

# Risk Stratification in Severe and Asymptomatic Mitral Valve Regurgitation: How Could Patients with Adverse Outcomes Be Identified?

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## ABSTRACT

### Objective

To assess the usefulness a score which might identify adverse outcomes in asymptomatic patients with severe organic mitral valve regurgitation using clinical, echocardiographic and exercise variables.

### Material and Methods

We assessed 375 asymptomatic patients with severe organic mitral valve regurgitation ( $61 \pm 10$  years, left ventricular ejection fraction [LVEF]  $67\% \pm 5\%$ ). The score performed included the presence of atrial fibrillation, end-diastolic diameter  $e^{\circ}40$  mm, effective regurgitant orifice  $55 \text{ mm}^2$ , left atrium volume  $>120 \text{ cm}^3$ , age  $>60$ , and exercise time  $<7$  minutes. The score ranged from 0 to 6.5.

The primary endpoint was the development of symptoms and/or left ventricular dysfunction, defined as a decrease in LVEF  $>5\%$  or LVEF  $<60\%$ . The secondary endpoints included isolated symptoms, isolated left ventricular dysfunction, sudden death and valvular surgery.

### Results

During a mean follow-up of  $10 \pm 3.5$  years, 145 patients (39%) presented the primary endpoint; 157 (42%) had symptoms, 99 (26%) ventricular dysfunction, 10 patients (2.6%) died (7 of cardiovascular causes) and 207 patients underwent surgery (55%). The incidence of the primary endpoint with a score  $< 2$ , between 2-3, and  $> 3$  was 2.3%, 26% and 78%, respectively. Primary event rate with a score  $< 2$ , 2-3 and  $> 3$  was  $2.3\% \pm 0.1\%$ ,  $28\% \pm 4\%$  and  $73\% \pm 9\%$ , respectively. The area under the ROC curve was 0.87.

### Conclusion

In asymptomatic patients with severe mitral valve regurgitation, a score using clinical, echocardiographic and exercise variables is useful to identify subgroups of patients at greater long-term risk.

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## Key words >

Regurgitation, Mitral Valve - Risk - Procedures, Thoracic Surgery - Prognosis

## Abbreviations >

|      |                                    |    |                      |
|------|------------------------------------|----|----------------------|
| LA   | Left atrium.                       | RF | Regurgitant fraction |
| EROA | Effective regurgitant orifice area | MR | Mitral regurgitation |
| EDD  | End-diastolic diameter             | LV | Left ventricle       |
| ESD  | End-systolic diameter              | RV | Regurgitant volume   |
| LVEF | Left ventricular ejection fraction |    |                      |

## BACKGROUND

Mitral regurgitation (MR) is a progressive condition with high incidence of events at long-term (heart failure, arrhythmias, death). (1-3) Therapeutic decision-making is based on the presence of symptoms, left ventricle dysfunction and severity of regurgitation. (1-3) This is particularly important as prognosis depends not only on these variables but also on the ca-

capacity of early detection of these events. Age should always be considered in terms of risk stratification, as elder patients are more likely to present postoperative complications. (1, 3, 8) In patients with asymptomatic and severe mitral valve regurgitation, functional capacity should be assessed, as limited stress testing is an objective measurement of disease progression. (5) Several studies have evaluated echocardiographic indices, and volume overload (represented

by ventricular diameters) and left atrium (LA) size might predict the outcomes of this condition. (1, 4, 6, 7) Left ventricular function, estimated through left ventricular ejection fraction (LVEF) is an index of contractility that may serve for patient's stratification together with ventricular size indices. (1, 4) End-diastolic diameter, end-systolic diameter and end-systolic wall stress have also demonstrated to have prognostic value. (1, 6) Nevertheless, these traditional indices present a moderate association with the presence of symptoms and evolution at the time of decision-making. (1, 6, 7) Left ventricular ejection fraction is an index currently used to assess ventricular function; however, it is not independent of load conditions. Currently, other indices are used to evaluate the degree of organic compromise - regurgitant volume (RV), regurgitant fraction (RF) and effective regurgitant orifice area (EROA). These parameters serve as a complement to provide information of the degree of valvular damage and volume overload. (4, 9)

The aim of this study was to assess the usefulness a score which might identify adverse outcomes in asymptomatic patients with severe mitral valve regurgitation using clinical, echocardiographic and exercise variables

## MATERIAL AND METHODS

### Study Population

We prospectively assessed 375 asymptomatic patients with organic mitral regurgitation.

