CHAPTER 1
INTRODUCTION

1.1. Background

Cardiovascular disease (CVD) is the leading cause of increased mortality globally, responsible for approximately 35% to over 50% of total deaths in Asia (WHO, 2020; Zhao, 2021; Ohira & Iso, 2013). Among the spectrum of CVD, acute coronary syndrome (ACS) represents the most severe form. Following an ACS episode, individuals encounter the risk of experiencing major adverse cardiovascular and cerebrovascular events (MACCE), including all-cause mortality, myocardial reinfarction, stroke, heart failure, and unplanned revascularization. The stratification of patient risk plays a pivotal role in guiding clinical decision-making and optimizing patient care and treatment (Huang, Dong & Duan, 2015; Wilson et al., 1998; Tikkanen et al., 2013).

Various parameters are utilized to predict adverse events following an episode of ACS, including serum biomarkers and risk scores. However, certain serum biomarkers are not routinely assessed in hospital setting due to the high expenses, particularly in low- and middle-income countries with limited resources. Moreover, the sensitivity and predictive performance of these parameters showed variability in different studies.

Several risk scores have been developed to stratify the risk in ACS patients, and are currently widely used worldwide, including the Global Registry of Acute Coronary Events (GRACE) score (Steg et al., 2002), Thrombolysis In Myocardial Infarction (TIMI) score (Morrow et al., 2000), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Supression Using InTegrilin (PURSUIT) score (Brilakis et al., 2003), and Can Rapid risk stratification of Unstable angina patients Supress ADverse outcomes with Early implementation of the American College of Cardiology/ American Heart Association guidelines (CRUSADE) score (Sánchez-Martínez et al., 2017). Nevertheless, it is important to note that most of these risk scores were developed in the Western world, involving predominantly Caucasian populations, and developed more than two decades ago, at a time when the era of primary percutaneous coronary intervention (PCI) had just begun (Van de Werf et al., 2008; O'Gara et al., 2013; Amsterdam et al., 2014; Roffi et al., 2016).

Additionally, there have been shifts in medical treatments for ACS, such as the use of dual antiplatelet therapy, ACEIs/ARBs, and β-blockers. These changes may render previous risk scores less applicable to today's ACS population. The majority of patients included in the TIMI and GRACE score were from Europe and the United States, with limited representation from Asia. Whether these risk scores remain suitable for the Asian population in the current era of widespread PCI adoption still requires evaluation.

Especially in Asia, a larger number of cardiac centers have been established throughout the countries. With the advent of advanced medical treatments and

trained operators, the utilization of PCI has become more widespread in this region (Fan et al., 2019), including in Indonesia. Consequently, it is imperative to update existing risk scores to reflect these evolving clinical settings specifically for Asia population. Secondly, ACS is characterized by its sudden onset, and the variables included in risk scores should be readily available for all ACS patients upon hospital admission. Thirdly, many risk scores are not commonly applied in clinical practice, most likely due to the considerable clinical workload and the intricate nature of these scoring systems. To enhance applicability, there is a need for a more concise and up-to-date risk score that is customized to the local population and aligns with contemporary clinical practices. This updated tool would serve as a valuable complement to the utilization of existing scoring systems, particularly within the Indonesian population.

Numerous studies have demonstrated that decreased renal function is an independent predictor of poor outcomes in patients with ACS. Notably, renal dysfunction can significantly impact cardiac function, leading to consequential implications for the trajectory and prognostic outcomes of ACS patients (Rangaswami et al., 2019; Ronco et al., 2010). Moreover, chronic kidney disease (CKD) is highly prevalent on a global scale and is associated with an elevated risk of unfavorable outcomes in patients hospitalized with ACS. The concurrent presence of these two conditions escalates the risk of mortality (Anon, 2020; Tonelli et al., 2006; Widimsky & Rychlik, 2010; Goldenberg, 2010; Marenzi, 2012). To date, no specific scoring system for ACS patients has been developed to focus on risk stratification based on whether patients have good or poor renal function upon hospital admission.

The main objective of this study was to develop a predictive model and validate a nomogram designed to forecast the incidence of in-hospital mortality and composite MACCE in ACS patients, considering the presence or absence of renal impairment. This was achieved using the latest and locally sourced data obtained from the Indonesian ACS registry.

1.2. Research Questions

In the present study, we posses several research questions:

1. What factors significantly predict in-hospital mortality and composite MACCE (i.e. all-cause mortality, shock, stroke, heart failure, and bleeding) in ACS patients and are included in the prediction model?
2. Does renal function affect the prediction model?
3. What machine learning (ML) method (i.e. Logistic Regression, Naïve Bayes, Gradient Boosting, or random forest) is most effective in predicting in-hospital mortality and MACCE in ACS patients within a South-East Asian setting?
4. How does the validation of this risk score (nomogram) compare with the developed GRACE and TIMI scores in predicting in-hospital mortality and composite MACCE in ACS patients?

