Editorial

4A score: prognostic value of clinical assessment in paucisymptomatic tricuspid regurgitation

Clasificación 4A: el valor pronóstico de la clínica en la insuficiencia tricuspídea paucisintomática

Joan Guzmán-Bofarull, Ilana Forado-Benatar, and Marta Farrero*

Unidad de Insuficiencia Cardiaca, Hospital Clínic de Barcelona, Barcelona, Spain

Tricuspid regurgitation (TR) is a highly frequent but classically overlooked condition. This heart valve disorder is slowly gaining prominence in cardiology circles, both from the clinical perspective and in the heart failure setting and in relation to imaging techniques and interventional cardiology. This is due to growing interest in the study of right ventricular congestion and function, associated with emerging techniques for percutaneous tricuspid repair. However, there is a lack simple and reproducible clinical tools that could help to stratify prognosis and the need for follow-up.

In an article published recently in *Revista Española de Cardiología*, González-Gómez et al.[1] proposed an intriguing clinical classification for patients with TR: the 4A score. In a cohort of 135 patients with severe isolated TR without previous decompensated heart failure events, the authors assessed the presence of 4 typical signs or symptoms in patients with significant TR: asthenia, anorexia, abdominal pain or distension, and ankle swelling. Based on the presence or absence of these signs/symptoms, patients were classified from A0 to A3. The primary study endpoint was cardiovascular death or hospital admission due to right heart failure. This simple classification, based on data easily obtained during a clinical assessment, was strongly associated with the presence of the primary endpoint: patients in classes A2 and A3 showed a higher incidence of events and a class worsening during follow-up.

TRICUSPID REGURGITATION

TR is a common finding in the echocardiography laboratory that is detected in up to 80% to 90% of the general population.[2] Advanced and symptomatic grades affect 4% of the population older than 75 years and 0.55% of the general population.[3] Considerable evidence has linked TR to elevated morbidity and mortality, independently of the degree of right ventricular dysfunction or the presence of pulmonary hypertension,[4] with 2 types of clinical consequences: exercise intolerance due to low cardiac output and symptoms of systemic venous congestion, as well as renal and hepatic dysfunction in advanced stages.

TR has historically been the forgotten valvular heart disease, and physicians mainly consider its management when patients require a left-sided valvular heart disease intervention. Isolated TR is underrepresented in studies and underestimated as a pathological entity. This has led to the underuse of the available diagnostic and therapeutic tools, which delays medical decisions, even in patients in advanced stages of the disease and with already unacceptable surgical risk.[3] The current clinical practice guidelines recommend the treatment of isolated TR if it is severe, symptomatic, and associated with right ventricular dilatation.[5] Percutaneous repair techniques are a burgeoning therapeutic alternative, although evidence supporting their long-term efficacy and clinical impact is still scarce.

An example of how TR has been overlooked is the classic clinical classification of patients with heart failure, the New York Heart Association (NYHA) scale. Used for the follow-up and management of patients with heart failure,[6] the NYHA scale is based on dyspnea on exertion, a highly representative symptom in patients with heart failure or largely left-sided valvular heart disease that is probably less important in tricuspid valve disease and right ventricular dysfunction.

Given the clinical presence of significant TR, its prognostic impact, and the current indications for invasive treatment, there is an urgent need to determine whether paucisymptomatic patients with right ventricular dysfunction or dilatation merit a more exhaustive follow-up or could benefit from an early intervention that may improve their prognosis before the intervention risk becomes unacceptably high or the intervention is futile.

This characteristic underscores the importance of the 4A classification proposed by González-Gómez et al.,[1] as the first classification with clinical data specifically aimed at evaluating TR that obtains prognostic information and is easily performed.

STUDY POPULATION: CHARACTERISTICS OF THE 4A COHORT

The patient cohort in the article by González-Gómez et al. has the classically described clinical characteristics of TR, such as a predominance of women (69%) and advanced age (78 years).[1]

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2023.02.008

* Corresponding author.
E-mail address: mfarrero@clinic.cat (M. Farrero).
✕ @MartaFarrero @JGuzmanBofarull @IForado

In general, the study population possessed clinical, analytical, and echocardiographic characteristics indicating a not particularly advanced condition:

- Most patients were in NYHA functional class I or II at the start of follow-up.
- Hepatorenal function was within normal limits, indicating that the population was in a relatively decongested splanchnic state.
- Left ventricular function was normal and the right ventricle was only slightly dilated, with normal tricuspid annular plane systolic excursion, fractional area change, and S' wave.

