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NARRATIVE REVIEW

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Revisiting tricuspid regurgitation: Historical insights and emerging research perspectives

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Abstract

Background: Tricuspid regurgitation (TR), defined as the failure of proper leaflet coaptation during systole, is a common but often underrecognized valvular disorder. TR continues to rise, primarily due to population aging and the broader application of advanced diagnostic imaging techniques. Recent studies have established a clear association between TR and increased morbidity and mortality, thereby challenging its historical perception as a benign condition.

Methods: The development of novel interventional therapies, combined with enhanced insight into the pathophysiology of right-sided heart failure, has prompted a shift towards earlier diagnosis and more proactive clinical management.

Aim: Several gaps between novel scientific advancements and clinical translation still make this disease deserving of further attention.

Discussion and Conclusion: In this review, we examine the most recent advances in understanding TR, which have enabled improved segmentation of affected patient populations. This progress has made it possible to identify key prognostic markers—particularly those related to disease progression—allowing for more accurate risk stratification and significantly more personalized treatment approaches.

KEYWORDS

arrhythmias, imaging, molecular markers, patient stratification, prognostic markers, tricuspid regurgitation, tricuspid valve

Tricuspid regurgitation (TR) is a silent valvular heart disease that predominantly affects the aging population.[1–4] The asymptomatic onset in early stages often leads to delayed diagnosis, by which time structural damage is already advanced, contributing to high relapse rates between patients.[5,6] This diagnostic delay becomes especially concerning given current global demographic trends.

The United States and Europe are undergoing a profound demographic transformation, characterized by rapid population aging.[7,8] As the demographic pyramid continues to invert, the population aged over 80 is expected to increase by nearly 50% within the next 15 years. This trend is anticipated to result in a substantial rise in age-related cardiovascular conditions,[9–11] underscoring the urgent need for heightened

clinical vigilance and earlier preventive strategies. Given that the prevalence of TR increases with age, and that its milder forms often remain clinically silent, significant underdiagnosis persists.[12,13] This evolving landscape highlights the critical need for proactive screening protocols and effective risk stratification, particularly among vulnerable groups, before the onset of irreversible disease progression.

TR was historically considered a benign or secondary condition. However, it is now recognized as an independent contributor to morbidity and mortality, largely due to its association with severe cardiovascular complications, particularly in patients with right-sided heart failure and arrhythmogenic profiles. Notably, several studies have demonstrated that moderate-to-severe TR is independently linked to increased mortality, regardless of biventricular function or the presence of pulmonary hypertension.[5] Although often regarded as a common and benign echocardiographic finding, TR becomes clinically significant when associated with pulmonary hypertension or right/left ventricular dysfunction.[14,15]

In a large retrospective study of 5223 patients, TR severity was correlated with reduced survival in men, independent of left ventricular ejection fraction (LVEF) or pulmonary artery pressure.[5] Mortality significantly increased with TR severity, including in cases of isolated TR, and was defined as regurgitation without concomitant major structural heart disease, which carries a particularly high burden of morbidity and mortality. Clinical consequences commonly include congestive heart failure, arrhythmias (especially atrial fibrillation) and increased need for permanent pacemaker implantation.[16,17]

Additional evidence indicates that moderate-to-severe isolated TR is associated with an approximately twofold increase in mortality risk and significantly higher rates of heart failure–related hospitalizations.[18] Furthermore, in-hospital mortality after isolated tricuspid valve surgery ranges from 7% to 10%, with late postoperative mortality approaching 40% during medium-term follow-up.[19]

In light of its broad clinical implications and consistent association with adverse outcomes, TR should no longer be viewed as a benign or incidental secondary finding. Indeed, TR should be recognized as a distinct and actionable therapeutic target. The evolving field of transcatheter tricuspid interventions, along with new insights into right-sided cardiac pathophysiology, offers an opportunity for earlier detection and more proactive, personalized management.

