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Bleeding during tooth extraction in patients with chronic kidney disease: A cross-sectional pilot study

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Abstract

Objective: This work measures the intra-operative bleeding in end-stage renal disease patients and assesses whether laboratory coagulation tests and nitrogenous compounds are related to a higher bleeding risk.

Methods: Laboratory tests were performed on the day of surgery and some patients with thrombocytopenia and values above the normal levels of international normalised ratio (INR), thrombin time (TT) and activated partial thromboplastin time (aPTT) were identified.

Results: Haemostatic time ranged from 2 to 35 min (mean of 8.51 min) after suture. Bleeding volume ranged from 0.02 to 67.06 mL (mean of 4.38 mL) and the bleeding volume *per* minute ranged from 0.05 to 2.10 mL/min (median of 0.6 mL/min). Only seven patients (16.27%) had abnormal bleeding (more than 0.6 mL/min). Spearman's coefficient showed weak correlations between bleeding volume (mL/min) and serum urea ($r = 0.226$), TT ($r = 0.227$), plasma urea ($r = 0.148$) and creatinine ($r = 146$), as well as very weak correlations with all other variables ($r < 0.140$) such as age, haemodialysis time, glycaemia, glycated haemoglobin, platelets, INR, aPTT and fibrinogen.

Conclusion: It was not possible to associate any laboratory test or nitrogenous compounds present in the blood and saliva with an increased bleeding.

KEYWORDS
bleeding, chronic kidney disease, end-stage renal disease, haemodialysis, nitrogenous compounds, oral surgery, tooth extraction

1 | INTRODUCTION

Chronic kidney disease (CKD) leads to other systemic impairments, such as imbalance of haemostasis. Several mechanisms contribute to changes in the coagulation system, but platelet dysfunction is the main factor accounting for haemorrhagic tendencies in CKD patients. Anaemia, uraemia and use of anticoagulant and antiplatelet medications also contribute to such a dysfunction (Andrade et al., 2022).

Increase in the levels of circulating urea in end-stage renal disease (ESRD) patients changes the platelet function, thus compromising adhesion, activation and aggregation of platelets (Almeras & Argilés, 2009; Dioguardi et al., 2016; Lisowska-Myjak, 2014).

Urea precludes the adhesion of receptors GPIb/IX/V present in the platelets' surface to the von Willebrand factor existing in the wall of the vessels. Platelet activation depends on this adhesion and secretion of dense granules containing ADP, serotonin, ATP and ionised calcium, which are reduced in ESRD patients and characterise

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the acquired storage pool defect. As a result of the change in the platelet activation, the GPIIb/IIIa receptors that bind to fibrinogen and allow platelets to bind to other platelets as well as to the vessel wall are not activated (Galbusera et al., 2009).

Another consequence of excessive urea is the diversion of l-arginine from the urea cycle, thus inducing the synthesis of nitric oxide (NO) and leading to the reduction of thromboxane A2 and ADP, which inhibits the platelet function (Galbusera et al., 2009; Hedges et al., 2007).

The harmful effects of the accumulation of urea and NO can be partially controlled by means of renal replacement therapies, such as haemodialysis. On the other hand, the need of using heparins to prevent blood coagulation during extra-corporeal circulation (Brandenburger et al., 2017; Ricci et al., 2016) may lead to thrombocytopenia (Gameiro et al., 2018).

Changes in the release of ADP and inactivation of prostacyclin are also triggered by red blood cells, but in ESRD patients red cells are reduced due to a reduced synthesis of erythropoietin (Andrade et al., 2022).

In addition, ESRD patients are more likely to have cardiovascular diseases because of their higher prevalence of risk factors such as hypertension, dyslipidaemia and haemodynamic abnormalities, which explains why many of them use platelet anti-aggregation agents (Natale et al., 2022).

All these factors together increase the likelihood of haemorrhagic events during or after tooth extraction in patients with ESRD. Some of these changes can be identified by laboratory tests, such as complete blood count and coagulogram, which reveal presence of anaemia, thrombocytopenia and alterations in intrinsic coagulation pathway (De Rossi & Glick, 1996). However, platelet function, platelet-vessel wall interaction and platelet–platelet interaction cannot be verified by these exams.