Inclusion criteria were as follows:

1. Organic etiology.
2. Severe mitral regurgitation according to standard echocardiographic criteria. (10, 11)
3. LVEF  $\geq$  60%.
4. Absence of symptoms (dyspnea or hospitalization due to heart failure) at the moment of inclusion.
5. Peak oxygen consumption  $\geq$  20 ml/kg/min.

Patients with associated valvular heart conditions (moderate to severe aortic regurgitation, moderate to severe aortic stenosis and significant and organic right valvular heart disease), mitral regurgitation secondary to ischemia or to cardiomyopathies, pericardial diseases, and history of coronary artery bypass graft surgery or heart valve surgery were excluded. Follow-up was completed in all cases. Annual assessment was achieved in 98% of patients.

### Clinical Data

All patients underwent complete clinical assessment.

### Echocardiography

Echocardiography was performed with Hewlett Packard (Sonos 5500, Image Point) or Toshiba HS140 scanners. Severity of mitral regurgitation was quantified by transthoracic Doppler echocardiogram (Colour Doppler, continuous wave Doppler and pulsed Doppler imaging). (10, 11)

Ventricular volumes and LVEF were estimated using the biplanar Simpson method. Left ventricular end-diastolic diameter (EDD) and end-systolic diameter (ESD) corrected for body surface area (BSA), LA size (anteroposterior dimension, area and volume), wall thickness, wall thickness/

EDD ratio, left ventricular mass and end-systolic stress were calculated in the classic fashion. (10-14) Valve lesions identified included involvement of one leaflet or both leaflets and a new flail leaflet (NFL). Effective regurgitant orifice area (EROA) was determined as an average of semi-quantitative measurements and proximal isovelocity surface area (PISA) method. (15, 16) Doppler interrogation was performed by two independent observers who were blind to clinical data.

### Exercise Stress Test

All patients underwent exercise stress testing using Bruce protocol, and exercise time was specially considered. Reasons to stop the test included hypotension (blood pressure fall of greater than 20mm Hg compared to basal values), ST depression greater than 2 mm, hypertension (blood pressure  $>$  220/110 mm Hg), dyspnea or persistent angina and/or severe ventricular arrhythmias (frequent couplets, R/T phenomenon or sustained ventricular tachycardia).

### Final Endpoints

Clinical examination and echocardiograms were performed at least once a year (time interval between tests varied according to the severity of the condition).

The primary endpoint was a composite of symptoms and/or LV dysfunction. In turn, secondary endpoints included: isolated symptoms, isolated LV dysfunction, cardiovascular mortality and valve surgery.

The presence of symptoms during follow-up was defined as functional class II-IV (NHA) dyspnea, angina, fatigue (physical exhaustion disproportionate to habitual exertion) or need of hospitalization due to congestive heart failure.

Left ventricular dysfunction was defined as EF  $<$  60% or a fall in EF  $>$  5% compared to basal values.

Deaths were classified as cardiovascular or non cardiovascular according to the information provided by the primary physician, medical reports or post mortem information when available.

Mitral valve replacement was decided by the primary physician who was informed about echocardiographic data such as ventricular and LA size, wall thickness, end-systolic stress, right and left ventricular function, pulmonary artery pressure and exercise stress test results. However, information about RV, RF and EROA was not systematically reported.

Patients who died of non cardiovascular causes were censored at the time of death, and those who remained alive free of valve replacement were censored at the end of follow-up.

### Statistical Analysis

Continuous variables are expressed as mean  $\pm$  standard deviation (SD) and discrete variables as percentages  $\pm$  confidence interval (CI).

Cut-points for each parameter analyzed were obtained from reports from a previous study published by our team. (17)

A logistic regression analysis among the clinical, echocardiographic and exercise testing variables examined was conducted in order to identify independent predictors of the primary combined endpoint (symptoms and/or LV dysfunction). A p value  $<$  0.01 was considered statistically significant.

