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Comparison between Conventional Cytology and Liquid-Based Cytology in the Tertiary Brazilian Navy Hospital in Rio de Janeiro

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Keywords
Cervical cancer screening · Liquid-based cytology · Conventional cytology

Abstract
Introduction: Cervical cancer screening is an important tool in public health. Liquid-based cytology (LBC) has been performed at the studied hospital for 7 years. The present study compares the performance of 2 LBC techniques with conventional cytology. ***Objective:*** Our objective is to verify the sensitivity for the detection of neoplastic and preneoplastic epithelial atypia, as well as the positive predictive value of the 3 methodologies. ***Methods:*** We analyzed retrospectively 24,529 cases and evaluated the conventional cytology, ThinPrep®, and BD SurePath® performance categorizing the results according to the Bethesda system. We also compared the level of unsatisfactory samples, the presence of elements from the squamocolumnar junction, and the detection of pathogenic microorganisms. ***Results:*** ThinPrep® (1.43%) showed superior sensitivity over BD SurePath® (0.91%) and conventional cytology (0.71%) in terms of the detection of high-grade lesions; however, in terms of squamous atypia as a whole (ASC-US+), BD SurePath® (6.44%) proved to be more sensitive than conventional cytology (5.28%) and ThinPrep® (3.73%). ***Conclusions:*** The results show the advantage of implementing LBC in routine screening for cervical lesions. In this study, BD SurePath® achieved the overall best performance considering the studied variables.

Introduction

Cervical cancer is the third most common cancer type amongst women in Brazil. In 2017, 6,385 women died from this disease. The crude mortality rate was 6.17 per 100 thousand. For 2020, 16,590 new cases of cervical cancer are estimated, corresponding to 7.4% of new cancer cases [1]. To prevent cervical cancer, cytology screening is a remarkable tool, especially in non-high-income countries.

In the 1920s, Babes [2] and Papanicolaou [3] were the precursors of cancer screening using exfoliative cytological techniques. The development of these techniques allowed for early diagnosis and the expansion of cervical cancer screening. The pioneering spirit of these researchers resulted in an evolutionary leap in public health. Pre-

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vention and early diagnosis are essential to reduce cancer-related morbidity and mortality.

Cervical cancer screening has been primarily carried out by conventional cytology. Several institutions are continually evaluating the results obtained after the implementation of liquid-based cytology (LBC). Tao et al. [4] compared 1,248,785 results from patients from an academic hospital in China between 2009 and 2014. The samples were processed using LBC, either BD SurePath® or ThinPrep®, and conventional cytology. They observed a significant increase in the detection of all categories considered abnormal after the establishment of LBC. Also, one of the topics evaluated was the adequacy of the sample. Conventional cytology showed a higher occurrence of unsatisfactory cases than LBC. In Turkey, Budak et al. [5] published a retrospective study to compare the results of cytological exams from 47,954 patients between 2008 and 2014, performed by conventional cytology and LBC. There was no significant difference regarding the occurrence of abnormalities.

Jeong et al. [6] studied 38,956 gynecologic cytopathology reports using conventional cytology and LBC (from 3 different manufacturers). It only addressed the incidence of unsatisfactory samples. The study concluded that LBC resulted in 1.26% of unsatisfactory samples, whereas conventional cytology resulted in 3.31%. In 2016, Rozemeijer et al. [7] retrospectively studied more than 6 million cytological reports on conventional cytology and 2 LBC (BD SurePath® and ThinPrep®). BD SurePath® showed a 12% increase in the detection of epithelial atypia (moderate dysplasia or more) compared with conventional cytology. ThinPrep® did not show any advantage compared with conventional cytology in terms of sensitivity. The incidence of unsatisfactory samples or the detection of pathogenic microorganisms was not addressed.

