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Magnitude of a Metabolic Risk Profile in Sepsis Scales in Patients with Pneumonia

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Received: 10 April 2021 Accepted: 4 May 2021 Published: 15 May 2021

Abstract

Introduction:The mortality of community acquired pneumonia (CAP) ranges from 5

Index terms— pneumonia, COVID 19, sepsis, prognostic scales.

adquirida en la comunidad (NAC) oscila entre el 5% y el 15%, dependiendo lógicamente de si el estudio ha sido realizado en la comunidad o en ámbito hospitalario, así como variando también según la edad. En México al 26 de Junio 2021 existen 2,498,357 casos confirmados por COVID y 232,346 muertes. Existen estudios demostrando que la enfermedad cardiovascular es un factor de riesgo para eventos de sepsis. Al no disponer de un marcador pronóstico único, es importante disponer de herramientas clínicas para estimar la probabilidad de muerte intrahospitalaria en pacientes sépticos y así identificar los pacientes de alto riesgo y mejorar el uso apropiado de las intervenciones médicas a realizar.

Objetivo: Conocer la magnitud de un perfil metabólico de riesgo en las escalas de sepsis en pacientes con neumonía Material y métodos: Estudio observacional, analítico de corte transversal en 117 pacientes por elegidos por muestreo no probabilístico de Junio 2019 a Diciembre 2020 en tres hospitales de la secretaria de salud de la ciudad de México con diagnóstico de neumonía adquirida en la comunidad y pacientes con infección por SARS-CoV-2. Se realizaron curvas ROC no paramétricas a partir de aquellas variables clínicas y bioquímicas que mostraron un área bajo la curva $>$ 50 % para las variables APACHE 25, SOFA 3 y PSI PORT 90. Se estableció un punto de corte con aquellas que presentaban mejor sensibilidad y especificidad con un posterior análisis multivariado mediante regresión logística binaria para calcular las razones de momio de cada variable ajustadas por edad. Se estableció el nivel de significancia con una $p < 0.05$, los datos fueron analizados con el programa Stata 14.

Resultados: Las variables que mejoran la sensibilidad y especificidad e impactan a las escalas pronosticas utilizando un modelo de regresión logistica fueron para "APACHE 25 gradiente alveolo arterial Grad(A-a)O2 en ambos grupos (OR=4.84 IC 6.88-95.3 p=0.0001). "SOFA 3" con proteina C reactiva (OR= 2.40 IC 1.21-6.74 p= 0.016), GA-A (OR=2.87 IC1.54-9.99 p=0.004), índice Tg/HDL (OR=2.81 IC1.01-1.06 p=0.005). Índice aterogénico únicamente en grupo "NAC" (OR=2.33 IC1.17-6.58 p= 0.020).

"PSI 90" mostro significancia en GA-A solo en grupo "COVID" (OR= 2.12 IC1. **??**0-13.88 Excluding COVID-19 pneumonia, communityacquired pneumonia (CAP) is a disease with an incidence of approximately 10 cases per 1000 inhabitants/year. The mortality of CAP ranges from 5% to 15%, depending logically on whether the study was performed in the community or in a hospital setting, as well as varying according to age (3).

Clinical prediction rules (CPR) are tools designed for decision making, containing three or more simple variables obtained from the clinical history, physical examination and/or ancillary tests. These rules are usually created by multivariate analysis and can predict the mortality of a disease and suggest a diagnosis or therapeutic course of action (4). The majority of RPC correspond to scoring systems. In recent years, most sepsis research has focused on early detection and care of acute sepsis. But few efforts have conceptualized sepsis as a preventable condition; identifying risk factors and developing a strategy for sepsis prevention could be a valuable effort to reduce the societal burden of this life-threatening and costly disease. (5) A new generation of scores, developed specifically to predict ICU admission, focuses on the severity of pneumonia itself rather than age and comorbid conditions.

