Impact of Tricuspid Regurgitation on Survival in Patients with Heart Failure – A Large Electronic Health Records Patient-level Database Analysis

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KEY POINTS

Question: What is the independent prognostic value of tricuspid regurgitation in patients with heart failure?

Findings: Using the Optum longitudinal database, a patient-level database that integrates multiple U.S.-based electronic health and claim records from several health care providers, we identified 435,679 patients with new heart failure diagnosis and both an assessment of the left ventricular ejection fraction and at least one year of history. Both moderate / severe prevalent tricuspid regurgitation (recorded prior to or within 28 days of the initial heart failure diagnosis) and incident tricuspid regurgitation (subsequent new cases thereafter) were associated with marked increases in mortality risk.

Meaning: Tricuspid regurgitation is not an innocent bystander in patients with heart failure and merits closer attention by cardiologists.

ABSTRACT

Importance. More evidence is needed to quantify the impact of tricuspid regurgitation (TR) on survival in patients with heart failure (HF).

Objective. To evaluate the independent and increment prognostic value of TR in patients with HF

Design. Using the Optum database, we collected all patients diagnosed with HF between 2008 and 2017. TR was graded as mild, moderate or severe and classified as prevalent (recorded prior to or within 28 days of the initial HF diagnosis) or incident (subsequent new cases of TR thereafter). For prevalent TR, the analysis was performed using a Cox proportional hazards model with adjustment for patient covariates. Incident TR was modelled as a time-updated covariate, as were other non-fatal events during follow-up.

Setting. Optum ©, a de-identified electronic health records (EHR) / claims dataset that integrates multiple U.S.-based electronic health and claim records from several health care providers

Participants. Patients with new HF diagnosis and both an assessment of the left ventricular ejection fraction (LVEF) and at least one year of history.

Main outcome measure. All-cause Mortality

Results. Between 2008-2017, we identified 435,679 patients with HF, at least one year of history and an LVEF assessment. Prevalence of mild, moderate and severe TR at baseline was 10.1%, 5.1% and 1.4% respectively. Over a median 1.5 years follow-up, 121,273 patients (27.8%) died and prevalent TR was independently associated with survival. Compared to patients with no TR at baseline, the adjusted hazard ratios for mortality were 0.99 (95% CI 0.97-1.01), 1.17 (95% CI 1.14-1.20) and 1.34 (95% CI 1.28-1.39) for mild, moderate and severe TR, respectively. In the 363,270 patients free of TR at baseline, incident TR (at least mild, at least moderate, or severe)

developed during follow-up in 12.1%, 5.1% and 1.1% respectively. Adjusted mortality hazard ratios for such new cases were 1.48 (95% CI 1.44-1.52), 1.92 (95% CI 1.86-1.99) and 2.44 (95% CI 2.32-2.57) respectively. These findings were consistent across all patient subgroups based on age, gender, rhythm, associated comorbidities, prior cardiac surgery, BNP/NT-proBNP and LVEF.

Conclusions. This is the first population-based evaluation of TR and patient survival in HF. Moderate and severe TR were associated with marked increases in mortality risk. This indicates that the occurrence of TR in patients with HF merits closer attention by cardiologists.

Keywords: tricuspid regurgitation, mortality, heart failure.

INTRODUCTION

Although present in over 1.6M individuals in the US, [1] tricuspid regurgitation (TR) has long been overlooked compared to left sided valve diseases. A recent epidemiological study estimated the prevalence of significant – moderate or greater - TR in the community to be as high as 0.55% (and up to 3% after 75 years of age), a prevalence similar to aortic valve stenosis (AS) or mitral valve regurgitation (MR).[2, 3] TR is a heterogeneous disease usually secondary to other conditions (mainly left-sided disease or pulmonary hypertension) [3, 4] and it is critical to account for these conditions to specifically evaluate the impact of TR on survival.

