv) were the most exposed in kidney transplant patients. On average, exposure to CT contributed 77% to H_T with a maximum of 89% for the ovaries and a minimum of 62% for the lungs. Conventional radiology provided on average 10% of H_T with a maximum of 25% for the lungs. Nuclear Medicine contributed on average 6.6% to $H_{T,}$ and the bladder (15%) and the colon (12%) were the most exposed organs. Interventional Radiology contributed on average 6.6% to $H_{T,}$ and peak exposures were in the liver (15%) and the lungs (11%).

Discussion

This study involving 14 nephrology units in Italy shows that radiation exposure attributable to medical imaging in haemodialysis and transplant patients is on average low. However, about 15% of haemodialysis patients and 6% of transplant patients have high or very high exposures to ionizing radiation. Radiation exposure was highly variable among centres suggesting substantially different clinical policies for the application of imaging studies in the haemodialysis and transplant populations.

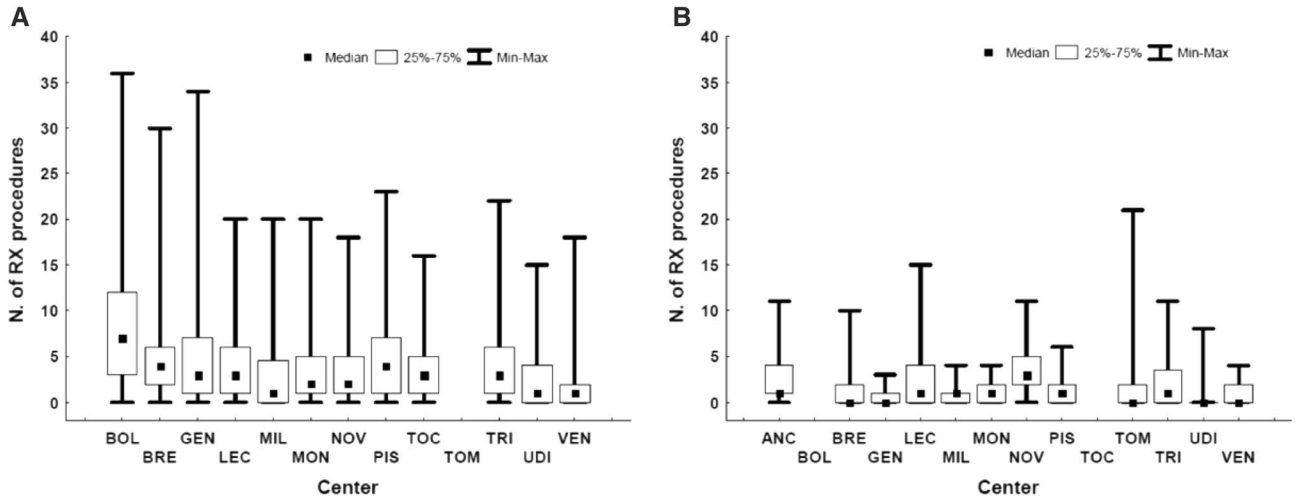

Fig. 1 Frequency distribution among centres of the number of radiological procedures. **a** Haemodialysis patients, **b** kidney transplant patients

Table 5 Number of radiological procedures, CED and total CED by procedure type

Haemodialysis Procedure	Number of examinations N (%)	CED (mSv per patient-year) Mean ± SD	Total CED mSv (%)
Overall total	3093 (100)	11.5 ± 24.9	8524 (100)
Conventional diagnostic radiology	2366 (76.5)	1.9 ± 2.6	1425 (16.7)
CT	426 (13.8)	7.5 ± 22.1	5519 (64.7)
Nuclear medicine	102 (3.3)	0.6 ± 2.5	468 (5.5)
Interventional	199 (6.4)	1.5 ± 7.8	1,114 (13.1)
Kidney transplant			
Overall total	836 (100)	4.4 ± 14.6	2116 (100)
Conventional diagnostic radiology	707 (84.6)	0.9 ± 1.5	447 (20.2)
CT	71 (8.5)	2.9 ± 13.1	1,402 (63.3)
Nuclear medicine	22 (2.6)	0.2 ± 1.1	77 (3.5)
Interventional	36 (4.3)	0.4 ± 3.7	130 (8.6)

CED Cumulative Effective Dose, *REID* Risk of Exposure-Induced Death.

