

# Comparative study of glomerular filtration rates estimated from serum cystatin C and serum creatinine in the follow-up of renal function in patients with neurogenic bladder due to HTLV-I infection

## *Estudo comparativo das taxas de filtração glomerular estimada através da cistatina C e creatinina séricas no acompanhamento da função renal dos pacientes com bexiga neurogênica por HTLV-I*

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### Abstract

**Background:** Patients with HTLV-I myelopathy and tropical spastic paraparesis (HAM/TSP) have a higher risk of developing chronic kidney disease, requiring follow-up of the renal function. **Objective:** To analyze the glomerular filtration rates (GFRs) estimated from CKD-EPI formulas for patients with HAM/TSP and neurogenic bladder taking into consideration the chronic kidney disease (CKD) staging in order to establish the best predictor for CKD in those patients. **Methods:** Retrospective longitudinal study conducted in the Salvador unit of "Rede SARAH de Hospitais", Bahia, Brazil. Data from 535 medical records was converted into glomerular filtration rate using the CKP-EPI formulas recommended in the 2013 KDIGO guideline "Guidelines for Evaluation and Management of CKD". The estimated GFRs were statistically compared and correlated. The association between disease status and estimated GFR value was also assessed. **Results:** Analysis of the agreement between results of the CKD-EPI cystatin C and CKD-EPI creatinine formulas showed the worst correlation strength (Cohen's Kappa: 0.40; Cramér's V<sup>2</sup>: 0.45). The highest agreement and correlation was observed between results from the CKD-EPI creatinine and CKD-EPI creatinine-cystatin C formulas (Cohen's Kappa: 0.69; Cramér's V<sup>2</sup>: 0.72). Using the 60 mL/min 24h cut-off point, and the classes recommended by KDIGO, the CKD-EPI cystatin C results for the cases group were systematically lower than those obtained by the other two formulas. **Conclusion:** The glomerular filtration rate (GFR) estimated by the CKD-EPI cystatin C proved to be, in this study, a better predictor of renal function in patients with HAM/TSP and neurogenic bladder.

**Keywords:** Glomerular filtration rate; CKD-EPI formulas; HTLV; Urinary Bladder, Neurogenic; Renal function.

### Resumo

**Fundamento:** Pacientes com mielopatia por HTLV-I e paraparesia espástica tropical (HAM/TSP) têm maior risco de desenvolver doença renal crônica, necessitando de acompanhamento rigoroso da função renal. **Objetivo:** Analisar as taxas de filtração glomerular (TFGs) obtidas a partir de fórmulas CKD-EPI para pacientes com HAM/TSP e bexiga neurogênica levando em consideração o estadiamento da doença renal crônica (DRC) a fim de estabelecer o melhor preditor de DRC nesses pacientes. **Método:** Estudo longitudinal retrospectivo realizado na unidade Salvador da Rede SARAH de Hospitais, Bahia, Brasil. Os 535 dados dos prontuários médicos foram convertidos em TFG a partir das fórmulas CKP-EPI conforme "Guidelines for Evaluation and Management of CKD" da KDIGO 2013. Os dados foram estatisticamente comparados e correlacionados. A associação entre o estado da doença e o valor estimado da TFG também foi avaliada. **Resultados:** A análise da concordância entre os resultados das fórmulas CKD-EPI cistatina C e CKD-EPI creatinina mostrou a pior força de correlação (Kappa de Cohen: 0,40; V2 de Cramér: 0,45). A maior concordância e correlação foi observada entre os resultados das fórmulas CKD-EPI creatinina e CKD-EPI creatinina-cistatina C (Kappa de Cohen: 0,69; V2 de Cramér: 0,72). Utilizando o ponto de corte de 60 mL/min 24h e a classificação preconizada pelo KDIGO, os resultados da CKD-EPI cistatina C para o grupo de casos foram sistematicamente inferiores aos obtidos pelas outras duas fórmulas. **Conclusão:** A taxa de filtração glomerular (TFG) estimada pelo CKD-EPI cistatina C mostrou-se, neste estudo, um melhor preditor da função renal em pacientes com HAM/TSP e bexiga neurogênica.