The occurrence relation of this research is as follows:

Validated nomogram = f (Demographic characteristics, clinical profile, coronary risk factors, diagnosis, supporting examinations, in-hospital treatment | confounders)

1.3. Objectives

In this research, we aimed:

1. to investigate and identify factors that significantly predict in-hospital mortality and composite MACCE in patients with ACS, and incorporate these factors into a comprehensive prediction model.
2. to assess the impact of renal function on the established prediction model for in-hospital mortality and composite MACCE in patients with ACS.
3. to determine the most effective ML method in predicting in-hospital mortality and MACCE in ACS patients within a South-East Asian setting.
4. to evaluate and compare the performance of the developed nomogram) with the existing GRACE and TIMI scores in predicting in-hospital mortality and composite MACCE among patients with ACS.

CHAPTER 2
RESEARCH METHODS

2.1. Study Population

The cohort was derived from the ACS Registry at the Makassar Cardiac Center, Dr. Wahidin Sudirohusodo Hospital from April 2018 to October 2022. ACS was defined as follows: (1) ST-segment elevation myocardial infarction (STEMI) in patients presenting with acute chest pain and persistent (>20 min) ST-segment elevation; (2) non-ST-segment elevation ACS (NSTE-ACS) in patients with acute chest discomfort but lacking persistent ST-segment elevation, exhibiting ECG changes that may encompass transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo-normalization of T waves; or the ECG may appear normal (Collet et al., 2021; Ibanez et al., 2018; Byrne et al., 2023).

Our cohort was divided into two datasets: 75% constituted the training cohort used for model development, while the remaining 25% served as the validation cohort to assess the performance of the best-fitted model within the population.

2.2. Inclusion and Exclusion Criteria

Patients meeting the following criteria were considered eligible for inclusion in the study: (1) age ≥ 18 years at presentation; (2) admission to the hospital with diagnosis of ACS (i.e. STEMI, NSTEMI, or unstable angina), and (3) the absence of serious concurrent illnesses such as trauma or gastrointestinal bleeding. All eligible patients are required to sign written informed consent.

However, we will exclude all fatal patients who immediately died at the Emergency Department before undergoing a complete examination, blood tests, and providing informed consent. To reduce patient selection bias, no other specific exclusion criteria were set, and we encouraged to enroll consecutive patients. The designated physician or study coordinator recorded demographic and clinical data, as well as details of in-hospital treatment.

2.3. Data Collection

Baseline characteristics, including age, gender, body mass index (BMI), clinical profiles at admission, medical history, diagnoses, physical examination, echocardiography, ECG, and treatment, were obtained from the Makassar ACS registry. For our initial dataset, missing values were filled by querying the hospital's electronic medical records, and variables with more than 25% missing values were excluded. We assumed that the remaining missing data were missing at random and employed multiple imputation techniques to address these missing values.

We calculated the admission GRACE and TIMI scores using a total of 33 parameters, with the conceptual framework illustrated in **Figure 1**. All parameters were collected within 24 hours of patient admission. The primary outcomes of the study were in-hospital mortality and composite MACCE, defined as any of the following events during hospitalization: all-cause mortality, shock, stroke, heart failure, or bleeding. The theoretical design and rationale for applying this research to ACS patients with and without renal impairment are depicted in **Figure 2**.

