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# Ionizing Radiation Exposure in Children with Vesicoureteral Reflux: Should We Be Alarmed?

## *Exposición a radiacion ionizante en niños con reflujo vesicoureteral: Debemos preocuparnos?*

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**Abstract**

**Objectives** Ionizing radiation imaging is commonly used for diagnosis and follow up in children with vesicoureteral reflux (VUR). We aim to measure the effective dose (mSv) in patients with VUR.

**Methods** We reviewed our electronic database of patients under 8-years-old with VUR. Primary endpoint was to calculate the effective radiation dose (ED). Absolute frequencies and percentages were reported for global qualitative variables. This study conducted a logistic regression model to calculate the odds ratio for radiation exposure. Analysis was performed using STATA version 14.0 (StataCorp LLC, College Station, TX, EEUU).

**Results** A total of 140 patients were found, 97 were assessed for eligibility. We included 59 patients in the final analysis. Mean age was 20 ± 17.9 months, 66% were females. Most cases of VUR were bilateral (44%) and high grade (93.4%). The lowest number of studies per patient was two, with a minimum radiation of 5.7 mSv. The highest radiation was estimated at 20.7 mSv corresponding to a total of five studies. Logistic regression showed that highest grades of VUR and age of first UTI episode were associated with higher ED (OR, 1.7; 95% CI, 0.87-3.31), (OR 1.02; 95% CI 0.97-1.07) respectively. A mean ED for children with VUR was estimated of 5.5 ± 3 mSv/year.

**Conclusion** In our study, the children with VUR were exposed to 5.5 mSv/year without counting the natural background radiation, which is alarming, and we believe should raise awareness worldwide in how we are unnecessarily diagnosing indolent VUR cases and following patients.

**Keywords**

- ionizing radiation
- children
- vesicoureteral reflux
- imaging diagnostic
- X-rays

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**Resumen**

**Objetivos** La imagenología por radiación ionizante es una herramienta usada frecuentemente para el diagnóstico y seguimiento de pacientes con reflujo vesicoureteral (RVU). El objetivo del presente trabajo es calcular la dosis estimada en milisieverts (mSv) de pacientes con RVU.

**Métodos** Se realizó una revisión retrospectiva de todos los pacientes menores de 8 años con RVU. El objetivo principal fue calcular la dosis de radiación efectiva recibida por los pacientes con base en los estudios imagenológicos realizados hasta el momento de la revisión de la base de datos. Las frecuencias y porcentajes fueron reportados para las variables cualitativas. Se realizó una regresión logística para calcular la asociación de factores de riesgo con la exposición a radiación. El análisis estadístico fue realizado con el programa STATA versión 14.0 (StataCorp LLC, College Station, TX, EEUU).

**Resultados** Se identificaron 140 patientes, de los cuales 97 fueron evaluados para coprobar su elegibilidad. En total, 59 pacientes fueron incluidos para el análisis final. La edad promedio de los pacientes fue de 20 ± 1,.9 meses, y 66% eran mujeres. La mayoría de casos fueron bilaterales (44%) y de alto grado (93,4%). El menor número de estudios realizados por paciente fue 2, con una dosis mínima de radiación acumulada de 5,7 mSv. La máxima radiación acumulada fue de 20,7 mSv, correspondiente a un total de 5 estudios. La regresión logística demostró que altos grados de reflujo y la edad a la cual tuvieron la primera infección se asociaban con mayores dosis de radiación efectiva (razón de probabilidades [RP]: 1.7; intervalo de confianza del 95% [IC95%]: 0,87–3,31), (RP: 1,02; IC95%: 0,97–1,07), respectivamente. Estimamos una dosis efectiva de radiación de 5,5 ± 3 mSv/año en nuestra población.