In patients with heart failure (HF), TR is highly prevalent with up to one third of patients having moderate or severe TR.[5, 6] Despite its high prevalence, the impact of TR on survival in patients with HF is disputed. While several recent studies have suggested a link between the presence and severity of TR to worse outcomes predominantly in the context of severely reduced systolic function [3, 5-9], other studies have found no independent association with survival.[10, 11] Furthermore, most studies on functional TR have been modest in size, often from single tertiary referral centers with inherent referral bias, have focused on HF with reduced ejection fraction (HFrEF) and have not considered HF as a global entity (i.e. inclusive of HF with preserved EF (HFpEF)). These uncertainties may contribute to why TR is not included in most HF prognostic scoring systems such as the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score [12] and why guidelines for TR management are vague and do not involve any class I indication for intervention.[13, 14]

Until now, evidence independently and incrementally linking TR to mortality in patients with HF in a large contemporary population with appropriate adjustment for associated

conditions has been lacking. Such evidence is essential in order to guide and enhance the development of new therapies and the design of appropriate clinical trials. Using the Optum longitudinal patient-level database, we aimed to evaluate in a large population-based study of patients with HF the independent and incremental impact of TR on mortality, when TR was diagnosed 1) prior to or at the time of the initial diagnostic of HF (prevalent TR) and 2) during the follow-up period of the initial diagnostic of HF (incident TR).

METHODS

Study design

Optum © de-identified electronic health records (EHR) / claims dataset is one of the largest databases in the United States, being derived from more than 85 healthcare provider organizations including 700 hospitals and 7,000 clinics. The database currently captures over 90 million patients. It integrates data from EHRs and from claim records from both ambulatory and inpatient settings and covers diagnosis and procedure codes, laboratory results, clinical observations and medications. In addition, Optum Analytics uses natural language processing (NLP) computing technology to extract critical facts from physician notes into structured datasets. The NLP data provides detailed information including disease signs and symptoms (see supplemental materials for more information regarding NLP). Data are certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules and managed according to Optum's customer data use agreements.

We identified all patients in the 2008-2017 period with an ICD 9 or 10 diagnosis code of HF (ICD-9 428, and ICD-10 I50) and an assessment of the LV function either qualitative (reduced/preserved LVEF) and/or quantitative (numerical value of the LVEF) and with at least one year of history in the dataset prior to the initial HF episode. As ICD-9 or 10 coding do not provide any indication regarding TR severity, it was assessed using NLP processing of EHR records and semi-quantitatively graded as absent, mild, moderate or severe.

Patients and disease characteristics

The Optum dataset contains a large number of demographic variables including age, gender, region, average income and race. Patients' baseline health status and comorbidities, including presence and severity of valvular heart disease (TR, MR and AS) were evaluated in the year before the HF diagnosis using ICD 9 and 10 diagnosis codes or NLP extraction. MR and AS were assessed as time updated covariates to account for their impact on survival. ICD-9/10 procedure and Common Procedural Terminology-4 (CPT) codes were used to extract relevant patient procedures. Cardiac procedures were evaluated as time updated variables to control for any potential impact on survival. Dialysis and PCI were assessed only during the patient's baseline period. Hospitalization and medication history were ascertained by analyzing patient records in the 12 months prior to the initial diagnosis of HF. Other parameters extracted from patient records in the twelve months prior to diagnosis were body mass index, systolic and diastolic blood pressure, creatinine, hemoglobin, INR, BNP, NT-proBNP, albumin, ALT, AST, bilirubin, systolic pulmonary artery pressure (SPAP), and numerical value of LVEF. LVEF was considered normal above 50%, moderately reduced between 30% and 50% and severely reduced below 30%. Values closest to the date of the index HF diagnosis were selected. Table 1 lists all covariates and the completeness of the aforementioned data.

Statistical analysis

TR was analyzed according to severity (none, mild, moderate, severe) and by whether it was prevalent (prior or at the time of the HF diagnosis) or incident (diagnosed afterwards, during patient follow-up in patients free of TR at baseline). Prevalent TR was defined as TR recorded up to 28 days after the date of the initial HF diagnosis. We used this 28-day period to capture TR diagnosed using an echocardiogram that might have been performed at the time of the HF

diagnosis but only captured in the system within the following 4 weeks after it was performed. Accordingly, time at risk began 28 days after HF diagnosis in all analyses.

Cumulative incidence of incident TR was assessed using the Kaplan Meier method. We assessed risk of death by TR severity using Kaplan Meier estimates and Cox proportional hazard models. Deaths were obtained from the Social Security Administration (SSA) Masterfile and censoring was based on the date of last documented encounter with the healthcare system.

