IJC Heart & Vasculature 55 (2024) 101511

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Development and validation of machine learning-derived frailty index in predicting outcomes of patients undergoing percutaneous coronary intervention

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ARTICLE INFO

Keywords:
Novel machine learning
Frailty index
Percutaneous coronary intervention
Asian

ABSTRACT

Introduction: Frailty is associated with increased mortality in patients with percutaneous coronary intervention (PCI). Existing operationalized frailty measurement tools are limited and require resource intensive process. We developed and validated a tool to identify and stratify frailty using collected data for patients who underwent PCI and explored its predictive power to predict adverse clinical outcomes post PCI.

Methods: Between 2014 and 2015, 1,732 patients who underwent semi-urgent or elective PCI in a tertiary centre were included. Variables including demographics, co-morbidities, investigations and clinical outcomes to 33 ± 37 months were analysed. Logistic regression model and Extreme Gradient Boosting (XGBoost) machine learning model were constructed to identify predictors of adverse clinical outcomes post PCI. The final models' predicted probabilities were assessed with area under receiver operating characteristic curve (AUC).

Results: With model analysis, frailty index (FI), age and gender were the 3 most important features for adverse clinical outcomes prediction, with FI contributing the most. After adjustment, the odds of FI to predict cardiac death and in-hospital death post PCI remained significant [1.94 (95 %CI1.79–2.10); $p < 0.001$, 2.04(95 %CI 1.87–2.23); $p < 0.001$ respectively]. The XGBoost machine learning models improved predictive power for cardiac death [AUC 0.83(95 %CI 0.80–0.86)] and in hospital death [AUC 0.83(95 %CI 0.80–0.86)] post PCI compared to logistic regression models.

Conclusion: The resultant model developed using novel machine learning methodologies had good predictive power for significant clinical outcomes post PCI with potential to be automated within hospital information systems.

1. Introduction

Population ageing represents both a challenge and triumph for cardiovascular medicine. The emergence of timely, well-designed healthcare structures for rapid treatment of acute coronary syndromes have resulted in increased life and health span. Consequently, there are increasingly older, co-morbid and vulnerable patients who require treatment for cardiovascular disease (CVD), with optimal assessment

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https://doi.org/10.1016/j.ijcha.2024.101511
Received 7 August 2024; Received in revised form 9 September 2024; Accepted 12 September 2024
Available online 21 September 2024

and management frailty being of increasing importance. The association of frailty and cardiovascular disease appears to be bidirectional [1]. Frailty appears to accelerate CVD onset and is associated with greater incidence of CVD [2]. CVD is associated with an estimated three-fold increase in incident frailty [3], with shared biological pathways such as insulin resistance, chronic inflammation, angiotensin 1R activation and obesity [4]. A recent systematic review suggested that frailty was associated with increased mortality in patients with acute coronary syndrome (HR=2.65; 95 %CI: 1.81–3.89, I2 = 60.2 %, P=0.02) compared to robust populations [5]. Patients with frailty who present with acute coronary syndrome were more likely to suffer from adverse events, such as arrhythmias, bleeding and mortality [6]. Patients with frailty were less likely to receive primary cardiac intervention, but paradoxically have reduced in hospital mortality if interventions were performed [7].

Despite this, frailty assessment is not routine in cardiology practice, and there is no consensus on optimal assessment tool for patient with CVD [8]. Additionally, existing operationalized frailty measurement tools have challenges limiting applicability to patients with CVD: subjectivity reduces inter-rater reliability and is subject to operator error [9], not always clinically feasible (e.g. frailty questionnaire in patient with delirium) [10] and requires a manual process that is resource intensive and difficult to scale to population level [11]. Increasingly, automated frailty measurement utilizing routinely collected data is purported as a possible solution [12].

We aimed to develop and validate a tool to identify and stratify frailty using routinely collected data for patients who received coronary angiography at a tertiary referral centre. We explored the predictive power of the tool to predict adverse outcomes after coronary angiography, and if machine learning methodologies might improve performance. Our primary outcome included cardiac and in-hospital mortality, and secondary outcomes included subsequent repeat coronary angiogram, congestive cardiac failure, myocardial infarction, and stroke.

