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Artículo Original

# El índice leucoglucémico es un predictor de mortalidad por todas las causas al año en pacientes cubanos con infarto agudo de miocardio con elevación del segmento ST

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INFORMACIÓN DEL ARTÍCULO

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**Conflictos de intereses**
Los autores declaran que no existen conflictos de intereses

**Abreviaturas**
**ILG:** índice leucoglucémico
**IAM:** infarto agudo de miocardio

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## RESUMEN

*Introducción:* El índice leucoglucémico (ILG) ha sido propuesto como marcador pronóstico de muerte en pacientes con infarto agudo de miocardio; sin embargo, no existe evidencia sobre su valor pronóstico al año.
*Objetivo:* El objetivo del estudio fue determinar el valor pronóstico del ILG en la mortalidad al año de pacientes cubanos con infarto agudo de miocardio con elevación del segmento ST.
*Método:* Los datos fueron obtenidos de las historias clínicas y el objetivo primario fue la muerte por todas las causas al año. El ILG se calculó con los valores al ingreso. Para el análisis se dividieron los pacientes en terciles de ILG, se construyeron curvas de características operativas del receptor y de supervivencia de Kaplan-Meier. Para el análisis multivariable se utilizó la regresión de Cox.
*Resultados:* Se analizaron 344 pacientes (mediana de edad, 68 años; el 65,7% masculino; un 25,6% diabéticos). La mortalidad fue de 25,6% y fue significativamente mayor en el tercil superior (55,7%; p<0,0001). Los pacientes fallecidos presentaron una mediana de ILG significativamente mayor que los sobrevivientes (2,18 y 1,34, respectivamente; p<0,0001). El área bajo la curva del ILG fue de 0,715 y el punto de corte: 2,2. Un valor de ILG mayor de 2,2 se asoció a una supervivencia significativamente menor (177 *vs.* 309 días; p<0,0001) y fue un predictor independiente de mortalidad (HR=3,56; IC 95%, 2,09-6,07; p<0,0001).
*Conclusiones:* El índice leucoglucémico es buen predictor de mortalidad al año, por todas las causas, en pacientes con infarto agudo de miocardio con elevación del segmento ST.
*Palabras clave:* Índice leucoglucémico, Infarto de miocardio, Mortalidad, Supervivencia, Leucocitos, Glucemia

## *The leucoglycaemic index is a predictor of one-year all-cause mortality in Cuban patients with ST-segment elevation acute myocardial infarction*

## ABSTRACT

*Introduction: The leuko-glycaemic index has been proposed as a prognostic marker of death in patients with acute myocardial infarction, but there is uncertainty*

*surrounding its prognostic value to predict one-year mortality.*
*Objectives: The aim of this study was to determine the prognostic value of leuko-glycaemic index for one-year mortality in Cuban patients with ST-segment elevation myocardial infarction.*
*Method: The data were obtained from the medical records and all cause one-year deaths was the primary endpoint. The leuko-glycaemic index was calculated from measurements at admission. The patients were divided into leuko-glycaemic index tertiles to be evaluated. Receiver operating characteristics and Kaplan-Meier survival curves were performed. Cox regression model was used for all multivariable analysis.*
*Results: Three hundred and forty-four patients were assessed (median age, 68 years; 65.7% males; 25.6% diabetic). The mortality rate was 25.6%, being significantly higher in the upper tertile (55.7%, p<0.0001). The deceased patients presented a median of leuko-glycaemic index significantly higher than the survivors (2.18 and 1.34 respectively, p<0.0001). The area under the curve for leuko-glycaemic index was 0.715 and its cut-off value was 2.2. Any leuko-glycaemic index value higher than 2.2 was associated with significantly lower survival (177 vs. 309 days, p<0.0001) and it was an independent predictor of mortality (HR=3.56, CI 95%, 2.09-6.07, p<0.0001).*
*Conclusions: The leuko-glycaemic index is a good predictor for all cause one-year mortality in patients with ST-segment elevation myocardial infarction.*
*Keywords: Leuko-glycaemic index, Myocardial infarction, Mortality, Survival, Leukocytes, Blood glucose*

## INTRODUCCIÓN

Las enfermedades cardiovasculares han incrementado progresivamente su presencia en todo el mundo, de tal modo que han llegado a ser la primera causa de mortalidad. A pesar de las mejoras sustanciales en las estrategias de reperfusión y la terapia médica, el infarto agudo de miocardio (IAM) permanece asociado a una morbilidad y mortalidad significativas[1].

La inflamación desempeña un papel importante en el desarrollo de la enfermedad aterosclerótica y la trombosis coronaria[2]. Estudios previos han demostrado que niveles elevados de marcadores inflamatorios están asociados con la gravedad de la enfermedad coronaria y con un peor pronóstico[3-5]. A pesar de existir novedosos marcadores (interleucinas, proteína C reactiva, homocisteína, péptidos natriuréticos, fibrinógeno, entre otros), el recuento de leucocitos y de sus componentes diferenciales constituye una herramienta rápida, universal y poco costosa para establecer la conducta a seguir y el pronóstico de estos pacientes[6,7]. Por su parte, la hiperglucemia inducida por la respuesta inflamatoria y adrenérgica al estrés isquémico, es frecuente y constituye un factor pronóstico independiente de muerte y complicaciones en el síndrome coronario agudo[8,9].

La asociación de estos 2 parámetros en el índice leucoglucémico (ILG) ha sido propuesta como un marcador pronóstico de muerte y complicaciones intrahospitalaria en los pacientes con IAM[10-13]. A pesar de ello, aun es necesario reproducir estos resultados en más estudios, así como evaluar su significado al año. Por estas razones, el objetivo de esta investigación fue determinar el valor pronóstico del ILG en la mortalidad por todas las causas al año, en pacientes cubanos con IAM con elevación del segmento ST.

## MÉTODO

### Población en estudio

Se incluyeron a los pacientes ingresados en el Hospital Universitario Arnaldo Milián Castro de Villa Clara (Cuba), con diagnóstico de IAM con elevación del segmento ST en el período comprendido entre enero de 2011 y diciembre de 2015. Se excluyeron aquellos con presencia de enfermedades infecciosas, inflamatoria sistémica o hematológica que pudiera alterar el recuento leucocitario, así como los pacientes para los cuales no se supo su estado al final del seguimiento (vivo o fallecido).

### Variables

Los datos se obtuvieron a partir de las historias clínicas. Se tomó la información relativa a los datos personales, antecedentes (edad, sexo, hábito de fu-

mar, hipertensión arterial, diabetes mellitus, IAM previo, fibrilación auricular, angina de pecho e insuficiencia cardíaca), clínica y laboratorio al ingreso (frecuencia cardíaca, tensión arterial sistólica y diastólica, clasificación Killip-Kimball, conteo de leucocitos, neutrófilos, linfocitos, glucemia y creatinina), y el tratamiento de reperfusión coronaria (trombólisis, intervención coronaria percutánea o ambas). Se tomó en cuenta la intervención coronaria percutánea realizada durante el ingreso ya que en nuestro centro no se realiza de forma primaria. La trombólisis se realizó con estreptoquinasa recombinante.

### Índice leucoglucémico

Para el cálculo del ILG se tuvo en cuenta que el leucograma y la glucemia hubieran sido realizados en el momento del ingreso. Se utilizó la siguiente fórmula ILG = (glucemia [mg/dl] × leucocitos [$10^6$/l])/$1000^{10}$.

### Definición del evento y seguimiento

Se definió como variable dependiente a la muerte por todas las causas de los pacientes diagnosticados con IAM con elevación del segmento ST, durante el período 2011-2015. Esta información se obtuvo combinando una encuesta de seguimiento telefónico a los 365 días del ingreso con los datos del registro provincial de mortalidad, del Departamento de Estadística de la Dirección Provincial de Salud Pública.

### Consideraciones éticas

La realización del estudio fue aprobada por el Comité de Ética de la institución. Los datos personales de los pacientes no fueron publicados y se siguieron los principios establecidos en la Declaración de Helsinki.

### Análisis estadístico

Los pacientes fueron divididos en 3 grupos según los terciles del ILG. La prueba de Kolmogorov-Smirnov fue usada para evaluar la distribución normal de las variables cuantitativas, que se expresaron como media ± desviación estándar y se compararon mediante ANOVA; las que no presentaron distribución normal se expresan como mediana y rango intercuartílico; para su comparación se utilizaron las pruebas U de Mann-Whitney y Kruskal-Wallis.

Para determinar las diferencias entre los grupos establecidos, según variables cualitativas, se usaron las pruebas estadísticas Chi-cuadrado y la exacta de Fisher, según correspondiera. Con el fin de determinar el poder discriminatorio del ILG como predictor de mortalidad al año se evaluó el área bajo la curva de características operativas del receptor (ROC), y se identificó el punto de corte óptimo. Se construyeron curvas de supervivencia utilizando el método de Kaplan-Meier, según los terciles y punto de corte de ILG; la supervivencia de estos grupos fue comparada a través del *test* Log-Rank.

Para determinar aquellos factores que de manera independiente se asociaron a la mortalidad, se utilizó la regresión de Cox univariable y multivariable. Se incluyeron en el modelo aquellas variables clínicamente significativas o posibles confusoras con independencia de su significación estadística, y aquellas que en el análisis univariable presentaron una significación p≤0,01. Se consideró estadísticamente significativo un valor de p bilateral <0,05.

Los datos fueron procesados con SPSS versión 20.0 y MedCalc versión 8.2.1, ambos para Windows.

## RESULTADOS

Se analizaron 344 pacientes consecutivos, la mayoría del sexo masculino (65,7%), y la mediana de la edad global fue de 68 años (rango intercuartílico 58-76). Destacan en los antecedentes personales que el 25% padecía de diabetes mellitus y había sufrido un IAM previo, el 64,2% presentaba hipertensión arterial y el 33,1% fumaba.

La mediana del ILG fue de 1,47. Se agruparon los pacientes según terciles de ILG que correspondieron a los percentiles 33 y 66, los cuales fueron 1,207 y 1,773, respectivamente. Al realizar un análisis de estos grupos, la mediana de la edad fue significativamente superior según aumentaba el ILG (**Tabla 1**). Las mujeres y los diabéticos se presentaron con una frecuencia significativamente mayor en los terciles más altos, mientras que los que tenían hábito de fumar predominaron en los más bajos. Otras características basales se detallan en la **tabla 1**.