First, we compared patients according to the level of prevalent TR (at the time of the HF diagnosis). In a second analysis, restricted to patients free from TR at baseline, we used time-updated categories of TR to explore the impact of incident TR on mortality. Each patient's follow-up was split into time spent before and after a diagnosis of TR.[15] Hazard ratios (HRs) for death therefore compared the hazard of death during time spent with mild, moderate or severe TR with the hazard during time spent without a diagnosis of TR (which also includes all patient time in patients who never had a diagnosis of TR throughout follow-up). At any given time, patients contributed time-at-risk only to the most severe category of TR for which they have received a diagnosis. For example, consider a patient with a diagnosis of mild TR followed by a diagnosis of moderate TR. From the time of diagnosis of moderate TR, the patient stopped contributing time to the mild TR category and began contributing time to the moderate TR category.

For both prevalent and incident TR, we first fitted unadjusted Cox models for mortality. Next, we adjusted for covariates in the MAGGIC risk score, an established multivariate model to predict mortality in HF patients.[12] Lastly, we adjusted for several other risk factors, including time-updated presence of MR and AS. We used multiple imputation with chained equations to impute data on missing covariates. We used 5 imputed datasets and combined estimates and

standard errors across datasets using Rubin's rules.[16] Sensitivity analyses used a complete case approach, restricting analyses to the subset of patients with complete information on all covariates. Multivariable Cox regression analyses were performed in the overall population and in pre-specified subsets based on age, gender, race, type of HF diagnosis, prior admission for HF, rhythm, ischemic or dilated cardiomyopathy, prior cardiac surgery, presence of permanent pacemaker (PPM), concomitant significant valve diseases (AS or MR), BNP/NT-proBNP, LVEF and SPAP.

Continuous variables were summarized using medians with interquartile ranges, categorical variables as counts and percentages. Analyses were performed in Stata version 15.1, statistical tests were two sided and a p-value <0.05 was considered as statistically significant.

RESULTS

Population

The initial study cohort consisted of 981,261 patients with a HF diagnosis in the period between 2008 and 2017, and either quantitative or qualitative information regarding LVEF. Less than one-year history in the dataset prior to the HF diagnosis was the main reason for exclusion (n=411,348; 75% of exclusions) and our final cohort consisted of 435,679 patients (see Supplementary Figure 1).

The median age at baseline was 73 years (interquartile range [IQR] 63-82) and 50.8% were female. At baseline, 363,270 (83.4%) patients had no TR, 44,003 (10.1%) had mild TR, 22,507 (5.1%) had moderate TR and 5899 (1.4%) had severe TR. Patients with moderate or severe TR were older, more frequently female, presented more frequently in AF, with associated MR, higher BNP/NT-proBNP and SPAP. They were also more commonly treated by diuretics and anticoagulant. Baseline characteristics of patients with and without TR are presented in Table 1.

Impact of prevalent tricuspid regurgitation on outcome

Over a median follow up of 1.5 years (IQR:0.5-3.1years), 121,273 (27.8%) patients died. Mortality risk was significantly associated with the severity of TR present at the time of HF diagnosis (Figure 1A). Unadjusted mortality rates at 2 years were 21.6% for patients free of TR, 24.0% for mild TR, 32.7% for moderate TR and 36.9% for severe TR. Compared to patients with no TR, unadjusted hazard ratios were 1.13 (95% CI, 1.11-1.15) for mild TR, 1.60 (95% CI, 1.57 -1.64) for moderate TR, and 1.85 (95% CI, 1.78-1.93) with severe TR (Figure 2). The

association was less strong with progressive adjustment for potential confounders. After adjustment for covariates in the MAGGIC risk score, hazard ratios compared to no TR were 1.06 (95% CI, 1.04 to 1.08) for mild TR, 1.35 (95% CI, 1.32 to 1.38) for moderate TR and 1.61 (95% CI, 1.54 to 1.68) for severe TR (Figure 2). Our final model also included adjustment for demographics, history of several comorbidities, presence of MR or AS, several biochemical markers, and procedures known to improve survival occurring during follow up (Figure 2). Fully adjusted hazard ratios compared to no TR were 0.99 (95% CI, 0.97-1.01) for mild TR, 1.17 (95% CI, 1.14-1.20) for moderate TR and 1.34 (95% CI, 1.28-1.39) for severe TR. Using complete analysis instead of multiple imputations gave very similar results.

