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Validation and Implementation of Topological Data Analysis and Machine Learning Techniques in Predicting Atrial Fibrillation Outcomes in Critically Ill Patients: The AFICILL Studies

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1. ABSTRACT

Non-valvular atrial fibrillation (NVAF) is the most common sustained arrhythmia observed in critically ill patients, linked to a higher risk of embolic and haemorrhagic events. Conventional tools, such as $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores, are ineffective for risk stratification and do not offer guidance for anticoagulation strategies in this population. Recently, we engineered new machine-learning (ML) models retrospective cohorts, with promising results; in this work, we aim to validate our ML models in a larger cohort.

We performed a retrospective analysis of all consecutive critically ill patients admitted to our step-down unit over a 10-year period who had a history of NVAF. We calculated classical risk scores and trained our ML models on pre-specified outcomes: the main outcome (MO) which was a composite of in-hospital death or intensive care unit (ICU) transfer, stroke/TIA, and major bleeding (MB) during the admission.

After eliminating trauma and non-critical patients, we obtained 2105 subjects, with 314 MO, 134 cardioembolic stroke/TIA and 227 MB. Classical risk scores (APACHE-II for MO, $CHADS_2$ and CHA_2DS_2-VASc for stroke/TIA, HAS-BLED for MB) performed poorly, while ML confirmed its accuracy in predicting outcomes also in this extended cohort (AUC APACHE-II:0.6397; 95%CI:0.6064-0.6729; AUC MO-ML:0.96; 95%CI:94.6-97.2; $p<0.0001$; AUC $CHADS_2$:0.5775; 95%CI:0.5332-0.6218; $p<0.0001$; AUC CHA_2DS_2-VASc:0.5793; 95%CI:0.5357-0.6228; AUC stroke/TIA-ML:0.95; 95%CI:94.3- 96.6; $p<0.0001$; AUC HAS-BLED:0.5089 95%CI:0.4786-0.5392; AUC MB-ML:0.973 95%CI 95.5–98.1; $p<0.0001$).

ML models can be considered as potential candidates in this setting to guide anticoagulant therapy. Multicenter, prospective cohorts will be necessary to establish their applicability in clinical practice.

2. INTRODUCTION

2.1 Atrial fibrillation: a general overview

2.1.1 Definition

The 2020 European Society of Cardiology (ESC) guidelines define atrial fibrillation (AF) as "a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction" with these electrocardiographic characteristics: "Irregularly irregular R-R intervals (when atrioventricular conduction is not impaired), absence of distinct repeating P waves, and irregular atrial activations" (Hindricks et al., 2021). This definition did not change during the time, and several authors and guidelines adopt this definition.

2.1.2 Classification

AF is classified as:

- ***Valvular AF (VAF)***: Atrial fibrillation occurring in the presence of moderate-to-severe mitral stenosis, moderate-to-severe mitral insufficiency or mechanical prosthetic heart valves, especially in mitral position (Hindricks et al., 2021).
- ***Non-valvular AF (NVAF)****:* Common, supraventricular arrhytmia, particularly relevant in outpatients for its increased stroke risk, but clinically important especially in a critical-care setting; this category may be further subdivided as follows:
  - ***New-onset (first-detected or recently diagnosed) NVAF***:
    Defined as the first documented episode of AF (irrespective of its duration or symptoms) (Camm et al., 2010). It may consist of brief, transient episodes difficult to detect in real time and without prior history or clear precipitating substrate. Management in acute settings is often more straightforward, as prompt cardioversion and correction of reversible triggers. Because these

episodes can be brief and under-recognized, conducting research on them is challenging; prospective studies including continuous rhythm monitoring or detailed arrhythmia registry analysis would be ideal.