En relación con las variables clínicas y de laboratorio al ingreso según terciles, no existieron diferencias en la tensión arterial sistólica y diastólica; sin embargo, la frecuencia cardíaca y los valores de glucemia, creatinina sérica, recuento de leucocitos, neutrófilos y linfocitos al ingreso fueron significativamente superiores en los pacientes de los terciles más altos. Igualmente estos grupos de pacientes presentaron peor clasificación Killip-Kimbal (> I). No se encontraron diferencias entre los pacientes de los distintos terciles en cuanto a los tratamientos de reperfusión coronaria (**Tabla 1**).

Durante la media de seguimiento de 278±8 días,

**Tabla 1.** Datos demográficos, clínicos, laboratorio y tratamiento.

| Variables | Global (n=344) | Valor del índice leucoglucémico (ILG) | | | p |
|---|---|---|---|---|---|
| | | Tercil 1 (n=114) | Tercil 2 (n=115) | Tercil 3 (n=115) | |
| **Antecedentes** | | | | | |
| Edad (años) | 68 [58-76] | 65 [55-74] | 69 [58-79] | 71 [61-77] | 0,006 |
| Sexo, femenino | 118 (34,3) | 28 (24,6) | 42 (36,5) | 48 (41,7) | 0,020 |
| Hipertensión arterial | 221 (64,2) | 65 (57,0) | 79 (68,7) | 77 (67,0) | 0,139 |
| Diabetes mellitus | 88 (25,6) | 11 (9,6) | 14 (12,2) | 63 (54,8) | 0,000 |
| Hábito de fumar | 114 (33,1) | 46 (40,4) | 41 (35,7) | 27 (23,5) | 0,020 |
| Infarto de miocardio previo | 86 (25) | 35 (30,7) | 26 (22,6) | 25 (21,7) | 0,225 |
| Fibrilación auricular | 11 (3,2) | 3 (2,6) | 4 (3,5) | 4 (3,5) | 1,000 |
| Angina | 96 (27,9) | 37 (32,5) | 28 (24,3) | 31 (27,0) | 0,378 |
| Insuficiencia cardíaca | 54 (15,7) | 13 (11,4) | 21 (18,3) | 20 (17,4) | 0,300 |
| **Datos clínicos y de laboratorio al ingreso** | | | | | |
| Frecuencia cardíaca (lpm) | 78 [68,5-90] | 74,5 [68-85] | 79 [67-98] | 84 [71-90] | 0,002 |
| TA sistólica (mmHg) | 120 [110-140] | 120 [110-140] | 120 [110-140] | 120 [100-140] | 0,195 |
| TA diastólica (mmHg) | 80 [70-85,5] | 80 [70-90] | 80 [70-90] | 70 [60-85] | 0,352 |
| Killip-Kimball > I | 141 (41,0) | 31 (27,2) | 48 (41,7) | 62 (53,9) | 0,000 |
| Leucocitos $mm^3$ | 11,2 [10,0-12,6] | 10,0 [8,6-11,0] | 12,0 [10,9-13,0] | 12,0 [10,4-13,2] | 0,000 |
| Neutrófilos $mm^3$* | 8,4±2,5 | 6,6±1,9 | 9,2±2,2 | 9,4±2,3 | 0,000 |
| Linfocitos $mm^3$** | 2,5±0,9 | 2,7±1,0 | 2,5±0,9 | 2,4±0,9 | 0,022 |
| Glucemia (mmol/L) | 6,8 [5,7-9,0] | 6,3 [5,5-8,2] | 6,8 [5,7-8,5] | 7,2 [5,8-12,3] | 0,011 |
| Creatinina (mmol/L)*** | 79,0 [65,0-103,0] | 77,0 [64,0-91,1] | 78,0 [64,0-103,0] | 93,0 [69,0-125,0] | 0,010 |
| **Tratamiento de reperfusión coronaria** | | | | | |
| Trombolisis | 151 (43,9) | 55 (48,2) | 44 (38,3) | 52 (45,2) | 0,295 |
| ICP | 51 (14,8) | 18 (15,8) | 19 (16,5) | 14 (12,2) | 0,611 |

Los datos se presentan como n (%), media ± desviación estándar o mediana [rango intercuartílico]. ICP, intervencionismo coronario percutáneo; ILG, índice leucoglucémico TA, tensión arterial.

* Disponible de 344 pacientes: 110 en Tercil 1 de ILG, 115 en Tercil 2 y 113 en Tercil 3.

** Disponible de 344 pacientes: 110 en Tercil 1 de ILG, 114 en Tercil 2 y 113 en Tercil 3.

*** Disponible de 344 pacientes: 100 en Tercil 1 de ILG, 107 en Tercil 2 y 106 en Tercil 3.

se registraron 88 muertes. La tasa de mortalidad fue de 25,6%, la cual se incrementó significativamente por terciles de ILG (p<0,0001) y alcanzó el 55,7% en el tercil 3 (**Figura 1**). La mediana de ILG entre los pacientes que sobrevivieron y fallecieron fue significativamente diferente, siendo mayor en los que fallecieron (1,34 *vs.* 2,18, respectivamente; p<0,0001).

El área bajo la curva del ILG fue de 0,715 (IC 95%: 0,664-0,762; p<0,0001). El valor de corte óptimo del ILG para predecir mortalidad fue 2,2; con una sensibilidad de 50% y especificidad de 85,9% (**Figura 2**).

Existieron diferencias significativas al comparar la supervivencia, que decreció según los terciles de ILG (p<0,0001). La supervivencia también fue significativamente menor (**Tabla 2** y **Figura 3**), en aquellos pacientes con un ILG > 2,2 (p<0,0001).

En el análisis multivariable, el ILG > 2,2 resultó un predictor de mortalidad al año por todas las causas (HR 3,562; IC 95%: 2,091-6,071; p<0,0001), independientemente de la edad, sexo, Killip-Kimball > I, tensión arterial sistólica, creatinina sérica y diabetes mellitus (**Tabla 3**).

## DISCUSIÓN

En el presente estudio se evaluó el valor pronóstico al plazo de un año del ILG en los pacientes con IAM con elevación del segmento ST. Varias investigaciones han confirmado la importancia del recuento de leucocitos y su diferencial como predictor de muerte y otros sucesos adversos a largo plazo. Núñez *et al*[6], en un estudio prospectivo en 1118 pacientes consecutivos con síndrome coronario agudo demuestra, durante un seguimiento promedio de 10 meses, que los pacientes con mayor conteo de glóbulos blancos en las primeras horas del ingreso poseen mayor probabilidad de fallecer. Otro estudio prospectivo[14] con 1037 pa-

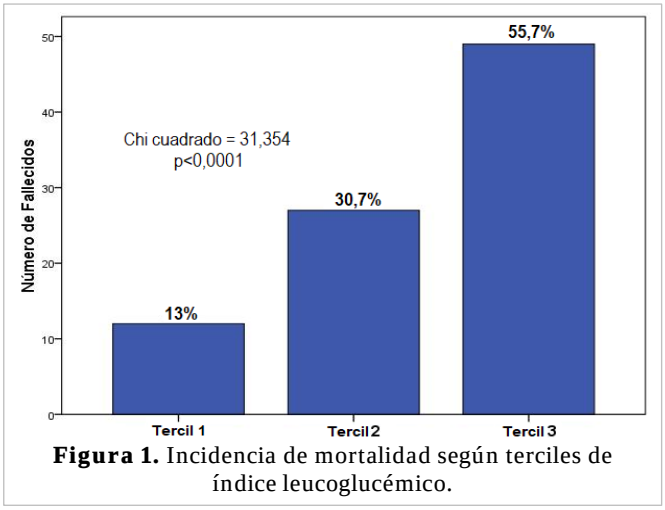


**Figura 1.** Incidencia de mortalidad según terciles de índice leucoglucémico.

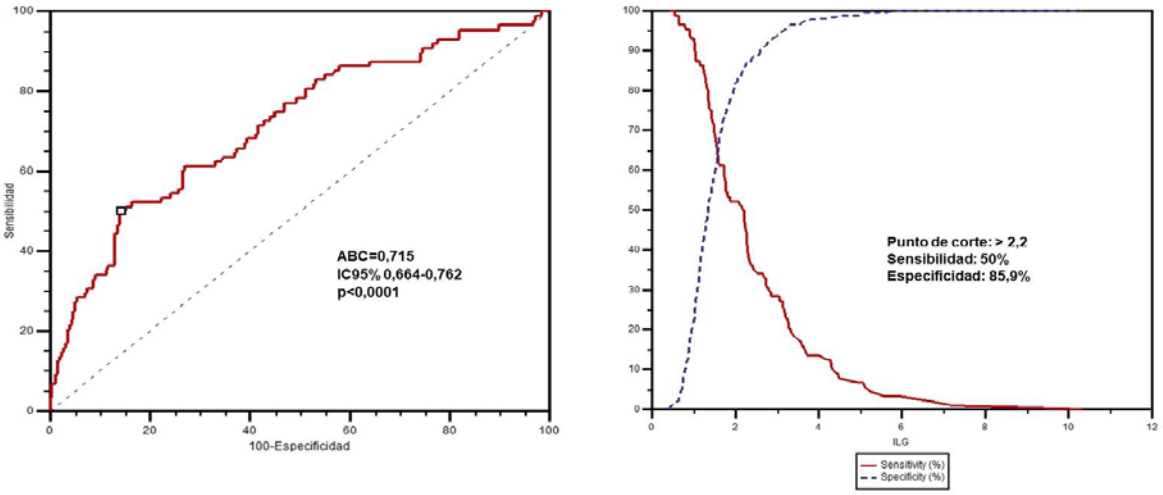


**Figura 2.** Curvas ROC que muestran la capacidad de discriminación y el punto de corte óptimo del índice leucoglucémico para predecir mortalidad. ABC, área bajo la curva; IC: intervalo de confianza.

