ORIGINAL ARTICLE

Prognostic Value of the Leuko-glycemic Index in Acute Myocardial Infarction. Results from the SCAR Multicenter Registry

Valor pronóstico del índice leucoglucémico en el infarto agudo de miocardio. Resultados del Registro Multicéntrico SCAR

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ABSTRACT

Background: Leukocytosis and hyperglycemia correlate with worse short-term prognosis in patients with acute coronary syndrome, but their new relationship, called leuko-glycemic index (LGI), has been scarcely evaluated.
Objectives: The aim of this study was to analyze the prognostic value of LGI in patients with ST-segment-elevation acute myocardial infarction (STEMI) and its added value to classical risk scores.
Methods: Patients diagnosed with STEMI from the SCAR (Acute Coronary Syndromes in Argentina) Multicenter Registry were analyzed. The final endpoint was death or in-hospital Killip-Kimball 3-4 (KK 3-4). The LGI was analyzed as a continuous variable and in quartiles according to 25, 50 and 75 percentile values.
Results: The study evaluated 405 out of 476 patients with final STEMI diagnosis. Presence of the primary endpoint significantly increased per LGI quartile: 0%, 7.60%, 9.30% and 30.60% ($p < 0.0001$). The LGI area under the ROC curve for the composite endpoint was 0.77 [(95% CI 0.71-0.88); $p = 0.0001$]; the best prognostic cut-off value was 1000. Presence of death or KK 3-4 was 0% and 13% in STEMI patients with LGI below or above 1000, respectively. In a multivariate logistic regression model, LGI was independently associated with death or KK 3-4. The area under the ROC curve of the TIMI risk score for STEMI was 0.58. The addition of LGI increased its discriminatory capacity to 0.66 ($p = 0.001$).
Conclusions: The LGI was an independent predictor of adverse outcome in STEMI patients (death or KK 3-4), adding prognostic value to the TIMI risk score.

Key words: Myocardial Infarction –Blood glucose - Leukocytes.

RESUMEN

Introducción: Se conoce que la leucocitosis y la hiperglucemia se correlacionan a corto plazo con peor pronóstico en pacientes con síndrome coronario agudo, pero su novel relación, denominada índice leucoglucémico (ILG), se ha evaluado escasamente.
Objetivos: Analizar el valor pronóstico del ILG en pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST) y su valor agregado a los puntajes de riesgo clásicos.
Material y métodos: Se analizaron los pacientes con diagnóstico de IAMCEST, del Registro Multicéntrico SCAR (Síndromes Coronarios Agudos en Argentina). El punto final analizado fue la muerte o Killip Kimball 3-4 (KK 3-4) en el período hospitalario. Se analizó el ILG tanto como variable continua como en cuartiles según los valores de los percentiles 25, 50 y 75.
Resultados: Se analizaron 405 de 476 pacientes con diagnóstico final de IAMCEST. La presencia del punto final fue significativamente creciente por cuartiles de ILG: 0%, 7,60%, 9,30% y 30,60% ($p < 0,0001$). El área bajo la curva ROC del ILG para el punto final combinado fue de 0,77 [(IC 95% 0,71-0,88); $p = 0,0001$]; el mejor valor de corte pronóstico fue de 1.000. La presencia de muerte o KK 3-4 fue del 0% y del 13% en los IAMCEST con ILG menor o mayor de 1.000, respectivamente. En un modelo de regresión logística multivariado, el ILG se asoció independientemente con muerte o KK 3-4. El área bajo la curva ROC del puntaje TIMI para IAMCEST fue de 0,58. El agregado del ILG incrementó su capacidad discriminatoria a 0,66 ($p = 0,001$).
Conclusiones: El ILG demostró que es un predictor independiente de mala evolución en el IAMCEST (muerte o KK 3-4), con valor aditivo al puntaje TIMI.

