Article

Socio Environmental and Haematological Profile of Landfill Residents (São Jorge Landfill – Sao Paulo – Brazil)

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Abstract: We are experiencing an unprecedented urbanization process that alongside with physical, social and economic developments is having a significant impact on population's health. Due to higher apprehensions of pollution, violence and poverty, our modern cities no longer ensure a good quality of life so they become unhealthy environments. This study aims to measure the socio-environmental and hematologic profile of residents of Santo André's landfill – "Bairro Espírito Santo" by using the contextualization of the studied area. The research method is Observational type and from Retrospective cohort and by convenience sampling in Santo André in the Greater ABC region. The study determined a socio environmental profile and the hematologic diseases screening related to a close location to the landfill. The disease manifests itself within a broad spectrum of symptoms that causes changes in blood count parameters. The full blood counts analysis was performed, indicating that the blood counts of residents living near the landfill led to positive hematological changes and diseases like Leukopenia, Anemia, Neutropenia and lymphocytosis were the most common changes. However it is considered that the proof of the relation of cause- effect to environmental exposures that may trigger chronic manifestations in humans requires specific studies that are often complicated.

Key Words: Landfill; Waste; Socio-environmental impact; Hematologic diseases

1 Introduction

Nowadays due to higher apprehensions of pollution, violence and poverty, cities no longer ensure a good quality of life and become unhealthy environments to the local inhabitants[1]. An unprecedented urbanization in our history, alongside with physical, social and economic developments is having a significant impact on population's health[1,2].

45   Alongside the continuous demographic growth there is an implicit relation with the amount of
46 resources that have to be consumed in order to sustain all Earth citizens. Therefore it recognized a
47 larger waste production what invariably affects a group of society dynamics.
48   Landfill deposition still remains as the main destination concerning waste management and it is
49 expectable that it will remain for the next decades[3,4,5]. It is estimated that at a worldwide scale more
50 than five million people die every year due to diseases related to waste[2]. The adverse effects of
51 municipal solid waste in the environment plus in public and individual health are widely
52 recognized by several authors[6] that point out a deficiency in the implemented systems and above it
53 the lack of a strong policy that emphasizes health safeguard[7].
54   The large amount of waste was not a concern from an extensive period due to the distance of
55 deposition sites to the urban areas. Meanwhile with the population growth it has been harsh to
56 soothe the distance among them[8]. Another arising problem connected to population growth is the
57 unsystematic occupation of dwellings in hazardous locations and quite vulnerable environmental
58 areas, where several are devoid of urban infrastructure (sanitation, electricity), among others[9,10].
59   It is scientifically proven that there are several impacts arising from landfill positioning whether
60 to population's health either to environment and air, water and soil pollution are the leading ones
61 that may affect Public Health. According to this way of thinking waste and its adequate treatment
62 and deposition became one of the major sanitary and environmental concerns to cities[3, 11, 12].
63   The Environmental degradation scenario is unquestionable and there is a lack of policies so that
64 the crisis can be reverted. The analysis complexity embracing all of impacts requires studies on the
65 various impacts of waste produced daily by the population[13, 14]. It is common knowledge that the
66 blood test can be an important tool for the evaluation of various situations, such as diagnosis and
67 progression of hematologic diseases, detection of infectious frames and therapeutic monitoring[15].
68   Therefore hemogram can guide the initial suspects supported by clinical files. It is inferred the
69 importance of the hematologic analysis as an important diagnosis tool providing useful information
70 for a better conduct in these cases.
71   It is necessary the adoption a set of measures that include politics globalization, government
72 social efficiency and social participation growth. It is the government duty to ensure that change is
73 possible but always sustained in clear objectives as well in results well defined and special actuation
74 properly defined.
75   Surrounding the landfill of San Jorge, there are situations that show how the environment has
76 suffered impacts either in looks either physical or social[19, 20]. The landfill began to operate in the 80s
77 and it is located in São Jorge District. Santo André's landfill is a facility that provides treatment and
78 disposal of solid waste produced in the county. Therefore it evolved from a non official dumping
79 location to a controlled one with good environmental practices. Nowadays it is an area destined to
80 receive solid waste produced in Santo André and provide the most suitable and green destination to
81 the waste.
82   The present study aims to assess the socio-environmental profile of residents in the landfill in a
83 residential area of Santo André – Bairro Espírito Santo. This field work will allow a better urban
84 planning and a greater social and environmental responsibility from all sectors in society.