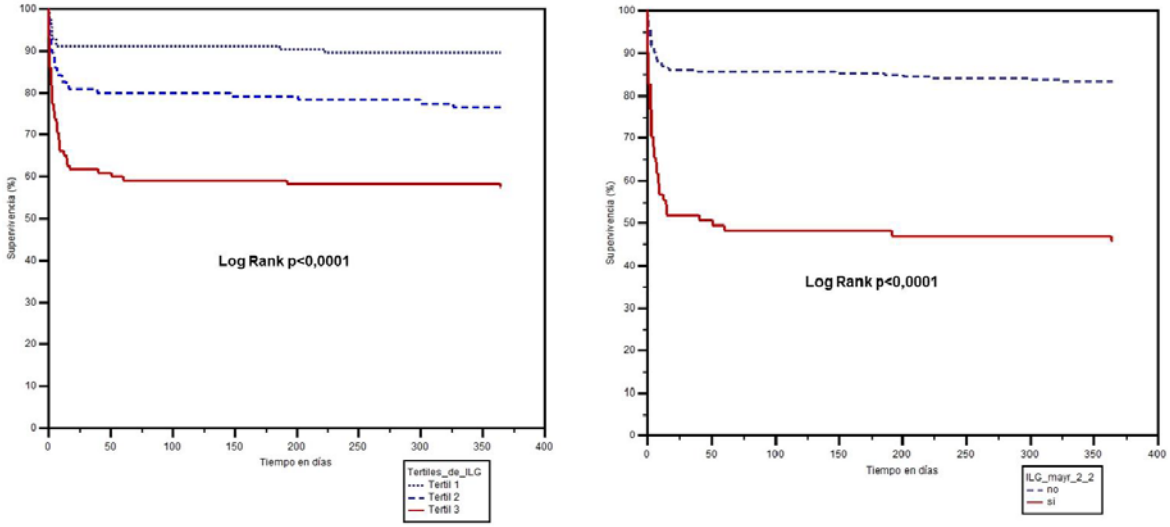


**Figura 3.** Curvas de supervivencia de Kaplan-Meier de los pacientes estudiados, a los 365 días, según terciles y punto de corte del índice leucoglucémico.

**Tabla 2.** Supervivencia según terciles y punto de corte del ILG.

| Variable | Media de supervivencia | Error típico | IC 95% | *p* (Log Rank) |
|---|---|---|---|---|
| Tercil 1 | 330,412 | 9,720 | 311,362-349,463 | <0,0001 |
| Tercil 2 | 288,983 | 13,417 | 262,685- 315,280 | |
| Tercil 3 | 217,313 | 16,363 | 185,242-249,384 | |
| ILG > 2,2 | 177,420 | 19,746 | 138,718- 216,122 | <0,0001 |
| ILG ≤ 2,2 | 309,962 | 7,842 | 294,592-325,332 | |
| Global | 278 753 | 8,171 | 262,739-294,767 | - |

ILG, índice leucoglucémico

**Tabla 3.** Modelos de riesgos proporcionales de Cox, uni y multivariable, para evaluar los factores predictores de mortalidad al año de los pacientes con IAM con elevación del segmento ST.

| Variables | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | *p* | *Hazard Ratio* | IC 95% | *p* | *Hazard Ratio* | IC 95% |
| ILG >2,2 | <0,0001 | 4,187 | 2,752-6,369 | <0,0001 | 3,562 | 2,091-6,071 |
| Killip Kimball>I | <0,0001 | 5,868 | 3,589-9,593 | <0,0001 | 3,502 | 2,083-5,888 |
| Sexo femenino | <0,0001 | 2,192 | 1,443-3,331 | 0,039 | 1,631 | 1,025-2,593 |
| Edad (años) | <0,0001 | 1,057 | 1,038-1,076 | <0,0001 | 1,040 | 1,020-1,061 |
| Creatinina (mmol/L) | <0,0001 | 1,005 | 1,003-1,006 | 0,002 | 1,004 | 1,001-1,006 |
| TA sistólica (mmHg) | <0,0001 | 0,972 | 0,964-0,981 | 0,002 | 0,986 | 0,977-0,995 |
| Diabetes mellitus | <0,0001 | 2,393 | 1,566-3,655 | 0,612 | 0,863 | 0,488-1,525 |

IC, intervalo de confianza; ILG, índice leucoglucémico; TA, tensión arterial.

cientes, y un tiempo de seguimiento medio de 23 meses, establece que el recuento leucocitario y su diferencial se asocia a un peor pronóstico. También se ha evaluado extensamente una arista de este marcador inflamatorio: el índice neutro-linfocitario, con sólidas evidencias que apoyan al conteo de glóbulos blancos y su diferencial como marcador independiente de mal pronóstico a largo plazo[15-21].

Se han propuesto numerosos mecanismos que explican dichos resultados. Los neutrófilos estimulados liberan radicales libres, enzimas proteolíticas y metabolitos del ácido araquidónico, los cuales aumentan el tamaño del infarto y llevan a la inestabilidad eléctrica del corazón mediante el daño endotelial, la activación de la cascada de la coagulación, la agregación leucocitaria y su deposición en las microarterias[2,22]. Las micropartículas derivadas de estos leucocitos polimorfonucleares activados pueden favorecer la cascada de la coagulación y perpetuar la formación de trombos, ya que pueden activar y favorecer la expresión de la P-selectina plaquetaria[23]. Además, niveles elevados de marcadores inflamatorios en sangre han sido observados en pacientes con insuficiencia cardíaca por varias causas, lo que sugiere la relación potencial con el fallo de bomba[24].

Por otra parte, la glucemia como marcador pronóstico a largo plazo en los pacientes con IAM también ha sido estudiada. En un valioso estudio con 11324 pacientes se demuestra que sus valores al ingreso constituyen un poderoso predictor de mortalidad a los 20 años de haber sufrido un IAM[25]. Planer *et al*[26], basados en los registros del ensayo clínico multinacional HORIZONS-AMI, establecen que la glucemia en las primeras 24 horas del ingreso es un predictor independiente de mortalidad a los 30 días y a los 3 años. Similar resultado se obtuvo en un estudio previo de Monteiro *et al*[27].

La hiperglucemia se relaciona con el tamaño del infarto, una clase Killip-Kimball mayor, baja fracción de eyección ventricular izquierda, *shock* cardiogénico, necesidad de resucitación por parada cardiorrespiratoria y concentraciones aumentadas de marcadores de necrosis miocárdica[28,29]. El aumento,

durante la hiperglucemia, de factores vasoconstrictores e inflamatorios, contribuye al daño de la función endotelial e incrementa la producción de radicales libres con el consiguiente estrés oxidativo[30]. Además, existe un estado de resistencia insulínica en el cual la lipólisis provoca liberación de ácidos grasos libres y estos dificultan el transporte de glucosa al interior de la célula miocárdica, y su oxidación genera aniones superóxido[8]. También produce una alteración en el metabolismo plaquetario y cambios en los mecanismos de señalización intraplaquetaria, que pueden contribuir al desarrollo de las complicaciones aterotrombóticas[31].

La evidencia teórica y práctica de los componentes del ILG por separado, como factores de peor pronóstico a corto y largo plazos, sugiere la lógica asociación de estos en un índice. Previas observaciones han demostrado que el ILG constituye un marcador de mal pronóstico durante la estadía hospitalaria. Quiroga *et al*[10] fueron los primeros en asociar el ILG a muerte y complicaciones durante la estadía hospitalaria, mientras que Benítez Díaz y colaboradores[13] fueron capaces de reproducir sus resultados pero con un período de seguimiento de 30 días. Entre otras investigaciones que confirman el valor pronóstico del ILG mediante análisis multivariable[11,12], destaca la de Hirschson *et al*[12] al analizar un total de 405 pacientes en 87 instituciones argentinas. Seoane *et al*[32] en otro contexto clínico, el postoperatorio de cirugía cardíaca, también demuestran –en 2743 pacientes– la utilidad del ILG como predictor de mala evolución intrahospitalaria.

No obstante, ninguno de los autores citados analiza el valor pronóstico del ILG para predecir mortalidad más allá de los 30 días; cuestión que evalúa la presente investigación y lo identifica como predictor independiente de mortalidad al año, después de ajustar otras variables de reconocido valor pronóstico. Además, en este trabajo se demuestra por primera vez que el mayor ILG es un buen predictor de menor supervivencia a los 365 días en los pacientes con IAM.

El punto de corte óptimo obtenido por curva ROC para predecir mortalidad al año fue de 2,2. Estos resultados difieren con el resto de las investigaciones analizadas. Quiroga *et al*[10], León-Aliz *et al*[11], Hirchson Prado *et al*[12] y Seoane *et al*[32] hallaron un valor de corte óptimo de 1,6; 1,158; 1,00 y 2,0, respectivamente. Estas diferencias pueden ser atribuidas fundamentalmente al período de análisis ya que todos evalúan el valor pronóstico del ILG a corto plazo, con muestras heterogéneas en cuanto a su tamaño y composición, y con objetivos finales primarios diferentes.

### Limitaciones del estudio

Se trata de la experiencia de una sola institución y el tamaño de la muestra es relativamente pequeño, aunque esto no impidió arribar a resultados sólidos. No se dispuso de los datos de la fracción de eyección del ventrículo izquierdo en la totalidad de la muestra, el estado de reperfusión miocárdica, ni la cantidad y gravedad de los vasos coronarios afectados. Además, la baja disponibilidad de intervención coronaria percutánea primaria influye en la pobre supervivencia intrahospitalaria de los pacientes, lo que determina la ocurrencia de menores eventos finales tras el alta hospitalaria.

## CONCLUSIONES

Los resultados que se derivan de este trabajo apoyan el basamento teórico y práctico del índice leucoglucémico como predictor de episodios adversos al año, en el contexto del infarto agudo de miocardio. Su sencillez, amplia disponibilidad, bajo costo y el hecho de ser parte de los exámenes paraclínicos de rutina que se realizan al momento del ingreso, en pacientes con síndrome coronario agudo, avalan aún más su potencial aplicación en la estratificación temprana de riesgo. Futuras investigaciones multicéntricas y con mayores muestras son necesarias para confirmar las observaciones realizadas, así como la capacidad pronóstica del índice leucoglucémico en asociación con escalas de riesgo.

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# The leucoglycaemic index is a predictor of one-year all-cause mortality in Cuban patients with ST-segment elevation acute myocardial infarction

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**Acronyms**
**AMI:** acute myocardial infarction
**LGI:** leuko-glycaemic index

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## ABSTRACT

*Introduction:* The leuko-glycaemic index has been proposed as a prognostic marker of death in patients with acute myocardial infarction, but there is uncertainty surrounding its prognostic value to predict one-year mortality.

*Objectives:* The aim of this study was to determine the prognostic value of leuko-glycaemic index for one-year mortality in Cuban patients with ST-segment elevation myocardial infarction.

