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Leukocyte ratios are useful early predictors for adverse outcomes of COVID-19 infection

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ABSTRACT

Leukocyte biomarkers, including the neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte-(MLR), platelet-to-lymphocyte (PLR) ratios and systemic immune-inflammation index (SII) have been associated with severity and mortality of patients with COVID-19. The purpose of this study was to evaluate the association of baseline leukocyte biomarkers calculated in the emergency department (ED) with the disease severity and mortality. This was a retrospective cohort study that evaluated 1,535 (mean age 57+18 years) patients with SARS-CoV-2 infection in the ED of a single reference center. Outcomes were severity, defined as intensive care unit (ICU) admission requirement, and in-hospital mortality. All leukocyte biomarkers were calculated in the ED before the hospital admission. Their ability to predict the severity and mortality was measured using receiver operating characteristic (ROC) curves. Severity and mortality were observed in 30.9% and 12.6% of the patients, respectively, and were significantly correlated with NLR, MLR, PLR and SII, but only NLR was independently associated with both outcomes on multivariate analysis. Analysis of ROC curves revealed that NLR (0.78 for severity and 0.80 for mortality) and SII (0.77 for severity and 0.75 for mortality) had the best ability to predict mortality, when compared to other ratios. The highest AUC was observed for NLR, employing cut-off points of 5.4 for severity and 5.5 for mortality. Leukocyte biomarkers, particularly NLR, are capable of predicting the severity and mortality of patients with SARS-CoV-2 infection and could be important adjunct tools to identify patients in the ED that are more prone to develop adverse outcomes.

KEYWORDS: Leukocyte biomarkers. COVID-19. Prognosis. Outcome. Critical care. Emergency department.

INTRODUCTION

Up to now, according to WHO Coronavirus (COVID-19) Dashboard, more than 430 million people were confirmed with SARS-COV-2, resulting in almost 6 million deaths worldwide[1–3]. The course of this infection is usually with no or mild to moderate flu-like respiratory symptoms that may evolve in a smaller subset of the patients to pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ failure, leading to a higher risk of death, particularly in older people with several comorbidities[4]. Clinical judgment for adequate triage of those patients with suspected or confirmed COVID-19 who could be discharged for outpatient care or alternatively admitted to the hospital or ICU is still a challenge for physicians. In this regard, several algorithms were proposed to assist physicians in the emergency department (ED) for decision-making toward hospitalization and ICU

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admission[5,6], including clinical and laboratory biomarkers associated with higher risk for adverse outcomes[7,8]. Organ dysfunction in COVID-19 has been associated with host-related uncontrolled inflammation triggered by viral infection[9] and several laboratory biomarkers including C-reactive protein, pro-calcitonin and blood leukocyte counts and ratios have been employed to assess the severity and mortality of the disease[5,6], but few are suitable to be used in the ED. Leucocyte ratios, including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII) and platelet-to-lymphocyte ratio (PLR), are inflammatory indices, which can be easily calculated after the results of whole blood count (WBC) that are readily and quickly available in every ED. In this regard, NLR has been useful to predict bloodstream infections in the ED[10], sepsis[11], pneumonia[12], and decompensated cirrhosis or acute on chronic liver failure[13]. Data concerning the prognostic role of MLR or SII of infectious diseases are scarce, but those aforementioned biomarkers were more closely associated with adverse outcomes related to cancer or cardiovascular diseases[14,15].

In COVID-19, several meta-analyses have disclosed an association between leukocyte biomarkers, including NLR, MMR and SII, disease severity and outcomes[16-20], but few studies were designed to evaluate the impact of those biomarkers assessed in the ED in the requirement for subsequent hospitalization, ICU admission and survival.

The purpose of this study was to evaluate their accuracy in the ED in predicting adverse outcomes of COVID-19 infection.