This work is aimed at measuring the intra-operative bleeding in ESRD patients undergoing tooth extraction and assessing whether laboratory tests for coagulation and nitrogenous compounds (i.e. urea and NO) in blood or saliva are related to higher bleeding events.

2 | MATERIALS AND METHODS

2.1 | Ethics

This study was approved by the local research ethics committee according to protocol number 2291623 as well as conducted according to recommendations set by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology). All the subjects signed an informed consent form.

2.2 | Study design and sampling

This is an observational cross-sectional study conducted with a convenience sample consisting of 43 patients with ESRD, who were consecutively selected at the Special Care Dentistry Centre of the University of São Paulo School of Dentistry (FOUSP) between June 2018 and November 2019.

2.3 | Inclusion & exclusion criteria

Male and female patients older than 18 years old undergoing haemodialysis and needing tooth extractions were included in the study.

Those patients using anti-coagulant medications other than heparin during haemodialysis were excluded.

2.4 | Anamnesis

The following data were collected during anamnesis: gender, age, comorbidities and medications in use. Further information on the patient was requested from the haemodialysis centre, such as haemodialysis time, diagnosis time, type of heparin used and type of access provided.

2.5 | Complementary tests

All patients underwent panoramic dental radiography and laboratory tests before surgery, namely: complete blood count (CBC), international normalised ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, urea, creatinine, platelet count, fasting glycaemia and glycated haemoglobin.

Moments before the surgical procedure, sialometry was performed and both saliva and blood were collected for determining the levels of NO and urea.

Sialometry was performed by using the method described by Falcão et al. (2013), in which a pair of cotton balls are placed into a universal collection container and then the whole set is weighed on a digital balance. Next, the cotton balls are placed on the mouth floor near the gingival edge. After 2 min, they are removed and placed into the container and the whole set weighed again. The weight difference is directly converted from g/min to mL/min as saliva has a very similar density to water, that is, $D = 1$ g/mL (Kubala et al., 2018).

The levels of NO and urea were determined in serum and saliva by means of automated enzymatic colorimetric assays, respectively, EnzyChromTM Nitric Oxide Synthase Assay and EnzyChromTM Urea Assay Kit (BioAssay Systems), according to the manufacturer's recommendations. The specimens were read by using a microplate reader (Stat Fax, model 2100, Awareness Technology) (Duarte et al., 2020, 2022).

2.6 | Tooth extraction and intra-operative bleeding measurement

All patients had appointment at 10 a.m. and made haemodialysis in the morning of the day before (at least 22 h before the surgery).

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Tooth extraction was performed by means of a minimally-traumatic surgical technique according to procedures described by Ghali et al. (2004). The surgical field was irrigated with saline solution during the procedure and both saliva and blood were aspirated into a collection flask. The patient's bleeding was measured by subtracting the amounts of fluid aspired, saline solution used for irrigation and saliva produced *per* minute (by sialometry). Patients having severe bleeding were submitted to local haemostatic measures in which tranexamic acid paste (macerated with saline solution) was used in an intra and/or extra-alveolar fashion according to the operator's criterion (Buhatem Medeiros et al., 2017; Franco et al., 2022).

Surgical time (i.e. from syndesmotomy to final suture) and haemostasis time (i.e. from suture to complete absence of bleeding) were measured in minutes.

Bleeding was considered to be abnormal when blood loss was greater than 0.6 mL per minute (Buhatem Medeiros et al., 2017).

The criteria set by Lockhart for definition of post-operative haemorrhagic complications were used as follows: bleeding lasting more than 12 h, need for the patient to seek medical attention, presence of large haematomas or ecchymosis and need for blood transfusion (Lockhart et al., 2003). All the patients were instructed to return immediately to the Special Dentistry Care Centre in case of bleeding, and only those presenting no residual bleeding were fully discharged.

2.7 | Statistical analysis

The resulting data were analysed by using statistical software (SPSS® for Windows, version 22.0, SPSS Inc.). Prior to the analyses, the Shapiro–Wilk normality test was used for confirming the non-parametric distribution of the data. Descriptive analysis was performed to obtain absolute and relative frequencies, central tendency measures and dispersion. Mann–Whitney test was used for comparing the groups regarding bleeding volume, medical history, laboratory tests and nitrogenous compounds in blood and saliva. Spearman's correlation test was used to correlate bleeding volume to independent variables. Statistically significant results were those with p values ≤ 0.05.