*Method:* The data were obtained from the medical records and all cause one-year deaths was the primary endpoint. The leuko-glycaemic index was calculated from measurements at admission. The patients were divided into leuko-glycaemic index tertiles to be evaluated. Receiver operating characteristics and Kaplan-Meier survival curves were performed. Cox regression model was used for all multivariable analysis.

*Results:* Three hundred and forty-four patients were assessed (median age, 68 years; 65.7% males; 25.6% diabetic). The mortality rate was 25.6%, being significantly higher in the upper tertile (55.7%, p<0.0001). The deceased patients presented a median of leuko-glycaemic index significantly higher than the survivors (2.18 and 1.34 respectively, p<0.0001). The area under the curve for leuko-glycaemic index was 0.715 and its cut-off value was 2.2. Any leuko-glycaemic index value higher than 2.2 was associated with significantly lower survival (177 vs. 309 days, p<0.0001) and it was an independent predictor of mortality (HR=3.56, CI 95%, 2.09-6.07, p<0.0001).

*Conclusions:* The leuko-glycaemic index is a good predictor for all cause one-year mortality in patients with ST-segment elevation myocardial infarction.

*Keywords:* Leuko-glycaemic index, Myocardial infarction, Mortality, Survival, Leukocytes, Blood glucose

## *El índice leucoglucémico es un predictor de mortalidad por todas las causas al año en pacientes cubanos con infarto agudo de miocardio con elevación del segmento ST*

## RESUMEN

*Introducción: El índice leucoglucémico (ILG) ha sido propuesto como marcador*

*pronóstico de muerte en pacientes con infarto agudo de miocardio; sin embargo, no existe evidencia sobre su valor pronóstico al año.*
*Objetivo: El objetivo del estudio fue determinar el valor pronóstico del ILG en la mortalidad al año de pacientes cubanos con infarto agudo de miocardio con elevación del segmento ST.*
*Método: Los datos fueron obtenidos de las historias clínicas y el objetivo primario fue la muerte por todas las causas al año. El ILG se calculó con los valores al ingreso. Para el análisis se dividieron los pacientes en terciles de ILG, se construyeron curvas de características operativas del receptor y de supervivencia de Kaplan-Meier. Para el análisis multivariable se utilizó la regresión de Cox.*
*Resultados: Se analizaron 344 pacientes (mediana de edad, 68 años; el 65,7% masculino; un 25,6% diabéticos). La mortalidad fue de 25,6% y fue significativamente mayor en el tercil superior (55,7%; p<0,0001). Los pacientes fallecidos presentaron una mediana de ILG significativamente mayor que los sobrevivientes (2,18 y 1,34, respectivamente; p<0,0001). El área bajo la curva del ILG fue de 0,715 y el punto de corte: 2,2. Un valor de ILG mayor de 2,2 se asoció a una supervivencia significativamente menor (177 vs. 309 días; p<0,0001) y fue un predictor independiente de mortalidad (HR=3,56; IC 95%, 2,09-6,07; p<0,0001).*
*Conclusiones: El índice leucoglucémico es buen predictor de mortalidad al año, por todas las causas, en pacientes con infarto agudo de miocardio con elevación del segmento ST.*
*Palabras clave: Índice leucoglucémico, Infarto de miocardio, Mortalidad, Supervivencia, Leucocitos, Glucemia*

## INTRODUCTION

Cardiovascular diseases have progressively increased their presence throughout the world, in such a way that they have become the leading cause of mortality. Despite significant improvements in reperfusion strategies and medical therapy, acute myocardial infarction (AMI) remains associated with significant morbidity and mortality[1].

Inflammation plays an important role in the development of atherosclerotic disease and coronary thrombosis[2]. Previous studies have shown that elevated levels of inflammatory markers are associated with the severity of coronary disease and with a worse prognosis[3-5]. Despite the existence of novel markers (interleukins, C-reactive protein, homocysteine, natriuretic peptides, fibrinogen, among others), counting leukocytes and their differential components is a rapid, universal and inexpensive tool to establish both prognosis and possible management[6,7]. Moreover, hyperglycemia caused by an inflammatory and adrenergic response to ischemic stress is frequent and constitutes an independent prognostic factor of death and complications in acute coronary syndrome[8,9].

The association of these 2 parameters in the leuko-glycaemic index (LGI) has been proposed as a prognostic marker of in-hospital death and complications in AMI patients[10-13]. However, it is still necessary to reproduce such results in more studies, as well as to evaluate their significance after one year. Hence, the objective of this study was to determine the prognostic value of LGI in all-cause mortality per year in Cuban patients with ST-segment elevation AMI.

## METHOD

### Study population

Patients admitted to the Hospital Universitario Arnaldo Milián Castro, Villa Clara (Cuba) were included, with a diagnosis of ST-segment elevation AMI in the period between January 2011 and December 2015. Those with presence of systemic hematological/ inflammatory infectious diseases, that may alter blood count, as well as patients with an unknown condition at the end of the follow-up (alive or deceased) were excluded.

### Variables

The data were obtained from the medical records. The information regarding personal data, background (age, sex, smoking habit, hypertension, diabetes mellitus, previous AMI, atrial fibrillation, chest pain and heart failure), clinical and laboratory tests at admission (heart rate, systolic and diastolic blood pressure, Killip-Kimball classification, blood count,

neutrophils, lymphocytes, glycemia and creatinine), and coronary reperfusion treatment (thrombolysis, percutaneous coronary intervention or both). The percutaneous coronary intervention performed during admission was taken into account since in our center it is not performed as a primary way. Thrombolysis was performed with recombinant streptokinase.

### Leuko-glycaemic index

For the calculation of LGI, we considered that the leukogram and blood glucose levels were performed at admission. The following formula LGI = (glycemia [mg/dl] × leukocytes [$10^6$/l])/1000 was used[10].

### Definition of the event and follow-up

We defined as a dependent variable death from all causes of patients diagnosed with ST-segment elevation AMI during the 2011-2015 period. This information was obtained by combining a telephone follow-up survey 365 days after admission with data from the provincial mortality registry, from the Statistics Department of the Provincial Directorate of Public Health.

### Ethical considerations

The study was approved by the Ethics Committee of the institution. The patients' personal data were not published and the principles established in the Declaration of Helsinki were followed.

### Statistical analysis

The patients were divided into 3 groups according to the LGI tertiles. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the quantitative variables, which were expressed as mean ± standard deviation and compared by ANOVA; those that did not present a normal distribution are expressed as median and interquartile range; the Mann-Whitney and Kruskal-Wallis U tests were used for comparison.

To determine the differences between the established groups, according to qualitative variables, Chi-square and Fisher's exact tests were used, as appropriate. In order to determine the LGI discriminatory power as a predictor of mortality per year, the area under receiver operating characteristic (ROC) curve was evaluated, and the optimal cut-off point was identified. Survival curves were constructed using the Kaplan-Meier method, according to the tertiles and LGI cut-off point; the survival of these groups was compared through the Log-Rank test.

To determine those factors independently associated with mortality, univariate and multivariable Cox regression was used. We included in the model those clinically significant variables or possible confounders regardless of their statistical significance, and those that in the univariate analysis presented a significance p≤0.01. A bilateral p value <0.05 was considered statistically significant.

The data was processed with SPSS version 20.0 and MedCalc version 8.2.1, both for Windows.

## RESULTS

A total of 344 consecutive patients were analyzed, most of them were male (65.7%), and the median of the overall age was 68 years (interquartile range 58-76). The personal history shows that 25% had diabetes mellitus and had suffered a previous AMI, 64.2% had high blood pressure and 33.1% smoked.

The median LGI was 1.47. The patients were grouped according to the LGI tertiles corresponding to the 33rd and 66th percentiles, which were 1.207 and 1.773, respectively. When analyzing these groups, the median age was significantly higher as the LGI increased (**Table 1**). Women and diabetics presented with a significantly higher frequency in higher tertiles, while those with smoking habit predominated in the lowest. Other baseline characteristics are detailed in **table 1**.

Regarding the clinical and laboratory variables at admission according to tertiles, there were no differences in systolic and diastolic blood pressure; however, the heart rate, blood glucose, serum creatinine, blood count, neutrophil and lymphocyte count at admission were significantly higher in patients in the higher tertiles. Similarly, these groups of patients presented worse Killip-Kimbal classification (>I). No differences were found between the patients from different tertiles in terms of coronary reperfusion treatments (**Table 1**).

During mean follow-up of 278 ± 8 days, 88 deaths were recorded. The mortality rate was 25.6%, which was significantly increased by LGI tertiles (p<0.0001) and reached 55.7% in tertile 3 (**Figure 1**). The median LGI among patients who survived and died was significantly different, being higher in those who died (1.34 vs. 2.18, respectively, p<0.0001).

The area under the LGI curve was 0.715 (95% CI:

**Table 1.** Demographic, clinical, laboratory and treatment data.

| Variables | Global (n=344) | Value of the leuko-glycemic index (LGI) | | | *p* |
|---|---|---|---|---|---|
| | | Tertil 1 (n=114) | Tertil 2 (n=115) | Tertil 3 (n=115) | |
| **Background** | | | | | |
| Age (years) | 68 [58-76] | 65 [55-74] | 69 [58-79] | 71 [61-77] | 0.006 |
| Sex. female | 118 (34.3) | 28 (24.6) | 42 (36.5) | 48 (41.7) | 0.020 |
| Hypertension | 221 (64.2) | 65 (57.0) | 79 (68.7) | 77 (67.0) | 0.139 |
| Diabetes mellitus | 88 (25.6) | 11 (9.6) | 14 (12.2) | 63 (54.8) | 0.000 |
| Smoking habit | 114 (33.1) | 46 (40.4) | 41 (35.7) | 27 (23.5) | 0.020 |
| Previous myocardial infarction | 86 (25) | 35 (30.7) | 26 (22.6) | 25 (21.7) | 0.225 |
| Atrial Fibrillation | 11 (3.2) | 3 (2.6) | 4 (3.5) | 4 (3.5) | 1.000 |
| Chest Pain | 96 (27.9) | 37 (32.5) | 28 (24.3) | 31 (27.0) | 0.378 |
| Heart failure | 54 (15.7) | 13 (11.4) | 21 (18.3) | 20 (17.4) | 0.300 |
| **Clinical and laboratory data on admission** | | | | | |
| Heart rate (bpm) | 78 [68.5-90] | 74.5 [68-85] | 79 [67-98] | 84 [71-90] | 0.002 |
| Systolic BP (mmHg) | 120 [110-140] | 120 [110-140] | 120 [110-140] | 120 [100-140] | 0.195 |
| Diastolic BP (mmHg) | 80 [70-85.5] | 80 [70-90] | 80 [70-90] | 70 [60-85] | 0.352 |
| Killip-Kimball>I | 141 (41.0) | 31 (27.2) | 48 (41.7) | 62 (53.9) | 0.000 |
| Leukocytes $mm^3$ | 11.2 [10.0-12.6] | 10.0 [8.6-11.0] | 12.0 [10.9-13.0] | 12.0 [10.4-13.2] | 0.000 |
| Neutrophils $mm^3$* | 8.4±2.5 | 6.6±1.9 | 9.2±2.2 | 9.4±2.3 | 0.000 |
| Lymphocytes $mm^3$** | 2.5±0.9 | 2.7±1.0 | 2.5±0.9 | 2.4±0.9 | 0.022 |
| Glycemia (mmol/L) | 6.8 [5.7-9.0] | 6.3 [5.5-8.2] | 6.8 [5.7-8.5] | 7.2 [5.8-12.3] | 0.011 |
| Creatinine (mmol/L)*** | 79.0 [65.0-103.0] | 77.0 [64.0-91.1] | 78.0 [64.0-103.0] | 93.0 [69.0-125.0] | 0.010 |
| **Coronary reperfusion treatment** | | | | | |
| Thrombolysis | 151 (43.9) | 55 (48.2) | 44 (38.3) | 52 (45.2) | 0.295 |
| PCI | 51 (14.8) | 18 (15.8) | 19 (16.5) | 14 (12.2) | 0.611 |

The data are presented as n (%), mean ± standard deviation, or median [interquartile range]. BP, blood pressure; LGI, leuko-glycaemic index; PCI, percutaneous coronary intervention.
* Available from 344 patients: 110 in Tertil 1 of LGI, 115 in Tertil 2 and 113 in Tertil 3.
** Available from 344 patients: 110 in Tertil 1 of LGI, 114 in Tertil 2 and 113 in Tertil 3.
*** Available from 344 patients: 100 in Tertil 1 of LGI, 107 in Tertil 2 and 106 in Tertil 3.

0.664-0.762, p<0.0001). The optimal LGI cut-off value to predict mortality was 2.2; with a 50% sensitivity and an 85.9% specificity (**Figure 2**).

There were significant differences when comparing survival, which decreased according to the LGI tertiles (p<0.0001). Survival was also significantly lower (**Table 2** and **Figure 3**), in those patients with an LGI>2.2 (p<0.0001).

In the multivariate analysis, LGI>2.2 was a predictor of one-year mortality for all causes (HR 3.562, 95% CI: 2.091-6.071, p<0.0001), regardless of age, sex, Killip-Kimball>I, systolic blood pressure, serum creatinine and diabetes mellitus (**Table 3**).

## DISCUSSION

In the present study, the prognostic value at 1-year LGI was evaluated in patients with ST-segment elevation AMI. Several investigations have confirmed the importance of blood count and its differential as a predictor of death and other long-term adverse

events. Núñez *et al*[6], in a prospective study of 1118 consecutive patients with acute coronary syndrome, showed, during an average 10 months follow-up, that patients with a higher white blood cell count in the first hours of admission were more likely to die. Another prospective study[14] with 1037 patients, and a mean 23 months follow-up, claims that blood count and its differential is associated with a worse prognosis. An edge of this inflammatory marker has also been extensively evaluated: the neutral-lymphocyte index, with solid evidence supporting the white blood cell count and its differential as an independent marker of poor long-term prognosis[15-21].

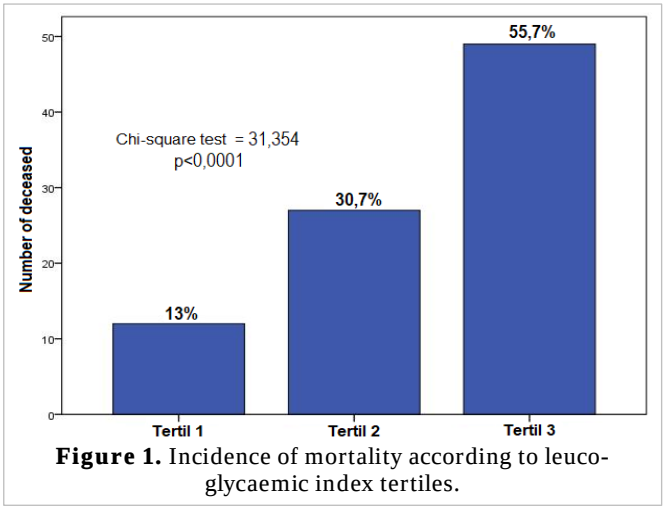


**Figure 1.** Incidence of mortality according to leuco-glycaemic index tertiles.

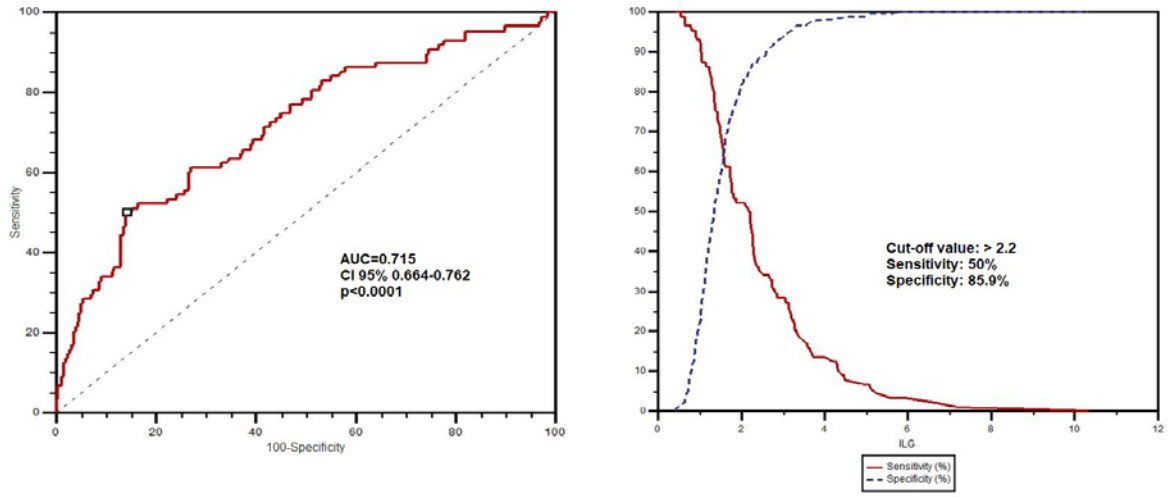


**Figure 2.** ROC curves showing the discrimination capacity and the optimal cut-off point of the leuco-glycaemic index to predict mortality. AUC, area under the curve; CI: confidence interval.

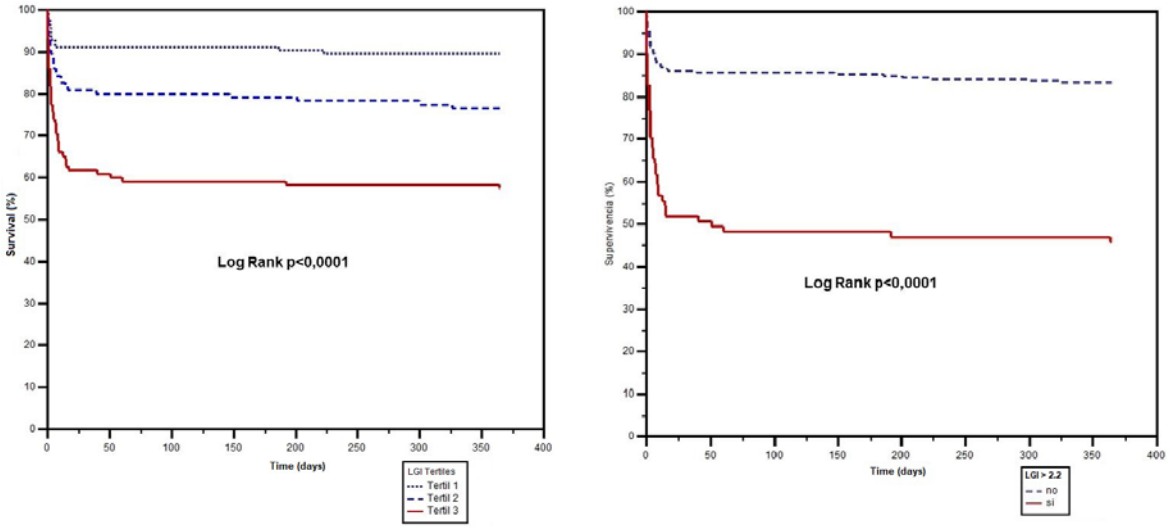


**Figure 3.** Kaplan-Meier survival curves of the patients studied, at 365 days, according to tertiles and leuco-glycaemic index cut-off point.

**Table 2.** Survival according to tertiles and LGI cut-off point.

| Variable | Survival average | Typical error | CI 95% | *p* (Log Rank) |
|---|---|---|---|---|
| Tertil 1 | 330.412 | 9.720 | 311.362-349.463 | |
| Tertil 2 | 288.983 | 13.417 | 262.685- 315.280 | <0.0001 |
| Tertil 3 | 217.313 | 16.363 | 185.242-249.384 | |
| LGI>2.2 | 177.420 | 19.746 | 138.718- 216.122 | <0.0001 |
| LGI≤2.2 | 309.962 | 7.842 | 294.592-325.332 | |
| Global | 278 753 | 8.171 | 262.739-294.767 | - |

LGI, leuko-glycaemic index

**Table 3.** Cox, uni and multivariable proportional hazards models to evaluate the predictors of mortality per year of patients with ST-segment elevation AMI.

| Variables | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | *p* | *Hazard Ratio* | CI 95% | *p* | *Hazard Ratio* | CI 95% |
| LGI >2.2 | <0.0001 | 4.187 | 2.752-6.369 | <0.0001 | 3.562 | 2.091-6.071 |
| Killip Kimball>I | <0.0001 | 5.868 | 3.589-9.593 | <0.0001 | 3.502 | 2.083-5.888 |
| Female sex | <0.0001 | 2.192 | 1.443-3.331 | 0.039 | 1.631 | 1.025-2.593 |
| Age (years) | <0.0001 | 1.057 | 1.038-1.076 | <0.0001 | 1.040 | 1.020-1.061 |
| Creatinine (mmol/L) | <0.0001 | 1.005 | 1.003-1.006 | 0.002 | 1.004 | 1.001-1.006 |
| Systolic BP (mmHg) | <0.0001 | 0.972 | 0.964-0.981 | 0.002 | 0.986 | 0.977-0.995 |
| Diabetes mellitus | <0.0001 | 2.393 | 1.566-3.655 | 0.612 | 0.863 | 0.488-1.525 |

BP, blood pressure; CI, confidence interval; LGI, leuko-glycaemic index.