**Palavras-Chave:** Taxa de filtração glomerular; Fórmulas CKD-EPI; HTLV; Bexiga Urinária, neurogênica; Função renal.

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Recebido em 28/08/2022 | Aprovado em 30/01/2023 | DOI: 10.21877/2448-3877.202300067

## INTRODUCTION

Human T-cell leukemia virus type-1 (HTLV-1) is an oncogenic human retrovirus that infects 10-20 million people all over the world. It is endemic in parts of the world including the Caribbean, parts of central Africa, southern parts of the United States and Brazil.<sup>(1)</sup> HTLV-1 causes diseases with different clinical outcomes such as adult T-cell leukemia/lymphoma,<sup>(2)</sup> and inflammatory neurologic disease, mainly HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP).<sup>(3)</sup> The later is insidious and progressive. It is characterized by unremitting myelopathic symptoms such as spastic paraparesis, lower limb sensory disturbance, and bladder/bowel dysfunction.<sup>(4)</sup> The neurogenic bladder originates from the thoracolumbar impairment expressed as hyperactivity of the detrusor bladder muscle. It is a risk factor for chronic kidney disease.<sup>(5,6)</sup>

For many decades, renal failure has been the factor with the greatest implication on morbidity and mortality of patients with spinal cord injury.<sup>(7)</sup> This makes the search for markers sensitive to the first signs of impaired kidney function in patients with HAM/TSP an important challenge for laboratory medicine.<sup>(5,7)</sup> The glomerular filtration rate (GFR) is considered the best overall index of kidney function in health and disease. GFR cannot be measured easily in clinical practice though. Instead, GFR is estimated from equations using serum creatinine and cystatin C, age, race, sex and body size.<sup>(8,9)</sup>

In clinical practice, the Cockcroft-Gault and MDRD (Modification of Diet in Renal Disease) formulas are still widely used but have recognized limitations for certain populations.<sup>(10,11)</sup> More recently, the Chronic Kidney Disease Epidemiology (CKD-EPI) consortium has proposed a group of novel equations for estimating glomerular filtration rate

(Table 1) which are included in the Kidney Disease: Improving Global Outcomes (KDIGO) association guidelines since 2013.<sup>(12)</sup>

These are currently widely recommended by medical societies and are reported in the literature as the formulas that provide better GFR estimation with the advantage of being able to use both creatinine and cystatin C alone or combined for the calculation.<sup>(13-17)</sup>

This work is, to the best of our knowledge, the first study to evaluate the performance of the CKD-EPI formulas in estimating glomerular filtration rates for adult patients with HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) with the objective to assess which one yields the most reliable GFR estimate for this group of patients.

## MATERIALS AND METHODS

### Study design

This retrospective longitudinal study was conducted using information collected at the SARAH Salvador Hospital (Bahia, Brazil) from 2002 to 2018 through the evaluation of laboratory data in electronic medical records of adult patients with HAM/TSP. This study was approved by the ethics committees of the Rede Sarah de Hospitais, Brazil and of the University Fernando Pessoa, Portugal.

### Data collection

The laboratory data was obtained from 535 medical records of adult patients with HTLV-I. Inclusion criteria were: age range between 16 and 60 years; clinical signs compatible with paraparesis and myelopathy; positive result for HTLV-I in serum and CSF samples; analytical results of serum creatinine and cystatin C obtained on the same day and diagnosis of

**Table 1**

CKD-EPI equations for estimating GFR.

