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RESEARCH ARTICLE

Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis

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Aims More evidence is needed to quantify the association between tricuspid regurgitation (TR) and mortality in patients with heart failure (HF).

Methods and results Between 2008–2017, using the Optum longitudinal database, a patient-level database that integrates multiple US-based electronic health and claim records from several health care providers, we identified 435 679 patients with new HF diagnosis and both an assessment of the left ventricular ejection fraction and at least 1 year of history. TR was graded as mild, moderate or severe and classified as prevalent (at the time of the initial HF diagnosis) or incident (subsequent new cases 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. Prevalence of mild, moderate and severe TR at baseline was 10.1%, 5.1% and 1.4%, respectively. Over a median follow-up of 1.5 years, 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% confidence interval (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 from 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. Findings were consistent across all patient subgroups based on age, gender, rhythm, associated comorbidities, prior cardiac surgery, B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide, and left ventricular ejection fraction.

Conclusions In this large contemporary patient-level database of almost half-million US patients with HF, TR was associated with a marked increases in mortality risk overall and in all subgroups. Future randomized controlled trials will evaluate the impact of TR correction on clinical outcomes and the causal relationship between TR and mortality.

Keywords Tricuspid regurgitation • Mortality • Heart failure

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Introduction

Although present in over 1.6 million individuals in the US,[1] tricuspid regurgitation (TR) has long been overlooked compared to left-sided valve diseases. Indeed, recent epidemiological data 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 stenosis (AS) or mitral regurgitation (MR).[2,3] Although highly prevalent, TR is often left untreated and less than 10 000 patient undergo tricuspid surgery per year in the US mostly at the time of mitral valve surgery.

Uncertainties regarding the impact of TR on outcome are related to its heterogeneous nature often secondary to other conditions (mainly left-sided disease or pulmonary hypertension),[3,4] so that it is critical to account for these conditions in appreciating TR effect on survival. In the context of heart failure (HF), these uncertainties are even most pronounced. TR is highly prevalent[5,6] but the impact of TR on survival in patients with HF is disputed. While recent studies suggested a link between TR and worse outcomes, predominantly in the context of severely reduced systolic function,[3,5–9] other studies found no independent association with survival.[10,11] Furthermore, most studies on functional TR have been modest in size, have focused on HF with reduced ejection fraction (HFrEF) and have not considered HF as a global entity inclusive of preserved ejection fraction (HFpEF) and have originated from single tertiary referral centres with inherent referral bias, but also with expert interpretation of TR severity, a notoriously complex evaluation.[12] The largest positive study emanates from a leading academic institution with advanced expertise regarding non-invasive TR assessment,[13] and it is uncertain whether these data are applicable to a wide variety of practices, imaging centres and practitioners. These uncertainties may explain why TR is not included in HF prognostic scoring systems such as the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score[14] and why valvular heart disease guidelines are vague for TR management in HF and do not involve class I indications for intervention.[15,16]

Hence, to fill the gaps of knowledge regarding TR in HF, it is essential to gather a very large cohort, evaluated in the routine practice of multiple centres/practitioners with coexisting conditions well defined for exhaustive adjustment and for definite characterization of TR independent prognostic implications in all HF types. Using the Optum longitudinal patient-level database, we gathered such a HF cohort and examined the independent and incremental association between TR and mortality, when TR was diagnosed (i) prior to or at the time of the initial HF diagnosis (prevalent TR) and (ii) during the follow-up period of the initial HF diagnosis (incident TR).

Methods

Study design

Optum© de-identified electronic health records (EHR)/claims dataset is one of the largest databases in the US, being derived from more than 85 health care provider organizations including 700 hospitals and 7000 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 provide detailed information including disease signs and symptoms (see following NLP section).[17,18] 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-9428 and ICD-10 I50) and an assessment of left ventricular function either qualitative [reduced/preserved left ventricular ejection fraction (LVEF)] and/or quantitative (numerical value of LVEF) and with at least 1 year of history in the dataset prior to the initial HF episode. As ICD-9 or 10 coding does not provide any indication regarding TR severity, it was assessed using NLP of EHRs and semi-quantitatively graded as absent, mild, moderate, or severe.

