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CRAX: A Simple Cardiovascular Risk Assessment Tool to Predict Risk of Acute Myocardial Infarction or Death

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Abstract

Background: Determining the risk of cardiovascular events is essential to optimize patient management.

Methods and Results: 5842 individuals underwent SPECT myocardial perfusion imaging (MPI) with 4.4 ± 1.2 years of follow up. Models (the CRAX tool) were derived to predict the cumulative risk of death and acute myocardial infarction (AMI) at 1-, 3-, and 5-years using clinical and MPI variables. Predictors of AMI and death included age, number of hospitalizations in the three years preceding MPI, and left ventricular ejection fraction (LVEF). Additional predictors of death were the use of pharmacological stress, and global stress total perfusion deficit (STPD), while transient ischemic dilation (TID), and ischemic total perfusion deficit (iTPD) change were predictive of AMI. CRAX predictions were significantly ($p < 0.001$) more accurate than clinical variables or MPI results alone, resulting in a significant net reclassification improvement (NRI, 7.5% for AMI, 14.5% death) compared to clinical variables alone. Accuracy for predicting major adverse cardiac events (MACE, comprising all-cause death, AMI, unstable angina, late revascularization) was comparable to that of AMI or death.

Conclusions: CRAX is a risk assessment tool that predicts the risk of AMI, death, or MACE, and improves prediction compared to clinical variables or MPI results alone.

Keywords

Myocardial perfusion imaging; gated SPECT; prognosis; acute myocardial infarction

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Disclosures:

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Introduction:

Despite advances in therapy, cardiovascular disease remains the leading cause of mortality worldwide [1]. Myocardial perfusion imaging (MPI) plays an important role in the evaluation of patients with suspected or known coronary artery disease, adding prognostic information independent from that provided by clinical risk factors alone [2, 3]. For example, in certain patient populations, normal single photon emission computed tomography (SPECT) MPI is associated with an annual cardiac event rate of < 1% [3, 4]; however, most studies have had limited patient follow-up (1–3 years), small numbers of hard events, and/or have focused on the predictive power of MPI without considering the independent additive value of clinical risk factors. Furthermore, many SPECT MPI studies to date are limited to varying degrees by technical factors. SPECT MPI is typically interpreted visually and is prone to intra- and inter-observer variability, with agreement reported to be 65–80% [5]. Objective automated quantitative approaches can achieve reproducibility as high as 96% [5]. Furthermore, the diagnostic performance of an automated approach has been shown to be at least as good as visual analysis by expert readers [6]. Despite this, only a few studies have reported on the predictive performance of fully-automated, computer based quantitative analysis [7, 8].

Risk prediction models combining multiple risk factors are in frequent use in many areas of medicine. Notably, the Fracture Risk Assessment (FRAX^R) Tool integrates clinical variables with imaging results (from dual-energy x-ray absorptiometry) in order to predict a patient's ten-year osteoporotic fracture probability [9]. Combining clinical variables with imaging resulted in improved fracture prediction, and was superior to the use of clinical or imaging variables alone [10].

Despite the importance of accurately assessing cardiovascular risk, a single, unified prediction tool has yet to emerge. The aim of this study was to develop a predictive model combining clinical variables with the results of automatically analyzed SPECT MPI in order to estimate the five-year risk of acute myocardial infarction (AMI), death, and major adverse cardiac event (MACE).

Materials and Methods:

Demographics

The study cohort and methods have been previously described in detail [6, 11, 12]. Briefly, we identified individuals who underwent attenuation-corrected stress-rest SPECT myocardial imaging at St. Boniface Hospital, Winnipeg, the cardiac center for the province of Manitoba (1.3 million), for suspected coronary artery disease between February 2001 and July 2008. We excluded subjects due to incomplete or corrupted scan data, and those undergoing a revascularization procedure during the first 3 months after scanning. In addition, studies being performed as follow-up to a previous scan were excluded from consideration. This retrospective study was approved by the institutional review board and the need for written informed consent was waived.

