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NARRATIVE REVIEW

Evaluation of renal function in the premature newborn

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Abstract

Background: Acute kidney injury is one of the most common injuries associated with the systemic inflammatory process in premature infants; it is related to the dysfunction of other organs and is considered a predictive marker of morbidity and mortality.

General objective: Describe clinical methods and biomarkers for evaluating renal function in premature newborns exposed to severe conditions such as mechanical ventilation, nephrotoxicity, and metabolic alterations. Analyzing these factors will allow us to detect AKI early and preserve nephrogenesis.

Methodology: This is a theoretical-descriptive study of documentary type that involves the search, analysis, and selection of electronic documents in databases published in PubMed, Scielo, and Cochrane, articles from systematic reviews, and complete bibliographical reviews, meta-analyses, consensus, and clinical practice guides in Spanish and English.

Expected results: The doctor involved in the care of the premature newborn knows the importance of the evaluation and preservation of renal function for effective decision-making, which is optimal in the integral management of patients with complex pathology in the early stages of life.

Keywords: MESH: Acute kidney injury, Preterm newborn, Renal function tests.

Introduction

Prematurity is defined as birth occurring before the 37th week of gestational age. In Ecuador, according to the latest figures from INEC 2018, 7.3% of premature births were registered, with a mortality of 6.0 per 1,000 inhabitants. The leading cause of death in children under one year of age is respiratory distress in the newborn, which corresponds to 16.6% (556 deaths), and the exact cause in children under 28 days of age is 24.8%, which corresponds to 493 cases [1, 2]. The epidemiology of acute kidney injury is not well established; different studies indicate incidence results related to some risk factors; however, all of them have shown that the presentation of neonatal acute kidney injury is ubiquitous and is associated with a poor prognosis [3].

In the Clinical Practice Guide for the Care of the Premature Newborn of Ecuador [4], strategies and protocols are established for the care of premature infants,

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emphasizing the cerebral, pulmonary, digestive-nutritional, and vascular levels; however, there are no guidelines that establish strategies that allow the preservation of renal functionality beyond specific support measures of medical knowledge to prevent AKI, such as avoiding exposure to nephrotoxic drugs and optimization of blood pressure and fluid balance according to gestational age.

The incidence of AKI in premature newborns ranges from 15-70% [5]. Of those admitted to neonatal intensive care units (NICUs), 30% develop AKI, with a 4.8-fold increased risk of mortality for neonates who do not have AKI [6]. In Ecuador, no population study has provided evidence of the incidence of AKI in premature infants.

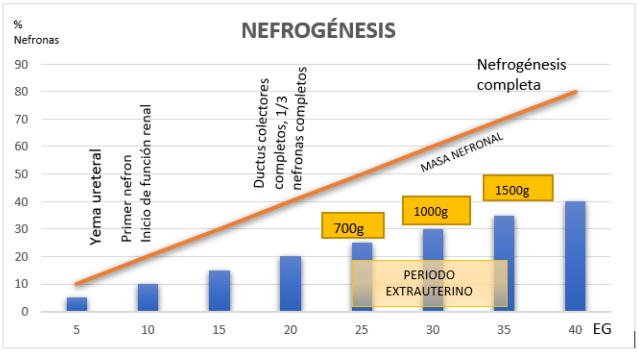
Nephrogenesis

During intrauterine growth, there is a relationship in the lung-kidney axis that is interrupted when an event such as preterm labor occurs. Nephrogenesis begins around the 9th week of gestational age (GA), and urine production at weeks 10-11 decreases at weeks 32-34 GA, with maximum output between weeks 24-30 GA. Sixty percent of nephron mass development occurs in the third trimester of pregnancy. Maturation continues within the first two years of life, reaching the adult population's glomerular filtration (GFR) values [7].

As a general criterion, the kidney grows 1.1 mm per week of gestational age and reaches approximately 1 million nephrons at birth. At 20 weeks, 300 ml/kg/day of fetal urine is produced, and it forms 90% of amniotic fluid. Ten to 15% of neonates undergo diuresis in the delivery room, 50% in the first eight hours, and 90% within 24 hours of birth [8].

