CorSalud 2016 Jul-Sep;8(3):153-163

Cuban Society of Cardiology

Original Article

Glycosylated hemoglobin and leukoglycemic index as prognostic determinations in acute coronary syndrome

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: April 23, 2016
Accepted: June 2, 2016

Competing interests
The authors declare no competing interests

Acronyms
ACS: acute coronary syndrome
HbA1c: glycosylated hemoglobin
LGI: leukoglycemic index

On-Line Versions:
Spanish - English

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ABSTRACT
Introduction: The acute coronary syndrome is one of the most frequent causes of morbidity and mortality worldwide, that is why it is important to find laboratory determinations of easy access, to help evaluating the prognosis of these patients.
Objective: To determine the prognostic value of the glycosylated hemoglobin (HbA1c) and the leukoglycemic index (LGI) in patients with acute coronary syndrome.
Method: A cross-sectional descriptive study was carried out in 142 diabetic and non-diabetic patients, with acute coronary syndrome, admitted to the Hospital Universitario Dr. Celestino Hernández Robau of Santa Clara, Cuba, from October 2012 to October 2013. The HbA1c, LGI, and complications after admission were evaluated during the study.
Results: A total of 40 diabetic and 102 non-diabetic patients were detected, with a mean age of 68.2 years and a prevalence of hypertension and dyslipidemia. As the LGI numbers increased, the frequency of complications in diabetics ($p=0.422$) and non-diabetics ($p=0.007$) also increased. The mean HbA1c of complicated diabetics (8.8%) was higher than that of non-diabetics (7.5%) ($p<0.01$). The 1443 of LGI values and 6.9% of HbA1c were established as complication predictors.
Conclusions: The joint evaluation of LGI and HbA1c was a predictor of high specificity and good sensitivity in both groups of study.
Key words: Leuko-glycemic index, Glycosylated hemoglobin A, Acute coronary syndrome, Risk assessment, Diabetes mellitus

Hemoglobina glucosilada e índice leucoglucémico como determinaciones pronósticas en el síndrome coronario agudo

RESUMEN
Introducción: El síndrome coronario agudo es una de las causas más frecuentes de morbilidad y mortalidad a nivel mundial; es importante encontrar determinaciones de laboratorio de fácil alcance que ayuden a valorar el pronóstico de estos pacientes.
Objetivo: Determinar el valor pronóstico de la hemoglobina glucosilada (HbA1c) y el índice leucoglucémico (ILG) en pacientes con síndrome coronario agudo.

Método: *Se realizó un estudio descriptivo transversal en 142 pacientes, diabéticos y no diabéticos, con síndrome coronario agudo, ingresados en el Hospital Universitario Dr. Celestino Hernández Robau de Santa Clara, Cuba, desde octubre de 2012 a octubre de 2013. Se evaluaron la HbA1c, el ILG y las complicaciones después del ingreso.*
Resultados: *Se encontraron 40 pacientes diabéticos y 102 no, con edad promedio de 68,2 años y predominio de hipertensión arterial y dislipidemia. A medida que aumentaron las cifras del ILG aumentó también la frecuencia de complicaciones en los diabéticos (p=0,422) y en los no diabéticos (p=0,007). La HbA1c media de los diabéticos complicados (8,8%) fue superior a la de los no diabéticos (7,5%) (p<0,01). Los valores 1443 del ILG y 6,9% de la HbA1c se establecieron como puntos de corte predictores de complicaciones.*
Conclusiones: *La valoración conjunta del ILG y la HbA1c resultó un predictor de alta especificidad y buena sensibilidad en ambos grupos de estudio.*
Palabras clave: *Índice leucoglucémico, Hemoglobina A glucosilada, síndrome coronario agudo, Medición de riesgo, diabetes mellitus*

INTRODUCTION

Acute coronary syndrome (ACS) is one of the most serious forms of coronary artery disease and one of the most frequent causes of morbidity and mortality in developed and developing countries[1,2].

In the United States, 60 million adults suffer from cardiovascular disease, which is responsible for 42% of all deaths a year, costing 218 billion dollars. Ischemic heart disease represents one of the main causes of death in both the United States and Europe as well, where Spain has a 40% mortality rate, within 60% of cardiac deaths, in general[3].