Natural language processing

We used Optum Analytics' proprietary 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 are harvested from the notes' fields within the EHRs 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 HF or tricuspid disease over time. Researchers using the NLP concepts can analyse and group the NLP verbatim texts harvested into large 'coded' sets of reported information as required.

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 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 percutaneous coronary intervention were assessed only during the patient's baseline period. Hospitalization and medication history were ascertained by analysing patient records in the 12 months prior to the initial diagnosis of HF. Other parameters extracted from patient records in the 12 months prior to diagnosis were body mass index, systolic and diastolic blood pressure, creatinine, haemoglobin, international normalized ratio, B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), albumin,

alanine aminotransferase, aspartate aminotransferase, bilirubin, pulmonary artery systolic pressure (PASP), 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

Tricuspid regurgitation was analysed according to severity (none, mild, moderate, severe) and by whether it was prevalent (prior or at the time of HF diagnosis) or incident (diagnosed afterwards, during patient follow-up in patients free from 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 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 Masterfile and censoring was based on the date of last documented encounter with the health care system.

First, we compared patients according to the level of prevalent TR (at the time of 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.[19] 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.[14] 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 five imputed datasets and combined estimates and standard errors across datasets using Rubin's rules.[20] 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, ischaemic or dilated cardiomyopathy, prior cardiac surgery, presence of permanent pacemaker, concomitant significant valve disease (AS or MR), BNP/NT-proBNP, LVEF and PASP.

Continuous variables were summarized using medians with interquartile ranges (IQR), categorical variables as counts and percentages. Analyses were performed in Stata version 15.1 (Stata Corp., College Station, TX, USA), 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 1-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 (online supplementary *Figure S1*).

The median age at baseline was 73 years (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 atrial fibrillation (AF), with associated MR, higher BNP/NT-proBNP and PASP. They were also more commonly treated with diuretics and anticoagulants. Baseline characteristics of patients with and without TR are presented in *Table 1*.

Prevalent tricuspid regurgitation and outcome

Over a median follow up of 1.5 years (IQR 0.5–3.1), 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 from TR, 24.0% for mild TR, 32.7% for moderate TR, and 36.9% for severe TR. Compared to patients with no TR, unadjusted HRs were 1.13 [95% confidence interval (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) for severe TR (*Figure 2*). The association was less strong with progressive adjustment for potential confounders. After adjustment for covariates in the MAGGIC risk score, HRs compared to no TR were 1.06 (95% CI 1.04–1.08) for mild TR, 1.35 (95% CI 1.32–1.38) for moderate TR, and 1.61 (95% CI 1.54–1.68) 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 HRs 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 HRs 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, ischaemic or dilated cardiomyopathy, prior cardiac surgery, presence of permanent pacemaker, concomitant moderate/severe AS or MR, BNP/NT-proBNP, LVEF and PASP. The association between TR and mortality was observed in all subgroups except PASP. In particular, a significant association between TR and mortality was observed in young and elderly patients, in patients in AF or in sinus rhythm, in patients with or without concomitant valvular or coronary artery disease, in patients whose HF episode was either ambulatory or in-hospital, patients with severely reduced

Table 1 Baseline characteristics by tricuspid regurgitation degree at baseline (prevalent tricuspid regurgitation)