85 *2 Method*

86   The research method is an observational with retrospective cohort study by convenience
87 sampling in Santo André in the Greater ABC region. The study consists of the elaboration of a socio
88 environmental profile and assessing the incidence and prevalence of hematological diseases related
89 not only the condition of housing but also to exposure to environmental contaminants from the
90 landfill. The study must be understood as a primary tracking diagnosis and it will be the kick off
91 about a transversal study to Espírito Santo inhabitants that will be performed in a near future.
92   The exposed group lives in the surroundings of the landfill. There is a total unawareness of the
93 reality of this people due to the fact that national entities do not have permission to enter in order to
94 study and help this community. Furthermore this study got a special permit to develop a campaign
95 in being the spinoff of a more transversal study. The community habits a place that was a dumping

96   place and actually it is the contiguous to the landfill; therefore the study aim was to establish
97   connections among the location and the community's health.
98   The study was conducted in two phases. The first phase consisted of a survey and research
99   profile of the residents as the following variables: age, gender, type of house, water treatment, water
100 supply and type of sewage, based on interviews and completing a questionnaire. The second phase
101 consisted of the collection of blood samples into two distinct groups: a group of people living in the
102 community (experimental group) and a group of random people attending a health facility located
103 in central city (control group).
104   According to the data obtained a descriptive and comparative analysis of the changes in
105 hematologic patterns among both groups.
106   The blood samples were performed through periferic venopucntion using the vacuum method.
107 After recovery the blood was added to the tube with EDTA. The samples were homogeneized for 10
108 minutes and evaluated through flux citometry with the ABX Pentra 120 equipment. The serial
109 evaluations were performed in blades using the Leishman method in order to obtain the procedures
110 approached. The analysis occurred according to the Good Biomedical Practices.
111   The questionnaires that contained any mistake or not properly filled in were excluded in order
112 to have viable data. The questionnaire was in Semasa database and it was performed according to
113 internal and national regulations.
114   In order to verify the investigation hypothesis the Qui-Square method and Fischer's exact test
115 were performed. The statistical interpretation was executed based on a significance level of $p \leq 0,05$
116 for a confidence interval of 95%. The non observation of the presupposes for the proper use of Qui
117 Square results in an descriptive analysis of the crossed tables ($N > 20$; $80Feq \geq 5$ e $Femin \geq 1,0$).
118   The sample was only gathered after the theme enlightening and only the authorization of the
119 individuals. The anonymity was guaranteed as well as the confidentiality of the data obtained.
120   The tools used were the application of questionnaires and the blood counts in order to correlate
121 the socio environmental conditions with hematologic changes.
122   All subjects gave their informed consent for inclusion before they participated in the study. The
123 study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved
124 by the Ethics Committee of Secretária Municipal de Saúde, Santo André (1.587.630).

125 **3 Results**

126 *3.1 First Phase*

127   Questionnaires were distributed with the purpose of establishing a profile of the socio
128 biographic towards location. In table 1 the most significant variables of the community.

129

Table 1. Socio Biographic Characteristics of the Inhabitants

	COMMUNITY SAMPLE	
	N	%
GENDER		
FEMALE	55	65,5
MALE	29	34,5
AGE GROUP		
[6-12[	7	8,3
[13-18[	6	7,1
[19-30[	30	35,7
[31-50[	31	36,9
[51-60[	8	9,5
[+60[	2	2,4

HOUSE TYPE		
BRICKS	53	63,1
WOOD	20	23,8
Mix	5	6,0
ANOTHER	6	7,1
INCOME*		
LESS THAN 2	67	79,8
BETWEEN 3-5	16	19,0
BETWEEN 5-10	1	1,2
PLUS 10	0	0,0
SEWAGE		
YES	54	64,3
No	30	35,7
TOTAL	84	100

* Minumm Wage (M.W) = 724 Reais

Of the several variables that were incorporated in the study and tabulated the appropriate statistical program, mentioned above are the best way of mirroring the social and demographic landscape of the target population. It is important to note that the variable "Sanitation" existing in table 1 corresponds to the presence of the official network of water, sewage and electricity.