**Conclusión** Nuestro estudio demuestra que pacientes con reflujo son expuestos a un promedio de 5,5 mSv/año sin contar la radiación de base a la que se exponen todos los humanos anualmente, lo cual resulta alarmante. Esto debe generar introspección al momento de evaluar pacientes con reflujo y evitar efectos a largo y mediano plazos.

**Palabras clave**

- radiación ionizante
- niños
- reflujo vesicoureteral
- diagnóstico imagenológico
- rayos X

## Introduction

According to a report on population exposure released on March 3, 2009, by the National Council on Radiation Protection and Measurements (NCRP), in 2006, Americans were exposed to more than 7 times as much ionizing radiation from medical procedures as in the early 1980's.[1] In 2006, ionizing radiation from medical imaging accounted for nearly one-half of the radiation exposure experienced by the population in the United States.[1]

Ionizing radiation may cause DNA damage, increasing the risk of future neoplams.[2–4] Studies of cancer following medical radiation exposure have shown that solid tumors usually start to be diagnosed a minimum of 10 to 15 years after exposure and usually do not appear until the children have reached adulthood. Several factors might predispose patients to cancer following radiation exposure, such as female gender (thyroid), age at exposure (younger children are more susceptible), attained age, underlying disease, and tobacco exposure. The most radiosensitive organ sites in children are the thyroid gland, breasts, bone marrow, brain, and skin. Radiation-related cancer risk is typically expressed as excess relative risk (ERR). An ERR of 1 corresponds to a doubling of the cancer rate in the exposed population compared to the unexposed population. It has been reported that ERR ranges from 0.4 to 32 after ionizing radiation in children, and with an ERR greater than 1 in most series.[1]

The risks in patients depend on the extent and amount of radiation exposure, which is particularly challenging in children. Furthermore, anatomical differences between adult and pediatric organs do have an impact on how exposure will have different implications for each population and their stochastic effects.[5,6] Therefore, the as low as reasonably achievable (ALARA) principle was proposed, and its purpose is to use the lowest radiation possible for diagnosis and treatment without compromising the quality of the image or the clinical outcomes.[4,5,12]

Ionizing radiation is commonly used for diagnosis and follow-up in children with vesicoureteral reflux, sometimes despite clinical guidelines recommendations; most clinicians have a tendency to overuse medical imaging with no impact on their clinical decisions.[7–9]

In the present study, we aim to measure the effective dose (in millisieverts, mSv) of ionizing radiation that patients with vesicoureteral reflux are exposed to in different medical imaging to estimate the possible risk of detriment to patients' health.

 

## Methods

### Study Population

After approval from the institutional review board, we retrospectively reviewed our electronic database of all patients under 8 years old with a diagnosis of vesicoureteral reflux at a tertiary care institution. We excluded all clinical records that had less than 10% of missing data in our database or a concomitant diagnosis of obstructive non-refluxing megaureter, ureterocele, congenital obstructive posterior urethral membrane (COPUM), hydronephrosis without vesicoureteral reflux, ureteropelvic junction obstruction, double collecting system without vesicoureteral reflux, solitary kidney, and horseshoe kidney. We used an 8-year-old cut off value given that, beyond this age, there is a growing tendency among clinicians to treat boys and girls with asymptomatic reflux in a conservative manner, having their antibiotic prophylaxis withdrawn and follow-up imaging suspended for several years.

### Endpoints

The primary endpoint was to calculate the effective dose of radiation exposure, in mSv, for patients with VUR; and for each study (dimercaptosuccinic acid [DMSA], diethylenetriamine-pentaacetic acid [DTPA], mercaptoacetyltriglycine [MAG3] renal scintigraphy, voiding cystourethrogram [VCUG], intravenous urography [IVU], and radionuclide cystography). The secondary endpoints were to evaluate the association between reflux severity and the effective radiation dose, the first febrile UTI, and the rate of VUR correction after surgery.