In Brazil, Etlinger-Colonelli et al. [8] analyzed 41,264 gynecological samples comparing conventional cytology and BD SurePath®. The increase in the detection of abnormal results rose from 7.80 to 11.57% when using LBC. The incidence of low-grade lesions (LSIL) was the main reason for the increase in sensitivity. As for the incidence of unsatisfactory samples, it was decreased from 3.50 to 0.25%. Longatto-Filho et al. [9] analyzed 218,594 conventional cytology and BD SurePath® samples. When using conventional cytology, 3% of the samples were unsatisfactory for analysis, whereas when using BD SurePath®, the rate was only 0.3%. As for the detection of high-grade lesions (HSIL), they observed the same percentage for both methods; however, the LSIL percentage was higher for LBC (2.2 vs. 0.7%). The index of positive results increased from 3% (conventional cytology) to 5.7% (LBC). In 2009, Beerman et al. [10] analyzed 86,469 gynecological cytology records from a database, in which 51,154 used conventional cytology and 35,315 used BD SurePath®. They observed a reduction in unsatisfactory samples with the use of LBC (0.30% for LBC vs. 0.89% for conventional cytology). They also noted a higher detection of cellular atypia when using LBC (2.97% for LBC vs. 1.64% for conventional cytology).

Simonsen et al. [11] studied 2 devices (Cervex-Brush® Combi vs. cervical brush + Ayre's spatula) for cervical harvesting in LBC, aiming to evaluate their effectiveness in obtaining endocervical cells, as well as the accuracy for detection of NIC 2+. They observed that Cervex-Brush® Combi was superior to the cervical brush + Ayre's spatula for endocervical sampling (82.7 vs. 74.6%) and more sensitive (48.6 vs. 33.9%) for detecting NIC 2+ lesions.

Kituncharoen et al. [12] compared the rates of unsatisfactory samples and the detection of epithelial abnormalities amongst 23,030 cervical samples collected by conventional cytology and BD SurePath®. They concluded that there was no difference in the occurrence of unsatisfactory samples (0.1 vs. 0.1%). The detection of high-grade and glandular squamous abnormalities was also the same. However, they observed that the detection of low-grade abnormalities in squamous cells was significantly greater with the LBC (7.7 vs. 11.5%). In 2019, Gupta et al. [13] compared the performance of a low-cost LBC technique (EziPREP®) with conventional cytology. It was a cross-sectional split-sample study conducted on 515 women. The rate of unsatisfactory samples favored conventional cytology (1 vs. 1.3%), but the differences in the detection of epithelial abnormalities and pathogenic microorganisms were not statistically significant, nor was the cytohistological correlation (96% for both techniques).

Pun et al. [14] conducted a comparative study between conventional cytology (1,180 samples) and LBC (1,160 samples). The percentage of unsatisfactory samples was lower in the LBC group (1.2 vs. 3.9%), and there was an increase in the detection of epithelial atypia (ASC-US+) when LBC was implemented (3.77 vs. 2.71%). Kaza et al. [15] compared conventional cytology and BD SurePath® in terms of their sensitivities for detecting pathogenic microorganisms. Their findings suggested that both methods are equally valuable for this purpose.

The main purpose of this study is to compare the sensitivity for the detection of neoplastic and preneoplastic epithelial atypia, as well as the positive predictive value of 3 methodologies, conventional cytology and LBC (BD

SurePath® and ThinPrep®), in a tertiary hospital in Rio de Janeiro, Brazil. We also assessed the samples' satisfactory rate, the presence of the elements of the squamocolumnar junction (SCJ), and the detection of pathogenic microorganisms.

Materials and Methods

Samples

This is a retrospective study where the cytology samples and reports were obtained from the Pathology Service in the tertiary care center of the Brazilian Navy Hospital, Hospital Naval Marcílio Dias (HNMD), Rio de Janeiro. This study obtained Institutional Ethics Committee clearance before the commencement of the research. The reference numbers are CONEP/Plataforma Brasil, CAAE 06468819.2.000.5256, and authorization 3.208.007, September 9, 2019.

The reports/samples were divided into 3 groups. The first group consisted of 10,742 samples prepared by conventional cytology from January 2007 to December 2016. The second group studied was represented by 1,258 samples from January 2012 to July 2013. They were processed using LBC ThinPrep® 2000 Hologic (Marlborough, MA, USA), and Ayre's spatula, endocervical sampling brush, and the PreservCyt® Solution were employed for harvesting the samples. In the third group, we analyzed 12,529 reports of gynecological cytology using LBC BD SurePath® from August 2013 to December 2018. For harvesting the samples, BD SurePath® Vial and Brush/Spatula Collection Kit were used.