As can be seen by observing Table 1 there is a female predominance and the age groups of 19 to 30 and 31 to 50 are the most prevalent in respondents. There is also a level of low income, the lack of a significant relation to the existence of sanitation difference. It was also verified that the income was inferior to 2 Minimum wages (M.W.) and it evidences that we face a special group in terms of economic capacity. It is also noted that there is a prevalence of the brick type of houses (63,1%) and (64, 3%) of them have sewage.

3.2 Second Phase

In order to obtain plausive conclusions to the case study it was necessary to compare the effects of the convenience sampling with another group of people that were not exposed to several and harmful environmental factors (Non Exposed Group) towards to the one's exposed (Exposed Group).

Of the 84 people individuals' described in table 1, 32 were randomly chosen and were designed as "Exposed Group". The Non-Exposed Group was interviewed at the same time as they did the blood sample. In total were interviewed 30 people which will correspond to the amount of blood samples.

As described earlier , so the importance of the two groups share the same characteristics , it appears that the percentages are significantly similar , where the female is the most prevalent, with 75 % in the " Group Exposed " and 66.7 % in " unexposed group " .

Regarding the age, the age range between 31-50 years was the most commonly reported, with 11 people (36.7%) in the "unexposed group" and 19-30 in the Exposed group with 13 persons (40.6 %).

It appears that the housing and financial realities are significantly different in different groups, of which 84, 4 % of the "Group Exposed" presents a less than two minimum wages income, while 56.7 % of the "non exposed group" has similar income .

Regarding the "Non-exposed group" it is observable a greater purchasing power, and therefore all of the respondents live in brick houses and nearly all have sanitation. In the table 2 it is described the exposure type according to socio biographic characteristics.

163   **Table 2.** Association of the socio biographic characteristics with the exposition type

SOCIO BIOGRAPHIC CHARACTERISTCS		NON EXPOSED		EXPOSED		TOTAL		x²; gl; p-value
		N	% COL UNA	N	% COL UNA	N	% COL UNA	
GENDER	Female	20	66,7	24	75	44	71	0,522; 1; 0,471
	Male	10	33,3	8	25	18	29	
	Total	30	100	32	100	62	100	
AGE GROUP	[6-12[	2	6,7	6	18,8	8	12,9	5,973; 5;0,309
	[13-18[	1	3,3	3	9,4	4	6,5	
	[19-30[	9	30	13	40,6	22	35,5	
	[31-50[	11	36,7	6	18,8	17	27,4	
	[51-60[	5	16,7	3	9,4	8	12,9	
	≥60	2	6,7	1	3,1	3	4,8	
	Total	30	100	32	100	62	100	
SEWAGE	Yes	29	96,7	22	84,4	51	82,3	8,269; 1; 0,004
	No	1	3,3	10	15,6	11	17,7	
	Total	30	100	32	100	62	100	
TYPE OF HOUSE	Brick	30	100	20	62,5	50	80,6	13,950; 1; <0,0001
	wood	0	0	12	37,5	12	19,4	
	Total	30	100	32	100	62	100	
INCOME	Less 2 MW	17	56,7	27	84,4	44	71	7,359; 2; 0,025
	Among 3- 5 MW	9	30	5	15,6	14	22,6	
	Among 5- 10 MG	4	13,3	0	0	4	6,5	
	Total	30	100	32	100	62	100	

164   According to the variables analysis i tis observed that both groups have significant association
165   to the variables sewage (p=0,004) house type (p<0,0001) and Income (p=0,025) with the exception of
166   the variables gender and age group (p>0,05).
167   It is noted that the totality of the individuals with sewage (82,3%) 94,4&% of them live in the
168   surroundings of the landfill.
169   According to house type the totality of the non exposed live in brick houses and from the total
170   of individuals that lives in this type (n=50) the majority (62, 5% is exposed to the landfill.
171   The total of individuals that own an income lower than 2 M.W is 44 (71%) as 27 of them (84, 4%)
172   is exposed to the landfill and (56,7%) correspond to the non exposed.
173   In order to verify the association among hematologic changes towards socio biographic
174   characteristics the next table was prepared. (Table 3)
175

