ORIGINAL ARTICLE

Performance of the European Society of Cardiology Algorithm for the Assessment of Chest Pain in Patients with Diabetes Mellitus

Evaluación del algoritmo de la sociedad europea de cardiología de dolor torácico en pacientes con diabetes mellitus

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ABSTRACT

Background: Patients with diabetes usually have higher troponin levels than the general population.
Objective: The aim of our study was to evaluate the performance of the European Society of Cardiology algorithm which uses high sensitivity cardiac troponin levels on admission and after 1 hour in these patients.
Methods: A total of 1,140 patients with chest pain and ECG without ST-segment elevation were evaluated. The algorithm stratifies patients in three risk groups: rule-out, observe and rule-in. We evaluated the performance of the algorithm to predict myocardial infarction at 30 days.
Results: A total of 124 patients (10.8%) had diabetes. None of the patients in the rule-out group (40.3%) presented myocardial infarction at 30 days. In the rule-in group (23.4%), the event occurred in 82.8% of cases and in 6.8% in the observe group (36.3%). Sensitivity and negative predictive value were similar in patients with and without diabetes (100% vs. 98.5%, P = 0.865 and 100% vs. 99.8%, P= 0.44), but the proportion of patients in the rule-out group was lower in diabetics (40.3% vs. 72.1%, P < 0.001). The accuracy of the algorithm to rule in patients was evaluated by its specificity which was lower in diabetics, but the positive predictive value was greater (90.9% vs. 97.2%, P < 0.001 and 83% vs. 76%, P < 0.001). The proportion of patients in the rule-in group was higher in diabetics (23% vs. 8.6%, P < 0.001).
Conclusion: The use of the algorithm in patients with diabetes revealed high sensitivity and negative predictive value to rule out, which was similar to that of the general population. Regarding the rule-in group, it had lower specificity but high positive predictive value. This performance makes the algorithm a useful tool for daily practice.

Key words: Diabetes mellitus - Non-ST elevated myocardial infarction - Acute coronary syndrome - Chest pain – Algorithms – Troponin - Sensitivity and specificity

RESUMEN

Introducción: Dado que los pacientes con diabetes tienen habitualmente niveles de troponina más elevados que la población general, nos propusimos evaluar el comportamiento del algoritmo de la Sociedad Europea de Cardiología que utiliza la medición de troponina de alta sensibilidad al ingreso y 1 hora después en estos pacientes.
Material y métodos: Se evaluaron 1140 pacientes que consultaron por dolor torácico con electrocardiograma sin supradesnivel del segmento ST. El algoritmo estratifica los pacientes en tres grupos de riesgo: "externar", "observar" e "internar". Se valoró el comportamiento del algoritmo para el evento infarto a 30 d.
Resultados: En total, 124 pacientes (10,8%) tenían diabetes. Ninguno de los clasificados como "externar" (40,3%) presentó infarto a 30 días. En los "internar" (23,4%), el evento se produjo en el 82,8%, mientras que en el grupo "observar" (36,3%), en el 6,8%. La sensibilidad y el valor predictivo negativo fueron similares entre pacientes con diabetes y sin esta (100% vs. 98,5% p = 0,865 y 100% vs. 99,8% p = 0,44), pero la proporción de pacientes para "externar" fue menor en diabéticos (40,3% vs. 72,1%, p < 0,001). En cuanto a la precisión para "internar" pacientes, la especificidad fue menor en diabéticos, pero el valor predictivo positivo fue mayor (90,9% vs. 97,2%, p < 0,001 y 83% vs. 76%, p < 0,001). La proporción de pacientes para "internar" fue mayor en diabéticos (23% vs. 8,6%, p < 0,001).
Conclusiones: El uso del algoritmo en pacientes con diabetes mostró una alta sensibilidad y un alto valor predictivo negativo para "externar" comparable a la población general. En cuanto al grupo "internar", presentó menor especificidad, pero alto valor predictivo positivo. Esto lo transforma en una útil herramienta para la práctica diaria.

