Association of NPAC score with survival after acute myocardial infarction

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Christien KH Li* [a, b], Jeffery Ho PhD* [a], Zhongzhi Xu[l], Ishan Lakhani [a], Yingzhi Liu MPH[c], George Bazoukis MD [d], Tong Liu MD PhD [e], Wing Tak Wong PhD [f], Shuk Han Cheng PhD [g], Matthew TV Chan MD PhD FANZCA [c], Lin Zhang [c, i], Tony Gin MD FANZCA FRCA [c], Martin CS Wong MD FESC FACC FFPH [h], Ian Wong PhD FRCPCH [j, k], William KK Wu PhD FRCPath* [c, i], Qingpeng Zhang PhD*[l], Gary Tse MPH PhD FESC FACC FRCP *[e]

[a] Laboratory of Cardiovascular Physiology, Li Ka Shing Institute of Health Sciences, Hong Kong, PR China

[b] Faculty of Medicine, Newcastle University, United Kingdom

[c] Department of Anesthesia and Intensive Care, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, PR China

[d] Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, Athens, Greece

[e] Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Tianjin Institute of Cardiology, Department of Cardiology, Second Hospital of Tianjin Medical University. Tianjin 300211, PR China

[f] School of Life Sciences, The Chinese University of Hong Kong, Hong Kong, PR China.

[g] Department of Biomedical Sciences, College of Veterinary Medicine and Life Science, City University of Hong Kong, Kowloon Tong, Kowloon, Hong Kong, PR China

[h] The Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, PR China

[i] State Key Laboratory of Digestive Disease, Institute of Digestive Disease, Li Ka Shing Institute of Health Sciences, and Shenzhen Research Institute, The Chinese University of Hong Kong, Shatin, Hong Kong, PR China

[j] Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, PR China

[k] University College London, United Kingdom

[l] School of Data Science, City University of Hong Kong, Hong Kong, PR China

***** Equal contribution

Correspondence to:

William KK Wu, PhD, FRCPath

Department of Anesthesia and Intensive Care, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, People's Republic of China.

Email: wukakei@cuhk.edu.hk

Qingpeng Zhang, BEng, MS, PhD

School of Data Science,

City University of Hong Kong, Kowloon Tong, Hong Kong, People's Republic of China.

Email: qingpeng.zhang@cityu.edu.hk

Gary Tse, MPH, PhD, FESC, FACC, FRCP

Laboratory of Cardiovascular Physiology, Li Ka Shing Institute of Health Sciences, Hong Kong, PR China

Email: gary.tse@doctors.org.uk

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ABSTRACT

Background: Risk stratification in acute myocardial infarction (AMI) is important for guiding clinical management. Current risk scores are mostly derived from clinical trials with stringent patient selection. We aimed to establish and evaluate a composite scoring system to improve short-term mortality classification after index episodes of AMI, independent of electrocardiography (ECG) pattern, in a large real-world cohort.

***Methods*:** Using electronic health records, patients admitted to our regional teaching hospital (derivation cohort, n=1747) and an independent tertiary care center (validation cohort, n=1276) with index acute myocardial infarction between January 2013 and December 2017 as confirmed by principal diagnosis and laboratory findings, were identified retrospectively.

Results: Univariate logistic regression was used as the primary model to identify potential contributors to mortality. Stepwise forward likelihood ratio logistic regression revealed that neutrophil-to-lymphocyte ratio, peripheral vascular disease, age, and serum creatinine (NPAC) were significant for 90-day mortality (Hosmer-Lemeshow test, P=0.21). Each component of the NPAC score was weighted by beta-coefficients in multivariate analysis. The C-statistic of the NPAC score was 0.75, which was higher than the conventional Charlson's score (C-statistic=0.63). Judicious application of a deep learning model to our dataset improved the accuracy of classification with a C-statistic of 0.81.

***Conclusions*:** The NPAC score comprised of four items from routine laboratory parameters and basic clinical information and can facilitate early identification of cases at risk of short-term mortality following index myocardial infarction. Deep learning model can serve as a gate-keeper to facilitate clinical decision making.