Many mechanisms have been proposed that explain such results. Stimulated neutrophils release free radicals, proteolytic enzymes and arachidonic acid metabolites, which increase the infarction size and lead to electric instability of the heart through endothelial damage, coagulation cascade activation, leukocyte aggregation and its deposition in microarteries[2,22]. Microparticles derived from these activated polymorphonuclear leukocytes can favor the coagulation cascade and perpetuate thrombi formation, since they can activate and favor the expression of P-selectin on the platelet[23]. In addition, elevated levels of inflammatory markers in the blood have been observed in patients with heart failure for several reasons, suggesting the strong relationship with pump failure[24].

On the other hand, glycemia as a long-term prognostic marker in patients with AMI has also been studied. A valuable study with 11324 patients shows that their admission values are a powerful predictor of mortality 20 years after having suffered an AMI[25]. Planer *et al*[26], based on the records of the multinational clinical trial HORIZONS-AMI, establish that glycemia in the first 24 hours of admission is an independent predictor of mortality at 30 days and at 3 years. Similar results were obtained in a previous study by Monteiro *et al*[27].

Hyperglycaemia is related to the size of the infarction, a greater Killip-Kimball class, low left ventricular ejection fraction, cardiogenic shock, need for resuscitation due to cardiorespiratory arrest and increased concentrations of myocardial necrosis markers[28,29]. The increase of vasoconstrictive and inflammatory factors during hyperglycemia contributes to the damage of endothelial function and increases the production of free radicals with the consequent oxidative stress[30]. In addition, there is a state of insulin resistance in which lipolysis causes free fatty acids to be released which hinders the transportation of glucose into the myocardial cell, and its oxidation generates superoxide anions[8]. It also produces an alteration in platelet metabolism

and changes in the intraplatelet signaling mechanisms, which may contribute to the development of atherothrombotic complications[31].

The theoretical and practical evidence of the LGI components separately, as factors of worse short and long term prognosis, suggests the logical association of these in an index. Previous observations have shown that LGI constitutes a marker of poor prognosis during hospital stay. Quiroga *et al*[10] were the first to associate LGI with death and complications during hospital stay, while Benítez Díaz *et al*[13] were able to reproduce their results but with a 30-day follow-up period. Among other studies confirming the prognostic value of LGI through multivariate analysis[11,12], highlights that of Hirschson *et al*[12] when analyzing a total of 405 patients in 87 Argentinians institutions. Seoane *et al*[32] in another clinical context (postoperative period of cardiac surgery) also demonstrate −in 2743 patients− the usefulness of LGI as a predictor of poor in-hospital outcome.

However, none of the cited authors analyzes the prognostic value of LGI to predict mortality beyond 30 days; which is evaluated in the present investigation and identified as an independent predictor of mortality per year, after adjusting other variables with recognized prognostic value. In addition, this work also demonstrates for the first time that the higher LGI is a good predictor of shorter survival at 365 days in patients with AMI.

The optimal cut-off point obtained by the ROC curve to predict mortality at one year was 2.2. These results differ with the rest of the analyzed researches. Quiroga *et al*[10], León-Aliz *et al*[11], Hirchson Prado *et al*[12] and Seoane *et al*[32] found an optimal cut-off value of 1.6; 1,158; 1.00 and 2.0, respectively. These differences can be attributed mainly to the analysis period and that all assess the prognostic value of LGI in the short term, with heterogeneous samples in terms of its size and composition, and with different primary end objectives.

### Study limitations

It is the experience of a single institution and the size of the sample is relatively small, although this did not prevent obtaining solid results. No data were available on the left ventricular ejection fraction, myocardial reperfusion state, or quantity and severity of the affected coronary vessels in the entire sample. In addition, the low availability of primary percutaneous coronary intervention influences the poor in-hospital survival of patients, which determines the occurrence of fewer final events after hospital discharge.

## CONCLUSIONS

The results from this work support the theoretical and practical basis of the leuko-glycaemic index as a predictor of adverse events per year, in the context of acute myocardial infarction. Its simplicity, wide availability, low cost and the fact of being part of the paraclinical routine examinations performed at admission, in patients with acute coronary syndrome, further support its potential application in early risk stratification. Future larger samples multi-center studies are necessary to confirm our observations, as well as the prognostic capacity of the leucoglycaemic index in association with risk scales.

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# The leucoglycaemic index is a predictor of one-year all-cause mortality in Cuban patients with ST-segment elevation acute myocardial infarction

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**Acronyms**
**AMI:** acute myocardial infarction
**LGI:** leuko-glycaemic index

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## ABSTRACT

*Introduction:* The leuko-glycaemic index has been proposed as a prognostic marker of death in patients with acute myocardial infarction, but there is uncertainty surrounding its prognostic value to predict one-year mortality.

*Objectives:* The aim of this study was to determine the prognostic value of leuko-glycaemic index for one-year mortality in Cuban patients with ST-segment elevation myocardial infarction.

*Method:* The data were obtained from the medical records and all cause one-year deaths was the primary endpoint. The leuko-glycaemic index was calculated from measurements at admission. The patients were divided into leuko-glycaemic index tertiles to be evaluated. Receiver operating characteristics and Kaplan-Meier survival curves were performed. Cox regression model was used for all multivariable analysis.

*Results:* Three hundred and forty-four patients were assessed (median age, 68 years; 65.7% males; 25.6% diabetic). The mortality rate was 25.6%, being significantly higher in the upper tertile (55.7%, p<0.0001). The deceased patients presented a median of leuko-glycaemic index significantly higher than the survivors (2.18 and 1.34 respectively, p<0.0001). The area under the curve for leuko-glycaemic index was 0.715 and its cut-off value was 2.2. Any leuko-glycaemic index value higher than 2.2 was associated with significantly lower survival (177 vs. 309 days, p<0.0001) and it was an independent predictor of mortality (HR=3.56, CI 95%, 2.09-6.07, p<0.0001).

*Conclusions:* The leuko-glycaemic index is a good predictor for all cause one-year mortality in patients with ST-segment elevation myocardial infarction.

*Keywords:* Leuko-glycaemic index, Myocardial infarction, Mortality, Survival, Leukocytes, Blood glucose

## *El índice leucoglucémico es un predictor de mortalidad por todas las causas al año en pacientes cubanos con infarto agudo de miocardio con elevación del segmento ST*

## RESUMEN

*Introducción: El índice leucoglucémico (ILG) ha sido propuesto como marcador*

*pronóstico de muerte en pacientes con infarto agudo de miocardio; sin embargo, no existe evidencia sobre su valor pronóstico al año.*
*Objetivo: El objetivo del estudio fue determinar el valor pronóstico del ILG en la mortalidad al año de pacientes cubanos con infarto agudo de miocardio con elevación del segmento ST.*
*Método: Los datos fueron obtenidos de las historias clínicas y el objetivo primario fue la muerte por todas las causas al año. El ILG se calculó con los valores al ingreso. Para el análisis se dividieron los pacientes en terciles de ILG, se construyeron curvas de características operativas del receptor y de supervivencia de Kaplan-Meier. Para el análisis multivariable se utilizó la regresión de Cox.*
*Resultados: Se analizaron 344 pacientes (mediana de edad, 68 años; el 65,7% masculino; un 25,6% diabéticos). La mortalidad fue de 25,6% y fue significativamente mayor en el tercil superior (55,7%; p<0,0001). Los pacientes fallecidos presentaron una mediana de ILG significativamente mayor que los sobrevivientes (2,18 y 1,34, respectivamente; p<0,0001). El área bajo la curva del ILG fue de 0,715 y el punto de corte: 2,2. Un valor de ILG mayor de 2,2 se asoció a una supervivencia significativamente menor (177 vs. 309 días; p<0,0001) y fue un predictor independiente de mortalidad (HR=3,56; IC 95%, 2,09-6,07; p<0,0001).*
*Conclusiones: El índice leucoglucémico es buen predictor de mortalidad al año, por todas las causas, en pacientes con infarto agudo de miocardio con elevación del segmento ST.*
*Palabras clave: Índice leucoglucémico, Infarto de miocardio, Mortalidad, Supervivencia, Leucocitos, Glucemia*

## INTRODUCTION

Cardiovascular diseases have progressively increased their presence throughout the world, in such a way that they have become the leading cause of mortality. Despite significant improvements in reperfusion strategies and medical therapy, acute myocardial infarction (AMI) remains associated with significant morbidity and mortality[1].

Inflammation plays an important role in the development of atherosclerotic disease and coronary thrombosis[2]. Previous studies have shown that elevated levels of inflammatory markers are associated with the severity of coronary disease and with a worse prognosis[3-5]. Despite the existence of novel markers (interleukins, C-reactive protein, homocysteine, natriuretic peptides, fibrinogen, among others), counting leukocytes and their differential components is a rapid, universal and inexpensive tool to establish both prognosis and possible management[6,7]. Moreover, hyperglycemia caused by an inflammatory and adrenergic response to ischemic stress is frequent and constitutes an independent prognostic factor of death and complications in acute coronary syndrome[8,9].

The association of these 2 parameters in the leuko-glycaemic index (LGI) has been proposed as a prognostic marker of in-hospital death and complications in AMI patients[10-13]. However, it is still necessary to reproduce such results in more studies, as well as to evaluate their significance after one year. Hence, the objective of this study was to determine the prognostic value of LGI in all-cause mortality per year in Cuban patients with ST-segment elevation AMI.

## METHOD

### Study population

Patients admitted to the Hospital Universitario Arnaldo Milián Castro, Villa Clara (Cuba) were included, with a diagnosis of ST-segment elevation AMI in the period between January 2011 and December 2015. Those with presence of systemic hematological/ inflammatory infectious diseases, that may alter blood count, as well as patients with an unknown condition at the end of the follow-up (alive or deceased) were excluded.