MATERIALS AND METHODS

Study design and population

This is a retrospective cohort study using data from electronic medical charts of all patients who were admitted in the emergency department of the Portuguese Hospital of Salvador, Bahia State, Brazil, from March 2020 to March 2021 with a clinical suspicion of SARS-CoV-2 infection leading to a collection of RT-PCR for COVID-19. All patients were followed based on hospital guidance that was constantly updated for evidence-based decision-making. In the ED, all patients were triaged according to the severity of their symptoms. Patients with mild symptoms were discharged for outpatient management while the results of RT-PCR were pending and advised to return to the ED in case of worsening of respiratory symptoms and/or health status. Those with moderate to severe symptoms were admitted to the emergency ward for laboratory and imaging evaluation at the attending physician's discretion, always including a complete blood count. All patients requiring admission to the hospital and to the ICU were managed by a dedicated group of physicians according to the available evidence-based data. A de-identified database comprising patients with respiratory symptoms admitted to the ED according to RT-PCR, with subsequent admission to the hospital ward, ICU or discharge from the ED, was created and updated on a daily basis.

Clinical and laboratory evaluation

White blood cell counts and ratios, including NLR, MLR, PLR and SII were calculated, as previously described[13]. Differential leucocyte counts were automatically produced for all white blood cell count estimation and reported to a minimum of three significant figures. Differential leucocyte counts were automatically produced using Sysmex® XT-4000i hematology analyzer equipped with flow cytometer.

Hospital admission and ICU referral directly from the ED were decided in accordance with the hospital guidance for COVID-19. Baseline leukocyte ratios were correlated with admission to the hospital and ICU and mortality. Only patients with COVID-19-confirmed infection by RT-PCR were included in this analysis. Subsequent admissions within 30 days were considered readmissions. Patients with more than one admission with RT-PCR confirming COVID-19 infection were considered as new infections only in those occurring in a time frame of more than 60 days. Outcomes were severity, defined as requirement for ICU admission, and mortality.

The study was approved by the Ethics Committee in Research of the Portuguese Hospital of Salvador, Bahia State.

Statistical analysis

Dichotomous variables are shown in text and tables as numbers and percentages and were compared using the chi-square test or Fisher's test, when appropriate. Continuous variables are reported as mean and standard deviation (SD) or as median and interquartile range, respectively, whether the distribution was normal or skewed, using the Student's t-test when appropriate. A p-value < 0.05 was considered significant. Variables associated with severity and mortality at univariate analysis with a p-value of < 0.10 were included in multivariate logistic regression modeling using stepwise elimination. All scores were further compared using receiver operator characteristic (ROC) curves. The area under the curve (AUC) provided the discriminative ability

of the score. In this analysis, a model with an AUC equal or greater than 0.7 was considered clinically useful. All leukocyte markers were compared to severe COVID-19 infection and mortality using ROC curves with respective 95% confidence interval (95% CI). The AUC provided the discriminative ability of the score and was compared as previously described[21]. Additionally, the prognostic score with the highest AUC obtained was considered a gold standard ROC curve. The other scores were compared to the gold standard using the Bonferroni-adjusted significance probability. In this analysis, models with an AUC equal to or greater than 0.7 were considered clinically significant. The Youden index was used to identify the optimal cut-off point for each score and the corresponding sensitivity and specificity with respective 95% CI. The software used for analysis was the Statistical Package for Social Sciences (IBM., Armonk, NY, USA), version 21.0 for Windows.

RESULTS

Six thousand four hundred and ninety-five subjects were admitted in the ED from March 2020 to March 2021 with respiratory and/or systemic symptoms compatible with COVID-19 (Figure 1). All were tested for SARS-CoV-2 infection. Three thousand six hundred and seven (56%) patients were positive to SARS-CoV-2 infection by RT-PCR. Among those subjects, 1,458 (40%) were admitted to the emergency ward for subsequent clinical, laboratory and imaging evaluation at the attending physician's discretion, and the remaining 2,068 were discharged for outpatient care. Of those discharged subjects, only 81 (4%) returned to the ED due to worsening clinical symptoms, requiring admission to the emergency ward. Eight hundred eighty-five (58%) and 476 (30.9%) subjects, respectively, were admitted to the hospital or to the ICU directly from the ED or after hospital admission. Forty-six subjects with missing data concerning baseline leukocyte ratios were excluded from the study. The demographics, clinical and laboratory features, leukocyte ratios and clinical outcomes of the 1,535 (799 women, mean age 57+18 years) subjects enrolled in the study are depicted in Table 1. Based on requirements for ICU, 476 subjects were considered to have severe COVID-19 infection. One hundred ninety-four subjects died, comprising 12.6% of hospitalized patients and 5% of those SARSCov-2 RT-PCR positive subjects evaluated at the ED.