Keywords: Cardiovascular; Heart disease; Mortality; Myocardial infarction; Neutrophil-to-lymphocyte ratio.

INTRODUCTION

Cardiovascular diseases pose a significant disease burden worldwide and are associated with considerable years of life lost, particularly in low- and middle-income countries [1, 2]. Given similar care settings and implementation of international guidelines, the long-term mortality following the first episode of acute myocardial infarction (AMI) was more than three-fold higher in developing countries as compared to that in European continents [3].

Infarction of the myocardium is characterized by a fluctuation in plasma leukocyte levels as part of the acute phase response [4]. Inflammation is key to its pathogenesis, placing an onus on the discovery and subsequent implementation of inflammatory biomarkers for risk stratification in clinical settings [5]. Following AMI, the absolute neutrophil count rises while circulating lymphocyte number decreases, leading to an elevation in the plasma neutrophil-to-lymphocyte ratio (NLR) [6]. Activated neutrophils invade the infarcted region and release various mediators that perpetuate the inflammatory process [4, 7]. This causes an increase in infarct size and consequently worsens the extent of myocardial ischemia [6], tissue injury and plaque damage [8]. By contrast, the ensuing reduction in plasma lymphocyte count following AMI occurs secondarily to enhanced apoptosis [9], and is probably associated with poorer prognosis in acute ST-elevation MI (STEMI) [10]. To date, a significant body of research has focused on STEMI given the high mortality given the extensive areas of myocardial involvement. However, it is recognized that a subset of non-STEMI patients remains at a high risk of mortality. Yet, risk stratification in NSTEMI can be challenging. A number of risk scores have demonstrated proven utility, but clinicians may be reluctant to use these during clinical practice at the bedside because of the time-consuming nature to calculate them [11]. Moreover, recent research has devised increasingly complex scores incorporating different novel biomarkers [12], which may not be readily available in all centers.

With a greater understanding of the mechanistic roles of both neutrophils and lymphocytes in AMI patients, NLR has recently emerged as a cost-effective biomarker for clinical outcomes in several cardiovascular diseases. NLR is a readily accessible biomarker for ongoing inflammation [13]. However, the discriminatory

power of neutrophil-to-lymphocyte counts alone for mortality remains sub-optimal [14], leading to the search of its combination with other hematological markers for risk stratification. While increasing the number of variables into a composite scoring system maximizes its predictability, it compromises the simplicity for clinical use.

Our study aim was to determine independent parameters including clinical risk factors and hematological parameters for short-term mortality in incident cases of acute myocardial infarction. A small set of significant parameters were identified for model simplicity. We developed a scoring system based on adjusted odds ratio for easy clinical use. A deep learning model was also developed as a gate-keeper to provide more accurate survival classification to facilitate clinical decision making.

METHODS

Study design, population and case identification

This retrospective single center observational study was conducted on consecutive admissions due to first episode of acute myocardial infarction using electronic health records registry database of the Prince of Wales Hospital, Hong Kong, between January 2013 and December 2017 (derivation cohort). The center is a university-affiliated teaching hospital with 173,114 discharges and registered in-hospital deaths per year collectively and the sole trauma center in the territory where 7.3 million people inhabited. The registry database is linked to a territory-wide Clinical Data Analysis and Reporting System (CDARS) with each patient identifiable with a unique reference identifier, enabling access to comprehensive medical records made in other government hospitals, which cover 90% tertiary care in the territory. Details of this administrative system have been published previously [15]. The external validation cohort was assembled retrospectively from an independent tertiary care hospital using the same search criteria (validation cohort).

