Severity of diastolic dysfunction predicts myocardial infarction

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ABSTRACT

Background: Diastolic dysfunction (DD) is known to be a predictor of mortality. However, the impact of DD on the risk for myocardial infarction (MI) is not well defined. We sought to examine whether DD is an independent predictor of risk of MI in patients with a preserved ejection fraction.

Methods: This was an observational study of consecutive patients who underwent an echocardiogram that showed normal systolic function and had $\geq$ 3 months of follow-up. DD was graded using the contemporaneous guidelines at the time of the echocardiogram. Subsequent MI was determined by an inpatient encounter with a primary diagnosis of MI.

Results: 129,476 patients were included (mean age 56 years; 58 % women). DD was present in 17.6 % of patients (13.6 % Grade I, 3.6 % Grade II, 0.4 % Grade III). Patients with DD were more likely to be older and have cardiovascular comorbidities. Survival free from MI was significantly lower as DD severity increased. Multivariate Cox proportional hazards modeling demonstrated that DD was an independent predictor of MI (hazard ratios [CI]: Grade I: 1.48 [1.33–1.66]; Grade II: 1.84 [1.57–2.16]; Grade III: 2.90 [1.98–4.25]).

Conclusion: Our data demonstrate that the risk of MI is significantly increased in the presence of DD, with higher risk at higher grades of DD. The increased risk associated with grade III DD is comparable to that from a prior history of percutaneous coronary intervention. These findings suggest that the severity of DD may be a useful tool in stratifying patients for risk of MI.

Left ventricular diastolic dysfunction (DD) is a common finding on echocardiography, but our understanding of the clinical implications of this finding remains limited, particularly in patients with normal systolic function. Diastolic dysfunction is a complex physiological entity [1] that is closely linked with heart failure with preserved ejection fraction (HFpEF). However, many patients without DD develop clinical heart failure and about a third of patients with HFpEF do not have echocardiographic evidence of DD [2,3].

Apart from its relationship with clinical HFpEF, DD has been shown to be associated with mortality and major adverse cardiovascular events [4,5]. However, these studies have been limited in size, and have in general examined an aggregate endpoint of mortality and other adverse cardiovascular outcomes. Although DD is associated with impaired coronary blood flow reserve [6,7], there has been no prior work specifically examining how DD influences the risk of future myocardial infarction (MI). In this study, we examined the association between DD and the risk of MI in a retrospective, observational analysis of patients at a large multi-hospital health care system.

1. Methods

This was a retrospective study of consecutive patients who underwent an echocardiogram between January 2010 and October 2022, that demonstrated normal systolic function (left ventricular ejection fraction $\geq$ 50 %). Patients who had less than three months of clinical follow-up were excluded. Because of the retrospective nature of the study, the need for informed consent was waived by the institutional review board, which approved this research protocol.

All echocardiograms were obtained as part of routine medical care. For patients with multiple echocardiograms, the follow-up data was collected following the first echocardiogram, though the patient was excluded if any subsequent echocardiograms showed systolic

dysfunction. DD was determined from the official echocardiogram report, whereby cardiology specialists graded DD using contemporaneous guidelines [8,9]. Patients for whom DD was reported as "indeterminate" or "incomplete data", or for whom diastolic function was not evaluated for other reasons (e.g. atrial fibrillation, mitral valve surgery) were excluded.

Clinical data were obtained from the University of Pittsburgh Medical Center's clinical analytics data warehouse. Collected data included demographic information (e.g. age, gender, race), physical examination (e.g. height, weight, body mass index (BMI)), and medical history (e.g. coronary artery disease, hyperlipidemia, diabetes, hypertension, heart failure, obesity, atrial fibrillation, chronic obstructive pulmonary disease, pulmonary hypertension, pulmonary embolism, vascular disease, chronic kidney disease, end-stage renal disease, history of stroke or transient ischemic attack, prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting (CABG), and active tobacco use). The primary endpoint of subsequent MI was determined by the presence of an inpatient admission with the primary diagnosis of MI, based on the documented International Classification of Disease (ICD) codes (ICD-9-CM code 410 and ICD-10 codes I21 and I22).

