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UTILIDAD DE LA GLICEMIA A LA ADMISIÓN EN LA UNIDAD DE CUIDADOS INTENSIVOS PEDIÁTRICA COMO PREDICTOR DE MORTALIDAD DE LOS PACIENTES HOSPITALIZADOS EN EL INSTITUTO NACIONAL DE SALUD DEL NIÑO, 2012-2013

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DEDICATORIA

A nuestras familias, quienes nos han acompañado física y espiritualmente durante este largo camino, y con cuyo ejemplo hemos aprendido y valorado todo sacrificio realizado en pos de un futuro mejor.

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A nuestros maestros, por guiarnos con paciencia durante la realización de este trabajo. A todo aquel que entiende el aporte de una investigación a la comunidad científica, transmite estos conocimientos y motiva a los demás a continuar dicha obra.

TABLA DE CONTENIDO

1.0 ARTÍCULO CIENTÍFICO

FULL TITLE:

Glycemia on admission and mortality in a Pediatric Intensive Care Unit

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ABSTRACT

Introduction. There is a high prevalence of mortality in the Pediatric Intensive Care Units (PICU) in developing countries. Association has been found between disglycemia and mortality in the PICU; however, there is a lack of standardization of the utility of such ranges. **Objectives**. To analyze the association between glycemia levels in PICU admission and mortality in patients hospitalized at Instituto Nacional de Salud del Niño (INSN). **Methods.** Retrospective cohort in PICU patients admitted to INSN between 2012 and 2013. A Poisson regression model with robust variance was used to quantify the association. Diagnostic Test performance evaluation was used to describe sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios for each range of glycemia. **Results.** 552 patients were included (Age range 5 to 79,8 months). The mean glycemia on admission was 121.3 mg/dL. Ninety two (16.6%) patients died during hospitalization. In multivariable analyses, significant associations between glycemia <65 mg/dL (RR: 2.01, 95%CI 1.14-3.53), glycemia >200 mg/dL (RR: 2.91, 95%CI 1.71-4.55), malnutrition (RR: 1.53, 95%CI 1.04-2.25), mechanical ventilation (RR: 3.71, 95%CI 1.17-11.76) and mortality at discharge were found. There was low sensitivity (between 17.39% and 39.13%) and high specificity (between 49.13% and 91.74%) for different glucose cut-off levels. **Conclusions**. There is an increased risk of death at discharge in patients who developed hypoglycemia and hyperglycemia on admission to the PICU. Certain glucose ranges (>200mg/dL and <65mg/dL) have a high specificity as predictors of death at discharge.

INTRODUCTION

Mortality in Pediatric Intensive Care Units (PICU) is high and developing countries are the most affected. Campos-Miño (1) analyzed this situation and found that the average Latin American PICU mortality was 13.29%, in contrast to 5% in European countries. In Peru, León (2) in 1996 and Tantaleán (3) in 2004 studied the mortality in Instituto Nacional de Salud del Niño (INSN) PICU and found percentages of 26% and 21%, respectively, which also showed marked differences compared with other countries.

The association between disglycemia and mortality has already been analyzed (4) (15). The association between hyperglycemia and mortality has been the most studied (16) (17). Umpierrez found that hyperglycemia (defined as serum glucose > 126 mg/dL) is a common finding in hospitalized patients and should be considered an important marker of poor clinical response and increased mortality, especially in patients admitted to critical care units (16) (17).

On the other hand, hypoglycemia is, for some authors, the most common alteration in the serum glucose concentration (7) and the most frequent metabolic disorder in childhood (18). The NICE-SUGAR study, done in critically ill patients, found an association between moderate and severe hypoglycemia (serum glucose levels of 41-70 mg/dL and <40 mg/dL, respectively) and increased risk of death, especially in patients with severe hypoglycemia and in those who sustained hypoglycemia for more than one day (6).

The assessment of the severity, clinical instability and prognosis are the main challenges to be faced in the pediatric intensive care unit, requiring effective and continuous assessment in critically ill patients (33). Currently, there are several scoring systems that

predict mortality in PICUs such as PRISM, PIM and its updates, and others, being PRISM the most commonly used. Although they have shown a good discriminative power (21), there are some drawbacks regarding their application (21) (23). The PRISM score is impractical due to the great amount of information required. The PIM score requires a complex mathematical formula to calculate the probability of death (24). The PRISM III score is not systematically used in developing countries because of its high cost and complexity (25). In Peru, two studies using the PRISM score found controversial results about its utility (3); one of them found significant differences between observed and expected mortality calculated through the PRISM (3).