	No TR (*n* = 363 270)	Mild TR (*n* = 44 003)	Moderate TR (*n* = 22 507)	Severe TR (*n* = 5899)
Characteristics of heart failure diagnosis				
Diagnosed with heart failure as inpatient	161 214 (44.4)	23 559 (53.5)	12 444 (55.3)	3206 (54.3)
Type of heart failure				
Preserved ejection fraction	217 602 (59.9)	29 102 (66.1)	14 054 (62.4)	3841 (65.1)
Reduced ejection fraction	145 668 (41.1)	14 901 (33.9)	8453 (37.6)	2058 (34.9)
Prior (within 1 year) admission for heart failure	107 799 (29.7)	16 855 (38.3)	8026 (35.7)	2087 (35.4)
Demographics				
Age, years	73.0 (62.0–81.0)	75.0 (65.0–82.0)	80.0 (70.0–84.0)	80.0 (69.0–84.0)
Female sex	179 877 (49.5)	23 215 (52.8)	14 095 (62.6)	4021 (68.2)
Comorbidities				
Prior/current smoker	226 980 (67.6)	29 120 (69.2)	14 176 (66)	3572 (63.8)
Hypertension	236 593 (65.1)	29 687 (67.5)	14 308 (63.6)	3331 (56.5)
Hyperlipidaemia	164 551 (45.3)	20 818 (47.3)	9196 (40.9)	2005 (34.0)
Diabetes without complications	110 885 (30.5)	12 947 (29.4)	5161 (22.9)	1154 (19.6)
Diabetes with complications	27 825 (7.7)	3232 (7.3)	1163 (5.2)	237 (4.0)
Pulmonary disease	49 456 (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	70 992 (19.5)	9344 (21.2)	4869 (21.6)	1264 (21.4)
Cancer	47 215 (13.0)	6363 (14.5)	2993 (13.3)	655 (11.1)
Dilated cardiomyopathy	20 329 (5.6)	2557 (5.8)	1164 (5.2)	281 (4.8)
Coronary artery disease	121 198 (33.4)	15 210 (34.6)	6808 (30.2)	1530 (25.9)
Myocardial infarction	47 282 (13.0)	6147 (14.0)	2477 (11.0)	467 (7.9)
Percutaneous coronary intervention	13 905 (3.8)	1656 (3.8)	562 (2.5)	71 (1.2)
Stroke	21 037 (5.8)	3319 (7.5)	1575 (7.0)	375 (6.4)
Cerebrovascular disease	34 535 (9.5)	5278 (12.0)	2414 (10.7)	524 (8.9)
Peripheral vascular disease	43 067 (11.9)	5893 (13.4)	2741 (12.2)	599 (10.2)
Moderate/severe mitral regurgitation	16 440 (4.5)	6403 (14.5)	7766 (34.5)	2506 (42.5)
Moderate/severe aortic stenosis	18 891 (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	86 708 (23.9)	12 897 (29.3)	9670 (43.0)	2917 (49.4)
Blood and echo measurements				
Creatinine, mg/dL	1.0 (0.8–1.4)	1.1 (0.8–1.4)	1.1 (0.8–1.5)	1.1 (0.9–1.5)
NT-proBNP, pg/mL	1636 (533–4213)	2167 (841–5190)	3550 (1678–7207)	3815 (1945–7922)
BNP, pg/mL	305 (117–694)	365 (154–766)	538 (278–1040)	603 (313–1120)
Pulmonary artery systolic pressure, mmHg	40 (31–49)	40 (33–48)	50 (42–60)	55 (43–69)
Left ventricular ejection fraction, %	55 (40–60)	55 (43–63)	55 (40–61)	55 (42–62)
Albumin, g/dL	3.7 (3.3–4.0)	3.6 (3.2–4.0)	3.6 (3.2–3.9)	3.6 (3.2–3.9)
Follow-up				
Time at risk, years	1.5 (0.5–3.1)	1.5 (0.5–3.1)	1.3 (0.4–2.9)	1.2 (0.4–2.8)
Died during follow-up	96 563 (26.6)	13 103 (29.8)	8976 (39.9)	2631 (44.6)
Pacemaker implantation	12 460 (3.4)	2019 (4.6)	1291 (5.7)	338 (5.7)
Any cardiac surgery (any procedure below)	14 248 (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 given as *n* (%) or median (interquartile range).
BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TR, tricuspid regurgitation.
Missing were as follows: prior/current smoker: 30717 (7.1%); creatinine: 71 438 (16.4%); NT-proBNP: 374 782 (86.0%); BNP: 301 684 (69.2%); pulmonary artery systolic pressure: 420 855 (96.6%); left ventricular ejection fraction: 53 799 (12.3%).

