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Simplified acute physiology score II and Mannheim peritonitis index are associated with in-hospital mortality in patients with abdominal sepsis admitted to ICU

Simplified acute physiology score II y Mannheim peritonitis index se asocian a mortalidad intrahospitalaria en pacientes con sepsis abdominal ingresados a la UCI

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Abstract

Objective: *The objective of this study was to assess the association and interaction of laboratory parameters, Simplified Acute Physiology Score II (SAPSII), Modified Shock Index (MSI), and Mannheim Peritonitis Index (MPI) with in-hospital mortality.* **Material and methods:** *We conducted a single-center case–control study. Adult patients with abdominal sepsis were included from May 2015 to May 2020. Baseline characteristics, laboratory parameters, SAPSII, MSI, and MPI scores at admission were collected. A principal component (PC) analysis was applied to evaluate variable interactions. In-hospital mortality risk was determined through logistic regression models.* **Results:** *One hundred and twenty-seven patients were identified, 60 of which were included for analyses. Non-survivors (48.4%) had a higher frequency of hypertension, lactate and MPI, and lower BE and alactic BE levels. Eight PCs were obtained, PC1 being a linear combination of pH, AG, cAG, alactic BE, bicarbonate, and BE. MPI (OR = 9.87, 95% CI: 3.07-36.61, p = 0.0002), SAPSII (OR = 1.07, 95%CI: 1.01-1.14, p = 0.01), and PC1 (OR = 2.13, 95%CI: 1.12-4.76, p = 0.04) were significantly associated with mortality in univariate analysis, while MPI (OR = 10.1, 95%CI: 3.03-40.06, p = 0.0003) and SAPSII (OR = 1.07, CI95%: 1.01–1.14, p = 0.02) remained significant after adjusting for age and sex.* **Conclusion:** *MPI and SAPSII were associated with mortality, although the interaction of laboratory parameters was not.*

Keywords: Septic shock. Abdominal sepsis. Mortality.

Resumen

Objetivo: *Evaluar la asociación e interacción de los parámetros de laboratorio, SAPSII, MSI y MPI con la mortalidad intrahospitalaria.* **Materiales y métodos:** *Nosotros realizamos un estudio de casos y controles de pacientes adultos con sepsis abdominal desde mayo 2015 a mayo 2020. Recolectamos las características basales, parámetros de laboratorio, SAPSII, MSI y MPI al ingreso. Se aplicó un Análisis de Componentes Principales. El riesgo de mortalidad intrahospitalaria se determinó mediante modelos de regresión logística.* **Resultados:** *Identificamos 127 pacientes, 60 de los cuales se incluyeron. Los no supervivientes (48,4%) tuvieron mayor frecuencia de HAS, lactato y MPI, y menores niveles de EB y EB aláctico. Se obtuvieron ocho Componentes Principales (PC), siendo PC1 una combinación lineal de pH, AG, cAG, EB aláctico, bicarbonato y EB. MPI (OR = 9.87, IC95%: 3.07-36.61, p = 0.0002), SAPSII (OR = 1.07, IC95%: 1.01-1.14, p = 0.01) y PC1 (OR = 2.13, IC95%: 1.12-4.76, p = 0.04) se asociaron significativamente con la mortalidad en el análisis univariado, mientras que MPI (OR = 10.1, IC95%: 3.03-40.06, p = 0.0003) y SAPSII (OR = 1.07, IC 95%: 1.01-1.14, p = 0.02) permanecieron significativos después del ajuste por edad y sexo.* **Conclusiones:** *MPI y SAPSII se asociaron con mortalidad, aunque la interacción de los parámetros de laboratorio no lo hizo.*

Palabras clave: *Choque séptico. Sepsis abdominal. Mortalidad.*

Introduction

Intra-abdominal infections are the second most frequent cause of sepsis worldwide, only surpassed by pneumonia. These infections can be classified as uncomplicated or complicated depending on their severity. Uncomplicated intra-abdominal infections seldom cause critical illness. On the contrary, complicated intra-abdominal infections, also referred to as "abdominal sepsis," lead to localized or diffuse peritonitis and subsequent sepsis[1]. Determinants of complicated infections include patient susceptibility, age, and comorbidities, among others[2].

Abdominal sepsis is distinguished by a systemic response to infection which initially develops within the organs of the abdominal cavity[3]. Up to ~5% of patients admitted to an intensive care unit (ICU) due to infectious diseases ultimately have abdominal sepsis[4,5]. Worldwide, it is a major cause of non-trauma deaths in emergency departments[6] with mortality rates being as high as 40%[7]. Therefore, prompt recognition of the infection site and early antimicrobial therapy are essential to reduce mortality[8]. A control on the source of infection should occur within 6-12 h after diagnosis since each hour of delay is associated with higher mortality rates[9].

Various scoring systems have been developed and validated to predict mortality in patients with abdominal sepsis, such as the Simplified Acute Physiology Score II (SAPSII), Modified Shock Index (MSI), and Mannheim Peritonitis Index (MPI), all of which allow for identification of patients at high mortality risk (e.g. MPI > 25 points)[10]. MPI is a mortality prediction index that assesses eight risk factors, with scores ranging from 0 to 47 points. Its sensitivity and specificity are deemed at 95.9% and 80%, respectively[11,12].

In addition, numerous biomarkers such as procalcitonin, neutrophil-to-lymphocyte ratio, and C-reactive protein have also been assessed as potential mortality predictors. Most studies have addressed them separately, and few studies have addressed them concurrently[13-17]. On the other hand, the role of acid-base disturbances, though considered important predictors of adverse outcomes in sepsis[18-20] since they reflect impairment at different levels of organ systems, has seldom been explored in the specific context of intra-abdominal infections, with the exception of serum lactate[21,22].

For the above reasons, the interaction between different scoring systems and laboratory parameters, as well as their weight on mortality in patients with abdominal sepsis, has not been extensively studied. Furthermore, laboratory tests that assess acid-base balance are vast in number, making the identification of those that better explain mortality a priority. Thus, the goal of this study was to assess the association of laboratory parameters, SAPSII, MSI, and MPI scores with in-hospital mortality among ICU patients with abdominal sepsis.