Palabras clave: Infarto agudo de miocardio - Leucocitos - Glucemia

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Abbreviations

CPK	Creatine phosphokinase	**LGI**	Leuko-glycemic index
AMI	Acute myocardial infarction	**KK**	Killip-Kimball
STEMI	ST-segment elevation acute myocardial infarction	**CRP**	C-reactive protein
HF	Heart failure	**ACS**	Acute coronary syndrome

INTRODUCTION

The purpose of stratifying patients with acute coronary syndrome (ACS) is to identify those at greater risk of presenting reinfarction, death or heart failure (HF) in order to define adequate strategies. Clinical predictors, as risk scores, which are easily and quickly implemented in the early phase of ACS, are widely used for this end. (1-3) Other markers, mainly inflammatory, have been evaluated to increase the precision of risk prediction. (4, 5) Previous studies have shown that leukocytosis and hyperglycemia correlate with worse short-term prognosis, (6, 7) but their novel relationship, called leuko-glycemic index (LGI) has been scarcely evaluated. The aim of this study was to determine the LGI value that predicts severe in-hospital events of death, or KK 3-4 in the first 24 hours following ST-segment elevation acute myocardial infarction (STEMI).

Another goal of the study was to define the added value of LGI to the TIMI score for STEMI.

METHODS

A multicenter cross-sectional study was performed with the information provided by the SCAR (Acute Coronary Syndromes in Argentina) Multicenter Registry developed by the Research Area and the Cardiovascular Emergency Council of the Argentine Society of Cardiology. It included consecutive ACS patients older than 18 years, in 87 centers throughout the country, during a 3-month inclusion period at each center, between June and September 2011. Patients with hematological or active infectious diseases were excluded from the study. Among the total sample population, patients with STEMI diagnosis (according to the classical criteria of the World Health Organization) were analyzed. Leukocyte count and fasting (at least 8 hours) blood sugar levels were assessed on admission.

The leuko-glycemic index was calculated as the product of fasting blood sugar (in mg/dL) and leukocyte count (on admission) in mm3 divided by 1000. The endpoint was in-hospital death or HF (KK 3-4).

Statistical analysis

Parametric or non-parametric distribution of continuous variables was analyzed using the Kolmogorov-Smirnov test, and kurtosis and skewness analyses. Continuous variables were compared using Student´s t test or the Mann-Whitney-Wilcoxon test according to their parametric or non-parametric distribution, and results were expressed as mean and standard deviation, or as median and the corresponding 25 and 75 interquartile range. Discrete variables were expressed as percentages and the chi-square test was used for comparison. The cross-product ratio was expressed as odds ratio (OR) with its corresponding 95% confidence interval (95% CI). ROC curves and the area under the ROC curve were used to analyze the discriminatory power of variables with respect to the primary endpoint cardiovascular events (Medcalc software version 11.6.1, Mariakerke, Belgium).

The LGI was analyzed as continuous variable per group of increasing concentration quartiles and by cut-off point established by the ROC curve.

A stepwise multivariate logistic regression analysis was performed, adjusting LGI according to variables that in the univariate analysis had a p value of 0.1 and other well-known historical counfounders. In this case, the LGI was entered in the model as a continuous variable and as categorical variable (by quartile groups).

A 5% two-tailed alpha error was considered as statistically significant. SPSS version 19.0 for Windows software package (Chicago, ILL, USA) was used for statistical analysis.

Ethical considerations

The study protocol was approved by the bioethics Committee of the Argentine Society of Cardiology, excluding the informed consent form as no sensitive data or clinical follow-up were required (in accordance to the Habeas Data Act No 25,326 on Protection of Personal Data).

RESULTS

Among the 476 STEMI patients from the SCAR registry, 405 patients with blood glucose and white cell count data on admission as the only selection criteria, were analyzed. Overall median age was 61 ± 12 years, 33% had more than 65 years and 24% were women. Sixty-four percent of patients were hypertensive and 22% were diabetic. Almost half of the population had history of dyslipidemia and 44% were active smokers; 14% had history of acute myocardial infarction (AMI), 2.4% of coronary artery bypass graft surgery and 10% of percutaneous coronary intervention. Table 1 shows baseline characteristics.