1 | PATHOPHYSIOLOGICAL MECHANISMS OF TR

TR is a heterogeneous condition arising from diverse anatomical and functional alterations involving the tricuspid valve (TV), right ventricle (RV) and right atrium (RA). Although traditionally viewed as a secondary effect of left-sided heart disease or pulmonary hypertension, recent evidence shows TR has distinct pathophysiology and prognostic significance.[4,20]

The TV is the largest, most anterior cardiac valve with three leaflets—anterior, posterior and septal—supported by a dynamic annulus and complex subvalvular apparatus. Variability in leaflet number and orientation is common and affects transcatheter therapies planning.[20] Three-dimensional echocardiography has substantially improved the assessment of leaflet coaptation and annular motion, enabling a more accurate diagnosis of TR mechanism and severity.[21]

TR is broadly classified as primary, when it results from intrinsic leaflet abnormalities (e.g. rheumatic disease, endocarditis, carcinoid syndrome), and secondary, when caused by annular dilation and/or leaflet tethering without intrinsic valve disease.[20,22] Secondary TR (STR), accounts for over 80% of cases, and is further stratified into atrial STR (A-STR) and ventricular STR (V-STR) phenotypes based on right-heart chamber remodelling.[21,22] A-STR is typically associated with atrial fibrillation and RA dilation, with preserved RV geometry and function. In contrast, V-STR reflects significant RV dilation, dysfunction and leaflet tethering.[22,23]

This pathophysiological distinction has relevant prognostic and therapeutic implications. Patients with A-STR demonstrate better natural history and clinical response to interventions compared to those with V-STR.[23,24] The recent consensus from the Tricuspid Valve Academic Research Consortium (TVARC) and the Partnership of Cardiovascular Research Tricuspid Focus Group (PCR Tricuspid Focus Group) reinforces the clinical utility of this classification.[22,23,25]

Complementing structural assessment, the 4A clinical classification, based on the presence of asthenia, ankle swelling, abdominal discomfort and anorexia, offers a simple yet powerful tool for symptom-based stratification. Patients with higher 4A classes have higher hospitalization and cardiovascular death rates, even if NYHA class is low.[26]

From a functional standpoint, progressive RA and RV remodelling due to chronic volume overload is central to TR progression. This remodelling leads to annular dilation and further leaflet malcoaptation, perpetuating a vicious cycle. Emerging echocardiographic techniques such as speckle-tracking-derived strain imaging have shown promise in identifying early RV and RA dysfunction.[22,27,28] These advances emphasize the evolving understanding of TR not as a benign secondary lesion but as an active and modifiable contributor to adverse outcomes, warranting dedicated diagnostic and therapeutic strategies. The

recently proposed Speckle-Tracking Echocardiography Ratio Index (STREI), which integrates RV-free wall longitudinal strain (RV-FWLS) and RA reservoir strain (RASr), independently predicts cardiovascular outcomes and enables enhanced risk stratification beyond traditional echocardiographic parameters.[29] As illustrated in Figure 1, patients with combined abnormalities in RASr and RV-FWLS are stratified into four prognostic groups, with progressively higher event rates, independent of TR severity or chamber dimensions. This stratification reflects the additive impact of atrial and ventricular dysfunction on right heart failure risk.

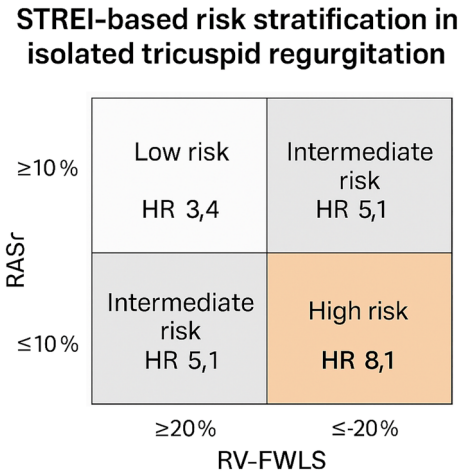

FIGURE 1 STREI-based risk stratification in isolated tricuspid regurgitation. Patients are stratified into four groups based on RASr (<10%) and RV-FWLS (>−20%), with incremental hazard ratios for the composite endpoint (HF hospitalization and mortality). (*Source*: Hinojar, Fernández-Golfín, et al., 2024).