Stress Testing and SPECT Imaging

Standard ^{99m}Tc -sestamibi or tetrofosmin rest/stress protocols were employed as previously described with treadmill testing or dipyridamole infusion with low-level exercise [13]. Adjunctive low level exercise was performed when feasible and not contraindicated (e.g., left bundle branch block). Dual-detector scintillation cameras with low-energy, high-resolution collimators (Vertex; Philips Medical Systems, Milpitas, CA) and gadolinium-153 line-source attenuation correction hardware and software (Vantage Pro; Philips Medical Systems, Milpitas, CA) were used to acquire MPI. Tomographic reconstruction was performed by AutoSPECT and Vantage Pro programs (Philips Medical Systems). Emission images were automatically corrected for non-uniformity, radioactive decay, center-of-rotation, and motion during acquisition. Filtered back-projection and Butterworth filters were applied to obtain the non-attenuation corrected MPI with an order of 10 and cut-off of 0.50 for rest MPI, and an order of 5 and cut-off of 0.66 for stress MPI. Non-attenuation correction images were used as it has previously been shown that the use of attenuation corrected images did not significantly improve the prognostic value of MPI [11].

Automated Image Analysis

A detailed overview of the image analysis is provided in [11]. Briefly, left ventricular segmentation, left ventricular contour quality control, and quantitation of left ventricular ejection fraction (LVEF) and global total perfusion deficit were performed with automated software without any user intervention (QGS-QPS software, Cedars-Sinai Medical Center, Los Angeles, CA, USA). All image analyses were performed by researchers at Cedars-Sinai Medical Center using de-identified image files to ensure blinding to all clinical information and outcomes. Automatically derived LV contours were visually verified by an experience technician and, if necessary, manually adjusted. Only 10% of rest/stress studies required visual correction of contours.

After the quality control step, all studies were processed in batch mode using QPS software to calculate global stress total perfusion deficit (sTPD) and ischemic total perfusion deficit (iTPD) as a percentage of the myocardium [14]. sTPD and rest TPD were measured independently for stress and rest scans, respectively, and iTPD was defined as their global difference: (sTPD minus rest TPD). Negative iTPD results were set to zero (i.e., no ischemia) for the analysis.

Clinical Information

In the Province of Manitoba, Canada, health services are provided to virtually all residents through a single public health care system. Registry data are regularly updated to capture loss of coverage due to migration or death (Vital Statistics). Manitoba Health maintains computerized databases of the physician services and hospitalizations provided for all persons registered with the system. Each physician service record includes information on the identity of the patient, the date of service, services provided, and a diagnosis, which is subsequently coded to a 3-digit International Classification of Disease-9-Clinical Modification (ICD-9-CM) code. After each hospitalization, a detailed abstract is created; prior to 2004, this included up to 16 diagnoses as 5- digit ICD-9-CM codes, and from 2004 onwards included up to 25 diagnoses as International Classification of Diseases-10-

Canadian Enhancements (ICD-10-CA) codes. Pharmacy-based prescription data for the province, collected through the Drug Programs Information Network (DPIN) are now also a part of the data repository. Our dataset included linkage to the population-based retail pharmacy system which identified use of statins, beta blockers, ACE inhibitors and long-acting nitrates (use defined as 6 months or more dispensed during the year following MPI) [15]. This data repository allows for the creation of a longitudinal record of health service utilization for an individual through a unique personal health identification number, anonymized to preserve patient confidentiality. The accuracy of these administrative data has been established for a wide range of clinical disorders, including prediction of death after acute myocardial infarction (AMI) [16, 17].

Outcomes

Follow-up was performed through the Manitoba Population Health Research Data Repository. The primary endpoints of the study were AMI, defined from hospital discharge diagnosis, or all-cause mortality, derived from vital statistics records. The composite endpoint of MACE, which included death from any cause, non-fatal AMI, unstable angina, late revascularization (including both percutaneous coronary intervention or coronary artery bypass grafting) was also examined. Subjects with early revascularizations (< 90 days following MPI) were excluded. Observations were censored at time of death, migration out of province, or end of data (March 31, 2012). The patients who moved out of the province (2.5%) were considered to have been lost to follow-up.