Basis of equation	Equation for estimating GFR
CKD-EPI creatinine (CDK-EPI <sub>Scr</sub> )	$141 \times \min(Scr/k, 1)^{\alpha} \times \max(Scr/k, 1)^{-1.209} \times 0.993^{Age} [x 1.018 \text{ if female}] [x 1.159 \text{ if black}]$ Where <i>Scr</i> is serum creatinine, <i>k</i> is 0.7 for females and 0.9 for males, $\alpha$ is -0.329 for females and -0.411 for males, <i>min</i> is the minimum of <i>Scr/k</i> or 1, and <i>max</i> is the maximum of <i>Scr/k</i> or 1.
CKD-EPI cystatin C (CDK-EPI <sub>Scys</sub> )	$133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age} [x 0.932 \text{ if female}]$ Where <i>Scys</i> is serum cystatin C, <i>k</i> is 0.7 for females and 0.9 for males, $\alpha$ is -0.329 for females and -0.411 for males, <i>min</i> is the minimum of <i>Scys/k</i> or 1, and <i>max</i> is the maximum for <i>Scys/k</i> or 1.
CKD-EPI creatinine-cystatin C (CDK-EPI <sub>Scr-Scys</sub> )	$135 \times \min(Scys/k, 1)^{\alpha} \times \max(Scys/k, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8, 1)^{-0.711} \times 0.995^{Age} [x 0.969 \text{ if female}] [x 1.08 \text{ if black}]$ Where <i>Scr</i> is serum creatinine, <i>Scys</i> is serum cystatin C, <i>k</i> is 0.7 for females and 0.9 for males, $\alpha$ is -0.248 for females and -0.207 for males, <i>min</i> is the minimum of <i>Scr/k</i> or 1, and <i>max</i> is the maximum of <i>Scr/k</i> or 1.

neurogenic bladder confirmed by the urologist. Individuals with pre-existing diseases with repercussion in reduced renal function, individuals outside the established age range and patients in whom the diagnosis of neurogenic bladder or HTLV-I myelopathy was not well established following the criteria of the “Guia do Manejo Clínico da infecção por HTLV<sup>(18)</sup>” were excluded from the study.

In the end, a group of 174 individuals who performed a total of 847 creatinine and cystatin C tests was selected. It was also possible to select a study control group composed of 32 individuals with asymptomatic HTLV-I who performed 44 creatinine and cystatin C tests.

### Statistical Methods

The laboratory data for creatinine and cystatin C were mathematically treated to be used in the CKD-EPI formulas.

The GFR results revealed to be non-normally distributed (Kolmogorov-Smirnov normality test), hence non-parametric tests were used in the statistical analysis. This analysis was performed using the SPSS<sup>®</sup> software version 26.0 (Statistical Package for the Social Sciences -IBM, Armonk, NY, USA), considering a significance level of 0.05 for all tests.

### Ethical standards

#### Compliance with ethical standards

- Research involves human and/or animal participation: No, the study involves retrospective database analysis.
- Informed Consent: I accept waiver of informed consent by the Hospital Ethics Committee (CEP number 3.281.307)

### RESULTS

Table 2 shows the result of the comparison of the Cases and Control groups, considering the gender and age variables. As can be seen, no statistically significant differences were found between the two groups with regard to these variables.

The estimated GFRs based on the laboratory data of serum creatinine and cystatin C using the three CKD-EPI formulas are compared in Table 3. Using the Friedman test, it is concluded that there are statistically significant differences between the GFRs estimated by the different CKD-EPI formulas for the cases group ( $p < 0.01$ ) but not for the control group ( $p = 0.22$ ). Additionally, it is noted that the CKD-EPI creatinine equation leads to statistically identical GFR estimates for both groups.

**Table 2**

Demographic characterization of the study groups regarding gender and age variables.

Characteristic	Cases (n=174) Median [IQR] or (%)	Controls (n=32) Median [IQR] or (%)	P
Age (years)	49 [13.1]	50 [21.1]	0.56†
Gender			
Women	124 (71)	24 (75)	0.66‡
Men	50 (29)	8 (25)	

†Median test; ‡Chi-square test.

**Table 3**

Comparison of GFRs estimated by the different CKD-EPI formulas for the case and control patients.

Group	CKD-EPI equation used for estimating GFR	Average GFR/ml/min 24h	IC 95% GFR/ml/min 24h
Cases	CKD-EPI <sub>cys</sub> <sup>1</sup>	83.2	81.4 – 84.9
	CKD-EPI <sub>Scr-cys</sub> <sup>2</sup>	93.4	91.7 – 95.1
	CKD-EPI <sub>Scr</sub> <sup>3</sup>	105.1	103.4 – 106.1
Controls	CKD-EPI <sub>cys</sub> <sup>1</sup>	103.5	97.4 – 109.6
	CKD-EPI <sub>Scr-cys</sub> <sup>2</sup>	105.0	98.3 – 111.7
	CKD-EPI <sub>Scr</sub> <sup>3</sup>	102.5	95.5 – 102.2

<sup>1</sup> $U = 27231.5$ ,  $p < 0.01$ ; <sup>2</sup> $U = 23196.0$ ,  $o = 0.01$ ; <sup>3</sup> $U = 16746.0$ ,  $p = 0.26$ .