- ***Pre-existing NVAF***:

  This group, often associated with more complex hemostatic and long-term management issues, can be sub-classified by the temporal pattern of AF:

  - ***Paroxysmal AF*****:** episodes that terminate spontaneously (or with intervention) within 7 days of onset (most often within 48 hours).
  - ***Persistent AF*****:** episodes that last > 7 days or require pharmacological or electrical cardioversion to restore sinus rhythm.
  - ***Long-standing persistent AF*****:** continuous AF lasting ≥ 12 months, when rhythm-control remains a therapeutic option.
  - ***Permanent AF:*** AF that is accepted as the long-term rhythm by patient and physician, with no further attempts to restore or maintain sinus rhythm planned (Camm et al., 2010).

2.1.3 Epidemiology

Globally, AF represents the most common sustained cardiac arrhythmia in adults, with an estimated 46.3 million individuals affected in 2016. Its prevalence is estimated to range between 2% and 4%, and a 2.3-fold increase is anticipated in the coming years, driven by population ageing, improved survival among patients with chronic diseases, and a growing number of diagnoses. In Europe, the lifetime risk of developing the most common type, the NVAF, at 55 years of age, is approximately 37%, corresponding to nearly one in three individuals. (Benjamin et al., 2019; Chugh et al., 2014).

2.1.4 Risk factors

Identifying individuals at elevated risk through structured screening programmes would allow earlier diagnosis and timely initiation of appropriate management.

Several predictive tools have been developed to estimate the risk of NVAF; however, none has yet been incorporated into routine clinical practice. The 2020 ESC guidelines describe a number of these models, including the FHS (Framingham Heart Study) score, which estimates the 10-year risk of NVAF onset, and the CHARGE-AF score, which provides a 5-year risk prediction. (Alonso et al., 2013; Schnabel et al., 2009).

These models incorporate recurrent variables that represent the major risk factors for AF, including age, body weight or body mass index, elevated blood pressure or ongoing antihypertensive therapy, and the presence of heart failure. The risk of developing NVAF increases with age and is influenced by genetic, clinical, and subclinical determinants. Overall, risk factors can be categorised as modifiable, partially modifiable, or non-modifiable.

- ***Modifiable risk factors:***
    - Lifestyle-related determinants, including smoking and alcohol consumption, noting that abstinence from alcohol has been shown to reduce arrhythmia recurrence. Coffee intake appears unlikely to contribute meaningfully to the onset of NVAF (Benjamin et al., 2019). Obesity also confers a progressively higher risk of NVAF with increasing body mass index (BMI), whereas weight reduction is associated with improvements in blood pressure, lipid profile, and the risk of developing type II diabetes mellitus all recognised risk factors for NVAF. Physical activity patterns, as high-intensity or endurance exercise (e.g., marathon running) is associated with an increased incidence and recurrence of AF. Conversely, moderate-intensity exercise should be encouraged to reduce overall cardiovascular risk. Notably, athletes exhibit a fivefold higher likelihood of developing NVAF compared with sedentary individuals, despite a lower prevalence of traditional cardiovascular risk factors (Giacomantonio et al., 2013).
    - Arterial hypertension, particularly systolic blood pressure (SBP) ≥160 mmHg or diastolic blood pressure (DBP) ≥95–100 mmHg, is a major determinant of NVAF risk, with a graded increase in risk for every 10–22 mmHg rise in SBP and every 10–11 mmHg rise in DBP (Benjamin et al., 2019) (Allan et al., 2017). Blood pressure is regarded as the most important aetiological and precipitating factor, and NVAF may be considered a clinical manifestation of

hypertension-mediated organ damage. Individuals with hypertension have approximately a 1.7-fold higher risk of developing NVAF; those with long-standing hypertension or inadequately controlled systolic blood pressure levels should be categorised as high-risk. Current evidence supports a target blood pressure of ≤ 130/80 mmHg to reduce adverse cardiovascular outcomes.