The dose of the radiolabeling agents for nuclear medicine studies was calculated with the ideal weight for the patients age on the date of the examination, given we did not have the exact weight for each time each imaged was taken. We calculated the effective dose of the nuclear studies using the World Health Organization (WHO) charts for the ideal weight-for-age reference[10] and using the nuclear medicine radiation dose tool created by the European Association of Nuclear Medicine.[11] The calculation of radiation dose for voiding cystourethrogram was the addition of a total dose of 5 abdominal x-rays (1 mSv assumed per abdominal radiograph).

Reflux grade was defined according to the International Reflux Study Committee;[12] 1 to 3 grade was considered low grade VUR, and 4 to 5 high grade VUR. The first urinary tract infection was defined as the first febrile infection reported in the clinical record. High effective radiation dose was defined as $> 3$ mSv/year.

### Statistical Analysis

Data collection and analysis were performed using the STATA 14.0 software (Stata Corp., College Station, TX, USA). Absolute frequencies and percentages were reported for global qualitative variables. The effective radiation dose (ED) was calculated following the European Association of Nuclear Medicine definition, which reads: ED depends on the dose equivalent to each tissue ($H_T$). For an exposed individual, the risk of radio-induced cancer or hereditary effects is the sum of the risks to each organ, given by the product of the tissue weighting factor $W_T$ (radiosensitivity weight) and the dose equivalent $H_T$" $ED = \Sigma H_T \times W_T$. The present study conducted a logistic regression model to calculate the odds ratio for radiation and reflux grade of severity. For quantitative variables, a Shapiro-Wilk normality test was used to determine the normal or non-normal distribution to report the corresponding measures of central tendency and dispersion.

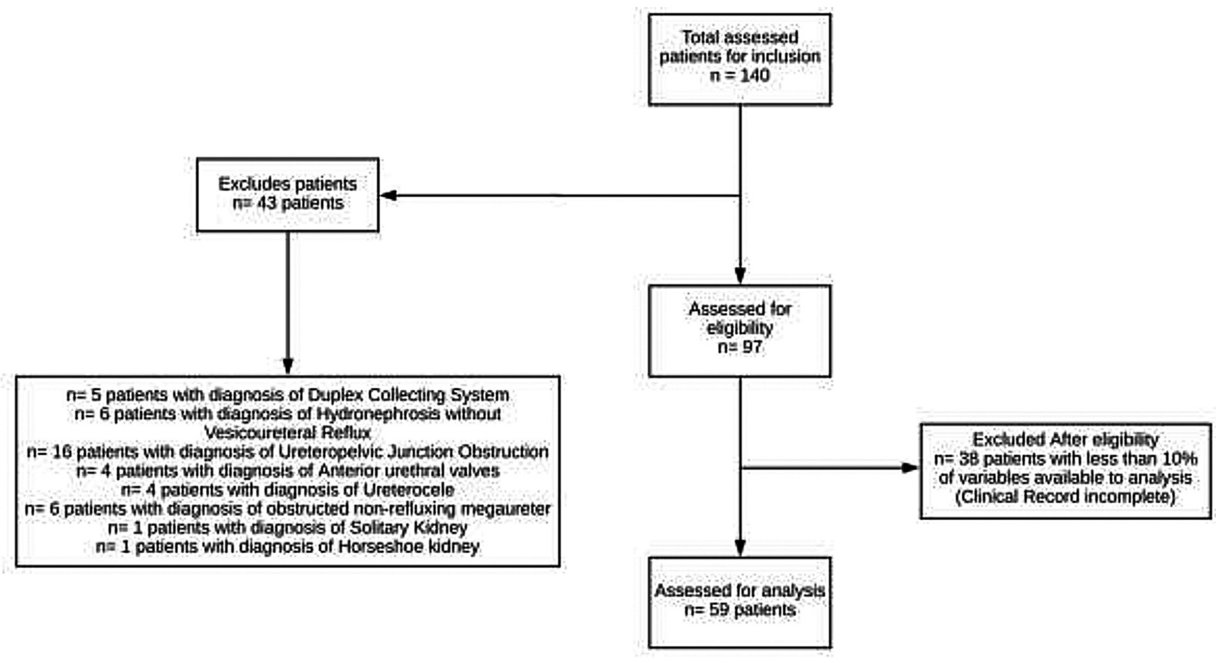


**Fig. 1** Patients flow chart indicating assessment for eligibility and exclusion.

 