Radiation is one of the most extensively studied carcinogens. Estimates of potential cancer risk from radiation are currently based on a linear no-threshold model, which is the model best supported by available epidemiological data [15]. According to the BEIR VII report [16], a radiation dose of the magnitude of 100 mSv can cause various types of neoplasias. As remarked, patients with end-stage renal disease have an excess risk for cancer as compared to the general population [2].

Doses of radiation from medical imaging procedures can be substantial in selected groups of patients who undergo repetitive imaging studies. A recent systematic review documented that ESRD is the condition entailing the highest risk of exposure to ionizing radiation, after cancer [17].

The median cumulative effective dose of ionizing radiation exposure in haemodialysis and transplant patients included in this study is within the limits of the natural background exposure. The cumulative dose was higher in haemodialysis (2.4 mSv per patient-year) than in transplant (0.4 mSv per patient-year) patients, possibly because of concerns about the nephrotoxic potential of iodinated contrast agents in transplanted patients.

The long-term risk due to the use of medical radiation should always be incorporated into the risk–benefit assessment of diagnostic and therapeutic imaging. However, profiling the risk–benefit is complex in ESRD patients, a selected group of patients with multiple co-morbidities and severe competing and confounding risks for death and cancer. While radiation exposure in this survey is reasonably low

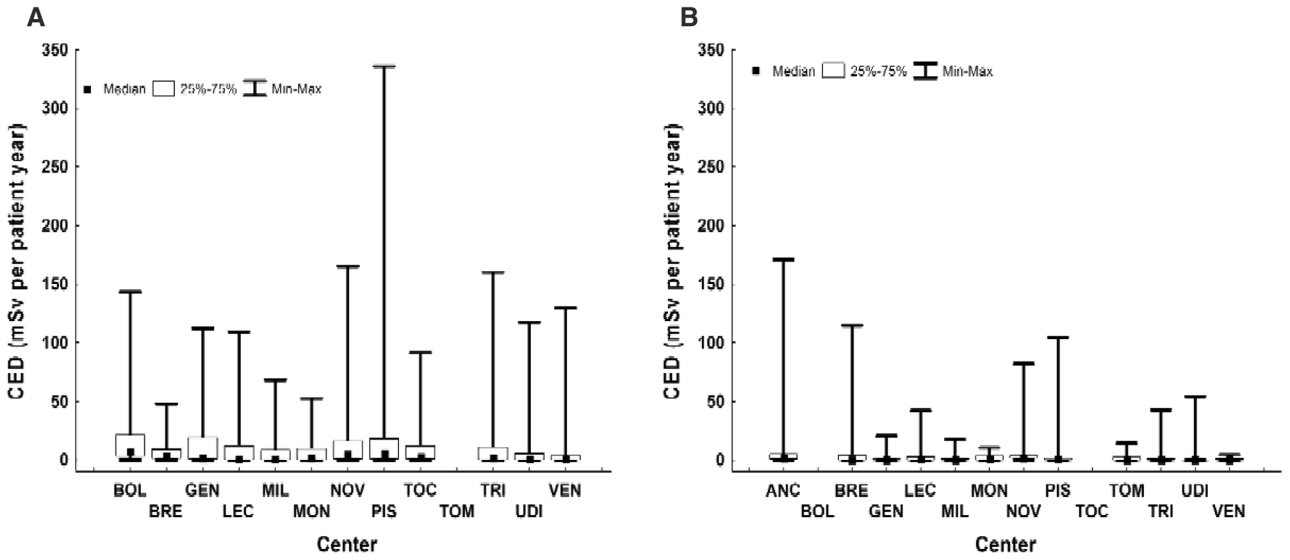

Fig. 2 Frequency distribution among centres of CED for all radiological procedures. **a** Haemodialysis patients, **b** kidney transplant patients