We determined in turn the predictive weight of each variable in relation to the coefficient of the model. (Table 1) Dichotomic variables identified as independent predictors of the model were: 1) atrial fibrillation, 2) ESD  $e^{*}$  40 mm, 3) EROA  $>$  55 mm<sup>2</sup>, 4) age  $>$  60 years, 5) exercise duration  $<$  7 minutes and 6) LA volume  $>$  120 cm<sup>3</sup>.

The Hosmer-Lemeshow test was used to measure logistic regression model calibration ( $p < 0.695$ , chi-square value: 1.24). Cut-points for each index were obtained from reports from a previous study published by our team.

Resampling models were validated for bootstrapping with 400 replications in order to exclude over adjustment. Concordance among data groups was excellent (maximum absolute error of likelihood prediction  $< 0.015$ ).

**Development of a Score from Independent Predictors of the Logistic Model**

Each predictor coefficient was divided by a common denominator (arbitrary). The constant was not included in the score. This information generated an individual score with the score for each variable. Risk groups were defined according to the estimation of the model and the score assigned for each of them. A score was generated with the score for each patient (ESD\* 1.5) + (age \* 1) + (EORA + 1.5) + (exercise duration \* 1) + (atrial fibrillation \* 1) + (LA volume + 0.5). Based on variables of the model, the maximum possible score was 6.5 (Table 1).

ROC curves were used to identify different score cut-points and thus it was possible to determine sensitivity and specificity of each risk score to predict primary outcomes.

Survival free of events in each subgroup of risk was assessed with the Kaplan-Meier method.

All calculations were performed using a software STATA 7.0, version 2001.

**RESULTS**

Mean age was  $61 \pm 10$  years, 63% were men and mean LVEF was  $67\% \pm 5\%$ . Causes of mitral regurgitation were degenerative disease (mitral valve prolapse) in 319 patients, rheumatic valve disease (46 patients) and infections in 10 patients. Table 2 shows basal characteristics of the study population and their relation with the risk score.

During a mean follow-up of  $10 \pm 3.5$  years, 10/375 patients (2.6%) died. The causes of death were sudden death (4 patients), congestive heart failure (3 patients) and 3 non cardiovascular deaths. The combined final endpoint was present in 145 patients (39%). Regardless of the primary endpoint, 157 patients (42%) developed symptoms and 99 patients (26%) presented LV dysfunction. Two hundred and seven patients (55%) underwent surgery.

Eighty six patients (23%) had a risk score  $< 2$ , 161 patients (43%) presented a score 2-3 and 128 patients (34%) had a score  $> 3$ . Table 3 shows the relationship between the different groups of risk, combined events and death. The relation between event rate, risk score, survival, presence of symptoms, ventricular dysfunction and valve surgery is described in Table 4.

Patients with a score  $> 3$  had the greatest risk of combined events ( $73\% \pm 9\%$ ) and heart valve surgery ( $84\% \pm 7\%$ ) compared to the other subgroups.

Combined event-free survival was 98% in the subgroup of patients with a score  $< 2$  (95% CI, 94-100), 71% in patients with a score 2-3 (95% CI 65-76) and 27% with a score  $> 3$  (95% CI 19-41) (Figure 1).

The risk score was able to identify combined events (area under the ROC curve 0.87) (Figure 2).

Sensitivity, specificity, negative predictive value and positive predictive value for a score  $> 3$  were 72%, 93%, 82% and 89%, respectively.

The score yielded a positive coefficient of 10.28 and a negative coefficient of 3.32.

After adjusting for sex, risk factors and LV wall stress, a MR score  $> 3$  was an independent predictor of combined events (adjusted relative risk = 4.56, 95% CI 2.3-6.3,  $p = 0.001$ ) and of global survival (adjusted relative risk = 5.4, 95% CI 2.7-8.3,  $p = 0.01$ ).

When the presence of symptoms was adjusted for sex and risk factors, the adjusted risk ratio for a score  $> 3$  was 3.8 (95% CI, 2.3-8.9,  $p = 0.01$ ) and using LV dysfunction as an isolated endpoint, a MR score  $> 3$  was an independent predictor with a relative risk of 4.1 (95% CI 2.6-9.1,  $p = 0.01$ ).

