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Performance of the Thrombolysis in Myocardial Infarction (TIMI) ST-elevation myocardial infarction risk score in a national cohort of elderly patients

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Abstract

Background—The TIMI ST-elevation myocardial infarction (STEMI) score was developed and validated in a randomized controlled trial population. We sought to assess its accuracy in a community-based cohort of elderly patients hospitalized with STEMI.

Methods—We evaluated the TIMI STEMI score in 47882 patients aged ≥ 65 years hospitalized with STEMI in US hospitals from 1994 to 1996. We assessed TIMI STEMI score discrimination and calibration for 30-day mortality and compared observed and published TIMI mortality rates.

Results—The cohort's median TIMI score was 6 (25th–75th percentile 4, 8). Thirty-day mortality rates were higher among patients with higher TIMI scores (TIMI score 2: 4.4% vs TIMI score >8 : 35.6%, $P < .0001$ for trend). However, the TIMI score provided only modest discrimination ($c = 0.67$) and calibration (goodness-of-fit $P < .0001$). Mortality rates for TIMI scores differed between patients who did and did not receive reperfusion therapy ($P < .0001$ for TIMI score $\times$ reperfusion therapy interaction). Thirty-day mortality rates in the cohort were higher than published TIMI estimates ($P = .001$; eg, TIMI score 2: 4.4% cohort vs 2.2% published rate).

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Conclusions—The TIMI score provided modest prognostic discrimination and calibration among elderly patients with STEMI. Our findings highlight the difficulties in applying risk scores developed in randomized controlled trial cohorts to elderly patients.

Elderly patients constitute the majority of patients hospitalized with acute coronary syndromes.

¹ Effective management of these patients requires an accurate estimation of their prognosis, and current risk-assessment tools span the spectrum from simple risk scores^{2,3} to complex multivariable models.^{4,5} One of the best known risk scores for patients hospitalized with ST-elevation myocardial infarction (STEMI) is the TIMI ST-elevation risk score (hereafter referred to as the TIMI score).⁶ Developed as part of the InTIME II trial,⁷ the TIMI score is a simple integer score that stratifies patients' prognosis and provides specific short-term mortality estimates.⁶

Generalizability and validity are the sine qua non of prognostic models. Although the TIMI score performed well in the randomized controlled trial (RCT) population in which it was developed and the TIMI 9A/B clinical trial cohort in which it was validated,⁶ it is unclear how accurate the TIMI score is when applied to elderly patients, a group that is not well represented in RCT populations.⁸ Community-based elderly patients are generally older, have a substantially higher comorbidity burden, and are treated at a more diverse spectrum of hospitals, with a variety of treatment strategies, compared with patients enrolled in RCTs.⁹ Of particular concern are the > 60% of community-based elderly patients with STEMI who do not receive fibrinolytic therapy.¹⁰ It is unclear whether prognostic data derived from InTIME II, a cohort in which all patients underwent fibrinolytic therapy, are applicable to elderly patients who did not receive any reperfusion therapy.

Our recent evaluation of a simple risk score for patients with STEMI found significant limitations in the use of risk indices derived in RCTs in community-based populations.¹¹ Because the simple risk score we evaluated was based on 3 variables,³ it is unknown how the more clinically detailed TIMI score may perform when assessed in an elderly community-based population. The 2 studies to date that have evaluated the performance of the TIMI score in nonrandomized trial cohorts have provided conflicting findings.^{6,12} An evaluation of the TIMI score in patients hospitalized in Olmsted County, Minnesota, found its performance to be poorer compared with another risk score, but this analysis was limited by the use of a homogenous, geographically restricted population and included patients treated in the pre-reperfusion therapy era.¹² In contrast, an evaluation of the TIMI risk score in the NRM3 cohort found the score performed sufficiently well and recommended the score be used for the triage of patients with STEMI.¹³ This study, however, was based upon patients drawn from a selected group of hospitals and limited by the evaluation of inhospital mortality, a nonstandardized end point susceptible to hospital differences in length of stay, discharge patterns, and interhospital transfer practices.¹⁴ Because these studies have different limitations, it is difficult to reconcile their findings. Thus, an additional assessment of the TIMI score's performance in more contemporary, generalizable community-based populations, using a standardized end point, is needed.

