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FULL RESEARCH PAPER
Coronary artery disease

Development and validation of a prognostic score integrating remote heart failure symptoms and clinical variables in mortality risk prediction after myocardial infarction: the PragueMi score

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Aims While heart failure (HF) symptoms are associated with adverse prognosis after myocardial infarction (MI), they are not routinely used for patients' stratification. The primary objective of this study was to develop and validate a score to predict mortality risk after MI, combining remotely recorded HF symptoms and clinical risk factors, and to compare it against the guideline-recommended Global Registry of Acute Coronary Events (GRACE) score.

Methods and results A cohort study design using prospectively collected data from consecutive patients hospitalized for MI at a large tertiary heart centre between June 2017 and September 2022 was used. Data from 1135 patients (aged 64 ± 12 years, 26.7% women), were split into derivation (70%) and validation cohort (30%). Components of the 23-item Kansas City Cardiomyopathy Questionnaire and clinical variables were used as possible predictors. The best model included the following variables: age, HF history, admission creatinine and heart rate, ejection fraction at hospital discharge, and HF symptoms 1 month after discharge including walking impairment, leg swelling, and change in HF symptoms. Based on these variables, the PragueMi score was developed. In the validation cohort, the PragueMi score showed superior discrimination to the GRACE score for 6 months [the area under the receiver operating curve (AUC) 90.1, 95% confidence interval (CI) 81.8–98.4 vs. 77.4, 95% CI 62.2–92.5, $P = 0.04$) and 1-year risk prediction (AUC 89.7, 95% CI 83.5–96.0 vs. 76.2, 95% CI 64.7–87.7, $P = 0.004$).

Conclusion The PragueMi score combining HF symptoms and clinical variables performs better than the currently recommended GRACE score.

Lay summary

- The prognosis of patients after myocardial infarction is heterogeneous. Thus, risk stratification is needed to identify and intervene patients at increased risk. While heart failure (HF) symptoms are associated with adverse prognosis, they are not used for patients' stratification.
- We have developed and internally validated the PragueMi score, which integrates clinical risk factors at the time of hospitalization and HF symptoms determined remotely by a questionnaire 1 month after hospital discharge.
- PragueMi score was able to better stratify patients' risk as compared with the currently recommended Global Registry of Acute Coronary Events score.

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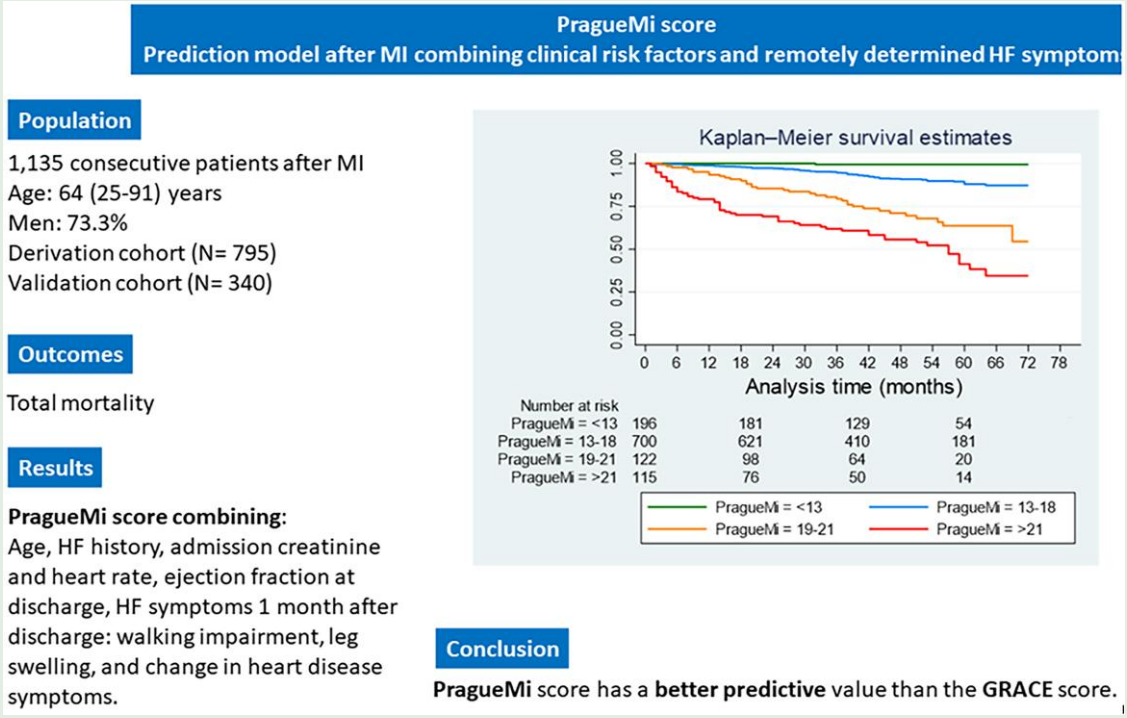
Graphical Abstract