Cuba also suffers the scourge, where the prevalence of coronary artery disease, besides increasing, is manifested earlier. In 2009 and 2010, heart disease was the leading cause of death in all ages, with mortality rate of 197.8 and 211.8; as well as 11.1 and 11.5 years of potential life lost. Villa Clara was the fourth province in the country with the highest heart-disease mortality rates, 210.4[4].

It is known that there is a link between thrombotic and inflammatory phenomena[3,5,6]. Leukocytosis is a marker that reflects the inflammatory and hypercoagulable state accompanying the atherogenic process in this syndrome[7-9]. Hyperglycemia on the other hand, plays a facilitating role in the development of acute myocardial infarction, not only by reinforcing the consequences of the cellular damage produced by acute ischemia, but also by its amplifying effect on the inflammatory response[10-13].

The leukoglycemic index (LGI) has been proposed as a prognostic marker of death and in-hospital complications of ACS, superior to each of them separately (blood glucose or leukocytes), with a greater utility during the patients in-hospital follow-up[14-16].

The white blood cell count and glycemia undoubtedly have a prognostic value, much more guaranteed by their easy availability and low cost. Their combined analysis, through LGI and glycosylated hemoglobin (HbA1c) calculation, could become a tool in the initial stratification of this type of patients. Therefore, this study aims to determine HbA1c and LGI values for predicting short-term complications of patients with ACS.

METHOD

A descriptive, cross-sectional study was conducted with 142 patients from 294, aged 35 or older, who entered were admitted to the Intensive Care Unit at *Hospital Universitario Dr. Celestino Hernández Robau* in Santa Clara, Cuba, the first 24 hours after ACS diagnosis, with or without ST segment elevation, from October 2012 to October 2013.

Those who had recently received blood transfusions (two months), had chronic kidney disease or liver dysfunction, and had a blood disorder such as recent anemia, hemolysis, or severe bleeding, were excluded; also those with previously known infectious, inflammatory, systemic or hematological diseases, and having hemoglobin variants.

The sample was divided into two groups according to the diagnosis or not of diabetes mellitus before admission, and the presence of complications at 30 days was investigated.

LGI description

Indicator that easily conjugates the inflammatory and metabolic response in ACS, after leukocyte count and glycemia determination. It was obtained by the following formula:

LGI = glycemia (mmol/L) x conversion factor x leucocytes (10^9/L), according to the formula LGI = [glycemia (mg/dL) x leucocytes (10^6/L)]/1000, proposed by Quiroga[15] and Reyes Prieto[16]. The reference formula was modified in order to perform the calculations and raise results, according to the International System of Units (SI).

Measurement: In real numbers, without unit of measure, with 4 reference ranges as used by Quiroga[15], being the first author to describe it and comprising the following categories:

- ≤ 800
- 801 - 1600
- 1601 - 2400
- ≥ 2401

The absolute, relative and mean ± standard deviation indicators were used.

HbA1c description

Laboratory test that measures HbA1c, which is an indicator of erythrocyte exposure to current glycemia levels[17].

Measurement: In real numbers, with unit of measure in percent of total hemoglobin, according to the National Glycohemoglobin Standardization Program (NGSP)[18], on a scale according to glycemic control goals in diabetics referred to in the Manual for the diagnosis and treatment of diabetic patients at primary health level[19].

- Good glycemic control: <6.5%
- Acceptable glycemic control: 6.5 - 7%
- Poor glycemic control: > 7%

For non-diabetic, on a scale according to Cuban consensus for type 2 diabetes mellitus in 2010[20].

- Values considered normal: < 5.6%
- Pre-diabetes or impaired glucose tolerance: 5.6 - 6.4%
- Figures considered for diabetes diagnosis: ≥ 6.5%

The same indicators as for the LGI were used.

Ethical considerations

The study was carried out in accordance with the World Medical Association Declaration of Helsinki and the regulations of the *Centro de Investigaciones Médicas (CIMED)*, and was reviewed and approved by the Scientific Committee of the Institution and discussed by the Research Ethics Committee.