In contrast, other characteristics of the study population suggested worse severity. For example, the TR grade was severe in 83% of the patients, massive in 13%, and torrential in 4%, and the prevalence of atrial fibrillation was high (up to 87%); the latter is typically associated with more advanced disease, greater remodeling, and worse clinical outcomes. Atrial fibrillation can be a major etiological cause in the TR subtype related to dilatation of the tricuspid annulus and growth of the right atrium. This subtype was present in 39% of the cohort patients.

Using the clinical classification proposed by González-Gómez et al.,[1] 50% of patients belonged to category A1 or higher (26% in A1, 11% in A2, and 13% in A3). This figure largely corresponded to the proportion of patients requiring diuretic treatment, which was 67%. This increased sensitivity for detecting patients with clinically significant disease compared with the NYHA functional classification or right ventricular ultrasound is highly relevant because it would permit us to identify patients falsely considered to be low risk by conventional measures and who would benefit from a more rigorous follow-up or early intervention.

All 3 severity grades of TR included in the cohort (severe, massive, and torrential) had similar scores with the 4A classification. This suggests that TR severity is not the main factor in the development of symptoms.

Finally, another pertinent aspect in the analysis of the characteristics of the study cohort is the authors' decision to exclude patients with TR secondary to uncorrected left-sided valvular heart disease. The decision was prudent because it allowed the authors to analyze a more homogeneous population, in which the signs and symptoms are more directly attributable to the predominant component of TR, without inference from left heart disease. However, the exclusion of these patients means exclusion of the most common cause of TR,[7] which limits direct extrapolation of this classification to the overall group of patients with TR.

4A CLASSIFICATION CHARACTERISTICS AND STUDY RESULTS

The value of the signs and symptoms chosen to comprise the 4A classification lies in 2 main aspects. On the one hand, they reflect both the classic congestion and low cardiac output of right heart failure. On the other hand, they are clinically accessible and easily evaluated as part of the standard medical record system and physical examination of all patients with heart failure.

One way to reduce subjectivity and improve the accuracy of clinical evaluation would be to consider a scale that grades each symptom or even incorporates objective variables such as the 6-minute walk test and cardiopulmonary exercise testing. Although this suggestion may be tempting in scientific terms, it would make the assessment more complex and less immediate and would erode the simplicity and accessibility of the 4A classification, which are its main advantages.

The primary endpoint chosen by the researchers was a composite of hospital admission due to heart failure and cardiovascular mortality. Overall, 39% of the patients showed the combined endpoint: 34% had heart failure and 5% experienced cardiovascular death after a median follow-up of 26 months. Patients classified in A2 and A3 showed an elevated incidence of events, similar to patients who had a class worsening to A2 and A3 during follow-up, whose risk of the primary endpoint practically doubled.

The authors separately analyzed the individual components of the 4A classification, which all showed good correlations with event onset. The main strength of the 4A score is the good correlation between the simple, accessible, and clinical classification and outcomes such as admission and death.

Although the classification is clinical, laboratory tests were also performed in the study. B-type natriuretic peptide levels were relatively low (median, 141 pg/mL) and provided no prognostic value for heart failure or death, which is probably expected in a population with normal left ventricular ejection fraction and predominant involvement of the right chambers. In future work, it would be interesting to analyze the levels of other biomarkers such as carbohydrate antigen 125 (CA125), because this biomarker has been more consistently associated with the development of right heart failure and systemic congestion.[8,9] Regarding liver function, gamma-glutamyl transpeptidase (GGT) level was an independent predictor of heart failure and cardiovascular mortality ($P > .001$), unlike the other liver enzymes. This finding corresponds well with the interpretation of GGT as a marker of liver congestion, a phenomenon predominant in TR, in contrast to liver ischemia, which is more related to aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[10] The recently published TRIO (Tricuspid Regurgitation Impact on Outcomes score) scale[11] identified 8 predictors of 10-year mortality in patients with moderate-to-severe TR: age, sex, creatinine concentration, congestive heart failure, lung disease, elevated heart rate, AST > 40 U/L, and TR severity. In this case, in contrast to the findings of González-Gómez et al.,[1] an AST value > 40 U/L was associated with mortality. This difference could be due to the inclusion of patients with left ventricular dysfunction and a lower grade of TR, in whom poor antegrade perfusion could play a more important role.