  - Elevated lipid level, specifically total cholesterol concentrations of ≥ 220–280 mg/dL (5.7–7.2 mmol/L), or for each incremental rise of 10–50 mg/dL (0.2–1.3 mmol/L); LDL-cholesterol levels ≥ 150 mg/dL, or for each 10–40 mg/dL (0.2–1.0 mmol/L) increase, and hypertriglyceridaemia are recognised contributors to NVAF risk (Benjamin et al., 2019).
  - Diabetes mellitus and pre-diabetes similarly confer a substantial increase in risk. The prevalence of NVAF in patients with diabetes mellitus is approximately twice that observed in non-diabetic individuals, and AF incidence rises in parallel with diabetes-related end-organ damage, including retinopathy and nephropathy. Treatment with metformin or pioglitazone may play a protective role by reducing the likelihood of NVAF onset (Aune et al., 2018).
- ***Non-modifiable or partially modifiable risk factors*** (Allan et al., 2017) (Aune et al., 2018):
  - Demographic variables, such as advanced age, male sex, caucasian ethnicity, and lower socioeconomic status.
  - Renal dysfunction and chronic kidney disease: present in 40–50% of patients with NVAF.
  - Height ≥ 173 cm or with each incremental increase of 1–10 cm.
  - Obstructive sleep apnoea syndrome (OSAS): approximately 50% of patients with NVAF have OSAS, compared to 32% of controls. Mechanisms by which OSAS contributes to NVAF include intermittent nocturnal hypoxaemia and hypercapnia, changes in intrathoracic pressure, sympathetic-vagal imbalance, oxidative stress, inflammation, and neurohormonal activation.
  - Cardiovascular diseases: Acute coronary syndromes are associated with NVAF incidence ranging from 2–23%, whereas in patients with myocardial infarction, the risk of new-onset NVAF is 60–77%. NVAF and heart failure frequently

coexist, with the onset and progression of each condition exacerbating the other. Over one-third of NVAF patients have valvular heart disease. Additional associated conditions include congenital heart defects, inherited cardiomyopathies, and arrhythmogenic disorders; for example, NVAF prevalence in short QT syndrome ranges from 18–70%, and in Brugada syndrome from 6–53%.

- Subclinical atherosclerosis, particularly coronary artery calcifications, increased carotid intima-media thickness, or carotid plaques.
- Chronic obstructive pulmonary disease (COPD).
- Genetic factors, including a family history of NVAF, susceptibility loci identified through genome-wide association studies (GWAS), or short QT syndrome.
- Inflammatory and autoimmune conditions, including elevated C-reactive protein (CRP), fibrinogen, autoimmune disorders, and thyroid dysfunction (TSH > 0.10–0.45 mU/L).
- Other factors, such as environmental pollution, sepsis, and psychosocial stressors.

All risk factors induce structural and functional alterations in the atrial chamber, which may be reversible or irreversible. These include fibrosis, resulting from atrial stretch; hypocontractility; inflammation; vascular remodelling; ischemia; secondary ion channel dysfunction; and intracellular calcium instability. Collectively, these changes promote ectopic atrial automaticity and conduction disturbances, increase the propensity of the atrium to initiate or sustain atrial fibrillation, and contribute to the hypercoagulable state associated with AF. Atrial hypocontractility, by reducing local endothelial shear stress, enhances the expression of plasminogen activator inhibitor, whereas ischemia-induced inflammation upregulates endothelial adhesion molecules and promotes endothelial cell detachment, resulting in exposure of tissue factor. NVAF itself further exacerbates many of these mechanisms, explaining its progressive nature (Hindricks et al., 2021).

A paradigmatic example of these alterations is observed in patients with heart failure, in whom the onset of NVAF is associated with hemodynamic changes due to pressure or volume overload, coupled with cellular modifications such as fibrosis and increased automaticity. These changes are closely related to established risk factors, including hypertension, diabetes, metabolic syndrome, and atherosclerosis.

The 2020 ESC guidelines emphasize the importance of comprehensive control and management of all risk factors as an integral part of AF treatment, aiming to reduce the incidence, recurrence, and overall burden associated with NVAF (Hohendanner et al., 2018).