Material and methods

Study design and patients

We conducted a single-center case–control study at the ICU of Hospital No. 14, Unidad Medica de Alta Especialidad (UMAE), Instituto Mexicano del Seguro

Social (IMSS) in Veracruz, México, from May 2015 to May 2020. Inclusion criteria were patients ≥ 18 years with diagnosis of abdominal sepsis, defined as evidence of organ dysfunction characterized but not limited to oliguria, and delayed capillary refill and hypotension with an increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2 points compared to baseline at admission, due to intra-abdominal infection regardless of etiology[23] who were admitted to the ICU, on invasive mechanical ventilation, and vasopressor support with norepinephrine. Patients with incomplete medical records, a diagnosis of non-abdominal sepsis, a do-not-resuscitate order, and pregnant patients were all excluded from the study. Consecutive convenience sampling of patients was performed.

All patients were managed according to Surviving Sepsis Campaign guidelines[24] and current Mexican Clinical Practice Guidelines[25]. The study protocol was approved by the Local Institutional Review Board (approval number: R-2019-1001-18) and the Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS) (approval number: 17_CI_11020_146).

Definitions of outcomes, exposures, cases, and controls

The primary outcome was in-hospital death. Thus, cases were defined as patients who died in-hospital, whereas controls were patients who survived until discharge. Both cases and controls identified amid the entire study period were ascertained through review of patient records. Exposures were defined as presenting with an MPI > 25 points at admission, as well as increasing SAPSII and MSI scores, and the interaction between blood gases and serum laboratory parameters.

Source of data

Data were collected by a Critical Care medicine specialist and a postgraduate year four (PGY-4) General Surgery resident physician. Baseline characteristics (age, sex, and body mass index [BMI]), comorbidities (diabetes mellitus, hypertension [HTN], chronic kidney disease, chronic heart disease), laboratory parameters (arterial pH, arterial partial pressure of oxygen [PaO_2], venous partial pressure of oxygen [PvO_2], arterial partial pressure of carbon dioxide [$PaCO_2$], venous partial pressure of carbon dioxide [$PvCO_2$], arterial oxygen saturation [SaO_2], central venous oxygen saturation [$ScvO_2$], lactate, bicarbonate [HCO_3], base excess [BE], venous-to-arterial carbon dioxide difference [$DvaCO_2$], arterial oxygen content [CaO_2], venous oxygen content [CvO_2], serum anion gap [AG], corrected serum anion gap [cAG], apparent strong ion difference [SIDa], effective strong ion difference [SIDe], strong ion gap [SIG], hemoglobin [Hb], chloride [$Cl-$], sodium [$Na+$], albumin [Alb], alactic base excess [alactic BE], creatinine [Cr], urea [Ur], brain natriuretic peptide [BNP], procalcitonin [PCT]), norepinephrine dose (mcg/kg/min), and PaO_2/FiO_2 (arterial partial pressure of oxygen/fraction of inspired oxygen ratio) were collected at ICU admission. MSI, MPI (Supplementary Table 1), and Simplified Acute Physiology Score II (SAPSII) (Supplementary Table 2) were calculated for all patients. Cutoff value for MPI was deemed at < 25 for statistical purposes[10]. Formulae for calculation of clinical and laboratory parameters (such as BMI, AG, SIDa, SIDe, SIG, alactic BE, PaO_2/FiO_2 ratio, $PvCO_2$, CaO_2, CvO_2 and MSI) are shown in supplementary Table 3. Age and sex were considered as confounding variables.

Statistical analysis

Sample size was calculated according to mortality risk estimates in patients with abdominal sepsis according to the MPI score since a relative risk of 3.62 has been reported for this scoring system[26]. We considered a mortality rate of 29.1% in the population of interest[27], obtaining a final sample size of 41 individuals, allowing for a possible loss of 20%, with an alpha of 0.05 and a statistical power of 80%.

Quantitative continuous variables were presented as median and interquartile range or as mean and standard deviation (SD) where applicable, whereas dichotomous variables were presented as absolute frequency and percentage (%). For comparison between survivors and non-survivors, the Mann–Whitney U test or Student's t-test was applied for quantitative continuous variables, while Chi-square (χ^2) or Fisher's exact test was applied for qualitative (categorical) variables.

A correlation analysis was also applied between laboratory variables by developing a correlation matrix with corresponding Spearman's rank correlation coefficients. Subsequently, an anti-image correlation matrix was applied to determine Kaiser–Meyer–Olkin measure of sampling adequacy (KMO).

A principal component analysis (PCA) was performed to reduce the laboratory dataset dimension and to increase interpretability. In addition, extraction communalities were estimated to acknowledge the proportion of explanation of the variance of each variable in the factor analysis; variables were considered important when they showed communality values > 0.9. Thereafter, principal components (PCs) were analyzed to obtain those that best explained total variance – defined as PC with eigenvalues > 1 and that altogether explained above 70% of the total variance. Similarly, a component score coefficient analysis was performed, defining high correlation components as those with absolute values > 0.5.

To determine the association of SAPSII, MSI, MPI, and PC with mortality, several logistic regression models were developed, considering each score and each PC as independent variables. MPI was introduced in the regression model as a binary variable (< 25 and > 25 points), while SAPSII and MSI were introduced as quantitative variables. Univariate analyses were performed followed by multivariate logistic regression models which were adjusted for age and sex to avoid model overfitting; variables were introduced by the Enter method. Collinearity assumptions were verified to assess that there was no collinearity of variables to create the multivariate models. Results are presented as regression coefficients (β) or Odds Ratios (OR) and 95% confidence intervals (95% CI). Model assumptions were verified by influential values of Cook's distance values (top 3 largest values) and standardized residuals. Goodness of fit of the multivariate logistic regression models was evaluated through Hosmer and Lemeshow test. Model performance was evaluated using the area under the curve (AUC) and Akaike information criterion (AIC). Statistical significance was defined as $p < 0.05$. All analyses and figures were performed using R studio V.1.0.153 and SPSS V.25.

Results

Out of 127 potentially eligible patients identified during the entire study period, 60 patients who met inclusion criteria were included for analyses (Fig. 1). Patient characteristics are shown in Table 1. Thirty-seven patients (61.7%) were female and mean age was 57.7 (SD: 16.7) years. Most patients were located in the > 60 years category (n = 29, 48.3%). HTN was the most frequent comorbidity (n = 27, 45%). Forty-four (73.3%) patients had a pH < 7.35 and 46 (76.7%) had a serum Cr > 1.2 mg/dl. Fifty (83.3%) patients had
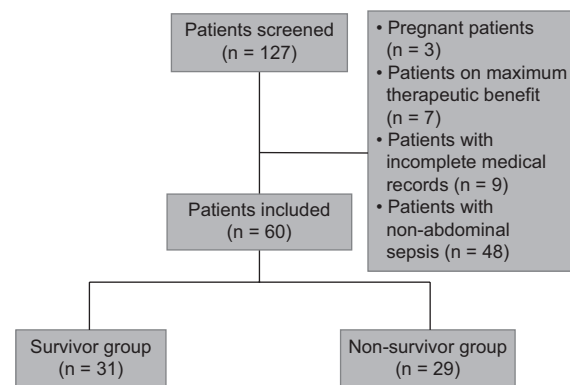

Figure 1. *Patient inclusion flowchart and reasons for exclusion.*

a MSI > 1.3 and 36 (60%) had an MPI score < 25 at admission. The most frequent SAPSII category was 64–77 points (n = 44, 73.3%). The mortality rate in the sample was 48.3% (n = 29). The non-survivor group had a higher frequency of HTN, higher lactate levels, and higher MPI scored, but lower BE and alactic BE levels. Comparison of characteristics of survivors against non-survivors is shown in table 1.