## Results

We assessed a total of 140 patients, and 43 were initially excluded; 97 were assessed for eligibility, and, of these, 38 patients were excluded for having an incomplete clinical record; We included 59 patients in the final analysis. (►**Fig. 1**) The mean time between the 1st study and the last one was 36 ± 32 months.

The mean age of the children at the 1st ionizing radiation study was 20 ± 17.9 months, and most of the patients were female (66.1%). Of the eligible patients 52.5% had no other associated conditions and 20.3% had chronic renal disease. (►**Table 1**) Most cases of VUR were bilateral (44%) and high grade (93.4%). Mean episodes of febrile urinary tract infections (UTIs) prior to surgical intervention were 2.9 ± 2.3. Interestingly, only 5% of all patients did not require surgery at the time of follow-up, and most surgeries for VUR used an extravesical reimplantation technique (Lich-Gregoir). Successful reflux correction was achieved in 74% of the patients; as aforementioned, this outcome was defined as no febrile UTIs after surgical intervention.

The total number of ionizing radiation studies for each patient is shown in ►**Figure 2**. The lowest number of studies per patient was 2, with a minimum radiation dose of 5.7 mSv. The highest radiation was estimated at 20.7 mSv, corresponding to a total of 5 studies, 4 of which were VCUGs. Of

**Table 1** Baseline demographic variables

| Variable | | | Total, n = 59 |
|---|---|---|---|
| Baseline characteristics | | | |
| | Age (months), mean (SD) | | 20 (17.9) |
| | Male (%) | | 33.9 |
| | Female (%) | | 66.1 |
| | Associated conditions | | |
| | | Antireflux surgery, (%) | 5 |
| | | CRD, (%) | 20.3 |
| | | Ectopic ureter, (%) | 8.5 |
| | | Nephropathy, (%) | 13.6 |
| | | None, (%) | 52.5 |
| | Diagnosis | | |
| | | Primary VUR (%) | 98 |
| | | Refluxing megaureter, (%) | 2 |
| | VUR laterality | | |
| | | Right, (%) | 27.1 |
| | | Left, (%) | 28.9 |
| | | Bilateral, (%) | 44 |
| | | UTIs before antireflux surgery, mean (SD) | 2.9 (2.3) |
| | | Age of first UTI (months), mean (SD) | 15.9 (16.4) |
| | Antireflux surgery | | |
| | Extravesical technique, (%) | | 64.4 |
| | Intravesical, (%) | | 3.4 |
| | Endoscopic (bulking agents) (%) | | 27.1 |
| | None, (%) | | 5.1 |
| | Reflux grade | | |
| | | I, (%) | 0 |
| | | II, (%) | 5.1 |
| | | III, (%) | 13.6 |
| | | IV, (%) | 29 |
| | | V, (%) | 50.8 |
| | | No data, (%) | 2 |

Abbreviations: CRD, ; SD, standard deviation; UTI, urinary tract infection; VUR, .

 