Figure 3A shows adjusted hazard ratios for prevalent moderate or severe TR according to pre-specified patient subgroups based on age, gender, race, type of HF diagnosis, prior admission for HF, rhythm, ischemic or dilated cardiomyopathy, prior cardiac surgery, presence of PPM, concomitant moderate / severe AS or MR, BNP/NT-proBNP, LVEF and SPAP. The association between TR and mortality was observed in all subgroups.

Impact of incident tricuspid regurgitation on outcome

Among the 363,270 patients free from TR at baseline, within 2 years, 12.1% developed at least mild TR, 5.1% had at least moderate TR, and 1.1% had severe TR (Figure 4). In patients with HF and no TR diagnosis, the 2-year mortality risk was 20.1%. Within 2-years of an incident diagnosis of TR the mortality risks were 26.9% for mild TR, 39.8% for moderate TR and 51.4% for severe TR (Figure 1B). Compared to patients with no TR, unadjusted hazard ratios were 1.59 (95% CI, 1.55-1.63) for mild TR, 2.64 (95% CI, 2.57-2.71) for moderate TR, and 3.61 (95% CI, 3.46-3.77) with severe TR (Figure 2). The association remained highly significant with

progressive adjustment for potential confounders and even mild TR was associated with an increased risk of mortality. Fully adjusted hazard ratios compared with no TR were 1.48 (95% CI, 1.44-1.52) for mild TR, 1.92 (95% CI, 1.86-1.99) for moderate TR and 2.44 (95% CI, 2.32-2.57) for severe TR. As for prevalent TR, the association between incident TR and mortality was observed in all patient subgroups (Figure 3B).

The increased hazard associated with an incident TR diagnosis was most marked in the early period after this diagnosis. Within the first month following diagnosis of severe TR, the adjusted hazard ratio compared with no TR was 6.10 (95% CI, 5.48-6.80) (Figure 5). The hazard ratio 1-3 months after diagnosis was 3.31 (95% CI, 2.94-3.72), and continued to steadily decline as time progressed after the diagnosis of severe TR. Beyond 2 years after diagnosis the hazard ratio for severe TR was 1.45 (95% CI, 1.29-1.62).

DISCUSSION

The results of the present study are based on a very large database coalescing electronic health and claim records from multiple sources and involving almost a half-million US patients with HF. This analysis provides unique insights into the importance of TR associated with HF. First, TR was commonly observed with HF, both in patients with reduced and preserved EF and the prevalence of TR increased with age, female gender, and with presence of concomitant AF and MR. Our main finding is that TR was significantly and independently associated with all-cause mortality, with increased mortality associated with increased TR severity. Furthermore, the association of TR with excess mortality was consistently observed in all pre-specified subgroups and independent of whether LVEF was reduced or preserved. In patients free of TR at baseline, incident TR was associated with increased mortality after adjustment for all covariates.

The evaluation of the impact of TR on survival is challenging due to the heterogeneity of the disease and the frequent association with other conditions. TR is predominantly functional in mechanism, i.e. secondary to other conditions such as left-sided heart diseases (either dilated/ischemic cardiomyopathy or left-sided valvular heart disease), pulmonary hypertension or AF.[3, 4] In a retrospective study of 5,223 patients who underwent a transthoracic echocardiogram at three Veterans Affairs Medical Center laboratories between 1998 and 2002, Nath et al. observed that mortality increased with increasing severity of TR.[7] However, this study was performed on a selected population, predominantly men, and more severe TR was associated with lower LVEF, leaving the intrinsic effect of TR on survival in doubt. Following this seminal paper, several studies also suggested that TR was associated with worse outcomes [3, 5, 6, 8, 9], while