Correlation coefficients among laboratory variables are shown in Figure 2. Highly positive correlation occurred between SIDa and SIG (p = 0.96), AG and cAG (p = 0.97), CaO_2 and Hb (p = 0.98), BE and alactic BE (p = 0.96), and $PaCO_2$ and $PvCO_2$ (p = 0.91), whereas perfect negative correlation was solely noted between SIDe and albumin (–1). The anti-image correlation matrix shows KMO values > 0.5 in all variables, which implies that all of the latter are suitable for PCA (Supplementary Table 4).

PCA retrieved 8 PC with the following eigenvalues: PC1 = 5.4, PC2 = 3.6, PC3 = 2.9, PC4 = 2.8, PC5 = 2.3, PC6 = 2.1, PC7 = 1.9, PC8 = 1.2 (Supplementary Table 5), and explaining: 20%, 13%, 11%, 10%, 9%, 8%, 7%, and 5% of the total variance, respectively. Altogether, the 8 PC explain 83% of the total variance, with a cumulative proportion of 93%. Table S6 shows laboratory variables that display high loading for PC: PC1: pH (–0.59), AG (0.9), cAG (0.92), alactic BE (–0.76), HCO_3 (–0.77), and BE (–0.78); PC2: PaO_2 (–0.46), lactate (–0.45), CaO_2 (0.51), SIDa (0.60), SIG (0.67), Hb (0.58), and Cl– (–0.58); PC3: PvO_2 (0.40), $PaCO_2$ (0.69), CvO_2 (0.68), and PCT (0.51); PC4: SIDe (–0.59), Na+ (0.56), Alb (0.59), Cr (–0.59), and Ur (–0.51); PC5: $ScvO_2$ (0.69) and $DvaCO_2$ (–0.47); PC6: $PvCO_2$ (0.63); and PC7: SaO_2 (0.45) and BNP (0.48). Table S6 also shows that variables PaO_2, PvO_2, PCT, Cr, $ScvO_2$, Ur, $PvCO_2$, SaO_2, and BNP contributed the

Table 1. Baseline characteristics of the study sample and comparison between survivors and non-survivors

Name of Variable	Total sample (n = 60)	Survivors (n = 31)	Non-survivors (n = 29)	p-value
Age, years*	57.7 (16.7)	55.6 (17.3)	60 (16)	0.31
Age categories**				
< 20	3 (5)	2 (6.5)	1 (3.4)	1.0
21–39	3 (5)	2 (6.5)	1 (3.4)	1.0
40–59	25 (41.7)	14 (45.2)	11 (37.9)	0.57
> 60	29 (48.3)	13 (41.9)	16 (55.2)	0.30
Female**	37 (61.7)	17 (54.8)	20 (69)	0.26
Male**	23 (38.3)	14 (45.2)	9 (31)	
Weight (kilograms)*	77.3 (19.7)	81.4 (19.5)	72.5 (19.2)	0.06
Height (meters)*	1.63 (0.9)	1.63 (0.09)	1.63 (0.09)	0.87
Body mass index, kg/m^2**				
< 29.9 (normal)	37 (61.7)	15 (48.4)	22 (75.9)	0.02
30–34.9 (obesity class I)	13 (21.7)	9 (29)	4 (13.8)	0.15
35–39.9 (obesity class II)	5 (8.3)	4 (12.9)	1 (3.4)	0.35
> 40 (obesity class III)	5 (8.3)	3 (9.7)	2 (6.9)	1.0
Comorbidities				
Diabetes mellitus**	21 (35)	8 (25.8)	13 (44.8)	0.12
Hypertension**	27 (45)	10 (32.3)	17 (58.6)	0.04
Chronic kidney disease**	6 (10)	2 (6.5)	4 (13.8)	0.41
Chronic heart disease**	6 (10)	1 (3.2)	5 (17.2)	0.09
Laboratory parameters at admission				
pH *	7.29 (0.08)	7.31 (0.07)	7.27 (0.08)	0.07
< 7.35**	44 (73.3)	20 (64.5)	24 (82.8)	0.11
Arterial partial pressure of oxygen (PaO$_2$), mmHg*	120.7 (54.4)	110.9 (56.4)	131.2 (51)	0.14
Venous partial pressure of oxygen (PvO$_2$), mmHg*	39.7 (9.4)	38.5 (8.1)	40.9 (10.7)	0.35
Arterial partial pressure of carbon dioxide (PaCO$_2$), mmHg*	33.9 (7.2)	35 (5.1)	32.7 (9)	0.24
< 60 mmHg**	4 (6.6)	4 (12.9)	0 (0)	0.11
Venous partial pressure of carbon dioxide (PvCO$_2$), mmHg*	39.6 (7.3)	40.8 (5.3)	38.2 (8.9)	0.19
Arterial oxygen saturation (SaO$_2$), %*	96.8 (3)	96.2 (3.4)	97.4 (2.5)	0.13
Central venous oxygen saturation (ScvO$_2$), %*	66.3 (12.7)	65.8 (11.3)	66.8 (14.3)	0.77
Lactate, mmol/L*	4.1 (2)	3.6 (1.5)	4.7 (2.3)	0.03
Bicarbonate (HCO$_3$), mmol/L*	16.3 (3.5)	17.1 (3.4)	15.4 (3.6)	0.07
Base excess (BE), mmol/L*	−9.5 (5.2)	−8.1 (5.5)	−11.1 (4.3)	0.02
Venous-to-arterial carbon dioxide difference (DvaCO$_2$), mmHg*	5.6 (3.1)	5.8 (2.2)	5.5 (3.9)	0.73
Arterial oxygen content (CaO$_2$), O$_2$ ml per 100 ml of blood*	12.3 (2.4)	12.2 (2.3)	12.3 (2.5)	0.95
Venous oxygen content (CvO$_2$), O$_2$ ml per 100 ml of blood*	8.2 (2.1)	8.1 (1.5)	8.3 (2.6)	0.68
Serum anion gap, mmol/L*	14.8 (6.4)	13.8 (4.4)	15.9 (7.9)	0.21
Corrected serum anion gap, mmol/L*	19.8 (6.6)	18.8 (4.4)	21 (8.3)	0.19
Apparent strong ion difference (SIDa), mmol/L*	−3.8 (5.1)	−4 (3)	−3.5 (6.8)	0.74
Effective strong ion difference (SIDe), mmol/L*	4.2 (1.5)	4.2 (1.4)	4.3 (1.6)	0.68
Strong ion gap (SIG), mmol/L*	−8 (5.4)	−8.2 (3.7)	−7.9 (6.8)	0.84
Hemoglobin (Hb), mg/dl*	9.2 (1.9)	9.2 (1.9)	9.1 (1.9)	0.78
< 7.0**	8 (13.3)	4 (12.9)	4 (13.8)	1.0
Chloride (Cl$^-$), mmol/L*	109.5 (6)	110.1 (5.2)	108.8 (6.7)	0.41
Sodium (Na$^+$), mmol/L*	140.7 (5.7)	141.1 (5.5)	140.2 (6)	0.57
Albumin (Alb), gr/dl*	24.8 (6.1)	25.1 (5.8)	25.5 (6.4)	0.68
Alactic BE, mmol/L*	−13.7 (6.3)	−11.7 (6.4)	−15.8 (5.6)	0.01
Creatinine (Cr), mg/dl*	2.8 (2.5)	2.7 (2.2)	3 (2.8)	0.58
> 1.2**	46 (76.7)	23 (74.2)	23 (79.3)	0.63
Urea (Ur), mg/dl*	97.3 (55.2)	86.7 (50.7)	108.5 (58.4)	0.12
Brain natriuretic peptide (BNP), ng/ml*	679.7 (836.6)	527 (614.4)	842.9 (1008.4)	0.15
Procalcitonin (PCT), ng/ml*	26.3 (23.9)	26.5 (26.7)	26 (21)	0.93
Scores at admission				
Modified shock index (MSI)**				
> 1.3	50 (83.3)	26 (83.9)	24 (82.8)	0.90