2. Methods

2.1. Data source

Between 1st January 2014 and 31st December 2015, 1,732 consecutive patients underwent percutaneous coronary intervention (PCI) for semi-urgent and elective indications our centre. We excluded patients who underwent PCI for ST-segment elevation myocardial infarction. Variables including demographics, diagnosis, co-morbidities, diagnostic imaging and laboratory results, outcomes to 33 ± 37 months were captured in a digital patient registry. The local ethics committee has approved the study.

2.2. Definition of frailty

A frailty index of 30 variables was constructed using previously established methodology [13], including demographics, medical history, laboratory results and coronary angiogram findings. Nominal and ordinal cut-points were assigned from established guidelines and literature, or from consensus from experts within the study team. Points were assigned to each variable (e.g. history of congestive cardiac failure: yes = 1-point and no = 0-points; body mass index: >27.5 = 2-points, 23–27.5 = 1-point, 18.5–23 or < 23 = 0-points). Supplementary Table 1 describes the variables, cut-off points and numerical scores for creation of the frailty index. A patient episode level index was calculated using the frailty index (consisting of 30 variables, 40 total points) defined in this study as the denominator and the patient's actual symptom points as the numerator. The resultant index was divided into ascending quartiles to form the cut-points for categorization: Robust, mild frailty, moderate frailty and severe frailty status.

2.3. Definition of outcomes

Primary outcomes include cardiac and in-hospital death. Secondary outcomes include subsequent coronary angiogram required, subsequent congestive cardiac failure, subsequent myocardial infarction, and subsequent stroke or transient ischemic attack. These secondary outcomes were combined into a composite adverse outcome using Boolean OR logic.

2.4. Missing data

A missing data analysis revealed a range of percentage missing data across the variables (0–35.3 %). Supplementary Table 2 displays the variables and missing data analysis. A recent study suggests that missing data is common in ageing studies and multiple imputation via classification and regression tree (CART) improves frailty index estimation and predictive power [14]. CART was therefore utilized for multiple imputation to create a complete dataset utilizing all variables within the frailty index.

2.5. Statistical analysis

Multicollinearity was investigated by way of correlation matrix of all variables. The ethnicity variable displayed weak but significant correlation with outcome variables and subsequently removed from further analysis. The dataset was randomly split into training (80 %) and validation (20 %) sets.

In the model-development phase, we constructed two predictive models: a conventional logistic regression model and Extreme Gradient Boosting (XGBoost) machine learning model. XGBoost is an ensemble learning method based on decision trees that is aware of sparse data, and is highly efficient and scalable [15]. Firstly, logistic regression for the outcomes were used to ascertain odds ratios with 95 % confidence intervals and significance of Odds Ratios were tested with *t*-test, Wald Chi-Squared Test method. Two separate risk models were created: the first utilizing frailty index only, and the second a combined age, gender and frailty index model. Secondly, we performed XGBoost model to analyze the contribution (importance) of each variable to different outcomes. After identifying the variables through XGBoost, we used included variables to construct the final machine learning algorithm.

The models' predicted probabilities were used to plot area under the receiver operating characteristic curve (AUC) as a measure of predictive power. To assess incremental improvement in prediction over baseline models and evaluate the degree of benefit, Net reclassification index (NRI) [16] and decision curve analysis (DCA) [17] were applied to the 'Frailty Index + Age + Gender (FI)' model in comparison to baseline 'Age + Gender' model in the training and test groups.

We further divided our cohort who received coronary angiogram into two groups for pre-planned subgroup analysis: those receiving elective PCI and those who presented with non-ST segment elevation myocardial infarction. All the analyses above were conducted using R software version R44.1.22, and p value < 0.05 was defined as statistically significant. All the analytics source code of the project can be accessed in https://github.com/nus-mornin-lab/frailty_cardiac.

3. Results

The mean population age was 61.12(±1.32) years and 19.4 % were female. Age as prevalence of co-morbidity and female gender increased concomitantly as frailty status worsened. There was generally a significant increase in prevalence of deranged physiology, abnormal laboratory and cardiac tests from robust to severe frailty status. Supplementary Table 3 displays full patient characteristics by frailty status as defined by the frailty index. There was a 6-fold increase in cardiac death (n = 7(1.6 %) to n = 45(10.4 %); p < 0.001) and in all-cause mortality (n = 13(3.0 %) to n = 84(19.4 %); p < 0.001) respectively from robust to severe

frailty status. For subsequent adverse events after PCI, there was a 9-fold increase in prevalence of subsequent congestive cardiac failure (n = 6 (1.4 %) to n = 58(13.4 %); p < 0.001), a 14-fold increase in prevalence of subsequent myocardial infarction (n = 4(0.9 %) to n = 56(12.9 %); p < 0.001) and a 4-fold increase in prevalence of subsequent stroke or transient ischemic attack (n = 9(2.1 %) to n = 42(9.7 %); p < 0.001) respectively from robust to severe frailty status. There was no significant difference with respect to bleeding complications across the robust-frailty spectrum. Table 1 displays patient demographics and outcomes by frailty status.