other studies did not find such association.[10, 11] Recently, a meta-analysis from seventy studies encompassing 32,601 patients concluded to an independent association between moderate or severe TR and mortality [17], but could not eliminate the effect of comorbidities on mortality. In addition, most studies were retrospective, single center, with various referral biases, often initiated in the early 1990s before the full implementation of current HF treatment standards, and almost exclusively centered on patients with HFrEF. In the present study, in a contemporary setting, with a sample size 15 times larger than the meta-analysis, and with an unselected diagnosis of HF (HFrEF and HFpEF documented by LVEF assessment), we were able to demonstrate and quantify the association of increasing TR severity and mortality. The Optum database with more than 90 million US patients of various age, gender, race, geographic area, insurance type and socioeconomic status strongly suggests the generalizability of our findings. The excess mortality associated with TR was observed after adjustment for multiple potential confounders. Moderate and severe TR were associated with a 17% and 34% increased risk of death, respectively. Furthermore, the association between TR and mortality was consistently observed in all subgroups (with similar magnitude) and independent of the methods of adjustment (multiple imputation or complete-case analysis). The incremental relationship between the severity of prevalent TR and mortality was further corroborated by a similar pattern observed with incident TR. The higher risk of death observed with incident TR over prevalent TR, at each grade of TR severity, could be explained by a survival bias. The hazard ratios according to the time of TR diagnosis (Fig 4) would support this hypothesis.

Several subsets deserve specific comments. Excess mortality associated with TR was observed both in patients with preserved and reduced LVEF. Most of the prior studies have focused on patients with reduced LVEF but in the present study, approximately two thirds of

patients presented with preserved EF, therefore enabling to extend conclusions regarding TR and mortality to all patients with HF, irrespective of HFrEF or HFpEF. It has been suggested in a single center study of 576 patients that the impact of TR on survival decreased as EF declined.[11] Our study, taking advantage of its large size, showed that the impact of TR was highly significant in all LVEF subsets including those with severely reduced LVEF (below 30%). TR is commonly observed in patients with either primary or secondary MR. In the present study, increase mortality rates were observed both in patients with associated MR and in patients free of MR; in addition, the impact of TR on survival remained significant after adjustment for MR. AF is also frequently associated with TR, both as cause and consequence of the disease. The impact of TR on survival was observed irrespective of the presence or absence of AF in this population. Hence, the present study conducted in a very large cohort of patients diagnosed and treated for HF, shows that TR is independently linked to excess mortality in all subsets of HF.

Clinical implications

Heart failure is a major burden [18, 19] and cause of morbidity and mortality with frequent association of TR. Prior studies have identified risk-factors and developed HF scoring systems in both patients with reduced and preserved LVEF to predict survival.[12, 20] However, none of those prognostic scoring systems have incorporated TR (presence or severity) into their modelling. TR has long been neglected due to lack of proven medical therapy and high mortality associated with surgery, reflected by the low rates of interventions performed throughout the patients' lifetime.[21, 22] This large cohort, extracted from a major segment of the US population (near population-based) clearly demonstrates that TR portends important prognostic information. Identification of TR either at the time or after an episode of HF, independently of any other

associated medical conditions and incrementally to any predictive risk score, should alert physicians. Those patients should be regarded as at increased risk of mortality and morbidity, deserve close attention and when possible, a more intensive medical management. Importantly, the development of TR within the following months after an index episode of HF was associated with an increased risk of mortality, further emphasizing the need for a rigorous follow-up of these patients. The impact of fast development of TR has also been suggested by others.[23]

At least two studies in different settings have shown that TR per se was responsible for an increased risk of mortality and morbidity. Patients with tricuspid flails, a model of isolated severe organic TR[24], and patients with isolated severe functional TR[25], which accounts for approximately 10% of all causes of severe TR [3, 4], incurred excess mortality and morbidity risks including new onset of AF and congestive HF. Mirroring functional MR, determining whether TR is a cause or marker for the observed increased mortality risk could not be determined from the current results. The results of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trials suggested that transcatheter correction, in selected patients with functional MR, have a positive impact on survival, HF hospitalizations and quality of life.[26, 27] There is a need for future randomized controlled trials to evaluate the benefit and timing of therapeutic interventions for TR. We expect that the rapid development of transcatheter therapies will offer a less invasive alternative to surgery and enable the medical community to evaluate the impact of TR correction on clinical outcomes.[28-32] Currently, TR correction is mainly performed at the time of concomitant mitral valve surgery and discrepancies between the number of patients suffering from TR and the number of tricuspid valve surgeries

performed in the US is consistent with the view that most TR patients are treated with conservative medical management.[21, 22]