It would therefore be useful to have alternative clinical predictors of mortality in the PICUs. Serum glucose is a simple measure, quick and easy to obtain, so it meets the criteria for being evaluated as a predictor in a dynamic environment such as PICU (26). The objective of this study was to determine the PICU admission glycemia levels that are associated with in-hospital mortality.

METHODS

Study Design

This study is a retrospective cohort performed at the PICU of the Peruvian INSN between 2012 and 2013. This referral center is a specialized institute of high complexity; its PICU has 23 beds (16 beds for acute and 7 for chronic patients) and recorded 409 hospital discharges in 2012 (34 monthly discharges) (27). The average length of stay (LOS) was 12 days. The Crude Mortality Rate recorded in 2012 in the service was 18.3% and the Net Mortality Rate, which only considers the subsequent deaths within 48 hours of admission, was 17.8% (27).

The study population consists of children between 29 days and 18 years of age admitted during the mentioned period, which were categorized by age groups (1-6 months, 7-12 months, 1-5 years, 6-15 years old, and > 15 years). Neither patients without serum glucose measurement amongst the first 24 hours of admission to PICU, nor those who stayed less than that time were considered. Patients without complete information of cause of death or anthropometric data and patients with diagnosis of diabetes mellitus or insulinoma were excluded.

A census of this population was done, which was composed of 552 patients. The main outcome was death at discharge of the PICU. The exposure variable was the glucose category, defined as the first serum glucose level measured at admission to the PICU obtained by venipuncture, expressed in mg / dL, taken from the medical registries, and categorized a priori into the following groups (3,4): Group 1 (<65 mg/dL), Group 2 (66-100 mg/dL), Group 3 (101-199 mg/dL), Group 4 (> 200 mg/dL).

Data collection

The study was approved by the Ethics Committee of the Universidad Peruana de Ciencias Aplicadas and the Oficina Ejecutiva de Apoyo a la Investigación y Docencia Especializadas (OEAIDE) from the INSN.

Medical records were used as a source of information. Data were collected by health workers of the PICU after capacitation. Death of patients was confirmed by clinical history and death certificate. The data were entered into a database in Microsoft Excel 2010 and quality control was performed by double digitization of data.

Statistical analyses

Data analysis was performed using the statistical package STATA 13.0. A p of <0.05 was considered significant.

For univariate analyses, the categorical variables were expressed as frequency (percentages). Continuous variables were described as mean and standard deviation or median and interquartile range.

For bivariate analyses, normality and homogeneity of variances were evaluated using the Shapiro-Wilk test and Levene test respectively. The comparison of categorical variables was performed using the Chi square test for parametrical variables and Fisher's exact for the non-parametrical ones.

For bivariate and multivariate analyses, Poisson regression models with robust variance were performed. Variables with a $p<0.05$ in bivariate analyses were considered for multivariable analyses. Associations were reported as relative risks (RR) and their 95% confidence intervals (CI). Glycemia between 66-100mg/dl (group 2) was considered as reference group for glucose categories and group etiology respiratory, for diagnosis on admission.

Additionally, the statistical methodology of diagnostic test evaluation was used to indicate the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios for each range of glycemia. A 95% CI was also provided.

RESULTS

769 patients were hospitalized in the PICU during the study period. 217 patients were excluded (neonates (n = 28), patients who stayed less than 24 hours in the PICU (n = 5), patients lacking anthropometric data (n = 95) and patients lacking glucose data (n = 89), resulting in 552 patients included in the analysis (Figure 1).