To address this issue, we sought to determine the prognostic value of the TIMI score among a nationally representative cohort of elderly patients hospitalized with STEMI. Using data from the Cooperative Cardiovascular Project (CCP), a Centers for Medicare & Medicaid Services initiative to improve quality of myocardial infarction (MI) care, we evaluated the prognostic calibration and discrimination of the TIMI score and the accuracy of its reported 30-day mortality rate estimates. Our objective was to determine how effective this well-known risk score derived from an RCT population, widely distributed via a public-access web site (www.timi.org, accessed November 27, 2002), performs when applied to a community-based cohort of elderly patients hospitalized with STEMI.

Methods

Cooperative Cardiovascular Project

The CCP included fee-for-service Medicare beneficiaries discharged from an acute care nongovernmental hospital in the United States with a primary discharge diagnosis of acute MI (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 410) between January 1994 and February 1996, with the exception of readmissions (code 410. × 2).¹⁵ These patients' records were centrally abstracted for detailed clinical data including medical history, presentation, in-hospital treatment, and outcomes. We limited our analysis to patients ≥65 years of age who presented with an ST elevation or a left bundle-branch block MI. Patients < 65 years of age (n = 17593), those without a clinically confirmed MI (n = 31186), readmissions for MI (n = 23773), and patients without documented ST elevation or a left bundle-branch block (n = 161458) were excluded from analysis. Patients who were admitted by means of interhospital transfer (n = 42177) were also excluded because we could not evaluate their status upon admission. In addition, 308 patients were excluded because we could not verify their vital status 30 days postinfarction. The remaining 55542 patients comprised the baseline sample.

TIMI score

The ST-elevation TIMI score is an integer score derived from 8 differentially weighted indicators ascertained upon admission. TIMI score indicators (and their associated point value) are age (2 points: 65–74 years, 3 points: 75 years and older), history of angina, diabetes, or hypertension (1 point), admission systolic blood pressure < 100 mm Hg (3 points), admission heart rate > 100 beat/min (2 points), admission Killip class II to IV (2 points), admission weight < 67 kg (1 point), anterior infarction or left bundle-branch block (1 point), and time to reperfusion therapy > 4 hours among patients who received reperfusion therapy (1 point).⁶ Because the CCP represents a cohort ≥65 years of age, the total possible TIMI score ranged from 2 to 14 for patients who received reperfusion therapy and 2 to 13 for patients who did not receive reperfusion therapy. Of the 55542 patients in the baseline sample, 7660 (13.8%) were excluded because they were missing data for the indicators used in the generation of the TIMI score. The remaining 47882 patients comprised the study cohort.

Statistical analysis

TIMI scores were evaluated for their association with mortality at 30 days using a χ^2 test of trend analysis. The accuracy of the TIMI score was determined by assessing its discrimination and calibration. Discrimination in 30-day mortality provided by the TIMI score was determined by deriving its *c* statistic (area under the receiver operating characteristic curve; 0.50 indicating chance discrimination and 1.00 perfect discrimination) for prediction of 30-day mortality from a logistic regression model.¹⁶ TIMI score calibration was assessed by visual inspection of calibration plots and by using the Hosmer-Lemeshow goodness-of-fit tests. We prespecified a Hosmer-Lemeshow test criterion of $P \leq .01$ as suggestive of poor calibration because of the oversensitivity of the Hosmer-Lemeshow test in large samples.

Because the TIMI score is not intended to be recalibrated in each population in which it is used (meaning the TIMI score mortality rates are presumed to be identical in other populations), we also examined the generalizability of published TIMI score data. TIMI score distributions and 30-day mortality rates in the CCP cohort were compared with TIMI score estimates derived from the InTIME II cohort⁶ using χ^2 analyses. Because the lowest possible TIMI score in the CCP cohort was 2, we restricted our comparison of risk score distributions and mortality estimates obtained in InTIME II to patients with a TIMI score of ≥2. TIMI score distributions from InTIME II were thus recalculated based on the 66% of the InTIME II cohort with a TIMI score of ≥2.⁶

Analyses were repeated stratifying patients by receipt of reperfusion therapy to determine whether mortality rates associated with TIMI scores were similar among patients who had undergone reperfusion therapy and those who had not using multiple logistic regression analysis with an interaction term for TIMI score and use of reperfusion therapy. Analyses were also repeated excluding 13300 patients with a history of cerebrovascular disease, admission systolic blood pressure >180 mm Hg, admission diastolic blood pressure >110 mm Hg, or those presenting in shock per InTIME II's enrollment criteria.⁶ All analyses were conducted using SAS 8.0 (SAS Institute, Cary, NC). Evaluation of the CCP database was approved by the Yale University School of Medicine Human Investigation Committee and conformed with the principles of the Declaration of Helsinki.