2.1.5 Use of thromboembolic and hemorrhagic risk scores in patients with AF

Thromboembolic and hemorrhagic risk in patients with AF

Patients with NVAF are at increased risk of cardioembolic events, and anticoagulant therapy represents a cornerstone of NVAF management, as it has been well established to reduce the risk of stroke or transient ischemic attack (TIA) by approximately 64% and overall mortality by 26%. However, patients with NVAF also carry an elevated bleeding risk, and often the risk factors for stroke/TIA and major bleeding (MB) overlap, complicating therapeutic decision-making. For this reason, the 2020 ESC guidelines recommend that anticoagulant therapy be guided by an assessment of both thromboembolic and bleeding risk, using the CHA_2DS_2-VASc and HAS-BLED scores, respectively, in order to appropriately balance risks and benefits. These scores currently represent the most reliable tools for predicting thromboembolic and hemorrhagic events (Lip et al., 2010).

The CHA_2DS_2-VASc Score

Several scoring systems have been developed to estimate stroke risk in patients with NVAF; however, the ESC 2020 guidelines identify the CHA_2DS_2-VASc score as the preferred tool for guiding anticoagulant therapy. This score has replaced the earlier CHA_2DS_2 score and incorporates the most common risk factors for stroke.

The CHA_2DS_2-VASc score has proven particularly effective in predicting thromboembolic events among low-risk patients (CHA_2DS_2-VASc = 0 for men, CHA_2DS_2-VASc = 1 for women), with observed thrombotic or mortality rates of less than 1%. Its predictive efficacy is comparatively lower in high-risk patients. The primary objective in developing this score, as proposed by Lip et al., was to optimize the identification of low-risk individuals who do not require anticoagulant therapy.

Specifically, the CHA$_2$DS$_2$-VASc score (Table 1) assigns 1 or 2 points, up to a maximum of 9, to the most significant stroke risk factors, including heart failure or left ventricular dysfunction, arterial hypertension, advanced age, prior stroke/TIA/thromboembolism, vascular disease, and female sex.

Table 1: CHA$_2$DS$_2$-VASc score according its original definition (Lip et al., 2010).

C	Congestive heart failure	1 point
H	Hypertension	1 point
A$_2$	Age ≥ 75 years	2 points
D	Diabetes mellitus	1 point
S$_2$	Stroke	2 points
V	Vascular disease	1 point
A	Age 65-74 years	1 point
Sc	Sex Category (female)	1 point

CHA_2DS_2-VASc Score, detailed components (Kim et al., 2018):

- Congestive Heart Failure (CHF) or Left Ventricular Dysfunction (1 point): "Congestive heart failure or dysfunction" refers to recent decompensated heart failure, regardless of left ventricular ejection fraction, including both heart failure with preserved and reduced ejection fraction, or the presence (even if asymptomatic) of moderate-to-severe left ventricular systolic dysfunction on cardiac imaging. Hypertrophic cardiomyopathy also contributes to increased thromboembolic risk.
- Hypertension (1 point): A history of arterial hypertension or current antihypertensive therapy may induce vascular changes that predispose to stroke. Well-controlled blood pressure (target SBP 120–129 mmHg and DBP < 80 mmHg) is associated with reduced risk of ischemic stroke, cardiovascular events, and mortality.
- Age ≥ 75 years (2 points): Most studies demonstrate increased risk from 65 years onward. Age is a continuous risk factor, but for practicality, 1 point is assigned for 65–74 years and 2 points for ≥ 75 years. Recent evidence suggests that stroke risk may begin as early as 50–55 years in Asian populations, indicating the potential need for modified risk scores in this ethnicity.
- Diabetes Mellitus (DM) (1 point): Diabetes is defined by treatment with oral hypoglycemics and/or insulin or fasting plasma glucose > 125 mg/dL (7 mmol/L). Stroke risk has been associated with diabetes duration (longer duration conferring higher thromboembolic risk) and the presence of end-organ damage such as retinopathy. Both type 1 and type 2 diabetes increase thromboembolic risk, with some evidence suggesting higher risk in patients < 65 years with type 2 diabetes compared to type 1.
- Stroke/TIA/Thromboembolism history (2 points): Previous ischemic stroke, TIA, or thromboembolism confers a particularly high risk. Risk is also increased in patients with prior intracranial hemorrhage, including hemorrhagic stroke.
- Vascular Disease (1 point): Peripheral vascular disease or myocardial infarction increases risk by 17–22%, particularly in Asian populations. Significant angiographic coronary artery disease is an independent risk factor in patients with

NVAF. Complex aortic atherosclerotic plaques may also indicate significant vascular damage.