Keywords Myocardial infarction • Heart failure • Symptoms • Risk prediction • Questionnaire • Mortality

Introduction

For optimal management of patients recovering from a myocardial infarction (MI), identification of individuals at increased risk of adverse outcomes is essential. This allows targeted proactive interventions in at-risk patients to improve their symptoms, function, and survival. The Global Registry of Acute Coronary Events (GRACE) score has been recommended by the guidelines to stratify patients' risk after MI.[1] However, discrimination of the GRACE model for 1-year mortality evaluated by the area under the receiver operating curve (AUC) is within the 0.82–0.89 range.[2] Thus, a better performing model is of clinical need.

Heart failure (HF) is a common complication of MI, developing in up to 40% of patients and increasing total mortality risk by three-fold.[3] The GRACE score evaluates HF using the Killip class. However, the Killip classification evaluates only pulmonary congestion, neglecting other HF symptoms. Furthermore, many patients develop HF symptoms early after hospital discharge. Interestingly, HF developing later after MI is associated with higher mortality risk as compared with HF developing at MI presentation.[4] Thus, evaluation of HF symptoms and signs is an important goal of post-discharge visits.

For decades, clinicians have been using unstructured questions on HF symptoms. Nevertheless, unstructured questioning is time-consuming, influenced by the physician's subjective interpretation, and may not be consistently done in all patients, and as such limits actionability. Our previous research showed that structured HF symptom evaluation using the Kansas City Cardiomyopathy Questionnaire (KCCQ) identifies HF symptoms in two out of five patients after MI[5] and identifies patients at increased mortality risk.[6] We hypothesized that the integration of HF symptoms with clinical risk factors may provide superior risk prediction after MI beyond the GRACE score. This may better define a high-risk group that may benefit from a more proactive approach and pharmacological and non-pharmacological therapy of HF.

The objectives of this study were as follows: (i) to select KCCQ items and clinical factors associated with total mortality risk after MI, (ii) to create a prognostic score (PragueMI score) based on identified variables in the derivation cohort, and (iii) to compare the predictive value of the PragueMi score against the GRACE score in the validation cohort.

Methods

Population

In this cohort design study, we have used data from the prospective Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry (AMBITION registry).[7] The registry collects clinical data and biospecimens from consecutive patients hospitalized for acute coronary syndrome since June 2017 at the Institute for Clinical and Experimental Medicine, Prague, Czech Republic, a tertiary heart centre with around-the-clock coronary intervention service. The Fourth Universal Definition of Myocardial Infarction has been used.[8] Patients underwent a detailed interview during their hospital stay, and additional information was obtained from medical record abstraction and laboratory studies. One month after discharge, patients were asked to complete the 23-item KCCQ. Because most patients did not have HF, in the questionnaire, we have replaced 'heart failure' with 'heart disease'. The patients had a choice of completing the KCCQ through an online application or on a paper form returned by regular mail.