1.1 | Predictors and Markers of TR Progression

TR progression is associated with demographic and clinical factors, including age, male sex, pulmonary hypertension and atrial fibrillation. However, these markers are not sufficiently sensitive to detect early structural or functional decline.[5,6] This limitation has hindered the timely identification of high-risk patients, underscoring the need for more refined predictive tools.

Imaging-based markers have emerged as critical elements in predicting TR progression. In a foundational study, Prihadi et al. demonstrated that tricuspid annular dilation, leaflet tethering and RA enlargement were independent predictors of worsening TR over time, even in patients with initially mild-to-moderate disease, highlighting the anatomical substrates of functional TR.[22,30] Similarly, Mutlak et al. showed that right atrial area alone was a powerful predictor of progression and adverse outcomes, suggesting that atrial remodelling may precede overt ventricular dysfunction.[3]

Recent advances in cardiac magnetic resonance (CMR) have further improved risk stratification. In a 2025 multicenter study, RMC parameters, particularly right ventricular end-diastolic volume index (RVEDVi) and RV ejection fraction, were independently associated with the future development of severe TR, regardless of baseline severity. Importantly, CMR also captured subclinical RV dysfunction missed by echocardiography, reinforcing its value in longitudinal monitoring.[31] These findings support the incorporation of CMR in select patients to identify early maladaptive changes.

Complementing anatomical and volumetric markers, strain-based functional indices have also become

TABLE 1 Functional, anatomical and clinical markers for risk assessment in TR.

Marker type	Specific parameter	Assessment tool	Key references
Functional	↓ TAPSE	2D/3D Echocardiography	Hinojar et al.[31]
Functional	↓ RV-FWLS (RV free-wall longitudinal strain)	Speckle tracking	Hinojar, Fernández-Golfín, et al.[29]
Functional	↓ RASr (RA reservoir strain)	Speckle tracking	Hinojar, Fernández-Golfín, et al.[29]
Anatomical	↑ Right atrial volume	CMR/3D Echo	Mutlak et al.[3]
Anatomical	↑ RV end-diastolic volume	CMR	Hinojar et al.[31]
Anatomical	↑ Leaflet tethering angle	3D Echocardiography	Prihadi, Van Der Bijl, et al.[22]
Clinical	4A (asthenia, ankle oedema, abdominal discomfort, anorexia)	Clinical exam/scoring system	González-Gómez et al.[26]
Traditional	Older age	Clinical history	Nath et al.[5]
Traditional	Male sex	Clinical history	Topilsky et al.[6]
Traditional	Pulmonary hypertension	Clinical history	Taramasso et al.[32]
Traditional	Atrial fibrillation	Clinical history	Topilsky et al.[6]

increasingly relevant. A recent prospective study demonstrated that declining RASr and RV-FWLS anticipated symptomatic worsening and adverse events, even in patients with moderate TR. These variables, consolidated into the STREI, provide a reproducible, non-invasive composite measure of right heart performance with prognostic value.[24]

As mentioned before, the 4A classification, which includes asthenia, ankle swelling, abdominal discomfort and anorexia, also offers a simple and effective way to quantify right-heart failure burden and predict adverse outcomes.[26]

Taken together, these findings collectively support a novel multimodal and multidimensional approach to risk assessment in TR. Moving beyond classical demographics, the integration of echocardiographic strain, cardiac MRI parameters and symptom-based scores may allow earlier identification of patients who will benefit most from timely intervention (Table 1).