The degree of agreement and correlation between the GFRs estimated by the three equations was measured utilizing the Cohen's Kappa and Cramér's  $V^2$  statistics. As shown in Table 4 the highest agreement was obtained between the GFR results estimated by the CKD-EPI creatinine and the CKD-EPI creatinine-cystatin C equations and the worst agreement and correlation was observed between estimates obtained using the CKD-EPI creatinine and CKD-EPI cystatin C equations.

In order to assess the impact of the GFR result variation on the clinical evaluation of symptomatic patients, a comparative analysis was performed between the estimated GFRs using the 60 mL/min<sub>24h</sub> cut-off point. As evidenced in Table 5, the

highest number of estimated GFR values for symptomatic patients below the 60 mL/min<sub>24h</sub> cut-off point was obtained using the CKD-EPI cystatin C formula. Furthermore, based on the results of the **chi-square test**, we can state that when the CKD-EPI cystatin C equation is used there was a significant association between predicted GFR and disease status ( $p = 0.01$ ) ( $p = 0.01$ ).

Using the classification proposed by KDIGO 2012 it is possible to distribute the estimated GFR as shown in Figure 1, confirming that CKD-EPI cystatin C produces systematically lower GFR estimates when compared to the data obtained by the other CKD-EPI formulas studied.

**Table 4**

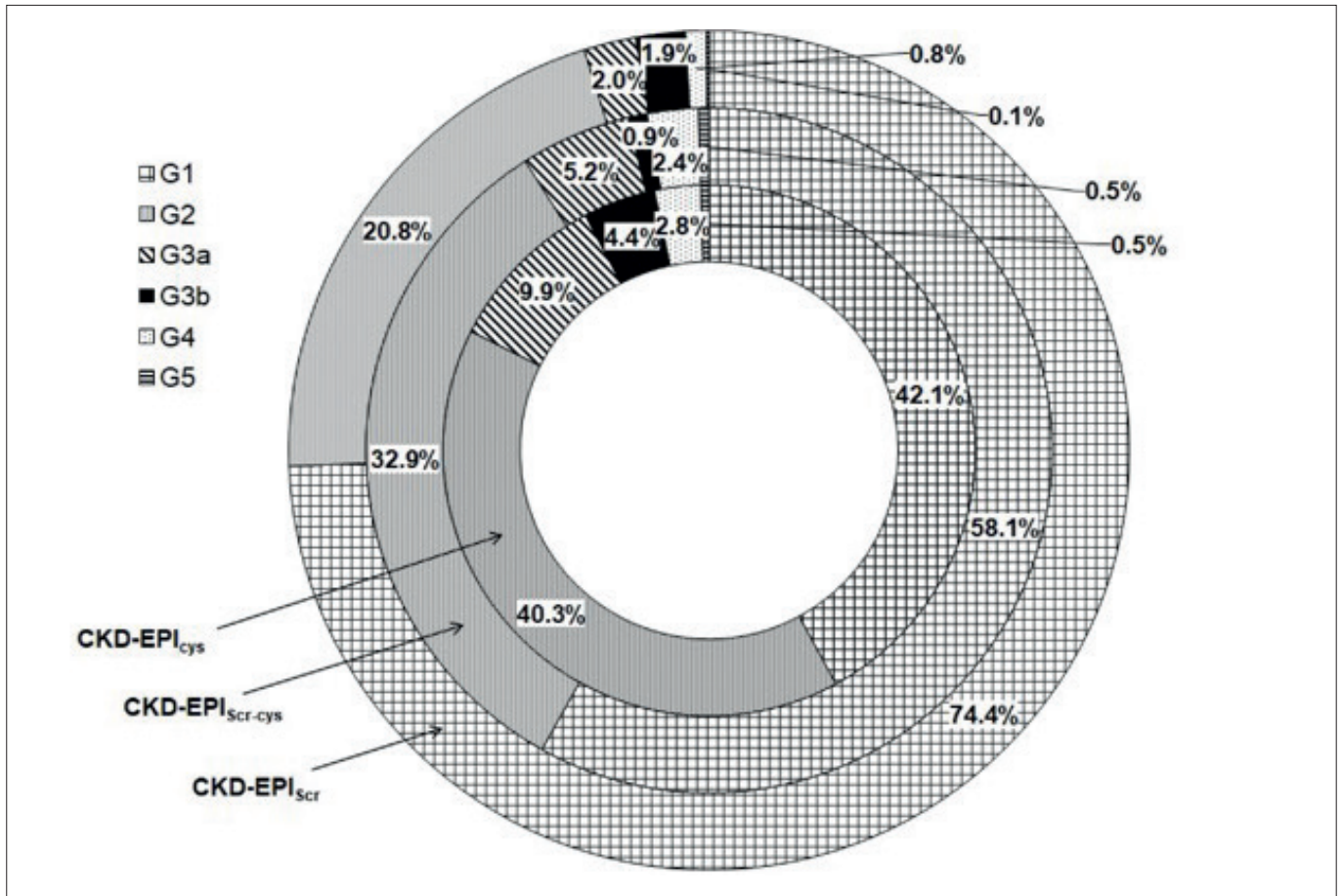
Inter-rater agreement and correlation analysis of the CKD-EPI formulas.