Using logistic regression, the odds ratio of the frailty index to predict in-hospital death was marginally higher than cardiac death at 2.22(95 % CI 2.05–2.41); p < 0.001 and 2.07(95 % CI 1.92–2.24); p < 0.001 respectively. The odds ratios of the frailty index to predict subsequent composite adverse events (bleeding complications or subsequent coronary angiogram required, or subsequent congestive cardiac failure, myocardial infarction or cerebrovascular event) were lower at 1.54(95 %CI 1.43–1.67); p < 0.001. The predictive power for cardiac, inpatient death and composite adverse events were moderate at AUC 0.67(95 %CI 0.63–0.71), 0.7(95 %CI 0.67–0.74) and AUC 0.66(95 %CI 0.61–0.70) respectively. Table 2 displays the odds ratios and predictive power for the frailty index to outcomes.

When adjusted for age and gender, the odds ratios for the frailty index to predict cardiac and in-hospital death, as well as composite adverse events remained significant [1.94 (95 %CI1.79–2.10); p < 0.001, 2.04(95 %CI 1.87–2.23); p < 0.001 and 1.51(95 %CI 1.40–1.64) p < 0.001 respectively]. Additionally, the odds ratios for the frailty index were greater than that of chronological age for all outcomes within the model. The addition of these variables to the logistic regression model improved the predictive power for cardiac and in-hospital death [AUC 0.76(95 %CI 0.73–0.80) and 0.78(95 %CI 0.74–0.81) respectively], but not composite adverse events.

According to the analysis results of each features' contribution by XGBoost model, the frailty index, age and gender were the top 3 most important features of the data set for prediction of the outcomes, with the frailty index contributing the most for all outcomes. The XGBoost machine learning models improved predictive power for cardiac death [AUC 0.83(95 %CI 0.80–0.86)] and in hospital death [AUC 0.83(95 %CI 0.80–0.86)] compared to logistic regression models, but not composite adverse events [AUC 0.66(95 %CI 0.62–0.71)]. Table 3A and 3B displays the odds ratios and predictive power for the frailty index, age and gender for outcomes using logistic regression and the XGBoost model respectively.

Table 4 displays the Net Reclassification index, which evaluates the improvement in risk prediction with the addition of the frailty index to a baseline 'Age + Gender' model. There is a statistically significant improvement in prediction of cardiac death [8.5 %(95 % CI 1.9 % – 15.1 %)], In hospital death [12 %(95 %CI4.9 %-19.1 %)] and composite adverse events [17.9 %(95 %CI 8.5 %-27.3 %)]. Fig. 1 displays the Decision Curve analysis for the three prediction models: 'Age + Gender' model; 'FI alone'; and 'FI+Age + Gender' model. The frailty index alone model shows additional benefit compared to the 'Age + Gender' only

Table 1
Patient demographics and outcomes by frailty status.