- Age 65–74 years (1 point).
- Sex Category (1 point): Female sex modifies stroke/TIA risk rather than serving as an independent risk factor.

Risk stratification based on CHA_2DS_2-VASc Score:

- CHA_2DS_2-VASc = 0: Low risk.
- CHA_2DS_2-VASc = 1: Intermediate risk.
- CHA_2DS_2-VASc ≥ 2: High risk.

It should be noted that the CHA_2DS_2-VASc score is not specific to NVAF, as its ability to predict thromboembolic events is similar in patients with or without atrial fibrillation. Nevertheless, it remains a useful predictor of other outcomes, including mortality, stroke, major cerebrovascular events, and thromboembolic events in high-risk patients, such as those with myocardial infarction, chronic pulmonary obstruction, or heart failure.

Future stroke risk prediction models should incorporate NVAF-specific factors, unlike the CHA_2DS_2-VASc score. These may include arrhythmia duration, left atrial or left atrial appendage anatomy and morphology, cardiac biomarkers, and electrocardiographic markers. Evidence suggests that including such parameters could improve the predictive capacity of these models. For example, each 10 mm increase in left atrial size has been associated with a 40–100% increase in stroke risk, while a larger or less mobile left atrial appendage confers a sixfold higher risk. Similarly, patients with elevated levels of troponin I or T and NT-proBNP have an increased risk compared with those with lower levels. Abnormal P-wave axis or morphology on the ECG is also associated with higher stroke risk (Maheshwari et al., 2019).

At present, the use of biomarker-based score, whether from blood or urin, does not provide additional information for treatment decisions guided by clinical risk scores such as CHA_2DS_2-VASc, and their routine use in clinical practice is limited by higher costs and practicality. Nevertheless, such biomarkers may be useful for risk stratification in low-risk patients or those with a single CHA_2DS_2-VASc risk factor (excluding female sex).

The HAS-BLED Score

Bleeding risk is assessed using the HAS-BLED score (Table 2), which assigns 1 or 2 points to factors including hypertension, impaired renal or liver function, prior stroke, history of bleeding, labile INR, age, and the use of medications or alcohol (Pisters et al., 2010).

Table 2: HAS-BLED score, according to its original definition (Pisters et al., 2010).

H	Hypertension	1 point
A	Abnormal renal and liver function	1 point each
S	Stroke	2 points
B	Bleeding	1 point
L	Labile INR	2 points
E	Elderly	1 point
D	Drugs or alcohol	1 point each

HAS-BLED Score, detailed components:

- Hypertension (1 point): defined as a systolic blood pressure > 160 mmHg.
- Abnormal renal and liver function (1 point each):
  - Renal dysfunction: defined as the need for dialysis, renal transplantation, or serum creatinine ≥ 200 µmol/L.
  - Liver dysfunction: refers to chronic liver disease (e.g., cirrhosis) or biochemical evidence of hepatic impairment, such as bilirubin levels > 2 times the upper limit of normal in combination with AST, ALT, or ALP values > 3 times the upper limit of normal.
- Stroke (1 point): Refers to a history of ischemic or hemorrhagic stroke.
- Bleeding (1 point): Includes a prior history of bleeding or a predisposition to bleeding, such as a bleeding diathesis or anemia.
- Labile INR (1 point): Labile INR refers to unstable or high INR values, or a low time in therapeutic range (TTR < 60%) calculated using the Rosendaal method. This parameter is only relevant in patients receiving vitamin K antagonists (VKAs).
- Elderly (1 point): Age > 65 years or extreme frailty.
- Drugs or alcohol (1 point each): Refers to concomitant use of medications such as antiplatelets or nonsteroidal anti-inflammatory drugs (NSAIDs), or excessive weekly alcohol consumption.