(Contd...)

Table 1. Baseline characteristics of the study sample and comparison between survivors and non-survivors *(Continued)*

Name of Variable	Total sample (n = 60)	Survivors (n = 31)	Non-survivors (n = 29)	p-value
Mannheim peritonitis index (MPI)**				0.001
≤ 25	36 (60)	26 (83.9)	10 (34.5)	
> 25	24 (40)	5 (16.1)	19 (65.5)	0.19
Simplified acute physiology score II (SAPSII)**				0.73
41–52	6 (10)	5 (16.1)	1 (3.4)	0.11
53–64	10 (16.7)	6 (19.4)	4 (13.8)	
64–77	44 (73.3)	20 (64.5)	24 (82.8)	
Other characteristics				
Arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2)**				
Mild	36 (60)	15 (48.4)	21 (72.4)	0.05
Moderate	22 (36.7)	15 (48.4)	7 (24.1)	0.05
Severe	2 (3.3)	1 (3.2)	1 (3.4)	0.96
Norepinephrine, mcg/kg/min**	0.39 (0.25)	0.43 (0.25)	0.34 (0.24)	0.16
ICU length of stay, days*	5.8 (4.2)	6.7 (3.7)	4.9 (4.6)	0.10
Duration of mechanical ventilation, days*	4.9 (4)	4.9 (3.4)	4.9 (4.6)	0.99

*Mean, (standard deviation);
**Frequency, (percentage).
FiO_2: fraction of inspired oxygen; ICU: intensive care unit; kg: kilogram; m²: square meter; mmHg: millimeters of mercury; O_2: oxygen; PaO_2: arterial partial pressure of oxygen.

Table 2. Univariate logistic regression analysis

Model	β	OR	95% CI	p-value
MPI	2.290	9.87	3.07-36.61	0.0002
SAPSII	0.071	1.07	1.01-1.14	0.01
MSI	−0.164	0.84	0.23-3.07	0.80
PC1	0.759	2.13	1.12-4.76	0.04
PC2	−0.232	0.79	0.46-1.32	0.38
PC3	0.191	1.21	0.73-2.05	0.46
PC4	−0.061	0.94	0.56-1.57	0.81
PC5	0.067	1.06	0.64-1.80	0.79
PC6	−0.347	0.70	0.40-1.19	0.20
PC7	0.051	1.05	0.63-1.77	0.84
PC8	0.52888	1.69	1.00-3.07	0.06

OR: odds ratio, 95% CI: 95% confidence interval; MPI: Mannheim peritonitis index; SAPSII: simplified acute physiology score II; MSI; modified shock index; PC: principal component.

least in terms of variation to factor analysis since they showed extraction values of 0.78, 0.85, 0.80, 0.84, 0.88, 0.55, 0.85, 0.82, and 0.77, respectively.

On logistic regression univariate analyses, MPI (OR = 9.87, 95% CI: 3.07-36.61, p = 0.0002), SAPSII (OR = 1.07, 95% CI: 1.01-1.14, p = 0.01), and PC1 (OR = 2.13, 95% CI: 1.12-4.76, p = 0.04) were significantly associated with patient in-hospital mortality (Table 2), whereas only MPI (OR = 10.1, 95% CI: 3.03-40.06, p = 0.0003) and SAPSII (OR = 1.07, 95% CI 1.01-1.14, p = 0.02) were significantly associated with mortality after adjusting for age and sex (Table 3). Both models MPI (Hosmer and Lemeshow = 0.40, AUC = 0.79, AIC = 73.37) and SAPSII (Hosmer and Lemeshow = 0.70, AUC = 0.70, AIC = 82.9) showed higher performance in comparison to PC1 (Hosmer and Lemeshow = 0.33, AUC = 0.66, AIC = 84.82). Model assumptions for MPI and SAPSII are shown in figures 3 and 4, respectively.

Discussion

We hypothesized that the scoring systems and laboratory parameters have different associations with in-hospital mortality in patients with abdominal sepsis. In logistic regression models, MPI, SAPSII, and PC1 were significantly associated with in-hospital mortality. Nevertheless, after adjusting for age and sex, only MPI, and SAPSII remained significantly associated with in-hospital mortality. In addition, we found that non-survivors showed a higher frequency of HTN, higher lactate levels, and higher MPI scores but lower BE and alactic BE levels.