Frailty status	Overall	Frail				p
		Robust	Mild	Moderate	Severe	
n	1732	433	433	433	433	
Age (mean (SD))	61.12(11.32)	59.33(10.84)	60.05(11.50)	61.67(11.27)	63.42(11.25)	<0.001
Gender = Male (%)	1396(80.6)	354(81.8)	370(85.5)	340(78.5)	332(76.7)	0.006
Ethnicity (%)						<0.001
Caucasian	2(0.1)	2(0.5)	0(0.0)	0(0.0)	0(0.0)	
Chinese	1033(59.6)	285(65.8)	266(61.4)	246(56.8)	236(54.5)	
Eurasian	7(0.4)	1(0.2)	2(0.5)	4(0.9)	0(0.0)	
Indian	220(12.7)	36(8.3)	47(10.9)	74(17.1)	63(14.5)	
Malay	286(16.5)	52(12.0)	62(14.3)	70(16.2)	102(23.6)	
Others	178(10.3)	56(12.9)	55(12.7)	38(8.8)	29(6.7)	
Sikh	6(0.3)	1(0.2)	1(0.2)	1(0.2)	3(0.7)	
Body Mass Index (mean (SD))	26.14(4.67)	24.67(3.56)	26.05(4.05)	26.22(4.77)	27.62(5.58)	<0.001
Smoking Status (%)						<0.001
Current Smoker	508(29.3)	73(16.9)	129(29.8)	147(33.9)	159(36.7)	
Ex-Smoker	278(16.1)	73(16.9)	72(16.6)	63(14.5)	70(16.2)	
Non-Smoker	946(54.6)	287(66.3)	232(53.6)	223(51.5)	204(47.1)	
Alcohol use (%)	38(2.2)	5(1.2)	3(0.7)	16(3.7)	14(3.2)	0.004
Co-morbidity						
Hypertension (%)	1228(70.9)	218(50.3)	279(64.4)	345(79.7)	386(89.1)	<0.001
Diabetes Mellitus (%)	730(42.1)	68(15.7)	124(28.6)	215(49.7)	323(74.6)	<0.001
Dyslipidaemia (%)	1340(77.4)	279(64.4)	311(71.8)	364(84.1)	386(89.1)	<0.001
Ischaemic Heart Disease (%)	1717(99.1)	425(98.2)	431(99.5)	430(99.3)	431(99.5)	0.084
Acute Myocardial Infarction (%)	1098(63.4)	190(43.9)	254(58.7)	304(70.2)	350(80.8)	<0.001
Cerebrovascular Disease (%)	144(8.3)	13(3.0)	23(5.3)	40(9.2)	68(15.7)	<0.001
Atrial Fibrillation (%)	120(6.9)	13(3.0)	16(3.7)	31(7.2)	60(13.9)	<0.001
Congestive Cardiac Failure (%)	220(12.7)	13(3.0)	30(6.9)	47(10.9)	130(30.0)	<0.001
Chronic Obstructive Pulmonary Disease (%)	47(2.7)	4(0.9)	9(2.1)	5(1.2)	29(6.7)	<0.001
Asthma (%)	70(4.0)	9(2.1)	10(2.3)	29(6.7)	22(5.1)	0.001
Peripheral Vascular Disease (%)	58(3.3)	5(1.2)	3(0.7)	12(2.8)	38(8.8)	<0.001
Outcomes						
Cardiac Death (%)	84(4.8)	7(1.6)	9(2.1)	23(5.3)	45(10.4)	<0.001
In-hospital Death (%)	148(8.5)	13(3.0)	17(3.9)	34(7.9)	84(19.4)	<0.001
Bleeding complication (%)	74(4.3)	17(3.9)	16(3.7)	20(4.6)	21(4.8)	0.811
Subsequent Coronary Angiogram required (%)	212(12.2)	34(7.9)	50(11.5)	56(12.9)	72(16.6)	0.001
Subsequent Congestive Cardiac Failure (%)	102(5.9)	6(1.4)	12(2.8)	26(6.0)	58(13.4)	<0.001
Subsequent Myocardial Infarction (%)	113(6.5)	4(0.9)	17(3.9)	36(8.3)	56(12.9)	<0.001
Subsequent Cerebrovascular Disease or transient ischemic attack (%)	71(4.1)	9(2.1)	8(1.8)	12(2.8)	42(9.7)	<0.001

Table 2
Odds Ratios and predictive power for frailty index (FI) for outcomes using logistic regression.

Outcomes	Training set N=1386					Test set N=346	
	OR	95 % Cl	p	AUC	95 % CI	AUC	95 % CI
Cardiac Death	2.07	1.92–2.24	<0.001	0.71	0.69–0.73	0.67	0.63–0.71
In hospital Death	2.22	2.05–2.41	<0.001	0.72	0.70–0.74	0.71	0.67–0.74
Composite Adverse Events	1.54	1.43–1.67	<0.001	0.63	0.61–0.66	0.66	0.61–0.70

OR: Odds ratio for increase in frailty stage; Composite Adverse events: bleeding complications or subsequent coronary angiogram required, or subsequent congestive cardiac failure, myocardial infarction or cerebrovascular event; AUC: Area under the Receiver Operating Characteristic Curve; 95% CI: Confidence Interval.