**DISCUSSION**

Natural history of mitral regurgitation is not well defined. Yet, prognosis is unfavorable once symptoms develop. Not all asymptomatic patients are candidates for heart valve surgery; however, when ventricular dysfunction develops during follow-up, surgery should be performed. In turn, mitral valve replacement or valve repair generate unpredictable changes in ventricular architecture. Current guidelines recommend

| Variable                        | $\beta$ coefficient | Odds | 95% CI     | Relative score |
|---------------------------------|---------------------|------|------------|----------------|
| Age > 60 years                  | 1.01                | 2.7  | (1.2-6.4)  | 1              |
| Atrial fibrillation             | 1.03                | 2.8  | (1.5-5.2)  | 1              |
| ESD $\geq 40$ mm                | 1.56                | 4.8  | (2.2-6.5)  | 1.5            |
| LA volume > 120 cm <sup>3</sup> | 0.59                | 1.8  | (1.07-3.7) | 0.5            |
| EROA > 55 mm <sup>2</sup>       | 1.58                | 4.9  | (2.4-6.3)  | 1.5            |
| Exercise duration < 7 minutes   | 1.04                | 2.9  | (1.9-5.5)  | 1              |
| EDD $\geq 65$ mm                | 0.21                | 1.23 | (0.79-3.9) | -              |
| New flail valve                 | 0.27                | 1.30 | (0.84-4.1) | -              |
| Constant                        | -2.74               |      |            |                |

**Table 1.** Multivariate logistic regression analysis for the combined final endpoint (symptoms and/or LV dysfunction). Determination of relative scores for each variable from the relative weight of the variable in the model

ESD: End-systolic diameter LA: Left atrium. EROA: Effective regurgitant orifice area. EDD: End-diastolic diameter

**Table 2.** Clinical and echocardiographic data of the study population

|  | Score < 2<br>(n = 86) | Score 2-3<br>(n = 161) | Score > 3<br>(n = 128) |
|--|-----------------------|------------------------|------------------------|
| Mean age $\pm$ SD (years)                        | 56 $\pm$ 7            | 63 $\pm$ 9             | 67 $\pm$ 4*            |
| Sinus rhythm n, (%)                              | 73 (84)               | 119 (73)               | 89 (69)                |
| Mean systolic arterial pressure $\pm$ SD (mmHg)  | 146 $\pm$ 23          | 132 $\pm$ 27           | 119 $\pm$ 21           |
| Mean diastolic arterial pressure $\pm$ SD (mmHg) | 74 $\pm$ 11           | 69 $\pm$ 12            | 66 $\pm$ 14*           |
| LA volume > 120 cm <sup>3</sup>                  | 16 (18)               | 53 (33)                | 103 (80)               |
| ESD $\geq$ 40 mm, n (%)                          | 9 (10)                | 41 (25)                | 85 (67)*               |
| EORA > 55 mm <sup>2</sup> , n (%)                | 6 (7)                 | 31 (19)                | 92 (72)*               |

SD: Standard deviation. mmHg: Millimeters of mercury. LA: Left atrium. ESD: End-systolic diameter EROA: Effective regurgitant orifice area.

\*  $p < 0,05$  compared to other groups.

**Table 3.** Association between score and risk of events.

| Score | Prevalence events* | Combined | Mortality |
|-------|--------------------|----------|-----------|
| < 2   | 86                 | 23%      | 0%        |
| 2-3   | 161                | 43%      | 2,5%      |
| > 3   | 128                | 34%      | 4,7%      |