2 | NATURAL HISTORY AND DISEASE TRAJECTORY OF TR

The natural history of TR is marked by a progressive decline in right heart structure and function, often occurring silently until evident clinical decompensation. Mild TR may remain stable for years, but in a significant proportion of patients, particularly those with predisposing anatomical or functional abnormalities, the condition evolves into moderate or severe regurgitation, with associated increases in morbidity and mortality.[33,34] Progression is typically driven by chronic volume overload, leading to right atrial and ventricular remodelling. As the annulus dilates and leaflet coaptation worsens, TR severity intensifies in a self-perpetuating loop. Concurrently, declining RV function and increased venous pressure contribute to hepatic congestion, renal impairment and exercise intolerance.[35]

Several studies indicate that in patients with initially mild-to-moderate TR, approximately 25–30% experience worsening grade over 5 years.[31,36,37] These patients frequently transition from asymptomatic to symptomatic status, often with signs of right-sided heart failure, including peripheral oedema, fatigue and abdominal bloating. In this context, early identification of patients with high-risk features is critical. The emergence of strain imaging and CMR has enabled the detection of subclinical changes that predict adverse remodelling. In particular, reductions in RV longitudinal strain and RA reservoir function are early signals of impending functional decline.[31]

Furthermore, disease trajectory may be influenced by comorbid conditions such as atrial fibrillation, pulmonary hypertension, and left-sided heart disease. The interplay of these factors contributes to clinical heterogeneity and underscores the need for individualized monitoring strategies. Hence, recognizing the full trajectory of TR from subclinical dysfunction to overt right heart failure is essential for optimizing the timing of intervention and improving patient outcomes.[38,39]

According to the 2025 ESC/EACTS Guidelines for the management of valvular heart disease, delayed referral remains a major determinant of poor outcomes in.

TR, as many patients undergo intervention only once severe RV or multiorgan dysfunction has developed. Historically, this contributed to the reported high in-hospital mortality rates for isolated tricuspid surgery. Contemporary series, however, consistently demonstrate that earlier intervention, before the onset of irreversible RV failure, is associated with substantially improved surgical outcomes. In this context, guideline recommendations highlight the indication for surgery not only in symptomatic patients with severe secondary TR, but also in asymptomatic patients with primary or secondary TR accompanied by RV dilatation or early functional deterioration. The guidelines also provide specific cut-off values of RV functional parameters (e.g. RV-FWLS, TAPSE and fractional area change) to aid in the detection of clinically relevant dysfunction, underscoring the importance of timely recognition of subclinical impairment.[40]

3 | CURRENT GRADING OF TR SEVERITY

The severity of TR has traditionally been classified into three grades: mild, moderate, and severe. While this approach remains foundational, recent data underscore its limitations, especially in distinguishing high-risk phenotypes within the 'severe' category. To address this gap, an expanded classification system has been proposed and validated in recent years.[40,41] This refined framework introduces two additional categories: massive and torrential TR, to stratify disease severity better and correlate with patient outcomes. Moreover, Hahn et al.[18,22] confirmed the clinical relevance of this extended framework by validating its prognostic value in real-world transcatheter tricuspid interventions. Their findings support the adoption of an expanded TR severity scale for decision-making in both medical and interventional therapy (Table 2).

The refined classifications of TR severity, including the additional categories of 'massive' and 'torrential' TR, are now explicitly acknowledged in the guidelines as carrying adverse prognostic significance and therefore represent a valuable extension to conventional grading Schemes.[41] In parallel, the recently introduced STREI index, which combines RASr and RV-FWLS, extends

TABLE 2 Traditional and expanded grading criteria and their impact on clinical implications.

Grade	Vena contracta width (cm)	Regurgitant jet area	Clinical description
Mild	<0.3	Small, central jet	Minimal regurgitation
Moderate	0.3–0.69	Moderate central jet	Often asymptomatic, may progress
Severe	≥0.7	Large central or eccentric jet	Associated with RV dysfunction
Massive	>1.0	Very large jet	Right heart dilatation, systemic effects
Torrential	>1.4	Holosystolic reversal in hepatic veins	Severe systemic congestion

these guideline-endorsed thresholds by complementing RV evaluation with RA functional assessment. This dual-chamber approach enables quantification of progressive changes in both RA and RV performance during the disease course, thereby unmasking earlier deleterious effects of TR.[29] Importantly, STREI stratification identifies distinct prognostic groups based on validated strain thresholds, providing incremental prognostic value beyond TR severity or chamber size. By integrating RA and RV functional impairment, this tool refines the assessment of right heart performance, offers a more comprehensive framework for risk stratification, and is likely to facilitate its translation into routine clinical practice alongside guideline-directed parameters.