To the best of our knowledge, this is the first study to simultaneously evaluate various scoring systems and biomarkers in abdominal sepsis patients. Our findings could suggest that initial and follow-up
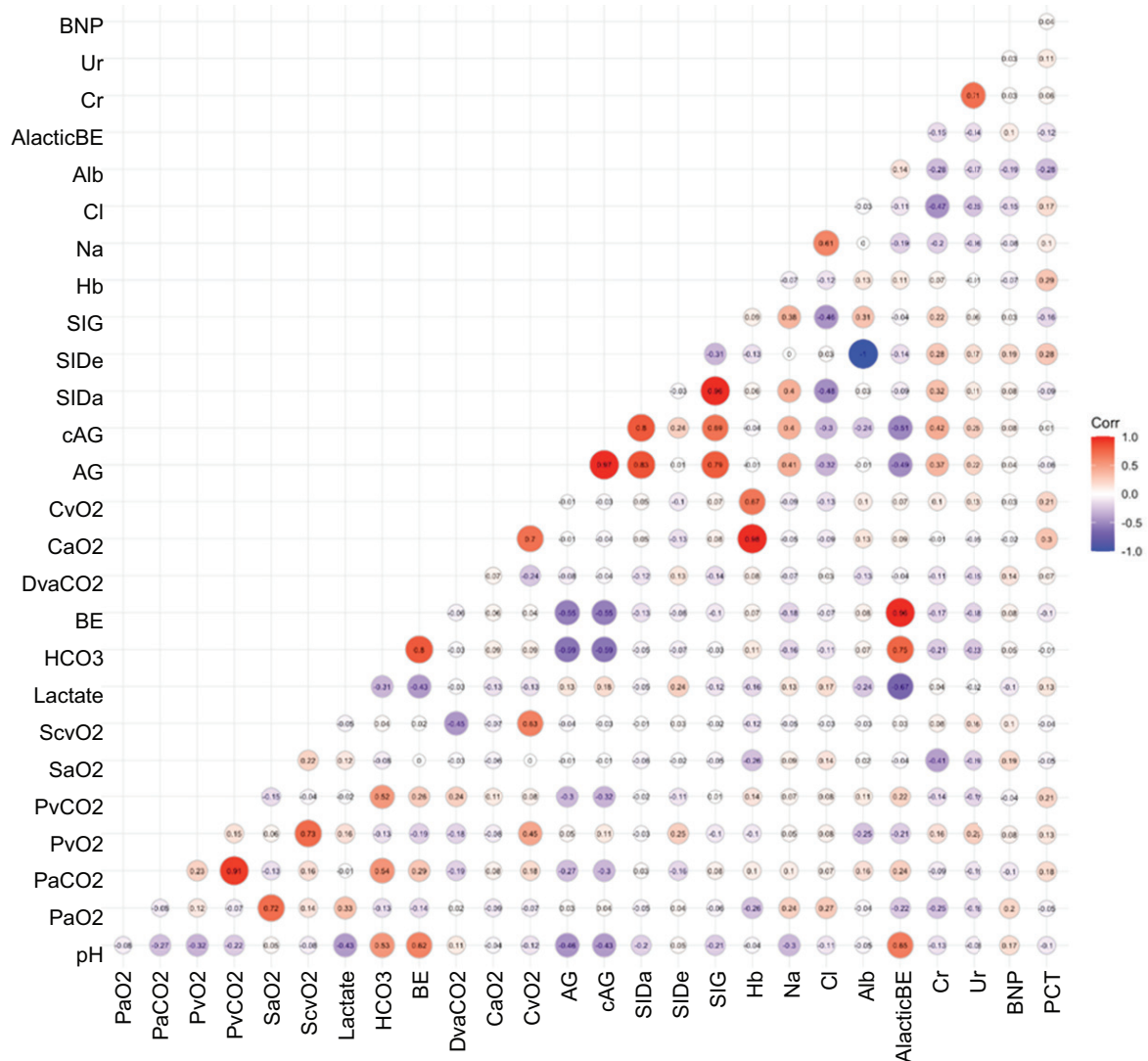
Figure 2. *Heat map. Red color indicates a positive correlation between variables, while blue color indicates a negative correlation.*

assessments of patients be based on the markers that were indeed associated with mortality. In that manner, the choice of a handful of relevant parameters could pave the way for a personalized medical approach in patients with abdominal sepsis. Nonetheless, it is also important to note that our findings are merely observational; hence, they should be viewed as hypotheses generators for future clinical studies, in which relevant markers are assessed as potential therapeutic targets.

Although PC1 – a linear combination of variables pH, AG, cAG, alactic BE, HCO_3^-, and BE – was not statistically significantly associated with the outcome after adjusting for confounders, acid-base disturbances still play an important role in abdominal sepsis-associated mortality and their prognostic value should not be underestimated. Acidemia (pH < 7.35) remains a potentially fatal condition, mainly due to its effect on the cardiovascular system. The classification of acidemia on various subtypes such as metabolic (BE < –2 mEq/L and $PaCO_2$ ≤ 42 mmHg), respiratory (BE ≥ –2 mEq/L and $PaCO_2$ > 42 mmHg), and mixed (BE < –2 mEq/L and $PaCO_2$ > 42 mmHg) acidemia is of paramount importance when determining appropriate treatment and prognosis. In fact, mortality in metabolic acidemia is as high as 11% when BE is < 6.7 mEq/L; in respiratory acidemia, it is of 6% when $PaCO_2$ is > 51 mmHg, and in mixed acidemia, it is of 13% when pH is < 7.23[28]. A persistent state of metabolic acidosis harbors negative consequences on patient outcomes and it may also indicate progression of underlying
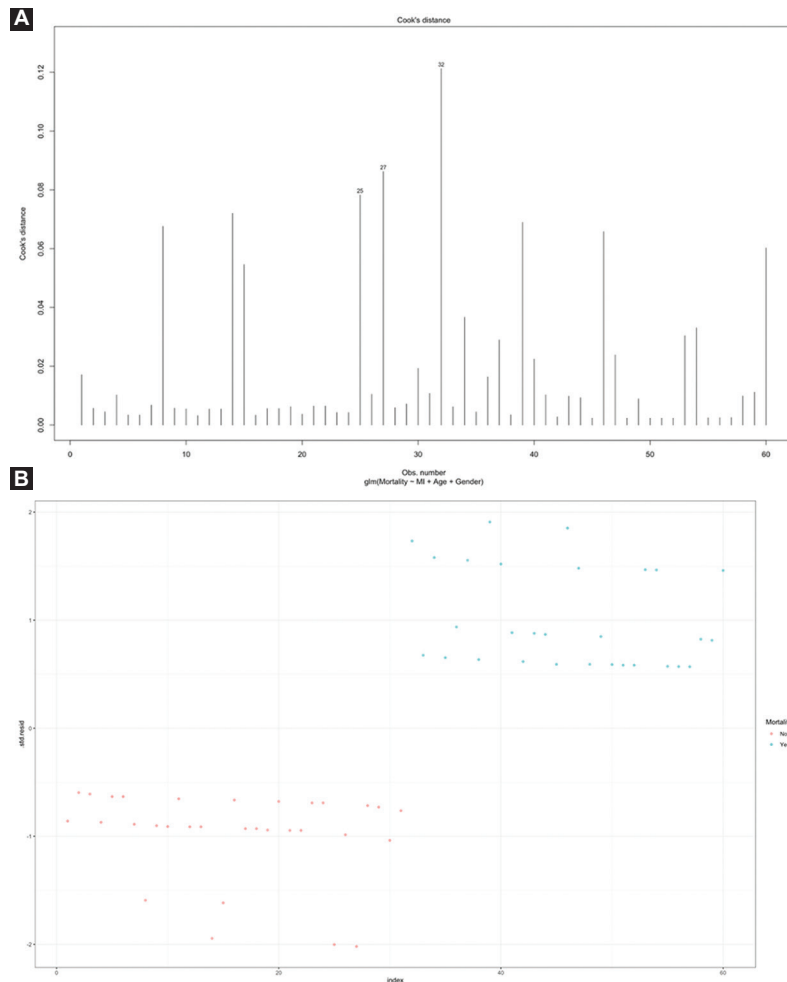
Figure 3. *Model assumptions for logistic regression analysis of MPI:* **(A)** *influential values by Cook's distance values for the top 3 largest values and* **(B)** *standardized residuals values.*