The inclusion criterion was hospitalization for MI between June 2017 and September 2022. Patients with missing KCCQ were excluded from this analysis. Death was ascertained through June 2023. Mortality data were provided by the Institute of Health Information and Statistics of the

Czech Republic (UZIS), which keeps a list of all deceased persons and dates of death in the Czech Republic by law. This study was approved by a local ethics committee and complies with the Declaration of Helsinki.

Primary outcome

The primary outcome of the analysis was all-cause mortality.

Global Registry of Acute Coronary Events score

The Eagle model estimates for death within 6 months after discharge was used.[9] Variables included in the model were age, heart rate, systolic blood pressure, creatinine level, troponin elevation, ST segment depression on initial electrocardiogram **(**ECG), previous history of MI and HF, and percutaneous coronary intervention (PCI).

Statistical methods

Continuous variables are presented as mean and SDs or medians and interquartile range (IQR). Nominal variables are shown as counts and percentages.

All consecutive patients hospitalized for MI between June 2017 and September 2022 were included in this analysis. No formal power calculation was performed.

To identify factors associated with mortality risk after MI, we have used restricted cubic splines adjusted for age. This allowed us to detect non-linear associations and to categorize continuous variables. We have used Cox regression with both forward and backward selection to identify factors independently associated with the mortality risk. Potential variables selection was based on a literature search and included the following factors: age, admission heart rate, systolic blood pressure, creatinine level, fasting glycaemia, glycated haemoglobin, haemoglobin, maximal troponin level, ST segment depression on initial ECG, ST-elevation myocardial infarction (STEMI), previous history of MI, HF or PCI, ejection fraction at hospital discharge, and KCCQ items. Variables independently associated with the mortality risk in the derivation cohort were used for the PragueMi score creation. We have used regression coefficients to create relative weights for each category. To compare the performance of the PragueMi score as compared with the GRACE score, we have used the following methods: (i) assessment of the difference in the area under the receiver operating characteristic curve (AUC), (ii) the Brier score, and (iii) the continuous net reclassification improvement (NRI).

The AUC is an overall measure of model discrimination. It measures the model's ability to distinguish between patients with and without events. The AUC ranges from 0 to 1, where 0.5 indicates a random classification and 1 signifies a perfect classifier. To compare differences in AUC, we have used the Delong–Delong test using the R riskRegression package.[10]

The Brier score is a measure of model calibration. It is calculated as the mean squared difference between the predicted probability and the actual outcome. The Brier score for a perfectly calibrated model is 0.[11] The riskRegression package was also used to calculate the Brier score at different time points.[10]

The NRI quantifies how well a new model reclassifies subjects—either appropriately or inappropriately—as compared with an old model.[12] We have used the R nricens package for continuous NRI calculation.

Statistical analyses were conducted with R statistical software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), SPSS version 25.0 (IBM Corporation, Armonk, NY, USA), and STATA version 17 (StataCorp, College Station, TX, USA). All statistical tests and confidence intervals were two sided with a significance level of 0.05.

Results

Population

Between June 2017 and September 2022, 1769 patients were hospitalized for MI. Of these, 69 (3.9%) had missing KCCQ due to death within 1 month after hospital discharge. In total, 1135 (66.8% of eligible) patients had available both clinical data and KCCQ that patients filled 1 month after hospital discharge. A comparison of patients with available and missing KCCQ is shown in Supplementary material online, *Table S1*.

