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Automated immature granulocyte count in patients of an intensive care unit with suspected infection

Contagem automatizada de granulócitos imaturos em pacientes de uma unidade de terapia intensiva com suspeita de infecção

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ABSTRACT

Introduction: Diagnosing infections in intensive care unit (ICU) patients is vital to provide appropriate therapies. Hematological analyzers perform automated immature granulocyte counts (IG) quickly and with no additional cost when compared to traditional microbiological cultures. Elevated IG is directly associated with infections and inflammation. **Objectives:** Evaluate IG as infection marker in adult inpatients at the ICU-Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC-UFPR), compared to cultures of biological materials (gold standard). **Material and methods:** Samples of 200 adult inpatients at CHC-UFPR ICU with suspected infection were used. Absolute (IG#) and relative (IG%) counts were performed on the Sysmex XN-3000. Cultures and blood cultures were performed either manually or on Bactec FX. Diagnostic accuracy and agreement for IG# and IG% were evaluated. **Results:** The reference intervals (RI) obtained for IG# and IG% were 0.06 × 10^3/µl and 0.6%, respectively, with sensitivity for both of 74.4% and specificity of 25.3% for IG#, and 26.6% for IG%. The receiver operating characteristic (ROC) curve showed cut-off value of 0.33 × 10^3/µl for IG#, sensitivity of 28%, specificity of 82.3%, and area under the curve (AUC) of 0.521. For IG%, cut-off value was 1.35%, sensitivity 44.6%, specificity 64.6%, and AUC 0.532. CV < 3% increased specificity to 88%. **Conclusion:** RI of IG% and IG# showed high sensitivity and are useful in screening for infection in ICU patients. The CVs demonstrated by the ROC curves showed high specificity and are helpful on the exclusion of sepsis diagnosis in ICU patients. IG was shown to be useful for screening and confirmation of infection in ICU patients.

Key words: intensive care units; automation laboratory; infection.

RESUMO

Introdução: *Diagnosticar infecções em pacientes da unidade de terapia intensiva (UTI) é vital para implementar terapias apropriadas. A contagem automatizada de granulócitos imaturos (IG) em analisadores hematológicos é rápida e sem custos adicionais. A taxa de IG elevada está associada a infecções.* ***Objetivos:*** *Avaliar IG como indicador de infecção em pacientes adultos da UTI do Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC-UFPR) em comparação com culturas de materiais biológicos (padrão-ouro).* ***Material e métodos:*** *Foram analisadas amostras de 200 pacientes adultos com suspeita de infecção da UTI do CHC-UFPR. As contagens automatizadas de granulócitos imaturos absolutas (IG#) e relativas (IG%) foram realizadas no Sysmex-XN-3000, e as culturas e as hemoculturas, manualmente ou no Bactec-FX. As características de desempenho de teste diagnóstico para IG# e IG% foram avaliadas.* ***Resultados:*** *Os intervalos de referência (IR) obtidos para IG# e IG% foram 0,06 × 10^3/µl e 0,6%, respectivamente, com sensibilidade para ambos de 74,4% e especificidade de 25,3% para IG# e 26,6% para IG%. A curva* receiver operating characteristic *(ROC) mostrou valor de corte de 0,33 × 10^3/µl para IG#, sensibilidade de 28%, especificidade de 82,3% e área sob a curva (AUC) de 0,521. Para IG%, o valor de corte foi de 1,35%, sensibilidade de 44,6%, especificidade de 64,6% e AUC de 0,532. Valores de corte de IG% < 3% aumentaram a especificidade para 88%.* ***Conclusão:*** *IRs de IG% e IG# apresentaram sensibilidade elevada e são úteis na triagem de infecção nos pacientes da UTI. Os valores de corte*

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demonstrados pelas curvas ROC apresentaram elevada especificidade, o que possibilitou a identificação adequada dos pacientes sadios. IG mostrou-se útil para triagem e confirmação de infecção em pacientes de UTI.