Strengths and Limitations

Firstly, Optum is a patient-level database that integrates multiple electronic health records based on clinical notes without structured common echocardiographic reports, which limits the analysis to the data considered notable by the managing physicians. The analysis of the clinical notes through the NLP process greatly enhances information granularity. However, the Optum database remains subject to errors, omission and misreporting, but conversely reflects routine clinical practice. In addition, the size of the HF population examined, unique in the literature, may minimize the importance of such errors and reduce the variation contributed by individual providers and institutions. Secondly, not all variables were available for all patients. Although a qualitative assessment of the LVEF was available for all patients by design, a numerical value was missing in 12.3% and BNP and NT-proBNP values were missing in a 68.9% and 85.7% respectively. However, our results and interpretation were unchanged when using multiple imputation for missing values or a complete-case analysis. We adjusted for all available potential confounders but SPAP was only available in a small proportion of the population. Although we acknowledge this is a limitation, SPAP was available in 14,824 patients which is three times larger than the total available number in the entire literature.[17] No information regarding right ventricular function was available and we were not able to account for this parameter. Thirdly, TR severity was graded semi-quantitatively. A quantitative assessment would have been desirable for TR severity [8, 9, 25] but it is not routinely performed in most institutions and an integrative multi-parametric approach is recommended by both the North American and

European Echocardiography and Cardiology Societies.[33] The present evaluation thus reflects current real-world practice. Finally, a causal relationship between TR and mortality will only be fully affirmed when the treatment of TR demonstrate a survival benefit for HF patients.

CONCLUSION

In this large contemporary patient-level database of almost half-million US patients with a background diagnosis of HF and LVEF assessment, both prevalent and incident TR were independently associated with an increased risk of death that was sustained after adjustment for extensive potential confounders. The excess mortality was associated with increased TR severity. These findings indicate that TR is not an innocent bystander in patients with HF and that the occurrence of TR in HF patients merits closer attention by cardiologists. Future randomized controlled trials will evaluate the impact of TR correction on clinical outcomes and may more conclusively demonstrate the causal relationship between TR and mortality.

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CONFLICT OF INTEREST

- David Messika-Zeitoun is a consultant for Edwards Lifesciences, Mardil and Cardiawave and receives research grants from Edwards Lifesciences and Abbott vascular.
- Patrick Verta is an Edwards Lifesciences employee
- John Gregson is a consultant to Edwards and MVrX and has received research funding from Boston Scientific.
- Stuart J. Pocock is a consultant to Edwards, Medtronic and Boston Scientific.
- Isabel Boero is a consultant for Edwards Lifesciences.
- Ted E. Feldman is an Edwards Lifesciences employee
- William T. Abraham has received consulting fees from Edwards Lifesciences and Abbott Vascular.
- JoAnn Lindenfeld a consultant for Edwards Lifesciences, Abbott Vascular, Boehringer-Ingleheim, Novartis, VWave, Impulse Dynamics, CVRx, Relypsa and receives research grants from Astra Zeneca.
- Jeroen Bax: Speaker fees from Abbott. The department of Leiden University Medical Center has received unrestricted research grants from Boston Scientific, Medtronic, Biotronik, Edwards Lifesciences and GE Healthcare.
- Martin Leon is an unpaid member of the Edwards Lifesciences medical advisory board. The Cardiovascular Research Foundation has received research grants from Edwards Lifesciences, Abbott, Boston Scientific and Medtronic.
- Maurice Enriquez-Sarano has received research grants from Edwards Lifesciences.

LEGEND OF FIGURES

Figure 1. Survival according to degree of tricuspid regurgitation (TR).

A) TR diagnosed at baseline (prevalent TR) and B) TR diagnosed during follow-up in patients free of TR at baseline (incident TR) *

*The analysis of incident TR includes only patients with no TR at baseline. For the analysis of incident TR, at the time of a diagnosis of TR patients are censored for the no TR category and begin contributing time at risk to the category of the new diagnosis (with time at risk starting again at time 0).

Figure 2. **Impact of the degree of tricuspid regurgitation (TR) on mortality risk.**

Risk is expressed as hazard ratios (95% confidence interval) relative to those with no TR.

*Factors in MAGGIC risk score: age, sex, current smoking status, systolic blood pressure, diabetes, pulmonary disease, serum creatinine, beta-blocker use, ACE/ARB use. We could not adjust for NYHA, PASP, because of a lack of availability.