Statistical analysis

Data was processed with SPSS 15.0 statistical software for Windows. The qualitative variables were expressed in absolute and relative frequencies; quantitative variables were expressed as mean ± standard deviation. The degree of association between the qualitative variables was determined by the Chi-square statistic; and Student t test for independent samples was used to compare the means of quantitative variables. In order to determine LGI and HbA1c accuracy as prognostic tests, ROC curves and determination of the C statistic were used, which is the value obtained from the area under the curve, which also allowed obtaining a cut-off value. Significant value was set at $p < 0.05$ and highly significant at $p < 0.01$. In addition, sensitivity, specificity, positive and negative predictive values were calculated.

RESULTS

The sample consisted of 142 patients, (28.2%) diabetic and 102 (71.8%) non-diabetic. Mean age was 68.2± 10.3 years and male predominated: 52.5% in diabetics and 60.8% in non-diabetics.

Regarding cardiovascular risk factors, 60% of diabetics and 62.7% of non-diabetics had a history of hypertension. Dyslipidemia was reported by 45% in the former and 46.1% in the latter, obesity in 37.5% of diabetics and smoking in 34.1% of non-diabetics. In addition, 35% of diabetics and 31.4% of non-diabetics had a family history of coronary artery disease.

Complications

47.5% of diabetic patients and 28.4% of non-diabetic had complications with a 0.905 variation coefficient in the former and 0.366 in the latter. Mortality was 47.4% in diabetics and 17.2% in non-diabetics, with a variation coefficient of 0.901 and 0.208 respectively.

LGI value

LGI mean value was 1890±848 in diabetic patients, white blood cell count 10.8±2.2, and fasting blood glucose 9.6±3.6. LGI average number for non-diabetics was 1237±488, white blood cell count was 9.8±2.2, and fasting blood glucose was 6.9±1.8 (**Table 1**).

It was observed that diabetic patients with LGI values below 800 had no complications according to the established ranges. They occurred in 30.8% of diabetics with LGI ranging from 801 to 1600, in 52.9% with values between 1601 and 2400, and in 66.7% of those with figures above 2400.

Non-diabetic patients with values below 800 had no complications. In the LGI range between 801 and 1600, only 12.1% had complications; from 1601 to 2400, 75%; and with values above 2400, all patients in the non-diabetic group had complications.

Strength of predictive value from LGI complications was established through statistic c, where an area under the ROC curve of 0.797 (95% confidence interval, 0.713-0.880) was evidenced. LGI's optimal value as a complications predictor in this study population was set up at the cut-off point raised from the exploratory analysis of the ROC curves for the best sensitivity and specificity values.

Table 1. LGI mean values and its components.

Analytical determinations	Mean ± SD		*t-Test*
	Diabetics	Non-diabetics	
Leukogram	10.8 ± 2.2	9.8 ± 2.2	p = 0.013
Glucose	9.6 ± 3.6	6.9 ± 1.8	p = 0.000
LGI	1890 ± 848	1237 ± 488	p = 0.000

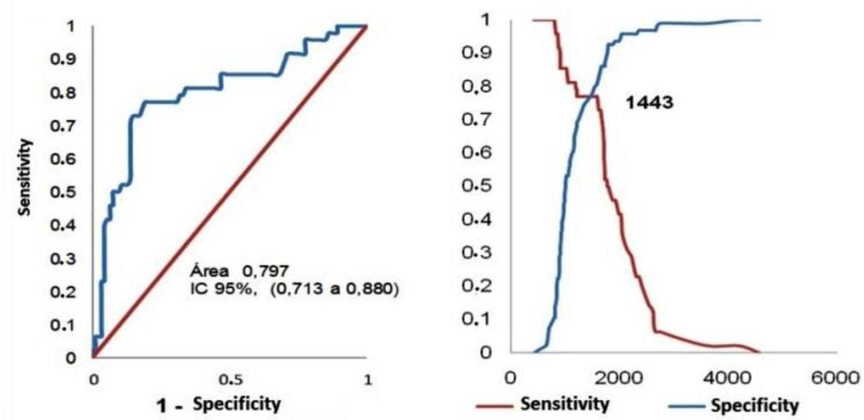

Figure 1. ROC curve and LGI cut-off point for prognostic value of complications in ACS patients.