Development of the CRAX tool

The Cardiovascular Risk Assessment (CRAX) tool was conceptually modeled after the FRAX^R tool with the goal of combining relevant clinical and imaging data in order to optimize the prediction of cardiovascular risk. It consists of a pair of mathematical models: one for the prediction of risk of AMI and another for all-cause death. Subjects were randomly assigned to the development (66.7%) or validation groups (33.3%). All subjects were assigned a random number between 0 and 1 using a random number generator. Those subjects with a number below 0.667 were assigned to the development group, the rest to the control group. Both models were developed using multivariable Cox proportional hazards regression backward elimination using data from the development group. The following candidate clinical variables were considered: age, sex, congestive heart failure, cardiomyopathy, angina, valvular disease, dysrhythmias, diabetes, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, and number of hospitalizations in the three years prior to MPI. In terms of candidate imaging variables, we considered the need for pharmacological stress vs exercise, transient ischemic dilation (TID), sTPD, iTPD, rest total perfusion deficit, and LVEF. Variables with $p < 0.05$ were retained in the models. Predictions for MACE were assessed using both the AMI and death models. We tested for two-way interactions between medication use and model-based risk predictions for AMI and death, and these were found to be non-significant (all $p > 0.05$). The CRAX calculator as an Excel spreadsheet has been included as a supplementary file for interested readers. This is not intended or approved for clinical use.

Statistical Analysis

Statistical analyses were performed using Statistica (Version 12.0, StatSoft, Inc., Tulsa, OK, USA). Categorical variables are presented as frequencies, and continuous variables as mean $\pm$ SD. All statistical analyses were two-tailed, and a p value of < 0.05 was considered significant. Categorical variables were compared with Pearson's chi-square, and continuous variables with Student's two sample t test. The 1-, 3- and 5-year cumulative incidence of AMI, death, and MACE were calculated for each risk tertile for both the development and validation groups. The number of surviving patients in each risk tertile for the AMI and death models are shown in Supplementary Table 1. Hazard ratios for each tertile (relative to the lowest risk tertile) were estimated from univariate Cox models. Stratification in AMI, death, and MACE risk was also assessed using receiver operating characteristic analysis. Area under the curve was calculated for the cumulative risk of AMI, death, and MACE for both the development and validation groups and compared. Receiver operating characteristic analyses were performed using IBM SPSS for Windows (Version 22.0). Improvements in risk prediction from using combined clinical and MPI variables, compared with models using the clinical variables or the MPI variables alone, were assessed using measures of model fit (log-likelihood ratio, pseudo- R^2 and the Wald test) and the chance in model fit tested using the log-likelihood ratio test. Impact on risk reclassification using the CRAX tool versus the clinical variables alone was studied using the Net Reclassification Improvement (NRI). The NRI [18] measures the impact of including an additional clinical variable on the classification of predicted risk, was calculated as per the method detailed by Pencina *et al* [18], and reported as recommended by Leening *et al* [19]. For individuals experiencing AMI or death in follow up, NRI events is the probability of moving 'up' to a higher risk tertile minus the probability of moving 'down' to a lower risk tertile. Conversely, for individuals who remain event-free in follow up, NRI non-events is the probability of moving into a lower risk tertile minus the probability of moving into a higher risk tertile. AMI five-year risk tertiles were defined as $<3.3\%$, 3.3% but $<10.5\%$ and 10.5% . Five-year risk of death tertiles were defined as $<9.4\%$, 9.4% but $<29.6\%$, and 29.6% .

Values of NRI events and NRI non-events greater than zero indicate an improvement in risk classification, whereas negative values indicate worse risk classification. An asymptotic test of significance for the null hypothesis of $\text{NRI}=0$ based upon the multinomial distribution was performed [18].

Results:

Population characteristics

We identified 8682 individuals who underwent SPECT MPI. After excluding 1787 subjects due to incomplete or corrupt data, 935 due to repeat studies or lack of AC data, and 118 with early revascularization (<3 months), a total of 5842 (67%) of the studies satisfied the eligibility criteria. During mean follow-up of 4.4 ± 1.2 years, the development group ($n=3896$) experienced a total of 682 (17.5%) deaths, 248 (6.4%) AMIs, and 1051 (27.0%) MACE, while the validation group ($n=1946$) experienced 314 (16.1%) deaths, 129 (6.6%) AMIs, and 500 (25.7%) MACE. Demographic information for the development and validation groups is summarized in Table 1. No statistically significant differences were

noted in the clinical factors or imaging variables between the development and validation subgroups.