Continuous data are presented as mean ± standard deviation. Categorical data are reported as frequency with percentage. Unadjusted time to event is presented with Kaplan-Meier curves, stratified by grade of DD. Log-rank testing was used to compare survival between these groups. Multivariable Cox proportional hazards models were developed to calculate hazard ratios for the outcome of MI by degree of DD, after adjustment for the clinical parameters included in the atherosclerotic cardiovascular disease (ASCVD) risk estimate from the pooled cohort equations i.e., using the following covariates: age, gender, diabetes, coronary disease, hypertension, hyperlipidemia, and current tobacco use (Model 1). Race was excluded from this analysis given the movement towards removing this social construct from quantitative risk scores [10]. The proportional hazards assumption was satisfied for all DD categories. Other clinical parameters (obesity, atrial fibrillation, chronic obstructive pulmonary disease (COPD), vascular disease, chronic kidney disease (CKD), end-stage renal disease (ESRD), history of stroke or transient ischemic attack (TIA), pulmonary hypertension, pulmonary embolism, prior PCI, and prior CABG were then added to the multivariable Cox model (Model 2), given their association with the risk of MI in our present dataset.

Given known gender differences in MI risk, the effect of gender on impact of DD was examined by adding an interaction term. In addition, separate sensitivity analyses 1) excluding all patients with prior PCI/ CABG or prior CAD and 2) including only patients with prior CAD was performed, to evaluate the impact of DD in a primary prevention vs. secondary prevention setting.

All analyses were performed in SPSS and with the Lifelines library for Python. Two-sided P values of < 0.05 were considered significant unless otherwise specified.

2. Results

There was a total of 129,476 patients with normal systolic function, with assessed DD and at least three months of follow-up included in this retrospective observational study. Of these, 106,693 (82.4 %) had normal diastolic function, while 17,586 (13.6 %) had grade I, 4,701 (3.6 %) had grade II, and 496 (0.4 %) had grade III DD. Median follow-up for the whole cohort was 43.5 months (range 3–154 months). A total of 1,813 patients (1.4 %) had a subsequent admission for MI during the follow-up period, the primary outcome of interest.

Table 1 shows the baseline characteristics of the study population. Patients with DD were notably older than those with no DD. Gender, race and BMI were comparable between groups. There was also no difference in average ejection fractions in this patient cohort with normal systolic function. The Elixhauer-based van Walraven comorbidity score increased with increasing levels of DD, indicating a higher prevalence of chronic comorbidities. The rates of every medical history factor listed in Table 1 were higher in the DD groups.

Over the duration of follow-up, there were 1,052 who were hospitalized with a primary diagnosis of MI among patients with normal diastolic function (1.0 %, mean follow-up 49 months), 539 in grade I DD (3.1 %, mean follow-up 52 months), 194 in grade II DD (4.1 %, mean follow-up 49 months) and 28 in grade III DD (5.6 %, mean follow-up 38 months). In an unadjusted Kaplan-Meier analysis, there was a significant lower survival free from MI by worsening grade of DD (Fig. 1, p < 0.001 by log-rank test). The Kaplan-Meier estimated survival free from MI at 5

Table 1
Patient Characteristics.