Table 1 Characteristics of the derivation and validation cohort

	Derivation cohort	Validation cohort
Total, No	795	340
Age, years	64.7 ± 11.5	63.7 ± 12.8
Female sex, *n* (%)	208 (26.2)	95 (27.9)
Risk factors		
Current smoking, *n* (%)	331 (41.6)	126 (37.1)
Arterial hypertension, *n* (%)	507 (63.8)	208 (61.2)
Diabetes, *n* (%)	153 (19.2)	72 (21.2)
CVD history		
Previous MI, *n* (%)	96 (12.1)	36 (10.6)
Heart failure history, *n* (%)	31 (3.9)	13 (3.8)
Previous PCI, *n* (%)	112 (14.1)	41 (12.1)
Previous CABG, *n* (%)	34 (4.3)	11 (3.2)
Previous stroke, *n* (%)	49 (6.2)	23 (6.8)
Clinical characteristics at MI presentation		
STEMI, *n* (%)	471 (59.2)	211 (62.2)
Heart rate, b.p.m.	76 ± 18	77 ± 19
Systolic BP, mmHg	144 ± 26	146 ± 25
Cardiac arrest, *n* (%)	23 (2.9)	11 (3.2)
Killip class		
I, *n* (%)	650 (81.8)	287 (84.4)
II, *n* (%)	115 (14.5)	42 (12.4)
III, *n* (%)	21 (2.6)	9 (2.6)
IV, *n* (%)	9 (1.1)	2 (0.6)
Creatinine, mmol/L	83.8 (71.5–100.5)	83.1 (70.5–100.6)
ST depression, *n* (%)	125 (15.7)	40 (11.8)
EF below 35%, *n* (%)	112 (14.1)	44 (12.9)
Outcomes		
Primary composite outcome, *n* (%)	105 (13.2)	43 (12.6)
Death, *n* (%)	103 (13.0)	43 (12.6)

CABG, Coronary artery bypass grafting; STEMI, ST-elevation myocardial infarction; BP, blood pressure; EF, ejection fraction.

Patients not included in this analysis due to missing KCCQ were slightly older and required more often cardiopulmonary resuscitation before hospital admission, while maximal troponin and mortality were similar in those included and not included in this analysis. The study CONSORT diagram is shown in Supplementary material online, *Figure S1*.

During a median follow-up of 46 months (IQR 29–61), 146 (12.9%) patients died. The study population was randomly split into derivation (70%, $n = 795$) and validation cohort (30%, $n = 340$).

Model development

Demographic characteristics of the 795 patients in the derivation cohort are shown in *Table 1*. Restricted cubic splines for age and age-adjusted continuous variables are shown in *Figure 1*. Based on cubic splines, categories of continuous variables were created and used in the multivariate Cox model. Forward and backward variable selection was used to create the final model. The final model included the following variables: age, HF history, admission creatinine and heart rate, ejection