3 | RESULTS

The sample consisted of 43 ESRD patients whose mean age was 52.28 years old (ranging from 23 to 78 years), with 41.9% being female and 58.1% male. The mean diagnosis time of CKD was 105.05 months (median of 96 months) and the mean time of haemodialysis was 69.63 months (median of 60 months). All patients used heparin during haemodialysis, 58.1% used unfractionated heparin and 20.9% used low-molecular-weight heparin. In 21% of the cases, the dialysis centre did not send information about the type of heparin used. The commonest types of access to haemodialysis were through arteriovenous fistula (76.7%), cathetre (16.3%) and arteriovenous prosthesis (7%), whereas the most used medications were anti-hypertensive (83.7%) and anti-platelet (72.1%) medication.

Laboratory tests of the patients were performed on the day of surgery and the results are listed in Table 1, whereas quantification of serum and blood nitrogenous compounds obtained by automated enzymatic colorimetric assays are listed in Table 2.

A total of 43 surgeries were performed, 26 (60.5%) in maxilla and 17 (39.5%) in mandible. Ten (23.3%) surgeries involved the extraction of multiple contiguous teeth (i.e. 2–4 teeth) and 33 (76.7%) involved the extraction of a single tooth.

The surgical time was 15 min, ranging from 5 to 44 min (i.e. from syndesmotomy to final suture). The haemostasis time (i.e. from suture to complete absence of bleeding) ranged from 2 to 35 min (mean = 8.51 min).

With regard to the bleeding volume during tooth extraction, we observed a median of 4.8 mL ranging from 0.02 to 67.06 mL. The bleeding volume *per* minute varied from 0.05 to 2.10 mL/min, with a median of 0.27 mL/min. Only seven patients (16.27%) showed abnormal bleeding (i.e. >0.6 mL/min), and none of them had post-operative complications according to the Lockhart criteria.

The use of local haemostatic measures (i.e. transamin) was necessary in three (7%) patients, which required the discontinuation of heparin during haemodialysis on the day after the tooth extraction. None of the three patients showed changes in the laboratory tests. Patient #1 and patient #2 showed, respectively, peri-operative bleedings of 10.6 mL for 24.03 min (0.441 mL/min) and 67.06 mL for 33.03 min (2.03 mL/min). They also had haemostasis times of 5 and 15 min after suture, with both patients using unfractionated heparin and presenting periodontal disease. Patient #3 had peri-operative bleeding of 7.8 mL for 20 min (0.39 mL/min) and haemostasis time of 35 min, in addition to using low-weight-molecular heparin and having longer haemostasis time (300 months). Only patient #1 was using oral anti-platelet medication (Table 3).

A total of 86 specimens were collected, in which 43 were saliva and 43 were serum, for identification and quantification of nitrogenous compounds (i.e. urea and NO) by using colorimetric assay.

Spearman's coefficient test showed that bleeding volume (mL/min) had a weak correlation with variables serum urea ($r = 0.226$), thrombin time ($r = 227$), blood urea ($r = 0.148$) and creatinine ($r = 0.146$), as well as a very weak correlation with other variables ($r < 0.140$) such as age, time of haemodialysis, glycaemia, glycated haemoglobin, platelets, PT/INR, APTT and fibrinogen.

The variable expressing the values of bleeding in mL/min was dychotomically categorised from the last quartile (p75), which represented the cases of higher volume of bleeding during tooth extraction. Therefore, we divided the sample of patients into 32 cases with bleeding ≤0.45 mL/min and 11 cases with bleeding >0.45 mL/min for evaluation of quantitative variables (Table 4).

Among the qualitative variables, only gender and presence of periodontal disease could be related to bleeding volume (Table 5).

4 | DISCUSSION

One of the motivations for carrying out this work was the fact that ESRD patients on haemodialysis show coagulation disorders due to

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TABLE 1 Pre-operative exams and laboratory clinical results of the 43 patients with ESRD.