Nephrogenesis in premature infants is different, being able to continue beyond birth up to 40 days, as long as it is ensured that extrauterine conditions are optimal, guaranteeing adequate hemodynamics, oxygenation, good nutrition, and avoiding the use of nephrotoxic drugs [9, 10].

Figure 1. Nephrogenesis. Percentage of nephrons according to gestational age, with events occurring in the embryonic period. Nephron mass at 24 s GA (700 g), 27 s GA (1000 g), 32 s GA (1500 g). A Birth from 25 weeks would produce extrauterine nephrogenesis that ends at six weeks of postnatal age.



Risk factors for AKI in the neonatal period

Depending on the origin of glomerular dysfunction, acute kidney injury has been divided into three groups: prerenal, intrinsic, and obstructive, associated with risk factors and gestational age of presentation.

Prenatal damage

- Prenatal use of nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme (ACE) inhibitors [11].
- Feto-fetus transfusion. AKI is associated with severe oligohydramnios and intrauterine growth retardation.
- Prenatal hyperglycemia, with alteration in the metanephros [12].

Prerenal

- Decreased blood volume: Perinatal hemorrhage (placental abruption, subgaleal hematoma) and dehydration.
- Sepsis: Necrotizing enterocolitis.
- Surgical correction of congenital abdominal defects (omphalocele, gastroschisis, etc.)

- Congenital heart disease: Heart failure or inadequate perfusion pressure, congenital heart disease associated with congestive heart failure. Myocardial dysfunction from perinatal hypoxia or sepsis [13].

Intrinsic or from the renal parenchyma

- Acute tubular necrosis. Hypoxic-ischemic encephalopathy.
- Drugs: Aminoglycosides (gentamicin, amikacin), glycopeptides (vancomycin), high osmolarity or ionic radiological contrast media defined as an osmolarity of 1,500-800 mOsmol/kg and including metrizoate, diatrizoate, and iothalamate [14].
- Tubulointerstitial nephropathy due to uric acid deposits.
- Glomerulonephritis. Maternal ANCA+ vasculitis, transplacental passage of maternal autoantibodies.
- Vascular injuries. Renal artery thrombosis. Renal vein thrombosis.
- Hemolytic uremic syndrome.
- Congenital anomalies: Agenesis. Hypoplasia-dysplasia.
- Polycystic kidney disease.
- Rarely: renal tubular dysgenesis, idiopathic diffuse mesangial sclerosis, congenital nephrotic syndrome [13].

Obstructive

- Urethral obstruction (posterior urethral valves. Stenosis). Ureterocele. Ureteropelvic, ureterovesical obstruction.
- Extrinsic tumors.
- Neurogenic bladder in patients with malformations of the neural tube.

In a prospective study with the participation of 206 preterm newborns between 27 and 36 weeks of gestation carried out by Mazaheri et al., it was determined that the factors associated with the development of AKI were prematurity, low birth weight, Apgar below 1 and 5 minutes and the need for mechanical ventilation, as well as the coexistence of sepsis [15].

Maur et al. described 200 term infants with sepsis, of whom 52 developed AKI [3]. Rhone et al. evaluated exposure to nephrotoxins, which is a modifiable factor, and found that 87% of NBs were exposed to at least one nephrotoxic agent in an average of 14 days [16].

Acute Kidney Injury Criteria

In 2013, pediatric neonatologists and nephrologists implemented the KDIGO (Kidney Disease Improving Global Outcomes; KDIGO) criteria [17] (Table 1) to provide a more appropriate definition of AKI for the newborn, offering a more reasonable starting point that will allow consistency across studies.

The 2017 AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) study, conducted on 990 patients, showed that the incidence of AKI is higher the younger the neonate's gestational age. Mortality in neonates with AKI was 10% in contrast to 1% in those without AKI ($P < 0.0001$). The more severe the AKI, the greater the mortality and days of hospitalization [18]. When we use the modified KDIGO criteria, taking serum creatinine and urine volume into account and classifying them according to their stages, it results in an incidence of 50% in highly preterm neonates associated with increased morbidity and mortality. The urinary output criteria need adaptations to longer time intervals or weight trends, while the CrS does not provide data on renal function alterations; instead, it is suggested to use the assay-specific CrS percentile values to better describe postnatal trends [19].

Kidney function assessment

The clinical history and the presence of maternal and neonatal risk factors determine a relevant role in the approach to evaluating renal function.