Unitermos: *unidades de terapia intensiva; automação laboratorial; infecção.*

RESUMEN

Introducción: *Diagnosticar infecciones en pacientes de la unidad de cuidados intensivos (UCI) es de suma importancia para proporcionar el tratamiento adecuado. El contaje automatizado de granulocitos inmaduros (GI) en analizadores hematológicos es rápido y sin costes adicionales. La elevada tasa de GI está asociada a infecciones.* ***Objetivos:*** *Evaluar GI como indicador de infección en pacientes adultos de la UCI del Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC-UFPR) en comparación a culturas de materiales biológicos (estándar de oro).* ***Material y métodos:*** *Se analizaron muestras de 200 pacientes adultos con sospecha de infección de la UCI del CHC-UFPR. Los conteos automatizados de granulocitos inmaduros absolutos (GI#) e relativos (GI%) se realizaron en el Sysmex-XN-3000, y los cultivos y hemocultivos, manualmente o en el Baetec-FX. Se han evaluado precisión diagnóstica y concordancia para GI# y GI%.* ***Resultados:*** *Los rangos de referencia obtenidos para GI# y GI% fueron 0,06 × 10^3/µl y 0,6%, respectivamente, con sensibilidad para ambos de 74,4% y especificidad de 25,3% para IG# y 26,6% para IG%. La curva* receiver operating characteristic *(ROC) ha mostrado valor de corte de 0,33 × 10^3/µl para IG#, sensibilidad de 28%, especificidad de 82,3% y área bajo la curva (AUC) de 0,521. Para GI%, el valor de corte ha sido 135%, sensibilidad de 44,6%, especificidad de 64,6% y AUC de 0,532. Valores de corte de GI% < 3% aumentaron la especificidad para 88%.* ***Conclusión:*** *Rangos de referencia de GI% y GI# presentaron sensibilidad elevada y son útiles en el triaje de infecciones en pacientes de UCI. Los valores de corte enseñados por las curvas ROC presentaron alta especificidad, permitiendo la identificación adecuada de los pacientes sanos. GI se ha mostrado útil para triaje y confirmación de infección en pacientes de UCI.*

Palabras clave: *unidades de cuidados intensivos; automatización de laboratorios; infección.*

INTRODUCTION

Intensive care unit (ICU) patients are in vulnerable state of health, undergoing several invasive procedures that expose them to the risk of contracting an infection. This can be related to the severity of the disease, physical, psychological and nutritional aspects, time of hospitalization and the employed treatment[1]. Such conditions favor the development of bacterial and fungal infections, being associated with increased morbidity and mortality rates in this population[2, 3].

When infection is suspected, laboratory tests are carried out, such as blood count, biochemical tests, and culture of biological materials, for the correct pathogen identification and the best antibiotic therapy plan. The cultures of specimens of the infectious site, such as urine culture, sputum specimen, and abscess material are performed to identify the microorganism causing the infection[2]. In the suspected bloodstream infection, two blood culture sets, at least, are collected to identify aerobic and anaerobic bacteria[4-6].

Highlighting the infectious site, as well as identifying its respective sensitivity profile, is essential for the correct antimicrobial therapy. However, the main disadvantage of culture is the time necessary for result release due to prolonged incubation periods, with other tests being necessary to help professionals in treatment decisions. The blood count is a test of more rapid conduction than the culture and it provides parameters that help evaluation. Patients with infection can present altered leukocyte counts, as well as the presence of immature cells of granulocyte lineage in the peripheral blood in case of acute infections, what can distinguish them from healthy patients[7].

Immature cells, or immature granulocytes (IG), which comprise the count of myelocytes, metamyelocytes, and promyelocytes, can be quantified by automatic blood count analyzers, such as the Sysmex XN 3000 (Sysmex Corporation, Kobe, Japan). In those instruments, IG is measured by flow cytometry in the white blood cell (WBC) Differential Fluorescence (WDF) channel, and differentiation is made based on the granularity of cells (side scatter) and on nucleic acid content (side fluorescence by the Lysercell WDF reagent)[8].

Diagnosis and treatment of infections are important to prevent complications such as sepsis, defined as ‘‘life-threatening

organ dysfunction caused by a dysregulated host response to infection", which induces a syndrome of physiologic pathological and biochemical abnormalities[9]. Sepsis is related to high mortality rate; this thesis can be proved in studies conducted with ICU patients in Brazil, where incidence of sepsis is 36.3% for each 1,000 patients/day, with a mortality rate of 55%, which can reach 63%[10, 11].

The objective of this study was to verify if automated IG count, obtained in the hematologic analyzer Sysmex 3000, can be used as a useful marker of early diagnosis for infection control in adult ICU patients of Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC-UFRP), in comparison with cultures of biological materials.