Within the development group, significant differences were noted between those with versus without clinical outcomes (AMI or death) for age, sex, the use of pharmacological stress, number of hospitalizations in the prior three years, sTPD, iTPD, LVEF, and TID (all $p < 0.05$) as shown in Table 2.

CRAX tool for AMI Prediction

In the CRAX model for AMI, independent predictors included the number of hospitalizations, age, TID, LVEF, and iTPD. All other factors considered were non-significant or collinear with other variables. Hazard ratios for the significant variables are shown in Table 3 (AMI) and Table 4 (death).

Cumulative incidences of AMI by CRAX risk tertile depicted in Figure 1 were similar in the development and validation groups. Similar area under the curve at five years were also seen for AMI prediction from the CRAX tool (0.718 95% CI [0.675, 0.762] vs 0.751 95% CI [0.719, 0.782], respectively). The area under the curve for AMI prediction in the validation group at 1-, 3-, and 5-years are shown in Table 5.

Hazard ratios for the middle and highest risk tertiles (referent lowest risk tertile) are shown in Table 6. Cumulative incidence of AMI in the lowest risk tertile was very low in the first three years ($< 1\%$), increasing to approximately 2% at 5 years. The 5-year risk of AMI in the highest risk tertile was approximately 13%, increasing most rapidly in the early years following imaging. The goodness of fit of the CRAX tool was evaluated using the Wald test and the pseudo- R^2 and compared to the use of clinical variables or imaging results alone. CRAX predictions were found to be significantly ($p < 0.001$) more accurate than those obtained from either clinical or imaging variables alone (Table 6).

CRAX tool for Death Prediction

For the CRAX death model, multivariate Cox regression showed that significant independent predictors of death included the number of hospitalizations in the prior three years, age, the use of pharmacological stress, LVEF, and sTPD. All other factors considered were non-significant or collinear with other variables. Table 4 shows the hazard ratios associated with the variables of the death model.

Cumulative incidences of death by risk tertile depicted in Figure 1 were similar in the development and validation groups. Similar area under the curve was also seen for death prediction from the CRAX tool (0.835 95% CI [0.819, 0.851] vs 0.835 95% CI [0.812, 0.858], respectively).

There was a low risk of all-cause death at 5-years for the lowest risk tertile ($< 4\%$) while the highest risk tertile demonstrated very high mortality (approximately 40%). As for AMI, the CRAX tool was significantly more accurate in predicting mortality than either clinical variables or MPI variables alone (Table 6).

CRAX tool for MACE prediction

MACE predictions using the AMI model were more accurate than those of the death models at 1-, 3-, and 5-years post MPI (area under the curve AMI model vs death model – 0.864 95% CI [0.841, 0.886] vs 0.852 95% CI [0.828, 0.876], 0.861 95% CI [0.842, 0.880] vs 0.851 95% CI [0.831, 0.871], and 0.821 95% CI [0.800, 0.842] vs 0.819 95% CI [0.798, 0.840], respectively). The area under the curve for MACE was comparable to those of AMI and death at all time points considered (Table 5). Hazard ratios for the middle and highest risk tertiles (referent lowest risk tertile) are shown in Table 6.

Risk Reclassification for AMI and Death

NRI analysis showed significantly improved risk reclassification using the CRAX tool compared to predictions based on the clinical variables alone with an NRI total of 7.5% ($p = 0.046$) for AMI (NRI events 3.9%, $p < 0.001$; NRI non-events 3.6%, $p < 0.001$), and an NRI total of 14.5% ($p < 0.001$) for death (NRI events 11.1%, $p < 0.001$; NRI non-events 3.3%, $p < 0.001$).

Discussion:

The purpose of this study was to develop and internally validate a simple cardiovascular risk assessment tool, which we have named CRAX. We found that fully automated, computer analyzed, SPECT MPI results combined with clinical information readily available at the time of the study can be useful in the long-term prediction of hard events, and was more accurate than the use of either clinical or MPI variables results alone. While several studies have examined the prognostic value of SPECT MPI, only a limited number of studies have examined the long-term (>3 years) prognostic implications [20–22], and these have either studied different, less commonly used perfusion agents [22] (i.e. Tl201) and/or were limited by sample size (<1000) [21, 23].