Table 1. Modified KDIGO criteria.

Stage	Serum creatinine	Urinary volume
0	No change or increase < 0.3 mg/dl	≥0.5 mL/kg/h
1	Increase ≥ 0.3 mg/dl in 48 h or ≥ 1.5-1.9 times the reference value ≤7 days	< 0.5 ml/kg/h for 6-12 h
2	≥ 2-2.9 times the reference value	< 0.5 mL/kg/h for ≥12 h
3	≥ 3 baseline or creatinine ≥ 2.5 mg/dl or dialysis required	< 0.3 mL/kg/h for ≥ 24 h or anuria ≥12 h

Neonatal Acute Kidney Injury Workshop, NIH (2013)
KDIGO: kidney disease improving global outcomes.

1. Maternal Factors:

- Ultrasound controls showing hydronephrosis or a single kidney and gestational age at diagnosis.
- Use of drugs and gestational age of administration to assess the potential for nephrotoxicity
- Family history of hereditary nephropathies such as autosomal recessive polycystic disease or congenital nephrotic syndrome.
- History of maternal diabetes.
- Amount of amniotic fluid at birth or a history of oligohydramnios considered as the maximum vertical column (MCV) < 2 cm, severe oligohydramnios/anhydramnios when it is less than 1 cm, or an amniotic fluid index (ALI) < 5 [20].

2. Neonatal factors

- Perinatal asphyxia
- Gestational age at birth
- History of bleeding, fluid loss, diarrhea, and increased insensible losses.
- Exposure to nephrotoxic drugs.
- Congenital heart disease.
- Congenital anomalies (anorectal malformation, tracheoesophageal fistula, diaphragmatic hernia, renal malformations, etc.)
- Neonatal sepsis

3. Physical examination of the Newborn

- Complete exploration that determines the gestational age using the Ballard Scale validated for extremely premature and full-term neonates after 24 hours of birth [21].
- Weight through the Fenton and Kim curves that allow showing the weight gain [22].
- Blood pressure and percentiles [23], taking blood pressure (BP) in neonates requires practice and technique. It is directly related to gestational age, postnatal age, weight, and maternal factors.
- State of hydration to reach euvolemia. Hypovolemia will prolong renal hypoflow, increasing the damage [24].

4. Complementary studies:

Urine analysis

In the first 24 hours of life, 7% of patients do not produce urine, and dripping or anuria for more than 48 hours is an urgent indication to perform renal and bladder ultrasound control before catheterizing the urinary tract, which should be done with extensive care for the risk of perforation.

Urinary output:

- o Term neonate: 1 ml/kg/hour
- o Premature neonate: 0.5 ml/kg/day,
- o Oliguria below this amount,
- o Polyuria: 3-6 ml/kg/hour, which causes a negative balance.
- Color, clear and transparent; any alteration with turbidity can indicate infection [11].
- The collection bag or cotton urine collection can be used for urinalysis and microscopic examination. Density does not correlate with osmolarity due to the usual presence of protein or glucose, but there are three possibilities:

a) Urinary density greater than or equal to 1010 with normal urine sediment, without hematuria or proteinuria, indicates prerenal acute kidney injury.

b) Urine density less than 1010 with normal urine sediment indicates intrinsic renal injury.

c) Variable changes in urine density and pathological sediment suggest the presence of nephritic and nephrotic syndromes, vascular thrombosis, interstitial nephropathies, or the presence of crystalluria and bacteriuria suggests obstructive pathology [25].

- Proteinuria less than 50 mg/dl is a frequent finding during the first days of life.
- Gross hematuria should be confirmed by urinary sediment; it is rare in the neonatal period.
- Glycosuria is common in preterm infants under 34 weeks GA.
- In suspected infection, the gold standard is ultrasound-guided suprapubic puncture for urine collection or collection by spontaneous urination based on bladder and lumbar region stimulation maneuvers [11].

Evaluation of Estimated Glomerular Filtration Rate and Serum Creatinine

The glomerular filtration rate increases rapidly after 20 weeks, reaching 10-20 ml/min/1.73 m^2 at 28-30 weeks, reaching a plateau of 20-30 ml/min/1.73 m^2 at week 35, which is maintained until week 40. The mean glomerular filtration rate at birth or the first three days of life varied with GA and increased within two weeks after delivery (Table 2).