The maximum HAS-BLED score is 9 points, with bleeding risk stratified as follows:

- HAS-BLED < 2: Low risk.
- HAS-BLED = 2: Intermediate risk.
- HAS-BLED ≥ 3: High risk.

The HAS-BLED score has demonstrated good accuracy in predicting bleeding events and identifying low-risk patients. All risk factors included in this score can be rapidly obtained from the patient's medical history or routine evaluations in NVAF patients (Lip, 2011).

Risk assessment is crucial in guiding anticoagulant therapy. It emphasizes the importance of managing modifiable risk factors, which should be addressed and reevaluated at each follow-up, as well as monitoring high-risk patients with non-modifiable factors more frequently (e.g., every 4 weeks rather than every 4–6 months). Identifying patients at high bleeding risk is also important for therapeutic decision-making, such as planning percutaneous coronary interventions (PCI).

Bleeding risk should be considered dynamic. Changes in bleeding risk profiles are among the strongest predictors of MB. One study demonstrated that modification of the hemorrhagic risk profile was associated with a 3.5-fold higher risk of MB at 3 months (Maheshwari et al., 2019).

2.2 Critical illness and critically ill patients

2.2.1 Critical illness and critically ill patients: how to define

In both clinical practice and research, a clear definition of “critical illness” and “critical care” is essential to ensure appropriate patient management and to allow accurate comparisons across studies. Divergent interpretations can substantially influence clinical decision-making and study design in emergency and intensive care medicine.

In 2022, a scoping review by Kayambankadzanja RK, Schell CO, Gerdin Warnberg M, et al., aimed to establish a common understanding of the terms “critical illness” and “critically ill patient” by analyzing existing definitions in the literature and conducting an open-ended survey among field experts. The proposed definition of “critical illness” is: “a state of severe health impairment, associated with dysfunction of one or more vital organs, with a high risk of imminent death if therapies are not applied, but with the potential for recovery” (Kayambankadzanja et al., 2022).

Particular attention is given to the concept of “reversibility”, which is critical in distinguishing critical illness from the natural process of dying. Without this aspect, all patients approaching death would be classified as critically ill; the inclusion of reversibility allows a meaningful differentiation between these fundamentally different conditions.

As highlighted in this definition, critical illness is "independent of the patient's underlying diagnosis or syndrome" and may occur in any clinical context.

"Critical care", in contrast, is defined as: "the identification, monitoring, and treatment of patients with critical illness through initial and ongoing support of vital organ functions" (Kayambankadzanja et al., 2022).

From this definition, it is evident that while specific resources may be required, they are not fundamental; the primary focus remains on the patient rather than the setting. What is indispensable is "vital organ dysfunction", emphasizing that the primary objective of critical care is the treatment of the critical illness itself, rather than the underlying condition (Kayambankadzanja et al., 2022).

2.2.2 The clinical complexity of the critically ill patients

As evident from the definitions and the challenges in proposing a common terminology, "critically ill patients are inherently complex". Caring for such patients involves a high degree of complexity in decision-making, requiring the assessment, monitoring, and support of vital functions, treatment of one or more organ failures, and the prevention of potentially life-threatening deterioration. In critical conditions, decisions must be made rapidly, often in clinical contexts where evaluating the risk, benefit balance is particularly challenging. Frequently, multiple comorbidities coexist and interact, for example, hepatic or renal dysfunction, respiratory failure, infections, electrolyte disturbances, and acidosis. Moreover, guidance for the management of critical conditions, including arrhythmias, is often limited (Kayambankadzanja et al., 2022).