MATERIAL AND METHODS

Study site, specimens and patients

This is an observational cross-sectional retrospective study conducted with 200 adult patients suspected of infection, with mean ages of 59 ± 16.7 years, with female predominance, hospitalized at the step-down unit, the adult ICU and the cardiac ICU of CHC-UFPR in the period from April to July 2017, with blood count and blood culture being ordered on the same day.

Absolute and relative automated counts of IG (IG# and IG%, respectively), as well as total leukocyte count (TLC) and neutrophil count (NC) were done from specimens collected in dipotassium ethylenediamine tetraacetic acid (K2-EDTA) of automated blood counts performed on the same date as blood culture. Patients were selected from the analysis of 200 blood cultures automatically in the instrument Bactec-FX (Becton Dickinson and Company, New Jersey, USA), with specimens separated into two groups: positive and negative. In negative blood cultures, by the Hospital Information System (SIH) of CHC-UFPR, data were collected regarding other cultures of microorganisms ordered on the same day as the blood culture, such as: aspirate, biopsy, stool test, catheter culture, fungal culture, bedsore, sputum, culture of liquids and cerebrospinal fluid (CSF), secretion of wound and abscess, tracheal and urine culture. At the end of the first analysis, patients were divided into patients with positive cultures and those with negative cultures. At SIH, data regarding patients' use of antibiotics, age, sex, and clinical data were also collected.

The reference interval (RI) for parameters IG# and IG% was obtained from the analysis of 200 adult outpatients, following the guidelines of the document C28-A3 of the Clinical and Laboratory Standards Institute [(CLSI), 2008][12]. The study was approved by the Ethics Research Committee of CHC-UFPR, under no. CAAE: 89702818.6.0000.0096. Individuals younger than 17 years, diagnosed with malignant or benign neoplasm and hematological diseases were excluded from the study.

Measurement principles of Sysmex XN-3000

A hematological analyzer Sysmex XN-3000 (Kobe, Japan), series number 25477, software version 00-19D, was used in this study. The instrument analyzes 100 specimens per hour and provides 31 reportable parameters in whole blood, besides conducting analysis of biological liquids. Differential leukocytes count was performed by WDF channel; and global leukocyte and erythroblast count, by white cell nucleated (WNR) channel. The WDF channel (neutrophils, lymphocytes, monocytes, eosinophils and IG) uses light scattering and fluorescence, separating cell groups based on internal complexity and content of deoxyribonucleic acid (DNA)/ ribonucleic acid (RNA). The WRN channel (leukocytes, basophils, and erythroblasts) also uses light scattering and fluorescence, but it separates cells by size and content of DNA/RNA[13].

Statistical analyses

The collected data were tabulated in the software Microsoft Office Excel 2016; data was analyzed by means of software IBM SPSS Statistics (Version 25, IBM Corporation, 2017, Armonk, NY, USA). Performance characteristics of the diagnostic test were evaluated for parameters IG#, IG%, TLC, and NC. The receiver operating characteristic (ROC) curve was analyzed with a 95% confidence interval (CI) for the estimate of the area under the curve (AUC), as well as sensitivity and specificity values of the cut-off values.

RESULTS

Characteristics of the population

Among the 200 analyzed patients, 79 presented negative cultures (39.5%) and 121, positive cultures (60.5%). A total of 172 patients used antimicrobials on the collection day; among these, 63 were patients with negative cultures (79.9% of this group), and 109, with positive culture (90.1%). Just 28 patients did not use antimicrobials. The population features are summarized in **Table 1**.

Out of the 121 positive cultures, 81 were blood cultures; 19, urine cultures; eight, respiratory cultures; two, CSF; 11, general cultures (biopsy, catheter, stool, bedsore, liquids and secretions).

TABLE 1 – Characteristics of the population

Characteristics	Total	Negative culture	Positive culture
Patients	200	79 (39.5%)	121 (60.5%)
Age	59.33 (17-90)	57.13 (17-90)	60.77 (21-90)
Male/female	89/111	31/48	58/63
Use of antimicrobials			
Yes	172 (86%)	63 (79.7%)	109 (90.1%)
No	28 (14%)	16 (20.3%)	12 (9.9%)

Among the etiological agents found, 49.6% (n = 60) of the evaluated infections were caused by Gram-positive (Gram+) bacteria: 27.3% (n = 33), by Gram-negative (Gram-) bacteria; 9.1% (n = 11), by Gram+ and Gram- bacteria; 13.2% (n = 16), by fungi; and 0.8% (n = 1) by mycobacteria (MB). **Table 2** presents the classification of patients by type of culture and groups of microorganisms.

