Prognostic Implication of Tricuspid Regurgitation in ST-segment Elevation Myocardial Infarction Patients

Ben Sadeh MD[1,3]*, Tamar Itach MD[2]*, Ilan Merdler MD MHA[1,3], Shir Frydman MD[2], Samuel Morgan BSc[3], David Zahler MD[2], Yogev Peri MD[1,3], Aviram Hochstadt MD[1,3], Yotam Pasternak MD MSc[2], Yan Topilsky MD[1,3], Shmuel Banai MD[1,3], and Yacov Shacham MD[1,3]

Departments of [1]Cardiology and [2]Internal Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

*These authors contributed equally to this study

ABSTRACT **Background:** Tricuspid regurgitation (TR) is associated with adverse prognosis in various patient populations but currently no data is available about the prevalence and prognostic implication of TR in ST-segment elevation myocardial infarction (STEMI) patients.

Objectives: To investigate the possible implication of TR among STEMI patients.

Methods: We conducted a retrospective study of STEMI patients undergoing primary percutaneous coronary intervention (PCI), and its relation to major clinical and echocardiographic parameters. Patient records were assessed for the prevalence and severity of TR as well as the relation to the clinical profile, key echocardiographic parameters, in-hospital outcomes, and long-term mortality. Patients with previous myocardial infarction or known previous TR were excluded.

Results: The study included 1071 STEMI patients admitted between September 2011 and May 2016 (age 61 ± 13 years; predominantly male). A total of 205 patients (19%) had mild TR while another 32 (3%) had moderate or greater TR. Patients with significant TR demonstrated worse echocardiographic parameters, were more likely to have in-hospital complications, and had higher long-term mortality (28% vs. 6%, $P < 0.001$). Following adjustment for significant clinical and echocardiographic parameters, mortality hazard ratio of at least moderate to severe TR remained significant (2.44, 95% confidence interval 1.06–5.6, $P = .036$) for patients with moderate to severe TR.

Conclusions: Among STEMI patients after primary PCI, the presence of moderate to severe TR was independently associated with adverse outcomes and significantly lower survival rate.

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KEY WORDS: echocardiography, percutaneous coronary intervention (PCI), ST-segment elevation myocardial infarction (STEMI), tricuspid regurgitation (TR)

Tricuspid regurgitation (TR) is a prevalent echocardiographic finding. Mild TR without other conditions is considered benign, while moderate to severe TR should prompt suspicion of other cardiac conditions such as significant pulmonary hypertension and right or left ventricular dysfunction [1,2].

The clinical impact of TR is still under investigation due to variation in the results of previous studies [3,4]. This variation was mainly associated with the heterogenous and numerous co-morbidities associated with TR that influenced clinical outcomes, such as low left ventricular ejection fraction (LVEF) [5], right ventricular (RV) [6] dilation and dysfunction, and pulmonary artery systolic pressure (PASP) [7], thus, leading to studies that tried to isolate TR from potential confounders. Recent studies had demonstrated association between severe isolated TR and excess mortality and morbidity in various patient populations [2,6,8], but lesser degrees of TR were associated as well with poor prognosis, especially in men [9]. Nonetheless, current management guidelines of TR patients are ambiguous and most often consider interventional therapy only at the time of mitral or aortic valve surgery [5].

To the best of our knowledge, to date, no study has evaluated the prevalence and possible prognostic implication of TR in ST-segment elevation (STEMI) patients. In the present study, we investigated the clinical profile, in-hospital outcomes, and long-term mortality associated with the presence of TR in STEMI patients treated with primary percutaneous coronary intervention (PCI).

PATIENTS AND METHODS

A retrospective, single-center observational study was performed at the Tel Aviv Sourasky Medical Center, a tertiary referral hospital with a 24/7 primary PCI service [10].