	No DD		DD Grade I		DD Grade II		DD Grade III	
	(n = 106,693)		(n = 17,586)		(n = 4,701)		(n = 496)	
Demographics								
Age, years (mean (SD)*	53	(17)	70	(12)	71	(13)	74	(14)
Women	61,870	(58 %)	10,281	(58 %)	2,727	(58 %)	286	(58 %)
Race (Black)	10,124	(9 %)	1,363	(8 %)	429	(9 %)	37	(7 %)
Weight, kg (mean (SD))	86	(24)	85	(22)	86	(25)	83	(22)
BMI, kg/m2 (mean (SD))	30	(8)	30	(7)	31	(8)	30	(7)
Medical History								
Ejection fraction, %	58	(5)	58	(5)	58	(5)	58	(6)
van Walraven score*	3	(6)	5	(7)	6	(8)	8	(8)
Coronary artery disease*	12,447	(12 %)	4,569	(26 %)	1,432	(30 %)	182	(37 %)
Hyperlipidemia*	43,556	(41 %)	11,244	(64 %)	3,045	(65 %)	320	(65 %)
Diabetes mellitus*	14,726	(14 %)	4,589	(26 %)	1,443	(31 %)	170	(34 %)
Hypertension*	44,645	(42 %)	11,947	(68 %)	3,438	(73 %)	372	(75 %)
Heart failure*	2,747	(3 %)	1,276	(7 %)	774	(16 %)	159	(32 %)
Atrial fibrillation*	6,285	(6 %)	1,499	(9 %)	799	(17 %)	198	(40 %)
Vascular disease*	3,853	(4 %)	1,280	(7 %)	395	(8 %)	54	(11 %)
Obstructive lung disease*	8,349	(8 %)	2,698	(15 %)	733	(16 %)	81	(16 %)
Chronic kidney disease*	4,222	(4 %)	1,702	(10 %)	716	(15 %)	109	(22 %)
Stroke or TIA*	6,672	(6 %)	2,156	(12 %)	638	(14 %)	96	(19 %)
Current tobacco use*	18,380	(17 %)	2,260	(13 %)	539	(11 %)	37	(7 %)
Prior PCI*	4,752	(4 %)	1,467	(8 %)	505	(11 %)	56	(11 %)
Prior CABG*	1,598	(1 %)	456	(3 %)	233	(5 %)	46	(9 %)

Values are n (%) unless otherwise stated. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.
(*) P < 0.01.
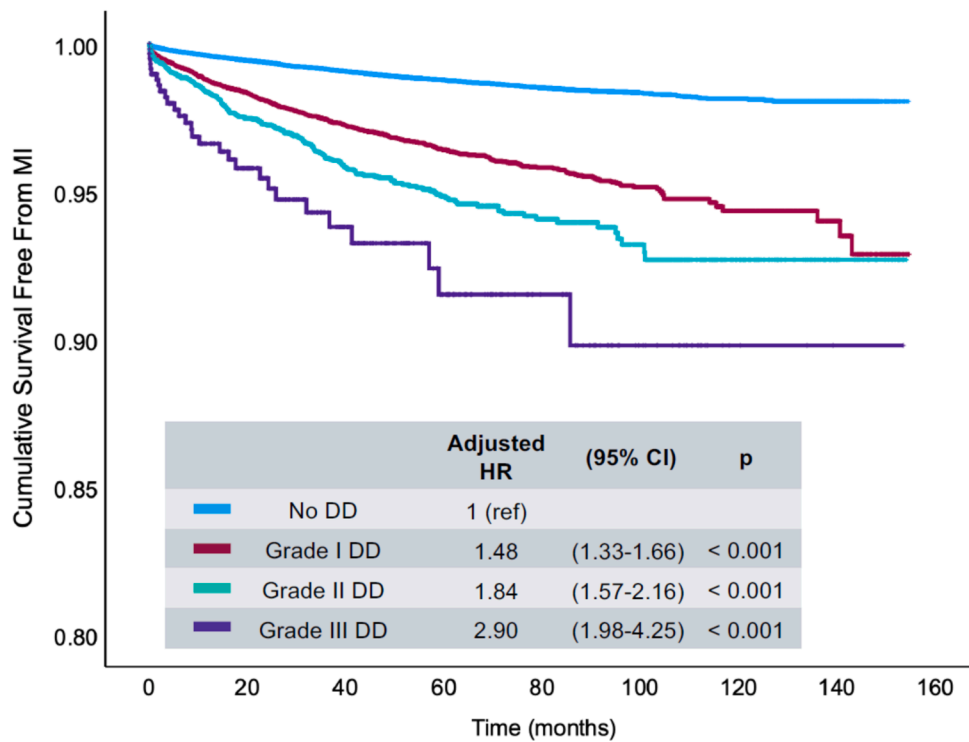
Fig. 1. Title: Survival Free from MI by Degree of Diastolic Dysfunction. Caption: Kaplan-Meier estimates of survival free from MI by degree of diastolic dysfunction (DD) show that that the risk of MI increases with worsening grade of DD. After adjustment for multiple comorbidities, the adjusted HRs demonstrate a significant, independent effect of diastolic dysfunction on MI risk. MI = myocardial infarction. HR = hazard ratio. CI = confidence interval.

years decreased with increasing grade of DD, with 98.8 % 5-year MI-free survival in normal diastolic function, 96.4 % in grade I DD, 94.9 % in grade II DD, and 91.5 % in grade III DD (Table 2).