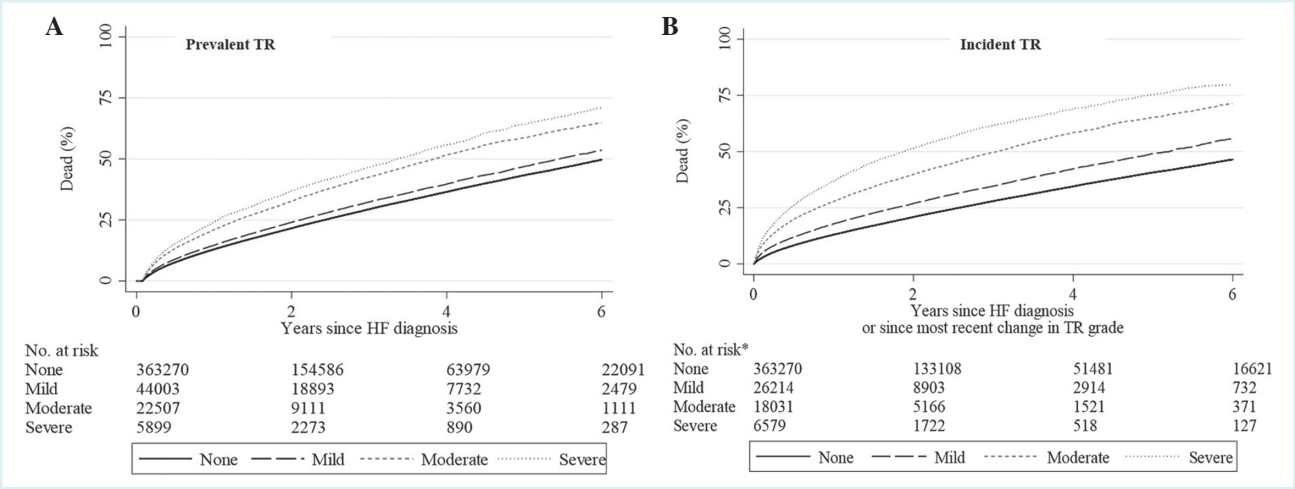

Figure 1 Survival according to degree of tricuspid regurgitation (TR). (*A*) TR diagnosed at baseline (prevalent TR) and (*B*) TR diagnosed during follow-up in patients free from TR at baseline (incident TR). *The analysis of incident TR includes only patients with no TR at baseline. For the analysis 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). HF, heart failure.