We evaluated 2139 consecutive patients admitted between September 2011 and May 2016 to the cardiac intensive care unit (CICU) with the diagnosis of acute STEMI. We excluded patients with a missing record of tricuspid valve echocardiographic

evolution (n=847) as well as patients with previous myocardial infarction (n=196) and known previous TR (n=25). The final cohort consisted of 1071 patients whose baseline demographic, cardiovascular history, clinical risk factors, treatment characteristics, and laboratory results were retrieved from their hospital electronic medical files. Diagnosis of STEMI was established in accordance with published guidelines including typical chest pain history, diagnostic electrocardiographic changes, and serial elevation of cardiac biomarkers [11]. Primary PCI was performed in patients with symptoms ≤ 12 hours in duration as well as in patients with symptoms lasting 12–24 hours if pain consisted at the time of admission. Family history was defined as first degree relative with a positive history of early coronary artery disease (≤ 50 male, ≤ 60 female). The duration of symptoms was defined as the time from symptom onset (usually chest pain or discomfort) to ER/catheterization laboratory admission. Assessment of survival following hospital discharge was determined from computerized records of the population registry bureau. The study protocol was approved by the local institutional Ethics Committee (Institutional Board Review number TLV-16-0224).

ECHOCARDIOGRAPHY

Following the performance of primary PCI, all patients underwent a screening echocardiographic examination within 6 to 72 hours of CICU admission. Relevant data were collected from the clinical echocardiographic exam reports. Echocardiography was performed using Philips IE 33 equipped with S5-1 transducers (Philips Healthcare, Andover, MA, USA) and GE Vivid 7 model equipped with M4S transducer (GE Healthcare, USA).

TR severity was determined using an integrative, semi-quantitative approach as recommended by the American Society of Echocardiography [12].

Regarding the gravity of tricuspid regurgitation, we first assessed the severity of valve regurgitation by evaluating specific signs that would point to either less than mild or severe regurgitation, including color jet area (thin small central vs. large > 50% jet area), vena contract (VC) width (< 0.2 cm or ≥ 7 mm), density of continuous Doppler jet (faint or dense and triangular), hepatic vein flow pattern (systolic dominant vs. systolic reversal), annular diameter (normal vs. dilated annulus with lack of valve coaptation), and RV and right atrial (RA) size (normal vs. dilated). If all of the signs and indices were concordant, we defined TR as less than mild or severe. If the signs or values of the qualitative or semiquantitative parameters were in the intermediate range between mild and severe, we defined TR as at least moderate to severe if the majority (five or more) of the signs and indices were concordant with severe TR [12].

None of the patients with severe TR had malcoaptation of valve leaflets. TR jet on Doppler echocardiography peak systolic pulmonary artery pressure (SPAP) was estimated using the modified Bernoulli formula (4 × TRV2max) + RAP, where TRV max is the peak systolic tricuspid regurgitation velocity at end expiration, and RAP is the right atrial pressure. Left ventricular (LV) diameters and interventricular septal and posterior wall width were measured from the parasternal short axis by means of a 2-dimensional (2D or a 2D-guided M-mode echocardiogram of the LV at the papillary muscle level using the parasternal short-axis view [13]. LV ejection fraction was calculated by the Biplane method of disks (modified Simpson's rule).Briefly, expiratory and inspiratory inferior vena cava (IVC) diameters and percent collapse were measured in subcostal views within 2 cm of the right atrium. IVC diameter > 2.1 cm that collapsed > 50% with a sniff suggested a normal RA pressure (assigned as 5 mmHg), whereas an IVC diameter > 2.1 cm that collapsed <50% with a sniff suggested a high RA pressure (15 mmHg). In patients with IVC diameter > 2.1 cm and no collapse (< 20%) with a sniff, RA pressure was upgraded to 20 mmHg. In indeterminate cases in which the IVC diameter and collapse did not fit this paradigm, secondary indices of elevated RA pressure were integrated. If uncertainty remained, RA pressure was left as intermediate value of 10 mmHg.