Overall, the performance of these scores appears superior to that of PSI or CURB-65. The inclusion of several biomarkers such as procalcitonin, endothelin-1, co-peptin, pro-atrial natriuretic peptide, or adrenomedullin; however, these biomarkers are unlikely to predict clinical deterioration due to hospital-acquired complications or decompensated comorbidities; it is even questionable whether they detect circulatory or respiratory failure in patients admitted very early in the course of their illness (6).

The Pneumonia Severity Index (PSI) was proposed by Fine et al. The PSI is the first model for assessing CAP. It includes three demographic variables, five comorbidities, five physical examination variables, and seven laboratory tests.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is the most commonly used critical illness evaluation system in clinical ICUs. It consists of three sections, namely acute physiology, age, and chronic health assessment. The acute physiology score consists of 12 physiological variables. (8,9) (7) The Sequential Organ Failure Assessment (SOFA) score was proposed by the European Society of Intensive Care Medicine. The SOFA score is primarily used to describe the onset and development of multiorgan dysfunction syndrome. Six systems are included in the model, namely the respiratory system, nervous system, hepatic system, cardiovascular system, coagulation system and renal system (10).

There are studies demonstrating that cardiovascular disease is a risk factor for sepsis events. The association between baseline cholesterol and sepsis rates remains unknown. As with coronary heart disease, a relationship between cholesterol and sepsis could provide an opportunity to potentially reduce an individual's long-term risk for the development of sepsis (11).

Metabolic syndrome (MetS) involves a group of metabolic abnormalities including centrally distributed obesity, decreased high-density lipoprotein cholesterol (HDL-C) concentration, elevated triglycerides (TG), high blood pressure, and hyperglycemia. MetS is also a risk factor for developing type 2 diabetes mellitus (DM2), heart disease, and stroke associated with arteriosclerosis which are causes of mortality. It is a risk factor for cardiovascular disease. Given the above, it is considered a public health problem, especially in westernized countries, with a prevalence of 39.7% in Mexico. (12,13) Mexican adults have a 71.2% prevalence of overweight and obesity, 25.5% have hypertension and 13.7% have type 2 diabetes mellitus. In people aged 50 to 59 years, dyslipidemia has a prevalence of 36.8%. A common phenotype in this age group was high Tg with low blood levels of HDLc (14).

In this context, a new index has been proposed to estimate cardiovascular risk, which considers the TG/HDL-C ratio. This index has been used in different types of populations, such as in subjects at high risk of coronary heart disease, in subjects with DM, and in patients with coronary heart disease; in all these studies, the TG/HDL-C ratio was an independent predictor of cardiovascular disease (15). Low HDL cholesterol and high triglyceride concentrations measured before or during hospitalization are strong predictors of a severe disease course. Lipid profile should be considered as a sensitive marker of inflammation and should be measured in patients with COVID-19 (16).

Compared with patients with mild or asymptomatic COVID-19, individuals with severe complications have a higher prevalence of comorbidities such as hypertension, cardiovascular disease, and type 2 diabetes mellitus. These comorbidities share the common metabolic disturbances of insulin resistance and dyslipidemia; the latter has been associated with severe COVID-19 (17).

Most patients with COVID-19 in the ICU develop ventilator-associated bacterial pneumonia (VAP), suggesting that both COVID-19 and bacterial infection may influence the lipid profile. (18) The Tg / HDLc ratio can be used as an early biochemical marker of severe COVID-19 prognosis with need for invasive mechanical ventilation. (19) Although the SOFA score is a simple and effective method to describe organ dysfunction in critically ill patients and to evaluate their evolution during their stay in the ICU, it does not allow distinguishing between acute, chronic or exacerbated chronic organ dysfunction, nor does it allow determining whether the organ dysfunction is secondary to the occurrence of an infectious condition or another condition that leads to this organ failure. (20) In the absence of a single prognostic marker, it is important to have clinical tools to estimate the probability of in-hospital death in septic patients in order to identify high-risk patients and improve the appropriate use of medical interventions.