Seventy-four percent of the 405 patients (n = 299) received reperfusion therapy: 19.01% (n = 77) were treated with fibrinolytics and 54.81% (n = 222) underwent primary percutaneous intervention. As shown in Table 2, there were no significant differences between the quartiles analyzed. In addition, the table shows that the upper LGI quartiles significantly correlated with anterior AMI and higher heart rate, fasting blood glucose, leukocyte count and total creatine phosphokinase (CPK) levels.

Fasting blood glucose was 106 mg/dL (95-139) and leukocyte count was 10,500/mm3 (8,770-13,000). Mean overall LGI was 1,176 (900-1,579). The LGI was analyzed as continuous and as categorical variable, dividing the population in quartiles according to 25 (n = 738), 50 (n = 975) and 75 (n = 1,401) percentiles.

Patients with the highest LGI values were associated with greater incidence of in-hospital second and third degree atrioventricular block, ventricular tachy-

Table 1. Baseline characteristics of the overall population and per leuko-glycemic index quartile

Variable	Overall	LGI 1st quartile	LGI 2nd quartile	LGI 3rd quartile	LGI 4th quartile	p
		0-738	739-975	976-1,401	>1,402	
n	405	53	137	121	94	ns
Age> 65 years, %	33	44	38	29	34	ns
Women, %	24	31	25	23	31	ns
BMI> 30, %	23	16	30	20	25	ns
Diabetes, %	22	6.9	12	14	46	0.0001
Hypertension, %	64	67	51	61	78	0.01
Smoking, %	44	51	44	47	42	ns
Dyslipidemia, %	45	48	21	27	54	ns
Sedentarism, %	67	82	61	50	80	0.0001
History of AMI, %	14	11	8.5	13	18	ns
History of CABG, %	2.4	0	6.40	3	1.40	ns
History of PCI, %	10	7.70	4.30	13.40	14	ns

The chi-square test for trend was used to perform the analysis between groups. BMI: Body mass index. CABG: Coronary artery bypass graft surgery. PCI: Percutaneous coronary intervention. ns: Non significant.

Table 2. Overall and by quartile clinical and laboratory characteristics

	Overall	LGI 1st quartile	LGI 2nd quartile	LGI 3rd quartile	LGI 4th quartile	p
		0-738	739-975	976-1,401	> 1,402	
n	405	53	137	121	94	
Anterior location, %	52	40	45	57	65	0.01
HR at admission > 100 bpm, %	20	6.80	13	13	34	0,002
SBP at admission < 100 mm Hg, %	10	6.90	14	4.40	14	ns
Total CPK, IU (x̄)	987	456	749	1,344	2,855	0.0001
Fasting blood sugar, mg/dL (x̄)	106	102	102	112	163	0.0001
Leukocyte count / mm3 (x̄)	10,500	6,123	8,900	10,800	11,455	0.0001
Creatinine> 1,3 mg/dL, %	15	16	20	11	17	ns
Fibrinolytics, %	19.01 (n = 77)	32.46 (n = 25)	20.77 (n = 16)	23.37 (n = 18)	23.37 (n = 18)	ns
Primary percutaneous coronary intervention, %	54.81 (n = 222)	17.56 (n = 39)	28.37 (n = 63)	29.27 (n = 65)	24.77 (n = 55)	ns
Second/third degree AV block, %	6	1	0	4	11	0.04
VT/VF, %	11	0	8	8	22	0.001
Asystolia, %	4.50	0	4	3	8	0.04
Death, %	6.70	0	4.50	3	13.50	0.02
KK 3-4, %	12	0	8	9	27	0.001
Death or KK 3-4, %	10	0	7.60	9.30	30.60	0.0001

The chi-square test for trend was used to perform the analysis between groups. Pearson´s test was used to analyze the correlation between continuous variables and the Mann-Whitney test to compare continuous and categorical variables.
HR: Heart rate. bpm: Beats per minute. SBP: Systolic blood pressure. CPK: Creatine phosphokinase. AV: Atrioventricular. VT/VF: Ventricular tachycardia/ventricular fibrillation. KK: Killip-Kimball.

cardia / atrial fibrillation and asystolia.