STATISTICAL ANALYSIS

Patients were divided into two groups according to the severity of TR: those with none to mild TR and those with moderate to severe TR.

All data were summarized and displayed as mean ± standard deviation for continuous variables unless stated otherwise, and as number (percentage) of patients in each group for categorical variables. The *p* values for the categorical variables were calculated with the chi-square test. Continuous variables were compared using the independent sample *t*-test or the Mann–Whitney U test. The Kaplan-Meier method and log-rank test were used to evaluate the association between the severity of TR and survival. To assess if TR grade was independently associated with outcome, we used multivariate Cox regression for the primary endpoint (all cause mortality) adjusted for all baseline variables found to be significant in the univariate analysis. We used SPAP cutoff of 36 mm/hg in the model as the European society of cardiology guidelines for the diagnosis and treatment suggest this value to diagnose possible pulmonary hypertension [14]. A two-tailed *P* value of < 0.05 was considered significant for all analyses. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 1071 patients were included in the study: 1039 (97%) with none to mild TR and 32 (3%) with moderate to severe TR. The mean patient age was 61 ± 13 years (range 40–91), with a majority male (80%). Demographic and clinical baseline parameters stratified by severity of TR are shown in Table 1. Patients with moderate to severe TR were significantly older, female and had increased prevalence of chronic kidney disease and hypertension.

Key echocardiographic parameters stratified by severity of TR are shown in Table 2. Patients having moderate to severe TR demonstrated lower ejection fraction and higher septal E/e ratio, SPAP, and RA area ($P < 0.05$ for all) compared to the none to mild TR group. There was no significant difference in TAPSE between the two groups.

Among patients with moderate to severe TR, the most common culprit artery was the left anterior descending coronary artery (14/32, 43%) and right coronary artery (14/32, 43%). The left circumflex coronary artery was the least imaged vessel (3/32, 9%).

IN HOSPITAL AND LONG-TERM OUTCOME

Patient with significant TR had higher rate of in-hospital complications [Table 3]. This included acute kidney injury, heart failure, arrhythmia bleeding and need for mechanical ventilation ($P < 0.05$ for all) [Table 3].

The 30-day mortality was significantly higher among patients with moderate to severe TR (4/32, 12.5%) compared to patients with none to mild TR (21/1039, 2.0%; $P < 0.001$).

LONG-TERM MORTALITY

Over a mean period of 2.3 ± 1.5 years, 71/1071 (6.6%) patients of the entire cohort died. Mortality was significantly higher among patients with moderate to severe TR (9/32, 28%) compared to patients with none to mild TR (62/1039, 6%, $P < 0.001$).

Multivariate Cox hazard analysis for moderate to severe TR adjusted for significant clinical and echocardiographic parameters is shown in Table 4. The mortality hazard ratios of moderate to severe TR (2.44, 95% confidence interval, 1.06–5.62; $P = 0.036$) remained significant even after adjustment for gender, family history, hypertension, estimated glomerular filtration rate (eGFR) < 60, EF < 50%, E/e′ ratio ≥ 15, and SPAP > 36.

DISCUSSION

The present study demonstrated that among STEMI patient population, the presence of moderate to severe TR was associated with significantly lower survival rate compared to patients with none to mild TR. TR was associated with excess mortality even when adjusted for demographic, clinical and other echocardiography parameters. To the best of our knowledge, this is the first report to date suggesting a possible prognostic implication of TR in STEMI patients.