1 II.

2 Material and Methods

An observational, analytical, cross-sectional study was conducted in 117 patients selected by nonprobabilistic sampling from June 2019 to December 2020 in three hospitals of the Secretary of Health of Mexico City who were admitted to the internal medicine service with a diagnosis of community-acquired pneumonia prior to the COVID 19 pandemic and patients with SARS-CoV-2 infection confirmed by a positive polymerase reaction test (PCR). They were grouped into two categories: the "CAP" group included 12 patients; the "COVID" group included 105 patients. Excluded were patients who refused to participate in the study; patients diagnosed with liver disease (hepatitis B, hepatitis C, autoimmune hepatitis, liver cirrhosis, hepatocellular carcinoma), dyslipidemia; patients on treatment with statins or other lipid-lowering drugs or using steroids 7 days prior to the study; patients with a clinical diagnosis of HIV, active pulmonary tuberculosis and patients discharged from the hospital during the three weeks prior to the study.

All patients received clinical laboratory sampling at baseline. All laboratory tests had completed the standardization and certification program. The severity scales to be studied were SOFA, APACHE and PSI PORT for both groups; therefore, clinical and biochemical parameters included in these scales were included. Based on the literature, cut-off points were established for severity and mortality scales in pneumonia APACHE with a score greater than 25 points corresponding to a mortality greater than 50% PSI PORT greater than 90 points indicating hospitalization requirement. SOFA greater than 3 points, taking this cutoff point because the sample "n" for SOFA less than 2, which is necessary in the operational definition of sepsis, was limited to 3 patients. Other variables included in the analysis were weight, height, body mass index, blood count, renal function tests (urea, blood nitrogen, creatinine), lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol), procalcitonin. In addition, the COVID included severity markers (D-dimer, Creactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin. Indices derived from the biochemical parameters analyzed, which have been associated with inflammatory activity or severity, were evaluated: triglycerides / HDL cholesterol, total cholesterol / HDL cholesterol (atherogenic index), partial oxygen pressure / fraction of inspired oxygen (PaO2 / FiO2), oxygen saturation / fraction of inspired oxygen (SaO2 / FiO2) and absolute neutrophils / absolute lymphocytes.

Descriptive statistics were performed by analyzing the distribution of the different continuous variables using the Shapiro Wilk test in the "CAP" group and the Kolmogorov Smirnov test in the "COVID" group; variables with non-normal distribution were found, so median and interquartile range were used as summary measures for these variables. The odds ratio (OR) with 95% confidence intervals (CI) was used as a measure of association to establish the advantage of one group over another. To establish differences in the frequencies according to the distribution of the variables, the chisquare test, Student's t-test, Mann Whitney test and Kruskal Wallis test with a significance level of 0.05 were used.

Nonparametric ROC curves were made from those clinical and biochemical variables that showed an area under the curve $>$ 50% for the variables APACHE 25, SOFA 3 and PSI PORT 90. A cutoff point was used to categorize these variables according to those with the best sensitivity and specificity; with these categorized variables, a binary logistic regression analysis was performed for the multivariate model to calculate the odds ratios of each variable adjusted for age. The significance level was established with a $p < 0.05$, the data were analyzed with the Stata 14.0 program.

The present study followed the ethical regulations in force at the hospital level. All the subjects surveyed, of legal age and capacity, signed the informed consent form; this study was classified as research without risk for the participants, collecting only pertinent data; the principle of confidentiality was maintained, taking into account personal identification by means of an alphanumeric code.

3 III.

4 Results

The contrast of the severity of pneumonia by hospital institution, according to the PSI/PORT, SOFA and APACHE scales, is shown in Table 1. No statistically significant differences were found in any of the scales evaluated (Kruskal Wallis 0.085, p = 0.958). 105 (89.7 %) participants who were diagnosed with COVID-19 represented 97.8 % of the patients at Hospital General Xoco, 90.6 % at Hospital General Tláhuac and 68.4 % at Hospital General de Ticomán. Overall, the highest percentage of patients were found in category 3 of the PSI PORT scale. The proportion of PSI class in both groups is shown in Figure **??**.