The 24,529 cytology results were plotted in a table and categorized according to the Bethesda system (TBS) [16]. The following variables were considered: negative for malignancy, ASC-US, LSIL, ASC-H, HSIL, squamous cell carcinoma, AGC, adenocarcinoma, and other malignant neoplasms. The presence of the following organisms was also evaluated: *Trichomonas vaginalis*, fungal organisms morphologically consistent with *Candida* spp., the shift in flora suggestive of bacterial vaginosis, bacteria morphologically consistent with *Actinomyces* spp., and cellular changes consistent with herpes simplex virus. We verified the sampling of the SCJ (the presence of endocervical cells and metaplastic cells) and the rate of unsatisfactory samples.

Whenever necessary, the patients were referred to colposcopy and biopsied, according to TBS and the Brazilian guidelines for cervical cancer screening [17]. Therefore, we correlated the cytology results of the patients that were biopsied with their histopathological result counterpart. The aim was to compare the positive predictive value for each of the cytology techniques (conventional cytology, ThinPrep®, and BD SurePath®). The data were obtained through direct search in registry books, Excel® sheets, medical records, cytology results plotted in the laboratory software Complab®, and printed medical files.

Statistics

We used Pearson's χ^2 test to check the existence of a significant difference between the techniques studied (conventional cytology, LBC ThinPrep®, and BD SurePath®) as to the proportion of occurrence of the test results. In cases where the difference was significant, we performed a post hoc test with Bonferroni correction. For cases in which there was a violation between observed and expected values ≥5, we applied Fisher's exact test. Table 1 presents statistical analysis.

Results

Between January 2007 and December 2018, during an 11-year study period, 24,529 cytology reports were reviewed and categorized, according to TBS. Table 2 presents all the reporting results for the 3 techniques we employed. We also assessed the rate of unsatisfactory samples and the sampling of the SCJ.

Interestingly, when we examined the specimen adequacy, the percentage of unsatisfactory samples was smaller for conventional cytology (0.20%) when compared with BD SurePath® (1.08%). Nonetheless, there was no statistical difference when comparing the 2 LBC, ThinPrep® (0.56%) and BD SurePath® (1.08%). The rate of unsatisfactory samples we observed for conventional cytology is significantly smaller, insofar as reflecting the continuing training of the gynecology staff of HNMD for a very long time. There is a residency medical program and a fellowship program in HNMD. We acknowledge that this rate might not be reproducible in all cases. Continuous education and quality management programs for sample takers may not be a reality for some institutions and hospitals. Therefore, we believe this is the key point why our unsatisfactory rate for conventional cytology was considerably small. Occasionally, the sample taker might not, for various reasons, accurately access the SCJ or even the cervix itself. It is a critical step in terms of the institutions' quality management program as a whole. The sample taker skills should not be taken for granted and might be assessed periodically.

In our daily routine, we observed that the main causes of unsatisfactory samples for conventional cytology are obscuring blood/white blood cells, interfering substances, and cellularity excess. The percentage of unsatisfactory samples we observed for LBC is comparable to the literature [6, 13, 14]. They were higher when comparing to LBC, possibly to the adaptation of the gynecology staff to the new technique when it was implemented. As for the LBC, we noticed that scanty squamous cellularity was the main reason for rejection.

The next evaluated point was the presence of organisms in the samples. We perceived no statistical difference between conventional cytology (7.52%) and ThinPrep® (5.80%), notwithstanding, BD SurePath® showed considerable superiority (16.94%).