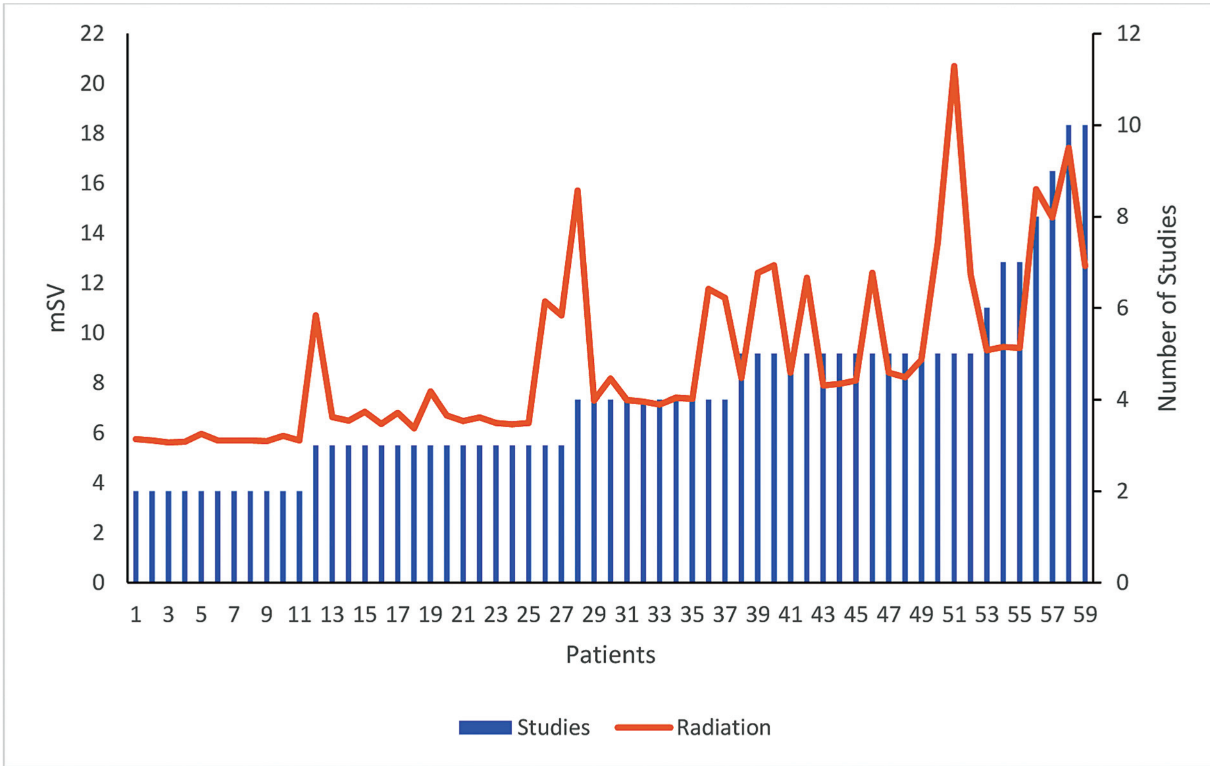


**Fig. 2** Number of studies per patient with estimated ionizing radiation (mSV).

the 59 children, only 2 had 10 or more studies with a radiation dose of 12.68 mSv and 17.42mSv.

The studies most commonly performed were: DMSA, DTPA, or MAG3 renal scintigraphy, VCUG, intravenous urography, and radionuclide cystography; These studies were always ordered by attending physicians. The frequency and radiation per study are shown in ►**Table 2**. On average, all patients had at least 2 DMSA scans, 11 patients underwent DTPA scans mostly before the VUR diagnosis, and, curiously, they were all ordered by the pediatrician or the pediatric nephrologist.

Of all studies performed, 51% of the total radiation given to all patients was from DMSA scans, followed by VCUG (31%). Mercaptoacetyltriglycine renal scintigraphy and intravenouse urography (IVU) corresponded to less than 2% of the total amount of accumulated radiation. (►**Fig. 3**)

Logistic regression analysis showed that highest grades of the severity of VUR were associated with higher effective radiation dose (odds ratio [OR], 1.7; 95% confidence interval [CI], 0.87-3.31). Age at the first UTI episode was associated with higher effective radiation dose (OR 1.02; 95% CI 0.97-1.07). (►**Fig. 4**) Finally, and considering a mean follow-up time of 36 months, we calculated a mean effective radiation dose for children with VUR of 5.5 ± 3 mSv/year.