In premature infants, the glomerular filtration surface area decreases, the glomerular filtration rate (GFR) is reduced by 30 ml/min/1.73 m^2, and several vasoconstrictor factors regulate renal hemodynamics and affect renal maturation [24].

Serum creatinine (Cr S)

It is produced endogenously from creatine and creatine phosphate due to metabolism in skeletal muscle. It is excreted in the urine by organic anion transporters by glomerular filtration and tubular secretion in the proximal convoluted tubule. Plasma concentrations vary with age by different combinations of muscle mass and glomerular filtration rate [26].

Table 2. The mean glomerular filtration rate at birth or within the first three days of life varies by gestational age

GA (weeks)	GFR* in the first 72 h of life	GFR* at 2 weeks of life
27	13.4	16.2
8	16.2	19.1
29	19.1	21.9
30	21.9	24.8
31	24.9	27.6
RNT	26.0	54.0

RNT. Term newborn. FG. Glomerular filtration (ml/min/1.73 m^2. EG. Gestational age

In the newborn, the creatinine concentration is generally high compared to the mother, and the RNPs present high levels, which indicates that the renal tubule is absorbing creatinine. The levels drop rapidly after birth; according to Ríos DR et al., in a study with the participation of 4808 neonates at 34.4 ± 5 weeks, they demonstrated a delay in the onset of glomerular filtration. It was inversely proportional to GA, and extremely preterm neonates had a longer delay in filtration onset during the first five days of life. The median steady-state creatinine concentration was <0.3 mg/dL [27].

Creatinine and creatinine clearance have been the most widely used biomarkers in the evaluation of renal function. Allegaert et al., in a study involving 217 extremely preterm infants, introduced the percentiles of creatinine values in the first 28 days of postnatal age [19] (Table 3).

There are positive or endogenous interferents such as proteins, glucose, acetoacetate, ascorbic acid, and uric acid, and negative interferents are the most crucial bilirubin that alters serum creatinine results. High bilirubin and fetal hemoglobin levels result in low creatinine values. Enzymatic creatinine measurements have superior specificity, accuracy, and precision and do not have harmful interference with fetal bilirubin and hemoglobin, which is why they are the choice in neonatology [28].

Serum creatinine is not a good marker of AKI; it measures GFR and not kidney damage. However, researchers used the calculation of volume-adjusted SCr = SCr x [ACT + current weight-birth weight]/ACT.

Table 3. Percentiles of serum creatinine values in a cohort of 217 extremely preterm newborns at 28 days of postnatal age.

Day of life	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Samples	206	190	205	198	182	171	145	157	140	128	117	112	92	133
P10	0.45	0.64	0.74	0.64	0.58	0.55	0.54	0.50	0.50	0.44	0.42	0.41	0.41	0.41
P25	0.52	0.75	0.81	0.76	0.7	0.67	0.64	0.60	0.57	0.55	0.51	0.50	0.47	0.48
P50	0.605	0.86	0.91	0.88	0.84	0.80	0.75	0.74	0.70	0.65	0.64	0.60	0.59	0.57
P75	0.74	0.95	1.03	1.03	0.97	0.94	0.89	0.88	0.83	0.79	0.79	0.76	0.70	0.66
P90	0.91	1,065	1.18	1.18	1.14	1.12	1.11	1.04	1.01	0.93	0.96	0.87	0.86	0.8
P95	0.98	1.16	1.22	1.29	1.25	1.28	1.17	1.12	1.15	1.05	1.03	0.92	0.96	0.85
Day of life	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Samples	101	96	99	79	85	62	123	72	66	86	64	fifty	54	111
P10	0.36	0.36	0.37	0.35	0.38	0.37	0.36	0.37	0.36	0.35	0.33	0.34	0.32	0.32
P25	0.44	0.44	0.43	0.42	0.42	0.40	0.39	0.40	0.40	0.41	0.38	0.37	0.37	0.36
P50	0.55	0.52	0.51	0.49	0.49	0.50	0.47	0.46	0.47	0.47	0.43	0.45	0.44	0.42
P75	0.63	0.61	0.60	0.61	0.57	0.62	0.54	0.54	0.54	0.52	0.52	0.51	0.50	0.48
P90	0.81	0.69	0.71	0.73	0.66	0.68	0.62	0.68	0.64	0.64	0.58	0.59	0.70	0.55
P95	0.87	0.73	0.78	0.81	0.73	na	0.68	0.72	na	0.67	na	na	na	0.59

Table 4 . Serum Cystatin C values in neonates.