Table 3A
Odds Ratios and predictive power for frailty index, age and gender using logistic regression.

Outcomes		Importance	Train		Test	
			AUC	95 %CI	AUC	95 %CI
Cardiac Death	FI	0.411	0.841	0.824–0.857	0.833	0.802–0.864
	Age	0.396				
	Gender	0.193				
In Hospital Death	FI	0.346	0.841	0.825–0.858	0.827	0.795–0.859
	Age	0.346				
	Gender	0.308				
Composite Adverse Events	FI	0.461	0.664	0.643–0.692	0.657	0.619–0.711
	Age	0.332				
	Gender	0.207				

Table 3B
Predictive power for frailty index, age and gender using XGBoost model.

Outcomes	Training set N=1386						Test set N=346	
	OR		95 % CI	p	AUC	95 % CI	AUC	95 % CI
Cardiac Death	Age	1.04	1.03–1.05	<0.001	0.77	0.75–0.78	0.76	0.73–0.80
	Gender	0.56	0.46–0.69	<0.01				
	FI	1.94	1.79–2.10	<0.001				
In hospital Death	Age	1.06	1.05–1.07	<0.001	0.80	0.78–0.82	0.78	0.74–0.81
	Gender	0.75	0.61–0.93	<0.01				
	FI	2.04	1.87–2.23	<0.001				
Composite Adverse Events	Age	1.02	1.01–1.02	<0.01	0.65	0.62–0.67	0.64	0.60–0.69
	Gender	1.06	0.85–1.33	> 0.1				
	FI	1.51	1.40–1.64	<0.001				

Table 4
Net Reclassification Index (NRI) in the Training and Testing Groups.

Outcomes		Training set				Test set			
		NRI	Lower	Upper	P value	NRI	Lower	Upper	P value
Cardiac Death	Age + Gender(Ref)								
	FI+Age + Gender	0.165	0.128	0.203	< 0.001	0.085	0.019	0.151	0.011
In hospital Death	Age + Gender(Ref)								
	FI+Age + Gender	0.162	0.126	0.197	< 0.001	0.120	0.049	0.191	< 0.001
Composite Adverse Events	Age + Gender(Ref)								
	FI+Age + Gender	0.151	0.099	0.203	< 0.001	0.179	0.085	0.273	< 0.001

model, and unsurprisingly, the 'FI+Age + Gender' model shows the greatest benefit compared to the other two models.

3.1. FI frailty index

Supplementary Table 4a and 4b displays the Odds Ratios and predictive power of the frailty index alone and age-gender adjusted frailty index for the subgroup receiving elective PCI and the subgroup with emergency presentation of acute coronary syndrome respectively. The predictive power of the frailty index and age-gender adjusted frailty index was even across both subgroups using logistic regression. The predictive power was good (AUC 0.73–0.81) for cardiac and in hospital

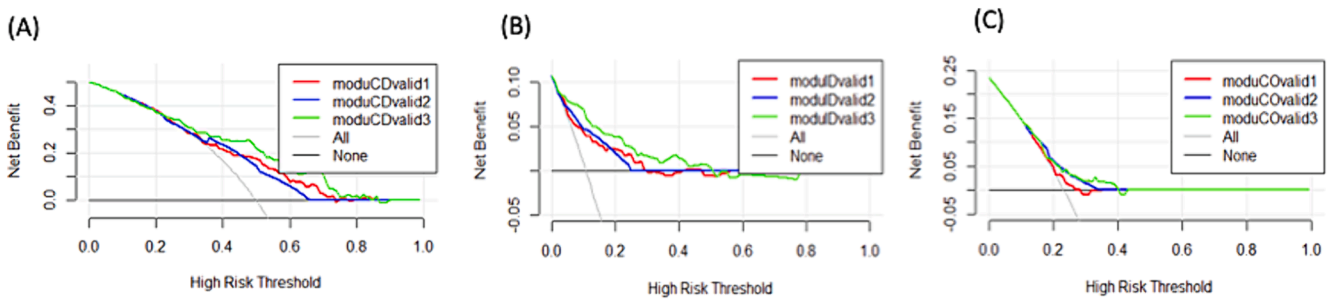

Fig. 1. Decision curve analysis (DCA) of the three prediction models. The net benefit curves for the three prediction models are shown. X-axis indicates the threshold probability for different outcomes and Y-axis indicates the net benefit. The pink line represents the Age + Gender model.The blue line represents the FI model. The green line represents the Age + Gender + FI model. The preferred model is the Age + Gender + FI model, the net benefit of which was larger over the range of other models. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