## Discussion

Radiation exposure in children with VUR is alarming, we found that in approximately 36 months of follow-up, most patients had at least 2 ionized imaging studies and approximately 5.7 mSv effective dose exposure. Fifty percent of all patients had 4 or more studies and more than 7 mSv of

**Table 2** Ionizing radiation imaging

| STUDY | PATIENTS | Studies per patient | SD | Radiation dose/study (mSv) | SD |
|---|---|---|---|---|---|
| DMSA scan | 59 | 2.1 | 1.1 | 1.5 | 0.9 |
| DTPA scan | 11 | 1.4 | 0.7 | 1.3 | 0.9 |
| MAG3 scan | 2 | 2.0 | 0.0 | 2.3 | 0.3 |
| VCUG | 58 | 1.3 | 0.6 | 6.5 | 3.0 |
| Intravenous urography | 2 | 1.5 | 0.7 | 3.8 | 1.8 |
| Radionuclide cystography | 17 | 1.2 | 0.4 | 1.2 | 0.4 |

Abbreviations: DMSA, dimercaptosuccinic acid; DTPA, diethylenetriamine-pentaacetic acid; MAG3, mercaptoacetyltriglycine; SD, standard deviation; VCUG, voiding cystourethrogram;

 

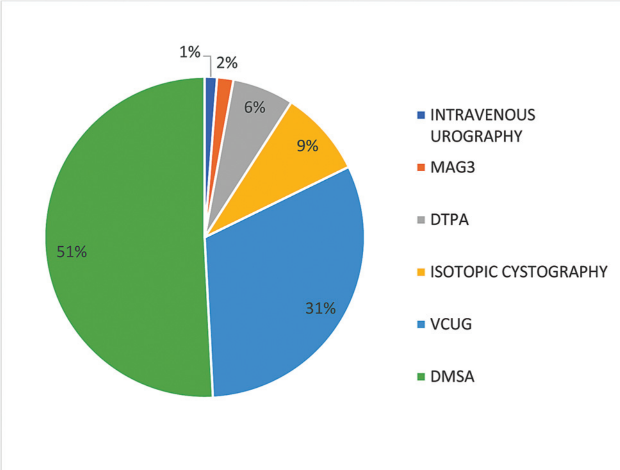


**Fig. 3** Frequency of diagnostic studies used in VUR assessment and follow-up.

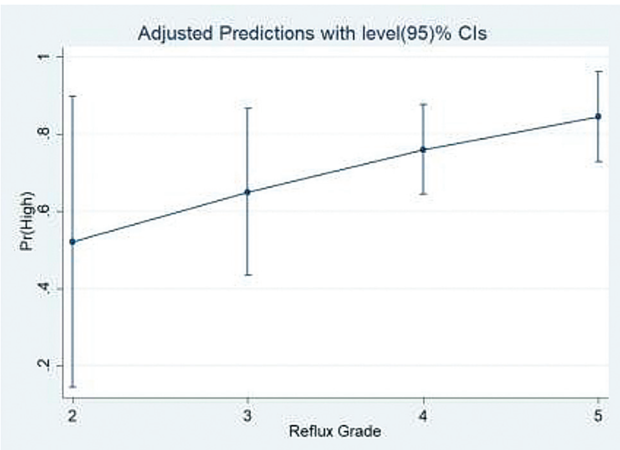


**Fig. 4** Radiation effective dose and VUR severity Grade.

effective dose. In general, the effective radiation dose in a year in patients with VUR at our institution was approximately 5.5 mSv/year with the additional natural background radiation sources, including radon, cosmic rays, terrestrial, and internal sources, that results in an effective dose of approximately 620 millirems (6.2 mSv) according to the American Association of Physicists in Medicine (AAPM).[13]