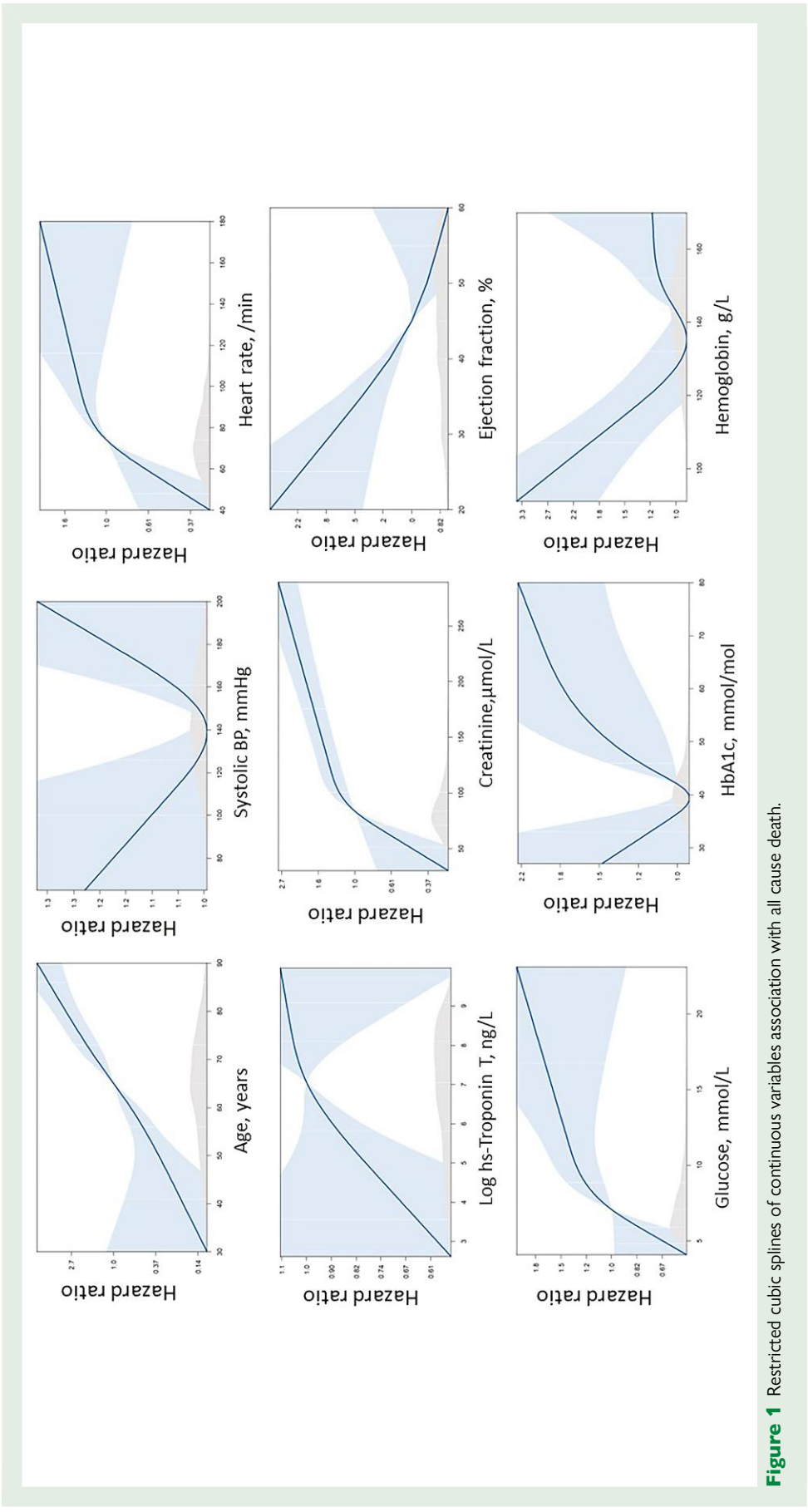


Figure 1 Restricted cubic splines of continuous variables association with all cause death.

Table 2 PragueMi score

No.	Variables	Levels	Score
1.	**Age, years**	≤45	1
		46–49	2
		50–69	4
		70–79	6
		≥80	10
2.	**Creatinine, μmol/L**	<100	1
		100–119	3
		120–159	4
		≥160	7
3.	**Heart rate, /min**	< 50	1
		50–69	3
		70–99	4
		≥100	7
4.	**Discharge EF, %**	≤35	3
		>35	1
5.	**Heart failure history**	No	1
		Yes	3
6.	**Walking 1 block on ground level**		
		Extremely limited	4
		Quite a bit limited	2
		Moderately limited	2
		Slightly limited	1
		Not at all limited	1
		Limited for other reasons	4
7.	**Compared with 2 weeks ago, have your symptoms of heart disease (shortness of breath, fatigue, or ankle swelling) changed? My symptoms have become**		
		Much worse	3
		Slightly worse	3
		Not changed	2
		Slightly better	2
		Much better	1
		I've had no symptoms	1
8.	**Over the past 2 weeks, how much has swelling in your feet, ankles, or legs bothered you? It has been**		
		Extremely bothersome	3
		Quite a bit bothersome	3
		Moderately bothersome	1
		Slightly bothersome	1
		Not at all bothersome	1
		I've had no swelling	1

Creatinine level and heart rate at hospital admission.
Walking impairment, change in symptoms, and leg oedema evaluated at 1 month after hospital discharge.

fraction at hospital discharge, and HF symptoms evaluated by the KCCQ 1 month after discharge, which included walking impairment, leg swelling, and the change in heart disease symptoms over the last 2 weeks. Based on the regression coefficients in the final model, the PragueMi score was developed (*Table 2*). In the derivation cohort, the PragueMi score showed superior discrimination and calibration as compared with the GRACE score (*Table 3*).