STUDY LIMITATIONS

Despite the value of this study and of the newly proposed clinical classification, it has some limitations, such as its observational and single-centre design and somewhat small population (albeit notable because it concerns a TR population). Second, the exclusion of patients with left-sided valvular heart disease limits the applicability of the 4A classification to this not insignificant population. Third, the long recruitment period and the differences in patient follow-up times may make it difficult to reach definitive conclusions regarding the course of this valvular heart disease. Fourth, the C statistic of 0.6 indicates a modest association, which could undermine the application of the score. Finally, 37 patients who underwent an intervention (14 percutaneous and 23 surgical) were excluded from the subsequent analysis. Accordingly, we do not know whether the 4A score improved after the intervention or whether the score was associated with an improved prognosis.

CONCLUSION AND FUTURE DIRECTIONS

In conclusion, the 4A classification proposed by González-Gómez et al.[1] is a new tool designed for the prognostic

stratification of patients with severe TR. This risk classification is simple and easily applied in the clinic and exhibits better discriminative and predictive power than the classic NYHA score. The items included are widely known signs and symptoms that have been grouped together to create a classification for patients with right-sided valvular heart disease.

The new classification enables us to detect symptomatic or paucisymptomatic patients who are not in advanced stages of the disease and who have potentially normal hepatorenal function and preserved right ventricular function.

The combination of this classification with blood tests, particularly GGT assessment, could help to identify a patient population with higher risk who would require a more rigorous follow-up or even surgical repair.

Looking to the future, it would be interesting to study the 4A classification in a second validation cohort to confirm its usefulness in clinical practice and evaluate its prognostic significance in a cohort including patients with left-sided valvular heart disease. In addition, it would be helpful to determine whether the inclusion of biomarkers such as GGT and CA125 could increase the sensitivity or specificity of this tool. Finally, valuable findings could be obtained by studying changes over time in the 4A classification based on treatment modifications, particularly percutaneous tricuspid repair, and identifying whether it maintains its prognostic value in this setting or even whether it is a good way to identify patients who would derive greater benefit from this technique.

FUNDING

CONFLICTS OF INTEREST

None of the authors have conflicts of interests related to the present article.

REFERENCES

1. González-Gómez A, Fernández-Golfín C, Rocío Hinojar R, et al. The 4A classification for patients with tricuspid regurgitation. *Rev Esp Cardiol.* 2023. http://dx.doi.org/10.1016/j.rec.2023.02.008.
2. Nishimura RA, Otto CM, Bonow RO, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines.2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:e57–e185.
3. Kadri AN, Menon V, Sammour YM, et al. Outcomes of patients with severe tricuspid regurgitation and congestive heart failure. *Heart.* 2019;105:1813–1817.
4. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of Tricuspid Regurgitation in Patients Diagnosed in the Community Setting. *JACC Cardiovasc Imaging.* 2019;12:433–442.
5. Vahanian A, Beyersdorf F, Praz F, et al. ESC/EACTS Scientific Document Group 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2022;43:561–632.
6. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. JAMA. 1953;153:891.
7. Dietz MF, Prihadi EA, van der Bijl P, et al. Sex-specific differences in etiology and prognosis in patients with significant tricuspid regurgitation. *Am J Cardiol.* 2021;147:109–115.
8. Miñana G, de la Espriella R, Mollar A, et al. Factors associated with plasma antigen carbohydrate 125 and amino pro-B-type natriuretic peptid concentrations in acute heart failure. *Eur Heart J Acute Cardiovasc Care.* 2020;9:437–447.
9. Núñez J, Bayés-Genís A, Revuelta-López E, et al. Optimal carbohydrate antigen 125 cutpoint for identifying low-risk patients after admission for acute heart failure. *Rev Esp Cardiol.* 2022;75:316–324.
10. Weisberg IS, Jacobson IM. Cardiovascular diseases and the liver. *Clin Liver Dis.* 2011;15:1–20.
11. Lara-Breitinger KM, Scott CG, Nkomo VT, et al. Tricuspid Regurgitation Impact Outcomes: A simple clinical risk score. *Mayo Clin Proc.* 2022;97:1449–1461.