Santoro et al.[41] demonstrated that patients with massive or torrential TR had significantly higher cardiovascular mortality and heart failure rehospitalization compared to those with severe TR (hazard ratio 2.48, 95% CI 1.25–4.93). These findings highlight the prognostic utility of distinguishing extreme TR phenotypes for guiding the timing of intervention and monitoring strategies. Similarly, Hahn et al.,[22] also confirmed that the massive/torrential categories were independently associated with poor procedural outcomes and reduced survival following transcatheter valve intervention, validating the need for refined risk stratification.

4 | EMERGING THERAPEUTIC STRATEGIES AND INTERVENTIONAL APPROACHES

Historically, TR was managed conservatively, with intervention reserved for patients undergoing left-sided heart valve surgery or in cases of advanced right heart failure.[35,41,42] However, increasing recognition of TR as an independent contributor to morbidity and mortality has catalysed a shift towards earlier and more targeted therapeutic strategies.

Surgical treatment of isolated TR has remained underutilized due to historically high operative risk and limited postoperative survival. In-hospital mortality rates range from 7% to 10%, with medium-term mortality approaching 40% (19 Scotti et al., 2022). These outcomes have prompted interest in less invasive, catheter-based alternatives, particularly in patients deemed high-risk for surgery. Recent years have witnessed significant advancements in transcatheter tricuspid valve interventions (TTVI), including edge-to-edge repair, annuloplasty devices and valve replacement systems.[25,43,44] Multiple observational registries, including TRILUMINATE and CLASP-TR,[45,46] have demonstrated favourable short-term safety and efficacy, with improvements in NYHA class, quality of life and reductions in TR severity (Table 3).

Guidelines currently recommend TTVI for symptomatic patients with severe or greater TR who are at prohibitive surgical risk, particularly when anatomy is favourable and right ventricular function is preserved or only mildly reduced.

Anatomical suitability and timing of intervention remain critical determinants of success. Predictors of poor outcome include advanced RV dysfunction, torrential TR, massive annular dilation and comorbidities such as severe pulmonary hypertension. As such, early referral and assessment by a multidisciplinary heart team are essential for optimizing outcomes. As interventional devices mature and prospective trials continue to validate their efficacy, transcatheter therapies are expected to redefine the management landscape of TR. The paradigm is shifting from passive observation to earlier, anatomy-guided intervention aimed at preventing irreversible right heart deterioration.

5 | MOLECULAR TOOLS AND BIOMARKERS IN TRICUSPID REGURGITATION: EMERGING INSIGHTS

Growing interest in the role of molecular signatures in TR has led to the identification of non-coding RNAs (lncRNAs), particularly microRNAs (miRNAs), as potential biomarkers for disease presence, progression and remodelling. In a pivotal study, we investigated the expression profile of circulating miRNAs in patients with isolated

functional TR, aiming to identify molecular signatures that could differentiate pathological TR from controls and healthy individuals. We reported a distinct pattern of upregulated and downregulated miRNAs in patients with TR, several of which are implicated in myocardial fibrosis, inflammation, and atrial remodelling.[47,48] Specifically, upregulated miRNAs included miR-125b, miR-21 and miR-199a, associated with fibrotic signalling pathways and TGF-β activation, whereas downregulated miRNAs miR-30a and miR-1 correlated with impaired myocardial relaxation and maladaptive RV adaptation.