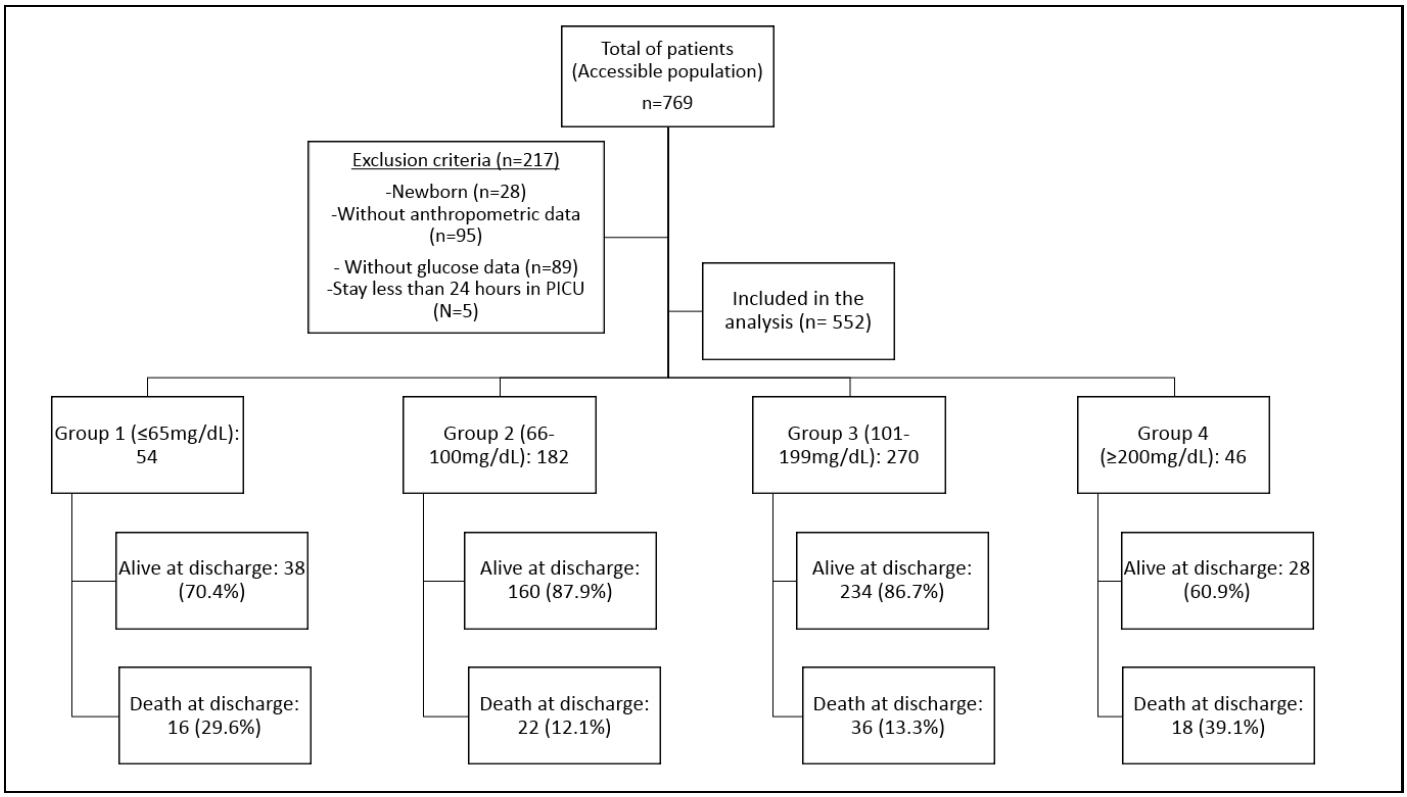

Figure 1. Flow chart of patients included in the analysis

The median age was 23 months (IQR = 5-79.75) and 52.3% were male. The mean blood glucose level on admission was 121.30 mg/dL. 48.9% presented glucose levels in Group 3 (101-199 mg/dL), followed by 33.0%, which presented in Group 2 (66-100mg/dL). 92 (16.7%) patients died. The most frequent diagnoses on admission were non-cardiovascular surgery (38.5%) and respiratory disease (23.2%). 83.5% of patients

required mechanical ventilation, 14.1% parenteral nutrition and 17.2% presented infection in the PICU (Table 1).

Patients characteristic	Total
Age, months (median, IQR)	23 (5.0 -79.8)
Gender (n,%)	
Male	289 (52.3)
Glucose (mean, SD)	121.30 (70.6)
Glucose group (n,%)	
< 65	54 (9.78)
66-100	182 (33.0)
101-199	270 (48.9)
>200	46 (8.3)
Diagnoses on admission (n,%)	
Respiratory	128 (23.2)
Infectious	97 (17.6)
Neurological	37 (6.7)
No cardiovascular surgery	213 (38.6)
Others	77(14.0)
Mechanical ventilation (n,%)	462 (83.5)
Obese (n,%)	4 (0.7)
Malnutrition (n,%)	114 (20.6)
Eutrophic (n,%)	434 (78.6)
Infection in PICU (n,%)	95 (17.2)
Parenteral nutrition (n,%)	78 (14.1)
Death at discharge (n,%)	92 (16.6)

Table 1. Demographic and clinical characteristics of the study population (n = 552)

There was a significant association between Glucose groups ($p < 0.001$), diagnoses on admission ($p < 0.001$), nutritional status ($p < 0.001$), infection in PICU ($p = 0.006$) and mechanical ventilation ($p < 0.001$), and death during hospitalization (Table 2).

