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ORIGINAL ARTICLE

Pediatric Index Mortality 3 (PIM3) Score as a predictor of mortality in pediatric critical care unit located at high altitude

Escala "Pediatric Index Mortality 3" (PIM3) como predictor de mortalidad en unidades de cuidado intensivo pediátrico ubicadas a gran altitud

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What do we know about the subject matter of this study?

The Pediatric Index of Mortality 3 (PIM3) is a widely used scale to predict mortality in pediatric intensive care units (PICUs) which is useful in the evaluation of the impact of interventions and quality of care. Its original model was validated in populations at sea level.

What does this study contribute to what is already known?

In patients admitted to PICUs located at an altitude above 2500 m.a.s.l., the PIM3 scale has low calibration and adequate discrimination as a predictor of mortality. The addition of serum lactate and the oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratio improve its predictive capacity.

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Abstract

The Pediatric Index of Mortality 3 (PIM3) is a scale that estimates the risk of mortality in children admitted to the Pediatric Intensive Care Unit (PICU) within the first hour of admission. **Objective**: to validate the PIM3 scale in pediatric population admitted to PICU at altitudes over 2,500 meters above sea level (m.a.s.l.), and to evaluate whether lactate and the oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) index improve its ability to predict mortality. **Patients and Method**: A prospective multicenter study was carried out in 10 PICUs in Colombia between November 2016 and June 2017. Variables were collected for the calculation of PIM3, serum lactate, and SpO2/FiO2 index. Their discrimination capacity was validated with the area under the ROC curve and calibration using the Hosmer Lemeshow goodness-of-fit test. **Results**: 2,803 admissions were included, with an overall mortality of 4.8% and a standardized mortality ratio of 1.1 (95%CI 1.00-1.3). PIM3 showed low calibration ($p < 0.001$) and adequate discrimination for the studied population (ROC 0.84; 95%CI 0.83-0.86). The addition of serum lactate and SpO2/FiO2 allowed a good calibration ($p = 0.75$) and maintained a high discrimination of mortality (ROC 0.86; 95%CI 0.84-0.87). **Conclusions:** The performance of the PIM3 scale has adequate discrimination, but low calibration in children admitted to PICU at above 2500 m. a. s. l. Lactate and SpO2/FiO2 variables improved its predictive ability.

Keywords:
Altitude;
Critical Illness;
Oxygen Saturation;
Lactic Acid;
Child Mortality;
Intensive Care Units;
Pediatrics

Introduction

Mortality prediction scales in pediatric intensive care units (PICUs) are tools to anticipate severity and evaluate the impact of interventions, where the Pediatric Index of Mortality 3 (PIM3) is one of the most widely used in pediatrics[1,2].

The development of populations at altitudes higher than 2,500 meters above sea level (m.a.s.l.) imposes unique physiological responses given by the decrease in barometric pressure that causes a drop in the inspired oxygen pressure and consequently in the alveolar pressure. Above 1,500 m.a.s.l., this value becomes unsustainable leading to an increase in ventilation and consequently to a predictable decrease in carbon dioxide pressure[3]. These changes can be attenuated under acclimatisation, but require prolonged exposure, are varied, and are genetically determined, so they can lead to pulmonary hypertension and polyglobulia[3-5]. Higher mortality among people living at high altitudes is caused by this, along with the sociocultural, economic, and nutritional conditions of contexts with limited resources, like the Latin American Andes[4,5], and is explained by a lower physiological reserve in respiratory diseases and pulmonary hypertension[3,6-8], leading to a different interpretation in the oxygenation indexes[3,5].

The PIM3 scale assumes standardized values at sea level due to the lack of data, so it's crucial to suggest a correction for altitude or the use of alternative indices, such as the oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratio, which is suitable for evaluating oxygenation disorders both separately and when integrated to mortality scales[9], avoiding arterial blood gases[10-11]. Similarly, it is thought important to include other markers[9,12,13], such as serum lactate, which may be less affected by altitude. Thus, the PIM3 scale performed better when lactate was included, according to a recent study[14].

The PIM3 scale has been validated in populations that were not included in the original study, with varying degrees of calibration and discrimination depending on factors such as demographic, geography, and healthcare features[15-21]. There are no multicenter studies that evaluate the performance of the PIM3 in populations located at high altitudes. The objective of this study is to determine the performance of the PIM3 scale in a pediatric population admitted to PICUs located at high altitudes and to evaluate whether serum lactate and the SpO2/FiO2 ratio improve the mortality prediction of the current model.