Table 3 Grace and PragueMi scores comparison in the derivation (Table A) and validation cohort (Panel B)

	Model discrimination			Model calibration		Reclassification		
Time (months)	Grace score AUC (95% CI)	PragueMi score AUC (95% CI)	*P*	Delta Brier score	*P*	NRI	NRI+	NRI−
Table A								
6	75.1 (64.7–85.4)	95.0 (91.5–98.4)	<0.0001	−0.4 (−0.7 to −0.1)	0.01	2.00 (1.98–2.00)	1.00 (1.00–1.00)	1.00 (0.98–1.00)
12	74.7 (66.7–82.7)	90.1 (84.5–95.7)	<0.0001	−0.8 (−1.3 to −0.2)	0.004	2.05 (1.97–2.23)	1.11 (1.00–1.27)	0.94 (0.93–1.00)
18	73.4 (66.0–80.8)	87.0 (81.1–92.9)	<0.0001	−1.3 (−2.0 to −0.6)	<0.001	2.47 (2.26–3.11)	1.60 (1.40–2.20)	0.87 (0.83–0.92)
24	72.2 (65.1–79.3)	86.4 (80.9–91.9)	<0.0001	−1.3 (−2.0 to −0.6)	<0.001	2.39 (2.08–2.54)	1.57 (1.28–1.71)	0.82 (0.80–0.85)
36	67.9 (61.4–74.4)	82.3 (76.4–88.1)	<0.0001	−1.7 (−2.6 to −0.8)	<0.001	1.85 (1.66–2.83)	1.45 (1.28–2.30)	0.39 (0.39–0.52)
Table B								
6	77.4 (62.2–92.5)	90.1 (81.8–98.4)	0.04	−0.5 (−1.1 to 0.1)	0.099	1.13 (0.42–1.34)	0.54 (0.16–0.80)	0.59 (0.25–0.72)
12	76.2 (64.7–87.7)	89.7 (83.5–96.0)	0.004	−0.7 (−1.4 to 0.0)	0.068	1.15 (0.85–1.72)	0.56 (0.20–1.00)	0.59 (0.51–0.78)
18	71.8 (60.7–82.8)	85.6 (76.5–94.6)	0.002	−1.4 (−2.3 to −0.4)	0.005	1.14 (0.88–1.40)	0.54 (0.30–0.88)	0.60 (0.38–0.65)
24	73.3 (64.0–82.5)	84.3 (76.5–92.1)	0.003	−1.4 (−2.4 to −0.4)	0.007	0.97 (0.64–1.38)	0.39 (0.08–0.74)	0.58 (0.54–0.65)
36	69.0 (59.7–78.2)	80.1 (72.1–88.2)	0.0009	−1.6 (−2.8 to −0.3)	0.016	0.85 (0.55–1.05)	0.27 (−0.02–0.49)	0.58 (0.52–0.68)