Table 3. Multivariate logistic regression analysis

Model	Variable	β	OR	95% CI	p-value
MPI[a]	MPI	2.318	10.1	3.03-40.06	0.0003
	Sex	−0.78	0.45	0.12-1.04	0.22
	Age	0.007	1	0.94-1.04	0.67
SAPSII[b]	SAPSII	0.069	1.07	1.01-1.14	0.02
	Sex	−0.687	0.5	0.16-1.51	0.22
	Age	0.0104	1.01	0.98-1.04	0.54
PC1[c]	PC1	0.661	1.93	1.01-4.44	0.08
	Sex	−0.319	0.72	0.23-2.25	0.57
	Age	0.011	1.01	0.98-1.04	0.48

All models were adjusted by sex and age.
[a]Hosmer and Lemeshow = 0.40, AUC = 0.79, AIC = 73.37;
[b]Hosmer and Lemeshow = 0.70, AUC = 0.70, AIC = 82.9,
[c]Hosmer and Lemeshow = 0.33, AUC = 0.66, AIC = 84.82.
AIC: Akaike information criterion; AUC: area under the curve; MPI: mannheim peritonitis index; SAPSII: simplified acute physiology score II: MSI; modified shock index;
PC: principal component.

causes. A standard base deficit clearance < 11% (within the first 24 h of ICU admission) increases the risk of mortality in patients with septic shock (< 11% = 65.1% mortality and > 11% = 36% mortality)[29]. A negative value of alactic BE indicates worsening of the renal function and, therefore, an impairment on the clearance of unmeasured anions and lactate. Thus, the more negative the alactic BE is, the greater the renal impairment and, most likely, the worse the prognosis[30]. Increased AG occurs mainly due to accumulation of unmeasured anions. Its highest utility is achieved when used on the differential diagnosis of metabolic acidosis, although it bears prognostic value as well. A recent study found that the greater the AG, the greater the mortality risk: AG $\geq$ 13 mEq/L (OR 1.02, 95% CI 0.75-1.40, p = 0.891), AG $\geq$ 15 mEq/L (OR 1.40, 95% CI 1.03-1.91, p = 0.031), and AG $\geq$ 17 mEq/L (OR 2.78, 95% CI 2.12-3.63, p < 0.001)[31].
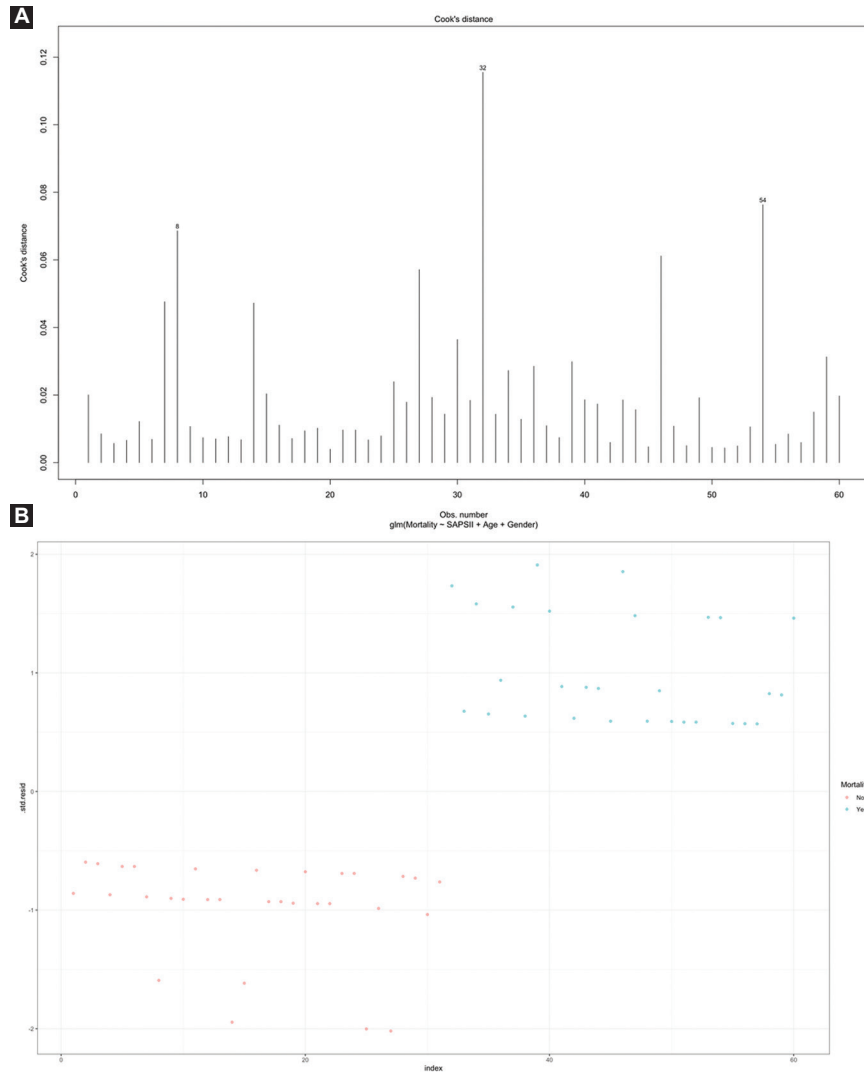
Figure 4. *Model assumptions for logistic regression analysis of SAPSII:* **(A)** *influential values by Cook's distance values for the top 3 largest values and* **(B)** *standardized residuals values.*