Patients and Method

Study design

We designed a prospective cohort study. Ten PICUs located in two cities in Colombia (Bogota, DC. and San Juan de Pasto in Nariño), located above 2,500 m.a.s.l were included. Two of them are dedicated primarily to the care of postoperative cardiovascular patients and the others are general PICUs. The study was approved by Research Ethics Committee of each institution, and the use of informed consent was not required due to the nature of the study.

Patient selection

Data for consecutive admissions to participating PICUs from November 1, 2016, to June 30, 2017 were collecter. All patients aged between 1 month and 16 years were included and discharges due to referral to

another PICU and those still hospitalized at the end of the study were excluded. Each center was responsible for data collection, validation, and submission.

Data collection

The data were recorded through an online electronic form on Google Forms® platform. The variables necessary for the calculation of PIM3 of the original study[1] were collected during the first hour of patient admission to the PICU and PICU mortality and other demographic variables were recorded to characterize the population. The measurement of serum lactate on admission and SpO2/FiO2 ratio was also included. For the FiO2 value, the value reported by devices such as mechanical ventilators, high-flow nasal cannulas, and Venturi masks was recorded, and for patients admitted with conventional flow nasal cannulas, it was roughly estimated using the formula for calculating the FiO2 provided[22]. For the PaO2/FiO2 variable, due to the altitude above sea level of the centers in this study, a reference value of 0.32 (not the usual 0.23 at sea level) was assumed for unavailable data because the usual PaO2 at this altitude has a mean of 60 mmHg.

Statistical analysis

The data were registered in spreadsheets from each center in the Google Sheets® platform, without providing the individual PIM3 value until the final analysis, to reduce information bias. The consolidated database was reviewed and processed with Microsoft Excel® 2016 software and the statistical data were analyzed in Stata® version 13.

General characteristics data were presented using the best measure of central tendency and according to the variable and its distribution, reporting medians and interquartile ranges (IQR) in most cases. The relationship of mortality observed with the main demographic variables, the PIM3 model variables, serum lactate, and the SpO2/FiO2 ratio was also measured. For quantitative variables Mann-Whitney test for difference of medians was used, while for nominal qualitative variables, a Chi-square test with Pearson's test or Fisher's exact test was used according to outcomes by group. $p < 0.05$ was considered significant.

Observed mortality was recorded and expected mortality was calculated by PIM3 score according to the original study[1], presenting the standardized mortality rate (SMR) with its 95% confidence intervals (95% CI). The calibration of the PIM3 score was defined as the degree of accuracy of the risk predictions made by the model, through the Hosmer-Lemeshow test by quartiles, centers, age ranges, and diagnostic groups. Adequate calibration was considered if the $p > 0.05$.

To measure discrimination, defined as the capacity to differentiate between patients who survived and those who died, a nonparametric ROC curve test was used with its global confidence intervals and using the same groups described above, with the highest value obtained corresponding to the best discrimination capacity. It was considered adequate if its value was greater than 0.7[2]. Finally, a logistic regression model was run to define which of the variables contributed significantly to the prediction of mortality, adding the 2 new variables.

Results

A total of 2,803 admissions were recorded for the 10 participating centers. 57% were male and 43% female with a mean age of 31 months (IQR 8-104). Respiratory disease was the main cause of admission (43%), with a PICU stay of 3 days (IQR 2-7), and a hospital stay of 11 days (IQR 6-22). There was a significant difference in mortality according to admission diagnoses, but not by age or sex (table 1).

Observed mortality was 4.85% (n =136), with a PIM3-predicted mortality of 4.4% (n =122, 95% CI 109-135), for an SMR of 1.1 (95% CI 1.0-1.3). By risk group, 25% of patients with a very high-risk diagnosis (33/131), 7% of high-risk patients (40/534), and 1% of low-risk patients (13/1023) died. In the individual variables, significant differences in mortality were observed in cases of cardiovascular postoperative admission with extracorporeal circulation, non-cardiac postoperative admission, use of mechanical ventilation, presence of fixed pupils to light, base excess, blood pressure, and oxygenation (table 2).

Regarding the performance of the PIM3 score, a low calibration ($p < 0.001$) and a high discrimination by the area under the curve of 0.84 (ROC 0.84; 95%CI 0.83-0.86) were obtained. In different subgroups, no significant differences were found in SMR or discrimination, but it was observed that calibration was lower in the lower quartiles of the score (lower risk), in cases without arterial blood gases, and diagnosis of cardiovascular, onco-hematological, and gastrointestinal/renal admissions (table 3).