** Further adjustments include adjustments for race, geographical region, type of heart failure (diastolic/systolic), BNP/NT-proBNP, body mass index, heart rate, albumin, MELD-XI score, comorbidities, medications use at baseline, time-updated status for mitral valve regurgitation and aortic stenosis, time-updated procedures (CABG, mitral valve repair, ablation, MAZE procedure, pacemaker implantation)

Figure 3. Adjusted hazard ratios of moderate and severe tricuspid regurgitation (TR) in selected patient subgroups relative to no TR.

A) prevalent TR and B) incident TR.

*Recorded in previous year. Cardiac surgery includes coronary artery bypass graft, mitral or aortic valve replacement

**Amongst the subset 14,824 patients with systolic pulmonary artery pressure measurements; other analyses use the full database

Figure 4. **Rates of incident mild, moderate and severe tricuspid regurgitation (TR) among the 363,270 patients free of TR at baseline.**

Figure 5: **Adjusted hazard ratios for mortality according to the time after occurrence of incident tricuspid regurgitation**.

Table 1: Baseline characteristics by presence of tricuspid regurgitation (TR) degree at baseline (prevalent tricuspid regurgitation).

	No TR N=363270	Mild TR N=44003	Moderate TR N=22507	Severe TR N=5899
Characteristics of heart failure diagnosis				
Diagnosed with heart failure as inpatient	161214 (44.4%)	23559 (53.5%)	12444 (55.3%)	3206 (54.3%)
Type of heart failure				
Diastolic	217602 (59.9%)	29102 (66.1%)	14054 (62.4%)	3841 (65.1%)
Systolic	140992 (38.8%)	14854 (33.8%)	8422 (37.4%)	2041 (34.6%)
Systolic + diastolic	4676 (1.3%)	47 (0.1%)	31 (0.1%)	17 (0.3%)
Prior (within one year) admission for heart failure	107799 (29.7%)	16855 (38.3%)	8026 (35.7%)	2087 (35.4%)
Demographics				
Age years	73.0 (62.0 to 81.0)	75.0 (65.0 to 82.0)	80.0 (70.0 to 84.0)	80.0 (69.0 to 84.0)
Female	179877 (49.5%)	23215 (52.8%)	14095 (62.6%)	4021 (68.2%)
Comorbidities				
Prior / current smoker	226980 (67.6%)	29120 (69.2%)	14176 (66%)	3572 (63.8%)
Hypertension	236593 (65.1%)	29687 (67.5%)	14308 (63.6%)	3331 (56.5%)
Hyperlipidemia	164551 (45.3%)	20818 (47.3%)	9196 (40.9%)	2005 (34.0%)
Diabetes without complications	110885 (30.5%)	12947 (29.4%)	5161 (22.9%)	1154 (19.6%)
Diabetes with complications	27825 (7.7%)	3232 (7.3%)	1163 (5.2%)	237 (4.0%)
Pulmonary disease	49456 (13.6%)	6292 (14.3%)	2604 (11.6%)	544 (9.2%)
Moderate to severe liver disease	2178 (0.6%)	362 (0.8%)	123 (0.5%)	52 (0.9%)
Moderate to severe renal disease	70992 (19.5%)	9344 (21.2%)	4869 (21.6%)	1264 (21.4%)
Cancer	47215 (13.0%)	6363 (14.5%)	2993 (13.3%)	655 (11.1%)
Dilated cardiomyopathy	20329 (5.6%)	2557 (5.8%)	1164 (5.2%)	281 (4.8%)
Coronary artery disease	121198 (33.4%)	15210 (34.6%)	6808 (30.2%)	1530 (25.9%)
Myocardial infarction	47282 (13.0%)	6147 (14.0%)	2477 (11.0%)	467 (7.9%)
Percutaneous coronary intervention	13905 (3.8%)	1656 (3.8%)	562 (2.5%)	71 (1.2%)
Stroke	21037 (5.8%)	3319 (7.5%)	1575 (7.0%)	375 (6.4%)
Cerebrovascular disease	34535 (9.5%)	5278 (12.0%)	2414 (10.7%)	524 (8.9%)
Peripheral vascular disease	43067 (11.9%)	5893 (13.4%)	2741 (12.2%)	599 (10.2%)
Moderate / severe mitral regurgitation	16440 (4.5%)	6403 (14.5%)	7766 (34.5%)	2506 (42.5%)
Moderate / severe aortic stenosis	18891 (5.2%)	4973 (11.3%)	2756 (12.3%)	674 (11.4%)
Pacemaker implantation	4073 (1.1%)	725 (1.6%)	423 (1.9%)	122 (2.1%)
Any cardiac surgery (any procedure below)	6782 (1.9%)	1356 (3.1%)	502 (2.2%)	167(2.8%)
Mitral valve replacement	776 (0.2%)	259 (0.6%)	178 (0.8%)	101 (1.7%)
Aortic valve replacement	2324 (0.64%)	654 (1.49%)	233 (1.04%)	64 (1.08%)
Coronary artery bypass graft	4725 (1.3%)	772 (1.8%)	236 (1.0%)	63 (1.1%)

