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The association of exposure to depleted uranium and markers of mineral and bone metabolism in chronic kidney disease patients; a prospective analytical, cross-sectional study

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ABSTRACT

Introduction: Environmental exposure to depleted uranium (DU) has raised growing concerns about its potential systemic toxicity, yet its impact on mineral and bone metabolism in patients with chronic kidney disease (CKD) remains poorly defined. Given that disturbances in vitamin D, calcium, parathyroid hormone (PTH), and phosphorus are central to the development of CKD-mineral and bone disorder, clarifying whether uranium burden contributes to these abnormalities may have important implications for risk stratification and clinical management in this vulnerable population.

Objectives: This prospective analytical study aimed to evaluate the correlation between internal exposure to DU and key markers of mineral and bone metabolism, including serum 25(OH)D, calcium, PTH, and phosphorus, in patients with CKD.

Patients and Methods: This cross-sectional study included 100 male patients with CKD who were referred to several hospitals and medical centers in Iraq from February to August 2024. After obtaining informed written consent, demographic and clinical data were recorded; a blood sample was collected for measurement of DU and assessment of markers of mineral and bone metabolism, including serum 25-hydroxyvitamin D (25(OH)D), calcium, PTH, and phosphorus, and these variables were subsequently analyzed using appropriate statistical methods.

Results: The results indicated that DU levels were significantly correlated with lower 25(OH)D concentrations (B = −0.015, 95% confidence interval [CI]: −0.028 to −0.001 and B = −0.016, CI: −0.030 to −0.001), reduced serum calcium (B = −0.003, 95% CI: −0.006 to −0.001 and B = −0.004, 95% CI: −0.007 to −0.001), and increased PTH (B = 0.022, 95% CI: 0.010 - 0.033 and B = 0.014, 95% CI: 0.002 - 0.026) in the unadjusted and adjusted (age and hemodialysis status) models, respectively. While no significant relationship emerged with serum phosphorus.

Conclusion: Greater internal exposure to DU was associated with a pattern of altered mineral and bone markers, with consistently lower 25(OH)D and calcium levels and higher PTH concentrations. A lack of link with phosphorus, suggesting that phosphate homeostasis may be maintained or shaped by additional determinants beyond uranium exposure in this setting.

Implication for health policy/practice/research/medical education:
In this study, we found that higher internal exposure to depleted uranium (DU) was linked to lower circulating 25-hydroxyvitamin D (25(OH)D) and calcium levels, together with higher parathyroid hormone (PTH) concentrations, pointing toward a shift in mineral and bone metabolism compatible with secondary hyperparathyroidism. At the same time, phosphorus levels did not show a meaningful association with uranium burden, suggesting that phosphate balance may be maintained or more strongly governed by other clinical or treatment-related factors in this setting.

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Original

Introduction

Chronic kidney disease (CKD) is a silent progressive condition defined by the presence of structural or functional abnormalities of the kidney lasting more than three months, classified according to cause, glomerular filtration rate (GFR) category, and albuminuria category (1-3). At present, CKD affects more than 10% of the general population worldwide, amounting to over 800 million individuals, with higher prevalence observed in older adults, women, and those living with diabetes mellitus or hypertension (4). A comprehensive systematic review and meta-analysis of 100 studies comprising nearly 7 million patients reported a global prevalence of CKD stages 1–5 of 13.4%, with stages 3–5 accounting for 10.6% of the global adult population (5). Meanwhile, CKD carries a substantial burden not only because of the risk of progression to end-stage kidney disease requiring renal replacement therapy, but also due to its strong and independent association with cardiovascular disease and premature death (6). The Global Burden of Disease studies have consistently shown that mortality attributed to CKD increased by more than 40% between 1990 and 2017, and the disease is projected to become one of the five leading causes of years of life lost globally by 2040 (7).