176   **Table 3.** Hematologic Changes discovered in individual's hemogram

Variable	Description	Yes		No		Total		X2; gl; p
		n	**% Linha**	**n**	**% Linha**	**n**	**% Coluna**	
GENDER	Female	20	45,5	24	54,5	44	29,0	0,522; 1 ; 0,470
	Male	10	55,6	8	44,4	18	71,0	
	Total	30	45,5	32	54,5	62	100	
AGE GROUP	[6-12[	5	62,5	3	37,5	8	12,9	NO PRESUPPOSES
	[13-18[	2	50,0	2	50,0	4	6,5	
	[19-30[	11	50,0	11	50,0	22	35,5	
	[31-50[	9	52,9	8	47,1	17	27,4	
	[51-60[	2	25,0	6	75,0	8	12,9	
	≥60	1	33,3	2	66,7	3	4,8	
	Total	30	48,4	32	51,6	62	100	
SEWAGE	Yes	25	49,0	26	51,0	51	82,3	NO PRESUPPOSES
	No	5	45,5	6	54,5	11	17,7	
	Total	30	48,4	32	51,6	62	100	
HOUSE TYPE	Brick	25	50,0	25	50,0	50	80,6	0,269; 1; 0,604
	Wood	5	41,7	7	58,3	12	19,4	
	Total	30	48,4	32	51,6	62	100	
INCOME	Less 2 MW	17	56,7	27	84,4	44	71	NO PRESUPPOSES
	Between 3-5 MW	9	30	5	15,6	14	22,6	
	Between 5-10 MW	4	13,3	0	0	4	6,5	
	Total	30	100	32	100	62	100	

177   During the analysis of the hematologic changes it was observed that there is no significant
178   association to any variable.
179   Relatively to the age group variable among the age groups of 6-12 and 51-60 there is a great
180   disparity among changes found. In an overall summit the majority (51, 6%) do not possess
181   hematologic changes.
182   Regarding the sewage variable there is a balance in terms of percentages and we infer that
183   (51,6%) does not have any hematologic changes. As regards income variable 44 individuals (71%)
184   have an inferior income of 2 Minimum wages.
185   In order to investigate the existence of association among the exposure type and hematologic
186   changes within individuals a statistical analysis was performed. The summit of results about
187   hemograms changes is summed in table 4.

188   **Table 4.** Relation among exposure type with hematologic change

			Hematologic Change		
			Change	**No change**	**Total**
EXPOSURE TYPE	NON EXPOSED	n	10	20	30
		% Line	33,3%	66,7%	100,0%
		% Column	33,3%	62,5%	48,4%
		% Total	16,1%	32,3%	48,4%
	EXPOSED	Count	20	12	32
		% Line	62,5%	37,5%	100,0%
		% Column	66,7%	37,5%	51,6%
		% of Total	32,3%	19,4%	51,6%

	Count	30	32	62
	% Line	48,4%	51,6%	100,0%
TOTAL	% Column	100,0%	100,0%	100,0%
	% of Total	48,4%	51,6%	100,0%

189                                    $\chi^2=5,274; gl=1; p=0,022$

190   By observing the table 4 it is noted an association among the variables of Exposure type and
191   Hematologic change as being significant in a statistical perspective (p<0,05). It is verified a pattern of
192   association among exposure and the presence/absence of hematologic changes (p=0,022).

193   The total exposed to landfill (32 cases), the majority had hematological disorders (62.5%). It was
194   found that of 30 cases where the presence of hematological abnormalities was found, most of these
195   are exposed to landfill (66.7%).

196   As noted in Table 4, there was an increase of approximately 50% for changes in screening
197   performed in the exposed group compared to the unexposed group, which indicates that the
198   population is not in the best health.

199   The chance of occurrence of hematological disorders is 3.33 times higher in subjects exposed to
200   the presence of the landfill compared to that presented hematological changes in the unexposed
201   group. It is recognized by the observation data, that 10 individuals from the non-exposed group
202   showed alterations in parameters, whereas the incidence in the exposed group was significantly
203   higher with 20 individuals to submit changes.

204   Diseases such as Leukocytosis, Anemia, Lymphocytosis and Neutropenia were the major
205   findings and changes are evident in the exposed group compared to the unexposed group.

206   **4 Discussion**

207   Analyzing the changes in vital functions of living beings, it is possible to know the effects of
208   exposure to pollutants aforementioned to its occurrence and existence of any more significant
209   damage[16, 21, 22, 23, 24].