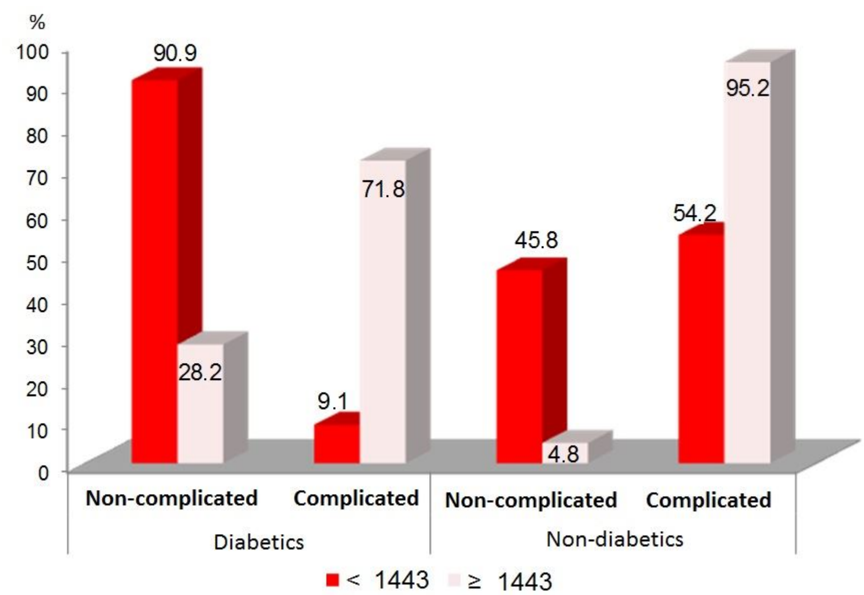

Figure 2. Complications according LGI cut-off point according to study group. Diabetics: χ^2=7,77 and p=0,047; non-diabetics: χ^2=28,41 and p=0,018; between groups: t=12,71 and p=0,042.

Hence it was 1443 without distinction between diabetics and no-diabetics (**Figure 1**).

71.8% of diabetics and 95.2% of non-diabetics presented complications with an LGI value higher than the calculated cut-off point. With LGI figures below 1443, 9.1% from the former had complications and 54.2% from the latter. In uncomplicated diabetics the proportion of patients with LGI values above 1443 was 28.2% and in non-diabetic 4.8% (**Figure 2**).

HbA1c value

With respect to HbA1c values, complicated diabetics had an average HbA1c value of 8.8±1.83%, and non-diabetic, 7.5±1.50% (**Figure 3**).

When assessing HbA1c as a predictor of complications in ACS patients, an area under the curve of 0.742 (95% confidence interval, 0.662-0.882) was obtained. The intersection between the best sensitivity and specificity values of this statistical procedure allowed determining the cut-off point for the appearance of complications in the value of 6.9% (**Figure 4**).

With HbA1c figures below that value, determined as cut-off point, 6.2% of diabetics and 13.1% of non-diabetics had complications. 75% of the former and 71.3% of the latter who had figures greater than or equal to 6.9% on this indicator, had some post-admission complications, as shown in **figure 5**.

In diabetic patients, HbA1c levels above 7% have an important clinical value. 72.5% of the cases in this study with such value had poor glycemic control. None of the patients with good glycemia control suffered complications. 5.3% of those who had an acceptable control had some complication after admission, and 94.7% from the total diabetics involved had poor glycemic control (**Table 2**).

28.4% of non-diabetics were in the pre-diabetic range. With these HbA1c figures, 20.7% from all non-diabetics had complications. 41.2% of the patients in this group had values of this indicator equal to or greater than 6.5%, from which 79.3% had complications (**Table 3**).