The contrast of clinical and sociodemographic characteristics according to the diagnosis of CAP or COVID-19 is presented in Table 2. The proportion of patients with pleural effusion, liver disease, and the pO2/FiO2and PSI/PORT indices, with their respective classes, were significantly higher in patients with CAP. In patients with a diagnosis of COVID-19, respiratory frequency, TG concentration, SOFA scale, and A-aO2 were higher than in the latter. No significant differences were found in cardiovascular risk parameters (BMI, TG/C-HDL index, complete lipid profile, diabetes mellitus and systemic arterial hypertension; $p > 0.05$) (Table 2).

The concentrations of D-dimer, ferritin, CRP, fibrinogen and the sO2/FiO2 index were only established in patients with a diagnosis of COVID-19.In these, D-dimer concentration correlated directly and significantly with TG/C-HDL index (Spearman's ? 0.205, 95 % CI 0.018 -0.378, p = 0.0277) and serum TG concentration (Spearman's ? 0.184, 95 % CI -0.001 -0.358, p = 0.0473).

In the ROC curve analysis, we found for the variable "APACHE 25" an area under the curve greater than 50% with confidence intervals greater than unity for the level of neutrophils, glycosylated hemoglobin, arterial alveolar gradient and borderline value in CI for the neutrophil-lymphocyte index. The variable "SOFA 3" obtained a significant area with C-reactive protein, arterial alveolar gradient, Tg/HDL index and atherogenic index (total cholesterol/HDL). "PSI PORTH 90" showed a significant curve with D-dimer, arterial alveolar gradient and lymphocyte neutrophil index (Table 3).

The multivariate model with binary logistic regression included the cut-off points according to the best sensitivity and specificity of the ROC curve, obtaining in the three scales an OR greater than unity with $p < 0.05$ only for Grad(A-a)O2 (arterial alveolar gradient). The "APACHE 25" scale showed a statistically significant OR for GA-A only. "SOFA 3" showed significant OR for C-reactive protein, arterial alveolar gradient, Tg/HDL index, however atherogenic index was only significant in the "CAP" group. "PSI 90 only showed a significant difference in the COVID group in arterial alveolar gradient (Table 4).

IV.

5 Discussion

The data obtained show that the scales analyzed in pneumonia increase their sensitivity and specificity by associating other biochemical variables not included in the scales, although they do so with different precision and with different cutoffs for each scale, despite being the same variable studied.

When correlating variables, we found a statistically significant association between HDL cholesterol and total triglycerides with markers of inflammation such as Dimero D and ferritin, results very similar to those found by Masana et al [16] even with a smaller population than their study, so we could infer that there is a proinflammatory state prior to and during hospitalization of patients with pneumonia that is aggravated by the addition of a septic process.

The calculation of Grad(A-a)O2 allows assessment of ventilation-perfusion inequality; it is conditioned by FiO2. In our multivariate study, Grad(Aa)O2 was an important parameter for establishing a risk profile with the highest statistical significance and OR for the three severity scales analyzed, but not for the parameters SaO2/FiO2 and PaO2/FiO2; However, Grad(A-a)O2 is only a reliable reflection of the alterations in the physiological shunt when there is cardiovascular stability, constant FiO2 and elevated PaO2 as mentioned in Sanchez Casado et al [22] in their work; however, with initial blood gases without other biochemical variables we can identify those patients with worse prognosis. This can be useful in an emergency department, especially in the context of the COVID 19 pandemic.

The neutrophil-lymphocyte index obtained statistical significance in the multivariate as a marker of severity for the APACHE scale; contradictorily to what was found by Che-Morales [23] the statistical significance was not in the community-acquired pneumonia group but in the group of COVID patients, a result that could be explained by the sample size of the CAP group. It should be noted that the cutoff point of the index > 7.2 for a PSI class III in the risk group of patients with pneumonia found by Che-Morales was similar to that reported in this work with a cutoff point > 7.79.