CKD-EPI equations	Cohen's Kappa K (n); p; Classification	Cramér's $V^2$ $V^2$ (n); p; Classification
CKD-EPI <sub>cys</sub> versus CKD-EPI <sub>Scr-cys</sub>	0.61 (891); <0.01; Substantial agreement	0.65 (891); <0.01; Moderate
CKD-EPI <sub>cys</sub> versus CKD-EPI <sub>Scr</sub>	0.40 (891); <0.01; Fair agreement	0.45 (891); <0.01; Moderate
CKD-EPI <sub>Scr-cys</sub> versus CKD-EPI <sub>Scr</sub>	0.69 (891); <0.01; Substantial agreement	0.72 (891); <0.01; Strong

**Table 5**

Comparative analysis between cases and controls considering the cut-off point of 60mL/min 24h.

Estimated GFR	Equation					
	CKD-EPI <sub>cys</sub>		CKD-EPI <sub>Scr-cys</sub>		CKD-EPI <sub>Scr</sub>	
	Cases	Controls	Cases	Controls	Cases	Controls
≥60ml/min 24h	698 (82%)	43 (98%)	771 (91%)	43 (98%)	806 (95%)	43 (98%)
<60ml/min 24h	149 (18%)	1 (2%)	76 (9%)	1 (2%)	41 (5%)	1 (2%)
Chi-square independent test results	$\chi^2=7.01$ , $p = 0.01$		$\chi^2 = 2.38$ , $p = 0.12$		$\chi^2 = 0.61$ , $p = 0.43$	



**Figure 1**

Categorization of the estimated GFR values (ml/min per 1.73 m<sup>2</sup>) using KDIGO 2012 staging.

High and moderate degrees of agreement were observed between the staging predicted by the CKD-EPI<sub>cys</sub> and CKD-EPI<sub>Scr-cys</sub> formulas for categories G1 (97%), G2 (57%), G4 (79%) and G5 (75%). The agreement percentages drop to 18% and 14% in the G3a and G3b categories, respectively. The agreement between GFR data between formulas CKD-EPI<sub>cys</sub> and CKD-EPI<sub>Scr</sub> is worse in almost all categories except G1 (92%). The comparative analysis between the CKD-EPI<sub>Scr</sub> and CKD-EPI<sub>Scr-cys</sub> formulas showed a better agreement in the G1 and G2 categories (75% and 72%), even so, lower than that observed in the staging predicted by the CKD-EPI<sub>cys</sub> and CKD-EPI<sub>Scr-cys</sub>. However, a better agreement was observed in the G3a category. Despite having presented agreements between 57% and 100% in the G4 and G5 categories, the reduction in the number of data analyzed does not allow any objective or relevant inference.