The most frequently isolated microorganism was coagulase-negative *Staphylococcus* (43 specimens), followed by *Candida* ssp. (13), *Klebsiella pneumoniae* (12), *Staphylococcus aureus* (eight), *Escherichia coli* (seven), *Enterococcus faecalis* (six) and *Pseudomonas aeruginosa* (five). The major microorganisms isolated in the samples are represented in **Table 3**.

Analysis of the diagnostic test characteristics

The RI obtained for parameters IG# and IG% was 0.06 × 10^3/µl and 0.6%, respectively. Sensitivity was obtained for both of 74.4%, with specificity of 25.3% for IG# and 26.6% for IG%. When ROC curve was analyzed, the cut-off value was 0.33 × 10^3/µl for IG#, presenting sensitivity of 28% and specificity of 82.3%, with AUC of 0.521. For IG%, the cut-off value was 1.35%, sensitivity of 44.6% and specificity of 64.5%, with AUC of 0.532. For IG%, when using a cut-off value of 3%, there was an increase of specificity to 88% and sensitivity of 19%. **Figure 1** shows ROC curves for IG#, IG%, TLC, and NC, with their appropriate cut-off values, found in the statistical analysis.

TABLE 2 – Patient classification by type of culture and main group of microorganism causing the infection

Type of culture	Positive cultures	Group of microorganism				
		Gram+	Gram-	Gram+ and Gram-	Fungi	MB
Blood cultures	81 (66.9%)	52	15	7	6	1
Urine culture	19 (15.7%)	3	10	0	6	0
Respiratory	8 (6.6%)	0	4	2	2	0
CSF	2 (1.7%)	1	0	0	1	0
General cultures	11 (9.1%)	4	4	2	1	0
Total	121 (100%)	60	33	11	16	1

CSF: cerebrospinal fluid; MB: mycobacteria.

TABLE 3 – Microorganisms isolated from cultures of biological specimens

Microorganisms isolated	Number of cases (n = 136)	
	n	%
Coagulase-negative *Staphylococcus**	43	31.6
Candida ssp.**	13	9.6
Klebsiella pneumoniae	12	8.8
Staphylococcus aureus	8	5.9
Escherichia coli	7	5.1
Enterococcus faecalis	6	4.4
Pseudomonas aeruginosa	5	3.7
Others***	42	30.9

**Cultures grown by skin bacteria (coagulase-negative* Staphylococcus, *Streptococcus of the group* viridans, *diphtheria toxoids,* bacillus *species,* Corynebacterium *spp.,* Micrococcus *spp.) were considered infectious agents when their positivity occurred in more than one blood culture bottle;* ***in three isolated* Candida albicans *cultures, two isolates of* Candida glabrata *and eight of* Candida *ssp.;* ****others: four* Acinetobacter baumannii*; four* Enterobacter aerogenes*; four* Enterococcus faecium*; four* Serratia marcescens*; three* Cryptococcus neoformans*; three* Enterobacter cloacae*; three* Proteus mirabilis*; three* Staphylococcus epidermidis*; two* Corynebacterium*; two* Streptococcus pneumoniae*; one* Burkholderia cepacia*; one* Citrobacter freundii*; one* Klebsiella ozaenae*; one* Morganella morganii*; one* Mycobacterium tuberculosis*; one* Propionibacterium acnes*; one* Pseudomonas putida*; one* Salmonella typhimurium*; one* Staphylococcus haemolyticus*; one* Streptococcus viridans.