As kidney function declines, a systemic disorder of mineral and bone metabolism known as CKD–mineral and bone disorder (CKD-MBD) develops, characterized by abnormalities in serum calcium, phosphorus, parathyroid hormone (PTH), and vitamin D (8,9). The underlying pathophysiology begins in the early stages of CKD, when reduced renal mass impairs the activity of 1α-hydroxylase in the proximal convoluted tubules, the principal site of conversion of 25-hydroxyvitamin D (25(OH)D) to its biologically active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (10). The resulting deficit in active vitamin D reduces intestinal calcium absorption, leading to hypocalcemia, which in turn stimulates compensatory secretion of PTH from the parathyroid glands (11). As CKD progresses, reduced renal phosphate excretion causes hyperphosphatemia, which further suppresses vitamin D activation and independently drives secondary hyperparathyroidism (12). The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline Update recommends regular monitoring of serum calcium, phosphate, PTH, and 25(OH)D beginning at CKD stage G3a, given their clinical importance as prognostic markers and as therapeutic targets (13).

Depleted uranium (DU) is a byproduct of uranium enrichment that is used in military munitions and armor; its widespread use in several conflict zones, including Iraq, has resulted in measurable environmental and human internal exposure in affected populations (14,15). The kidney is recognized as the primary target organ of uranium's chemical toxicity, with uranium ions concentrating in the cortical and juxtaglomerular regions of the kidney and binding to the brush border membrane of proximal tubular cells, thereby disrupting tubular reabsorption of calcium and phosphate; a review of epidemiological and experimental data demonstrated that uranium exposure increases urinary excretion of calcium and phosphate, biomarkers of proximal tubular dysfunction, and may thereby contribute to secondary disturbances in bone and mineral metabolism (16). Furthermore, Kurttio et al found, in a population chronically exposed to natural uranium through drinking water, that higher uranium intake was associated with elevated markers of bone resorption in men, suggesting that bone may constitute an additional target of uranium's chemical toxicity beyond the kidney (17). Given that CKD patients already exhibit compromised proximal tubular function and impaired vitamin D activation, the possible additional burden imposed by DU exposure on mineral and bone metabolism in this vulnerable group warrants dedicated investigation, which forms the basis of the present study.

Objectives

This prospective analytical study aimed to evaluate the correlation between internal exposure to DU and key markers of mineral and bone metabolism, including serum 25(OH)D, calcium, PTH, and phosphorus, in patients with CKD.

Patients and Methods

Study design and participants

This prospective analytical cross-sectional study enrolled Iraqi adults with CKD between 10 February and 10 August 2024, drawing participants from several hospitals and outpatient medical centers across Iraq. Eligible patients were randomly selected from nephrology clinics and dialysis units to provide a heterogeneous sample of individuals at different stages of CKD and with varying exposure profiles to DU.

Inclusion and exclusion criteria

This study included adult (more than 18 years) CKD patients who were referred to the selected nephrology clinics or hemodialysis units of hospitals and medical centers in Iraq during the study duration. Patients were required to have stable clinical status, complete baseline laboratory data for DU, 25(OH)D, calcium, PTH, and phosphorus, and to provide informed consent. Individuals were not enrolled if they had acute kidney injury, known primary disorders of calcium–phosphate metabolism, active malignancy, advanced liver disease, or current use of high-dose vitamin D or mineral supplements likely to markedly alter mineral metabolism. In addition, patients with incomplete data, those unwilling to participate, or those with documented heavy-metal exposure unrelated to DU (for example, occupational lead exposure) were excluded.

Data collection

Data were collected at a single study visit using a standardized protocol applied across all selected hospitals and medical centers in Iraq. After obtaining informed consent, trained research staff interviewed each eligible patient to record demographic information, clinical history, and hemodialysis status using a structured case report form. Venous blood samples were then collected under fasting or routine pre-dialysis conditions, processed according to local laboratory standards, and analyzed for DU, 25(OH)D, calcium, PTH, and phosphorus using the same reference laboratories and assay methods for all participants.

Blood samples and laboratory measurements

Venus blood samples were collected before each dialysis session. Approximately 8 mL of venous blood was drawn from each subject without the use of a tourniquet and divided into two portions. One portion was placed in tubes containing K_3-ethylenediaminetetraacetic acid (K_3-EDTA) for DU concentration measurement, and the other was placed in a sterile tube for serum preparation. After clot formation, samples were centrifuged, and serum was aliquoted and stored at −20°C until analysis.