Based on extrapolation models from nuclear accidents and atomic bomb survivors, Brenner et al. estimated that the use of computed tomography (CT) may account for 1.5 to 2% of all future cancers in the United States.[14] Also, another study estimates that radiation dose from a single CT exam in a 1-year-old child is higher than that for adults.[15] It is essential to consider that most of the studies on nuclear medicine have exposure to radiation. So, whenever ionizing radiation images are used, it is recommended to balance the risk against the benefits or the clinical impact that the study would have on the patient's treatment.[3,4]

Radiation risk in children is aggravated by their longer lifespan following exposure, as there is a long time over which radiation-induced cancers may occur.[6,16] Due to the high sensitivity to radiation, lifetime radiation risk from even one ionized study in a pediatric patient is a relevant factor that triggers health complications due to radiation exposure[12]. Adverse effects of ionizing radiation exposure are higher in pediatric patients compared to adults.

The risks of ionizing radiation in children are related to the cumulative dose received.[6,12,14,15,17,18] In a cohort study of individuals who underwent CT when they were younger than 22 years of age, compared with those who received a cumulative radiation dose < 5 mGy, the risk of subsequent leukemia tripled for those who received a cumulative radiation dose ≥ 30 mGy, and the risk of a subsequent brain tumor increased up to 3-fold for those who received a cumulative radiation dose ≥ 50 mGy.[19] Our study presents critical data, as we believe we are exposing children with VUR to high doses of radiation for follow-up of a condition that, in most cases, does not require treatment and has a high likelihood of spontaneous resolution. With the new available contrast enhanced ultrasound technologies that have been proposed for follow-up and diagnosis of patients with VUR, we may be able to safely monitor and diagnose these patients.[20,24]

Dimercaptosuccinic acid renal scan was the most requested ionizing radiation study. On average, each patient had almost two DMSA scans. Moreover, DMSA renal scintigraphy, represents almost half of all the exposed radiation, followed by the voiding cystourethrogram, which represents 31% of all the radiation exposure in our patients.[21–23] The indications of those studies are not a subject of matter of this article, but in our research, we found out that 242 studies were performed, each patient with VUR underwent on average 4.1 studies. Dang et al., from 1996 to 2005 noted in their study that children had lower findings (65.5%) than adults (77.6%) from ionizing studies, leading them to concluded that approximately 35% of CT scans performed on children had no impact on their diagnosis.[1,24]

We found that patients with higher reflux grade were more predisposed to a higher effective radiation dose. Also, patients who underwent surgical VUR correction tend to be more exposed to ionizing radiation than those who were managed conservatively. The only association we could find was that pediatricians were actively screening for VUR resolution in patients treated surgically and were asymptomatic. Our results should rise awareness on how to reduce the need for ionizing imaging and how results do really impact decision making.

Our limitations are that the study has a retrospective and cross-sectional designed, all the data has been obtained from clinical records. Also, it does not consider the protocols of each institution for ionized studies. Our results are based on the ideal weight of the patient at the moment of the study and not the real weight given the difficulty to withdraw the weight from all the clinical records, and it may be a selection bias due that all patients were from one pediatric referral center. Another limitation is that given the children in our study were from a high-volume pediatric referral center, most cases of VUR were high grade and were more complex to treat, that is why, most of our patients required surgical intervention at some point, which is not usually seen at most pediatric urology practices.

 

## Conclusion

In our study, the children with VUR were exposed to 5.5 mSv/year without counting the natural background radiation, which is alarming, and we believe should raise awareness worldwide in how we are unnecessarily diagnosing indolent VUR cases and following patients with ionizing radiation studies without a clinical denotation. Physicians involved in the care of children with VUR must be aware of the risk of excessive ionizing radiation and try to minimize the use of this diagnostic modality.

## Declarations

### Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Nicolas Fernandez, Luis Villarraga and Julian Chavarriaga. The first draft of the manuscript was written by Nicolas Fernandez, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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No funding was available for this project.

### Conflict of Interests

The authors have no conflict of interests to declare.

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