These alterations were consistent with the imaging findings of right atrial and ventricular dysfunction, suggesting that circulating miRNAs may serve as early, non-invasive indicators of structural remodelling in functional TR. Notably, miRNA expression also correlated with RA reservoir strain and RV free-wall strain, indicating potential utility in refining risk stratification when combined with imaging biomarkers like STREI.[47]

Complementing these findings, Tian et al. also performed an integrated transcriptomic analysis in myocardial tissue from TR patients, identifying several lncRNA–miRNA–mRNA networks associated with immune response and fibrosis.[49] These include CERS6-AS1/miR-539-5p/TRPM5 and DLX6-AS1/miR-497-5p/CXCL8 axes. These molecular interactions highlight active remodelling pathways in the right heart and may represent future therapeutic targets (Table 4).

The immune system may play a key role in advanced TR. Although TR is primarily viewed as a structural or

TABLE 3 Comparison between surgical and transcatheter interventions for the treatment of the tricuspid valve.

Feature	Surgical repair/replacement	TTVI
Indication	Often secondary to left-sided surgery or severe symptomatic TR	Severe symptomatic TR in high-risk surgical candidates
Invasiveness	Highly invasive (open-heart)	Minimally invasive
Perioperative mortality	7–10%	<5% (in recent registries)
Long-term survival	~60% at 5 years	Data emerging, promising early results
Eligibility	Limited in frail/elderly patients	Broader candidacy with anatomical selection
Techniques	Valve repair or replacement	Edge-to-edge repair, annuloplasty or valve implantation
Recovery time	Prolonged	Shorter hospital stays
Guideline position	Recommended in selected surgical patients	Emerging Class IIb–IIa (depending on anatomy and risk)

TABLE 4 The role of molecular biomarkers in the diagnosis and prognosis of TR.

Marker	Type	Biological role/mechanism	Clinical application	References
miR-125b/miR-21/miR-199a	Circulating miRNAs	Fibrosis, TGF-β pathway activation	TR diagnosis, fibrosis monitoring	Hinojar, Moreno-Gómez-Toledano et al.[47]
miR-30a/miR-1	Circulating miRNAs	Contractility, RV maladaptation	Risk stratification in functional TR	Hinojar, Moreno-Gómez-Toledano et al.[47]
CERS6-AS1/miR-539-5p/TRPM5	lncRNA–miRNA–mRNA axis	Calcium signalling, immune modulation	Molecular profiling, tissue targeting	Tian et al.[49]
DLX6-AS1/miR-497-5p/CXCL8	lncRNA–miRNA–mRNA axis	Inflammation, extracellular matrix remodelling	Biomarker discovery, fibrosis response	Tian et al.[49]
ADRA1A, TRPM5, CXCL8 (hub genes)	mRNAs	Cardiomyopathy-associated signalling	Target discovery, disease classification	Tian et al.[49]

mechanical valvular disorder, immune-mediated mechanisms can exacerbate its severity through multiple pathways. Recent studies have shown that in advanced stages of TR, immune cells release proinflammatory cytokines that promote structural remodelling of the heart. This inflammation-driven remodelling, especially affecting the right ventricle and tricuspid annulus, can trigger or worsen functional TR.[50] Similarly, proteomic analyses have indicated that a higher burden of comorbidities is linked to systemic inflammation, which correlates with increased E velocity, higher E/e' ratio and the presence of TR.[51] However, the exact role of inflammation in the early development of TR remains unclear and warrants further research.

Together, these data support a multimodal biomarker strategy, wherein circulating and tissue-based molecular markers complement strain imaging for early identification of patients at risk of progression, even in the absence of overt clinical decompensation.

6 | GAPS IN KNOWLEDGE, REGULATORY CHALLENGES, AND FUTURE DIRECTIONS

Despite a growing recognition of the clinical relevance of TR, significant challenges remain in understanding, diagnosing and managing this condition comprehensively.