Table 1. Statistical analysis – TBS results

Interpretation/result	Multiple comparison	Methodology	Post hoc
NILM	<0.0001	Conventional × Thinprep®	0.2700
		Conventional × BD Surepath®	<0.0001
		Thinprep® × BD Surepath®	<0.0001
ASC-US	<0.0001	Conventional × Thinprep®	**0.0042**
		Conventional × BD Surepath®	**0.0042**
		Thinprep® × BD Surepath®	**<0.0001**
LSIL	0.0985	Conventional × Thinprep®	Not calculated
		Conventional × BD Surepath®	Not calculated
		Thinprep® × BD Surepath®	Not calculated
ASC-H	0.0002[a]	Conventional × Thinprep®	**0.0002**
		Conventional × BD Surepath®	0.1126
		Thinprep® × BD Surepath®	**0.003**5
HSIL	0.0385[a]	Conventional × Thinprep®	0.7772[a]
		Conventional × BD Surepath®	0.0113[a]
		Thinprep® × BD Surepath®	0.5201[a]
Carcinoma	0.0047[a]	Conventional × Thinprep®	1.0000[a]
		Conventional × BD Surepath®	**0.0016**[a]
		Thinprep® × BD Surepath®	0.3810[a]
AGC (either NOS or favor neoplastic)	0.4678[a]	Conventional × Thinprep®	0.5810[a]
		Conventional × BD Surepath®	0.5033[a]
		Thinprep® × BD Surepath®	0.3186[a]
Adenocarcinoma	0.0102[a]	Conventional × Thinprep®	0.2466[a]
		Conventional × BD Surepath®	0.0044[a]
		Thinprep® × BD Surepath®	1.0000[a]
Other malignant neoplasms	0.1478[a]	Conventional × Thinprep®	Not calculated
		Conventional × BD Surepath®	Not calculated
		Thinprep® × BD Surepath®	Not calculated
Unsatisfactory	<0.0001	Conventional × Thinprep®	**0.0271**[a]
		Conventional × BD Surepath®	**<0.0001**
		Thinprep® × BD Surepath®	0.1083
Organisms	<0.0001	Conventional × Thinprep®	0.0940
		Conventional × BD Surepath®	**<0.0001**
		Thinprep® × BD Surepath®	**<0.0001**
SCJ sampling	<0.0001	Conventional × Thinprep®	**<0.0001**
		Conventional × BD Surepath®	**<0.0001**
		Thinprep® × BD Surepath®	**<0.0001**

Bold: statistically significant difference. ASC-US, epithelial atypia; LSIL, low-grade lesions; HSIL, high-grade lesions. [a] Fisher's exact test.

Cervical intraepithelial neoplasia most commonly occurs at the SCJ, a transitional zone. Sometimes, it is a challenge to obtain an adequate sample. When we analyzed the sampling of the SCJ, meaning the presence of well-preserved endocervical and squamous metaplastic cells, the technique that showed the best result was BD SurePath® (67.08%), followed by ThinPrep® (50.40%) and conventional cytology (39.53%). These results endorse the better sensitivity for detecting atypia when using BD SurePath®.

From the total of 24,529 cytology reports, we recognized 1,419 results considered atypical/abnormal, mean-

Table 2. Number of Pap tests from 2007 to 2018 according to results (TBS) using conventional cytology, BD SurePath®, and ThinPrep®

	Conventional cytology (10,742), *n* (%)	BD SurePath® (12,529), *n* (%)	ThinPrep® (1,258), *n* (%)
Interpretation/result			
NILM	10,154 (94.52)	11,588 (92.49)	1,204 (95.71)
ASC-US	295 (2.75)	436 (3.48)	15 (1.19)
LSIL	143 (1.33)	197 (1.57)	12 (0.95)
ASC-H	29 (0.27)	49 (0.39)	13 (1.03)
HSIL	30 (0.28)	61 (0.49)	4 (0.32)
Carcinoma	17 (0.16)	4 (0.03)	1 (0.08)
AGC (either NOS or favor neoplastic)	34 (0.32)	47 (0.38)	2 (0.16)
Adenocarcinoma	17 (0.16)	5 (0.04)	0 (0.00)
Other malignant neoplasms	1 (0.01)	7 (0.06)	0 (0.00)
Unsatisfactory	22 (0.20)	135 (1.08)	7 (0.56)
Organisms	808 (7.52)	2,122 (16.94)	73 (5.80)
SCJ sampling	4,246 (39.53)	8,405 (67.08)	634 (50.40)

ASC-US, epithelial atypia; LSIL, low-grade lesions; HSIL, high-grade lesions.

Table 3. Grouped atypical/abnormal results

	ASC-US LSIL, *n* (%)	ASC-H HSIL carcinoma, *n* (%)	AGC (either NOS or favor neoplastic) adenocarcinoma, *n* (%)	Other malignant neoplasms, *n* (%)	Total, *n* (%)
Conventional cytology	438 (4.08)	76 (0.71)	51 (0.47)	1 (0.01)	566 (5.28)
BD SurePath®	633 (5.05)	114 (0.91)	52 (0.42)	7 (0.06)	806 (6.44)
ThinPrep®	27 (2.15)	18 (1.43)	2 (0.16)	0 (0.00)	47 (3.73)
Total	1,098 (11.27)	208 (3.05)	105 (1.06)	8 (0.07)	1,419 (15.45)

ASC-US, epithelial atypia; LSIL, low-grade lesions; HSIL, high-grade lesions.

ing ASC-US or higher (Table 3). They were categorized into 4 different groups: ASC-US and LSIL; ASC-H, HSIL, and carcinoma; AGC (either NOS or favor neoplastic) and adenocarcinoma, and other malignant neoplasms.