Palabras clave: Diabetes mellitus - Infarto del miocardio sin elevación del ST - Síndrome coronario agudo - Dolor en el pecho – Algoritmos – Troponina - Sensibilidad y especificidad

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Abbreviations

PCI	Percutaneous coronary intervention	**AMI**	Acute myocardial infarction
CCA	Cine coronary angiography.	**NSTEMI**	Non-ST-segment elevation myocardial infarction
CABGS	Coronary artery bypass graft surgery	**ACS**	Acute coronary syndrome
ED	Emergency department	**hs-cTn**	High-sensitivity cardiac troponin
DM	Diabetes mellitus	**Hs-cTnT**	High sensitivity cardiac troponin T
ECG	Electrocardiogram	**NPV**	Negative predictive value
ESC 0/1-h	European Society of Cardiology 0 h/1 h algorithm	**PPV**	Positive predictive value

INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes of mortality and disability worldwide. Therefore, timely stratification of patients with symptoms suggestive of AMI is crucial to provide rapid and effective treatment. Furthermore, rapid exclusion of AMI reduces emergency department (ED) length of stay, accelerates the identification and treatment of the real cause of the symptoms and avoids significant costs for the health care system. (1, 2)

Patients with diabetes mellitus (DM) deserve special attention as they represent a vulnerable group with greater incidence of AMI and frequently with atypical presentation.

The last European guidelines for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation suggest the 0 h/1 h algorithm (ESC 0 h/1 h) to stratify patients using high sensitivity cardiac troponin (hs-cTn) assays on admission and absolute changes of its levels within 1 hour. (3) The cutoff values have been uniformly established for all the population, but there is scarce evidence if these levels can be extrapolated to patients with DM who seem to have elevated chronic baseline hs-cTn levels compared with patients without this disease. For this reason, the use of the algorithm proposed by the European Society of Cardiology for the assessment of chest pain may have different results in this population.

The aim of our analysis was thus to validate this algorithm in a population of DM patients evaluated in a reference center of our country.

METHODS

We conducted an observational, descriptive, single-center study between January and August 2018. Data from 1,335 patients >18 years who presented at the ED with symptoms suggestive of ACS and without ST-segment elevation in the electrocardiogram (ECG) were prospectively collected.

Inclusion criteria

- Patients >18 years with DM who presented at the ED with suspected ACS.

Exclusion criteria

– Non-cardiac chest pain
– Admission indicated by other physician
– Impossibility to follow up
– ST-segment elevation
– Hemodynamic instability or arrhythmias

Routine patient assessment

All the patients underwent clinical assessment which included history taking, physical examination, routine lab tests including serial hs-cTn levels, 12-lead ECG, chest-X ray, continuous ECG monitoring and pulse oximetry. The ESC 0 h/1 h algorithm had been incorporated to the standard local procedures for the evaluation of patients with suspected non-ST-segment elevation myocardial infarction (NSTEMI). The decision of how to treat each patient was left at the discretion of the treating physician who was free to void any recommendation emerging from the ESC 0/1-h algorithm.

ESC 0/1-h algorithm

The ESC 0/1-h algorithm must always be used with all the clinical information available, including the ECG, to classify patients with suspected NSTEMI as rule-out, observe and rule-in, according to hs-cTn levels obtained on admission and at 1 h (Figure 1).

Follow-up

A 30-day follow-up period after the index event was carried out in all patients at the outpatient clinic or by telephone call.

Events

The presence of cardiovascular events was analyzed by a cardiologist who was not involved in the initial treatment of the patients, based on the results of the lab tests, echocardiography, functional tests, cine coronary angiography (CCA) or computed tomography coronary angiography (CTCA). This physician was in charge of assigning the final events.

Definitions

- Patients with DM were defined as those who self-reported having DM or who were regularly medicated with antidiabetic drugs.
- The diagnosis of AMI was based on the fourth universal definition which includes detection of a rise and/or fall of hs-cTn values with at least one value above the 99th percentile upper reference limit and at least one of the following: symptoms of ischemia, new or presumed new significant ST-T changes or left bundle branch block in the ECG, development of pathological Q waves, loss of viable myocardium or regional wall motion abnormality, identification of intracoronary thrombus by angiography or autopsy. (4)
- The diagnosis of ACS was based on the recommendations of the Argentine Society of Cardiology guidelines. (5)

Troponin measurement

Our laboratory uses Elecsys Troponin T high-sensitive (hs-cTnT) assay (Roche Diagnostics) with a cut-off value of 14 ng/L which represents the 99th percentile of a healthy refer-