Results

Patient characteristics

Patients in the study cohort were predominantly white, 76 years of age on average, and slightly less than half were female. Reperfusion therapy was provided to 17579 patients (36.7%), with 14858 patients (84.5% of patients receiving reperfusion therapy) receiving fibrinolytic therapy and 2721 patients receiving a primary percutaneous transluminal coronary angioplasty. Patients who received reperfusion therapy were younger and a greater proportion were male, white, and had fewer comorbid conditions and less severe presentation at admission than patients who did not receive reperfusion therapy (Table I).

TIMI score performance

The median TIMI score for the cohort was 6. Fewer than 2% of patients were assigned a score of 2, the lowest possible score in the CCP cohort (because all patients received at least 2 points for being ≥ 65 years), and more than 15% were assigned a TIMI score > 8 (Table II).

The 30-day mortality rate in the study cohort was 20.1%. Thirty-day mortality rates varied 8-fold between patients with a TIMI score of 2 (4.4%) and patients with TIMI scores > 8 (35.6%, $P < .0001$ for trend) (Table III). The TIMI score provided only modest prognostic discrimination ($c = 0.67$). TIMI score calibration was also modest as the Hosmer-Lemeshow goodness-of-fit test did not meet the prespecified test criterion (goodness-of-fit $P < .0001$). Visual inspection of the calibration plot also confirmed shortfalls in calibration as mortality rates observed in CCP were higher than those predicted by the TIMI score for patients with lower TIMI scores.

Use of reperfusion therapy and TIMI score performance

TIMI score distributions varied based on patients' receipt of reperfusion therapy. Patients who received reperfusion therapy had lower median TIMI scores than patients who did not receive reperfusion therapy (Table II). In addition, 30-day mortality rates for each TIMI score varied based on whether patients were treated with reperfusion therapy ($P = .0001$ for interaction). Patients who did not receive reperfusion therapy had higher mortality rates than patients who did receive reperfusion therapy for the same TIMI score (Table III).

Among patients who received reperfusion therapy, the TIMI score exhibited satisfactory calibration (goodness-of-fit $P = .03$, exceeding prespecified Hosmer-Lemeshow criterion) and modest discrimination ($c = 0.69$). Calibration (goodness of fit $P < .0001$) and discrimination ($c = 0.63$) were worse among patients who did not receive reperfusion therapy. Findings were similar when analyses were repeated among the smaller cohort of patients who met InTIME II enrollment criteria.

Comparison with published TIMI score data

TIMI score distributions in the CCP cohort differed from those reported in the InTIME II cohort ($P < .001$) (Figure 1, A). The median TIMI score in the InTIME II cohort (after excluding 34% of patients with a TIMI score of 0 or 1) was 4 and the TIMI score exhibited a left-skewed distribution toward lower values. In contrast, the median TIMI score among patients in the CCP score was 6 and the TIMI score exhibited a right-skewed distribution. Published TIMI score distributions were particularly different for patients who did not receive acute reperfusion therapy ($P < .001$) (Figure 1, B).

Published 30-day mortality estimates for the TIMI score were lower than those observed for patients in the CCP cohort with TIMI scores of ≤ 8 ($P < .001$) (Figure 2, A). Thirty-day mortality rates among patients who received reperfusion therapy were clinically comparable to published TIMI score mortality data. However, published 30-day mortality estimates for TIMI scores were lower than the observed 30-day mortality rates for patients who did not receive reperfusion therapy ($P < .0001$) (Figure 2, B). The extent of discordance between 30-day mortality rates for TIMI scores in the CCP cohort and those reported in InTIME II is summarized in Figure 3. Findings were similar when analyses were repeated among patients who met InTIME II enrollment criteria.