The incidence of the final endpoint (death or KK 3-4) significantly increased per LGI quartile: 0%, 7.60%, 9.30% and 30% ($p < 0.0001$), respectively.

The area under the ROC curve was 0.77 (95% CI 0.71-0.88; $p = 0.0001$). The best cut-off value for the final endpoint was 1000.The area was significantly greater in non-diabetic than in diabetic patients: 0.79 (95% IC 0.67-0.90) vs. 0.65 (95% CI 0.44-0.85); $p = 0.02$. The final endpoint of death or KK 3-4 was 0% and 13% in patients with LGI below or above 1000, respectively.

In a multivariate logistic regression model, adjusted by age, female gender, diabetes, hypertension, previous AMI, anterior location, heart rate and systolic blood pressure LGI was independently associated with death or KK3-4. This association was observed with LGI entered as continuous or as categorical variable between the fourth and the first quartile: OR 1.01 (95% CI 1.00-1.10; $p = 0.001$) and OR 3.40 (95% CI 1.40-7.90; $p = 0.003$), respectively (Table 3).

Conversely, when the TIMI score (8) for STEMI was analyzed, the area under the ROC curve was 0.58 (95% CI 0.51-0.76). The area under the curve in-

creased to 0.66 (95% CI 0.60-0.91; p = 0.02) when LGI (above 1000) was added to the score. In non-diabetic patients, the discriminatory power was significantly greater when LGI was added to the TIMI score for STEMI: 0.69 (0.58-0.80) vs. 0.55 (0.42-0.68) for the STEMI score alone.

DISCUSSION

Our findings showed that LGI assessment in patients admitted with STEMI diagnosis is an independent predictor of death or severe HF (KK 3-4), as a significant correlation was found with severe cardiovascular events (30.60% of events in the upper quartile).

Since the 50s, it is known that leukocytosis is a frequent finding in AMI (9, 10). Previous studies have shown that it is not the only expression of infarct size, (11) but that inflammation is also an essential part of the atherogenic process, with numerous markers involved both in the genesis and prognosis of ACS, as C-reactive protein (CRP), the complement system, myeloperoxidase and interleukin 6 (IL-6). (12-14) However, most of these markers are costly and not widely available, especially in developing countries.

In a recent study we evaluated the relationship between cardiovascular complications and white blood cell count in a cohort of patients with high risk ACS referred for coronary angiography (PACS-BLANCOS), and found a significant correlation between white blood cell count and the incidence of events and greater anatomical complexity. (15)

In ACS registries, the prevalence of diabetic patients is around 20% and diabetes is one of the most important predictors at 30 days, doubling mortality in this population. (16)

Despite the pathophysiology of hyperglycemia in AMI is not fully understood, it has been suggested to be more than a mere marker of adrenergic response, and its control has been studied in the field of ACS due to its association with increased in-hospital morbidity and mortality, even in non-diabetic patients. (17-22)

It has been postulated that hyperglycemia frequently found in patients with infarction might correspond to a relative insulin deficit, associated with increased lipolysis and the consequent availability of free fatty acids. In normal conditions, free fatty acids are the preferred myocardial energetic substrate, but in ischemic conditions, they have a toxic effect on the myocardium, producing more energy consumption, cellular membrane damage, calcium overload, arrhythmias and finally contractile dysfunction. Excess free fatty acids can be partially inhibited with beta-blockers, which can in part explain the beneficial effect of these drugs in infarction. (23-26)

In a meta-analysis of patients with infarction, Capes showed that hyperglycemia is associated with increased risk of death and HF, both in patients with or without diabetes. (27-29)

On the other hand, as previously postulated, hyperglycemia could be a marker of myocardial injury size in STEMI rather than an epiphenomenon of extensive myocardial injury. However, there are contradictory data on STEMI infarct size and admission hyperglycemia. (30) Nonetheless, in the national SCAR registry, the main cause of death in STEMI patients was cardiogenic shock, (31) so LGI could be an alternative tool adding prognostic information.