Risk assessment for both AMI and death using the CRAX model significantly outperformed models using only clinical variables or MPI results, as shown by comparing the goodness of fit measures. Interestingly, SPECT MPI results alone had the least predictive value. Our NRI analysis showed that the use of CRAX lead to an important number of risk reclassifications, for both AMI and death, when compared to the next most predictive model consisting of clinical variables alone.

Our findings are in line with those of other groups which have examined the prognostic implications of combining clinical variables and SPECT results. Multiple studies have shown that the combination of SPECT and clinical data results in a significant improvement in risk reclassification [24–27]; however, our study is one of the largest to date, and has examined the impact on long-term (5 years) prognostication. In addition, our approach in creating the CRAX tool differs from many of these studies in that we limited the overall number of input variables, and relied on clinical variables which would be known (i.e., age) or easily available (i.e., number of hospitalizations) to the physician at the time of interpretation.

SPECT MPI data which has been quantified by a completely automated analysis has advantages over conventional MPI interpretation in terms of reproducibility, and has the potential to reduce the effects of inter- and intraobserver variability and bias [28]. Furthermore, it has been shown that fully automated quantification of myocardial SPECT, on a per-patient basis, has equivalent accuracy to an expert reader [6].

Both models in the CRAX tool share similar clinical variables but differ in their dependence on MPI results. In addition to patient age, the number of hospitalizations in the three years preceding MPI was an important clinical predictor. Other studies have previously identified this variable as an important predictor of death [29] as well as AMI [30].

Numerous studies have suggested that TID is of limited prognostic value when present on an otherwise normal MPI study [31]. In comparison, our results suggest that, while TID is not a significant predictor of death, it is one of the most important predictors of AMI, as reported previously [31]. LVEF, a well-established prognostic factor of both death [32] and AMI [33], was also predictive of both in our models.

Small perfusion defects had no significant effect on our outcome measures. In particular, iTPD 4.5 and sTPD 14.5 were not predictive of AMI or death, respectively, after covariate adjustments, confirming that mild ischemia or up to a moderate amount of scar was not a major risk factor for adverse outcomes. A recent article by Betancur et al [34] reported much lower TPD cutoffs for prediction of major cardiac outcomes, likely related to different primary outcome measures as the latter also included revascularization and unstable angina. In our study, we predicted MACE using models optimized for AMI and death prediction.

The use of pharmacological stress has previously been shown to be associated with a higher risk of cardiac events, even with normal or near-normal MPI results. In particular, a meta-analysis [35] showed this to be one of the most important predictors of major adverse cardiac events. In our study, inability to exercise, independent of any other results on the perfusion study, was an effective predictor of overall mortality, but not AMI. While the increased event rate seen in patients undergoing pharmacological stress has been attributed to the fact that these patients are generally older with more comorbidities [35], we found that inability to exercise had prognostic significance independent of age and hospitalization rate, which can be thought of as a surrogate for comorbidities. Our results showed that patients in the lowest risk tertile have a very low risk of AMI and death in the first three years following an MPI. However, we saw a gradual increase in AMI risk beyond three years. This highlights the importance of long-term follow-up and confirms the notion of the limited 'nuclear warranty period' [36], even in low-risk patients.

Some limitations of this study need to be acknowledged. This was a single-centre, retrospective cohort study and is prone to the limitations inherent to this study design. Our internal validation group was drawn from the same population as our development group. Independent prospective validation in a different population would be an important next step. Our analysis did not include the effects of late post-MPI management (more than 3 months after scanning). We are therefore unable to comment on the effects that management

would have on subsequent risk of AMI or death. Finally, since cause of death information is not reliably coded, we modeled all-cause mortality rather than cardiovascular mortality.