Discussion

Our evaluation of the TIMI score in a national, community-based population of elderly patients hospitalized with STEMI found the TIMI score provided only modest prognostic discrimination and calibration. Furthermore, published estimates of the 30-day mortality rates for TIMI scores were lower than those observed in the CCP cohort. Together, these data indicate the TIMI score may not accurately predict prognosis among elderly patients with STEMI.

Our evaluation of the TIMI score highlights how a risk score that may be associated with mortality at the population level may not provide accurate estimates of mortality for individual patients.¹⁷ The limited calibration of the TIMI score resulted in mortality predictions that underestimated 30-day mortality rates for patients with lower TIMI scores. Shortfalls in discrimination, in contrast, indicate that the TIMI score cannot accurately differentiate between a patient's death or survival with 30 days of their MI. Risk scores with a c statistic > 0.80 are believed to provide sufficient discrimination for use with individual patients.¹⁸ We found the TIMI score's c statistic to be 0.67, lower than the c statistic of 0.78 reported in InTIME II, TIMI 9A/B ($c = 0.75$),⁶ and evaluations using the NRMI ($c = 0.74$)¹³ and Olmsted County cohorts ($c = 0.73$).¹² Poor calibration and discrimination indicate that patients' mortality risks are inaccurately assessed by the TIMI score. This may be problematic if patients with a low risk are assigned to higher TIMI score groups and undergo interventions they do not necessarily need, or if those with a higher risk are assigned to lower TIMI score groups and do not receive interventions from which they could possibly benefit.

The TIMI score is not only used to generate a risk score for a patient, but also to predict that patient's risk of 30-day mortality based on published estimates.⁶ However, we found published TIMI score 30-day mortality rates underestimated 30-day mortality rates in the CCP, particularly for patients with lower TIMI scores. This is not attributable to the older age of the CCP cohort because the TIMI score explicitly incorporates age into its calculation. Underestimates of 30-day mortality for patients may alter physicians' treatment decisions. A physician contemplating a treatment strategy based on a patient's mortality risk may not pursue a strategy because the 30-day mortality risk reported by the TIMI score fails to meet a prespecified threshold, although the patient's actual mortality risk may be much higher.

Differences in mortality rates for each TIMI score based on receipt of reperfusion therapy were also documented in an evaluation of the TIMI score in the NRM1 3 cohort.¹³ It is not clear what factors may account for these reperfusion therapy–associated differences. Our findings were similar when analyses were conducted in the cohort of CCP patients who met InTIME II enrollment criteria, a proxy for reperfusion therapy eligibility, suggesting that higher mortality rates in patients who did not receive reperfusion therapy are not entirely attributable to reperfusion-ineligible patients. Although reperfusion therapy will contribute to differences in outcomes, the 10.7% difference in 30-day mortality rates between patients who received reperfusion therapy and those who did not is larger than would be expected due to therapy alone.¹⁹ Instead, it appears as though use of reperfusion therapy may be acting as a marker for patients' overall risk. Patients who received reperfusion therapy have characteristics that are more similar to patients in the InTIME II cohort than patients who did not receive reperfusion therapy. Poorer TIMI score accuracy among elderly patients who do not receive reperfusion therapy is concerning given that more than two thirds of all elderly patients with STEMI do not receive reperfusion therapy.¹⁰

The performance of the TIMI score in the CCP cohort underscores the limitations of applying data obtained from RCT populations or similarly selected groups to community-based patient cohorts. Although RCTs are the best environment in which to assess treatment efficacy, their selected patient populations do not provide an optimal environment in which to develop widely generalizable risk scores. This limitation is particularly acute for elderly patients who are under-represented in trials of MI therapies.⁸ Indeed, some of the differences in TIMI score performance between the InTIME cohort and our evaluation may reflect the 14-year difference in median ages (62 vs 76 years) between both populations. In addition, RCTs exhibit selection in patient enrollment, even within trial eligibility criteria,²⁰ by preferentially selecting patients with fewer comorbidities who are at lower risk than non-enrolled patients in the community.²¹ The near 3-fold difference in 30-day mortality rates between the InTIME II cohort (6.7%) and the CCP cohort (20.1%) underscores the magnitude of these differences. The modest performance of the TIMI score when applied to the higher-risk CCP population indicates the TIMI score is sensitive to the overall mortality rate in the cohort in which it is tested. This phenomenon, known as poor spectrum transportability,²² is confirmed by the TIMI score's superior performance in the lower-risk subset of CCP patients who received reperfusion therapy. This limitation, however, is not specific to the TIMI score alone. Other risk scores that estimate prognosis from RCT cohorts or populations that differ from those in which the scores will ultimately be applied will similarly provide less accuracy. A more effective approach would be to develop and validate risk scores from observational data sets or other resources that more accurately represent the patients in which the risk score will later be used.