2.4. Conceptual Framework

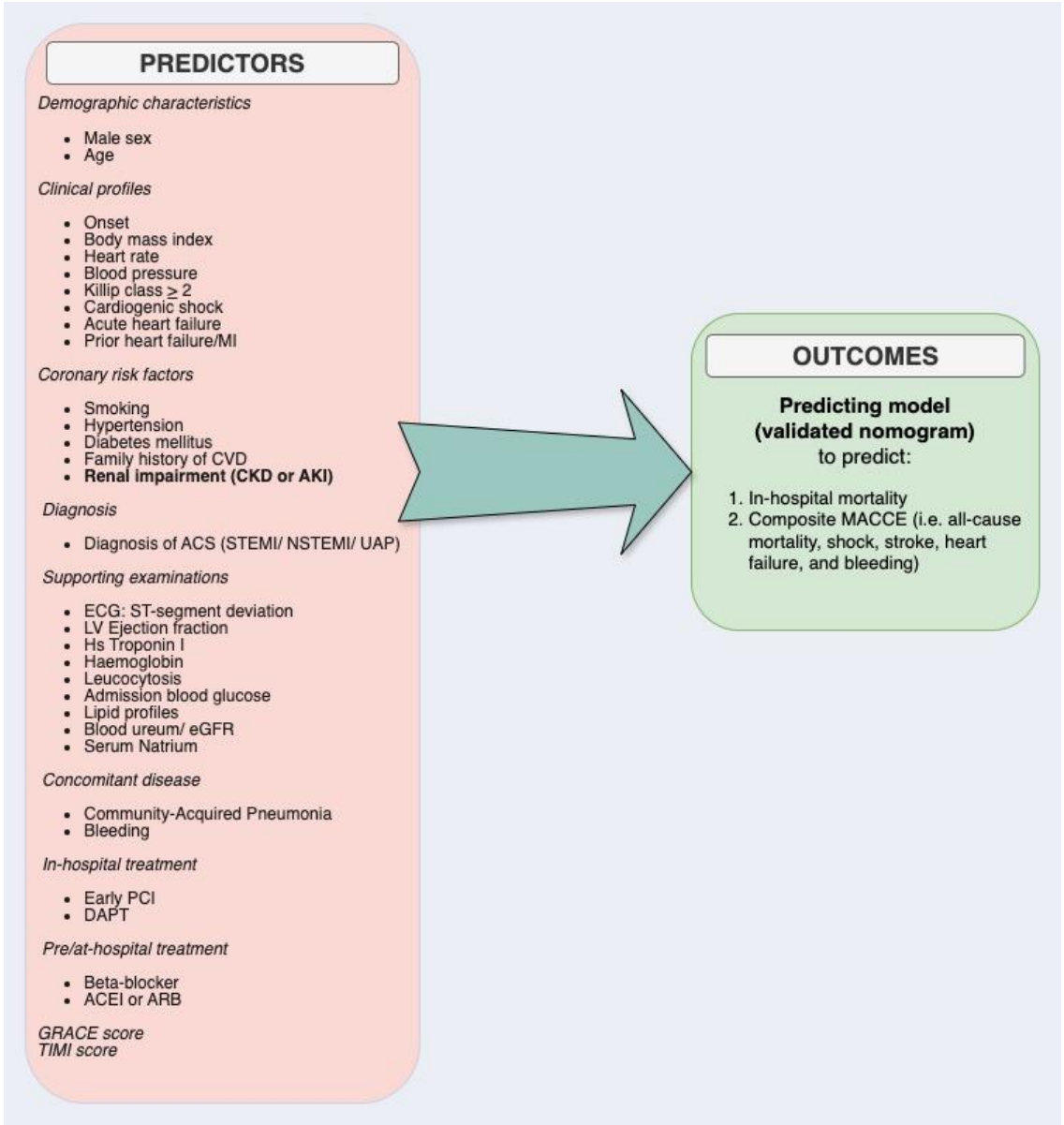

Figure 1. Conceptual framework in the development of a predicting model

2.5. Theoretical design

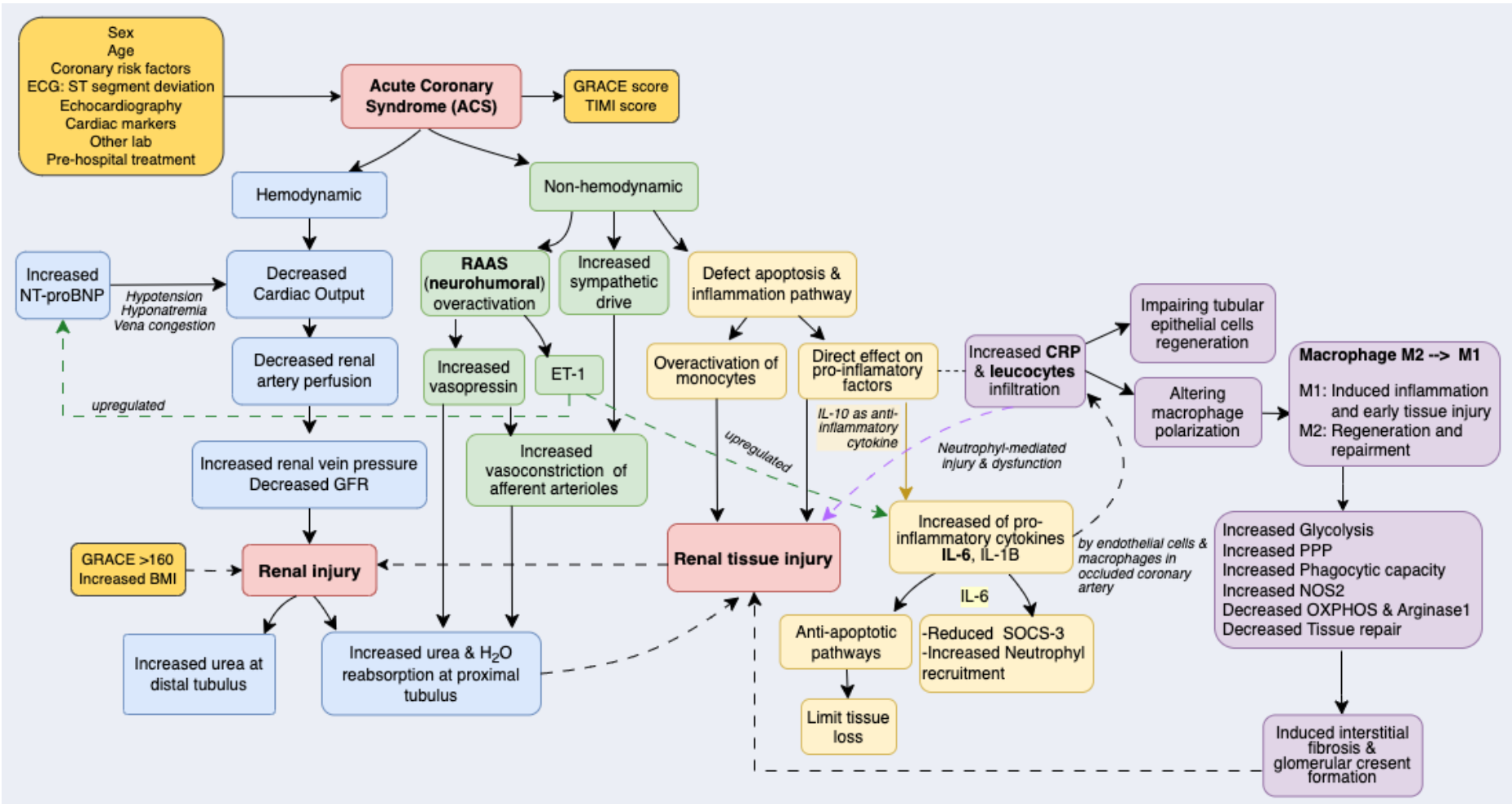

Figure 2. Pathomechanism involved in the cardio-renal crosstalk (*source: original figure*)

2.6. Statistical Analysis

Continuous variables were presented as mean ± standard deviation, while categorical variables were described using numbers and percentages. To compare differences between two groups for continuous variables, we employed the Independent t-test. For categorical variables, we used Pearson's Chi-square test or Fisher's Exact test, as appropriate.

Using a Bernoulli distribution, we randomly grouped the participants into two cohorts: the training cohort (n=1410, 74.6%) and the validation cohort (n=480, 25.4%). The events/outcomes between the two groups were statistically comparable, with in-hospital death rates of 7.8% versus 6.5% (p=0.333) and composite MACCE rates of 34.6% versus 32.3% (p=0.354).

For the development of the nomogram, we initiated the process with a combination of univariate analysis and an comprehensive literature review of existing ACS risk models to identify significant risk factors associated with in-hospital mortality and the occurrence of MACCE. This effort aimed to identify candidate predictors for our model. We included a total of 30 candidate predictors in the construction of our prediction model. We selected the significant independent variables, calculated their corresponding regression coefficients, and thereby established an optimal logistic model.