Uranium assessment technique

The uranium assessment was carried out using CR-39 solid-state nuclear track detectors with a thickness of 400 µm, which were cut into 130 small pieces to serve as individual measurement units. One drop of whole blood (approximately 45 µL) was carefully pipetted onto each piece and allowed to dry over an area of about 1.0 × 1.0 cm^2 on the detector surface. Each blood-coated piece was then paired with another detector fragment to create a sandwich configuration, secured with transparent adhesive tape, before irradiation at the Advanced Nuclear Laboratory, Department of Physics, College of Education for Pure Sciences (Ibn Al-Haytham), University of Baghdad, Iraq. Thermal neutrons from an Americium–Beryllium source were used to irradiate the samples for one week in a thermal neutron flux of 3.024×10^9 n/cm^2, inducing fission tracks in the CR-39 detectors. After irradiation, the detectors were chemically etched in 6.25 N NaOH at 60 °C for approximately four hours and then thoroughly rinsed with water to remove residual etchant and reveal the latent tracks. The resulting fission track densities were subsequently counted under an optical microscope at 400 ×magnification, and these counts were conducted to estimate uranium concentrations in the blood samples.

Outcome measurement

The measured outcome included assessing the association between internal exposure to DU in blood samples and key parameters of mineral and bone metabolism, including serum 25(OH)D, calcium, PTH, and phosphorus, in patients with CKD.

Statistical analysis

Statistical analyses were performed using SPSS software, version 27 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables, including age, DU, 25(OH)D, calcium, PTH, and phosphorus, was examined using the Kolmogorov–Smirnov test to assess normality. Given that both parametric and nonparametric methods yielded comparable results and *P* values, parametric tests were ultimately selected because of their greater statistical efficiency and accuracy. Bivariate associations between DU and each biochemical parameter were first evaluated using Pearson's correlation coefficient with 95% confidence intervals, followed by univariate and multivariable linear regression models in which serum 25(OH)D, calcium, PTH, and phosphorus served as dependent variables and DU concentration as the main independent predictor, with final models adjusted for age and hemodialysis status. A two-sided *P* value < 0.05 was considered indicative of statistical significance.

Results

This study included 100 CKD male patients, with a mean age of 54.81 ± 15.02 years, of whom 50 were undergoing hemodialysis at the time of assessment, while the remaining half were not receiving hemodialysis treatment. The average DU concentration was approximately 200.1 µg/L. Serum 25(OH)D levels were low, with a mean of roughly 14.0 ng/mL. The mean serum calcium level was 7.9 mg/dL, serum PTH showed a mean value of 8.6 pg/mL, and serum phosphorus averaged 5.1 mg/dL in this population (Table 1).

The correlation analysis demonstrated that higher DU concentrations were modestly but significantly associated with lower serum 25(OH)D levels and reduced calcium levels. In contrast, DU showed a moderate positive significant correlation with PTH concentrations, suggesting that a higher uranium burden may be linked

Table 1. Demographic characteristics laboratory test data

Qualitative variables	Frequency	Percent
Gender		
Male	100	100
Female	0	0
Under hemodialysis		
Yes	50	50
No	50	50
Quantitative variables	**Mean**	**SD**
Age (year)	54.81	15.02
DU (µg /L)	200.07	86.87
25(OH)D (ng/mL)	14.01	6.01
Calcium (mg/dL)	7.87	1.11
PTH (pg/mL)	8.57	5.28
Phosphorus (mg/dL)	5.08	1.43

DU: Depleted uranium, 25(OH)D: 25-hydroxyvitamin D, PTH: Parathyroid hormone, SD: Standard deviation.

with secondary hyperparathyroidism. No meaningful relationship was observed between DU and serum phosphorus, indicating that phosphorus homeostasis appeared largely independent of uranium levels in this cohort (Table 2).

The univariate linear regression indicated that increasing DU levels were significantly associated with lower 25(OH)D concentrations and reduced serum calcium, while showing a positive correlation with PTH; no significant relationship emerged with serum phosphorus. When we adjusted variables for potential confounders such as age and hemodialysis status, the inverse associations with 25(OH)D and calcium persisted, and the positive correlation with PTH remained statistically significant, although slightly attenuated, whereas phosphorus continued to show no meaningful association with DU (Table 3).