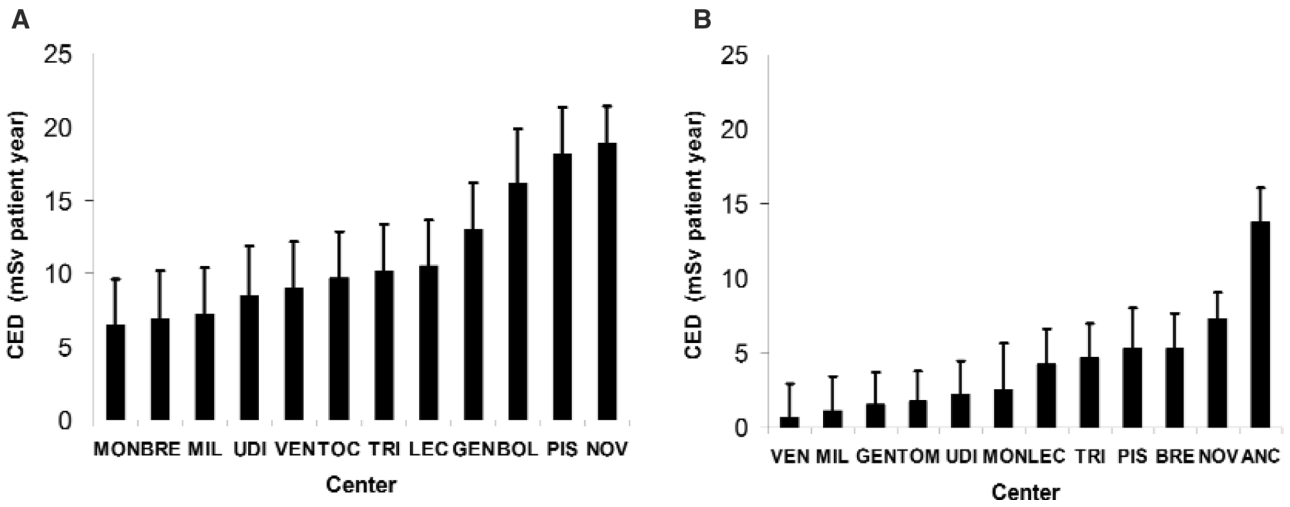

Fig. 3 Average of CED among centres. Points represent least square averages; vertical bars represent 95% confidence intervals. **a** Haemodialysis patients, **b** kidney transplant patients

when considering the whole population, it is not negligible when considering the most exposed subgroups. For instance, when selecting only patients in the upper fourth quartile, the average CED (37.7 and 16.5 mSv patient-year for haemodialysis and kidney transplant, respectively) is equal to or higher than the median CED in patients with gastric cancer (52.3 mSv for 47 months) [18], or lung cancer (84 mSv for 36 months) [19].

Haemodialysis patients with previous myocardial infarction, diabetes and without previous cancer were subjected on average to lower CED. Although statistically significant, the very weak negative correlations between CED and age and haemodialysis vintage could hardly be interpreted as being clinically relevant. In kidney transplant patients the only demographical variable associated with a lower CED was male sex, whilst the presence of comorbidities was not associated with different CEDs.

The substantial between-centre variability in patient' exposure to ionizing radiation is a relevant finding of the present study. The variability was striking for transplant patients, for whom we observed a 20-fold variation between the minimum and maximum average radiation exposure among different centres.