The model encompassed a comprehensive set of variables, including patient demographic, medical history, clinical profiles, echocardiography and electrocardiography findings, serum biomarker, pharmacological treatment, and angiographic parameters. The final model, designed to predict in-hospital mortality and composite MACCE in ACS patients, was presented as a nomogram for ease of use. This risk model was subsequently tested on a validation cohort. Model performance was assessed using key metrics, including the area under the receiver operating characteristic curve (AU-ROC) and decision curve analysis. All statistical tests were two-sided, and a significance level of $p<0.05$ was considered significant. The statistical analyses were conducted using SPSS version 28 for Mac (IBM, USA), R software version 3, and Orange Data Mining version 1.35 for Windows.

2.7. Development and comparison of machine learning algorithms to predict in-hospital mortality and MACCE

2.7.1 Machine learning algorithms

Machine learning algorithms can significantly enhance the prediction of CVD events by analyzing large, complex datasets and identifying patterns that traditional statistical methods might overlook. We implemented several ML algorithms namely logistic regression, naive bayes, gradient boosting, and random forest to predict in-hospital mortality and in-hospital MACCE. In this study we use ***Orange Datamining software*** **(v.3.37)** an open-source Python-based data mining application with a graphical user interface

(Demšar et al., 2013). It allows people with no knowledge of programming to apply Machine Learning as well as advanced data processing, analysis, and visualization using a point-and-click, drag-and-drop interface.

The general workflow for developing machine learning models used in this study is shown in **Figure 5** below.