Non-cardiovascular post-operative admission, presence of fixed pupils, base excess, PaO2/FIO2 ratio, and diagnostic categories maintained statistical significance in the multiple logistic regression model (table 4).

Serum lactate was recorded in 1,037 cases (37%) with a significant difference between survivors and death (1.4 [0.9-2.3] vs. 2.8 [1.4-7.9] mmol/L, $p < .001$). For SpO2/FiO2, a reliable FiO2 was obtained in 1,867 cases (67%) and, in 869 cases, it was calculated indi-

rectly, and overall it was found that there was a significant difference between survivors and death (245 [163-363] vs. 213 [100-376] mmol/L, p < 0.001). When these variables were included in the predictive model, individually significant changes were found for serum lactate (OR 1.134; 95%CI 1.051-1.223) and SpO2/FiO2 (OR 0.997; 95%CI 0.996-0.999). Performance was measured, obtaining adequate calibration (Hosmer-Lemeshow test, 4 groups; p = 0.75) and high discrimination with AUC-ROC of 0.86 (95%CI 0.84 -0.87) (table 5).

Discussion

This multicenter study, evaluated the performance of the PIM3 scale in high-altitude conditions, above 2,500 m.a.s.l., evidencing a low calibration and high discrimination capacity of the test. The low calibration is evident in lower-risk patients, in the absence of arterial blood gases, and in diagnosis of non-respiratory admission. Finally, alteration of serum lactate and SpO2/FiO2 were associated with higher mortality and their inclusion in the predictive model improved calibration and discrimination.

For the PIM3 score, eight validation studies in Asia, Europe, South America, and Africa[15,21,23] have been published. The majority were completed at a single center, with the most significant ones coming from Italy[16], Argentina[20], and South Africa[21]. The first one demonstrated adequate calibration and discrimination of PIM3, which is related to the similar living conditions with the original study population. In contrast, the calibration and discrimination in the remaining ones were comparable to ours because of the similarity in population characteristics with our patients. Our low calibration is expected due to a number of factors that were not taken into account when calculating the score. These factors may be influenced by living at a high altitude with limited access to and opportunities for ICU admission, pathologies that are more severe in their later stages, and a higher prevalence of illnesses that are not listed under the risk categories, such as malnutrition or chronic diseases[4,5,24], which worsen the functional reserve when faced with acute imbalances[25]. The decreasing monitoring of arterial blood gases in the first hour in patients with respiratory disorders, which is required to input the prediction model, is another important and increasingly common aspect in PICU. However, we think that in the future, risk classification using non-invasive indicators should be encouraged.

With this consideration we sought to evaluate the effect of incorporating serum lactate and SpO2/FiO2 measurements into the PIM3 model on calibration and discrimination. This analysis was recently proposed by Morris et al. retrospectively in critical

Table 1. Demographic characteristics of children with severe disease at high altitude and comparison to clinical outcomes

	Total	Survivors	Death	p*
	2803	2667	136	
Sex				
Female. n (%)	1193 (43%)	1131 (42%)	62 (46%)	0.464
Male. n (%)	1610 (57%)	1536 (58%)	74 (54%)	
Age range (months). n (%)				
1– 12	969 (35%)	909 (34%)	60 (44%)	0.075
13 – 24	310 (11%)	299 (17%)	11 (8%)	
25 – 72	668 (24%)	643 (24%)	25 (18%)	
73 – 156	614 (22%)	589 (22%)	25 (18%)	
157 – 192	241 (9%)	2.268 (8%)	15 (11%)	
Diagnostic groups. n (%)				
Respiratory	1206 (43%)	1185 (44%)	21 (15%)	0.000
Cardiovascular (including postoperative)	273 (10%%)	242 (9%)	31 (23%)	
Neurologic	229 (8%)	208 (8%)	21 (15%)	
Hematologic/oncologic	167 (6%)	152 (6%)	15 (11%)	
Gastrointestinal/ Renal	137 (5%)	127 (5%)	10 (7%)	
Postoperative noncardiac	460 (16%)	455 (17%)	5 (4%)	
Other	331 (12%)	298 (11%)	33 (24%)	

*Pearson´s Chi square test

Table 2. Characteristics of Paediatric index of Mortality 3 (PIM3) from all admission and comparison to clinical outcomes