Our findings raise concerns about the validity of the TIMI score. A broader concern is the question of whether a prediction model, valid or otherwise, has clinical utility in the initial management of patients with confirmed STEMI. Clinical prediction models are developed to facilitate decision making in cases of uncertainty to improve clinical outcomes.^{23–26} Risk scores, such as the TIMI non–ST-elevation score,²⁷ can inform the management of patients with unstable angina because treatment options are determined by patients' prognosis. There is, however, little clinical uncertainty in the initial management of patients presenting with STEMI. Current guidelines clearly indicate the use of reperfusion therapy, aspirin, β -blockers, angiotensin-converting enzyme inhibitors, and other therapies where clinically appropriate.²⁸ The decision to use these therapies is independent of patients' predicted mortality risks. Stated more directly, it is irrelevant whether a patient has a TIMI score of 1 or 9 when the decision to initiate aspirin therapy is being considered. Risk scores may be helpful after the initial management of STEMI when patients are being considered for interventions,²⁹ but the TIMI score and other mortality prediction models are not developed to support clinical decision making in this context. Furthermore, neither the TIMI score nor other prediction models for

STEMI have demonstrated that use of their risk estimates will improve patient outcomes.³⁰ In light of the limited clinical uncertainty in the initial management of patients presenting with STEMI and the lack of demonstrated benefit associated with the use of risk scores, the clinical utility of the TIMI score and other prediction models remains as yet unproven.

Our study has certain issues to consider in its interpretation. We limited our analysis to patients ≥ 65 years of age and thus cannot evaluate the performance of the TIMI score among patients < 65 years of age. However, elderly patients comprise the majority of patients hospitalized with STEMI and the majority of deaths among patients with STEMI.³¹ In addition, age is explicitly incorporated into the calculation of the TIMI score. Thus, differences in patients' ages should not influence the TIMI score's accuracy other than modifying the risk score each patient is assigned. In addition, there is no indication from the TIMI score developers that the risk score groups or their mortality estimates are not applicable to elderly patients. Although some authors have suggested that differences in risk score performance may reflect differences in outcome assessment,³² our evaluation of short-term mortality makes this criticism unlikely.

Conclusion

Although the TIMI score identified a 30-day mortality gradient when evaluated in a nationally representative, community-based cohort of elderly patients hospitalized with STEMI, it provided only modest prognostic discrimination and calibration. TIMI score accuracy was worse for the more than two thirds of patients who did not receive reperfusion therapy. Published TIMI score 30-day mortality estimates were lower than those observed in the CCP cohort, indicating clinicians would underestimate patients' mortality risks if using TIMI score mortality figures. Finally, it is unclear how the TIMI score would augment clinical decision making concerning patients with STEMI given that the initial management of these patients is clearly specified by clinical guidelines. In light of our findings, we suggest caution in the use of the TIMI score for prognostic assessments among elderly patients with STEMI.

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Figure 1.

A, TIMI score distribution. The figure represents the distribution of CCP patients according to their TIMI scores. For point of reference, the TIMI score distribution from the InTIME II cohort is also provided. x-axis, TIMI score; y-axis, proportion of patients. **B**, TIMI score distribution. The figure represents the distribution of CCP patients who received reperfusion therapy and CCP patients who did not receive reperfusion therapy according to their TIMI scores. For point of reference, the TIMI score distribution from the InTIME II cohort is also provided. x-axis, TIMI score; y-axis, proportion of patients.

Figure 2.

A, Thirty-day mortality by TIMI score. Thirty-day mortality rates for CCP patients according to TIMI score. For point of reference, 30-day mortality rates provided for the TIMI score (obtained from InTIME II) are also provided. x-axis, TIMI score; y-axis, 30-day mortality rate.

B, Thirty-day mortality by TIMI score. Thirty-day mortality rates for CCP patients according to TIMI score and use of reperfusion therapy. For point of reference, 30-day mortality rates provided for the TIMI score (obtained from InTIME II) are also provided. x-axis, TIMI score; y-axis, 30-day mortality rate.