Discussion

The present study examined the relationship between internal DU burden and a panel of mineral and bone metabolism markers, specifically serum 25(OH)D, calcium, PTH, and phosphorus, in a cohort of 100 male patients with CKD. The findings revealed that higher DU levels were independently associated with lower 25(OH)D concentrations, reduced serum calcium, and elevated PTH in both unadjusted and adjusted regression models, while no significant association was detected with serum phosphorus. These results offer clinically relevant insights into the metabolic burden imposed by uranium exposure in a population already predisposed to the mineral and bone disorder (MBD) and warrant careful examination in the context of existing literature.

The inverse association between DU exposure and serum 25(OH)D concentrations observed in the present study is consistent with broader evidence implicating nephrotoxic heavy metals in the disruption of vitamin D metabolic pathways (16). The kidney is the primary site for the conversion of 25(OH)D to its biologically active form, $1,25(OH)_2D$, a reaction catalyzed by the enzyme 1α-hydroxylase within the proximal tubular epithelium (18). Uranium preferentially accumulates in and damages the proximal convoluted tubules of the kidney, targeting the S2 and S3 segments, where mitochondrial dysfunction, oxidative stress, and apoptosis collectively impair tubular cell viability and enzymatic activity (16). It is mechanistically plausible, therefore, that uranium-induced proximal tubular injury compromises 1α-hydroxylase function and, by extension, disrupts the activation of circulating 25(OH)D, leading to its accumulation and the relative deficiency of active vitamin D metabolites observed clinically.

Supporting this mechanistic framework, Zamoiski et al conducted a cross-sectional study in 512 adolescents from Torreón, Mexico, and reported that urine uranium concentrations were positively associated with serum $1,25(OH)_2D$, with a mean increase of 2.2 pg/mL per doubling of urinary uranium. Although this finding reflects a positive association with the active metabolite rather than 25(OH)D itself, it underscores uranium's capacity to interfere with the renal vitamin D activation cascade, a dynamic that may manifest differently in populations with pre-existing renal insufficiency where tubular compensation is limited (19). The present cohort of CKD patients represents a substantially more vulnerable substrate in which tubular 1α-hydroxylase activity is already impaired, potentially amplifying uranium's

Table 2. The correlation between DU with vitamin D, calcium, PTH, and phosphorus

Dependent variables	DU (µg /L)		
	r	95% CI	*P* value*
25(OH)D (ng/mL)	- 0.211	- 0.392 – [- 0.016]	0.034
Calcium (mg/dL)	- 0.234	- 0.412 – [- 0.040]	0.019
PTH (pg/mL)	+ 0.354	0.169 – 0.515	<0.001
Phosphorus (mg/dL)	+ 0.033	- 0.160 – 0.228	0.742

DU: Depleted uranium, 25(OH)D: 25-hydroxyvitamin D, PTH: Parathyroid hormone, CI: Confidence interval. *Pearson coefficient correlation

Table 3. The association between DU and vitamin D, calcium, PTH, and phosphorus using univariate and multivariate linear regression

Dependent variables		DU (µg /L) (Independent variable)		
		B	95% CI	*P* value
Unadjusted	25(OH)D (ng/mL)	- 0.015	- 0.028 – [- 0.001]	0.034
	Calcium (mg/dL)	- 0.003	- 0.006 – [- 0.001]	0.019
	PTH (pg/mL)	+ 0.022	0.010 – 0.033	<0.001
	Phosphorus (mg/dL)	+ 0.001	- 0.003 – 0.004	0.742
Adjusted*	25(OH)D (ng/mL)	- 0.016	- 0.030 – [- 0.001]	0.037
	Calcium (mg/dL)	- 0.004	- 0.007 – [- 0.001]	0.004
	PTH (pg/mL)	+ 0.014	0.002 – 0.026	0.019
	Phosphorus (mg/dL)	+ 0.001	- 0.003 – 0.004	0.621

DU: Depleted uranium, 25(OH)D: 25-hydroxyvitamin D, PTH: Parathyroid hormone, CI: Confidence interval, B: Unstandardized coefficients. *Adjusted for age and being under hemodialysis.

deleterious effect on circulating 25(OH)D. It is also noteworthy that air pollution, environmental chemicals, and heavy metal co-exposures have been identified as modulators of the vitamin D endocrine system through multiple pathways, including interference with cutaneous photosynthesis and hepatic hydroxylation, further contextualizing uranium as one of several environmental contributors to vitamin D dysregulation.