SOFA was the scale that obtained the most statistically significant variables; sensitivity and specificity increase when lipid profile variables are included, especially the triglyceride level. As analyzed by Lee-Park et al [21] in their study, including the triglyceride level in the SOFA scale improves sensitivity and specificity in the ROC curve; however, in our study the greatest impact on this scale was the inclusion of the Tg/HDL index, as in the study by Alcántara Alonso et al [19] When the triglyceride/HDL index is associated, a greater OR is observed with very narrow confidence intervals in the multivariate analysis; in our study, the cut-off point was 5.41 as opposed to 7.45 according to that reported by Alcántara, however in our study the sample was not directed only to patients who developed mechanical ventilation or to a type of pneumonia, a situation that could explain this difference in value but which is one of the strengths of this study; despite this discordance the influence of this index is clear; this index has been related to insulin resistance and increased cardiovascular risk and little has been studied in processes of acute inflammation such as sepsis.

Regarding C-reactive protein, similarities were found to reports by Huang et al [24] in meta-analysis of Chinese studies with an n over 5000 patients where an elevated CRP >10 mg/L was associated with an unfavorable outcome (RR) 1.84 (1.45, 2.33), $p<0.001$. A sensitivity of 51%, a specificity of 88%, and an area under the curve (AUC) of 0.84. We found a cut-off point of >12.2mg/L (OR) 2.40 (1.21-6.74), $p=0.016$ sensitivity 66%, specificity 50%. (AUR) of 0.57 for a probability of obtaining a SOFA greater than 3 points in both pneumonia groups; a result that reinforces that it is an important variable to consider as a prognostic factor, not only in patients with COVID-19, but also in patients with community-acquired pneumonia. In contrast to the aforementioned study, Procalcitonin, D-dimer and ferritin did not obtain statistical significance in the multivariate, only D-dimer in the ROC curve for the PSI scale.

Among the limitations of this study, it is possible that the size of the sample n influenced the wide confidence intervals found in the significant variables when performing the logistic regression; however, some of the significant variables found in the linear correlations did not obtain the expected result, especially for the community-acquired pneumonia group when performing the multivariate analysis, which could lead to a type B error. The heterogeneity of the groups in each hospital site and treatment established could influence the result obtained in this study.

The lipid and respiratory profile could be extrapolated to other severity scales not analyzed in this study, such as Logistic Organ Dysfunction Score (LODS), Early Warning Score (NEWS), Graham COVID, Brescia COVID, MuLBSTA score, among others, adapting them by adding the variables proposed in this study and obtaining a new scale applicable to the Mexican population.

V.

6 Conclusions

There are parameters not included in the severity scales used in patients with pneumonia, which are accessible, inexpensive and quickly obtained when a patient is admitted to the hospital, increasing their sensitivity and specificity. New indexes derived from lipid profile such as Tg/HDL, atherogenic, blood biometry, neutrophil/lymphocyte index and respiratory profile such as alveolar arterial gradient have an indirect impact

on the prognosis and severity of a patient with pneumonia, not only in community-acquired pneumonia but also in patients with COVID 19 pneumonia. The proposed variables improve the ability to identify patients at risk of poor short-term outcomes compared to the already known scales. [1]

Introduction
he current virus named SARS-CoV-2, initially called 2019-nCov (2019 novel coronavirus), emerges in December 2019 in

Figure 1:

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Global Journal of Medical Research	Pneumonia severity scale PSI/PORT SOFA APACHE	Ticomán General Hospital 73.5 (RIC 44.5 -105) 67 (RIC 65 -82) Hospital 2 (RIC 2 -3.5) 3 (RIC 2 -6) 11.5 (RIC 3 -16.5) 12 (RIC 7 -17) Xoco General	Tláhuac General Hospital 75.5 (RIC 66 -100) 3 (RIC 2 -7) 8.5 (RIC 7 -15)

[Note: KFigure 1:]

Figure 2: Table 1 :