## DISCUSSION AND CLINICAL REPERCUSSION

The early detection of kidney disease is essential in the clinical follow-up of patients with neurogenic bladder. This makes the identification of a laboratory marker that allows assessment of the first signs of the disease, desirable.<sup>(2)</sup> In this sense serum creatinine and cystatin C, are particularly useful because they allow the estimation of GFR, considered the best overall index of kidney function, without the need to collect 24-hour urine or use invasive methods with exogenous markers.<sup>(9,19)</sup> The challenge associated with using the GFR is that the different formulas currently used to estimate GFR can lead to disparate values which can create uncertainty in assessing kidney function. Several studies have already pointed out differences in the performance of the CKD-EPI formulas according to the population profile.<sup>(20,21)</sup> MacDiarmid

and collaborators conducted a study with individuals with spinal cord injury, and concluded that the GRF estimates obtained from the Cockcroft-Gault formula did not correlate with the gold standard.<sup>(22)</sup> This led those researchers to recommend the use of urinary creatinine determination as an option for estimating GFR for those patients. Macdiarmid and collaborators argued that the medullary filtration rate could be reduced without changing the serum creatinine associated with the age factor.<sup>(22)</sup> Stevens conducted studies with CKD patients and concluded that the GFR equations that employ cystatin C are more accurate.<sup>(20)</sup> This research also showed that the CKD-EPI creatinine-cystatin C equation was more reliable for some age groups. Van Deventer and collaborators in studies conducted with South African individuals with various comorbidities such as high blood pressure, diabetes and HIV also concluded that CKD-EPI cystatin C formula produces more reliable GFR estimates.<sup>(23)</sup>

According to the literature, the determination of GFR based on creatinine is more imprecise when applied to patients with reduced muscle mass.<sup>(17,22)</sup> In the studied population, there is a reduction in muscle mass as a consequence of HTLV-associated paraparesis.<sup>(24)</sup> This fact may explain the worse performance of the joint cystatin and creatinine formula evidenced by the results, especially in the G3 stages and also the overestimation of the GFR by the creatinine formula for the categories G1, G2, G3a, G3b and G4 when compared to the cystatin C formula.

As demonstrated by studies, in the present work, the ability of the CKD-EPI cystatin C formula to detect early GFR reduction was also evidenced, especially in the staging ranges with greater renal impairment. In any case, it will be necessary to make a comparison with a gold standard in order to unequivocally demonstrate this better predictive power.

## CONCLUSIONS

Patients with spinal cord injury and neurogenic bladder require close monitoring of renal function because of the risk of developing chronic kidney disease. Thus, early laboratory diagnosis and clinical evaluation are crucial for clinical follow-up and prevent the onset of cardiovascular complications with an impact on mortality. The findings of the present study indicate that the GFRs estimated using cystatin C are systematically lower, showing that GFR estimated from the CKD-EPI cystatin C equation is a better predictor of renal function in patients with HAM/TSP and neurogenic bladder. The imprecision of the formulae based on creatinine seem to

be linked with the muscle mass loss and decrease in mobility that afflicts patients with HAM/TSP.

## LIMITATIONS

This study was carried out in a single rehabilitation hospital in the city of Salvador. Due to the racial miscegenation in the state of Bahia the black race was assumed to calculate the creatinine-dependent GFRs. The data obtained in this study did not show a homogeneous distribution in the result ranges, having a small number of GFR values in the lower classification ranges. It was not possible to use the gold standard for the determination of GFR due to the scarcity of available data.

## ACKNOWLEDGEMENTS

To the SARA Network of Hospitals and Fernando Pessoa University for the support of the professional team and academic support.

## AUTHORS' CONTRIBUTION INDICATION-TAXONOMY CREDIT

**Araújo, Luciana:** Conceptualization (leadership), Data curation (equal), Formal Analysis (supporting), Investigation, Methodology (equal), Project administration (equal), Original draft writing. **Catita, José:** Methodology (equal), Project administration (equal), Supervision (equal), Writing-reviewing and editing (equal). **Barreira, Sérgio:** Methodology (equal), Project administration (equal); Supervision (equal), Writing-reviewing and editing (equal). **Santos, Alfredo:** Data curation (equal), Formal Analysis (leadership). **Coutinho, Elaine:** Conceptualization (supporting), Formal Analysis (supporting), Methodology (equal).

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