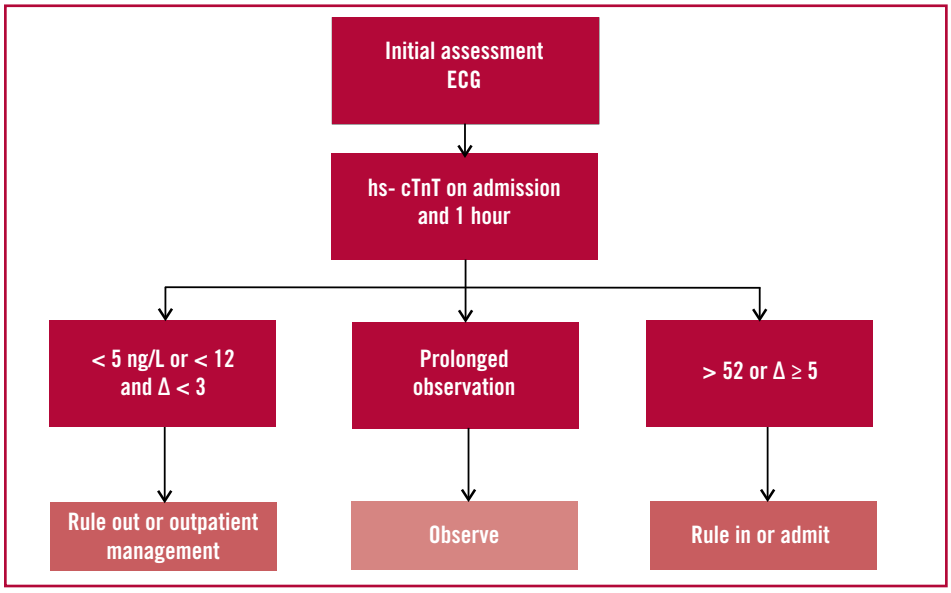

Fig. 1. Structure of the European Society of Cardiology algorithm with high sensitivity cardiac troponin T

ECG: Electrocardiogram; hs-cTnT: High sensitivity cardiac troponin T

ence population, with a 10% coefficient of variation for 13 ng/L, a limit of blank of 3 ng/L and a limit of detection of 5 ng/L. (6)

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, or median and interquartile range, according to their distribution. The Kolmogorov-Smirnov test or the Shapiro-Wilk test was used for normality, as applicable. The chi square test or Fisher's exact test were used to compare categorical variables and continuous variables were analyzed using Student's t test or the Mann-Whitney U test, depending on their distribution. ROC curves were built. The absolute differences were analyzed with their 95% confidence intervals for predictive values.

A type I error ≤5% (two-tailed P value <0.05) was considered statistically significant. All the statistical calculations were performed using IBM SPSS 25.0 software package (for Mac iOS).

Ethical considerations

All the patients signed an informed consent form to be included in the study. Patients were clearly informed about the purpose of the study, the confidentiality of the data provided and the mechanisms used to protect their identity. They were informed that their participation was voluntary and that they could refuse to participate in the study without any consequences or differences in their medical care, as well as their right to withdraw their consent at any time if they so wished.

During the recruitment process, the investigator provided verbal explanation to the patient of the information included in the informed consent and answered all the participant's questions about the study. The consent was submitted for approval by the institutional review board, which is under the regulations of the Central Review Board.

The investigators implemented measures to protect the confidentiality of all the information according to the Argentine personal data protection law 25,326, so the identity of the patients and all their personal data will remain anonymous, and that only the researchers and the members of the learning, teaching and research ethics committee will have access to this data, if required.

The study was conducted following national ethical standards (Law 3301 of the city of Buenos Aires, National Law for Good Clinical Practice on Research in Human Subjects, and the Declaration of Helsinki, among others).

RESULTS

After applying the inclusion and exclusion criteria, 1,140 of the total 1,351 patients were included in the study; 1,016 (89,2%) did not have DM (group 1) and 124 (10.8%) had DM (group 2). Patients with DM were older, had more cardiovascular risk factors (hypertension and dyslipidemia) and more comorbidities (history of AMI or myocardial revascularization, peripheral vascular disease, or chronic kidney disease). The values of hs-cTnT at 0 h and 1 h were significantly higher in this group of patients (Table 1).

The total incidence of ACS and AMI was 17.3% and 8.1%, respectively, and was significantly higher in the group with DM (group 1 14.4% with ACS and 7.9% with AMI; group 2 41,5% with ACS and 22% with AMI; P <0.01).