Even though PCT helps predict the occurrence of intra-abdominal infections after definitive surgery for intestinal fistulae[32], infected necrotizing pancreatitis[33], and it is also an early biomarker of intra-abdominal infections in post-operative patients with gastrointestinal malignancies[34], this biomarker might not be as useful when used as a predictor of mortality in patients with abdominal sepsis, based on our findings.

We would like to draw attention to the fact that out of all the laboratory parameters included in PC1, HCO_3 is also coincidentally an item in one of the scores associated with mortality (SAPSII). Although the statistical significance of PC1 was lost during multivariate analysis, this finding suggests that there might be room for including new laboratory parameters into the existing scoring systems that could further improve mortality risk estimates[35,36].

In accordance with their AIC values, we conclude that MPI and SAPSII scoring systems are both equally associated with mortality. Differences observed in OR values are due to the taxonomy of the variables themselves, but the strength of association with mortality is not any different among them (Table 3). In our study, we considered MPI cutoff values as reported on the original paper[37], proving significant association with in-hospital mortality, which is consistent with the literature[38]. Nonetheless, other studies have used cutoff values of > 21, while displaying sensitivity of 97.5% and AUC of 0.976.[39] In addition, SAPSII showed optimal performance, in similar fashion to that reported by Sánchez-Casado et al.[40]

Besides association with mortality, SAPSII has also been associated with overall length of hospital stay[41].

Finally, we want to emphasize that our findings are consistent with the literature regarding the relationship between HTN and adverse outcomes in sepsis patients since non-survivors showed a higher frequency of HTN. A recent study by Garg et al. showed that male gender, HTN, SOFA > 9, and increased creatinine were predictors for mortality in adult patients with diagnosis of sepsis requiring ICU care[42]. Moreover, it appears that HTN, along with other chronic medical conditions, might increase the risk of incident sepsis episodes[43].

Limitations of our study include its retrospective nature, as well as potential sampling bias due to convenience sampling, and having used a selective study cohort, which limits generalizability of results. Since this study was developed in a low-resource hospital in Mexico, we were unable to assess important predictors which were unavailable (i.e., C-reactive protein, interleukin-6), whereas other variables were not presented since they are already included in the scores (i.e., leukocytes and bilirubin). In addition, we did not evaluate specific causes of abdominal sepsis. Another limitation is that even when the sample size was calculated to encounter differences in the main outcome according to MPI scores, it is possible that the study was underpowered to detect differences according to PCA groups. Furthermore, PCA is a technique for reducing the dimensionality of large datasets which can be challenging to interpret; for instance, it is difficult to acknowledge the most important characteristics of the dataset after calculating PC. Although reduction of dimensionality is useful, it does not come without a cost, given that the loss of information is a necessary part of this type of analysis. Balancing dimensionality reduction and loss of information are mandatory when applying PCA.

Conclusion

MPI and SAPSII are both equally associated with in-hospital mortality in abdominal sepsis patients admitted to the ICU. Acid-base disturbances play an important role in abdominal sepsis-related mortality, although they were not significantly associated with in-hospital mortality in our study when adjusting for age and sex. Larger studies are needed to confidently evaluate the association of pH, AG, cAG, alactic BE, HCO_3, and BE with mortality in these patients to better understand pathophysiology of abdominal sepsis.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Supplementary data

Supplementary data are available at 10.24875/CIRU.22000219. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

References

1. Boldingh QJ, de Vries FE, Boermeester MA. Abdominal sepsis. Curr Opin Crit Care. 2017;23:159-66.
2. Weledji EP, Ngowe MN. The challenge of intra-abdominal sepsis. Int J Surg. 2013;11:290-5.
3. Schein M, Wittmann DH, Wise L, Condon RE. Abdominal contamination, infection and sepsis: a continuum. Br J Surg. 1997;84:269-72.
4. Volakli E, Spies C, Michalopoulos A, Groeneveld AJ, Sakr Y, Vincent JL. Infections of respiratory or abdominal origin in ICU patients: what are the differences? Crit Care. 2010;14:R32.
5. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med. 2002;28:108-21.
6. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017;12:29.
7. De Waele J, Lipman J, Sakr Y, Marshall JC, Vanhems P, Barrera Groba C, et al. Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. BMC Infect Dis. 2014;14:420.
8. Kerrigan SW, Martin-Loeches I. Public awareness of sepsis is still poor: we need to do more. Intensive Care Med. 2018;44:1771-3.
9. Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y, et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014;18:R87.
10. Sharma R, Ranjan V, Jain S, Joshi T, Tyagi A, Chaphekar R. A prospective study evaluating utility of Mannheim peritonitis index in predicting prognosis of perforation peritonitis. J Nat Sci Biol Med. 2015;6:49.
11. Salamone G. Mannheim peritonitis index (MPI) and elderly population: prognostic evaluation in acute secondary peritonitis. G Chir. 2016;27:243.
12. Muralidhar VA. Efficacy of mannheim peritonitis index (MPI) score in patients with secondary peritonitis. J Clin Diagn Res. 2014;8:NC01-3.

13. Xiao Z, Wilson C, Robertson HL, Roberts DJ, Ball CG, Jenne CN, et al. Inflammatory mediators in intra-abdominal sepsis or injury-a scoping review. Crit Care. 2015;19:373.

14. Tan WJ, Ng WQ, Sultana R, de Souza NN, Chew MH, Foo FJ, et al. Systematic review and meta-analysis of the use of serum procalcitonin levels to predict intra-abdominal infections after colorectal surgery. Int J Colorectal Dis. 2018;33:171-80.

15. Saucedo-Moreno EM, Fernández-Rivera E, Ricárdez-García JA. Hipoalbuminemia como predictor de mortalidad en sepsis de origen abdominal. Cir Cir. 2020;88:481-4.