Disease severity and mortality were significantly higher in males and older subjects (Table 2). Patients with severe COVID-19 infection had significantly higher WBC, neutrophil, lymphocyte and platelet counts, as well as with all leukocyte ratios, including NLR, MLR, PLR and SII (Table 2). Likewise, except for lymphocyte, monocytes and platelet counts, all other markers, including WBC, neutrophil and all leukocyte ratios were also associated with mortality (Table 2). On univariate analysis (Table 3), age, male gender, NLR, MLR, PLR and length of stay (LOS) were significantly associated with disease severity, but only age, NLR and LOS were independently associated with severe COVID-19. Likewise, age, male gender, NLR, MLR, PLR and LOS were significantly associated with

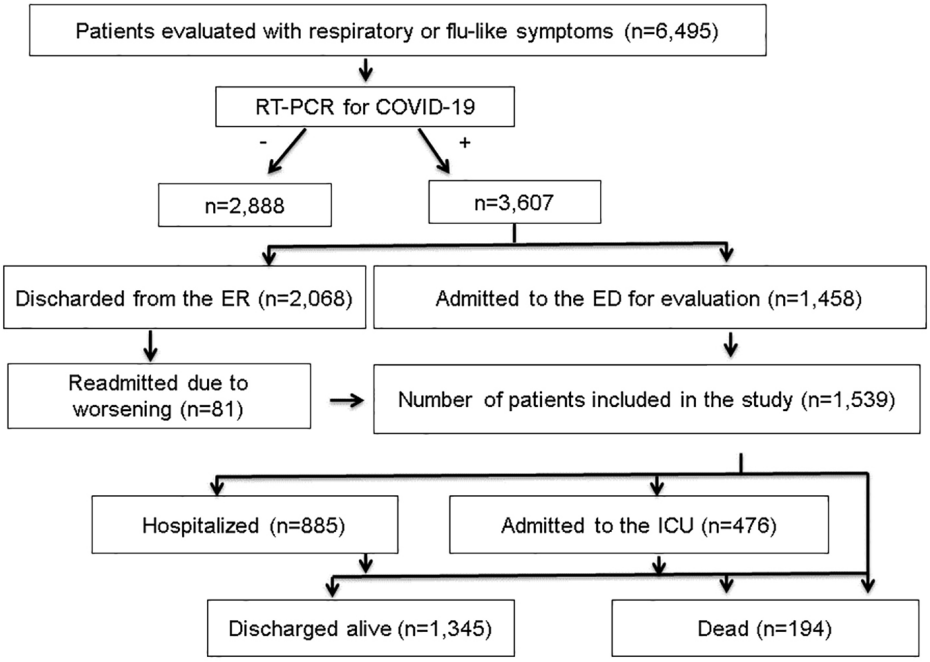

Figure 1 - Flowchart of patients included in the study.

Table 1 - Clinical and laboratory features of patients admitted to the emergency room (n = 1,535).

Demographics	
Age (years)	56.9±18.4
Gender	
Female	798 (52%)
Male	737 (48%)
Leukocyte biomarkers	
Leukocytes[a]	7.5 [4.9-8.8]
Neutrophils[a]	5.3 [2.9-6.8]
- Monocytes[a]	0.6 [0.4-0.7]
Lymphocytes[a]	1.8 [0.7-1.7]
Platelets[a]	229.5 [173.0-270.0]
NLR[a]	6.63 [1.95-7.73]
MLR[a]	0.56 [0.29-0.70]
PLR[a]	237 [125-279]
SII[a]	1,595 [409-1,756]
Outcomes	
Severity	476 (30.9%)
Mortality	193 (12.6%)

[a]Expressed by median (25^{th}–75^{th}); NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio; SII = systemic immune-inflammation index; PLR = platelet-to-lymphocyte ratio. Severity was defined based on the requirements for admission in the intensive care unit.

an increased risk for death, but only age and NLR were independently linked to mortality (Table 3).