TR is a common echocardiographic finding [15], but it has been disregarded due to the thought that it is a clinically insignificant condition. The clinical impact and outcome of TR are difficult to assess, given its heterogeneity and the association with numerous co-morbidities. Hence, management guidelines of TR patients remain ambiguous due to conflicting studies results [9,16,17].Pivotal studies suggested that untreated TR is associated with excess mortality and cardiac events [7,17]. TR had been associated in previous studies with additional car-

Table 1. Baseline characteristics

Variables	None to mild tricuspid regurgitation (n=1039)	Moderate to severe tricuspid regurgitation (n=32)	*P* value
Age (years)	60.9 ± 12.9	75.4 ± 9.7	< 0.001
Gender (male)	841 (80.9%)	16 (50%)	< 0.001
Diabetes mellitus	219 (21.1%)	11 (34.4%)	0.081
Hyperlipidemia	449 (43.2%)	16 (50%)	0.473
Family history	255 (24.5%)	3 (9.4%)	0.048
Smoking	540 (52%)	10 (31.3%)	0.03
Hypertension	422 (40.6%)	23 (71.9%)	0.001
eGFR	77.22 ± 23.86	62.08 ± 28.49	< 0.001
C-reactive protein	12.72 ± 28.63	22.84 ± 42.4	0.205
CAD severity			
1-vessel disease	475 (46%)	10 (32.3%)	0.265
2-vessel disease	307 (29.7%)	9 (29%)	
3-vessel disease	248 (24%)	12 (38.7%)	

CAD = coronary artery disease, eGFR = estimated glomerular filtration rate, LV = left ventricle
Continuous variables are expressed as mean ± SD. Categorical Variables are expressed as number and percentage.

Table 2. Echocardiographic parameters stratified by severity of tricuspid regurgitation

Parameter	None to mild tricuspid regurgitation (n=1039)	Moderate to severe tricuspid regurgitation (n=32)	*P* value
E/E'	11.8 ± 4.7	15.8 ± 6.7	0.01
E/E' ⩾ 15	200(20%)	15(51%)	< 0.001
EF (%)	46.79 ± 7.62	41.09 ± 7.26	< 0.001
EF<50%	618 (57%)	29 (90%)	< 0.001
RA area (cm 2)	16.6 ± 3.5	19.6 ± 5.7	0.01
SPAP (mmHg)	26.6 ± 7.9	39.0 ± 16.0	< 0.001
SPAP > 36 mmHg	114 (15%)	17 (53%)	< 0.001
TAPSE (mm)	21.5 ± 4.8	19.4 ± 3.7	0.31

EF = ejection fraction, RA = right atrial; SPAP = systemic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion
Continuous variables expressed as mean ± SD. Categorical variables are expressed as number and percentage.

diovascular outcomes. It has been shown that TR is a common finding in patients with left-sided valvular disease. Significant TR in this circumstance is considered as a late-stage marker and is associated with poor outcome and worse prognosis [7,17,18]. Therefore, patients undergoing left valve surgery with severe functional TR (FTR) have a class I indication for concomitant tricuspid valve surgery [19]. In patients undergoing transcatheter aortic valve replacement (TAVR) the impact of preoperative significant TR was associated with almost a twofold increase in 2-year mortality [18].

TR is also common among patients with chronic heart failure (CHF), due to the pathophysiology of CHF resulting in right ventricular dilatation, and the development of FTR which, consequently, generating further right ventricular dilatation and worsening of TR [20]. Studies indicate a strong impact of TR on the clinical outcome in CHF patients, where TR was significantly related to mortality [21].

Recent studies have demonstrated that moderate to severe TR is associated with poor outcome, even in the absence of left ventricular dysfunction or pulmonary hypertension [3,7,9], implying that tricuspid valve repair or replacement may lead to a survival benefit. However, to date, TR patients are rarely referred for isolated surgical tricuspid valve repair, and these are mostly performed during other planned cardiac surgery [5]. In the era where percutaneous repair procedures are on the rise, more research on percutaneous approaches for TR is needed [22].

Limited data exist on the prevalence and prognostic value of significant TR in STEMI patients undergoing PCI. In the setting of acute occlusion of the right coronary artery leading to inferior myocardial infarction (MI), RV involvement, and concomitant severe TR, tricuspid papillary muscle rupture (PMR) had been reported as a rare complication [23,24].