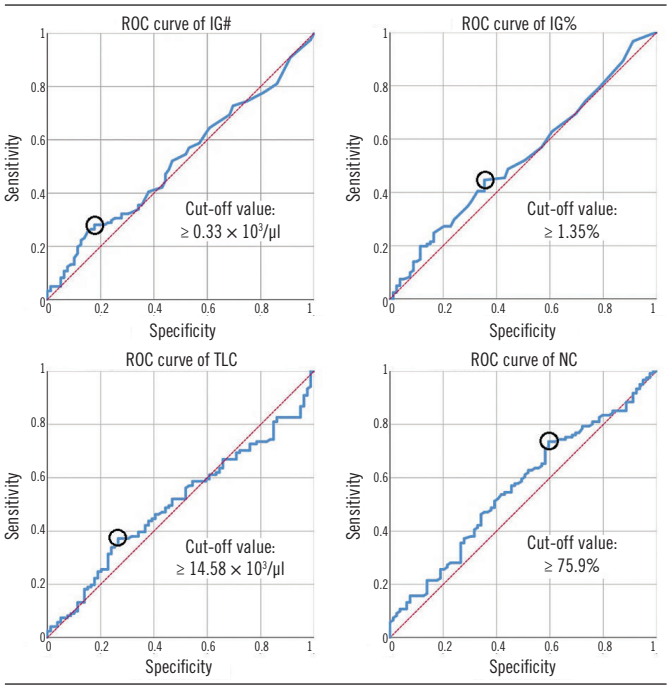

FIGURE 1 – *ROC curve and cut-off values for IG#, IG%, TLC, and NC*

ROC: receiver operating characteristic; IG#: absolute automated count of immature granulocytes; IG%: relative automated count of immature granulocytes; TLC: total leukocyte count; NC: neutrophil count.

The characteristics of diagnostic tests are presented in **Table 4**.

Figure 2 demonstrates the capture percentage of RIs and cut-off values, by means of ROC curve for IG%, IG#, TLC and NC (%) regarding the groups of microorganisms identified in the cultures. In 87.5% of the cases of infections caused by fungi, IG%

was above the reference value of 0.6%; and IG#, above 0.06 $\times 10^3$/µl in 93.8% of the cases of fungal infections. For the infections caused just by Gram- and Gram+ bacteria and by both groups of bacteria, IG# and IG% values were above RI in approximately 70% of the cultures. Cut-off values of IG# ≥ 0.33 × 10^3/µl and of IG% ≥ 1.35% identified 37.5% and 68.8% of the cultures positive for fungi respectively. Cut-off values of TLC ≥ 14.585 × 10^3/µl and NC ≥ 75.9% identified 37.5% and 81.3% of positive cultures for fungi, respectively. The cultures grown by both bacteria Gram- and Gram+ presented IG% ≥ 1.35% and NC ≥ 75.9% in 63.6%, respectively, and IG# ≥ 0.33 × 10^3/µl and TLC ≥ 14.585 × 10^3/µl in 54.5%. Infections by Gram- and Gram+ bacteria were detected in 66.7% and 76.7% whenever NC was ≥ 75.9%, respectively. The only culture grown by MB had its value altered for IG# and IG%.

TABLE 4 – Characteristics of the diagnostic test when comparing IG# and IG% values in positive and negative cultures

	Cut-off values	Sens	Spec	AUC	95% CI
IG#	> 0.06 × 10^3/µl	74.4%	25.3%	0.521	0.44-0.602
IG%	> 0.6%	74.4%	26.6%	0.532	0.45-0.613
IG#	≥ 0.33 × 10^3/µl	28%	82.3%	0.521	0.44-0.602
IG%	≥ 1.35%	44.6%	64.6%	0.532	0.45-0.613
IG%	≥ 3%	19%	88%	0.532	0.45-0.613
TLC	≥ 14.58 × 10^3/µl	37.2%	73.4%	0.503	0.422-0.583
NC	≥ 75.9%	73.6%	40.5%	0.562	0.481-0.642

IG#: absolute automated count of immature granulocytes; IG%: relative automated count of immature granulocytes; TLC: total leukocyte count; NC: neutrophil count; Sens: sensitivity; Spec: specificity: AUC: area under the curve; CI: confidence interval.

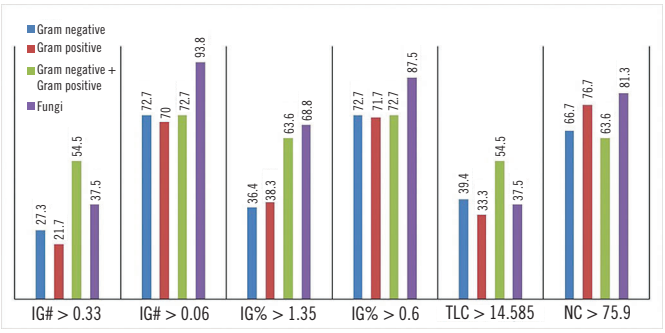

FIGURE 2 – *Cut-off values of IG#, IG%, TLC and NC, and capture percentage by group of microorganism*

IG#: absolute automated count of immature granulocytes; IG%: relative automated count of immature granulocytes; TLC: total leukocyte count; NC: neutrophil count.