In a multivariable Cox proportional hazards model incorporating the components of the ASCVD pooled cohort equations as well as grade of DD, the grade of DD was independently associated with risk of MI. The hazard ratio associated with DD increased with worsening DD grade (Grade I: HR 1.4 [95 % CI: 1.37–1.72]; Grade II: HR 1.99 [95 % CI: 1.70–2.34]; Grade III: HR 3.13 [95 % CI 2.14–4.57]) (Table 3, Model 1).

To ensure the robustness and independence of the effect of DD, Model 2 included additional predictors of MI in the present dataset. In this model, obesity, COPD, vascular disease, CKD, ESRD, history of stroke or transient ischemic attack and history of PCI were associated with increased risk of MI, while atrial fibrillation was associated with slightly decreased MI risk. History of pulmonary hypertension, pulmonary embolism, or prior CABG were not significantly associated with increased risk. After multiple adjustment, DD remained significantly associated with increased risk of MI (Fig. 1) with increasing risk at higher grades of DD (Grade I: HR 1.48 [95 % CI: 1.33–1.66]; Grade II: HR 1.84 [95 % CI: 1.57–2.16]; Grade III: HR 2.90 [95 % CI 1.98–4.25]) (Table 3, Model 2).

Separate sensitivity analyses of the impact of DD were performed by 1) excluding patients with prior PCI/CABG, 2) excluding patients with

Table 2
Kaplan-Meier Cumulative Risk of MI by Degree of DD.

Diastolic Dysfunction	Cumulative Risk % (95 % CI)					
	1-year		3-years		5-years	
Normal	0.4	(0.4–0.4)	0.8	(0.8–0.9)	1.2	(1.1–1.3)
Grade I	1.2	(1.0–1.4)	2.5	(2.3–2.8)	3.6	(3.2–3.9)
Grade II	1.5	(1.2–1.9)	3.8	(3.2–4.4)	5.1	(4.3–5.8)
Grade III	3.4	(1.8–5.0)	5.7	(3.4–8.1)	8.5	(4.9–12.1)

CI = confidence interval.

Table 3
Multivariable Predictors of MI by Cox Proportional Hazards.

Predictor	Model 1		Model 2	
	HR	95 % CI	HR	95 % CI
Diastolic Dysfunction				
Grade I DD	1.54	(1.37–1.72)	1.48	(1.33–1.66)
Grade II DD	1.99	(1.7–2.34)	1.84	(1.57–2.16)
Grade III DD	3.13	(2.14–4.57)	2.90	(1.98–4.25)
ASCVD risk factors				
Female gender	0.79	(0.72–0.87)	0.81	(0.74–0.89)
Age (per year)	1.03	(1.03–1.04)	1.03	(1.03–1.04)
Diabetes	1.84	(1.66–2.05)	1.63	(1.46–1.82)
CAD	2.39	(2.15–2.66)	1.67	(1.48–1.89)
Hypertension	1.29	(1.15–1.45)	1.21	(1.08–1.36)
Hyperlipidemia	0.82	(0.74–0.92)	0.78	(0.7–0.88)
Current tobacco use	1.83	(1.62–2.06)	1.76	(1.56–1.99)
Additional predictors				
Obesity			1.19	(1.08–1.32)
Atrial fibrillation			0.83	(0.7–0.97)
COPD			1.21	(1.06–1.38)
Vascular disease			1.4	(1.21–1.61)
CKD			1.42	(1.22–1.65)
ESRD			2.13	(1.63–2.77)
History of stroke/TIA			1.18	(1.02–1.35)
History of PCI			2.22	(1.94–2.53)

Abbreviations as in tables 1 and 2.

any known CAD, and 3) including only patients with known CAD. In all three populations, increasing severity of DD continued to be associated with increased MI risk (Supplemental Table 1). Of note, in the analysis of only patients with known CAD, female gender, obesity, atrial fibrillation, and COPD were no longer significant independent predictors of MI.