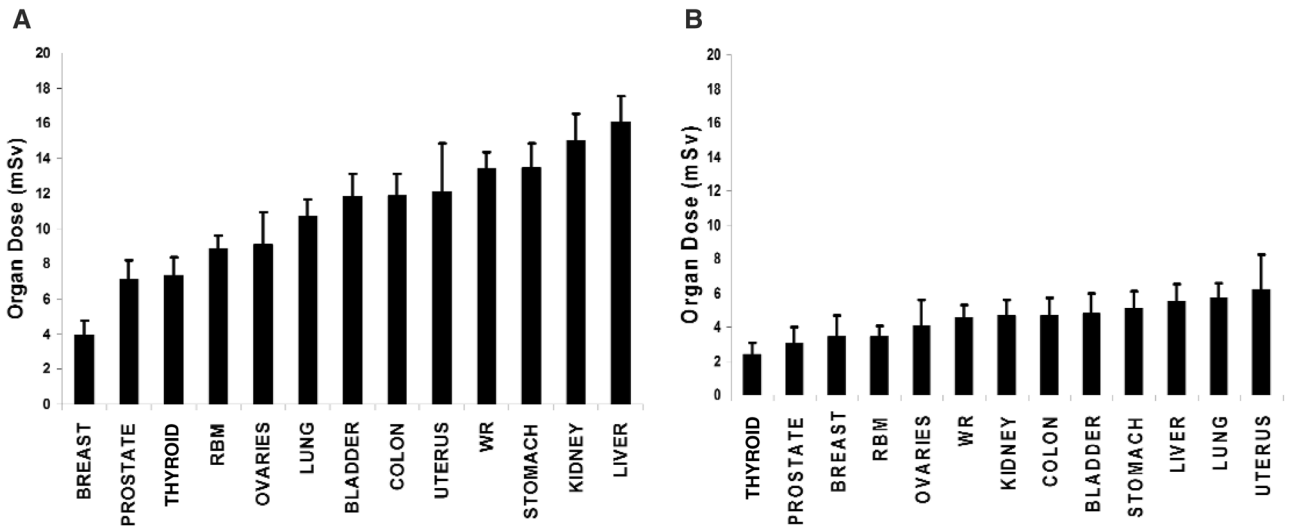

Fig. 4 Average of cumulated organ doses. Points represent least square averages; vertical bars represent 95% confidence intervals. **a** Haemodialysis patients, **b** kidney transplant patients

A meta regression with the average CED per centre as the dependent variable and anagraphic, clinical and comorbidities as the independent variables failed to identify any statistically significant predictor of the average CED in either haemodialysis or kidney transplant centres.

Awareness of the risk of exposure to ionizing radiation remains unsatisfactory among clinical nephrologists. Patients are followed up based on local protocols by applying radiological examinations at disparate time-intervals which results in a highly variable intensity of exposure depending on the local clinical policies. Protocol harmonization and education of nephrologists on the risks of radiation exposure are of obvious importance to limit such risk in these populations.

The source of ionizing radiation exposure was variable across organs or tissues. Nuclear medicine contributed to more than 12% of the exposure of the bladder and the colon. This observation goes along with the fact that the excretion of most radionuclides is via the urinary and gastrointestinal systems. Interventional radiology was responsible for 18% of the exposure of the liver and the lungs, which are the most exposed organs during cardiac procedures such as coronary angiography or percutaneous angioplasty. On the other hand, conventional radiology provided the maximum contribution in the lung (25%), while CT was responsible in 89% of the exposures of the ovaries and uterus.

Some limitations in our survey should be acknowledged. First, there are uncertainties about the assumptions concerning the shape and the geometry of exposed organs and the estimation of effective doses and measured dosimetric indexes. However, the methods we applied are the standard ones used worldwide to estimate the risk of exposure to ionizing radiation [20]. The fact that our observations are limited to a single country is another limitation. Therefore, findings in the present study cannot be generalized to other countries. International surveys are needed to confirm whether the risk of excessive exposure to ionizing radiations in some subgroups of haemodialysis and transplant patients also applies to countries other than Italy. Shared, evidence-based protocols limiting the application of imaging studies implying exposure to ionizing radiation is of obvious importance for reducing the risk of such exposures among these populations.

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Compliance with ethical standards

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