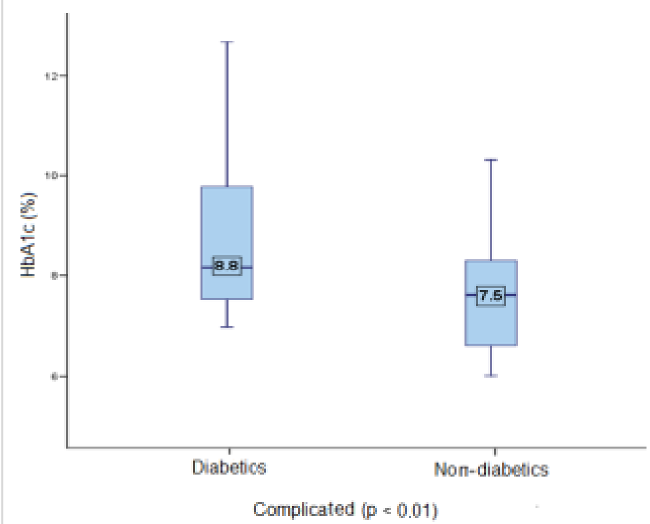

Figure 3. Mean values of HbA1c in complicated patients according to study group.

Table 2. Diabetic patients according to complications and glycemic control.

HbA1c (%)	Complicated		Non- complicated		Total	
	Nº	%	Nº	%	Nº	%
< 6.5	0	0	3	14.3	3	7.5
6.5 – 7	1	5.3	7	33.3	8	20.0
> 7	18	94.7	11	52.4	29	72.5
Total	19	47.5	21	52.5	40	100

χ^2 = 88.37; p=0.001

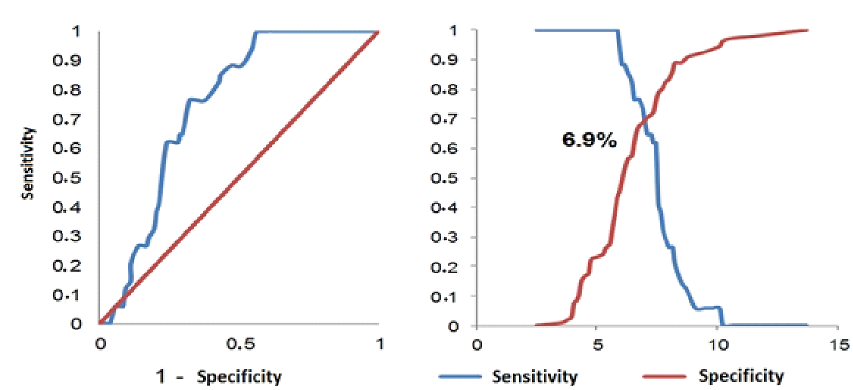

Figure 4. HbA1c ROC curve and cut-off point for the prognostic value of complications in ACS patients.

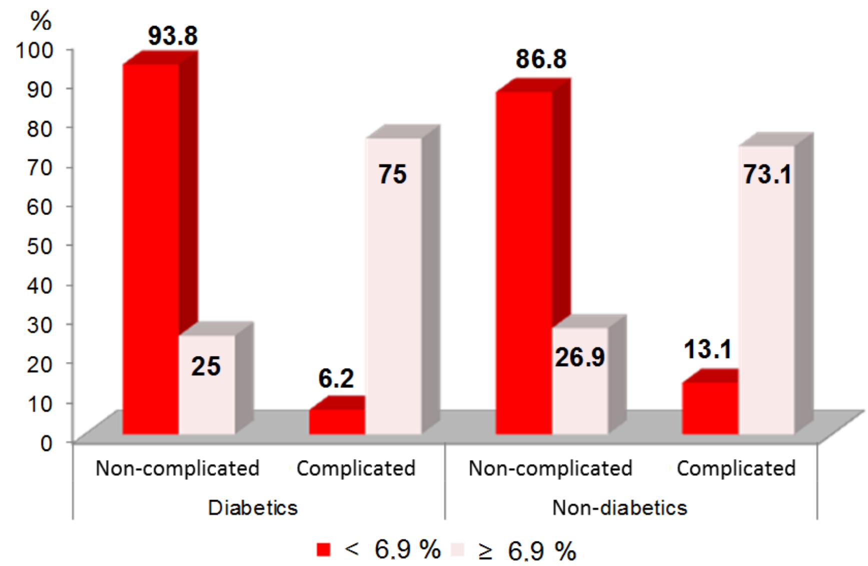

Figure 5. Complications according to HbA1c cut-off value according to study group. Diabetics: χ^2=30,12 and p=0,012; non-diabetics: χ^2=6,63 and p=0,005; between groups: t=1,885 and p=0,041.