PIM3	Total 2803	Survivors 2667	Deaths 136	p*
Elective admission. n (%)	431 (15%)	407 (15%)	24 (18%)	0.452
Admission from a bypass cardiac procedure. n (%)	123 (4%)	109 (4%)	14 (10%)	0.001
Admission from a non-bypass cardiac procedure. n (%)	61 (2%)	55 (2%)	6 (4%)	0.067
Admission from a noncardiac procedure. n (%)	340 (12%)	339 (13%)	1 (1%)	< 0.001
Mechanical ventilation. n (%)	855 (31%)	777 (29%)	78 (57%)	< 0.001
Pupils fixed to light. n (%)	58 (2%)	19 (1%)	39 (29%)	< 0.001
Base excess. Median (IQR)	0 (0-4)	0 (0-3)	5 (0-12)	< 0.001
SBP (mmHg). Median (IQR)	102 (92-113)	102 (93-113)	92 (64-110)	< 0.001
(SBP*SPB)/1000 (mmHg). Median (IQR)**	10.4 (8.5-12.8)	10.4 (8.6-12.8)	8.4 (4.0-12.1)	< 0.001
100*FiO2/PaO2. Mediana (IQR)	0.32 (0.32-0.33)	0.32 (0.32-0.32)	0.33 (0.32-1.0)	< 0.001
Low-risk diagnosis. n (%)	1.023 (37%)	1.010 (38%)	13 (10%)	< 0.001
High-risk diagnosis. n (%)	534 (19%)	494 (19%)	40 (29%)	0.002
Very high-risk diagnosis. n (%)	131 (5%)	98 (4%)	33 (24%)	< 0.001

IQR: inerquiartile range; SBP (Systolic blood pressure). *Pearson´s Chi square test or Fisher´s exact test for nominal data. Wilcoxon signed-rank test for continuous variables.

Table 3. PIM 3 Calibration. discrimination. and Standardized Mortality Ratio (SMR) by age. diagnostic group and risk group

Standardized Mortality Ratio									Calibration		Discrimination		
Variable	N	Observed(O)		Expected(E)		SMR	CI 95%		$\Sigma(O-E)^2/E$*	p*	AUC	CI95%	
Total	2.803	136	4.9%	122	4.4%	1.1	1.0	1.3	30.9**	0.000	0.84	0.83	0.86
Quartiles of mortality risk													
First quartile (0-0.2%)	702	7	1.0%	1	0.2%	6.3	0.0	21.2	30.9	0.000	0.61	0.42	0.79
Second quartile (0.2-1.3%)	701	9	1.3%	4	0.6%	2.0	0.0	5.7	4.5		0.56	0.35	0.76
Third quartile (1.3%-3.7%)	700	18	2.6%	14	2.0%	1.3	0.1	2.5	1.3		0.57	0.44	0.70
Fourth quartile (3.7-99.9%)	700	102	14.6%	103	14.6%	1.0	0.8	1.2	0.0		0.81	0.76	0.86
Arterial blood gases													
Available	1.038	82	7.9%	87	8.4%	0.9	0.7	1.1	0.3	0.001	0.77	0.70	0.84
Not-available	1.765	54	3.1%	34	2.0%	1.4	1.1	2.1	11.1		0.89	0.84	0.93
Age range (months)													
1-12	969	60	6.2%	45.6	4.7%	1.4	0.9	1.7	4.5	0.056	0.85	0.79	0.91
13-24	310	11	3.5%	13.9	4.5%	0.8	0.8	2.0	0.6		0.84	0.68	0.99
25-72	668	25	3.7%	25.0	3.7%	1.1	0.3	1.8	0.0		0.89	0.83	0.95
73-156	614	25	4.1%	27.2	4.4%	0.9	0.3	1.5	0.2		0.81	0.70	0.91
157-192	241	15	6.2%	10.2	4.2%	1.5	0.0	3.1	2.3		0.77	0.61	0.93
Diagnostic group													
Respiratory	1.206	21	1.7%	25.8	2.1%	0.81	0.17	1.46	0.9	0.016	0.70	0.58	0.82
Cardiovascular	273	31	11.4%	20.7	7.6%	1.50	0.69	2.31	5.2		0.85	0.78	0.92
Neurologic	229	21	9.2%	21.3	9.3%	0.99	0.20	1.77	0.0		0.84	0.72	0.96
Hematologic/oncologic	167	15	9.0%	10.3	6.2%	1.45	0.00	3.07	2.1		0.77	0.62	0.91
Gastrointestinal/Renal	137	10	7.3%	7.3	5.3%	1.38	0.00	3.67	1.0		0.77	0.62	0.93
Postoperative	460	5	1.1%	10.5	2.3%	0.48	0.00	2.07	2.9		0.75	0.41	1.00
Other	331	33	10.0%	26.1	7.9%	1.27	0.63	1.91	1.8		0.88	0.82	0.94

SMR: Standardized Mortality Ratio; CI.: Confidence interval; AUC: Area under curve; *Hosmer-Lemeshow test **Global calibration used deciles.