According to the protocols adopted in the studied hospital, the patients are followed after 6 months whenever they have results of ASC-US or LSIL. We observed the following rates of detection for this group: BD SurePath® (5.05%), followed by conventional cytology (4.08%) and ThinPrep® (2.15%).

According to TBS [16] and the Brazilian guidelines for cervical cancer screening [17, 18], whenever the patients have a result of ASC-H or higher, they are referred to colposcopy and biopsy. Hence, in the next group of results, we investigated ASC-H, HSIL, and squamous cell carcinoma, and we verified the following results for each technique: ThinPrep® (1.43%), BD SurePath® (0.91%), and conventional cytology (0.71%). We did not observe any statistical difference between ThinPrep® versus BD SurePath®, both techniques proved to be superior to conventional cytology.

We assume the higher percentage of the ThinPrep® atypical results (1.43%) resemble false-positive results when compared with conventional cytology and BD SurePath®. This is critical when choosing the ideal technique, but it should be correlated to the positive predictive value (PPV).

In our study, 321 patients were reported with a result of ASC-H or higher. They were referred to colposcopy and biopsy, but only 200 patients returned to the hospital and were effectively biopsied. Accordingly, we compared their cytology reports with their histopathological result counterpart (Table 4). Then, we assessed the PPV for each of the techniques. We observed the following PPV: Thin-

Table 4. PPV and correlation between cytology and histology

	Patients biopsied, *n* (%)	Correlated histology × cytology, *n* (%)	Discrepant correlation histology × cytology, *n* (%)	PPV, %
Conventional cytology	93 (0.87)	74 (0.69)	19 (0.18)	79.6
BD SurePath®	86 (0.69)	68 (0.54)	17 (0.14)	79.1
ThinPrep®	21 (1.67)	13 (1.03)	8 (0.64)	61.9

PPV, positive predictive value.

Table 5. Statistical analysis for grouped atypia

Grouped atypia	Technique	Frequency, %	*p* value	Post hoc	Bonferroni (*p* value)
ASC-US, LSIL	Conventional cytology	4.08	**<0.0001**	Conventional × ThinPrep®	**0.0031**
	BD SurePath®	5.05		Conventional × BD SurePath®	**0.0012**
	ThinPrep®	2.15		ThinPrep® × BD SurePath®	**<0.0001**
ASC-H, HSIL, carcinoma	Conventional cytology	0.71	**0.0007**	Conventional × ThinPrep®	**0.004**
	BD SurePath®	0.91		Conventional × BD SurePath®	**0.012**
	ThinPrep®	1.43		ThinPrep® × BD SurePath®	0.393
AGC (either NOS or favor neoplastic), adenocarcinoma	Conventional cytology	0.48	**0.2560**	Conventional × ThinPrep®	Not calculated
	BD SurePath®	0.42		Conventional × BD SurePath®	Not calculated
	ThinPrep®	0.16		ThinPrep® × BD SurePath®	Not calculated
Epithelial total atypia	Conventional cytology	5.28	**<0.0001**	Conventional × ThinPrep®	0.0908
	BD SurePath®	6.44		Conventional × BD SurePath®	**0.0001**
	ThinPrep®	3.73		ThinPrep® × BD SurePath®	**0.0005**

Bold: statistically significant difference. ASC-US, epithelial atypia; LSIL, low-grade lesions; HSIL, high-grade lesions.

Prep® (61.9%), conventional cytology (79.6%), and BD SurePath® (79.1%).

As we summarized our data considering the presence of atypical/abnormal cells, whether squamous or glandular, we verified that BD SurePath® detected more of these cells (6.44%) in comparison with conventional cytology (5.28) and ThinPrep® (3.73%) (Table 5). These results associated with the PPV indicate that, in our study, the most sensitive technique for cervical cancer screening is BD SurePath®. We did not observe any statistical difference between the results observed when using ThinPrep® and conventional cytology.