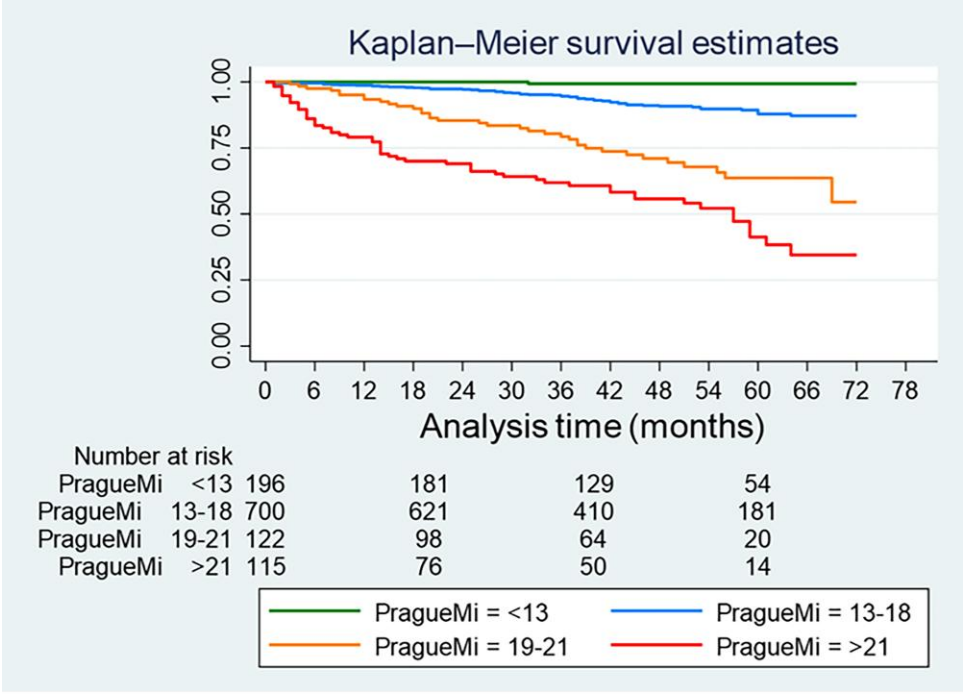


Figure 2 Kaplan–Meier survival curves by PragueMi categories.

Table 4 PragueMi score performance in different subgroups

Variables	AUC (95% CI)	P
Sex		
Male	0.87 (0.85–0.89)	0.41
Female	0.91 (0.87–0.94)	
Age, years		
≤60	0.94 (0.91–0.96)	0.19
>60	0.84 (0.81–0.87)	
eGFR, mL/min/1.73 m^2		
<60	0.83 (0.78–0.87)	0.87
≥60	0.84 (0.82–0.87)	
Diabetes		
No	0.89 (0.87–0.91)	0.63
Yes	0.86 (0.81–0.90)	
Ejection fraction, %		
>40	0.87 (0.84–0.89)	0.58
<40	0.89 (0.85–0.93)	
MI type		
Non-STEMI	0.86 (0.83–0.89)	0.41
STEMI	0.90 (0.88–0.92)	

eGFR, estimated glomerular filtration rate; STEMI, ST-elevation myocardial infarction.

Model validation

The validation cohort included 340 patients. The PragueMi score showed superior discrimination and calibration as compared with the GRACE score (*Table 3*). Over several study time points, PragueMi improved the continuous NRI, significantly improving both event and non-event NRI (*Table 3*). While the AUC and Brier scores were similar in the derivation and validation cohort, NRI was lower in the validation cohort probably due to lower statistical power in a smaller cohort.

Risk categories of the PragueMi score

Due to similar model performance in the derivation and validation cohort, we have combined them and created PragueMi risk categories based on observed risk. The Kaplan–Meier curves by PragueMi score categories are shown in *Figure 2*. The 196 patients (17.3% of the study cohort) with PragueMi score of <13 had excellent prognosis, with 100% event-free survival at 2 years. On the other hand, event-free survival in patients with PragueMi > 21 (10% of the study cohort) was 82.1% at 6 months and 77.8% at 1 year. The PragueMi score performance was consistent in different subgroups (*Table 4*).

Discussion

In this study, we show that HF symptoms evaluated remotely using a questionnaire possess an important prognostic value that adds to clinical risk factors. Our PragueMi score based on five clinical variables and three HF symptoms has superior discrimination, calibration, and risk reclassification properties as compared with the currently guideline-recommended GRACE score based only on clinical risk factors.

The prognosis of patients after MI is very heterogeneous.[13] Thus, the identification of patients at increased mortality risk is of clinical need. This allows a personalized approach to secondary prevention with intervention targeted at individuals that benefit the most.

Until now, the prediction models after MI have been only based on clinical risk factors, neglecting patients' symptoms. However, for

decades, clinicians have been searching for HF symptoms in patients after MI to identify at-risk individuals and to modify treatment accordingly.[14] Yet, this approach is time-consuming, influenced by provider skills and subjective interpretation.[15] Patient-reported outcomes coupled with modern telemedicine options allow the remote collection of patients' symptoms and empower patients to become a valuable source of clinically important data, without increasing the burden on the provider.[15]

Several previous studies have shown the utility of the KCCQ to predict prognosis in patients after MI.[6,16,17] No previous study evaluated the utility of combining patient-reported outcomes with clinical risk factors after MI. As KCCQ was developed for HF patients, not all items are relevant in patients after MI. In this study, we have identified that among the 23 KCCQ items, walking limitation, leg oedema, and change in heart disease symptoms over the last 2 weeks have the greatest predictive value among patients after MI.