The present study provides evidence that moderate to severe TR can serve as a possible prognostic marker among STEMI patients. We found that among STEMI patients undergoing primary PCI, with no known previous TR, the prevalence for moderate to severe TR was 2.7%. These patients suffered more in-hospital complications and worse long-term outcomes. These results imply that in patients with moderate to severe TR, additional follow-up after PCI is needed. Once released from the hospital these patients should be followed by a cardiologist, undergo an additional echocardiographic exam to track progression of TR severity and possibly electrocardiogram exam due to a high prevalence of arrythmias. An extra emphasis should be placed on balancing of cardiovascular risk factors for these patients.

Although the reason for higher mortality among STEMI patients with significant TR is still unclear, we postulate that the presence of TR after STEMI could be a marker of decreased RV function and contractility. It has been shown that the presence of severe TR can be attributed to RV akinesis in the settings of inferior MI or to ischemic impairment of the tricuspid valve [23]. Moreover, increasing severity of TR is allied with RV dila-

Table 3. Complications at the time of hospitalization

Parameter	None to mild tricuspid regurgitation (n=1039)	Moderate to severe tricuspid regurgitation (n=32)	*P* value
30-day mortality	21 (2.0%)	4 (12.5%)	< .001
AKI	103 (9.9%)	10 (31.2%)	< 0.001
IABP	33 (3.2%)	6 (18.7%)	< 0.001
In hospital CABG	17 (1.6%)	1 (3.4%)	0.42
Mechanical ventilation	44 (4.3%)	6 (18.7%)	< 0.001
HF	91 (8.8%)	9 (28%)	< 0.001
Bradycardia	39 (3.8%)	5 (15.6%)	< 0.001
VT/VF	92 (8.9%)	4 (12.5%)	0.37
AF	41 (3.9%)	4 (12.5%)	0.01
Stent Thrombosis	19 (1.8%)	0 (0%)	0.46
Bleeding	43 (4.1%)	5 (15.6%)	0.001

AKI = acute kidney injury, IABP = intra-aortic balloon pump, CABG = coronary artery bypass graft; VT/VF = ventricular tachycardia/ventricular fibrillation AF = atrial fibrillation.

Table 4. Multivariate Cox hazard analysis for long-term mortality adjusted for significant clinical and echocardiographic parameters.

Parameter	Hazard ratio	95% Confidence interval	*P* value
Gender	1.47	0.83–2.62	0.18
Family history	0.51	0.18–1.43	0.20
hypertension	0.87	0.49–1.55	0.65
E < 50%	1.08	1.04–1.11	< 0.001
E/E' ≥ 15	2.34	1.24–4.41	0.01
eGFR < 60 ml/min	2.92	1.66–5.18	< 0.001
SPAP >36 mmHg	1.55	0.83–2.87	0.17
TR moderate-severe	2.44	1.06–5.62	0.036

EF = ejection fraction, eGFR = estimated glomerular filtration ratio, SPAP = systolic pulmonary artery pressure

tion, dysfunction, and elevated right atrial pressure, thus leading to a worse outcomes [20]. In addition, the association between enlarged RV and increased mortality was demonstrated in previous studies [25], elucidating that RV function after STEMI has important prognostic implications. Nevertheless, from our understanding the RV function influence on outcomes only partly explains the association between significant TR among STEMI patients and mortality. From our data only 5/32 (16%) patients with moderate to severe TR had RV dysfunction and/or dilation, this can imply previous impermanent or pulmonary hypertension leading to FTR; therefore, additional research is needed to illuminate the matter.

LIMITATIONS

We acknowledge several important limitations of our study. This single-center retrospective and non-randomized observational study was retrospective nature. The study was subjected to selection bias, and therefore the results point toward association, and not cause and effect. The relatively small number of patients with moderate to severe TR represents a fragile dataset with changes in results possible if data from single patients is changed.