The ESC 0/1 h algorithm classified group 2 as follows: 50 patients (40%) as rule-out, 45 (36%) as observe and 29 (23%) as rule-in. Among rule-out patients, 10 (20%) were finally interpreted as ACS and underwent CCA, but none of them met AMI criteria. However, 18% underwent revascularization (percutaneous coronary intervention [PCI] in 14% and coronary artery bypass graft surgery [CABGS] in 4%). Among rule-in patients, 26 (93%) were interpreted as ACS (82.8% with AMI); 86% underwent CCA and 62% required revascularization (PCI in 34.5% and CABGS in 27.5%). Of note, 31% of the patients did not require revascularization and 44% of those undergoing revascularization underwent surgical treatment. Of the 45

patients (36%) assigned to the "observe" group, 32% were interpreted as ACS and 27% underwent CCA, but only 6.8% presented AMI; among them, 18% underwent revascularization (PCI in 16% and CABGS in 2.3%),

Without considering the cardiovascular events diagnosed during the index consultation, only one event was reported at the 30-day follow-up period (Table 2).

According to these results, the safety to rule out, quantified by sensitivity for NSTEMI, was similar in both groups (group 1 98.5% vs. group 2 100%, P=0.865) and the negative predictive value (NPV) was also similar (99.8% vs. 100%, P=0.44). Yet, the efficacy to rule out patients was significantly lower in group 2 (72.1% vs. 40.3%, P <0.001). Regarding the accuracy of the algorithm to rule in patients, the specificity, was greater in group 1 compared with group 2 (97.2% vs. 90.9%, P <0.001), but the positive predictive value (PPV) was higher in group 2 than in group 1 (76% vs. 83%, P < 0.001). Thus, the efficacy to rule in was significantly higher in group 2 (8.6% vs. 23%, P < 0.001) (Table 3).

Table 1. Baseline characteristics of the general population and of patients with diabetes

	Group 1 (without DM) n = 1,016	Group 2 (with DM) n = 124	*p*
Age (years)	60 (49-71)	64 (51-76)	<0.001
Male sex	1,477 (64%)	75 (60.4 %)	0.345
Pain-to-consultation time (hours)	4 (2-12)	4 (2-12)	0.543
Cardiovascular risk factors			
Hypertension	466 (45.9%)	103 (83.1%)	<0.001
Hypercholesterolemia	425 (41.8%)	94 (75.8%)	<0.001
Smoking habit	138 (13.6%)	19 (15.3%)	0.336
History			
Previous AMI	143 (14.2%)	31 (25%)	<0.001
Previous PCI	225 (22.1%)	42 (33.9%)	<0.001
Previous CABGS	67 (6.6%)	19 (15.3%)	<0.001
Peripheral vascular disease	19 (1.9 %)	10 (8.1%)	<0.001
Stroke/TIA	10 (1 %)	0	<0.001
Chronic kidney failure	10 (1 %)	7 (5.6%)	<0.001
Troponin value			
hs-cTnT on admission (ng/L)	8 (5-12)	13 (8-27)	<0.001
hs-cTnT 1 h (ng/L)	9 (6-15)	13 (8-27)	<0.001

DM: Diabetes mellitus; PCI: Percutaneous coronary intervention; CABGS: Coronary artery bypass graft surgery; TIA: Transient ischemic attack; hs-cTnT: High-sensitivity cardiac troponin T

Table 2. Management of patients with diabetes by algorithm groups

	Rule-out n = 50	Observe n = 45	Rule-in n = 29	*p*
Management				
Outpatient basis	36 (73.5%)	31 (70.5%)	1 (3.4%)	<0.001
Procedures within 30 days				
Functional test	7 (14.3%)	4 (9.1%)	0	<0.001
CTCA	1 (2%)	0	2 (6.9%)	<0.001
Coronary angiography	10 (20%)	12 (27.3%)	25 (86.2%)	<0.001
Revascularization	9 (18.1%)	8 (18.1%)	18 (62%)	<0.001
PCI	7 (14%)	7 (15.9%)	10 (34.4%)	<0.001
CABGS	2 (4.1%)	1 (2.3%)	8 (27.5%)	<0.001
30-day outcome				
Acute coronary syndrome	10 (20%)	14 (31.8%)	26 (93.1%)	<0.001
Index visit	10 (20%)	14 (31.8%)	27 (93.1%)	
Myocardial infarction	0	3 (6.8%)	24 (82.8%)	<0.001
Index visit	0	3 (6.8%)	24 (82.8%)	<0.001
Total mortality	1 (2%)	0	0	
Cardiovascular mortality	1 (2%)	0	0	

CTCA: Computed tomography coronary angiography; PCI: Percutaneous coronary intervention; CABGS; Coronary artery bypass graft surgery.