GA	PNA (days)	Range	Upper limit	Lower limit
≤28 (n=15)	0-3	1.2-2.1	1.18 (1.02-1.34)	2.02 (1.86-2.18)
	4-6	1.3-2.3	0.99 (0.75-1.23)	2.11 (1.87-2.35)
	7-10	1.2-2.4	0.90 (0.53-1.28)	2.55 (2.16-2.92)
	11-15	1.5-2.2	1.35 (1.15-1.56)	2.39 (2.18-2.60)
	22-30	1.4-2.5	1.20 (0.86-1.54)	2.83 (2.50-3.17)
29-32 (n=40)	0-3	0.3-2.1	1.01 (0.88-1.14)	2.11 (1.99-2.24)
	4-6	1.1-1.9	1.12 (0.98-1.25)	1.95 (1.82-2.09)
	7-10	1.2-2.4	1.18 (1.03-1.33)	2.31 (2.16-2.47)
	11-15	1.4-2.4	1.27 (1.08-1.46)	2.48 (2.29-2.66)
	16-21	1.3-2.8	1.06 (0.89-1.23)	2.29 (2.12-2.46)
	22-30	1.4-2.3	1.31 (1.15-1.47)	2.37 (2.21-2.53)
33-36 (n=72)	0-3	1.2-2.5	1.18 (1.10-1.27)	2.17 (2.08-2.25)
	4-6	1.1-2.1	1.15 (1.04-1.27)	2.20 (2.09-2.32)
	7-10	1.0-2.2	1.07 (0.95-1.18)	2.32 (2.20-2.43)
	11-15	11-2.2	1.25 (1.11-1.40)	2.19 (2.05-2.33)
	16-21	1.4-2.2	1.38 (1.26-1.50)	2.23 (2.11-2.35)
	22-30	1.3-2.1	1.19 (1.07-1.31)	2.08 (1.96-2.21)
≥37 (n=119)	0-3	0.9-2.9	1.01 (0.93-1.10)	2.28 (2.19-2.36)
	4-6	0.5-2.1	0.92 (0.84-0.99)	1.92 (1.85-2.00)
	7-10	1.0-2.0	1.06 (0.99-1.13)	1.96 (1.89-2.03)
	11-15	1.1-2.2	0.97 (0.85-1.10)	2.12 (2.00-2.25)
	16-21	1.1-2.2	0.88 (0.70-1.05)	2.21 (2.04-2.39)
	22-30	1.0-2.4	0.80 (0.56-1.04)	2.33 (2.09-2.57)

GA: Gestational age. PNA Postnatal age

They found a lower incidence of AKI, 18.8% vs. 27.9%, concluding that this approach differentiates changes in current renal function from changes elicited by fluid volume [29].Recently, a specific eGFR for preterm and athermic infants (mean age three days postnatal period, Jaffe compensated) (eGFR= 2.32 x [weight (g)/CrS (µmol/L)] has been suggested. This formula worked best in comparison with the original neonatal Schwartz formula [30].

Cystatin C (CysC)

It is a serum protease inhibitor polypeptide (PM13 kDa) constantly produced by nucleated cells. Unlike serum creatinine, its concentration is not affected by muscle mass or sex, and its value depends on age: it is higher at birth, it decreases at 12 months, and does not depend on gestational age; it does not cross the placenta, it does not reflect maternal renal function, and it can measure fetal and postnatal GFR. Recently, a study measured serum CysC that demonstrated a sensitivity of 93% and specificity of 96% with a cutoff of 1.3 mg/dl predicting AKI in neonates with RDS, in contrast to those who were healthy [8].