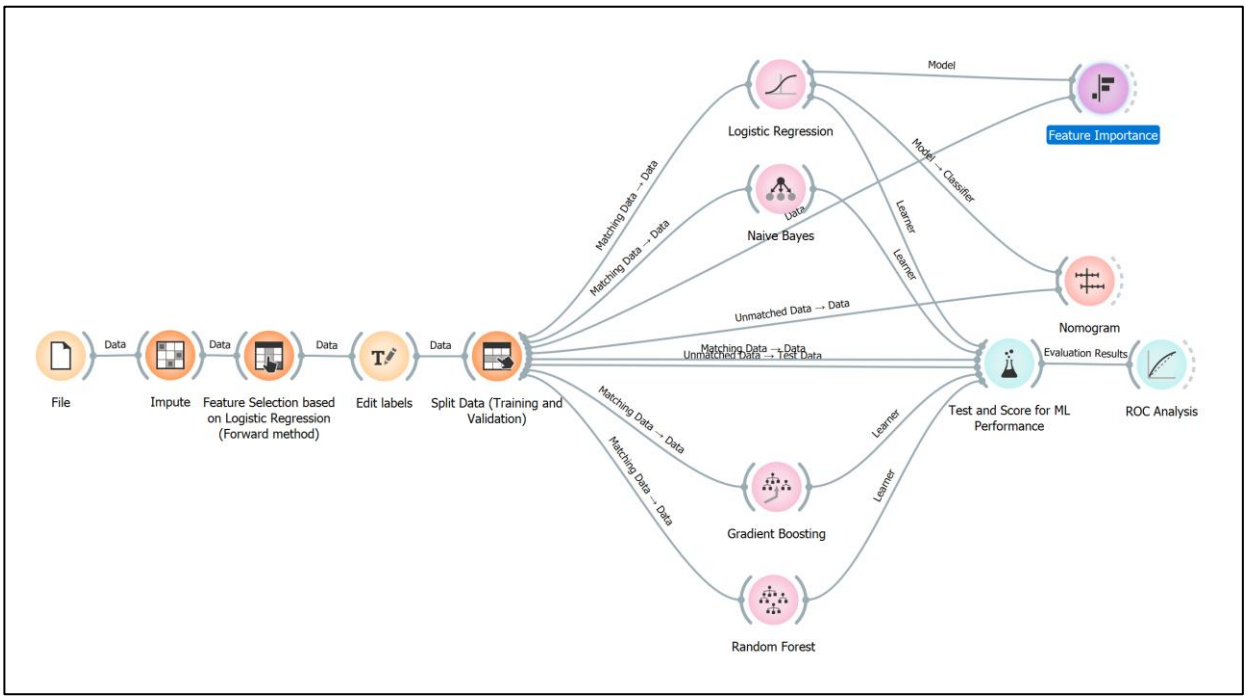

Figure 3. Orange3 workflow for developing and testing the performance of machine learning algorithm in predicting in-hospital mortality and MACCE

1. Logistic regression (LR)

One of machine learning method for developing an algorithm is LR, The LR is one of supervised learning methods which creates a mathematical model that uses probability to predict and classify each category in the binary outcome variables based on the selected predictors. In simple definition, LR can predict the likelihood of occurrence of specific outcome.

2. Naïve Bayes (NB)

Naive Bayes is a probabilistic machine learning algorithm for classification task based on “Bayes Theorem”. It assumes that the features in a dataset are conditionally independent given the class label, an assumption which often does not hold in real-world scenarios but still allows for efficient and effective classification. The algorithm calculates the posterior probability of each class given the input features and assigns the class with the highest probability to the each of row in the dataset or instance.

3. Gradient boosting (GBoost)

The GBoost, is a type of supervised machine learning, relies on decision trees for making predictions. It combines multiple weak models, like decision trees, into a single, stronger model. GBoost optimizes an objective function, such as the value of log loss for classification, by evaluating the gradient at each point. This algorithm iteratively improves the model by adding new trees until the final model meets predefined criteria, enhancing its performance and accuracy.

4. Random forests (RF)

RF is supervised learning method used commonly for classification. It operates by constructing a multitude of decision trees during training and outputting the mode of the classes (classification) of the individual trees. This technique improves predictive accuracy and controls overfitting by averaging multiple decision trees, each trained on different random subsets of the data and features. RF is robust to noise and capable of handling large datasets with high dimensionality, making it a versatile and powerful tool in machine learning for various applications, including feature selection, outlier detection, and handling missing data (Demšar et al., 2013).

2.7.2. Imputation

We observed missing data ranging from 1 - 10% on several predictors, we applied data imputation to these missing values based on information from the other variables, a separate model is constructed for imputing missing value on each predictor. We used a 1-NN learner for imputing a missing value in each of the features, which takes the value from the most similar patterns derived from a model. 1-NN learner is capable of handling missing values for both numeric and categoric predictors.

2.8. Nomogram development

A nomogram is a visual tool that allows clinicians to estimate the probability of a specific outcome based on multiple predictor variables. Developing nomograms is crucial for visualizing machine learning models and enhancing our understanding of predictor variables. Nomograms provide a visual representation of the model's output, allowing researchers and clinicians to intuitively interpret the impact of different factors on the predicted outcome (Li et al., 2021). By visualizing the contribution of each predictor, nomograms facilitate the identification of key drivers, aiding in clinical decision-making and risk stratification (Balachandran et al., 2015). Additionally, nomograms offer a user-friendly tool for communicating complex model results to non-technical audiences, promoting knowledge dissemination and fostering communication between clinician and patients. On this study we build two nomograms for each outcome, i.e. in-hospital death and in-hospital MACCE.

2.9. Research Ethics

The research protocol was approved by the Institutional Review Board of the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia, as indicated by reference letter No. 514/UN4.6.4.5.31/PP36/2022 (supplement). All patients or their legally authorized representatives provided written informed consent. All procedures conducted in this study involving human participants adhered to the principles outlined in the Declaration of Helsinki and local regulation.