Finally, comparison of outcome associated with echocardiograms

performed before 2016 and after 2017 was performed to evaluate the impact of the changes in DD diagnostic criteria in 2016. While the prevalence of DD decreased under the updated guidelines (24.0 % prior to 2016 vs 15.0 % after 2017), its impact on the risk of MI persisted (Supplemental Table 2).

The impact of gender on the association of DD with risk of MI was studied with the addition of an interaction term. For this analysis, a simplified model was used where DD was considered either present or absent, i.e., the grade of dysfunction was not considered (Supplemental Table 3). The simplified model without (HR 1.59 [95 % CI: 1.43–1.76]; and 0.82 [95 % CI: 0.74–0.90], respectively) and with (HR 1.39 [95 % CI: 1.21–1.60]; and 0.73 [95 % CI: 0.64–0.82], respectively) interaction term remained significant for both DD and gender. There was also noted to be a significant interaction between female gender and DD (HR 1.32 [95 % CI: 1.09–1.59]), indicating that the presence of DD had a larger impact on the risk of MI in women compared to men.

3. Discussion

DD is an increasingly common clinical finding, with some studies suggesting a prevalence of isolated DD significantly higher than systolic dysfunction [11]. DD is characterized by impaired LV relaxation, increased LV stiffness and impaired LV diastolic recoil, all of which lead to elevated LV filling pressures [1]. Echocardiographic markers of each of these components are combined to make the diagnosis of diastolic dysfunction. DD on echocardiogram is associated with the subsequent development of clinical heart failure [12], as well as the subsequent reduction in ejection fraction [13]. However, across multiple studies, independently of the risk of future heart failure, DD appears to portend a risk of poor cardiovascular outcomes, including cardiac events, cardiovascular death and all-cause death [5]. To our knowledge, no study has specifically sought to examine the independent relationship between isolated DD and MI.

Understanding the factors that contribute to an individual's risk of MI are critical in delivering appropriate preventative medical care. In current clinical practice, the 2013 pooled cohort equations (PCE) for estimating 10-year risk atherosclerotic cardiovascular disease are commonly used [14]. These equations factor in age, race, gender, smoking status, blood pressure, diabetic status, and cholesterol levels to estimate risk. While the PCE work well in estimating risk on a population level [15], there are likely additional risk factors that affect an individual's risk of cardiovascular disease. In this study, we examined whether the presence of DD by echocardiography was independently predictive of the risk of MI.

Among the 129,476 patients included in the study, there was a 17.6 % prevalence of DD and a 1.4 % rate of admission for myocardial infarction. Risk of MI in DD has previously been assessed as part of composite cardiovascular endpoints in several small studies. An elevated E/e' ratio (one of the four variables evaluated in the 2016 DD criteria) was associated with higher incidence of a composite endpoint of MI, stroke or cardiovascular death in patients with type 2 diabetes [16], and was associated with a higher incidence of cardiac events in patients with hypertension [17]. Kuznetsova et al. examined echocardiographic markers of DD and found that those with signs of elevated LV filling pressures has a significantly elevated risk of cardiac events (HR 4.5 [95 % CI 1.7–11.7]) and cardiovascular events (HR 2.2 [95 % CI 1.0–4.8]) [18]; reduced mitral annular e' velocity was the most predictive marker of cardiac events, defined as a composite endpoint of MI, heart failure, angina, new atrial fibrillation and significant arrhythmia. In each of these studies, the limited study size of 500–1000 patients and the overall low event rates restricted the ability to examine individual types of cardiac events.