The ROC curve for AMI in group 1 (Figure 2) was 0.960 (95% CI, 0.941-0.980) and 0.947 for group 2 (Figure 3) (95% CI, 0.903-0.990), with no significant differences (P=0.028).

DISCUSSION

In this analysis we evaluated the performance of the ESC 0/1-h algorithm to stratify diabetic patients with acute chest pain according to the risk of presenting NSTEMI or ACS without ST-segment elevation.

Initially, we verified that these patients had higher baseline values of hs-cTnT than those without DM, even without coursing a NSTEMI. This could be due to multiple factors: advanced age, kidney disease, metabolic syndrome or microvascular dysfunction. (7-11) In this study, diabetic patients were older and had greater prevalence of hypertension, chronic coronary artery disease and kidney dysfunction, in line with international publications. This situation was the main reason to evaluate the performance of the algorithm in scenarios of "chronically" higher values than those of the population without diabetes.

A direct pathophysiologic mechanism could justify this increase in troponin values which has been observed even in patients with recent diagnosis of DM and in those without evidence of macrovascular dysfunction, hypertension or kidney dysfunction. (12-14) An independent association between chronic hyperglycemia and troponin elevation has been demonstrated, which persists even after adjustment for baseline characteristics of patients and comorbidities. In addition, a previous study by Yiu et al. revealed an association between arterial stiffness measured by pulse wave velocity and elevated troponin levels in patients with DM without established macrovascular disease. (15) Therefore, other factors besides the traditional cardiovascular risk factors could play an important role.

Table 3. Performance of the algorithm in patients with and without diabetes

	Group 1 (without DM) n = 1,016	Group 2 (with DM) n = 124	Difference	*p*
Sensitivity to rule out	98.5 (95.6-100)	100	0.5 (0.2. 0.8)	0.865
NPV to rule out	99.8 (98-100)	100	0.2 (0.1. 0.5)	0.445
Proportion of patients to rule out	733 (72.1%)	50 (40.3 %)		<0.001
Specificity to rule in	97.2 (96-98.4)	90.9 (83.3-98.95)	–6.3 (–10. –2)	<0.001
PPV to rule in	76 (70.1-84)	83 (76.1-88)	–7 (–11. –4)	<0.001
Proportion of patients to rule in	87 (8.6%)	29 (23 %)		<0.001

DM: Diabetes mellitus; NPV: Negative predictive value; PPV: Positive predictive value