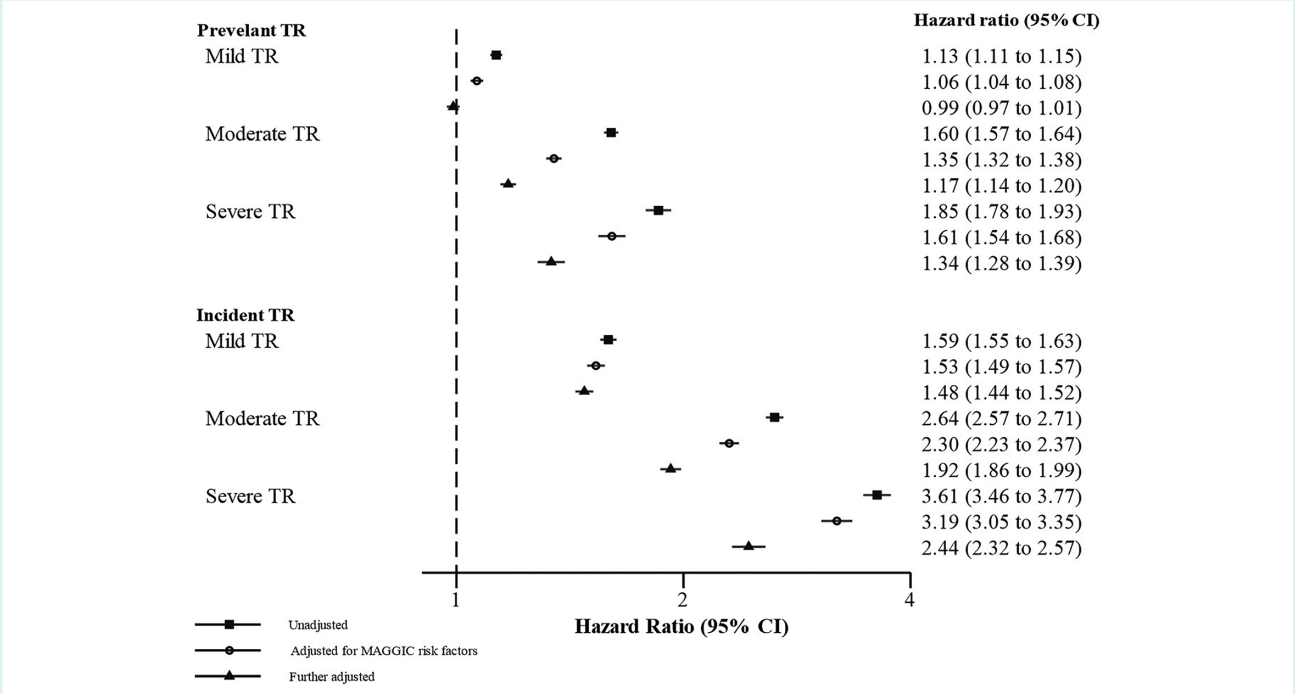

Figure 2 Impact of the degree of tricuspid regurgitation (TR) on mortality risk. Risk is expressed as hazard ratios [95% confidence interval (CI)] relative to those with no TR. *Factors in the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score: age, sex, current smoking status, systolic blood pressure, diabetes, pulmonary disease, serum creatinine, beta-blocker use, angiotensin-converting enzyme/angiotensin receptor blocker use. We could not adjust for New York Heart Association class, pulmonary artery systolic pressure, because of unavailability. **Further adjustments include adjustments for race, geographical region, type of heart failure (diastolic/systolic), B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide, body mass index, heart rate, albumin, MELD-XI score, comorbidities, medication use at baseline, time-updated status for mitral regurgitation and aortic stenosis, time-updated procedures (coronary artery bypass graft, mitral valve repair, ablation, Maze procedure, pacemaker implantation).