Table 3. Non-diabetic patients according to HbA1c complications and ranges.

HbA1c (%)	Complicated		Non- complicated		Total	
	Nº	%	Nº	%	Nº	%
< 5.6	0	0	31	42.5	31	30.4
5.6 – 6.4	6	20.7	23	31.5	29	28.4
≥ 6.5	23	79.3	19	26.0	42	41.2
Total	29	28.4	73	71.6	102	100

χ^2 = 79.08; p=0.049

Table 4. LGI/HbA1c complications relation and predictive values according to study group.

Leuco-glycemic index	HbA1c (%)	Complications					
		Diabetics			Non-diabetics		
		Sí	No	Total	Sí	No	Total
≥ 1443	≥ 6.9	16	6	22	13	3	16
< 1443	< 6.9	0	5	5	1	56	57
Other variants		3	10	13	15	14	29
Total		19	21	40	29	73	102
Risk prediction statistics							
Sensitivity		0.73			0.81		
Specificity		1.00			0.98		
Positive predictive value		1.00			0.93		
Negative predictive value		0.45			0.95		
Relative Risk		1.83			18.26		

LGI and HbA1c combined value

According to cut-off points calculated for each determination, 16 out of 22 diabetic patients and 13 out of 16 non-diabetic who simultaneously had LGI ≥ 1443 and HbA1c ≥ 6.9% had complications. None of the 5 diabetics and only 1 out of 57 non-diabetic patients who presented figures below these values had short-term complications after admission (**Table 4**)

DISCUSSION

Age, male sex, presence of risk factors and previous manifestations of coronary artery disease are variables associated with a greater severity of ischemic heart disease and, therefore, increase the probability for an unfavorable outcome[14].

These patients average age was over 65 years, which coincides with Cabrerizo[14,21] and Cid Álvarez[22], and differs from Quiroga[15] and Juárez Baizabal[23] results.

Cardiovascular risk is more common in men than in women. However, male predominance is only up to 50 years, from where risks are similar in both sexes[24-26]. This equality, as age increases, may be due to the estrogen concentrations decrease in postmenopausal women[14]. The predominance of male patients with coronary artery disease was similar to that found by other authors[15,16,23,27].

Cardiovascular risk factors are related to most acute coronary disease events[28]. A meta-analysis of nine large prospective studies found a significant relationship between diastolic arterial hypertension and the risk of ischemic heart disease; likewise, the isolated increase in systolic blood pressure is also associated with an increase in cardiovascular risk. Results from the present study are consistent with other several researches[14-16,21,24,27,29].

Dyslipidemia presented a similar behavior. Cabrerizo[14] and McCune[27] analyzed this risk factor and reported high lipid values in patients with coronary artery disease. All forms of hyperlipidemia associated with an increase in plasma levels of total cholesterol, low density lipoproteins, or both, are associated with an increased risk of ischemic heart disease. Hypertriglyceridemia is also associated with increased atherosclerotic risk, although it is difficult to separately determine the role of each factor in the risk of ischemic heart disease[30].

On the other hand, diabetics have two- to three-fold risk of cardiovascular disease than non-diabetics[14]. Although this disease was not a predominant risk factor in the present study, the frequency obtained was similar to that found by other authors[14,16,21-24,29]. As it is known, atherosclerosis occurs earlier, more intense, more diffuse, and progresses more rapidly in diabetics[31,32].

Authors such as Monteiro et al.[11], Zamora and Marrugat[33], and Palma Gámiz[34] have pointed out that diabetic patients have a greater propensity for cardiovascular disease and a worse prognosis in an ACS course compared to non-diabetics. In fact, diabetes mellitus has been defined as a cardiovascular disease of metabolic origin[24]. Quiroga[15] points out that, due to the facilitating role of hyperglycemia in the development of ACS and the reinforcement of the consequences of cellular damage caused by acute myocardial ischemia, the negative influence of diabetes and hyperglycemia on the prognosis of ACS patients it is likely to expect a negative influence of diabetes and hyperglycemia in ACS patients' prognosis. In the sample studied, diabetic patients presented complications in greater proportion than non-diabetics, which coincides with Capes[35], Vivas[36] and Currie[37] findings. It has been established in several studies[13,16,35,38-41] that during an ACS, hyperglycemia can occur in patients with and without diabetes mellitus diagnosis. Similarly, white blood cell count rises and eventually is indicated as an independent marker of morbidity and mortality in these patients[8,16,21,41,42]. This fact was evidenced by the high mean values of these indicators present in the sample studied.