2.10. Study Flowchart

Flowchart of the present study is described in **Figure 4.**

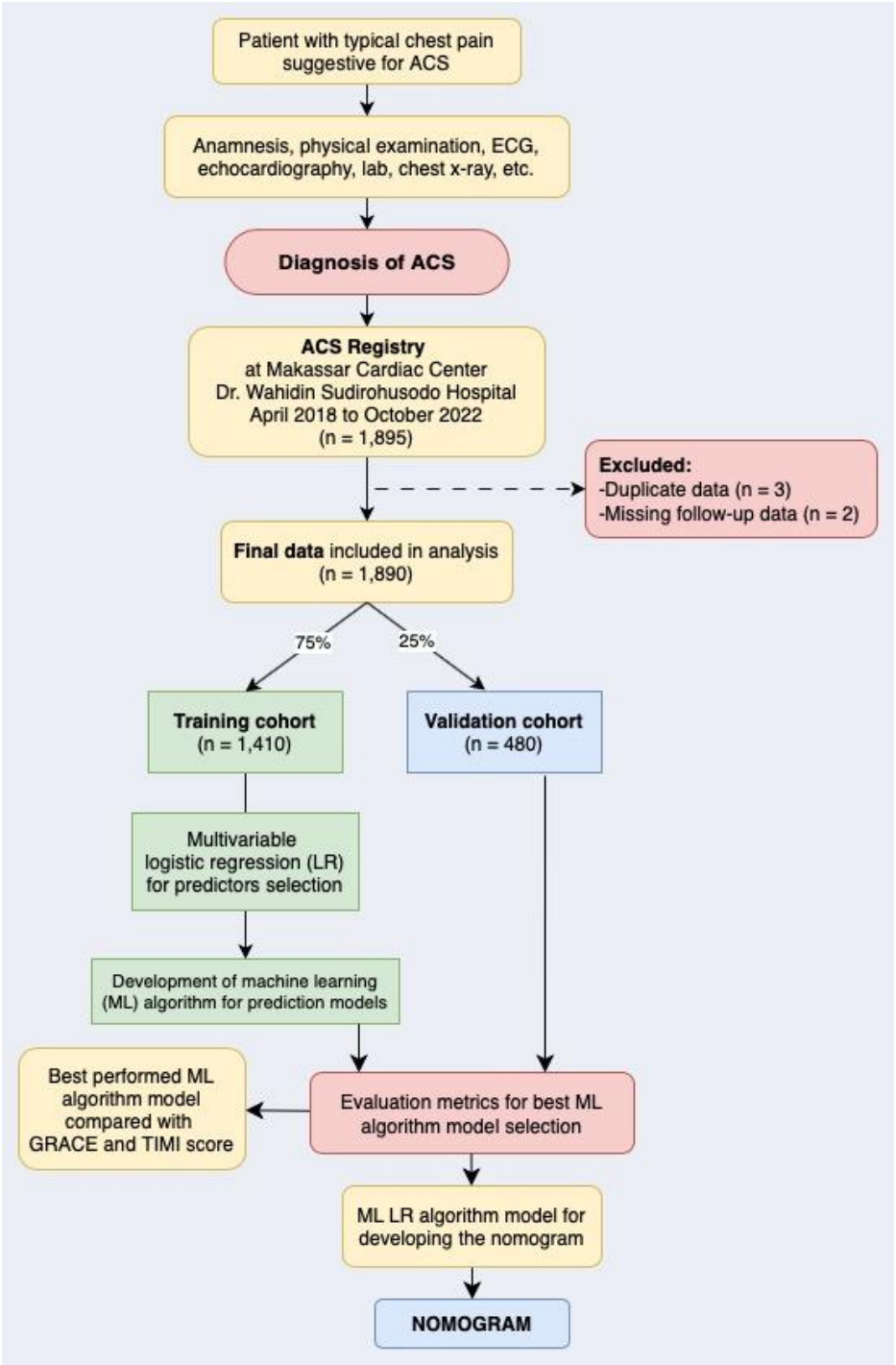

Figure 4. The study flowchart, from data collection to nomogram development

2.11. Operational Definitions and Objective Criteria

Table 2.1. Definitions and cut-offs of included variables

Variables	Operational definitions	Scale	Measurement	Tools	Objective Criteria or SPSS coding
Obese	Obesity is a chronic, progressive disease of caloric energy storage that manifests as excess visceral or subcutaneous lipid deposition. Obesity is defined as a body mass index (BMI) value of 30.0 kg/m2 (kg per m2 of body surface) or higher in Western countries or **25.0 kg/m2 or higher in Asian** body types (Mathis, Tanaka & Hiramatsu, 2022).	Binary	Body mass index (BMI)	Medical record	Obese: if **BMI $\geq$ 25 kg/m^2** Obese: Yes = 1 No = 0
Killip Class	The Killip classification is a system used in individuals with an acute myocardial infarction, taking into account physical examination and the **development of heart failure** in order to predict and stratify the risk of mortality (de Mello et al., 2014; DeGeare et al., 2001).	Ordinal	• Killip-Kimbal Class • Physical examination: elevated JVP, auscultation of S3, rhonci, peripheral or lung oedema	Medical record	4. **Killip I**: no clinical signs of heart failure, 5. **Killip II**: with rales in the lungs, third heart sound (S3), and elevated jugular venous pressure, 6. **KillipIII**: with acute lung oedema(ALO),and 7. **Killip IV**: with cardiogenic shock or arterial hypotension (measured as SBP < 90 mmHg), and evidence of peripheral vasoconstriction (oliguria, cyanosis, and diaphoresis) (de Mello et al., 2014; DeGeare et al., 2001).

Cardioge-nic shock	Patient was categorized as cardiogenic shock (CS) if diagnosis of CS was stated in medical record. Cardiogenic shock is caused by severe impairment of myocardial performance that results in diminished cardiac output, end-organ hypoperfusion, and hypoxia. Clinically this presents as hypotension refractory to volume resuscitation with features of end-organ hypoperfusion requiring pharmacological or mechanical intervention (Vahdatpour, Collins & Goldberg, 2019).	Binary	• Systolic BP • MAP • Mental status • Urine output • Hemodynamic (cardiac index and PCWP) • Cold extremities • Diaphoresis • Serum lactate • Serum creatinin • Blood gas analysis	Medical record	**SHOCK Trial (1999)** (Vahdatpour, Collins & Goldberg, 2019): • SBP <90 mm Hg for >30 min or vasopressor support to maintain SBP >90 mm Hg • Evidence of end-organ damage (UO <30 mL/h or cool extremities) • Hemodynamic criteria: CI <2.2 and PCWP >15 mm Hg **IABP-SOAP II (2012)** (Vahdatpour, Collins & Goldberg, 2019): • MAP <70 mm Hg or SBP <100 mm Hg despite adequate fluid resuscitation (at least 1 L of crystalloids or 500 mL of colloids). • Evidence of end-organ damage (AMS, mottled skin, UO <0.5 mL/kg for 1 h, or serum lactate >2 mmol/L) **ESC-HF Guidelines (2016)** (Vahdatpour, Collins & Goldberg, 2019): • SBP <90 mm Hg with appropriate fluid resuscitation with clinical and laboratory evidence of end-organ damage • Clinical: cold extremities, oliguria, AMS, narrow pulse pressure. Laboratory: metabolic acidosis,