### Variables

The data were obtained from the medical records. The information regarding personal data, background (age, sex, smoking habit, hypertension, diabetes mellitus, previous AMI, atrial fibrillation, chest pain and heart failure), clinical and laboratory tests at admission (heart rate, systolic and diastolic blood pressure, Killip-Kimball classification, blood count,

neutrophils, lymphocytes, glycemia and creatinine), and coronary reperfusion treatment (thrombolysis, percutaneous coronary intervention or both). The percutaneous coronary intervention performed during admission was taken into account since in our center it is not performed as a primary way. Thrombolysis was performed with recombinant streptokinase.

### Leuko-glycaemic index

For the calculation of LGI, we considered that the leukogram and blood glucose levels were performed at admission. The following formula LGI = (glycemia [mg/dl] × leukocytes [$10^6$/l])/1000 was used[10].

### Definition of the event and follow-up

We defined as a dependent variable death from all causes of patients diagnosed with ST-segment elevation AMI during the 2011-2015 period. This information was obtained by combining a telephone follow-up survey 365 days after admission with data from the provincial mortality registry, from the Statistics Department of the Provincial Directorate of Public Health.

### Ethical considerations

The study was approved by the Ethics Committee of the institution. The patients' personal data were not published and the principles established in the Declaration of Helsinki were followed.

### Statistical analysis

The patients were divided into 3 groups according to the LGI tertiles. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the quantitative variables, which were expressed as mean ± standard deviation and compared by ANOVA; those that did not present a normal distribution are expressed as median and interquartile range; the Mann-Whitney and Kruskal-Wallis U tests were used for comparison.

To determine the differences between the established groups, according to qualitative variables, Chi-square and Fisher's exact tests were used, as appropriate. In order to determine the LGI discriminatory power as a predictor of mortality per year, the area under receiver operating characteristic (ROC) curve was evaluated, and the optimal cut-off point was identified. Survival curves were constructed using the Kaplan-Meier method, according to the tertiles and LGI cut-off point; the survival of these groups was compared through the Log-Rank test.

To determine those factors independently associated with mortality, univariate and multivariable Cox regression was used. We included in the model those clinically significant variables or possible confounders regardless of their statistical significance, and those that in the univariate analysis presented a significance p≤0.01. A bilateral p value <0.05 was considered statistically significant.

The data was processed with SPSS version 20.0 and MedCalc version 8.2.1, both for Windows.

## RESULTS

A total of 344 consecutive patients were analyzed, most of them were male (65.7%), and the median of the overall age was 68 years (interquartile range 58-76). The personal history shows that 25% had diabetes mellitus and had suffered a previous AMI, 64.2% had high blood pressure and 33.1% smoked.

The median LGI was 1.47. The patients were grouped according to the LGI tertiles corresponding to the 33rd and 66th percentiles, which were 1.207 and 1.773, respectively. When analyzing these groups, the median age was significantly higher as the LGI increased (**Table 1**). Women and diabetics presented with a significantly higher frequency in higher tertiles, while those with smoking habit predominated in the lowest. Other baseline characteristics are detailed in **table 1**.

Regarding the clinical and laboratory variables at admission according to tertiles, there were no differences in systolic and diastolic blood pressure; however, the heart rate, blood glucose, serum creatinine, blood count, neutrophil and lymphocyte count at admission were significantly higher in patients in the higher tertiles. Similarly, these groups of patients presented worse Killip-Kimbal classification (>I). No differences were found between the patients from different tertiles in terms of coronary reperfusion treatments (**Table 1**).

During mean follow-up of 278 ± 8 days, 88 deaths were recorded. The mortality rate was 25.6%, which was significantly increased by LGI tertiles (p<0.0001) and reached 55.7% in tertile 3 (**Figure 1**). The median LGI among patients who survived and died was significantly different, being higher in those who died (1.34 vs. 2.18, respectively, p<0.0001).

The area under the LGI curve was 0.715 (95% CI:

**Table 1.** Demographic, clinical, laboratory and treatment data.

| Variables | Global (n=344) | Value of the leuko-glycemic index (LGI) | | | *p* |
|---|---|---|---|---|---|
| | | Tertil 1 (n=114) | Tertil 2 (n=115) | Tertil 3 (n=115) | |
| **Background** | | | | | |
| Age (years) | 68 [58-76] | 65 [55-74] | 69 [58-79] | 71 [61-77] | 0.006 |
| Sex. female | 118 (34.3) | 28 (24.6) | 42 (36.5) | 48 (41.7) | 0.020 |
| Hypertension | 221 (64.2) | 65 (57.0) | 79 (68.7) | 77 (67.0) | 0.139 |
| Diabetes mellitus | 88 (25.6) | 11 (9.6) | 14 (12.2) | 63 (54.8) | 0.000 |
| Smoking habit | 114 (33.1) | 46 (40.4) | 41 (35.7) | 27 (23.5) | 0.020 |
| Previous myocardial infarction | 86 (25) | 35 (30.7) | 26 (22.6) | 25 (21.7) | 0.225 |
| Atrial Fibrillation | 11 (3.2) | 3 (2.6) | 4 (3.5) | 4 (3.5) | 1.000 |
| Chest Pain | 96 (27.9) | 37 (32.5) | 28 (24.3) | 31 (27.0) | 0.378 |
| Heart failure | 54 (15.7) | 13 (11.4) | 21 (18.3) | 20 (17.4) | 0.300 |
| **Clinical and laboratory data on admission** | | | | | |
| Heart rate (bpm) | 78 [68.5-90] | 74.5 [68-85] | 79 [67-98] | 84 [71-90] | 0.002 |
| Systolic BP (mmHg) | 120 [110-140] | 120 [110-140] | 120 [110-140] | 120 [100-140] | 0.195 |
| Diastolic BP (mmHg) | 80 [70-85.5] | 80 [70-90] | 80 [70-90] | 70 [60-85] | 0.352 |
| Killip-Kimball>I | 141 (41.0) | 31 (27.2) | 48 (41.7) | 62 (53.9) | 0.000 |
| Leukocytes $mm^3$ | 11.2 [10.0-12.6] | 10.0 [8.6-11.0] | 12.0 [10.9-13.0] | 12.0 [10.4-13.2] | 0.000 |
| Neutrophils $mm^3$* | 8.4±2.5 | 6.6±1.9 | 9.2±2.2 | 9.4±2.3 | 0.000 |
| Lymphocytes $mm^3$** | 2.5±0.9 | 2.7±1.0 | 2.5±0.9 | 2.4±0.9 | 0.022 |
| Glycemia (mmol/L) | 6.8 [5.7-9.0] | 6.3 [5.5-8.2] | 6.8 [5.7-8.5] | 7.2 [5.8-12.3] | 0.011 |
| Creatinine (mmol/L)*** | 79.0 [65.0-103.0] | 77.0 [64.0-91.1] | 78.0 [64.0-103.0] | 93.0 [69.0-125.0] | 0.010 |
| **Coronary reperfusion treatment** | | | | | |
| Thrombolysis | 151 (43.9) | 55 (48.2) | 44 (38.3) | 52 (45.2) | 0.295 |
| PCI | 51 (14.8) | 18 (15.8) | 19 (16.5) | 14 (12.2) | 0.611 |

The data are presented as n (%), mean ± standard deviation, or median [interquartile range]. BP, blood pressure; LGI, leuko-glycaemic index; PCI, percutaneous coronary intervention.
* Available from 344 patients: 110 in Tertil 1 of LGI, 115 in Tertil 2 and 113 in Tertil 3.
** Available from 344 patients: 110 in Tertil 1 of LGI, 114 in Tertil 2 and 113 in Tertil 3.
*** Available from 344 patients: 100 in Tertil 1 of LGI, 107 in Tertil 2 and 106 in Tertil 3.

0.664-0.762, p<0.0001). The optimal LGI cut-off value to predict mortality was 2.2; with a 50% sensitivity and an 85.9% specificity (**Figure 2**).

There were significant differences when comparing survival, which decreased according to the LGI tertiles (p<0.0001). Survival was also significantly lower (**Table 2** and **Figure 3**), in those patients with an LGI>2.2 (p<0.0001).

In the multivariate analysis, LGI>2.2 was a predictor of one-year mortality for all causes (HR 3.562, 95% CI: 2.091-6.071, p<0.0001), regardless of age, sex, Killip-Kimball>I, systolic blood pressure, serum creatinine and diabetes mellitus (**Table 3**).

## DISCUSSION

In the present study, the prognostic value at 1-year LGI was evaluated in patients with ST-segment elevation AMI. Several investigations have confirmed the importance of blood count and its differential as a predictor of death and other long-term adverse

events. Núñez *et al*[6], in a prospective study of 1118 consecutive patients with acute coronary syndrome, showed, during an average 10 months follow-up, that patients with a higher white blood cell count in the first hours of admission were more likely to die. Another prospective study[14] with 1037 patients, and a mean 23 months follow-up, claims that blood count and its differential is associated with a worse prognosis. An edge of this inflammatory marker has also been extensively evaluated: the neutral-lymphocyte index, with solid evidence supporting the white blood cell count and its differential as an independent marker of poor long-term prognosis[15-21].