death, but moderate for composite adverse outcomes (0.62–0.66). The age-gender adjusted XGBoost machine learning model improved the predictive power for cardiac death and in hospital death compared to logistic regression models, but the more so for the elective subgroup compared to those presenting with acute coronary syndrome [AUC 0.95 (95 %CI 0.93–0.98) elective subgroup versus AUC 0.86 (95 %CI 0.83–0.89) emergency subgroup for cardiac death and [AUC 0.93 (95 % CI 0.90–0.96) elective subgroup versus AUC 0.80 (95 %CI 0.77–0.84) emergency subgroup for in hospital death respectively]. Again, the predictive power for composite adverse events were not improved by the XGBoost model. Supplementary Table 5 displays the predictive power for frailty index, age and gender by XGBoost model.

4. Discussion

With increasing recognition that frailty assessment for patients with cardiovascular disease valuably contributes to prognostication, shared outcome driven decision-making and healthcare redesign for elderly population, widespread operationalized frailty assessment is not yet the norm. We report the development and validation of a frailty index that utilizes routinely collected data as part of patient care, in a cohort of patients who received PCI. In keeping with frailty literature [18,19], prevalence of co-morbidity and female gender increased concomitantly as frailty status worsened. We found the frailty index had significant predictive discrimination for important outcomes such as cardiac death, in hospital death and adverse events (subsequent myocardial infarction, congestive cardiac failure, cerebrovascular event and need for further coronary angiogram). We found the predictive power of the frailty index was moderate to good for all these outcomes and exceeded that of chronological age. Additionally, the frailty index significantly improved prediction for all outcomes when added to chronological age and gender. The application of novel gradient boosting machine learning methodology appeared to improve prediction of the outcomes over traditional statistical methods ie logistic regression. Subgroup analysis (elective PCI versus acute coronary syndrome) found the predictive power for the outcomes were even across both groups. Additionally, when machine learning methodology was applied, the predictive power increased, but preferentially for the elective group over those presenting with acute coronary syndrome.

There are several factors to consider when developing the ideal tool to risk stratify patients prior to PCI. Firstly, it would be based on data collected as a part of routine care. Secondly, the variables to build the risk prediction model would ideally encompass past and within-episode care data up until the point of coronary angiogram to be useful for prognostication and to aid clinical decision making prospectively. Thirdly, the risk tool should be explainable, comprised of elements known to be associated with significant clinical outcomes. Lastly, the tool should have prognostic significance and excellent predictive performance for important clinical outcomes. The frailty index arguably contains many of these elements which make it an attractive tool to improve clinical practice.

While risk stratification models for patients receiving PCI exist, majority do not consider the clinical syndrome of frailty. Most risk models that encompass frailty in this patient group were small retrospective observational studies. Studies that have utilized routinely collected data, have utilized claims-data [7] or diagnostic codes [20] which are only available retrospectively long after the care episode. Table 5 displays the studies of risk scores in patients who received PCI or acute coronary syndrome. The predictive performance for cardiac death and in hospital of the frailty index is comparable or exceeds other non-frailty or existing frailty risk models for patients who require PCI or present with acute coronary syndrome.

As frailty gets increasingly recognized, there is a growing search for more accurate and convenient ways to measure frailty. Apart from the derivation of frailty index in our studies, other means evaluated to assess frailty in a patient include digital wearables. These digital wearables have made frailty assessment more convenient for patients, especially elderly patients with less motivation to wear devices for lengthy duration [21]. However, these tools will take time due to limitations from connectivity of digital devices and elderly patient's familiarity with technological devices [22]. Till then, the frailty index serves as an established way to measure frailty.