					elevated serum lactate, elevated serum creatinine Cardiogenic shock: Yes = 1 No = 0
Acute heart failure (AHF)	Heart failure is a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated JVP, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise (McDonagh et al., 2021). AHF refers to rapid or gradual onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical atten tion, leading to an unplanned hospital admission or an emergency department visit (McDonagh et al., 2021).	Nominal	• Sign and symptom of HF • ECG • Pulse oxymetry • Echocardiography • Initial laboratory (i.e. troponin, serum creatinine, electrolytes, BUN or urea, TSH, liver function tests, D-dimer, and procalcitonin when pulmonary embolism or infection are suspected, arterial blood gas analysis in case of respiratory distress, and lactate in case of hypoperfusion) • Chest x-ray • Lung ultrasound • Other specific evaluations	Medical record	Four major clinical presentations of AHF can be described with possible overlaps between them. Patient was categorized as having AHF if one of the following diagnosis was stated in medical record (McDonagh et al., 2021): 4. Acute Decompensated Heart Failure 5. Acute Lung Oedema 6. Isolated Right Ventricle Failure, and 7. Cardiogenic Shock.

Diabetes Mellitus (type 2 DM)	Patient was categorized as having type 2 DM if diagnosis of DM was stated in medical record.	Binary	• HbA1c • Fasting plasma glucose (FPG) • Oral glucose tolerance test (OGTT) • Random plasma glucose (RPG)	Medical record	Diagnosis of type 2 DM is made by (Richardson et al., 2020): 1. an A1c ≥6.5%, 2. a fasting glucose ≥126 mg/dL, 3. a 2h post 75 gm glucose load glucose of ≥200 mg/dL, or 4. a random glucose ≥200 mg/dL with symptoms, confirmed by a repeat or second test. Type 2 DM: Yes = 1 No = 0
Current smoker	An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes (Centers for Disease Control and Prevention, 2017).	Binary	Questionnaire	Interview	Current smoker: Yes = 1 No = 0
Hyperten-sion	In health care settings that include the physician's office, hyper- tension is diagnosed when BP is 140/90 mmHg or greater, ideally using an electronic device and following standard protocols for measurement, including repeat measurements (Buelt, Richards & Jones, 2021).	Binary	Blood pressure	Using electronic sphygmomanometer	Patient was categorized as having hypertension if diagnosis of hypertension was stated in medical record. Hypertension if: blood pressure ≥ 140/90 mmHg Hypertension: Yes = 1 No = 0