Ji-Hyun Lee et al. provided cystatin C values in healthy neonates from the first 30 days of life (Table 4) and showed that for RNPs with a postconceptional age of <28-32 weeks, there was a gradual decrease in CysC of 1.60 ±0.21 in the first three days, 1.50 mg/l on the fourth-sixth day of life, and then a gradual increase up to 22-30 days. They concluded that CysC increases 48 hours before the renal resistance index and creatinine in critically ill neonates who develop AKI [31]. Of specific importance to neonates, steroid administration and hyperthyroidism can also affect cystatin C by increasing its concentration, while in hypothyroidism, CysC is decreased [32].

Neutrophil gelatinase-associated lipocalin (NGAL)

It has bacteriostatic properties and participates in innate immunity. At the renal level, it is used with a marker in blood and urine that increases renal injury. This marker predicts AKI long before creatinine is affected, showing a specificity of 87% with oscillating threshold values of 140-157 ng/mL. Urinary NGAL had a cutoff value of 18-162 ng/ml with a sensitivity of 89.7% [33]. In prospective experimental studies, investigators have concluded that elevated levels of NGAL can determine the risk of AKI early, even in patients asphyxiated on the first day of life, but not in those with patent ductus arteriosus [29].

Interleukin 18

Monocytes, macrophages, and proximal tubule cells produce the IL-1 family of proinflammatory cytokines. Its concentration in patients with acute lung injury predicted the occurrence of acute kidney injury within 24 hours with an OR greater than 4.22 (95% CI 2.90-6.14; in particular, sensitivity and specificity of 0.58 and 0.75, respectively). IL18 exhibits a time course, with an initial rise time of 4-6 h and a peak concentration of 12 h, and remains elevated for 48 h [35].

Epidermal Growth Factor (EGF)

It is a modulating protein produced by the salivary glands present in milk. Its values decrease in children with kidney injury and neonates with asphyxia [8].

Uromodulin or urinary Tamm-Horsfall protein

It is a protein secreted by the epithelial cells of the loop of Henle, has a protective role, and reduces renal inflammation. Low uromodulin concentrations in urine are a sensitive indicator for a loss of renal function. High birth weight, inflammation, and diabetes raise their values, while nephrectomy produces a decrease [37].

Kidney Injury Molecule (KIM 1)

It is an epithelial cell adhesion protein that contains an immunoglobulin-binding end. KIM-1 is a type 1 transmembrane protein located in the proximal tubules and has shown increased expression after ischemic or toxic renal injury in experimental and clinical studies [38].

Other bookmarks

In addition to the changes in these markers, the changes associated with AKI should be assessed:

- Hyponatremia: the result of water intake that cannot be excreted.
- Hyperkalemia: decreased GFR due to reduced potassium secretion, tissue rupture with intracellular potassium release, and metabolic acidosis resulting in transcellular movement of potassium [24].
- Hyperphosphatemia: secondary to reduced excretion of phosphate.
- Hypocalcemia: secondary to hyperphosphatemia.

Conclusions

The physiological changes precede the damage of the renal parenchyma; the lower the gestational age, the greater the presentation of AKI, added to risk factors such as nephrotoxic drugs and the alteration of urinary output, blood pressure figures, and urinalysis can detect it, early predicting AKI.

The minimum screening of renal function in the premature newborn should include the moment of the first urination, adequate and meticulous recording of the fluid balance, recording of blood pressure, clinical examination, an inspection of urine, elemental and microscopic analysis of urine, and bladder and kidney ultrasound with Doppler.

Newborns with AKI are predisposed to developing chronic kidney injury and require monitoring of blood pressure, urinalysis, and renal function during later growth. The study of renal function in premature newborns is still limited. It is necessary to research a biomarker whose demonstration of specific use can improve treatment, reduce some outcomes of epidemiological interest, and improve survival.

Abbreviations

ACT: Total body water.
AKI: acute kidney injury.
Scr: serum creatinine.
GFR: glomerular filtration rate.

Supplementary information

No supplementary materials are declared.

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Author contributions

Joanna Granda Jiménez: Conceptualization, data curation, formal analysis, fundraising, research, writing - original draft.
Franklin Loachamin Caiza: Methodology, project administration, resources, Software, supervision, validation, visualization, revision, and editing.
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Ethics committee approval and consent to participate

Not required for narrative reviews.

Publication Consent

Not required when patient-specific images, radiographs, and studies are not published.

Conflicts of interest

The authors declare they have no conflicts of interest.

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