How may we use this tool? Recommendations for PCI in a semi-urgent or elective setting in older patients remain poorly defined compared to younger patients as most older patients were excluded. The latest guideline for coronary artery revascularization [23] has suggested for careful consideration of risks and benefits including frailty and patient's preference in the decision making for PCI. In this vulnerable group of co-morbid elderly patients with an uncertain role of PCI, our frailty risk model serves as a useful tool which provides clinicians with a fairer assessment of risk. As a result, communications with patients and their family members on management of CVD may benefit from better informed risk estimation. The 30 variables used in the formulation of the frailty index in our study are standard required medical information for patients routinely undergoing PCI and are easily retrieved from electronic health records if available in individual institutions. The next step in implementation and testing of tool would be to conduct a prospective trial for elderly patients undergoing PCI in our institution for "real world setting" data.

This study has some important limitations. The study has been limited by missing data for some of the predictor variables. However, we have utilized appropriate methodologies to impute data, optimizing the risk prediction models. The study utilizes retrospective single-centre patient registry data. However, the predictor variables are derived from data elements that are collected as part of routine patient care. Prospective validation of this tool at different clinical sites is therefore a research priority as discussed. Additionally, these data elements make it suitable to automate this the risk prediction model using clinical

Table 5
Studies with risk stratification models in patients who received percutaneous coronary intervention or acute coronary syndrome.

Authors, Year	N	Study cohort	Risk Score	Findings and outcomes
Singh et al, 2013 [24]	7640	Patients who received PCI	New Mayo Clinic Risk Score	AUC MACE 0.74AUC periprocedural death 0.89
Moscucci et al, 2001 [25]	16,592	Patients who received PCI	–	AUC in hospital mortality 0.90
Wu et al, 2006 [26]	96,136	Patients who received PCI	New York PCI risk score	AUC in hospital mortality 0.886
Singh et al, 2011 [27]	628	Patients who received PCI	Mayo Clinic Risk Score Mayo Clinic Risk Score + Fried Frailty	AUC all-cause mortality 0.628 AUC all-cause + MI 0.573 AUC all-cause mortality 0.675 NRI 22 % p = 0.13 AUC all-cause + MI 0.607 NRI 16 % P=0.038
Damluji et al, 2019 [28]	469,390	Admitted with Acute Myocardial Infarction	Claims-based Frailty Index	In hospital mortality OR 1.43, (95 %CI 1.39–1.46)
Murali-Krishnan et al, 2015 [6]	745	Patients who received PCI	Clinical Frailty Scale	30-Day mortality HR 4.8 (95 % CI 1.4–16.3)1-year mortality HR 5.9 (95 % CI 2.5 to 13.8)
Hermans et al, 2019 [29]	206	Admitted with ST Elevation Myocardial Infarction	Safety Management Programme (VMS) score	30-day all-cause mortality OR 9.6 (95 %CI 1.6–56.9)30-day serious adverse event OR 2.9 (95 % CI 1.1–7.9)
Kurobe et al, 2021 [30]	266	Admitted with ST Elevation Myocardial Infarction	Clinical Frailty Scale	MACE OR 1.39 (95 %CI 1.08–1.79) Bleeding events HR 3.77 (95 %CI 1.16–12.19)
Calvo et al., 2018 [31]	259	Admitted with ST Elevation Myocardial Infarction	FRAIL scale	In hospital mortality OR 3.96 (95 %CI 1.16–13.56)
Nishihira et al, 2020 [32]	546	Admitted with ST Elevation Myocardial Infarction	Impairment of walking, cognition and ADLs	All-cause mortality HR 1.81 (95 %CI 1.23–2.65)
Dodson et al, 2018 [33]	129,330	Admitted with Acute Myocardial Infarction	Impairment of walking, cognition and ADLs	Bleeding OR 1.33 (95 %CI 1.23–1.44) vulnerable/mild frailtyOR 1.44 (95 %CI 1.23–1.44) moderate/severe frailty
Yoshioka et al, 2019 [34]	354	Admitted with ST Elevation Myocardial Infarction	Clinical Frailty Scale	All-cause mortality HR 2.34 (95 %CI 1.43–3.85)
Segichi et al, 2020 [35]	412	Admitted with Acute Myocardial Infarction	Modified Katz index	In hospital mortality OR 1.212, (95 %CI 1.00–1.47)
Nguyen et al, 2019 [6]	324	Admitted with acute coronary syndrome	Reported Edmonton Frail Scale	In-hospital mortality OR 3.02 (95 %CI 1.35–6.75)30-day mortality: OR 3.28 (95 % CI 1.59–6.76) Arrhythmia OR 2.24 (95 % CI 1.32–3.8)HAP OR 2.27 (95 % CI 1.24 4.17)
Campo et al, 2020 [36]	402	Admitted with acute coronary syndrome	SPPB Clinical Frailty Score Edmonton Frail ScaleGrip strength	All-cause mortalitySPPB OR 0.74 (95 %CI 0.63–0.85) Clinical Frailty Score OR 1.34 (95 %CI 0.94–1.92) Edmonton Frail Scale OR 1.33 (95 %CI 1.13–1.56)
Kwok et al, 2019 [37]	7,398,572	Admitted with acute coronary syndrome	HFRS	Bleeding OR 2.08 (95 %CI 1.79–2.41)In hospital stroke OR 7.84 (95 %CI 6.93–8.86) In hospital death OR 2.57(95 %CI 2.18–3.04)
Alonso Salinas et al, 2017 [38]	234	Admitted with Acute Myocardial Infarction	SHARE-FI	Death or non-fatal reinfarction or major bleeding HR 2.54 (95 %CI 1.12–5.79)
Blanco et al, 2017 [39]	236	Admitted with acute coronary syndrome	Edmonton Frail Scale	All-cause mortality Score 4–6 HR 1.53(95 %CI 0.74–3.16) Score > 6 HR 3.60(95 %CI 1.70–7.63)
Kang et al, 2015 [40]	352	Admitted with acute coronary syndrome	Clinical Frailty Score	All-cause mortality HR 5.393 (95 %CI 1.48 – 19.69)
Sanchis et al, 2014 [41]	342	Admitted with acute coronary syndrome	Fried Score	All-cause mortality AUC 0.76 HR 1.25 (95 %CI 1.15–1.36)
Gharacholou et al, 2012 [42]	545	Patients who received PCI	Fried Score	lower SF-36 scores, lower SAQ scores for physical limitation, and lower SAQ scores for quality of life
Graham et al, 2013 [43]	183	Admitted with acute coronary syndrome	Edmonton Frail Scale	Mortality HR 3.49(95 %CI 1.08–7.61)
Borovac et al, 2022 [44]	429,070	Admitted with ST	HFRS	All-cause mortality was