In the present study, we have decided to evaluate HF symptoms 1 month after hospital discharge instead of evaluating them during the hospital stay. This decision was based on the fact that in many patients, HF symptoms develop later after discharge due to left ventricular remodelling. Furthermore, functional requirements for everyday living are higher outside of the hospital; thus, the patient may not recognize the newly developed limitations during the hospital stay.

In clinical settings, the PragueMi score may be particularly useful during post-discharge outpatient visits and also for remote monitoring of patients after discharge to identify high-risk patients who may benefit from closer follow-up and advanced therapies. As compared with other prediction scores that are based only on clinical variables, a potential barrier of the PragueMi score is that it also requires patients' symptoms evaluation. However, it includes only three easy-to-answer questions, which may also be answered remotely before the outpatient visit using an online questionnaire or dedicated app, thus decreasing the burden on providers. Furthermore, identifying HF symptoms before the outpatient visit may help to streamline the visit to this important issue.

Among discharged patients, the PragueMi score > 21 identified 10% of the population as very high risk, with 18% 6-month and 22% 12-month mortality rates, respectively. Timely identification of these patients followed by initiation or up-titration of HF pharmacotherapy and referral for advanced HF therapies such as heart transplant and left ventricular assist device has the potential to improve prognosis in these high-risk patients. Based on results of the STRONG-HF[18] study with rapid up-titration of HF pharmacotherapy, a meta-analysis of sodium-glucose transport protein 2 inhibitors use in HF,[19] and sacubitril–valsartan studies results,[20] we estimate that a multifactorial intervention targeted at these high-risk patients may decrease the mortality risk by at least 20–30%. Future randomized studies will be needed to test whether clinical decision-making based on the PragueMi score will lead to an improvement in clinical outcomes.

Study limitations

First, this is a single-centre study; thus, the model performance was only internally validated. Because no previous study systematically collected KCCQ 1 month after hospital discharge, we were unable to externally validate our model. This may limit the generalizability of our findings. However, the characteristics of our cohort are very similar to other recent cohorts of patients after MI.[21] In the future, the performance of our model needs to be tested in other cohorts. Second, due to missing KCCQ in some patients, our results may be the subject of a selection bias. However, while there were some statistically significant differences between patients with and without KCCQ available, clinically these differences are negligible. Thus, we assume that these missing data do not affect the generalizability of our results. Furthermore, in this study, we have identified the three most predictive items of the KCCQ. This reduction in the number of questions may improve the response rate in future studies. Third, data required for the PragueMi score were collected at different time points. Automated data collection of in-hospital data together with remote HF symptoms evaluation online or using an app may help to integrate PragueMi score into everyday practice without additional burden on clinicians.

The strengths of our study include a well-defined systematically collected cohort of consecutive MI patients with multiple clinical factors and remote HF symptoms evaluated as possible predictors of mortality risk.

Conclusion

Heart failure symptoms evaluated remotely using a questionnaire possess an important prognostic value that adds to clinical risk factors. The PragueMi risk score combines these predictors and has superior discrimination, calibration, and risk reclassification properties compared with the guideline-recommended GRACE score. Future studies will have to address whether clinical decision-making based on the PragueMi score can significantly improve the care of patients after MI.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

P.W. conceived and designed the study and analysed the data. J.M., D.J., M.Ž., M.Š., and M.K collected the data. All authors were involved in writing and revising the manuscript and approved the final version. P.W. is the guarantor of this work and as such has full access to all the data and takes responsibility for the integrity of all data and the accuracy of the data analysis.

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Conflict of interest: none declared.

Data availability

The data that support the findings of this study are available from the corresponding author (P.W.) upon reasonable request.

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