Variables	Median	Interval	Minimum value	Maximum value	Reference values (RV)
Red blood cells (cells/mm^3)	4155	2560	2999	5550	4000–5200
Haemoglobin (g/dL)	12.4	8.2	7.9	16.1	12–16
Haematocrits (%)	37.9	25.8	24.7	50.5	36–46
MCV (fL)	91.9	32.9	73.8	106.7	80–100
MCH (pg)	30.0	10.3	24.2	34.5	26–34
MCHC (g/dL)	32.6	7.1	27.7	34.8	31–37
RDW (%)	14.2	7.2	12.1	19.3	to 14.9
Leukocytes (cells/mm^3)	5910	8610	3160	11,770	4500–11,000
Lymphocytes (cells/mm^3)	1416	2213	588	2801	1000–4800
Platelets (cells/mm^3)	195	301	115	416	150–400
INR	1.10	0.20	1.00	1.20	1.00
APTT (s)	31.8	24.4	23.3	47.7	25.4–36.9
TT (s)	15.4	6.2	13.2	19.4	10.3–16.6
Fibrinogen (mg/dL)	355	629	217	846	200–393
Blood urea (mg/dL)	76	138.3	39	151.0	17–49
Creatinine (mg/dL)	7.26	12.24	3.59	15.83	0.50–0.90
Glycated haemoglobin (%)	6.0	7.0	5.0	12.0	<5.7% normal From 5.7% to 6.4%: higher risk of diabetes (pre-diabetes) ≥6.5%: diabetes

Abbreviations: APTT, Activated partial thromboplastin time; INR, International normalised ratio; MCH, Mean corpuscular haemoglobin; MCHC, Mean corpuscular haemoglobin concentration; MCV, Mean corpuscular volume; RDW, Red cell distribution width; TT, Thrombin time.

TABLE 2 Quantification of nitrogenous compounds in saliva and serum.

Variables	Median	Interval	Minimum value	Maximum value
Urea in saliva (mg/dL)	29.51	44.32	18.07	62.39
Nitric oxide in saliva (μmol/L)	20.01	43.82	7.19	51.01
Urea in serum (mg/dL)	55.64	47.81	33.88	81.69
Nitric oxide in serum (μmol/L)	10.37	15.25	5.66	20.91

Note: Reference values for urea: 16–40 mg/dL; nitric oxide: 10.3–66.8 μmol/L.

complications of the chronic kidney disease and medications used during the treatment of the kidney dysfunction. These facts would make the patients more susceptible to haemorrhagic events and these still are one of the preoccupations regarding the dental treatment of such patients (Costantinides et al., 2018; Römer et al., 2022).

In the present study, a few changes were observed in the pre-operative laboratory tests of ESRD patient's. The median values of laboratory tests characterised a group of patients in which at least 50% of them had an adequate clinical condition, since complete blood count, coagulogram and glycaemia were found to be within the normality range. It is true that there were patients with changes compatible with anaemia, leukopenia and lymphopenia, but these findings are common in patients with ESRD and the values found are not clinically significant, except the levels of haemoglobin (Tefferi et al., 2005).

Coagulogram showed that there were patients with thrombocytopenia and values above the normality range for INR, TT and APTT, but none characterised an increase in the risk of bleeding (Chee et al., 2008; Slichter, 2004). Fibrinogen was the only laboratory variable drawing attention because of the extremely high values (i.e. more than twice of the maximum reference value) (Gameiro et al., 2018). Fibrinogen plays essential roles in coagulation and platelet aggregation, in addition to increasing the plasma viscosity (Goldwasser et al., 2004). In this sense, patients with ESRD have an already-increased plasma viscosity as a result of low-grade sustained inflammation and its decreased depuration (Pavord & Myers, 2011; Shlipak et al., 2003).

On the other hand, as already expected in ESRD patients, urea and creatinine had very high values. Because urea was related to changes in the platelet function and to an increase in bleeding, one could expect to find a higher volume of bleeding in these patients or a greater difficulty in primary haemostasis.

In our study, by assessing the intra-operative bleeding of the patients, it was possible to identify some increased bleeding despite the fact that the great majority of them showed a normal bleeding volume (below 0.6 mL/min) (Buhatem Medeiros et al., 2017), as only three patients had to use local haemostatic

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TABLE 3 Clinical characteristics of the patients needing to use local haemostatic agents to stop bleeding.