ROC curves were used to assess the ability of those leukocyte markers calculated in the ED to predict disease severity and in-hospital mortality (Figure 2). In this respect, NLR showed the best discriminative ability to predict severity and mortality (AUC 0.78; 95% CI 0.76-0.81, $p < 0.001$ and AUC 0.80, 95% CI 0.75-0.82; $p < 0.001$ respectively), when compared to other leukocyte ratios. The most discriminative cut-off point was determined using the highest Youden index for each biomarker. Those results and the corresponding sensitivity and specificity values are depicted in Table 4. Among those aforementioned leukocyte counts and ratios, NLR, PLR, SII and neutrophil count and NLR and SII exhibited AUC values greater than 0.70 previously considered relevant to predict severity and mortality, respectively (Table 4). NLR had the highest discriminative power to distinguish those patients with non-severe COVID-19 from their counterparts with severe conditions, as well as those subjects who survived the infection from those who didn't. The discriminative cut-off points of NLR for severity and mortality were 5.4 and 5.5, respectively.

DISCUSSION

Virus-induced cytokine storm leading to an unregulated

Table 2 - Clinical and laboratory features of patients admitted to the emergency ward according to demographics, leukocyte counts and ratios.

Features	Severity			Mortality		
	Yes	No	*p*	Yes	No	*p*
Demographics						
Age (years)	67.9±15.7	52±17.3	**0.001**	73.5±13.7	54.5±17.7	**0.0001**
Gender			0.001			0.03
Female	216 (45.4%)	583 (55%)		86 (44.6%)	712 (53.1%)	
Male	260 (54.6%)	477 (45%)		107 (55.4%)	630 (46.9%)	
Leukocyte biomarkers						
Leukocytes	9.3±8.1	6.8±3.9	**0.0001**	9.4±5.7	7.3±5.6	**0.0001**
Neutrophils	7.2±4.6	4.5±2.6	**0.0001**	7.8±5.2	5.0±3.1	**0.0001**
Lymphocytes	1.4±3.7	1.9±3.8	0.02	1.4±3.7	1.8±3.8	0.27
Monocytes	0.6±0.5	0.6±0.3	0.9	0.6±0.4	0.6±0.4	0.68
Platelets	238.3±105.5	225.6±75.5	0.006	225.0±112.6	230.2+82.3	0.44
NLR	11.6±12.7	4.4±5.2	**0.0001**	14.7±15.4	5.5±6.9	**0.0001**
MLR	0.7±0.6	0.5±0.4	0.0001	0.8±0.7	0.5±0.4	0.0001
PLR	325.5±323.7	197.1±132.8	0.0001	371.8±441.6	217.5±155.3	0.0001
SII	2947.0±4867.2	988.1±1235.3	0.0001	3698.4±6209.6	1293.2±2070.3	0.0001

NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio; SII = systemic immune-inflammation index; PLR = platelet-to-lymphocyte ratio.

Table 3 - Univariate and multivariate variables associated with severity and mortality in subjects with COVID-19.

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Severity						
Age	1.06	1.05-1.065	< 0.001	1.030	1.020-1.040	**< 0.001**
Male gender	1.47	1.18-1.83	< 0.001			
NLR	1.6	1.3-1.87	< 0.001	1.060	1.031-1.090	**< 0.001**
MLR	2.87	2.18-3.76	< 0.001			
PLR	1.004	1.003-1.005	< 0.001			
LOS	1.25	1.22-1.28	< 0.001	1.2	1.16-1.23	**< 0.001**
Mortality						
Age	1.073	1.061-1.086	< 0.001	1.049	1.035-1.063	**< 0.001**
Male gender	1.41	1.04-1.90	< 0.001			
NLR	1.09	1.074-1.114	< 0.001	1.04	1.020-1.060	**< 0.001**
MLR	2.805	2.071-3.798	< 0.001			
PLR	1.003	1.002-1.004	< 0.001			
LOS	1.03	1.02-1.04	< 0.001			

Odds ratio are expressed as 95% CI (confidence interval); NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio; SII = systemic immune-inflammation index; PLR = platelet-to-lymphocyte ratio.