An incident case of acute myocardial infarction was identified using the principal diagnosis that denoted an initial episode of medical care for acute myocardial infarction (ICD-9 codes 410.00-52) (**Supplementary Table 1**), regardless of anatomical sites, and an elevation of high-sensitivity cardiac troponin T (hs-cTnT). 100 random cases of patients with ICD-9 coding on MI were sampled and compared

with case notes. All patients (100%) were confirmed to have an MI. Patients less than 18 years old or with malignancies were excluded. Laboratory results on the different haematological parameters in the same hospital stay were recorded. Complete blood count was performed using automated haematology analyzer. NLR was calculated from absolute neutrophil and lymphocyte counts derived from the same venous blood specimen. We used the time point of NLR estimate closest to that of peak troponin T (NLR_t) for establishing our risk score. The selection of NLR_t for use in analysis was based upon multiple runs of the kaplan-meier survival model using multiple NLR time points, which in turn revealed that the best statistical accuracy (AUC/C-statistics) was achieved with NLR measurements taken closest to peak troponin rather than the first NLR during admission. This study was reported according to the STROBE guidelines for observational studies [16].

Data extraction

Baseline characteristics such as patient demographics, principal diagnosis, co-morbidities, cardiac medication use, laboratory findings, and clinical outcomes of all-cause in-hospital, 30-day and 90-day mortality from the time of AMI diagnosis, length of hospital stay, and 28-day emergency re-admission were extracted. Concurrent morbidities were identified according to Charlson's framework using codes from the International Classification of Diseases 9^{th} edition. Concurrent morbidities were marked as positive if they were present during point of incident MI diagnosis. The use of antiplatelet agents, anticoagulants, fibrinolytic agents, lipid regulating drugs, and corticosteroids on admission was also identified.

Statistical analysis

Descriptive statistics were presented as number (percentage), mean±standard deviation or median [interquartile range] as appropriate. Normality was determined by Kolmogorov-Smirnov test. Study population was stratified into NLR quartiles by Tukey's Hinges 25^{th}, 50^{th} and 75^{th} percentiles. Comparison across groups was conducted using Chi-square Mantel-Haenzel test for trend and simple linear regression for categorical and continuous variables, respectively. For variables that were not normally distributed, Kruskal-Wallis test was applied to compare the

difference in median values. One-way ANOVA with Tukey's post-hoc test was used to compare mean difference of NLR values detected at different time periods after admission. The relation between clinical and laboratory parameters and study outcomes was explored using univariate logistic regression. Variables with $P<0.05$ were further analyzed using stepwise forward likelihood ratio logistic regression. Appropriate adjustments were made for age, sex, laboratory parameters, cardiac medication use, and different co-morbidities. The simplest multivariate model was selected based on Hosmer-lemeshow test for goodness of fit. To account for missing data, we used mean imputation (<10% missing) or random imputation (>10% missing). Crude and adjusted odds ratios (OR) were reported in 95% confidence intervals (CI). To develop a scoring system, the significant variables in the final multivariate logistic regression model were included. Briefly, a point assigned to a variable would be equivalent to the halved value of adjusted odds ratio, rounded up to the nearest integer. This method was previously published by our research team [17]. Correlation between NLR and other inflammatory markers was evaluated using Pearson correlation with 95% CI generated by bootstrapping. Diagnostic performance of biomarkers was evaluated by Harrel's C-statistic and receiver operator curve using cut-offs determined by Youden's J statistic. Both the derivation cohort and validation cohort were retrieved from the same administrative database and analyzed using the same method as described. There was no overlap in the patient cohorts between the derivation and validation cohort. This was confirmed by comparing patient identification number between the two cohorts. All statistical analysis was conducted using IBM SPSS for Windows version 24.0 (IBM Corp, Armonk, NY, USA). Statistical significance was set as two-sided P-value of less than 0.05.