The study included only patients with their first MI who were undergoing primary PCI and with no previously known TR. Therefore, the results cannot be generalized to all STEMI patients with TR. The group with moderate to severe TR was small, patients were significantly older, female and with chronic kidney disease. While we attempted to adjust for confounding factors using the multivariate Cox hazard model TR may be regarded as a marker rather than cause in this population. Data regarding medical and AICD treatment post discharge are not present or available and may prohibit further comprehensive analysis of the data.

Finally, data were collected retrospectively from echocardiographic reports that were recorded and analyzed by different sonographers. An echocardiographic exam is highly operator dependent, which may be subjective, even though it was determined by echocardiography experts. Because echocardiography was performed only after PCI for all patients, possible improvement of TR after PCI could have not been assessed. Patients having TR were more likely to be older and female. Older, female patients raise suspicion of heart failure with preserved ejection fraction, which frequently is accompanied by moderate/severe TR and is associated with substantial risk for mortality, which might explain findings in the present study.

CONCLUSIONS

Among STEMI patients after primary PCI, the presence of moderate to severe TR was a marker of lower survival rate. Our results should be interpreted with caution and more research is needed in the future with prospective randomized trials.

Correspondence

Dr T. Itach
Dept. of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
Phone: (972-3) 697-3222
Fax: (972-3) 697-3704

email: itachtamar@gmail.com

References

1. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999; 83 (6): 897-902.
2. Sadeghpour A, Hassanzadeh M, Kyavar M, et al. Impact of severe tricuspid regurgitation on long term survival. *Res Cardiovasc Med* 2013; 2 (3): 121.
3. Bar N, Schwartz LA, Biner S, et al. Clinical outcome of isolated tricuspid regurgitation in patients with preserved left ventricular ejection fraction and pulmonary hypertension. *J Am Soc Echocardiogr* 2018; 31 (1): 34-41.
4. Topilsky Y, Inojosa JM, Benfari G, et al. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. *Eur Heart J* 2018; 39 (39): 3584-92.
5. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary. *Circulation* 2014; 129 (23): 2440-92.
6. Schwartz LA, Rozenbaum Z, Ghantous E, et al. Impact of right ventricular dysfunction and tricuspid regurgitation on outcomes in patients undergoing transcatheter aortic valve replacement. *J Am Soc Echocardiogr* 2017; 30 (1): 36-46.
7. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014; 7 (12): 1185-94.
8. Sagie A, Schwammenthal E, Newell JB, et al. Significant tricuspid regurgitation is a marker for adverse outcome in patients undergoing percutaneous ballon mitral valvuloplasty. *J Am Coll Cardiol* 1994; 24 (3): 696-702.
9. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004; 43 (3): 405-9.
10. Arbel Y, Shacham Y, Finkelstein A, et al. Red blood cell distribution width (RDW) and long-term survival in patients with ST elevation myocardial infarction. *Thromb Res* 2014; 134 (5): 976-9.
11. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary. *Circulation* 2013; 127 (4): 529-55.
12. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation. *J Am Soc Echocardiogr* 2017; 30 (4): 303-71.
13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16 (3): 233-70.
14. Bossone E, D'Andrea A, D'Alto M, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc *Echocardiog.* 2013; 26 (1): 1-14.
15. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999; 83 (6): 897-902.
16. Messika-Zeitoun D, Thomson H, Bellamy M, et al. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg* 2004; 128 (2): 296-302.
17. Sagie A, Schwammenthal E, Newell JB, et al. Significant tricuspid regurgitation is a marker for adverse outcome in patients undergoing percutaneous ballon mitral valvuloplasty. *J Am Coll Cardiol* 1994; 24 (3): 696-702.
18. Barbanti M, Binder RK, Dvir D, et al. Prevalence and impact of preoperative moderate/severe tricuspid regurgitation on patients undergoing transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2015; 85 (4): 677-84.
19. Mahesh B, Wells F, Nashef S, Nair S. Role of concomitant tricuspid surgery in moderate functional tricuspid regurgitation in patients undergoing left heart valve surgery. Eur *J Cardio-Thoracic Surg* 2013; 43 (1): 2-8.