6.1 | Scientific and translational gaps

Large-scale, randomized clinical trials dedicated exclusively to TR remain scarce. As a result, much of the current evidence relies on retrospective cohorts or post hoc analyses, limiting the strength of current recommendations.[52] Furthermore, TR is still frequently diagnosed at advanced stages, often when right ventricular dysfunction and irreversible atrial remodelling have already occurred.[53]

While imaging advances such as strain echocardiography and indices like STREI have improved early detection,[29] the integration of molecular markers, particularly circulating and tissue-based miRNAs and lncRNA networks,[47,49,54] is still lacking in clinical practice. Despite compelling data from recent studies, these biomarkers have not yet been validated in prospective trials, nor incorporated into risk-stratification algorithms or clinical guidelines. This reflects a translational bottleneck, where high-throughput molecular insights fail to influence bedside decision-making.

6.2 | Regulatory and implementation barriers

From a regulatory perspective, TTVI remains under provisional classifications (Class IIb in ESC and ACC/AHA guidelines), with restricted reimbursement policies in many healthcare systems.[55,56] The lack of standardized clinical endpoints for right heart failure complicates device approval and trial comparability. Imaging variability and incomplete patient phenotyping (e.g. absence of torrential TR in some datasets) further fragments the evidence base. Moreover, there is no validated tool for early identification of 'progressors', patients with mild or moderate TR at risk of advancing to massive/torrential disease.[57,58] This leads to late referrals, missed windows of intervention and suboptimal outcomes.

6.3 | Future directions

To address these gaps, several key priorities emerge: (i) standardize TR classification and phenotyping, incorporating extended severity scales and novel strain-derived indices. (ii) Validate and operationalize molecular biomarkers (e.g. circulating miRNAs, lncRNA-mRNA axes) in multicentre clinical studies to refine early detection and monitor therapeutic response. (iv) Harmonize imaging protocols and integrate multimodal risk models,

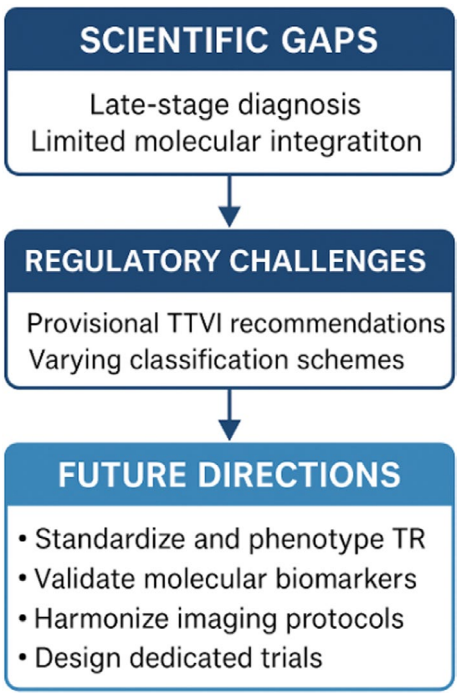

FIGURE 2 Bridging the knowledge-to-practice gaps in TR.

combining molecular, anatomical, and functional parameters. (v) Design dedicated TR trials with patient-centred endpoints and long-term follow-up, including high-risk or subclinical populations. (vi) Promote cross-disciplinary collaboration between basic scientists, imaging experts and regulatory bodies to accelerate the translation of mechanistic discoveries into actionable tools (Figure 2).

In summary, bridging the knowledge-to-practice gap in TR requires coordinated efforts across the scientific, clinical and regulatory spectrum. By embracing precision medicine tools and fostering earlier, evidence-based intervention, the field can move beyond observational inertia and transform patient care.

AUTHOR CONTRIBUTIONS

Writing—original draft preparation: C.Z. and C.G-C.; writing—review and editing: M.S., G.V., J.L.Z. and R.H. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

This is an original manuscript and has not been previously published or submitted to another journal.

There are no conflicts of interest related to the study design or its results.

DATA AVAILABILITY STATEMENT

Anonymized data will become available to interested parties for non-commercial reasons after publication upon reasonable requests made to the corresponding author. Data requestors will need to sign a data access agreement.

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