Deep learning model

The proposed NPAC score framework is highly interpretable and convenient for clinical use, but such statistical models-based framework fails to capture the higher-order interactions among multiple risk factors that are essential for characterizing and categorizing disease progression. With this in mind, we also proposed a deep learning-based framework constructed using Scikit-learn, a free software machine

learning library for the Python programming language. The proposed deep learning framework is a neural network with one input layer (four neurons, representing the four variables in NPAC), one output layer (one neuron, representing the classification outcome), and multiple hidden layers in between. An activation function controls the amplitude of the output of each neuron and modifies all inputs so that it is able to capture the complex higher-order interactions between all inputs. Specifically, the proposed deep learning model has two hidden layer with eight neurons in each layer. The commonly used Rectified Linear Unit (ReLU) is adopted as activation function before the final output. The sigmoid function was used to generate the final association outcome, because it shrinks the final output values into an S-shaped curve ranged from 0 to 1 (the same as the logistic function used in logistic regression). For both derivation cohort and validation cohort, clinical data from half of the patients are used to train the parameters of the deep learning model and data from the remaining are used to test the validity and generalization ability of the trained model.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki (2013 version), and was approved by the Joint Clinical Research Ethics Committee of the Chinese University of Hong Kong and Hospital Authority New Territories East Cluster. All information was anonymized with all potential patient identifiers removed upon return of database searches.

RESULTS

Baseline characteristics

From 2013 through 2017, 2249 unique cases with principal diagnosis of first episode of acute myocardial infarction were identified. Of these, 122 patients (5.4%) had incomplete laboratory data, and were therefore removed from subsequent analysis. A total of 2127 patients were finally included in this study. The mean age (standard deviation) was 71.08 ± 14.04 years. The majority was male (65.5%). Of note, the proportion of elders (≥65 years) was over-represented in the female group as compared to the male group (85.7& vs 57.2%, P<0.001). The highest NLR and peak

troponin T were detected at overlapping median time of 5.7h (interquartile range: 0-13.1) and 9.5h (IQR:3-24) from admission, respectively. With reference to the percentiles of NLR_t, the study population was stratified into four NLR_t quartiles. Comparing to the lower quartile group with NLR ≤2.92, the upper NLR_t quartile group (≥9.51) had higher level of C-reactive protein, peak troponin T, creatine kinase, and serum creatinine. The level of C-reactive protein (r=0.276, 95% $CI_{bootrstrap}$ 0.206-0.353, P<0.001), peak troponin T (r=0.123, 95% $CI_{bootrstrap}$ 0.080-0.172, P<0.001) and creatine phosphokinase (r=0.133, 95% $CI_{bootrstrap}$ 0.069-0.201, P<0.001) was correlated with NLR_t. Multi-morbidities, defined as the composite of 30-day mortality, 90-day mortality, and in-hospital death, were highly prevalent in the upper NLR_t quartile group (50.2%) as compared to the lower quartile group (35.6%), reaching statistical significance (OR=1.82, 95% CI 1.43-2.33, P<0.001). However, the use of anti-platelets, anticoagulants, and lipid regulating drugs was less common in the upper NLR_t quartile group (**Supplementary Table 2**). There were 18.1% missing data for mortality. Comorbidities in **Supplementary Table 2** is defined as the presence of one or more additional medical conditions that co-occur with the incident MI. Similarly, the medications listed in the table refers to the medications that patients are taking at the point of incident MI.

Association of NLR with clinical outcomes

The NLR at 6h of admission was significantly higher than that measured in 7h to 24h (mean difference=2.26, 95% CI 0.82-3.69, P<0.001). The ratio remained stable after 6h until discharge or death (P>0.62). The AMI population can be separated into patients with ST-elevated myocardial infarction (STEMI) (n=766) and non-STEMI (NSTEMI) (n=1361). The NLR_T in STEMI took a median value of 5.89 (IQR: 3.25-10.32) while median NLR_T for NSTEMI yielded a median value of 4.64 (IQR: 2.74-9.00). The Mann-Whitney U-test confirmed that there was a significant difference between the median NLRt (P<0.001). In univariate analysis, NLR_t≥ 9.51 was associated with in-hospital death (OR=3.46, 95% CI: 2.41-4.96), 30-day mortality (OR=2.75, 95% CI: 1.95-3.86) and 90-day mortality (OR=3.20, 95% CI: 2.32-4.40) (**Supplementary Table 3).** After adjusting for the other 3 items in the NPAC score, high NLR_t remained as an independent risk factor for in-hospital mortality (aOR=2.96, 95% CI 2.26-3.89), 30-

day mortality (aOR=2.43, 95% CI 1.86-3.17), and 90-day mortality (aOR=2.73, 95% CI 2.12-3.51) (**Figure 1**; **Supplementary Table 4**).