210   It is considered that proving the cause-effect connection with environmental exposures that
211   may trigger chronic manifestations in humans requires specific studies that prove costly and time
212   consuming[25, 26, 27, 28]. It is necessary that the data must be collected in the field so as to be compared
213   with experimental observations in order to demonstrate the process and how the interactions occur
214   so as to study the dynamics[14].

215   The effects of human exposure to environmental pollutants are manifested typically in the long
216   term and are masked by other causes. Adding to this, the fact that the probability of harmful
217   elements synergy and exponentiation of the risk is generally unknown and there is thus extremely
218   difficult for corroboration by a science based on laboratory tests, without incorporating other
219   relevant factors, such as corporate interests, industrial, or professional regulators who stand against
220   the recognition of the effects on human health[18, 22, 24, 28].

221   Given these considerations and also relying on the limitations of the health system itself in
222   identifying peculiarities in the epidemiological profile of the population; a methodology was
223   defined that aims the total understanding of the exposure process. There are five parameters that are
224   difficult to materialize such as individual characteristics, duration of exposure, frequency of
225   exposure, average time and "contact rate", never forgetting that the characteristics of the individual
226   vary by age, gender, occupation, and body weight[29].

227   The focus of the study is the exposure of individuals to organisms, as well as to social, economic
228   and environmental processes in anticipation of models that focus historically in the monitoring and
229   maintenance of health[19, 20]. There have been published several papers that address the role that the
230   landfill can hold on people's health[28,29,30]. There is no doubt that a landfill should be viewed from a
231   holistic point of view, in that it must manage the direct and indirect that it may exercise near the
232   same impact[3, 16, 30].

233   Despite the existence of Federal Government programs for vulnerable populations, do not
234   show an improvement of living conditions of this community[11,12]. As a tool to promote the respective

235   indicative and screening improvements to minimize ongoing risks potentiating of the CBC taking
236   into account all capabilities of this method of monitoring. CBC integrates a set of parameters that
237   describes the number and characteristics of some elements in the blood. The CBC is composed of
238   three basic determinations include (or red series), leukocytes (white or series) Review of
239   erythrocytes and platelets (platelet or series)[31].

240   The lymphocytosis is characterized by an increase in the number of lymphocytes (sub-group of
241   white blood cells). The disease neutropenia indicates a low number of neutrophils that are a subset
242   of leukocytes that originate in the bone marrow, thus revealing an immune susceptibility. The
243   increase of leukocytes is a sign of a viral infection, i.e. near the landfill people tend not to viral and
244   bacterial infections[31]. The disease leukocytosis reveals an increased number of leukocytes that
245   reveals the existence of infection since they are the elements that are linked to fighting immune
246   system to foreign bodies. The higher leukocytosis, may be more contaminated landfill, can be
247   interpreted as a parameter to reveal deepening to establish causal links. The disease of anemia is
248   more complex, so the causes are more comprehensive and diversified, which immediately implies a
249   more detailed investigation into these cases[31, 32, 33].

250   The Lymphocytosis, Neutropenia and Leukocytosis diseases can be understood as correlated
251   despite having opposite directions of growth, as previously conveyed[33].

252   The results express the presence of discrepancies in the health of the Holy Ghost Quarter
253   population, compared with the other subjects in the study, which requires the completion of further
254   studies detect the most common causes and the consequences for the residents of order to enable the
255   development of a continuous and systematic supervision for the same programs. It is suggested that
256   in-depth study for potential replacement of the group under study so that based on the results of this
257   study primary health problems resulting from exposure were identified in comparison with the
258   non-treatment group.

259   The problems derived from municipal solid waste are current and without a proper equation[34].
260   There is no alternative but to a behavioral change in relation to waste, given the reduction in its
261   creation and gradually implement a use of technologies that are within our technical capabilities and
262   leverage resources to gradually acquire greater control over the environmental and health effects
263   caused by waste. [35]

264   The prevention and control of public health consequences related to urban solid waste lack of
265   information and epidemiological data, in which causal relationships can be established. There is a
266   colossal deficiency in studies on the recovery of degraded areas for disposal of urban solid waste. In
267   this context, this article seeks to contribute to a consolidation of the state of art related to the theme,
268   in order to contribute to awareness of the elements aimed at improving the quality of urban cities
269   and hence the quality of life of citizens[29, 34].