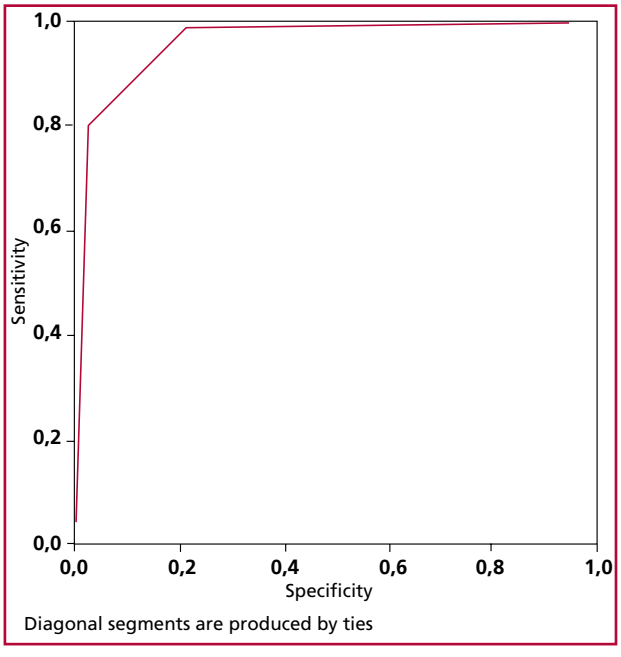

Fig. 2. ROC curve for AMI at 30 days in patients without diabetes

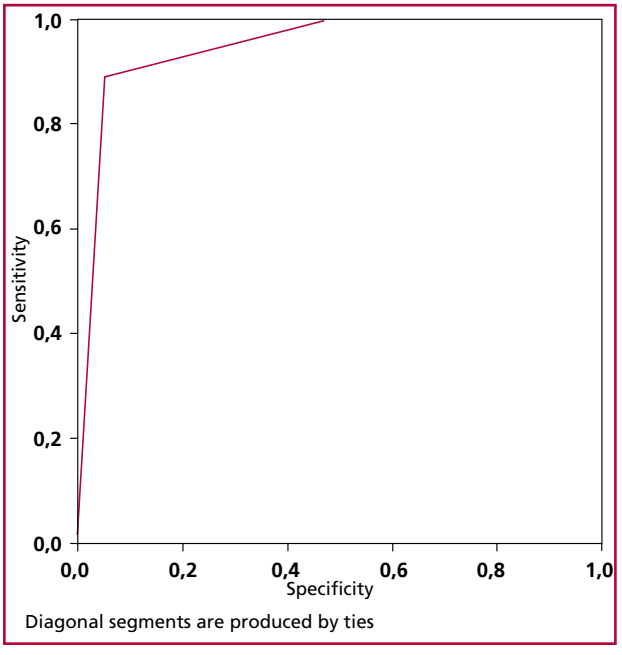

Fig. 3. ROC curve for AMI at 30 days in patients with diabetes

In 2019, Haller et al. also evaluated the performance of the ESC 0/1 h algorithm in patients with DM and they also found that the algorithm had high sensitivity and NPV to rule out patients, but the proportion of patients discharged was lower than in the general population. (16) This could precisely be due to the elevated baseline hs-cTn values presented by patients with DM, even without an ACS. Optimizing the cutoff value would perhaps increase the efficacy of the method.

Among patients in the rule-in group, those with DM have greater cardiovascular risk and are more likely to present other types of myocardial injury mimicking AMI. This is evidenced by the percentage of patients classified as rule-in that did not require revascularization, despite elevated hs-cTn levels, and would explain the greater specificity of the algorithm in patients without DM. Conversely, the high prevalence of coronary artery disease in this subgroup would explain the high PPV found.

The NPV of the algorithm for the rule-out group was as high as in the group without diabetes. Although this outcome is favorable, some concepts deserve to be clarified, as they may have an impact when these results are applied to daily practice: 1) the endpoint of the algorithm is AMI and that is why we evaluated its performance with this event. However, ruling out myocardial infarction is not the same as ruling out an acute coronary syndrome and, for this reason, we were interested in analyzing this endpoint. Muller et al., who designed the original algorithm, argued that ACS is a "softer" endpoint than AMI, and thus, used the latter. We agree with this concept, bearing in mind that when AMI is ruled out, the patient should not be discharged immediately. 2) In our study population, all the patients revascularized in the rule-out group underwent revascularization during the index visit and not after discharge because the emergency physician decided to admit the patients despite the "rule-out" label, based mainly on the clinical characteristics of chest pain.

Unlike the study by Haller et al., in which the ESC 0/1-h algorithm only defined management in 52% of the patients, in our population the algorithm allowed us to resolve the management of about 63% of the cases, which is still far from the 80.7% observed in the general population.

As a diagnostic algorithm should be safe and easy to implement, our findings support the use of the ESC 0/1 h algorithm in patients with DM.

LIMITATIONS

It should be noted that this study was conducted in a cardiac care delivery center where the first contact with the patient is a cardiologist. As this does not occur in all the centers and the experience in the evaluation of patients with chest pain has an impact on the outcomes, it would be important to validate these results in centers with other characteristics.

On the other hand, the definition of DM that we used in this study, based on the use of antidiabetic drugs (97%) and self-report could have misdiagnosed the prevalence of this condition.

CONCLUSIONS

The use of the ESC 0/1 h algorithm in patients with DM revealed sensitivity and NPV to rule out similar to that of the general population, but with lower efficacy that could be improved by using higher cutoff levels. Specificity was lower in the rule-in group but had high PPV. This performance makes the algorithm a useful tool for the stratification of patients in daily practice.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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