The NPAC score design

Stepwise forward logistic regression analysis based on Hosmer-Lemeshow test was performed (P>0.20). This allowed selection of the simplest best-fit model, the NPAC score comprising of binary parameters including high $\underline{N}LR_t$, peripheral vascular disease, age ≥ 65 years old, and median serum creatinine of the upper quartile **(Supplementary Table 4).** Kaplan-Meier analysis showed that patients with an NPAC score greater or equal to five had 37% increased risk for death in 90-days (Hazard ratio=1.373, 95% CI 1.099-1.715, P=0.005). In non-STEMI, the risk was higher (HR=1.506, 95% CI=1.15-1.97, P=0.003) (**Figure 2**). A weighted score was assigned based on exponential transformation of the respective beta coefficients in the multivariate logistic regression model. NPAC score was accurate in the survival classification of 90-day mortality in both STEMI (C-statistic: 0.758±0.023) and non-STEMI patients (0.747±0.016). The ability of our NPAC score to risk-stratify 90-day mortality was significantly better than that of Charlson's score in STEMI (0.651±0.028) and non-STEMI (0.623±0.021) cohorts.

External validation

The NPAC score was validated against a cohort of index episodes of AMI derived from an independent tertiary care center. The C-statistic of 0.715±0.015 confirmed the strong stratification power for 90-day mortality. Kaplan-Meier analysis confirmed a significantly higher mortality risk in 90 days amongst patients with NPAC score greater than five (HR=1.315, 95% CI 1.067-1.619, P=0.010). Distribution of NPAC score is depicted in **Supplementary Figure 1**.

The proposed deep learning model exhibited better performance due to its capability to capture the high-order interactions among the included variables. The details of the neural network architecture are depicted in **Figure 3**. The C-statistic is 0.808 for the derivation cohort and 0.742 for the validation cohort, indicating the good survival stratification ability of the identified NPAC parameters.

DISCUSSION

In this large cohort study, we developed and validated a rapid and easy-to-use risk stratification tool for acute myocardial infarction. The timing for percutaneous coronary intervention in non-STEMI population is important [17]. As such, we developed the four-variable NPAC scoring system for short-term mortality risk stratification in patients experiencing their first episode of AMI, regardless of ST-elevation. The NPAC scoring system consists of age, history of PVD, serum creatinine and NLR_T. When the NPAC score was applied across all outcome measures, the highest accuracy was found with 90-day mortality. Furthermore, the accuracy of the NPAC scoring system was found to be superior to the Charlson comorbidity index in risk-stratifying short-term mortality in both STEMIs and NSTEMIs. Subsequently when the NPAC score was used for external validation on more than 1,200 patients from another independent tertiary center. An important aspect of involving the Charlson index is to illustrate the 'law of diminishing returns' with regard to scoring systems. The Charlson comorbidity index is used to predict one-year mortality, which include 22 components. However, when additional significant parameters derived from the univariate analysis were added to the existing NPAC score, accuracy (AUC) was lowered. It was also noted that the use of corticosteroids is associated with increase in neutrophils in patients, which may skew the NLR results. This was proven when NLR means were found to be significantly different between the corticosteroid and non-steroid users. Regardless, omitting the corticosteroid users did not alter the statistical significance of NPAC score parameters on the 90-day mortality risk classification.

We further proposed a neural network-based risk stratification model since the progression of the prognosis of MI is based on the latent higher-order interactions among multiple risk factors, providing significant improvement in the survival classification power for mortality. These interactions are too complicated to be captured by traditional statistical models but are essential for characterizing and classifying disease progression. State-of-art machine learning techniques (e.g. neural network) are considered black-box models as their complex architecture of hidden layers obfuscate their internal decision processes. The neural network-based

framework, which has superior stratification power, moves quickly towards our life and can serve as a supplementary “gatekeeper” for clinical decision-making.