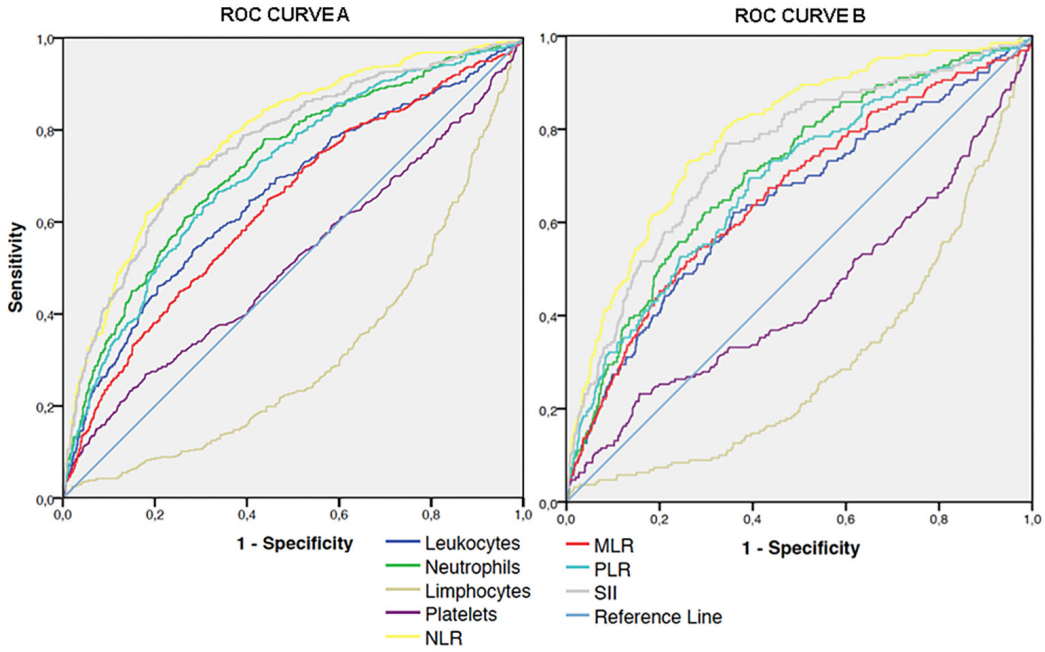

Figure 2 - Comparison of leukocyte markers calculated in the emergency department in their ability to predict A) severity and B) mortality of patients with COVID-19. NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio; SII = systemic immune-inflammation index; PLR = platelet-to-lymphocyte ratio.

inflammatory syndrome resulting in multi-organ failure is the hallmark of severe COVID-19 infection[9]. It is usually associated with systemic signs of inflammation, including leukocytosis with relative neutrophilia and lymphopenia and increased circulating levels of pro-inflammatory biomarkers, such as C-reactive protein, ferritin, and interleukin[6-8]. Several studies up to now have already linked the circulating biomarkers of COVID-19-associated hyperinflammation with an increased risk of organ failure and death. Although based on variables easily available in all hospitals, the prognostic value of NLR in patients with COVID-19 was rarely described in previously published research. This study demonstrated that several leukocyte markers are associated either with COVID-19 severity or

Table 4 - Comparison of leukocyte biomarkers in their ability to predict severity and mortality using ROC curve analysis in patients with COVID-19.

Markers	AUC	95% CI	Cut-off point	Sensitivity (%)	Specificity (%)	*p* Value
Severity						
WBC count	0.66	0.63-0.69	6,300	70	53	< 0.001
Neutrophil count	0.72	0.70-0.75	4,200	77	60	< 0.001
Lymphocyte count	0.31	0.28-0.34	778	58	20	< 0.001
Platelet count	0.51	0.48-0.55	1,880	64	35	0.414
NLR	0.78	0.76-0.81	5.4	70	76	< 0.001
MLR	0.63	0.60-0.67	0.4	70	60	< 0.001
PLR	0.71	0.68-0.74	180	70	60	< 0.001
SII	0.77	0.74-0.79	728	80	60	< 0.001
Mortality						
WBC count	0.64	0.59-0.68	7,000	64	58	< 0.001
Neutrophil count	0.70	0.66-0.74	4,261	78	51	< 0.001
Lymphocyte count	0.30	0.26-0.34	798	50	25	< 0.001
Platelet count	0.44	0.39-0.49	190	55	34	0.013
NLR	0.80	0.75-0.82	5.5	74	71	< 0.001
MLR	0.66	0.61-0.70	0.45	70	55	< 0.001
PLR	0.69	0.64-0.73	182	75	53	< 0.001
SII	0.75	0.70-79	735	84	53	< 0.001