Characteristic	Total	Dead	Alive	p
	n (%)	n (%)	n (%)	
Glucose				<0.001
<65 mg/dL	54 (9.8)	16 (29.6)	38 (70.4)	
66- 100mg/dL	182 (33.0)	22 (12.1)	160 (87.9)	
101-199 mg/dL	270 (48.9)	36 (13.3)	234 (86.7)	
>200 mg/dL	46 (8.3)	18 (39.1)	28 (80.9)	
Age*				0.330
1-6 months	163 (29.5)	35 (21.5)	128 (78.5)	
7-12 months	66 (12.0)	12 (18.1)	54 (81.8)	
1-5 years	160 (29.0)	21 (13.1)	139 (86.9)	
6-15 years	141 (25.5)	21 (14.9)	120 (85.1)	
15-18 years	22 (4.0)	3 (13.6)	19 (83.6)	
Gender				0.790
Male gender	289 (52.4)	47 (16.3)	242 (83.7)	
Female gender	263 (47.6)	45 (17.1)	218 (82.9)	
Diagnoses on admission				<0.001
Respiratory	128 (23.1)	26 (20.3)	102 (79.7)	
Infectious	97 (17.6)	29 (29.9)	68 (70.1)	
No cardiovascular surgery	213 (38.6)	11 (5.1)	202 (94.8)	
Neurological	37 (6.7)	5 (13.5)	32 (86.4)	
Others	77 (14.0)	21 (27.2)	56 (72.7)	
Nutritional status*				0.009
Obesity	4 (0.7)	0 (0)	4 (100.0)	
Malnutrition	114 (20.6)	33 (29.0)	81 (71.0)	
Eutrophic	434 (78.6)	59 (16.6)	375 (83.4)	
Mechanical ventilation*				<0.001
Yes	462 (83.5)	89 (19.3)	373 (80.7)	
No	90 (16.5)	3 (3.3)	87 (96.7)	
Parenteral nutrition				0.101
Yes	78 (14.1)	18 (23.1)	60 (76.9)	
No	474 (85.9)	74 (15.6)	400 (84.4)	
Infection in PICU				0.006
Yes	95 (17.2)	25 (26.3)	70 (73.7)	
No	457 (82.8)	67 (14.7)	390 (85.3)	

* Fisher's exact test

Table 2. Association between patient characteristics and death during hospitalization

However, multivariate analyses showed that the following variables remained associated with mortality during hospitalisation: glucose <65 mg/dL (RR: 2.01, 95%CI 1.14- 3.53),

glucose >200 mg/dL (RR: 2.91, 95%CI 1.71-4.55), malnutrition (RR: 1.53, 95%CI 1.04-2.25) and mechanical ventilation (RR: 3.71, 95%CI 1.17-11.76) (Table 3).

Variable	Crude analyses			Adjusted analyses		
	RR	95% CI	p	RR	95% CI	p
Group 1 <65 mg / dL	2.45	(1.38-4.32)	0.002	2.01	(1.14-3.53)	0.015
Group 2 66-100 mg/ dL	1.00	(Reference)		1.00	(Reference)	
Group 3 101-199 mg /dL	1.10	(0.67-1.81)	0.699	1.41	(0.86-2.30)	0.172
Group 4> 200 mg / dL	3.23	(1.89-5.51)	<0.001	2.91	(1.71-4.55)	<0.001
Respiratory diagnosis	1.00	(Reference)		1.00	(Reference)	
Infectious diagnosis	1.47	(0.92-2.32)	0.099	1.51	(0.95-2.38)	0.076
Non cardiovascular surgery diagnosis	0.25	(0.13-0.49)	<0.001	0.31	(0.15-0.63)	0.001
Neurological diagnosis	0.66	(0.27-1.61)	0.367	0.85	(0.37-1.99)	0.724
Others	1.34	(0.81-2.21)	0.249	1.22	(0.71-2.08)	0.466
Malnutrition	2.14	(1.47-3.12)	<0.001	1.53	(1.04-2.25)	0.030
Mechanical Ventilation	5.77	(1.86-17.85)	0.002	3.71	(1.17-11.76)	0.025
Infection in the PICU	1.79	(1.19-2.68)	0.004	1.21	(0.79-1.86)	0.369

Table 3. Bivariate and Multivariate analyses for death during hospitalization

In the diagnostic test analysis (Table 4), low sensitivity values were found for all ranges of glucose for prediction of mortality. However, a high specificity (91.7%) was found for glucose values of <65 mg/dL and for values >200 mg/dL (93.9%). Neither the positive nor the negative likelihood ratios could be considered of significant clinical value.