It should be noted that there are in fact many other well-validated risk scores, such as the TIMI [18] and GRACE scores [19], that have demonstrated usefulness in risk stratification. With the TIMI score, it was validated on a fairly complicated prognostication scheme specifically in patients with unstable angina and NSTEMI on non-specific endpoints including all-cause mortality, new or recurrent MIs. Calculation of the score usually involves the help of an online calculator, rendering it inconvenient within an acute clinical setting. On the other hand, the NPAC score covers both NSTEMIs and STEMIs and works on a simplified dichotomous approach for both the parameters and the resulting score as compared to the graded-score approach in TIMI. Similarly with the GRACE score, a nomogram-scoring algorithm will make risk stratification more difficult in the absence of an online scoring calculator. The NPAC score also addresses short-term (90-day) all-cause mortality while the GRACE score is more commonly used for 6 months to 3 years post-discharge mortality prediction. Other scoring systems such as the syntax score, which has been shown to predict long-term clinical outcomes using angiographic results, was found to be associated with 30-day mortality [20]. However, the syntax was not originally designed to assess short-term mortality and the inconvenience of angiography is needed. With an increased understanding that MIs are inflammatory processes mediated by activated neutrophils and secondary apoptosis of lymphocytes, it is essential for markers reflecting this phenomenon to be integrated into existing scoring systems.

The high discriminatory power of the NPAC scoring system can facilitate the identification of high-risk patients regardless of ST elevation. Being a composite biomarker that accounts for two interrelated, albeit different, arms of the immune system, it comes as no surprise that many studies have examined the relationship between NLR and adverse outcomes in myocardial infarction patients [21]. It has been shown that NLR, in comparison to other WBC markers such as absolute neutrophil or lymphocyte counts, have superior prognostic ability in predicting clinical outcomes in AMI patients [17].

Utilizing a large AMI population, this cohort study is the first to show that NLR following peak troponin T could risk-stratify short-term mortality along side other parameters. Patients with STEMIs were also observed to have a significantly higher median NLR_T in comparison to those with NSTEMIs. This lends support to previous studies that have used mean NLR during hospital stay to predict similar clinical outcomes in STEMI and NSTEMI separately [6, 8, 14]. Furthermore, females were found to be at a higher risk of death. This is probably attributable to their older mean age than the male group. The older age in women in relation to increased mortality risk was previously reported [22].

NLR_T was evaluated because of the ease of clinical applicability as troponins are also known to be positively associated with the inflammatory severity and myocardial damage, serving as the most appropriate reflection of maximum inflammation during an AMI [23]. $NLR_T > 50^{th}$ percentile (> 5.11) was found to be a more accurate risk-stratifier compared to general NLR_T (NLR_T of all values), which suggests improved reliability when the NLR_T score is higher. This is also in keeping with existing studies, which used NLR values between 3.3 and 7.4 as cutoffs. However, $NLR_T > 75^{th}$ percentile was found to be less accurate than $NLR_T > 50^{th}$ percentile. The accuracy of $NLR_T > 50^{th}$ percentile improved further when used in combination with the Charlson Comorbidity score ($NLR_T > 50^{th}$ percentile + Charlson score), achieving statistical significance across all clinical outcomes. However, given the complexitity of Charlson comorbidity index that might be counterintuitive in clinical practice. As such, there is a need to incorporate NLR_T and elements of the Charlson index into simpler scoring system for clinical convenience.

Despite these results, the difficulty remains in determining a standardized NLR cut off value that can be incorporated within clinical setting due to numerous non-disease related factors influencing NLR levels. First and foremost, there is evidence to support the existence of gender- and age-based differences in NLR in non-patient populations, wherein men [24] and the elderly [25] have both been found to have higher NLR values. Furthermore, other factors not limited to genetic factors, environmental factors, body mass index (BMI), and smoking have been found to be associated with increased NLR [24, 26-29]. NLR can also be transiently elevated by many physiological factors, particularly catecholamine release in

response to psychological or physical stresses [6, 30]. Overall, multiple factors have the potential to alter either positively or negatively influence the NLR in turn diminishing its true prognostic capability for assessing clinical outcomes in patients. As such, more research into the modification of the NLR index has to be conducted to correct for these potential confounders.