Age and comorbidities add further complexity. Critically ill patients are often older adults: individuals over 65 years account for 15% of intensive care unit (ICU) admissions and are projected to comprise at least one-quarter of ICU patients by 2060. Older patients frequently present with multiple chronic conditions in addition to the acute event, which increases vulnerability and worsens outcomes, including short- and long-term mortality. Common comorbidities include hypertension, diabetes, chronic obstructive pulmonary disease, heart failure, malignancies, and cognitive impairment. These conditions contribute to geriatric syndromes, encompassing pressure ulcers, incontinence, falls, functional decline, and delirium. ICU admission increases the risk of geriatric syndromes by 2.6-fold.

Age and comorbidities also increase the risk of frailty, a syndrome characterized by multisystem physiological decline, reduced physiological reserves, and diminished capacity to respond to stressors. Age-related changes further compound the complexity of critically ill patients. Cognitive decline, due to loss of gray and white matter volume and integrity, reduced cerebral blood flow and oxygenation, slower metabolism, altered neurotransmitter production and activity, and endothelial dysfunction leading to increased blood–brain barrier permeability, increases vulnerability to neurological insults. Acute brain dysfunction and delirium are frequent in the ICU, and long-term cognitive impairment is commonly observed in ICU survivors.

Cardiovascular changes with aging contribute to greater hemodynamic instability during acute illness. Autonomic imbalance, reduced parasympathetic tone, and increased sympathetic activity predispose to cardiovascular disease. Age-related reductions in heart rate, sinoatrial node impulses, atrioventricular conduction, valvular calcification, vascular rigidity, and myocardial fibrosis reduce left ventricular compliance and filling. Consequently, these patients are less able to tolerate intravascular volume changes: hypovolemia reduces cardiac output and may precipitate acute kidney injury (AKI), whereas hypervolemia leads to cardiac dysfunction and pulmonary edema. Aging also increases susceptibility to arrhythmias, which further compromises hemodynamic stability.

Respiratory system vulnerability increases with age. Impaired mucociliary clearance, connective tissue changes in the pulmonary parenchyma, loss of alveolar units, and decreased lung elasticity reduce forced expiratory volume and vital capacity. Muscle mass loss, diminished cough strength, and impaired secretion clearance further predispose to aspiration and respiratory failure. Consequently, the need for mechanical ventilation rises significantly with age, increasing the risk of ventilator-induced lung injury and acute respiratory distress syndrome (ARDS).

Nutritional status and metabolism are critical considerations. Pre-existing malnutrition predisposes patients to anemia, functional decline, and sarcopenia. Critical illness typically progresses from an acute phase characterized by hemodynamic and metabolic instability with marked catabolism, to a phase of muscle atrophy and metabolic stabilization. ESPEN guidelines recommend early oral or enteral nutrition, progressing to full caloric intake within 3–7 days, or parenteral nutrition if enteral feeding is contraindicated, particularly in cases of intestinal failure, albeit with associated morbidity and mortality risks.

Renal function is also compromised with age and critical illness. Progressive loss of renal mass and nephrons increases the risk of AKI, especially in the context of hypotension or reduced cardiac output, dehydration, or impaired renal autoregulation. Management of AKI, including renal replacement therapy, requires careful hemodynamic assessment due to increased risk of instability, reduced cardiac reserve, autonomic dysfunction, bleeding, and neurological complications.

Older critically ill patients are also at increased risk of infection due to immunosenescence.

Sarcopenia is associated with greater disease severity, prolonged mechanical ventilation, longer ICU and hospital stays, and increased mortality. Early physiotherapy can reduce ICU and hospital length of stay and improve physical function at six months, although survival benefits are not consistently observed.