Conclusion:

SPECT MPI has significant prognostic value and plays an important role in the prediction of clinical endpoints. Combining the results of SPECT MPI with clinical information in a single model enhances the predictive power of the test and may be useful in clinical practice for long-term prognostication. These results have the potential to translate into improved, individualized risk-assessment predictions which may result in better patient management and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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New knowledge gained

This work has provided a novel and simple risk prediction, built from clinical and MPI variables, which was shown to result in improved risk prediction over the use of clinical or MPI variables alone. This in itself represents a novel finding. In addition, numerous articles have examined the prognostic value of using clinical information or imaging results alone; however, relatively few authors have attempted to synthesize both sources of information into a single predictive framework. We believe that, in addition to our results, this approach itself is novel, represents the logical evolution of cardiovascular risk prediction models, and is an approach which should be pursued by other authors in order to optimize cardiovascular risk prediction models.

Abbreviations

CRAX	Cardiovascular risk assessment
SPECT	Single photon emission computed tomography
MPI	Myocardial perfusion imaging
AMI	Acute myocardial infarction
MACE	Major adverse cardiac event
LVEF	Left ventricular ejection fraction
TID	Transient ischemic dilatation
NRI	Net reclassification improvement
iTPD	Ischemic total perfusion defect

sTPD Stress total perfusion defect

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Fig. 1. 5-year cumulative incidence of death (top row) or AMI (bottom row) for both the development (left column) and validation (right column) cohorts stratified by CRAX risk tertile: lowest (green), middle (blue), and highest (red). AMI five-year risk tertiles were defined as <3.3%, 3.3% but <10.5% and 10.5%. Five-year risk of death tertiles were defined as <9.4%, 9.4% but <29.6%, and 29.6%

TABLE 1:

Baseline characteristics of the development and validation groups, including both clinical and imaging variables. No statistically significant differences were observed between the two group in any of the variables considered in our model.

	Development Group	Validation Group	p-value
N	3896	1946	
Age in years (SD)	64.7 (12)	65.1 (11.5)	0.19
Male sex (%)	2061 (52.9)	998 (51.3)	0.24
Number of hospitalizations (SD)	1.5 (2.4)	1.4 (2.3)	0.13
Pharmacologic stress (%)	2328 (59.8)	1189 (61.1)	0.32
sTPD (SD)	10.3 (11.9)	9.7 (11.5)	0.080
iTPD (SD)	3.1 (4.9)	3 (4.7)	0.23
LVEF (% ,SD)	55.6 (14.8)	56.1 (14.7)	0.32
TID (SD)	1.03 (0.13)	1.03 (0.13)	0.94
Duration of follow-up in years (SD)	4.4 (1.2)	4.4 (1.2)	0.53
AMI (%)	248 (6.4)	129 (6.6)	0.70
Death (%)	682 (17.5)	314 (16.1)	0.19
MACE (%)	1051 (27.0)	500 (25.7)	0.30

SD=Standard deviation, TID=transient ischemic dilatation, LVEF=left ventricular ejection fraction, sTPD=stress total perfusion deficit, iTPD=ischemic total perfusion deficit, AMI=acute myocardial infarction, MACE=major adverse cardiac event

TABLE 2:

Baseline characteristics of the development group according to outcome.

	No Death	Death	p-value	No AMI	AMI	p-value
N	3214	682		3648	248	
Age in years (SD)	63.3 (11.9)	71 (10.6)	<0.001	64.4 (12.0)	67.9 (11.7)	<0.001
Male sex (%)	1642 (51.1)	419 (61.4)	<0.001	1671 (52)	451 (66.1)	<0.001
Number of hospitalizations (SD)	1.11 (1.8)	3.3 (3.6)	<0.001	1.3 (2.2)	3.2 (3.9)	<0.001
Pharmacologic stress (%)	1738 (54.1)	590 (86.5)	<0.001	1874 (58.3)	553 (81.0)	<0.001
sTPD (SD)	9.0 (11.1)	16.3 (13.6)	<0.001	9.9 (11.7)	15.9 (13.7)	<0.001
iTPD (SD)	2.9 (4.8)	4.2 (5.1)	<0.001	3.0 (4.8)	5.1 (6.0)	<0.001
LVEF (%; SD)	57.4 (13.6)	47.2 (17.6)	<0.001	56.1 (14.7)	48.4 (15.4)	<0.001
TID (SD)	1.02 (0.13)	1.05 (0.13)	<0.001	1.03 (0.13)	1.07 (0.13)	<0.001

SD=Standard deviation, TID=transient ischemic dilatation, LVEF=left ventricular ejection fraction, sTPD=stress total perfusion deficit, iTPD=ischemic total perfusion deficit

TABLE 3:

Hazard ratios for final variables in the AMI model derived from the developmental group.