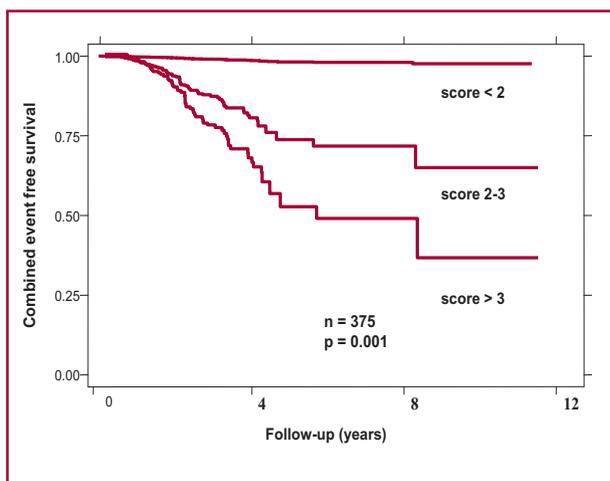
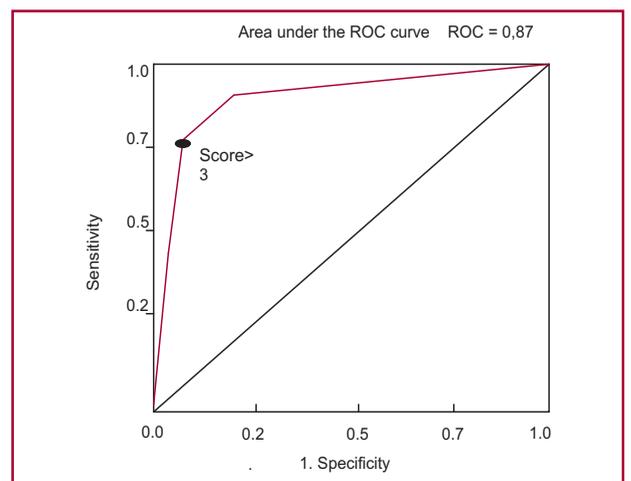
\*Combined events: symptoms and/or LV dysfunction (decrease in LVEF > 5% or LVEF < 60%).

**Table 4.** Relation between event rate and mitral regurgitation score.

| Score | Combined event<br>(n = 145; 39%) | Symptoms<br>(n = 157; 42%) | Ventricular dysfunction**<br>(n = 99; 26%) | Heart valve surgery<br>(n = 207; 55%) |
|-------|----------------------------------|----------------------------|--|---------------------------------------|
| < 2   | 2.3 $\pm$ 0.1                    | 3.1 $\pm$ 0.4              | 0.1 $\pm$ 0.06                             | 19 $\pm$ 5                            |
| 2-3   | 28 $\pm$ 4                       | 41 $\pm$ 4                 | 35 $\pm$ 7                                 | 57 $\pm$ 8                            |
| > 3   | 73 $\pm$ 9                       | 82 $\pm$ 9                 | 71 $\pm$ 6                                 | 84 $\pm$ 7                            |

\*Combined event: symptoms and/or LV dysfunction (decrease in LVEF > 5% or LVEF < 60%).

\*\*LV dysfunction (decrease in LVEF > 5% or LVEF < 60%).

**Fig. 1.** Relationship between combined event free survival and mitral regurgitation score.**Fig. 2.** ROC curve for combined events (symptoms and/or LV dysfunction) related to mitral regurgitation score.

mitral valve replacement in patients with left ventricular dysfunction (LVEF < 60%) and ventricular dilatation (ESD  $\geq$  40 mm); nevertheless, other weight variables should be considered for risk stratification.

(1-4) Mitral regurgitation is a condition that produces deep changes in ventricular function and afterload; therefore, although contractility indices (LVEF) are useful, they may not represent the real contractile

status of the LV. In addition, volume overload represented not only by left ventricular size but also by quantitative indices, such as RF, RV and EORA, must also be considered. (4, 9)

Both EDD and LA size are well-known indices of volume overload that express the hemodynamic impact of mitral regurgitation. (1, 4, 6, 17). End-systolic diameter greater than 40 mm has been considered an independent predictor of poor preoperative and postoperative outcomes in terms of morbidity and mortality. We have previously reported greater mortality rates in patients with ESD between 40-44 mm and  $e''$  45 mm compared to those with ESD < 40 mm. (17) In turn, progression to postoperative heart failure and ventricular dysfunction was greater in the subgroup of patients with DFS > 40 mm.

A negative stress test with exercise duration > 7 minutes is an objective measurement of functional capacity that allows identifying which patients will develop symptoms. (18) A recent study has assessed the predictive capacity of exercise duration related to postoperative morbidity and mortality in patients with organic MR. Postoperative risk for death and symptoms persistence was 5 times and 6 times greater in the group of patients with exercise duration < 7 minutes, respectively. (18)