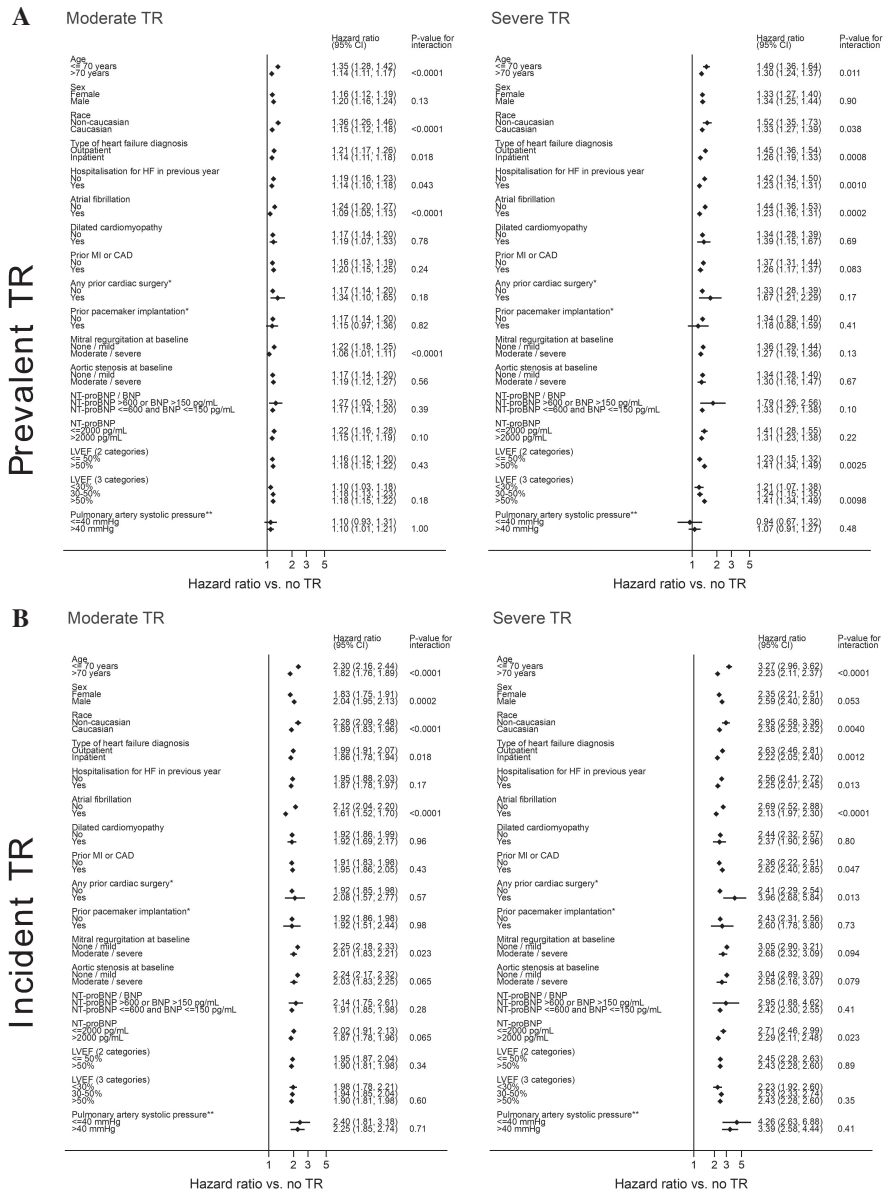

Figure 3 Adjusted hazard ratios of moderate and severe tricuspid regurgitation (TR) in selected patient subgroups relative to no TR. (*A*) Prevalent TR and (*B*) incident TR. *Recorded in previous year. Cardiac surgery includes coronary artery bypass graft, mitral or aortic valve replacement. **Amongst the subset of 14 824 patients with pulmonary artery systolic pressure measurements; other analyses use the full database. BNP, B-type natriuretic peptide; CAD, coronary artery disease; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

or preserved ejection fraction and patients with normal or mildly elevated BNP values.

Incident tricuspid regurgitation and 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 HRs 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) for 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

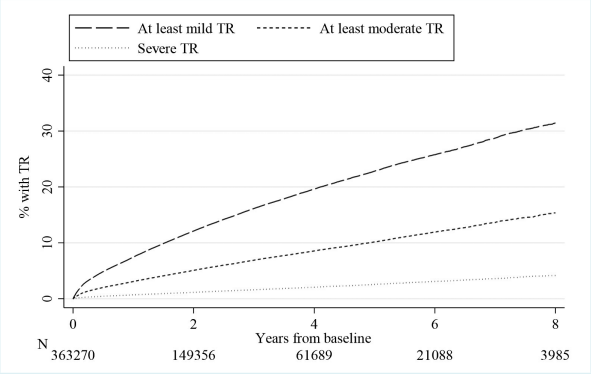

Figure 4 Rates of incident mild, moderate and severe tricuspid regurgitation (TR) among the 363 270 patients free from TR at baseline.

adjusted HRs 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. The association between incident TR and mortality was observed in all patient subgroups (*Figure 3B*). It is worth noting that using patients free from TR at baseline and during follow-up as reference did not change our findings and the association between TR and mortality.

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 HR compared with no TR was 6.10 (95% CI 5.48–6.80) (*Figure 5*). The HR 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 HR 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. TR was commonly observed with HF, both in patients with reduced and preserved ejection fraction and the prevalence of TR increased with age, female gender, and with the presence of concomitant AF and MR. Our main finding is that TR – both prevalent and incident – 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.

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/ischaemic cardiomyopathy or left-sided valvular heart disease), pulmonary hypertension or AF.[3,4] In a retrospective study of 5223 patients who underwent a transthoracic echocardiogram at three Veterans Affairs Medical Center laboratories between 1998 and 2002, Nath *et al.*[7] observed that mortality increased with increasing severity of TR. 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 70 studies encompassing 32 601 patients concluded to an independent association between moderate or severe TR and mortality,[21] but could not eliminate the effect of comorbidities on mortality. In addition, most studies included in the meta-analysis were retrospective, single centre, with various referral biases, often initiated in the early 1990s before the full implementation of current HF treatment standards, and almost exclusively centred 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 excess mortality associated with TR was observed after adjustment for multiple potential confounders. Moderate and severe TR was 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 HRs according to the time of TR diagnosis (*Figure 4*) would support this hypothesis. Importantly, the Optum database with more than 90 million US patients of various age, gender, race, geographic area, insurance type and socioeconomic status support the generalizability of our findings. In addition, evaluation of TR severity was performed by unselected and numerous care providers extending applicability of our findings regarding the association of TR in HF with mortality to most routine clinical practice.