	Hazard Ratio	95% CI	p-value
Age per 10 year increase	1.17	[1.05, 1.31]	0.005
TID per 0.1 increase	1.15	[1.05, 1.26]	0.002
LVEF per 10% decrease	1.30	[1.20, 1.42]	<0.001
1 hospitalization in the prior 3 years	2.31	[1.50, 3.55]	<0.001
2 hospitalizations in the prior 3 years	4.68	[3.05, 7.19]	<0.001
3 or more hospitalizations in the prior 3 years	6.91	[4.71, 10.1]	<0.001
iTPD > 4.5	1.42	[1.02, 1.96]	0.036

iTPD=ischemic total perfusion deficit, TID=transient ischemic dilatation, LVEF=left ventricular ejection fraction

TABLE 4:

Hazard ratios for final variables in the mortality model derived from the developmental group.

	Hazard Ratio	95% CI	p-value
Age per 10 year increase	1.47	[1.36, 1.58]	<0.001
Pharmacological stress	1.84	[1.45, 2.32]	<0.001
LVEF per 10% decrease	1.30	[1.22, 1.37]	<0.001
1 hospitalization in the prior 3 years	2.53	[1.92, 3.33]	<0.001
2 hospitalizations in the prior 3 years	3.73	[2.81, 4.96]	<0.001
3 or more hospitalizations in the prior 3 years	6.61	[5.13, 8.52]	<0.001
sTPD > 14.5	1.41	[1.06, 1.87]	0.018

sTPD=stress total perfusion deficit, LVEF=left ventricular ejection fraction

TABLE 5:
Area under the curve (AUC) for prediction of AMI, death, and MACE in the validation group at 1-, 3-, and 5-years post MPL.

Endpoint	1-year			3-years			5-years		
	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC
AMI	0.863	[0.825, 0.901]	0.794	[0.756, 0.832]	0.718	[0.675, 0.762]			
Death	0.849	[0.812, 0.886]	0.870	[0.847, 0.893]	0.835	[0.812, 0.858]			
MACE (predicted from AMI model)	0.864	[0.841, 0.886]	0.861	[0.842, 0.880]	0.821	[0.800, 0.842]			
MACE (predicted from death model)	0.852	[0.828, 0.876]	0.851	[0.831, 0.871]	0.819	[0.798, 0.840]			

TABLE 6:
Hazard ratios for AMI, death, and MACE for each risk tertile from the CRAX tool (referent lowest risk tertile).

	AMI				Death				MACE (from AMI model)				MACE (from death model)			
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p	Hazard ratio
1st Tertile (lowest risk)	1	Referent	N.A.	1	Referent	N.A.	1	Referent	N.A.	1	Referent	N.A.	1	Referent	N.A.	1
2nd Tertile (middle risk)	3.22	[1.69, 6.17]	< 0.001	4.02	[2.28, 7.09]	< 0.001	4.17	[2.86, 6.09]	< 0.001	3.93	[2.69, 5.74]	< 0.001	3.93	[2.69, 5.74]	< 0.001	3.93
3rd Tertile (highest risk)	7.37	[4.02, 13.53]	< 0.001	19.04	[11.48, 32.62]	< 0.001	14.92	[10.48, 21.24]	< 0.001	14.04	[9.87, 19.98]	< 0.001	14.04	[9.87, 19.98]	< 0.001	14.04

TABLE 7:

Goodness of fit measures for the CRAX tool, clinical variables alone, and MPI variables alone.

	AMI			Death		
	CRAX	Clinical variables	MPI variables	CRAX	Clinical variables	MPI variables
Wald statistic	160.4	132.8	56.1	639.2	575.8	352.2
Pseudo-R²	0.52	0.47	0.19	0.74	0.64	0.53
Likelihood Ratio	182.6	157.0 *	51.9 *	639.2	575.8 *	352.2 *

* p-value <0.001 versus CRAX from the log-likelihood ratio test.