Odds ratio are expressed as 95% CI (confidence interval); WBC = white blood cell; NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to-lymphocyte ratio; SII = systemic immune-inflammation index; PLR = platelet-to-lymphocyte ratio.

mortality, but only NLR, besides age, was independently correlated with both outcomes. NLR levels were also shown to have a better performance to predict ICU admission and mortality, when compared to several other variables with different discriminative cut-off points for disease severity and mortality.

In the current study, the cut-off 5.5 for the NLR, obtained on the day of ED admission, could predict outcomes and mortality with an accuracy of over 70%, strengthening the applicability of this marker in clinical practice. Although it was previously reported that leukocyte ratios could predict COVID-19-associated outcomes, our study differs from others. We included a large sample size to show that NLR, early determined in the ED, has prognostic value. Several studies, performed in China[21-25], the Middle-East[26], Europe[27,28] and the United States[29,30], revealed that leukocyte ratios, particularly NLR, are reliable biomarkers to better assess the prognosis of subjects with SARS-CoV-2 infection, corroborating the evidence for using this marker in clinical practice. Several meta-analyses involving those reports, as well as several other studies, endorsed the association between NLR levels and disease severity and mortality[31-36]. However, the significant clinical heterogeneity in these studies regards the moment the ratios were calculated.

Some studies reported a different cut-off, obtained by ROC curve analysis, to discriminate patients with benign outcomes from those with adverse ones. In this regard, NLR levels ranging from 3.3 to 5.87 and 4.0 to 11.75 were respectively associated with either disease severity[21-23,30] or mortality[24,25,29,30,37]. Most of the studies came from China with less than a hundred patients enrolled[36]. Recently, one Brazilian study[37] has suggested an NLR cut-off point of 10 to discriminate those patients with a higher risk of death. However, patients were assessed at an advanced disease stage. All patients had an extremely severe clinical picture, as approximately 90% of them were on mechanical ventilation and one-third died in the hospital. This precludes the use of the cut-off point of 10 for early prognostic predictions.

Different cut-off points observed for NLR may reflect the heterogeneity associated with disease severity and mortality reported in different parts of the world. This may be related to differences in access to health care and management of COVID-19, as well as in the frequencies of concurrent comorbidities and different responses to severe inflammation in populations with different ethnical or racial backgrounds.

Despite this variability, our study reinforces the concept that leukocyte ratios, particularly NLR, are useful

biomarkers, which can be easily employed in the ED to assess the prognosis of patients with COVID-19. Due to its higher discriminative ability to assess disease severity, NLR may turn out to become a valuable laboratory parameter to aid emergency care physicians in decision-making toward hospitalization of COVID-19 patients, because it is usually readily available and automatically calculated with the WBC count.

Limitations

It is important, however, to highlight that our study has several limitations due to its retrospective design, absence of comorbidity stratification, not being able to control confounders, as well as an adequate evaluation of several other concurrent biomarkers known to increase the disease morbidity and mortality. We believe that prospective and multicentric studies are important to assist in the decision-making process.

CONCLUSION

In summary, leukocyte biomarkers, particularly NLR, are capable of predicting the severity and mortality of patients with SARS-CoV-2 infection and could be important adjunct laboratory biomarkers in the ED to identify subjects with COVID-19-associated hyperinflammation requiring hospitalization for adequate surveillance.

AUTHORS' CONTRIBUTIONS

PLB conceived the study; PLB and LC supervised data collection; JPF, PPCS and PLB collected the data; RCD and JPF searched for reference articles in the literature for analysis; APM, DV, LC and AQF drafted the manuscript, and all authors contributed substantially to its revision; PLB takes responsibility for the paper as a whole.

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