Glycaemia (mg/dL)	Sensibility (%)	Specificity (%)	Positive predictive value	Negative predictive value	Positive Likelihood ratio	Negative Likelihood ratio
≤ 65	17.4	91.7	29.6	84.7	2.1	0.9
66-100	23.9	65.2	12.1	81.1	0.7	1.2
101-199	39.1	49.1	13.3	80.1	0.8	1.2
>200	19.6	93.9	39.1	85.4	3.2	0.9

Table 4. Performance of the ranges of glucose as predictors of mortality at discharge

DISCUSSION

Patients with hypoglycemia or hyperglycemia at the admission to the PICU showed an increased risk of death at discharge. The group with the highest risk of death was the one with glucose levels >200mg/dL followed by those with glucose levels <65 mg/dL.

With respect to children with hyperglycemia, these findings are consistent with those of Park et al. (28), who showed that patients with hyperglycemia >300mg/dL had a higher death rate at discharge, compared to patients who had glycemia between 100 and 199mg/dL. The results are also similar to those made by Klein et al., who studied 1550 hospitalized children in the PICU, concluding that patients with glucose levels >200 mg/dL on the first day of PICU admission had significantly higher mechanical ventilation time, longer stay in the PICU and lower survival rate compared with those who had normal blood glucose (29).

It has been proposed that the liberation of stress hormones as epinephrine and cortisol, induced by disease, leads to hepatic glycogenolysis mediated by catecholamines, as well as direct sympathetic stimulation of glycogen breakdown that leads to hyperglycemia (28). Furthermore, use of intravenous dextrose, plus the exogenous use of glucocorticoids and catecholamines might contribute to an increase in glucose levels. On the other hand, hyperglycemia has multiple effects on the body, such as immunosuppression, which leads to infection, increase of blood pressure and natriuretic peptide levels, platelet hyperactivity, which lead to thrombotic events and neuronal damage that can induce cerebral ischemia and death (28).

The association between hypoglycemia and mortality has also been studied before. A study in pediatric population at the Befelatanana University Hospital (Madagascar) (4) found that children with hypoglycemia (glycaemia <40mg/dL) had the highest risk of death (RR: 12.2, 95% CI: 6.2–23.7), followed by those with hyperglycemia (glycemia >150 mg/dL) (RR: 2.5, 95% CI: 1.0–6.2). The authors also found that children with hypoglycemia had a greater decrease in consciousness, more vomit frequency, and higher incidence of severe illness, severe dehydration and severe malnutrition. Similarly, Osier et al (7) in the Kilifi District Hospital in 1999, found that mortality of patients with hypoglycemia was higher than those with normoglycemia, especially in patients with severe signs of disease (prostration or deep breathing) and severe malnutrition. In addition, Egi in 2010 (11) found similar results regarding the association between hypoglycemia and death in critically ill patients at discharge.

Hypoglycemia causes impairment of autonomic function, release of inflammatory mediators and cytokines, alteration of blood flow and composition, white-cell activation and vasoconstriction. Severe hypoglycemia is associated with a prolonged QT interval and fatal cardiac arrhythmias (6). These events can answer to a causal relationship, but hypoglycemia can be only a result of disease processes, which is responsible of death, and not the cause. (6) In this case, hypoglycemia could be used like a marker of the predisposition of death.

In contrast to the results found in this study, Blesa et al (30), Freire et al (31) and Larrondo et al (32) concluded that glycemia during the first twenty-four hours was not a prognostic factor for mortality in critically ill patients. However, they found a linear relation between elevated levels of glucose and severity of the disease; therefore they concluded that blood

glucose monitoring remains useful and necessary, because its dysfunction expresses metabolic instability.