LGI easily matches these laboratory variables. Leon-Aliz *et al.*[43,44] report results similar to ours, where the appearance of complications was directly related to LGI increase, regardless the presence or absence of diabetes mellitus. Quiroga[15] and Reyes Prieto[16] give equal prognostic value to this indicator. However, different results have been presented on this subject. Quiroga[15], who pioneered these studies, reports a figure of 1600 LGI having a strong association with in-hospital complications; Reyes Prieto[16] points it out in 1550; while León-Aliz *et al.*[43] report 1158.

1443 cut-off value obtained in this study with statistic c=0.797 −which assigns a good prognostic value− differs from the cut-off values mentioned above, which could be a reflection of a differentiated behavior in terms of glycemia figures in different populations, where factors related to diet, lifestyle and environment are very important; as well as samples size and performance of analytical determinations under different laboratory conditions.

Regardless the differences found in cut-off points, a strong association between LGI high figures above these values and the onset of complications is evidenced in each of the referred studies, which indicates it as a prognostic marker for complications in ACS, a fact that was corroborated in the present study.

Hyperglycemia produces hemodynamic changes and increased arrhythmogenicity, atherosclerotic plaque instability and impaired immune response, with increased morbidity and mortality[14,45,46]. Leukocytosis, on the other hand, favors microvascular obstruction and lesion extension[44], and may even lead to ventricular dysfunction[9,14]. Therefore, considering that LGI depends on these determinations figures, it is not surprising that patients with this indicator values higher than the determined cut-off point have a higher frequency of complications.

In this study, HbA1c also showed higher mean values in complicated diabetic patients compared to non-diabetic ones (p<0.01). Its cut-off point of 6.9% does not differ from that reported by Cid Álvarez *et al.*[22], who established 7% in ACS patients. Meanwhile, Liu *et al.*[47] suggest that this can be estimated in a 5-8% range. It should be noted that, like the LGI cut-off value obtained in this research, that of HbA1c is consistent with the values that other authors have obtained from c=0.742, which gives it the category of good predictor.

In other investigations[23,24,27] HbA1c prognostic importance in diabetic patients with coronary heart disease has been commented, and an inadequate metabolic control has been reported in the majority of diabetic patients with this disease, results that coincide with those found in the present study in which 72.5% of them had figures above 7% and a higher frequency of complications, with a statistically significant difference. So it can be inferred that the majority of diabetic patients with HbA1c above 7% are more likely to have complications.

On the other hand, the existence in the study sample of non-diabetic patients with HbA1c levels similar to those of diabetics reveals an insufficient glucose metabolism regulation, suggesting the presence of a "pre-diabetic" stage, as several studies reveal[24,27,38]. However, Liu *et al.*[47] and Ashraf *et al.*[48] reported that high HbA1c levels constitute an independent prognostic factor of mortality in non-diabetic ACS patients, but not in patients with diabetes. Others, such as Chan *et al.*[49] and Rasoul *et al.*[50], found no association between this indicator values and the occurrence of complications in their patients, so those findings do not agree with these of the present study.

LGI and HbA1c combined assessment proved to be a predictor with excellent specificity in both study groups, with a sensitivity of 0.73 (good) in diabetics and of 0.81 (excellent) in non-diabetics, which allows evaluating both combined determinations as good predictors of short-term ACS complications.

No previous studies were found to correlate the prognostic value of LGI and HbA1c overall levels in ACS patients. However, the results of this investigation confirm that, in the case of a patient who has suffered an ACS, the presence of high LGI and HbA1c levels enables to predict with good precision the incidence of short-term complications.

CONCLUSIONS

LGI together with HbA1c with high values –above 1443 and 6.9% respectively– constitute a short-term complications predictor of high specificity and good sensitivity in patients who have suffered an ACS, despite the presence or not of diabetes mellitus.

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