STRENGTHS AND LIMITATIONS

There are several strengths of this study. Firstly, this was the largest cohort study examining NLR. Secondly, this is the first scoring system derived from a real-world cohort that included NLR for risk stratification purposes in both STEMI and NSTEMI, which was externally validated using a separate cohort. Thirdly, the score is simple and can easily be calculated by busy clinicians to quickly identify high-risk individuals. Fourthly, the gate-keeping deep learning model provides more accurate survival stratification to reduce Type II error ("false negative") and facilitate clinical decision making. However, several limitations of our study should be noted. Firstly, this is limited by its retrospective nature and biases inherent in this type of studies remain. Secondly, data were obtained from an administrative database with some data not being captured by it, which is primarily responsible for the 18% missing mortality information. For example, genetic factors, smoking statuses, hematological disorders, AMI severity, cause of death and post-procedural parameters were not accessible [19]. Thirdly, both internal and external validations of the NPAC score were done within the context of a Hong Kong population. This suggests potential validation of this score in other countries and ethnic groups to extend its use beyond a local population. Furthermore, the added value of the NPAC score to other existing, well-established risk scores, such as the TIMI or GRACE scores, was not determined, as all of the constituent components of these scores could not be obtained. Finally, medications recorded on CDARS only reflected in-hospital medications and not medications prior to admission, which could have a impact on patient outcomes. Despite these limitations, our study is the first to include a large sample size while combining NLR with other clinical and laboratory parameters to yield a more robust NPAC scoring system for survival classification in short-term mortality.

CONCLUSIONS

The four-item NPAC score comprised of clinical and laboratory variables would provide an easy and rapid risk assessment tool for 90-day risk of mortality following acute myocardial infarction. This shall facilitate an early identification of high-risk population, in particular for non-STEMI patients, who warrants early arrangement of percutaneous interventions. Future prospective studies should be conducted to evaluate the utility of this scoring system to guide management.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Christien KH Li: Study conception, manuscript drafting, data-analysis and data collection

Jeffery Ho: data collection and data analysis

Zhongzhi Xu: Data-analysis, deep learning model and critical appraisal

Ishan Lakhani: Data collection and data analysis

Yingzhi Liu: Deep learning model and data collection

George Bazoukis: Critical appraisal and data analysis

Tong Liu: Critical appraisal and data collection

Wing Tak Wong: Critical appraisal and data collection

Shuk Han Cheng: Data collection

Matthew TV Chan: Critical appraisal

Lin Zhang: Minor critical appraisal and manuscript drafting

Tony Gin MD: Critical appraisal and data collection

Martin CS Wong: Methodology for scoring system development

Ian Wong: Methodology for scoring system development and minor editing

William KK Wu: Critical appraisal and minor editing

Qingpeng Zhang: data collection, critical appraisal, methodology development

Gary Tse: Study conception and manuscript editing

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Figure Legends

Figure 1. Receiver operating curve analysis of risk-stratifying accuracy of NPAC score for 90-day all-cause mortality following the first episode of acute myocardial infarction in (A) all patients, (B) ST-segment elevation, and (C) non-ST-segment elevation.

Figure 2. Kaplan Meier curves in (A) derivation cohort and (B) validation cohort.

Figure 3. The architecture of the adopted neural network.

Supplementary materials

Supplementary Table 1. ICD-9 codes used for case identification.

Supplementary Table 2. Baseline characteristics.

Supplementary Table 3. Univariate binary logistic regression for 90-day all-cause mortality.

Supplementary Table 4. Multivariate binary logistic regression for 90-day all-cause mortality and NPAC scoring system

Supplementary Figure 1. Distribution of NPAC score in (A) derivation and (B) validation cohort.

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