270   The supporting research of this kind is a priority. The development of greater technical training,
271   in view of the environmental and health issues, as well as the involvement of professionals in
272   integrated waste management systems, in the medium and long term, these variables enter in
273   projects and plans[13, 35, 36].

274   Data from this study should be compared with other data, may involve a characterization of the
275   epigenetic profile of the population[37] and to a characterization of the study areas for the presence of
276   particulate material[38]. The challenge is to continue collecting more valid and reliable data in order to
277   achieve an extrapolation between environmental and respective consequences for the health of
278   population's risk factors to make a comparison to a national and global scale. [16] The study described
279   is the first step in a thorough all the *Espírito Santo* community study.

280   The data obtained in this study indicate that screening strategies for prevention and health
281   promotion should include joint actions established between citizens and the management of services
282   and always aimed at improving living conditions, particularly targeted to urban planning,
283   implementation educational programs, as well as awareness for behavior change, once isolated
284   actions are considered ineffective in reducing any aggravation[36-39].

285   It can be inferred that this study has a purpose of consolidating knowledge which contribute to
286   the prevention and detection of known and unknown to the public and environmental

287 exposure-related adverse health effects[38, 39]. The study should be understood as a primary screening
288 indication of some pathologies. In addition to being able to assess the state of health of the patient
289 may be indicative of the state of pollution of landfill insofar as the conditions are reflected in the
290 landfill people.

291 We must identify priorities at the community level, so that the understanding of environmental
292 health problems is essential. Sustainable planning is a tool for achieving proceeds with an
293 implementation of a research-oriented future intervention, and thus addresses the issues of greatest
294 importance. However, this process is not simple in communities characterized by persistent health
295 disparities and a lack of historical confidence in health professionals[38, 39].

296 The primary findings, based on elaborate study were anemia, leukocytosis, Lymphocytosis and
297 Neutropenia. These data show this to be a group with greater immune susceptibility, adding that
298 some elements of the exposed already have infections that are consistent with exposure to
299 contaminants, supporting the existence of a pattern. Aiming at the promotion of Health suggests the
300 continuity of the project monitoring, in order to obtain a greater number of clairvoyance that
301 support the trace output made and described.

302 Based on the study, the exposed group has 3.33 times more likely to develop hematological
303 abnormalities, with reference to its exposure to the landfill with the group that was not exposed.

304 Although the results show only the Holy Spirit occurred in the neighborhood, in the Greater
305 ABC region also provide important information for the expansion of knowledge concerning the
306 assessment of this risk in residential areas around the planet clues. The demand for a thorough
307 investigation is urgent with a view to broadening and disseminating information related to the
308 potential effects of human exposure to contaminants from multiple sources that affect public health.

309 Future investigations may include concepts like the Nano Particles and the term Epigenetics, in
310 order to promote a holistic view of the causes, mechanisms and consequences that flow from human
311 to a multitude of organism's exposure, thus completing the present study and scientific knowledge,
312 thus eliminating cross existing limitations.

5 Conclusion

314 The full blood counts analysis was performed and it was discovered that the blood counts of
315 residents living near the landfill had positive results in hematological changes and diseases like
316 Leukopenia, Anemia, Neutropenia and lymphocytosis were the most frequently encountered
317 changes. However it is considered that the proof of the relation of cause- effect to environmental
318 exposures that may trigger chronic manifestations in humans requires specific studies that are often
319 costly and time-consuming.

Author Contributions: This research was conducted as part of the doctoral thesis in Health Sciences, Faculty
of Medicine of ABC - BRAZIL, and its line of research is public health. Vivianni Wanderley is the author of this
thesis. All authors contributed significantly to the successful completion of this work both intellectually and
financially. So they conceived and designed the study plan. Fernando Fonseca, Rodrigo Raimundo, Eriane
Savoy, José Domingues and Ana Ferreira conducted sampling and interviews, analyzing the data. Cleonice
Pinto, Hating Silva and Rodrigo Raimundo did the statistical analysis of data. Vivianni Wanderley conducted
the study and manuscript revisions. André Quiaios, Susana Passion, João Figueiredo, Roger Alvarenga and
Amaury Junior made relevant comments on the manuscript. Finally, all authors read and approved the final
manuscript.

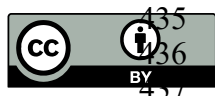**Conflicts of interest:** The authors declare no conflict of interest.

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