DISCUSSION

Among the positive cultures observed in this study, blood culture was more prevalent, with 66.9% of total. The main found pathogen was the Gram+ bacterium coagulase-negative *Staphylococcus* (31.6%). This finding differs from other epidemiological studies about infections in ICU patients, in which the main found pathogen was *Staphylococcus aureus*[14, 15]. The Gram- bacterium *Klebsiella pneumoniae* (8.8%) and fungi of the genus *Candida* ssp. (9.6%) were the most frequently isolated in their groups, as observed in the work by Secretaria do Estado da Saúde do Paraná (2018), where such agents were also the main causing agents of nosocomial infections in 2017[16].

The reference values obtained by means of analysis of outpatients presented normality intervals between 0-0.06 × 10^3/µl for IG# and 0%-0.6% for IG%. Those values were the same as those obtained by Monteiro (2016)[17] – who used blood donor patients as a control group – and similar to those found by Bruegel *et al*. (2004)[18] – which defined IG# < 0.06 × 10^3/µl and IG% < 5% as normal values for the parameters[17, 18]. Higher values were found by Senthilnayagam *et al*. (2012)[14]: IG# ranged from 0.01-0.09 × 10^3/µl, and IG% from 0.2%-0.8%. The cut-off value obtained in the ROC curve was higher than that found in the reference interval, with IG# ≥ 0.33 × 10^3/µl and IG% ≥ 1.35%. Ansari-Lari *et al*. (2003)[7] and Senthilnayagam *et al*. identified that IG% values above 3% are considered optimal identification values of infection/sepsis, with specificity above 90% for both. That value was near the one found in this study, which presented specificity of 88% with this cut-off value.

Using RI as cut-off value, a sensitivity of 74.4% for both parameters IG# and IG% was found, a value in line with the literature[14, 19, 20]. However, a 25.3% specificity for IG# and a 26.6% for IG% was below the observed in other studies[14, 19, 21, 22]. This difference between the established results can be attributable to some biases of the study, as the use of antibiotics up to specimen collection; insufficient or incomplete investigation; infection caused by microorganisms of difficult growth or uncommon in laboratory practice; and clinical alterations related to inflammatory and not to infectious processes (for example, the inflammatory response syndrome). Although the culture is considered gold standard for diagnosis of sepsis, negative results are observed in around 40%-60% of cultures grown in patients with this clinically established condition[23, 24].

Despite the recommendations to collect cultures before the use of antibiotic therapy, 86% of the patients in this study were using the medication. The use of antimicrobials decreases the chances of positivity in the culture, because they have a bactericidal effect or bacteriostatic action, what can inhibit bacterial growth[3, 6, 25]. Another limitation of the study is being retrospective, because data collection depends on correct ordering of laboratory tests and adequate and precise filling in of data and indications of tests in the system, which can influence a more complete and significant analysis of the obtained results.

When using RI as cut-off value in infections, which presented higher sensitivity in the study, we observed that in fungi-caused infections, values of IG# and IG% were altered in 93.8% and 87.5% of the cases, respectively; in the other groups, just in 70% of the cultures. Similar result was found for NC (cut-off value > 75.9%): 81.3% of fungal infections; 76.7% of Gram-; and for the other groups, approximately 65%. With the IG cut-off value found in the ROC curve, which increased specificity and decreased sensitivity, there was decreased of relationship of groups, being fungi (68.8%) and Gram- (63.6%) with highest percentages in IG% and Gram- and Gram+ together in IG#; in the other groups, percentages were lower than 40%.

Several studies demonstrated relevance of IG automated count, which presented higher specificity, sensitivity and precision when in comparison with the manual count, which differs in relation to the quantity of cells counted and in its application in clinical practice, because it presents significant increase in patients with neonatal sepsis and in adults, also being related to higher severity of infection when IG is elevated[14, 26-30].

With perspectives of continuation of this work, the need was observed for a more detailed analysis on patients' clinical status, based on, as recommended by Singer *et al*. (2016)[9], signs and symptoms of each one comparing them with the parameters established by the score of Sequential Organ Failure Assessment (SOFA). This clinical and laboratory combination will allow greater likelihood in the obtained data, besides improving the use of IG% and IG#.

CONCLUSION

With the values of RI of IG% and IG#, sensitivity presented itself elevated, being fundamental in the screening of infection of ICU patients. The cut-off values demonstrated by ROC curves presented high specificity, what enabled the exclusion of the sepsis diagnosis in the ICU patients. All things considered, IG values are useful for screening, confirmation, and exclusion of infection in ICU patients.

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