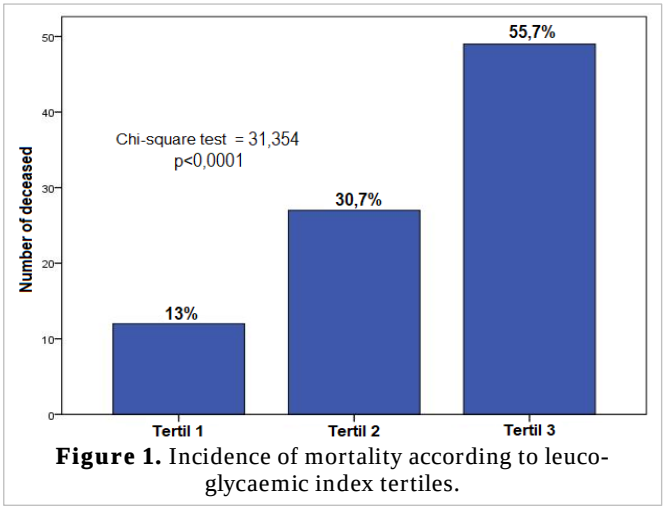


**Figure 1.** Incidence of mortality according to leuco-glycaemic index tertiles.

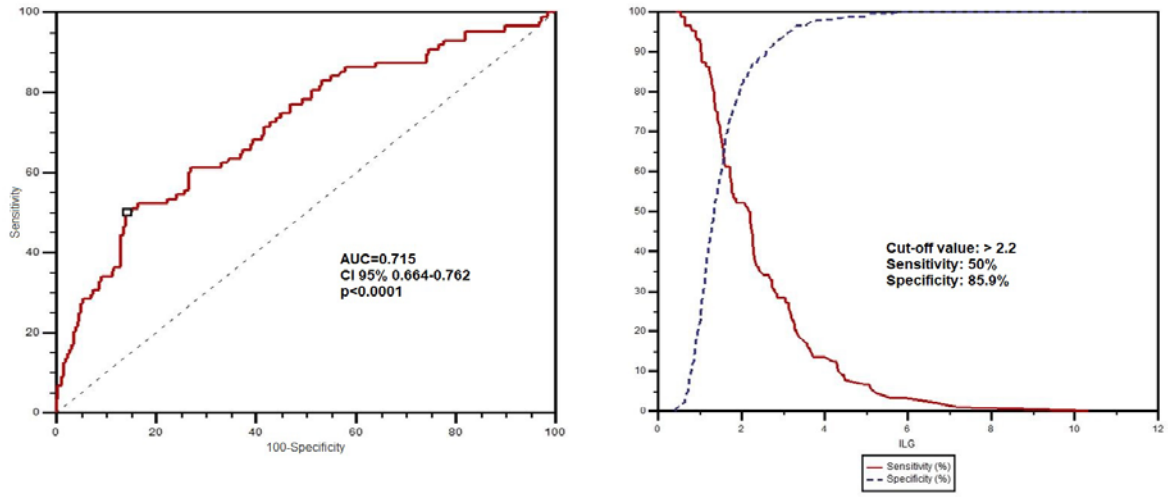


**Figure 2.** ROC curves showing the discrimination capacity and the optimal cut-off point of the leuco-glycaemic index to predict mortality. AUC, area under the curve; CI: confidence interval.

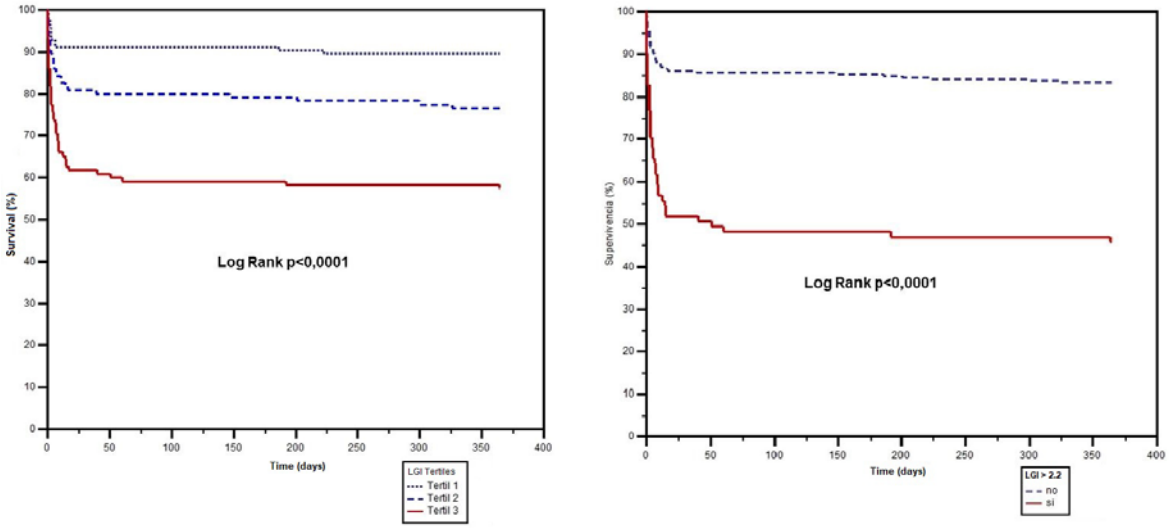


**Figure 3.** Kaplan-Meier survival curves of the patients studied, at 365 days, according to tertiles and leuco-glycaemic index cut-off point.

**Table 2.** Survival according to tertiles and LGI cut-off point.

| Variable | Survival average | Typical error | CI 95% | *p* (Log Rank) |
|---|---|---|---|---|
| Tertil 1 | 330.412 | 9.720 | 311.362-349.463 | |
| Tertil 2 | 288.983 | 13.417 | 262.685- 315.280 | <0.0001 |
| Tertil 3 | 217.313 | 16.363 | 185.242-249.384 | |
| LGI>2.2 | 177.420 | 19.746 | 138.718- 216.122 | <0.0001 |
| LGI≤2.2 | 309.962 | 7.842 | 294.592-325.332 | |
| Global | 278 753 | 8.171 | 262.739-294.767 | - |

LGI, leuko-glycaemic index

**Table 3.** Cox, uni and multivariable proportional hazards models to evaluate the predictors of mortality per year of patients with ST-segment elevation AMI.

| Variables | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | *p* | *Hazard Ratio* | CI 95% | *p* | *Hazard Ratio* | CI 95% |
| LGI >2.2 | <0.0001 | 4.187 | 2.752-6.369 | <0.0001 | 3.562 | 2.091-6.071 |
| Killip Kimball>I | <0.0001 | 5.868 | 3.589-9.593 | <0.0001 | 3.502 | 2.083-5.888 |
| Female sex | <0.0001 | 2.192 | 1.443-3.331 | 0.039 | 1.631 | 1.025-2.593 |
| Age (years) | <0.0001 | 1.057 | 1.038-1.076 | <0.0001 | 1.040 | 1.020-1.061 |
| Creatinine (mmol/L) | <0.0001 | 1.005 | 1.003-1.006 | 0.002 | 1.004 | 1.001-1.006 |
| Systolic BP (mmHg) | <0.0001 | 0.972 | 0.964-0.981 | 0.002 | 0.986 | 0.977-0.995 |
| Diabetes mellitus | <0.0001 | 2.393 | 1.566-3.655 | 0.612 | 0.863 | 0.488-1.525 |

BP, blood pressure; CI, confidence interval; LGI, leuko-glycaemic index.

Many mechanisms have been proposed that explain such results. Stimulated neutrophils release free radicals, proteolytic enzymes and arachidonic acid metabolites, which increase the infarction size and lead to electric instability of the heart through endothelial damage, coagulation cascade activation, leukocyte aggregation and its deposition in microarteries[2,22]. Microparticles derived from these activated polymorphonuclear leukocytes can favor the coagulation cascade and perpetuate thrombi formation, since they can activate and favor the expression of P-selectin on the platelet[23]. In addition, elevated levels of inflammatory markers in the blood have been observed in patients with heart failure for several reasons, suggesting the strong relationship with pump failure[24].

On the other hand, glycemia as a long-term prognostic marker in patients with AMI has also been studied. A valuable study with 11324 patients shows that their admission values are a powerful predictor of mortality 20 years after having suffered an AMI[25]. Planer *et al*[26], based on the records of the multinational clinical trial HORIZONS-AMI, establish that glycemia in the first 24 hours of admission is an independent predictor of mortality at 30 days and at 3 years. Similar results were obtained in a previous study by Monteiro *et al*[27].

Hyperglycaemia is related to the size of the infarction, a greater Killip-Kimball class, low left ventricular ejection fraction, cardiogenic shock, need for resuscitation due to cardiorespiratory arrest and increased concentrations of myocardial necrosis markers[28,29]. The increase of vasoconstrictive and inflammatory factors during hyperglycemia contributes to the damage of endothelial function and increases the production of free radicals with the consequent oxidative stress[30]. In addition, there is a state of insulin resistance in which lipolysis causes free fatty acids to be released which hinders the transportation of glucose into the myocardial cell, and its oxidation generates superoxide anions[8]. It also produces an alteration in platelet metabolism

and changes in the intraplatelet signaling mechanisms, which may contribute to the development of atherothrombotic complications[31].

The theoretical and practical evidence of the LGI components separately, as factors of worse short and long term prognosis, suggests the logical association of these in an index. Previous observations have shown that LGI constitutes a marker of poor prognosis during hospital stay. Quiroga *et al*[10] were the first to associate LGI with death and complications during hospital stay, while Benítez Díaz *et al*[13] were able to reproduce their results but with a 30-day follow-up period. Among other studies confirming the prognostic value of LGI through multivariate analysis[11,12], highlights that of Hirschson *et al*[12] when analyzing a total of 405 patients in 87 Argentinians institutions. Seoane *et al*[32] in another clinical context (postoperative period of cardiac surgery) also demonstrate −in 2743 patients− the usefulness of LGI as a predictor of poor in-hospital outcome.

However, none of the cited authors analyzes the prognostic value of LGI to predict mortality beyond 30 days; which is evaluated in the present investigation and identified as an independent predictor of mortality per year, after adjusting other variables with recognized prognostic value. In addition, this work also demonstrates for the first time that the higher LGI is a good predictor of shorter survival at 365 days in patients with AMI.

The optimal cut-off point obtained by the ROC curve to predict mortality at one year was 2.2. These results differ with the rest of the analyzed researches. Quiroga *et al*[10], León-Aliz *et al*[11], Hirchson Prado *et al*[12] and Seoane *et al*[32] found an optimal cut-off value of 1.6; 1,158; 1.00 and 2.0, respectively. These differences can be attributed mainly to the analysis period and that all assess the prognostic value of LGI in the short term, with heterogeneous samples in terms of its size and composition, and with different primary end objectives.

### Study limitations

It is the experience of a single institution and the size of the sample is relatively small, although this did not prevent obtaining solid results. No data were available on the left ventricular ejection fraction, myocardial reperfusion state, or quantity and severity of the affected coronary vessels in the entire sample. In addition, the low availability of primary percutaneous coronary intervention influences the poor in-hospital survival of patients, which determines the occurrence of fewer final events after hospital discharge.

## CONCLUSIONS

The results from this work support the theoretical and practical basis of the leuko-glycaemic index as a predictor of adverse events per year, in the context of acute myocardial infarction. Its simplicity, wide availability, low cost and the fact of being part of the paraclinical routine examinations performed at admission, in patients with acute coronary syndrome, further support its potential application in early risk stratification. Future larger samples multi-center studies are necessary to confirm our observations, as well as the prognostic capacity of the leucoglycaemic index in association with risk scales.

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