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 ejection fraction, 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 centre study of 576 patients that the impact of TR on survival decreased as ejection fraction declined.[11] Our study, taking advantage of its large size, showed that the association between TR and mortality was highly significant in all LVEF subsets, including those with severely reduced LVEF (<30%). TR is commonly observed in patients with either primary or secondary MR. In the present study, increased mortality rates were observed both in patients with associated MR and in patients free from MR; in

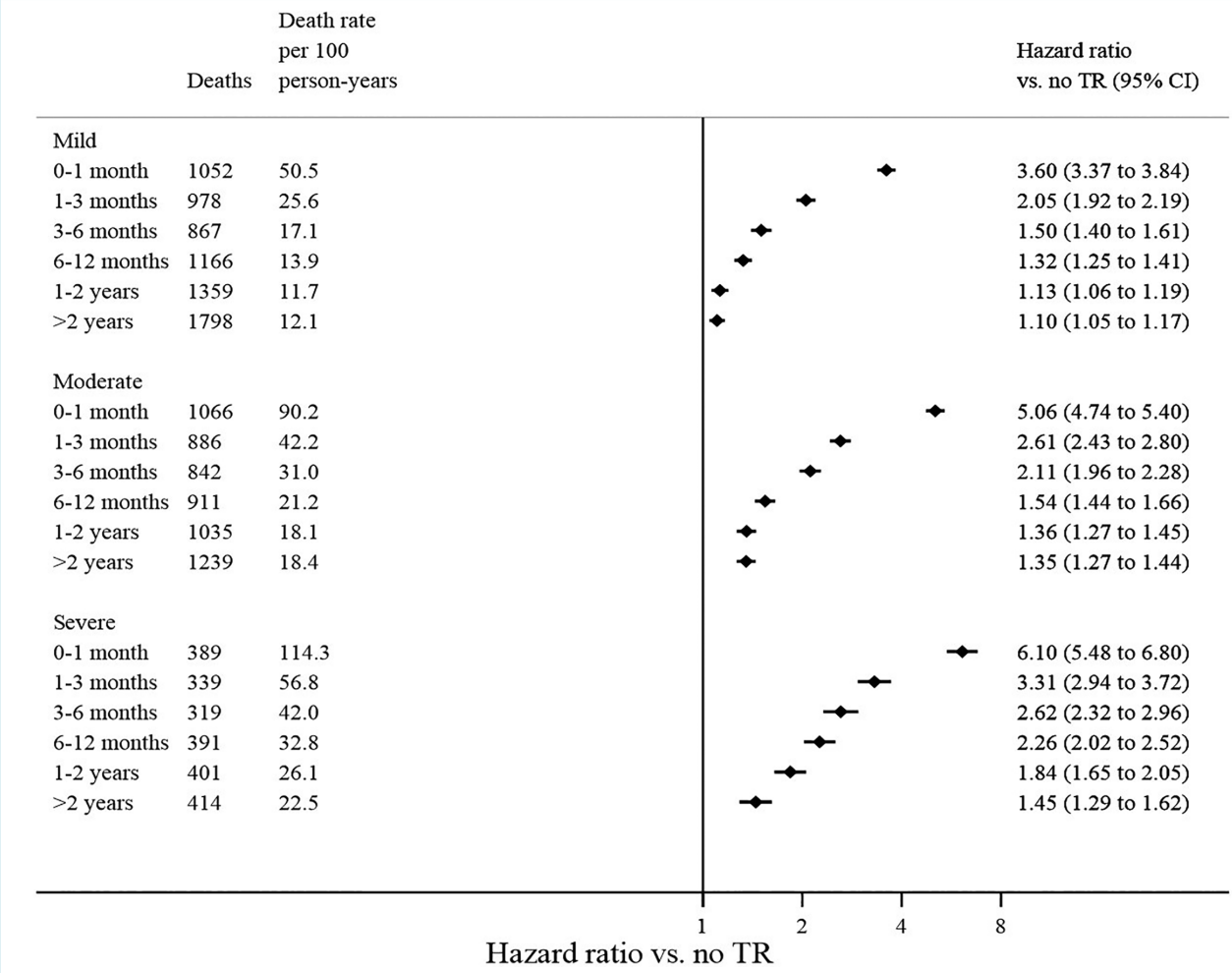

Figure 5 Adjusted hazard ratios for mortality according to the time after occurrence of incident tricuspid regurgitation (TR). CI, confidence interval.