The scale of our study, looking at over one hundred thousand patients, allows us to examine MI as an independent outcome. In unadjusted Kaplan-Meier analyses, the risk of MI was found to increase with increasing severity of DD, with patients with grade III diastolic dysfunction having an 8.5 % cumulative risk of MI over 5 years. The increased risk associated with DD was robust despite correction for traditional cardiovascular risk factors, as well as other possible predictors of cardiovascular disease. In the adjusted Cox model, the additional risk from the presence of grade II diastolic dysfunction was higher than the risk from diabetes, current tobacco use, or prior history of coronary artery disease, and the risk from the presence of grade III diastolic dysfunction was on par with that from a prior history of percutaneous coronary intervention (Fig. 2). Female gender was shown to be protective, with HR 0.79 [95 % CI: 0.72–0.87] in Model 1, which is consistent with the well-described lower cardiovascular risk in women [14]. However, an interaction analysis suggests that the impact of DD on MI risk is greater in women than in men, suggesting that that cardiovascular benefit of female gender is negated or even reversed in the presence of DD. Interestingly, contrary to conventional wisdom, hyperlipidemia had a statistically significant hazard ratio of less than 1 across all tested models. The cause of this finding is not clear, but as the hyperlipidemia variable represents a chart diagnosis of hyperlipidemia rather than persistently elevated lipids, it is possible that a substantial number of patients with hyperlipidemia but without coronary artery disease have appropriately treated lipid levels and the protective hazard ratio represents well-managed hyperlipidemia and/or the pleotropic benefits of statin medications. Further analysis using laboratory data would be necessary to further elucidate this.

To ensure the robustness of the demonstrated effects of DD on the risk of MI, we conducted several sensitivity analyses to examine how this effect may differ in a primary prevention versus secondary prevention setting. In doing so, we found that DD was associated with increased MI risk across all populations. In addition, though our dataset demonstrated a significant decrease in the rate of diagnosis of DD due to changes in diagnostic guidelines in 2016, which has previously been well described [19], we found no difference in the impact of DD on MI risk before 2016 versus after 2017, allowing for a lag for adoption of the new guidelines.

The mechanisms underlying the relationship between DD and MI remain unclear. DD is associated with elevated left ventricular filling pressures and elevated wall stress [20]. It is possible that, in the setting of underlying coronary artery disease with unstable atherosclerotic plaques, these elevated wall stresses can lead to excess stress in vulnerable regions of plaque, leading to plaque rupture and type I MI. In addition, elevated wall stress is associated with elevated myocardial oxygen demand [21], and DD is associated with decreased coronary flow reserve [6]. Under conditions of systemic physiological stress, the combination of these factors may lead to a supply–demand mismatch, causing a type II MI. It is also worth noting that heart failure, which is often associated with DD, can result from acute coronary syndrome, thus providing further mechanistic links between DD and MI [22].

It remains unclear whether DD is a valuable target for reducing the risk of MI. While it has been shown that weight loss and reduction in blood pressure can lead to improvement in echocardiographic DD [23,24], the overall impact on cardiovascular risk is less defined. In a sub-analysis of the LIFE study of losartan for hypertension, normal diastolic function while on antihypertensive treatment was associated with a reduced risk of heart failure, but no change in risk of MI or cardiovascular mortality [25]; however this study did not distinguish between those who had normal diastolic function at baseline and those whose diastolic dysfunction normalized after treatment with losartan.