Hyperglycemia and leukocytosis have been previously studied together, (32) but there is little evidence on the predictive information added by the combined index.

Quiroga Castro recently published results in 101 STEMI patients showing that LGI is a predictor of clinical events, death, postinfarction angina and HF at 30 days. A limitation was that the study was performed in a single center, with a low number of patients and softer endpoints than in our analysis. (33) Nevertheless, Quiroga Castro´s work is original, as according to our records it was the first time that blood glucose and white blood cell count were analyzed together as an index. In previous studies we analyzed LGI in different clinical scenarios: non-ST-segment elevation ACS patients and the total population of the SCAR registry. In both cases, LGI significantly predicted a higher rate of cardiovascular events. (34, 35)

In the present study, LGI demonstrated a higher predictive value in the group of non-diabetic patients, evidencing added clinical value, as non-diabetic (or unknown diabetic) patients could be underestimated in one of the risk scores, such as the TIMI score.

In our cohort, the TIMI score for STEMI patients showed poor discriminatory power (area under the ROC curve: 0.58).

The incorporation of LGI (cut-off point > 1000) to the TIMI score improved its discriminatory capacity (area under the ROC curve: 0.66) (see Figure 1 A) and even more significantly in non-diabetic patients (see Figure 1 B), where LGI showed a greater added value in risk stratification.

Moreover, we believe that LGI allows better assessment of risk in patients underestimated by the TIMI score in whom hyperglycemia and leukocytosis

Table 3. Multivariate logistic regression analysis for death or Killip-Kimball 3-4

Variable	OR	95% CI	p
LGI 4/1 quartile	3.40	1.4-7.9	0.003
Quantitative LGI	1.01	1.00-1.10	0.001
Age (per year)	1.02	1.06-1.17	0.03
SBP (per mmHg)	1.03	1.1-1.60	0.004
HR (per bpm)	1.03	1.01-1.20	0.001
Prior AMI	2.10	0.9-9	0.06
Diabetes	1.30	0.4-3.30	0.4
HT	1.40	0.4-3.30	0.3
Anterior location	2	0.7-3.,50	0.,1

LGI: Leuko-glycemic index. bpm: Beats per minute. SBP: Systolic blood pressure. HR: Heart rate. AMI: Acute myocardial infarction. HT: Hypertension.

represent an evident indicator of greater clinical risk of severe HF and in-hospital death.

Regarding its usefulness and clinical application, given its simplicity and low cost, it could be valuable in low complexity centers, since according to the SCAR Multicenter Registry 21% of 87 centers had no available troponin.

Bedside LGI calculation could become a complementary tool in daily practice to identify patients at greater clinical risk, especially in the case of non-diabetic patients.

Finally, we assume that a greater LGI could be associated with infarct size and its severe complications, as observed in the upper quartile with higher CPK level, independently of the reperfusion strategy used.

In this sense, a significant correlation was found between CPK and LGI values analyzed as continuous variables.

Study limitations

The probable bias in the results of the present study could be attributed to the selected population admitted in high complexity centers, with high reperfusion rate and available primary percutaneous coronary intervention.

CONCLUSIONS

In the population of patients with ST-segment elevation AMI, LGI > 1000 in the first 24 hours after the event was an independent predictor of death or severe HF, especially in non-diabetic patients, and an alternative tool adding value to the TIMI score.

The LGI is a simple, low cost tool allowing restratification of non-diabetic patients with low TIMI score, at greater risk of death or severe HF (KK 3-4). This index is probably associated with greater infarct size and severe complications.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms in the web / Supplementary Material).

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