Table 4. Multiple logistic regression model for PIM3

PIM3 Variables	Original PIM3 β*	Model of the sample* β*. 95%CI			p
Elective admission.	-0.5378	0.3343	-0.5538	1.2223	0.461
Admission from a bypass cardiac procedure	-1.2246	-0.4990	-1.5827	0.5847	0.367
Admission from a non-bypass cardiac procedure	-0.8762	-0.6431	-1.8947	0.6086	0.314
Admission from a noncardiac procedure	-1.5164	-2.9543	-5.0116	-0.8971	0.005
Mechanical ventilation	0.9763	0.1793	-0.3290	0.6877	0.489
Pupils fixed to light	3.8233	2.8513	2.1220	3.5806	0.000
Absolute Base excess	0.0671	0.0591	0.0194	0.0988	0.004
SBP (mmHg)	-0.0431	-0.0136	-0.0459	0.0188	0.411
(SBP * SBP)/1000 (mmHg)	0.1716	0.0021	-0.1874	0.1915	0.983
100*FiO2/PaO2	0.4214	0.5837	0.1801	0.9872	0.005
Low-risk diagnosis	-2.1766	-1.1295	-1.7932	-0.4657	0.001
High-risk diagnosis	1.0725	0.6650	0.1637	1.1663	0.009
Very high-risk diagnosis	1.6225	1.6795	1.0630	2.2961	0.000
Constant	-1.7928	-2.4895	-4.0113	-0.9677	

SBP: Systolic blood pressure. *Logistic coefficient

Table 5. Logistic regression model of the newly derived model by adding Lactate and SpO_2/FIO_2

Model Variables****	β*	OR**	IC 95%**		p***
Pupils fixed to light (yes/no)	0.369	18.057	8.756	37.239	0.000
SBP (mmHg)	-0.015	0.985	0.976	0.994	0.001
FiO_2/PaO_2	0.482	1.619	1.093	2.399	0.016
Postoperative admission					
Bypass cardiac procedure	-2.837	0.059	0.008	0.429	0.005
Non- bypass cardiac procedure	-0.140	0.869	0.304	2.488	0.794
Noncardiac procedure	-0.168	0.845	0.402	1.777	0.657
Diagnostic group					
Very high risk (yes/no)	1.581	4.861	2.601	9.084	0.000
High risk (yes/no)	0.535	1.707	1.033	2.822	0.037
Low risk (yes/no)	-1.259	0.284	0.146	0.554	0.000
Lactate	0.126	1.134	1.051	1.223	0.001
SpO_2/FiO_2	-0.003	0.997	0.996	0.999	0.004
Constant	-1.378				

SBP: Systolic blood pressure ; SpO2: Pulse oximeter oxygen saturation; *Logistic regression coefficient;**OR: odds ratio. CI: Confidence Interval ****Newly Derived Model using PIM3 and Adjusted according to the best logistic regression model This model maintain good calibration (p = 0.18) and a high discrimination. AUC 0.86 (CI. 95% 0.84 - 0.87).

care units in the United Kingdom, New Zealand, and Australia and its adjustment to the PIM2 and PIM3 scales[14]. In our study, we were able to demonstrate that incorporating lactate and SpO2/FiO2 into the model improved the prediction of mortality with good calibration and high discrimination, so we propose incorporating these elements as predictors of mortality.

The good performance of the SpO2/FiO2 ratio may be explained by the same altitude of the admission unit, given that many patients required additional oxygen supports and infrequently saturation points high enough to invalidate the SpO2/FiO2 ratio were observed, as occurs more frequently in measurements at sea level[25,26], with the advantage of incorporating an index widely available in real-time in most patients, unlike PaO2/FiO2.

The strength of this study is that it is the first prospective, multicenter validation at high altitudes. Our main limitations were the exclusion of newborns, unlike the original model, and the fact that it is a high-altitude population, therefore, it cannot be extrapolated to populations at other altitudes.

Conclusion

The mortality reported in our high-altitude PICUs is higher than expected for the PIM3 scale, which showed low calibration and good mortality discrimination. The addition of serum lactate and SpO2/FiO2 ratio improves the predictive model of mortality and should be considered in future versions of the scale if validated in other populations.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights 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 correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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