Vitamin D deficiency is exceptionally prevalent in patients with CKD, with published data indicating that the majority of CKD patients, including those on maintenance hemodialysis, exhibit suboptimal 25(OH)D concentrations (20,21). A cross-sectional study in CKD patients (stages 3–5) found that vitamin D deficiency (defined as <20 ng/mL) was present in 63.8% of participants, and 86.1% had suboptimal vitamin D levels overall, with a mean serum vitamin D of 18.4 ± 7.2 ng/mL (21). The additional burden imposed by DU exposure in the current study suggests that uranium contamination may function as an aggravating, independent determinant of vitamin D insufficiency in CKD populations living in conflict-affected or industrially contaminated regions. Given that low 25(OH)D concentrations in CKD patients are independently linked to increased all-cause mortality, cardiovascular risk, and accelerated bone disease (22-24), the clinical significance of uranium-associated vitamin D suppression deserves targeted attention in nephrology practice.

The finding of a significant negative association between DU levels and serum calcium, which persisted after adjustment for age and hemodialysis status, aligns with established evidence that uranium exposure disturbs calcium homeostasis through both renal and skeletal mechanisms. Uranium has been demonstrated to accumulate in bone tissue, where the uranyl ion (UO_2^{2+}) competes with and partially displaces calcium at bone mineral crystal surfaces, thereby disrupting the structural integrity of hydroxyapatite and the normal calcium exchange between bone and extracellular fluid (25). In a landmark epidemiological study among Finnish residents exposed to naturally elevated uranium in drinking water, Kurttio et al reported that uranium intake was associated with increased urinary excretion of calcium and phosphate, consistent with uranium-induced proximal tubular dysfunction and impaired renal calcium reabsorption; the authors proposed that leakage of calcium into urine, by disturbing tubular reabsorption, could secondarily reduce circulating calcium concentrations and stimulate bone resorption (17).

The significant positive association between DU exposure and serum PTH, observed in both unadjusted and adjusted regression models, represents one of the most clinically consequential findings of this study. Secondary hyperparathyroidism is a defining feature of CKD-MBD, driven classically by the triad of decreased $1,25(OH)_2D$ production, hypocalcaemia, and phosphate retention (26,27). The present data suggest that uranium burden adds a further, exogenous stimulus to PTH secretion, likely acting through its adverse effects on both vitamin D activation and serum calcium, as described in the preceding sections. The depression of 25(OH)D and calcium concentrations associated with higher DU levels would logically reduce the negative feedback on the parathyroid glands, thereby releasing tonic inhibition of PTH secretion and driving a compensatory rise in circulating PTH.

This pattern closely parallels the well-characterized sequence of events in CKD-MBD, where reduced renal 1α-hydroxylase activity leads to $1,25(OH)_2D$ deficiency, impaired intestinal calcium absorption, hypocalcaemia, and consequent parathyroid gland stimulation (10). The surveillance studies of Persian Gulf War veterans exposed to DU from retained shrapnel fragments, conducted over more than 30 years, have demonstrated a biologically plausible and statistically significant reduction in bone mineral density in the high urinary uranium subgroup, accompanied by elevated markers of bone resorption (urine N-telopeptide). Although direct PTH measurement was not consistently the focus of those studies, the observed bone loss and elevated resorption markers are consistent with a state of heightened parathyroid activity (28). In the Persian Gulf War veteran cohort evaluated in 2019 and again in 2024, bone resorption measured by N-telopeptide was significantly elevated in those with the highest uranium burden, and this was accompanied by a significant decrease in bone mass compared with the low-uranium subgroup (28,29). These longitudinal findings, taken together with the cross-sectional associations in the present study, build a consistent evidence base linking uranium exposure to hyperparathyroidism-mediated bone resorption.

Lead exposure has also been reported to disturb PTH and calcium metabolism through analogous mechanisms, further supporting the concept that nephrotoxic metals share common disrupting effects on the parathyroid–vitamin D–calcium axis. In a study of lead-exposed jewellery workers in Bangladesh, significantly altered serum calcium and PTH concentrations were documented, consistent with metal-induced interference with parathyroid feedback regulation (30). Taken collectively, the available evidence supports the notion that uranium, like other divalent metal cations with nephrotoxic potential, disrupts mineral and bone homeostasis through a convergent pathway involving proximal tubular injury, vitamin D axis suppression, hypocalcaemia, and compensatory PTH elevation.