We have previously reported that EORA was the best predictor of ventricular dysfunction and development of symptoms in asymptomatic patients with severe MR; in addition, this parameter was useful to identify the presence of symptoms and late events. Indices of valve lesion (such as EORA) are relevant for patient follow-up and for a better differentiation between symptomatic and asymptomatic patients. It has been demonstrated that in patients with EORA  $^3$  55 mm<sup>2</sup> the likelihood to develop symptoms due to MR was > 80%; when the change rate of the EROA was > 15%, the probability of events at 3-year follow-up was 60% and 80% in symptomatic and asymptomatic patients, respectively. (19) It takes a while to calculate EORA, as it requires estimation of rings diameters and of time-velocity integrals at the left ventricular outflow tract and through the mitral valve; yet its reproducibility is high. (15, 16) Changes in EROA throughout ventricular systole in patients with organic valve disease can lead to overestimation of the overall degree of regurgitation. (20)

When paroxysmal or permanent atrial fibrillation – a marker of progression of the disease – develops, early intervention increases survival free of symptoms and of heart failure. (21, 22)

For all the aforementioned reasons, we assessed the usefulness of a score that incorporated simple and reproducible variables with the objective of a better risk stratification to identify patients with unfavorable prognosis. (1, 4, 23) The association of clinical, exercise and echocardiographic variables already known allows identifying mortality risk, progression of left ventricular dysfunction and need of heart valve sur-

gery. This is important because early surgical indication will depend not only on surgical technique used but also on the capacity of association of the variables mentioned above.

### Study Limitations

The choice of a combined endpoint is a matter of opinion, especially because it attributes the same value to events of diverse clinical relevance. Anyway, development of symptoms and/or ventricular dysfunction has similar clinical relevance to be considered primary endpoint according to the point of view of the authors.

This score should be compared with current criteria for prognostic stratification in mitral regurgitation.

Levels of atrial natriuretic peptide were not determined in this study. This may be a weight variable for risk stratification. (24, 25) Nevertheless, the predictive capacity and the accuracy of this score are high even in absence of this hemodynamic parameter.

### CONCLUSION

In asymptomatic patients with severe mitral valve regurgitation, a score using clinical, echocardiographic and exercise variables is useful to identify subgroups of patients at greater long-term risk.

### Competing interests

None declared.

### RESUMEN

#### Estratificación de riesgo en la insuficiencia mitral grave asintomática: ¿cómo se podría identificar a los pacientes con evolución adversa?

##### Objetivo

Evaluar un puntaje que incorpore variables clínicas, ecocardiográficas y de ejercicio que identifiquen peor evolución en pacientes con insuficiencia mitral grave de causa orgánica asintomáticos.

##### Material y métodos

Se evaluaron 375 pacientes asintomáticos con insuficiencia mitral grave de causa orgánica (61 ± 10 años, 63% hombres, fracción de eyección del ventrículo izquierdo [FEVI] 67% ± 5%). Se elaboró un puntaje basado en la presencia de fibrilación auricular, diámetro de fin de sístole  $^3$  40 mm, orificio regurgitante efectivo > 55 mm<sup>2</sup>, volumen auricular izquierdo > 120 cm<sup>3</sup>, edad > 60 años, tiempo de ejercicio < 7 minutos. El rango del puntaje fue de 0-6,5.

El punto final primario fue desarrollo de síntomas y/o disfunción ventricular (caída de la FEVI > 5% o FEVI < 60%). Los puntos secundarios fueron síntomas aislados, disfunción ventricular aislada, muerte cardíaca y cirugía valvular.

##### Resultados

Durante un seguimiento promedio de 10 ± 3,5 años, 145 pacientes (39%) presentaron el punto final primario; 157 (42%) presentaron síntomas, 99 (26%) disfunción ventri-

cular, 10 (2,6%) fallecieron (7 de causa cardíaca) y se operaron 207 pacientes (55%). El punto final primario con puntaje < 2 fue del 2,3%, con puntaje 2-3 fue del 26% y con puntaje > 3 fue del 78%. La tasa de eventos primarios con puntaje < 2, 2-3 y > 3 fue del 2,3% ± 0,1%, 28% ± 4% y 73% ± 9%, respectivamente. El área bajo la curva operador-receptor fue de 0,87.

### Conclusión

En pacientes asintomáticos con insuficiencia mitral grave, la utilización de un puntaje que considere variables clínicas, ecocardiográficas y de ejercicio permite identificar subgrupos de mayor riesgo a largo plazo.

**Palabras clave** > Insuficiencia de la válvula mitral - Riesgo - Cirugía torácica - Pronóstico

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