(continued on next page)

Table 5 (*continued*)

Authors, Year	N	Study cohort	Risk Score	Findings and outcomes
		Elevation Myocardial Infarction		4.5 % in the low-risk group, 28.9 % in the intermediate-risk group and 31.1 % in the high-risk group

PCI Percutaneous Coronary Intervention; AUC Area under the Receiver Operating Characteristic Curve; MACE major adverse cardiovascular events; NRI Net Reclassification Index OR Odds Ratios; ADL activities of daily living HAP hospital acquired pneumonia; SPPB short physical performance battery; MPI Multidimensional Prognostic Index HFRS Hospital Frailty Risk Score; SHARE-FI Survey of Health Ageing and Retirement in Europe Frailty Index.

information systems, further reducing clinician burden. Other limitations include imbalance in the database with 3.6 % in-hospital death, 3.8 % cardiac death, and 0.4 % composite outcome. For cases where the data contained a large number of negative case samples and small percentage of positive case samples, we considered a stratified sampling method to divide the data set. For such cases with heterogenous distribution, we ensured that the proportion of the test data representing the minority class was similar to the training data as much as possible. Lastly, while the tool identifies patients with frailty and is able to grade severity, it does not identify specific dimensions of frailty (e.g. cognitive frailty) for targeted intervention.

5. Conclusion

We report the development and validation of a frailty index using novel machine learning methodologies utilizing data routinely collected as a part of patient care in a cohort of patients who received PCI. The resultant machine learning model had good predictive power for significant clinical outcomes including cardiac and in hospital death and has the potential to be automated within hospital information systems.

Funding Source

This study is supported by two grants: NUHS (NUHSRO/2020/099/RO5 + 6/Seed-Mar/05) and NMRC (MOH-000770). This work was supported by the Cisco-NUS Accelerated Digital Economy Corporate Laboratory (Award I21001E0002, funded by A*STAR, CISCO Systems (USA) Pte. Ltd, and National University of Singapore).

All authors declare no conflict of interest.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [John Soong reports financial support was provided by Ministry of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper].

Acknowledgement

None. This study is supported by two grants: NUHS (NUHSRO/2020/099/RO5+6/Seed-Mar/05) and NMRC (MOH-000770).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101511.

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