The lack of a significant association between DU exposure and serum phosphorus is a noteworthy finding that warrants careful interpretation. At first consideration, this might appear discordant with the established nephrotoxic mechanisms of uranium, given that proximal tubular injury typically impairs sodium-phosphate cotransporter

(NaPi-IIa) activity, the very mechanism through which uranium enters tubular cells, and is expected to reduce tubular phosphate reabsorption (16). Indeed, Kurttio et al reported that uranium exposure through drinking water was associated with increased fractional urinary excretion of phosphate in their population, suggesting some degree of phosphaturic effect (17).

Overall, the present study demonstrates that greater internal DU burden is independently and consistently associated with a characteristic pattern of disturbed mineral and bone metabolism in CKD patients, manifesting as lower serum 25(OH)D, reduced calcium, and elevated PTH concentrations, while phosphate homeostasis remains unaffected. This pattern is mechanistically coherent with uranium's known nephrotoxic effects on the proximal tubular epithelium, where impairment of 1α-hydroxylase activity, disruption of tubular calcium reabsorption, and suppression of vitamin D–mediated parathyroid feedback converge to produce the hormonal profile observed. The findings align with, and extend, prior evidence from Persian Gulf War veteran surveillance cohorts documenting uranium-associated impairment of bone mineral density and bone resorption markers, as well as experimental evidence linking uranium to calcium and vitamin D pathway disruption. Against the background of the already high burden of vitamin D deficiency and secondary hyperparathyroidism that characterizes CKD populations globally, uranium exposure represents an additional, modifiable, and potentially amenable target for clinical intervention. Screening for elevated uranium burden in CKD patients residing in regions with known DU contamination, particularly those in conflict-affected areas of Iraq, may be warranted, and clinicians should be alert to the possibility that uranium exposure could be amplifying the severity of CKD-MBD in this vulnerable group. These observations underscore the need for prospective, multi-center studies with longitudinal follow-up to establish the clinical trajectory of uranium-associated mineral and bone disease in CKD and to evaluate whether reduction of uranium burden translates into improvement of the mineral metabolism profile.

Conclusion

Based on the study results, we conclude that higher internal exposure to DU is associated with a more disturbed mineral and bone metabolism profile, characterized by lower 25(OH)D and calcium levels alongside elevated PTH concentrations. The absence of a clear association with serum phosphorus implies that phosphorus regulation may be relatively preserved or influenced by additional factors beyond uranium burden in this population.

Limitations of the study

First, its cross-sectional design precludes any inference of causality between DU exposure and disturbances in mineral and bone metabolism, and residual confounding by unmeasured factors cannot be ruled out despite adjustment for age and hemodialysis status. Second, the sample was restricted to 100 male CKD patients from selected Iraqi centers, which limits statistical power for subgroup analyses and may reduce the generalizability of the results to women, other ethnic groups, earlier CKD stages, or non-Iraqi populations. Third, although biochemical markers and DU were carefully measured at a single time point, the lack of repeated measurements, detailed dietary data, environmental exposure histories, and information on vitamin D supplementation or phosphate binders may have introduced measurement error and additional confounding. Finally, the use of routine clinical assays and a single method for uranium quantification, while practical, may be influenced by analytical variability, and external validation in larger, independent cohorts using complementary exposure assessment techniques is warranted.

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Authors' contribution

Conceptualization: Seyed Alireza Mesbah-Namin and Ihsan Maher Abdulameer.
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Supervision: Seyed Alireza Mesbah-Namin and Arif Sami Malik.
Validation: Sameera Ahmed Ebrahiem.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical issues

The research was conducted under the principles of the Declaration of Helsinki. Informed written consent was taken from all participants. This study was conducted at several hospitals and outpatient medical centers across Iraq and was derived from the Ph.D project of Ihsan Maher Abdulameer (No: 9920332004), approved by the ethics committee of the Tarbiat Modares University, Tehran, Iran, under the ethical code (#IR.MODARES.

REC.1403.111). Other ethical approval was obtained from the ethics committees of all Iraqi institutions participating in the study, including the Iraqi hospitals. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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