Figure 3.

Difference between CCP and InTIME II 30-day mortality rates by TIMI score. Difference in 30-day mortality rates observed in the CCP cohort and those reported with the TIMI score (from InTIME II) by TIMI score. Positive numbers indicate a higher mortality rate observed in CCP than reported in InTIME II, whereas negative numbers indicate a higher mortality rate in InTIME II compared to CCP. x-axis, TIMI score; y-axis, difference in 30-day mortality rates.

Table I

Patient characteristics

Characteristics	Received reperfusion therapy				P	InTIME II*
	Overall	Yes	No			
n	47882	17579	30303		–	15060
Demographics						
Median age, y (IQR)	76 (70, 82)	73 (69, 77)	83 (78, 88)		< .0001	62 (52, 70)
Age > 75 y	54.7	38.6	64.0		< .0001	13.7
Female	48.6	43.2	51.8		< .0001	24.7
White	90.7	91.9	90.0		< .0001	94.5
Medical history						
Current smoker	16.0	21.1	13.1		< .0001	44.7
Diabetes	29.9	23.7	33.5		< .0001	13.9
Angina	55.6	58.7	53.8		< .0001	21.2
Hypertension	60.9	57.0	63.2		< .0001	30.4
MI	27.8	20.2	32.2		< .0001	16.0
PCI	6.2	7.6	5.4		< .0001	4.5
CABG	10.7	7.8	12.3		< .0001	2.7
Admission characteristics (%)						
Median systolic BP, mm Hg (IQR)	141 (120, 164)	140 (120, 161)	142 (120, 165)		< .0001	140 (122, 155)
Systolic BP < 100 mm Hg	8.6	9.1	8.3		.0019	2.6
Median heart rate, beat/min (IQR)	84 (70, 102)	76 (63, 90)	90 (74, 108)		< .0001	74 (63, 86)
Heart rate > 100 beat/min	25.8	12.3	33.6		< .0001	7.7
Anterior infarction or LBBB	64.3	57.8	68.1		< .0001	42.7
Killip class II–IV	51.6	38.0	59.4		< .0001	12.6
Median weight, kg (IQR)	73 (61, 83)	75 (66, 85)	70 (59, 81)		< .0001	77 (69, 86)
Weight < 67 kg	36.6	28.0	41.7		< .0001	19.2
Time to reperfusion therapy >4 h	–	5.6	–		–	24.3

BP, Blood pressure; CABG, coronary artery bypass graft surgery; IQR, interquartile range or 25th to 75th percentile of distribution; LBBB, left bundle-branch block; PCI, percutaneous coronary intervention.

* As reported by Morrow et al. 6

Table II

Distribution of TIMI score, overall and by reperfusion therapy status

	Received reperfusion therapy					
	Overall			Yes		
	n	%	n	%	n	%
n	47882	—	17579	—	30303	—
Median TIMI score	6	—	5	—	7	—
25th, 75th percentile	4, 8	—	4, 7	—	5, 8	—
TIMI score						
2	793	1.7	550	3.1	243	0.8
3	4244	8.9	2600	14.8	1644	5.4
4	6961	14.5	3633	20.7	3328	11.0
5	7352	15.4	3158	18.0	4194	13.8
6	7919	16.5	3050	17.4	4869	16.1
7	7032	14.7	2051	11.7	4981	16.4
8	6066	12.7	1299	7.4	4767	15.7
>8	7515	15.7	1238	7.0	6277	20.7
						< .0001
						< .0001

Table III

TIMI score and 30-day mortality rates

	Overall	InTIME II predicted [*]	Received reperfusion therapy		P
			Yes	No	
Overall	20.1		13.3	24.0	< .0001
TIMI score					< .0001
2	4.4	2.2	3.4	6.6	
3	6.2	4.4	4.4	8.9	
4	9.7	7.3	7.4	12.3	
5	15.3	12.4	11.6	18.0	
6	18.8	16.1	13.9	21.9	
7	24.7	23.4	19.3	26.9	
8	26.7	26.8	24.4	27.3	
>8	35.6	35.9	36.1	35.7	
P for trend	< .0001	< .001	< .0001	< .0001	

^{*} As reported by Morrow et al.⁶