STEMI	Patient was categorized as STEMI if diagnosis of STEMI was stated in medical record.	Binary	ECG	Medical record	Based on ESC 2017 and AHA/ACC 2013 guidelines, STEMI is defined as (Ibanez et al., 2018; Anderson, 2013): ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: **at least two contiguous leads** with ST-segment elevation ≥ 2.5 mm in men < 40 years, ≥ 2 mm in men ≥40 years, or ≥ 1.5 mm in women in leads V2–V3 and/or ≥ 1mm in the other leads (in the absence of LVH or left bundle branch block LBBB).
NSTE-ACS	Patient was categorized NSTE-ACS if diagnosis of NSTEMI or unstable angina was stated in medical record.	Nominal	• Sign and symptoms • ECG • Hs Troponin I	Medical record	Non-ST-segment elevation ACS (NSTE-ACS) in patients with acute chest discomfort but lacking persistent ST-segment elevation, exhibiting ECG changes that may encompass transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo-normalization of T waves; or the ECG may appear normal (Collet et al., 2021).

					The pathological correlate at the myocardial level is cardiomyocyte necrosis (NSTEMI) or, less frequently, myocardial ischaemia without cell damage (unstable angina) (Collet et al., 2021).
Early Invasive strategy	Patient was categorized to have an early invasive strategy if stated in medical record. Early coronary angiography (<24 h from diagnosis of ACS) and PCI/CABG of the infarct-related artery if indicated (Byrne et al., 2023).	Binary	N/A	Medical record	Early invasive strategy: Yes = 1 No = 0
GRACE score	The 'Global Registry of Acute Coronary Events' (GRACE) as a clinical risk prediction tool for estimating the cumulative 6-month risk of death or myocardial infarction (Timóteo et al., 2014). High-risk NSTE-ACS patients (e.g. ruled in as NSTEMI as per the 0 h/1 h or 0 h/2 h ESC algorithms, with dynamic ST-segment or T wave changes, with transient ST-segment elevation, or with a **GRACE risk score >140**) should be considered for an early invasive strategy (i.e. undergoing angiography within 24 h).	Conti-nous	The variables including: 1. Creatinine level, 2. Heart rate, 3. Systolic BP, 4. Killip class, 5. Age, 6. Cardiac arrest at admission, 7. ST-segment deviation, and 8. Elevated cardiac enzyme level.	Physical examination, medical record.	Interpretation (Tscherny et al., 2020): **Total GRACE Score (1 to 372 points)** Predicts in hospital and 6-month risk of death or MI **Non-ST Elevation Acute Coronary Syndrome** **Mortality in hospital** Score <109: Low risk - Mortality <1% Score 109-140: Intermediate risk - Mortality 1-3% Score >140: High risk - Mortality >3% **Mortality at 6 months** Score <89: Low risk - Mortality <3% Score 89-118: Intermediate risk - Mortality 3-8%

					Score >118: High risk - Mortality >8% **ST-Elevation Acute Coronary Syndrome** **Mortality in hospital** Score <126: Low risk - Mortality <2% Score 126-154: Intermediate risk - Mortality 2-5% Score >154: High risk - Mortality >5% **Mortality at 6 months** Score <100: Low risk - Mortality <4.5% Score 100-127: Intermediate risk - Mortality 4.5-11% Score >127: High risk - Mortality >11%
TIMI score	• The TIMI risk score for UA/NSTEMI predicted the risk of a combined end-point of death, MI or urgent revascularization within two weeks after presentation. • The TIMI risk score for STEMI predicted the risk of 30-day mortality.	Conti-nous	**TIMI for STEMI** (Morrow et al., 2000): 1. Age ≥ 75 2. DM/HT or angina 3. Systolic BP <100 4. HR >100 5. Killip II-IV 6. Weight <67 kg 7. Anterior ST-Elevation or LBBB 8. Time to treatment >4 hours **TIMI for NSTE-ACS** (Antman et al., 2000): 1. Age ≥ 65	Physical examination, medical record	**TIMI for STEMI** (Morrow et al., 2000): Risk score total: 0-14 **Risk for 30-day mortality** Score 0: 0.8% Score 1: 1.6% Score 2: 2.2% Score 3: 4.4% Score 4: 7.3% Score 5: 12% Score 6: 16% Score 7: 23% Score 8: 27% Score >8: 36%

			2. ≥ 3 CAD risk factors (HT, DM, dyslipidemia, family history of CAD, smoking) 3. Known CAD 4. ASA use in past 7 days 5. Severe angina (≥ 2 episodes in 24 hours) 6. ECG: ST changes ≥0.5 mm 7. Positive cardiac marker		**TIMI for NSTE-ACS** (Antman et al., 2000): Risk score total: 0-7 Score 0-2 : low risk Score 3-5 : intermediate risk Score 6-7: high risk