Atrial fibrillation	86708 (23.9%)	12897 (29.3%)	9670 (43.0%)	2917 (49.4%)
Blood and echo measurements				
Creatinine, mg/dl	1.0 (0.8 to 1.4)	1.1 (0.8 to 1.4)	1.1 (0.8 to 1.5)	1.1 (0.9 to 1.5)
NT-proBNP, pg/mL	1636 (533 to 4213)	2167 (841 to 5190)	3550 (1678 to 7207)	3815 (1945 to 7922)
BNP, pg/mL	305 (117 to 694)	365 (154 to 766)	538 (278 to 1040)	603 (313 to 1120)
Systolic pulmonary artery pressure, mmHg	40 (31 to 49)	40 (33 to 48)	50 (42 to 60)	55 (43 to 69)
Left ventricular ejection fraction, %	55 (40 to 60)	55 (43 to 63)	55 (40 to 61)	55 (42 to 62)
Albumin, g/dL	3.7 (3.3 to 4.0)	3.6 (3.2 to 4.0)	3.6 (3.2 to 3.9)	3.6 (3.2 to 3.9)
Follow-up				
Time at risk, years	1.5 (0.5 to 3.1)	1.5 (0.5 to 3.1)	1.3 (0.4 to 2.9)	1.2 (0.4 to 2.8)
Died during follow up	96563 (26.6%)	13103 (29.8%)	8976 (39.9%)	2631 (44.6%)
Pacemaker implantation	12460 (3.4%)	2019 (4.6%)	1291 (5.7%)	338 (5.7%)
Any cardiac surgery (any procedure below)	14248 (3.9%)	2603 (5.9%)	1213 (5.4%)	430 (7.3%)
Mitral valve replacement	2669 (0.7%)	601 (1.4%)	496 (2.2%)	270 (4.6%)
Aortic valve replacement	6439 (1.8%)	1452 (3.3%)	598 (2.7%)	163 (2.8%)
Coronary artery bypass graft	7996 (2.2%)	1180 (2.7%)	497 (2.2%)	163 (2.8%)

Values are number of patients (percentage) or median (inter-quartiles)

Missing were as follows: Prior / current smoker: 30717 (7.1%); Creatinine: 71438 (16.4%); NT-proBNP: 374782 (86.0%); BNP: 301684 (69.2%); Systolic pulmonary artery pressure: 420855 (96.6%); Left ventricular ejection fraction: 53799 (12.3%)

SUPPLEMENTARY MATERIALS

Natural language processing

We used Optum Analytics' proprietary Natural Language Processed (NLP) data for determination of the concepts related to cardiac and valvular disease. The Optum Analytics NLP system was developed using vocabulary from the Unified Medical Language System that includes multiple medical dictionaries such as the Logical Observation Identifiers Names and Codes (LOINC), the Systemized Nomenclature of Medicine-Clinical Terms (SNOMED-CT), and RxNorm, a listing of generic and branded drugs (among others). NLP Concepts are identified and created based on broad topics such as medications, signs, disease and symptoms, measurements, observations, etc. The data is harvested from the notes' fields within the Electronic Health Records provided to Optum Analytics. The data used for development of each NLP concept is de-identified and accuracy is verified through a series of Quality Assurance steps prior to release for use. Each NLP concept included in the data is associated with a unique subject record and a date of observation; allowing longitudinal tracking of concepts such as heart failure or tricuspid disease over time. Researchers using the NLP concepts can analyze and group the NLP verbatim texts harvested into large "coded" sets of reported information as required.

Figure S1. Flow chart of the population