This study has limitations. It is a retrospective study from a single healthcare system, with clinical outcomes assessed based on readmissions within the system. As such, it is possible that admissions for MI that occurred outside of this single system were not included in this analysis. However, the healthcare system encompasses more than 40 hospitals, so a vast majority of readmissions are likely in-network. In addition, because the outcome of MI was measured based on hospital admissions using diagnosis codes rather than angiography, it is likely that the measured outcome includes both type I MI due to plaque rupture events and type II MI related to myocardial supply–demand
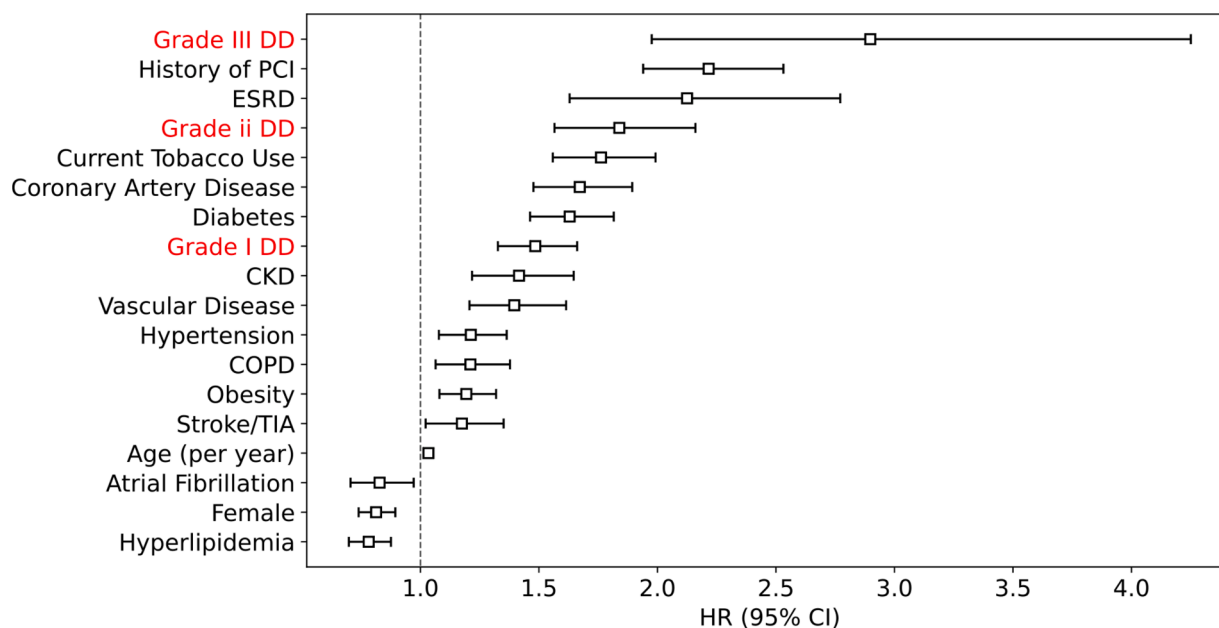
Fig. 2. Title: Diastolic Dysfunction Substantially Increases Risk of MI. Caption: The increased risk of MI from grade II and grade III DD are comparable to the risk of known coronary artery disease and prior PCI, respectively. CI = confidence interval; CKD = chronic kidney disease; ESRD = end-stage renal disease; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

mismatch. To reduce the risk of capturing these secondary events, readmissions were only included if the primary diagnosis for the admission was MI. Finally, DD is generally not reported in the presence of atrial fibrillation, significant mitral valve disease (including mitral annular calcification, mitral stenosis, or prior mitral surgery), and ventricular paced rhythm, and is reported as indeterminate if the available data is insufficient to determine the presence of dysfunction. As a result, among all patients with echocardiograms with normal systolic function and more than 3 months of follow-up, 23.4 % were excluded from this analysis due to inability to assess the presence of DD. In addition, the reason why the echocardiogram was clinically ordered by the treating physician is not available.

In conclusion, our results demonstrate that the risk of MI is significantly increased in the presence of DD, with higher risk at higher grades of DD. The increased risk associated with grade III DD is comparable to that from a prior history of percutaneous coronary intervention. These findings suggest that the severity of DD may be a useful tool in stratifying patients for risk of MI.

Short tweet.

The risk of MI increases with worsening diastolic dysfunction. Grade II DD increases MI risk as much as known CAD, and Grade III as much as prior PCI. #HeartFailure.

CRediT authorship contribution statement

Tanmay A. Gokhale: Writing – original draft, Conceptualization. **Mehak Dhande:** Writing – review & editing. **Suresh Mulukutla:** Writing – review & editing. **Oscar C. Marroquin:** Writing – review & editing, Conceptualization. **Floyd Thoma:** Data curation. **Aditya Bhonsale:** Writing – review & editing. **Krishna Kancharla:** Writing – review & editing. **Andrew Voigt:** Writing – review & editing. **Alaa A. Shalaby:** Writing – review & editing. **N.A. Mark Estes:** Writing – review & editing. **Sandeep K. Jain:** Writing – review & editing. **Samir Saba:** Writing – original draft, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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