	Patient #1	Patient #2	Patient #3	Reference values
INR	1.14	1.13	1.16	1.00
APTT	33.5	27.7	31.8	25.4–36.9
TT	14.9	15	16.5	10.3–16.6
Fibrinogen (mg/dL)	355	400	275	200–393
Platelets ($\times 10^3/mm^3$)	195,000	148,000	158,000	150–400
Saliva urea (mg/dL)	49.05	36.18	25.3	16–40
Serum urea (mg/dL)	73.83	55.32	55.4	16–40
Saliva nitric oxide (μmol/L)	26.76	38.96	11.96	10.3–66.8
Serum nitric oxide (μmol/L)	12.76	16.81	9.21	10.3–66.8
Anti-platelet medication (ASA)	Yes	No	No	
Type of heparin	Unfractionated heparin	Unfractionated heparin	Low-molecular-weight heparin	
Haemodialysis time (months)	14	96	300	
Extracted teeth	2 (17 and 18)	1 (47)	1 (27)	
Bleeding volume (mL)	10.6	67.06	7.8	
Periodontal disease	Yes	Yes	No	
Surgical time (min)	24	33	20	
Haemostasis time (min)	5	15	35	
Bleeding volume per minute (mL/min)	0.44	2.03	0.39	

Abbreviations: APTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; INR, International normalised ratio; TT, thrombin time.

TABLE 4 Comparison between bleeding volume *per* minute during tooth extraction (less or greater than 0.45 mL/min) and quantitative variables.

Variables	Bleeding volume ≤0.45 mL/min $n=32$	Bleeding volume >0.45 mL/min $n=11$	p[a]
Age (years)	48.5 (51.0)	51.0 (45.0)	0.606
Diagnosis time (months)	96.0 (284.0)	60.0 (132.0)	0.474
Haemodialysis time (months)	54.0 (295.0)	60.0 (140.0)	0.823
Haemoglobin (g/dL)	12.3 (8.2)	12.5 (2.8)	0.656
Platelets ($\times 10^3/mm^3$)	198.0 (301)	186.0 (159)	0.504
INR	1.10 (0.20)	1.10 (0.20)	0.927
APTT	32.0 (24.4)	30.9 (19.7)	0.638
TT	15.3 (5.1)	15.6 (6.2)	0.184
Fibrinogen (mg/dL)	355 (629)	364.5 (234)	0.738
Serum urea (mg/dL)	76.0 (117)	89.0 (66.0)	0.215
Creatinine (mg/dL)	7.38 (11.07)	6.63 (11.72)	0.707
Glycated haemoglobin (%)	6.2 (9.0)	5.8 (4.7)	0.687
Systolic arterial pressure (mmHg)	140 (70)	140 (60)	0.855
Diastolic arterial pressure (mmHg)	80 (40)	80 (30)	0.906
Haemostasis time (min)	5 (33)	10 (25)	0.119
Saliva urea (mg/dL)	29.51 (43.84)	30.58 (24.46)	0.738
Saliva nitric oxide (U/L)	20.86 (43.82)	16.85 (35.17)	0.627

Note: Results expressed in median and interval for each nitrogenous compound.

Abbreviations: APTT, activated partial thromboplastin time; INR, International normalised ratio; TT, thrombin time.

[a]Mann Whitney's test.

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TABLE 5 Comparison between bleeding volume *per* minute during tooth extraction (less or greater than 0.45 mL/min) and qualitative variables.

Variables	Bleeding volume during tooth extraction (mL/min)			
	N	Median	Interval	*p*[a]
Gender				
Female	18	0.16	1.15	0.045
Male	25	0.34	2.06	
Type of anti-coagulation				
Low-molecular-weight-heparin	09	0.28	1.31	0.830
Unfractionated heparin	25	0.25	2.08	
Systemic arterial hypertension				
Yes	37	0.25	2.08	0.441
No	06	0.36	1.01	
Diabetes mellitus				
Yes	17	0.18	2.06	0.449
No	26	0.28	2.02	
Current smoking				
Yes	07	0.26	1.89	0.895
No	36	0.27	2.08	
Current alcohol consumption				
Yes	06	0.26	0.27	0.916
No	37	0.26	2.08	
Use of anti-hypertensive drugs				
Yes	25	0.29	2.08	0.631
No	18	0.26	1.31	
Use of oral hypoglycemic drugs				
Yes	02	0.08	0.10	0.089
No	41	0.28	2.08	
Use of anti-platelet drugs				
Yes	31	0.26	2.08	0.797
No	12	0.27	1.99	
Use of vasodilator drugs				
Yes	11	0.46	1.99	0.068
No	32	0.24	2.08	
Use of insulin				
Yes	10	0.17	1.31	0.307
No	33	0.29	2.08	
Type of tooth extraction				
Single tooth	33	0.26	2.06	0.698
Multiple teeth	10	0.30	2.02	
Tooth extracted due to periodontal disease[b]				
Yes	11	1.13	2.05	<0.01
No	32	0.18	0.54	
Use of extra-alveolar medication				
Yes	04	0.41	1.66	0.086
No	39	0.25	2.08	
Flap opening				
Yes	01	0.16	-	0.519
No	42	0.27	2.08	
Tooth sectioning				
Yes	02	0.39	0.03	0.419
No	41	0.26	2.08	
Total	43	3.34	71.26	-