As for other variables associated with mortality in critically ill patients, Sambany et a.l (4) found a significant association between hepatomegaly and coma and death. Furthermore, in the study of Srinivasan et al. (14), infusion of vasoactive substances such as epinephrine was found to be associated with mortality. In adults, Freire et al (31) reported that the severity of illness measured by the APACHE II scale, severe hypoalbuminemia, severe lactic acidosis and mechanical ventilation showed association with mortality independently.

One of the strengths of our study is the fact of being a census of the attended pediatric population. In addition, we made the differentiation between surgical and medical causes, in comparison with similar studies. Lastly, to our knowledge, this is the first study in Latin-American population addressing this issue.

Our study had some limitations. There are some variables that were not taken into consideration because we were not able to gather their information and which could influence the association between glucose and mortality, such as the use of glucocorticoids or exogenous catecholamines, insulin therapy, disease severity measured by usual scales and nutrition 12 hours prior to admission (4). We also did not consider when, during his or her stay in ICU, variables like mechanic ventilation started.

It would be very useful to count on a marker that can distinguish between patients with increased likelihood of death of those who do not, therefore achieve better distribution of

material and human resources, a goal that becomes more important when referring to developing countries (3). This marker should be simple, readily available and fast, helpful in a dynamic environment like PICUs. Measuring serum glucose meets these characteristics and so we evaluated it as a predictor of death at discharge.

Our study showed a significant association between glucose and mortality at both extremes of the spectrum: hyperglycemia and hypoglycemia. Using these ranges of glucose as markers for mortality yielded very high specificities, but suboptimal positive likelihood ratios. Pediatric intensivists should perform a careful monitoring of blood glucose, especially during the first twenty-four hours since alterations in its levels are linked to adverse patient outcomes and to an increase of the risk of death at discharge. Taking these findings on account can allow these health professionals to identify the most vulnerable patients and establish an early and appropriate treatment in order to prevent mortality (33).

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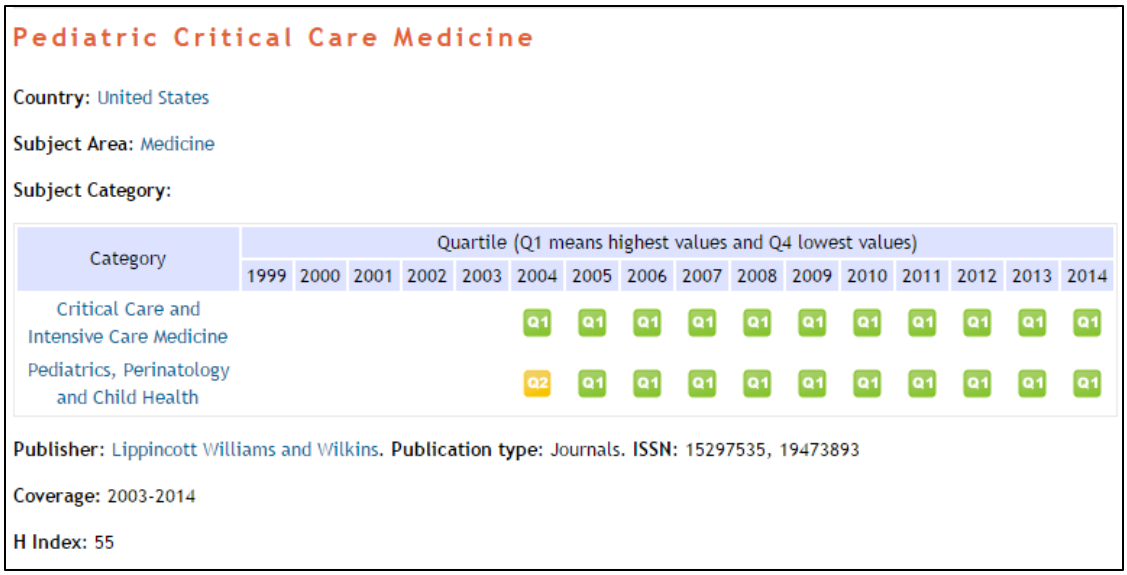

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Desde el 25 de febrero del 2016, el artículo se encuentra en proceso de revisión por parte de la revista "Pediatric Critical Care Medicine". Nos comprometemos a corregir las observaciones planteadas por la revista y, en caso sea rechazado, se enviará a otra revista indizada en SCOPUS.

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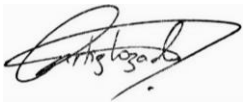

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