20. Neuhold S, Huelsmann M, Pernicka E, et al. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. *Eur Heart J* 2013; 34 (11): 844-52.

21. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J.* 2002; 144 (3): 524-9.

22. Landes U, Kerner A, Segev A, et al. Transcatheter tricuspid valve-in-valve implantation in patients with tricuspid bioprosthetic valve degeneration at high surgical risk: a multicenter case series. *IMAJ* 2017; 19 (3): 156-9.

23. Walker JR, Mousavi N, Horlick E, Seifer C, Jassal DS. Tricuspid valvular papillary muscle rupture with intractable hypoxia: a rare complication post MI. *J Am Soc Echocardiogr* 2009; 22 (7): 863.e1-863.e3.

24. Goldstein JA. Pathophysiology and management of right heart ischemia. *J Am Coll Cardiol* 2002; 40 (5): 841-53.

25. Lewis JF, Webber JD, Sutton LL, Chesoni S, Curry CL. Discordance in degree of right and left ventricular dilation in patients with dilated cardiomyopathy: recognition and clinical implications. *J Am Coll Cardiol* 1993; 21 (3): 649-54.

It's surprising how much memory is built around things unnoticed at the time.

Barbara Kingsolver (born 1955), novelist, essayist, and poet

Capsule

TIM-3 restrains anti-tumor immunity by regulating inflammasome activation

T cell immunoglobulin and mucin-containing molecule 3 (TIM-3), first identified as a molecule expressed on interferon-γ producing T cells1, is emerging as an important immune-checkpoint molecule, with therapeutic blockade of TIM-3 being investigated in multiple human malignancies. Using conditional knockouts of TIM-3 together with single-cell RNA sequencing, **Dixon** and colleagues demonstrated the singular importance of TIM-3 on dendritic cells (DCs) in which the loss of TIM-3 on DCs, but not on CD4+ or CD8+ T cells, promotes strong anti-tumor immunity. Loss of TIM-3 prevented DCs from expressing a regulatory program and facilitated the maintenance of CD8+ effector and stem-like T cells. Conditional deletion of TIM-3 in DCs led to increased accumulation of reactive oxygen species resulting in NLRP3 inflammasome activation. Inhibition of inflammasome activation, or downstream effector cytokines interleukin-1β (IL-1β) and IL-18, completely abrogated the protective anti-tumor immunity observed with TIM-3 deletion in DCs. Together, these findings reveal an important role for TIM-3 in regulating DC function and underscore the potential of TIM-3 blockade in promoting anti-tumor immunity by regulating inflammasome activation.

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Eitan Israeli

Capsule

COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets

Delorey and colleagues generated single-cell atlases of 24 lung, 16 kidney, 16 liver, and 19 heart autopsy tissue samples and spatial atlases of 14 lung samples from donors who died of COVID-19. Integrated computational analysis uncovered substantial remodelling in the lung epithelial, immune, and stromal compartments, with evidence of multiple paths of failed tissue regeneration, including defective alveolar type 2 differentiation and expansion of fibroblasts and putative *TP63+* intrapulmonary basal-like progenitor cells. Viral RNAs were enriched in mononuclear phagocytic and endothelial lung cells, which induced specific host programs. Spatial analysis in lung distinguished inflammatory host responses in lung regions with and without viral RNA. Analysis of the other tissue atlases showed transcriptional alterations in multiple cell types in heart tissue from donors who contracted COVID-19, and mapped cell types and genes implicated with disease severity based on COVID-19 genome-wide association studies. This foundational dataset elucidates the biological effect of severe SARS-CoV-2 infection across the body, a key step towards new treatments.

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Eitan Israeli