Discussion/Conclusion

In 2012, the Pathology Service of Hospital Naval Marcílio Dias implemented LBC, an extraordinary technique promoting a breakthrough in cervical harvesting, sample fixation, and preparation of slides. The fixation process consists of collecting cervical cells with a brush and dispersing the material in a preservative liquid right on site, for further processing and assembly of the slides in the laboratory, using an automated and controlled methodology. It was a milestone considering advances in the following aspects:

1. Higher potential for detecting epithelial lesions
2. Diminishing interferences (such as red blood cells and leukocytes) that obscure the slides in conventional cytology
3. Better distribution of epithelial cells in the preservative liquid medium in the slide, thereby reducing the overlap of cells
4. Better sampling of the cells onto the slide as the entire collection of cells is transferred to the flask with the preservative medium
5. Cells are better preserved, therefore better dyed and more likely to be morphologically examined

6. Shorter slide scrutiny time
7. Use of the residual sample for molecular tests for HPV detection

Implementing HPV testing and LBC is still a challenge to non-high-income countries. Besides the clear relationship between HPV and cervical cancer, implementing both methodologies in these countries is part of a complex strategy of public health in the context of screening programs. The World Health Organization (WHO) considers that better screening tests may result in more effective programs [19]. In public health, it should be affordable considering the financial investment, the training of personnel involved, and easy access for patients to the screening and treatment [20]. The global outcome of this investment may overcome the burden of the incidence and mortality of cervical cancer, as soon as these technologies become more and more affordable.

When the hospital decided to implement LBC at the Pathology Service, we chose 2 different technologies. Initially, we used ThinPrep® and then we switched to BD SurePath®. This study compared the performance between these 2 LBC and conventional cytology, searching for answers that could corroborate to better results proposed by LBC.

Both ThinPrep® and BD SurePath® showed unsatisfactory rates compared with other studies. However, these results surprisingly did not excel conventional cytology since it already had a low occurrence of unsatisfactory samples in the studied institution (0.2%).

According to the literature, LBC detected more low-grade lesions (ASC-US + LSIL) compared with conventional cytology; notwithstanding, in our study, we observed this result only with BD SurePath®. In contrast, ThinPrep® distinguished more grouped high-grade lesions (ASC-H + HSIL + carcinoma) compared with BD SurePath® and conventional cytology. Despite this regard, when we analyzed the PPV, ThinPrep® presented more false-positive cases since its PPV was lower than BD SurePath® and conventional cytology. We did not observe any difference when detecting glandular atypia. Considering that the noblest purpose of cervical screening is the detection of neoplastic and preneoplastic lesions, we conclude the superiority of LBC over conventional cytology as a screening method. Embodied in this conclusion is the advantage of BD SurePath® regarding the sensitivity for detecting epithelial atypia as a whole (ASC-US+ and glandular atypia) and ThinPrep® for the detection of high-grade lesions (ASC-H+). BD SurePath® was the technique that better sampled the SCJ compared with the others. This assumption might corroborate to the better sensitivity observed.

Ultimately, BD SurePath® detected more than twice the presence of organisms compared with conventional cytology, but we did not observe any advantage in this scope when analyzing the results from ThinPrep®. This situation surprised us, considering that some studies do not show an advantage when comparing LBC with conventional cytology. It is an important observation, especially in non-high-income countries, where cervical cancer screening is still not as effective as it should be. In these countries, women usually seek gynecologists when they have complaints related to infectious processes. In Brazil, the price of LBC is still a barrier when we think of implementing this technology in our Public Health System; on the other hand, it is more important to evaluate the cost benefits of how this technology can improve cervical cancer screening in our society.

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Statement of Ethics

The study obtained Institutional Ethics Committee clearance before the commencement of the research, assuring the ethical and legal aspects of the study. The reference numbers are CONEP/Plataforma Brasil, CAAE 06468819.2.000.5256, and authorization 3.208.007, September 9, 2019.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Antônio Carlos Almeida de Oliveira: screening/analyzing all the samples studied and substantial contribution to the conception of the work and acquisition, analysis and interpretation of

data for the work, and writing of the draft and final version of the article. Miguel Fontes Domingues: screening/analyzing all the samples studied and substantial contribution to the conception of the work and acquisition, analysis and interpretation of data for the work, and writing of the draft and final version of the article. Paulo Murilo Neufeld: guidance in the initial phase of project definition and article evaluation. Marcos Fleury: guidance in the initial phase of project definition and article evaluation. José Firmino Nogueira Neto: conception of the study from the draft, planning, monitoring the execution, discussion of statistical analysis, and contribution to the final version of the article.

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