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				Year 2021 7
Variable Age Sex Weight Size BMI Institutionalized patients Patients with pleural effusion	Community-acquired pneumonia "CAP" n=12 60.1 (± 18.5) years 33.3 % men, 66.7 % women 76.3 (RIC 65 -80) kg 1.60 (1.58 -1.60) m 28.4 (± 5.4) kg/m2 0 % present 25 % present	COVID-19 "COVID" n=105 56.6 (± 15.7) years 59 % men, 41 % women 76 (RIC 67 -90) kg 1.62 (1.57 -1.70) m 29.0 (± 6.0) kg/m2 2.9 % present 1 % present	p value 0.479 a 0.125 b 0.628 c 0.464 c 0.830 a > 0.999 b *0.003 b	Volume XXI Issue VIII Version I (D D D D)
Neoplasia	16.7% present	2 % present	0.055 b	
Liver disease Heart disease Cerebral vascular disease Chronic kidney disease	16.7% present 8.3 % present 8.3 % present 0 % present	1 % present 2 % present 5 % present 4 % present	*0.029 b 0.288 b 0.498 b > 0.999 b	Medical Research
Diabetes mellitus Systemic arterial hypertension Altered alertness Respiratory frequency	25 % present 58.3 % present 33.3 % present 20 (RIC 19-27) breaths/minute	42.6 % present 37 % present 26 % present 24 (RIC 22-28) breaths/minute	0.354 b 0.212 b 0.731 b *0.003 c	Global Journal of
Heart rate	90 (RIC 87.5-120.5) beats/minute	90 (RIC 80-104) beats/minute	0.861 c	
Systolic blood Pressure	113.7 (± 14.3) mm Hg	122.3 (± 18.7) mm Hg	0.126 a	
Body temperature	36.5 (RIC 36 -37.1) °C	36.4 (RIC 36 -36.8) °C	0.996 c	
Ph	7.39 (RIC 7.38 -7.46)	7.44 (RIC 7.4 -7.47)	0.260 c	
BUN	24 (RIC 18.5-36.5)	20.7 (RIC 15-34.6)	0.404 c	
Serum sodium	134.5 (± 4.3) mEq/L	134.6 (± 6.1) mEq/L	0.966 a	
Hematocrit	41.4 (± 2.7) %	38.7 (± 11.6) %	0.670 a	

[Note: K © 2021 Global Journals Magnitude of a Metabolic Risk Profile in Sepsis Scales in Patients with Pneumonia a Student's t-test; b Fisher's exact test; c Mann Whitney test; d Spearman's x2 test.]

Figure 3: Table 2 :

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SCALE	VARIABLE	Cut-off point	Area under the curve (AUR)	Sensibility	Specificity
APACHE 25	Arterial alveolar gradient Neutrophil/lymphocyte ratio	284 7.79	% 72 58	% 76.4 68.9	% 65.4 42.1
SOFA 3	Absolute neutrophils	6.6	62 57	72.4	43.8
	Glycosylated hemoglobin	7.62	57 66	72.7	53.3
	C-reactive protein Arterial alveolar gradient Tg/Hdl Ratio	12.2 188.9 5.41	58	66.0 75.0 63.0	50.0 50.0 44.7
	Atherogenic index (Col/hd l)	4.78	62	65.7	50.0
PSI PORT 90	Arterial alveolar gradient	238	60	70.8	60.4
	D-dimer	709	60	77.4	47.7
	Neutrophil/lymphocyte ratio	8.55	56	63.4	48.6

Figure 4: Table 3 :

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SCALE	VARIABLE	OR	IC	P
	ARTERIAL ALVEOLAR GRADIENT > 284	4.84	6.88-95.3	0.0001
APACHE 25				
	NEUTROPHIL/LYMPHOCYTE INDEX > 7.79	1.96	0.99-5.33	0.050*
	C-REACTIVE PROTEIN > 12.2	2.40	1.21-6.74	0.016
	ARTERIAL ALVEOLAR GRADIENT > 188.9	2.87	1.54-9.99	0.004
SOFA 3				
	TG/HDL RATIO > 5.41	2.81	1.01-1.06	0.005
	ATHEROGENIC INDEX (CHOL/HDL) > 4.78	2.33	1.17-6.58	0.020

Figure 5: Table 4 :

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