[a]Mann Whitney's test.

[b]The diagnostic criteria used to determine the need for dental extraction due to periodontal disease were clinical or radiographic attachment loss greater than 2/3 of the root length and dental mobility (grade 3).

agents. Nevertheless, it was not possible to associate any laboratory result or nitrogenous compound in the blood and saliva with increased bleeding.

The only positive correlation found involved two clinical parameters, namely, presence of periodontal disease and gender. The positive correlation with gender was marginal ($p = 0.045$) and probably casual. On the other hand, it has been often observed that periodontal disease can potentially increase the risk of bleeding (Franco et al., 2022; Medina et al., 2018; Morimoto et al., 2009; Scully & Wolff, 2002). Periodontal disease activates several inflammatory pathways which can be involved in unexpected bleeding (Goerge et al., 2008), but perhaps the nitro-oxidative stress is not the most important pathway in ESRD patients as one of the main players in this event, the salivary NO (Mani Sundar et al., 2013), cannot be associated with bleeding.

It is important to emphasise that no patient showed intra- or post-operative haemorrhagic event, and although increased bleeding occurred in a few patients, such a situation was easily controlled with local haemostatic measures. However, laboratory coagulation results and nitrogenous compounds (i.e. urea and NO) in blood and saliva are not related to a greater intra-operative bleeding.

Perhaps the low volume of bleeding presented by the patients is linked to low-degree systemic inflammation and a possible hypercoagulability state represented by the levels of fibrinogen (Gäckler et al., 2019; Kim et al., 2017). This hypothesis is supported in the literature, in which changes in the coagulation of ESRD patients are considered to be complex because the signs of increased risk of bleeding (e.g. decrease in the capacity to generate thrombin and platelet dysfunction) (Gäckler et al., 2019) are mixed with the pro-thrombotic characteristics, which in turn, seem to be augmented by haemodialysis. The mechanisms of interaction between pro-factors and anti-coagulation in these patients still have to be further studied (Pavlou et al., 2021).

It is important to remind that the laboratory tests available to evaluate coagulation have been long questioned as tools for predicting the risk of bleeding (Chee & Greaves, 2003).

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As a pilot study, this work has limitations such as sample of small size, heterogeneity of the variables and cross-sectional study design.

In the present study, an increase in bleeding during and after tooth extractions was a rare event in patients with ESRD and, if occurred, it would be easily controlled with local haemostatic measures. The existing laboratory tests seem not to have enough sensitivity to predict such events as well as nitrogenous compounds present in blood and saliva.

AUTHOR CONTRIBUTIONS

Marilia Andrade Figueiredo: Investigation; writing – original draft; writing – review and editing; methodology; conceptualization; validation; visualization; formal analysis; project administration. **Natalia Silva Andrade:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; project administration. **Andrés Blanco Carrión:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; project administration. **Janaina Braga Medina:** Formal analysis; project administration; methodology; validation; visualization; writing – review and editing; writing – original draft; investigation; conceptualization. **Marina Gallottini:** Formal analysis; project administration; methodology; validation; visualization; writing – review and editing; writing – original draft; investigation; conceptualization. **Karem L. Ortega:** Formal analysis; project administration; methodology; validation; visualization; writing – review and editing; writing – original draft; investigation; conceptualization.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PATIENT CONSENT STATEMENT

All the subjects signed an informed consent form.

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