addition, the association between TR and mortality remained significant after adjustment for MR. AF is also frequently associated with TR, both as a cause and consequence of the disease. Association between TR and mortality was observed irrespective of the presence or absence of AF in this population. TR prevalence increases with age but association between TR and mortality was observed irrespective of age. It is worth noting that we did not observe an association between prevalent TR and mortality in the subset in whom PASP was measured. It is likely due to a limited statistical power as PASP was only measured in 3.4% of the population and an association with mortality was observed for incident TR independently of PASP. 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[22,23] and a 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.[14,24] 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.[25,26] 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, and deserve close attention. 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.[27]

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,[28] and patients with isolated severe functional TR,[29] 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 a marker for the observed increased mortality risk could not be determined from the current results. More specifically, severity of right ventricular dilatation would be a critical parameter to account for as clearly established as important prognostic factor.[30] It is highly probable that patients with advanced right ventricular consequences are likely the ones that will benefit the less of tricuspid valve interventions. The most common interpretation of the discordant results of the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trials is that transcatheter correction has a positive impact on survival, HF hospitalizations and quality of life in selected patients with functional MR.[31,32] Recent observational studies evaluating the impact of TR correction have provided contradictory results[33,34] and there is a critical need for randomized controlled trials aiming to evaluate the benefit and timing of therapeutic interventions for TR. 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.[35–39] 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 are consistent with the view that most TR patients are treated with conservative medical management.[25,26]

Strengths and limitations

Firstly, Optum is a patient-level database that integrates multiple EHRs 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 system greatly enhances information granularity. However, the Optum database remains subject to errors, omission and misreporting, but conversely reflects routine clinical practice. We thus cannot exclude that TR prevalence might have been underestimated if it was neither mentioned in clinical notes nor in echocardiographic reports. In addition, the size of the HF population examined, unique in the literature, minimizes the importance of such errors and reduces the variation contributed by individual providers and institutions. Secondly, not all variables were available for all patients. Although a qualitative assessment of 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 PASP was only available in a small proportion of the population. Although we acknowledge this is a limitation, PASP was available in 14 824 patients, which is three times larger than the total available number in the entire literature.[21] Right ventricular size and function are important prognostic factors.[30] Previous studies have suggested that, in patients with reduced ejection fraction, TR was an independent determinant of poor outcome after adjustment for right ventricular function and pulmonary pressure.[8,13] No information regarding right ventricular size and function was available in the present study and we were not able to account for them in the model assessing the independent prognostic value of TR on outcome. Thirdly, TR severity was graded semi-quantitatively. A quantitative assessment would have been desirable for TR severity[8,9,29] but it is not routinely performed in most institutions and an integrative multiparametric approach is recommended by both the North American and European Echocardiography and Cardiology Societies.[12] The present evaluation thus reflects current real-world practice. Fourthly, mean follow-up duration was relatively short mainly due to the recent enrolment of patients (median February 2015, IQR Dec 2012–Aug 2015). Nevertheless, mortality rate was high and enabled us to show the strong association between TR and mortality. Finally, a causal relationship between TR and mortality will only be fully affirmed when the treatment of TR demonstrates 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 a higher risk of death that increased with TR severity overall and in all subgroups based on age, gender, rhythm, associated comorbidities, prior cardiac surgery, BNP/NT-proBNP and LVEF, and association between TR and mortality was sustained after adjustment for extensive potential confounders. Occurrence of TR in HF patients merits closer attention by cardiologists and future randomized controlled trials will evaluate the impact of TR correction on clinical outcomes and demonstrate the causal relationship between TR and mortality.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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