16. Tai H, Zhu Z, Mei H, Sun W, Zhang W. Albumin-to-fibrinogen ratio independently predicts 28-day mortality in patients with peritonitis-induced sepsis. Mediators Inflamm. 2020;2020:7280708.

17. Arbutina DD, Milic L, Cuk VV, Juloski JT, Radulovic R, Starcevic A, et al. Significance of biomarkers in early diagnosis of abdominal sepsis. Chirurgia (Bucur). 2022;117:30.

18. Mukherjee S, Das S, Mukherjee S, Ghosh PS, Bhattacharya S. Arterial blood gas as a prognostic indicator in patients with sepsis. Indian J Med Microbiol. 2020;38:457-60.

19. Eckmann C, Sanchez-Garcia M. Monitoring treatment response in abdominal sepsis with procalcitonin-if only! Crit Care. 2013;17:1017.

20. Jung B, Molinari N, Nasri M, Hajjej Z, Chanques G, Jean-Pierre H, et al. Procalcitonin biomarker kinetics fails to predict treatment response in perioperative abdominal infection with septic shock. Crit Care. 2013;17:R255.

21. Li Y, Chen L, Xing C, Ding C, Zhang H, Wang S, et al. Changes in serum lactate level predict postoperative intra-abdominal infection after pancreatic resection. World J Surg. 2021;45:1877-86.

22. Mahmoodpoor A, Shadvar K, Saghaleini SH, Koleini E, Hamishehkar H, Ostadi Z, et al. Which one is a better predictor of ICU mortality in septic patients? Comparison between serial serum lactate concentrations and its removal rate. J Crit Care. 2018;44:51-6.

23. Hecker A, Reichert M, Reuß CJ, Schmoch T, Riedel JG, Schneck E, et al. Intra-abdominal sepsis: new definitions and current clinical standards. Langenbeck's Arch Surg. 2019;404:257-71.

24. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304-77.

25. Secretaría de Salud. Diagnóstico y Tratamiento de Sepsis Grave y Choque Séptico en el Adulto. México; 2009. Available from: http://www.cenetec.salud.gob.mx/interior/gpc.html

26. Shakya VC, Pangeni A, Karki S, Sharma LR. Evaluation of Mannheim's peritonitis index in prediction of mortality in patients with non-traumatic hollow viscus perforation peritonitis. J Nepal Health Res Counc. 2021;19:179-84.

27. Blot S, Antonelli M, Arvaniti K, Blot K, Creagh-Brown B, de Lange D, et al. Epidemiology of intra-abdominal infection and sepsis in critically ill patients: "AbSeS", a multinational observational cohort study and ESICM Trials Group Project. Intensive Care Med. 2019;45:1703-17.

28. Mochizuki K, Fujii T, Paul E, Anstey M, Uchino S, Pilcher DV, et al. Acidemia subtypes in critically ill patients: an international cohort study. J Crit Care. 2021;64:10-7.

29. Sánchez Díaz JS, García Gómez G, Peniche Moguel KG, Monares Zepeda E, Martínez Rodríguez EA, Calyeca Sánchez MV. Aclaramiento del déficit de base estándar como pronóstico de mortalidad en choque séptico. Med Crítica. 2019;33:298-304.

30. Gattinoni L, Vasques F, Camporota L, Meessen J, Romitti F, Pasticci I, et al. Understanding lactatemia in human sepsis. Potential impact for early management. Am J Respir Crit Care Med. 2019;200:582-9.

31. Sun T, Cai C, Shen H, Yang J, Guo Q, Zhang J, et al. Anion gap was associated with inhospital mortality and adverse clinical outcomes of coronary care unit patients. Biomed Res Int. 2020;2020:1-11.

32. Ren H, Ren J, Hu Q, Wang G, Gu G, Li G, et al. Prediction of procalcitonin for postoperative intraabdominal infections after definitive operation of intestinal fistulae. J Surg Res. 2016;206:280-5.

33. Rau B, Steinbach G, Gansauge F, Mayer JM, Grünert A, Beger HG. The potential role of procalcitonin and interleukin 8 in the prediction of infected necrosis in acute pancreatitis. Gut. 1997;41:832-40.

34. Domínguez-Comesaña E, López-Gómez V, Estevez-Fernández SM, Mariño Padín E, Ballinas-Miranda J, Carrera-Dacosta E, et al. Procalcitonina y proteína C reactiva como marcadores precoces de infección intraabdominal postoperatoria en pacientes operados de cáncer gastrointestinal. Cir Esp. 2014;92:240-6.

35. Steele L, Hill S. Using sepsis scores in emergency department and ward patients. Br J Hosp Med. 2019;80:C120-3.

36. Kammar-García A, Castillo-Martínez L, Mancilla-Galindo J, Villanueva-Juárez JL, Pérez-Pérez A, Rocha-González HI, et al. SOFA score plus impedance ratio predict mortality in critically ill patients admitted to the emergency department: retrospective observational study. Healthcare (Basel). 2022;10:810.

37. Wacha H. Mannheim peritonitis index-prediction of risk of death from peritonitis : construction of a statistical and and validation of an empirically based index. Theor Surg. 1987;1:169-77.

38. Malik AA, Wani KA, Dar LA, Wani MA, Wani RA, Parray FQ. Mannheim Peritonitis index and APACHE II--prediction of outcome in patients with peritonitis. Ulus Travma Acil Cerrahi Derg. 2010;16:27-32.

39. Sedano C, Lizano L, Balbin J, Condor I, Atencio J, Villalba C. Eficacia del Índice de Mannheim en pacientes con peritonitis secundaria de un hospital de Huancayo, Perú. Rev Medica Hered. 2019;30:12.

40. Sánchez-Casado M, Hostigüela-Martín VA, Raigal-Caño A, Labajo L, Gómez-Tello V, Alonso-Gómez G, et al. Escalas pronósticas en la disfunción multiorgánica: estudio de cohortes. Med Intensiva. 2016;40:145-53.

41. Das K, Ozdogan M, Karateke F, Uzun AS, Sozen S, Ozdas S. Comparison of APACHE II, P-POSSUM and SAPS II scoring systems in patients underwent planned laparotomies due to secondary peritonitis. Ann Ital Chir. 2014;85:16-21.

42. Garg R, Tellapragada C, Shaw T, Eshwara VK, Shanbhag V, Rao S, et al. Epidemiology of sepsis and risk factors for mortality in intensive care unit: a hospital based prospective study in South India. Infect Dis (Auckl). 2022;54:325-34.

43. Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S, Howard G. Chronic medical conditions and risk of sepsis. PLoS One. 2012;7:e48307.