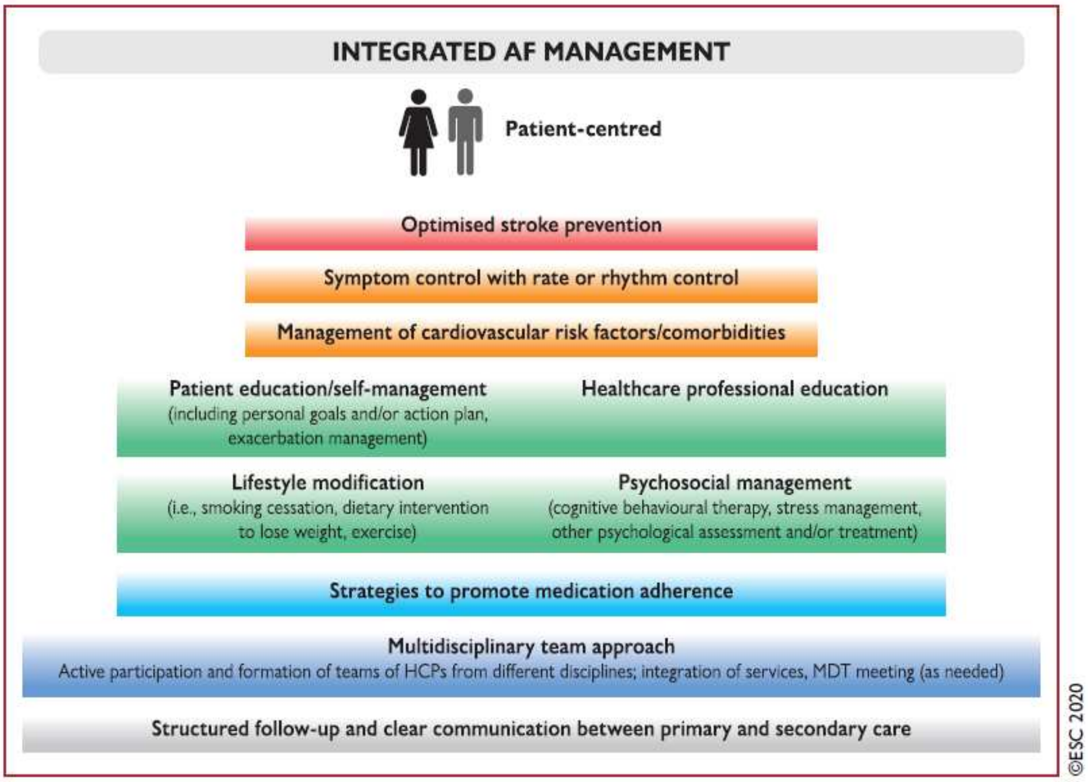
Finally, polypharmacy must always be considered.

In summary, the complexity of the critically ill patient arises from a combination of the acute illness, frailty, pre-admission functional status, geriatric syndromes, and comorbidities. These factors interact synergistically, producing a state of diminished health and markedly reduced life expectancy, exceeding the sum of the individual risk factors.

2.2.3 The critically ill patient with AF: importance of a multidisciplinary approach

So far, the complexity of the critically ill patient has been emphasized, but attention must also be paid to the complexity of the patient with NVAF. As highlighted in the 2020 ESC Guidelines, NVAF is a condition sufficiently complex to require a multidisciplinary approach capable of optimizing patient management and improving clinical outcomes (Figure 1).

Figure 1: Components of integrated AF management (Hindricks et al., 2021).



AF: atrial fibrillation; HCP: healthcare professional; MDT: multidisciplinary team.

At first glance, the complexity of the NVAF patient is evident in the difficulty of defining a simple and comprehensive classification. This is due to the multitude of factors involved in NVAF management, continuous advances in monitoring, the variety of risk assessment tools, and the evolving therapeutic options. Rather than attempting to classify the arrhythmia, the focus has shifted toward a structured characterization, considering the specific domains relevant to both treatment and prognosis.

The 2020 ESC Guidelines propose the “4S-AF scheme”, which evaluates:

- Stroke risk.
- Symptom severity, assessed using the European Heart Rhythm Association (EHRA) symptom score (Table 3).
- Severity of AF burden, evaluating the duration and spontaneous termination of NVAF episodes.

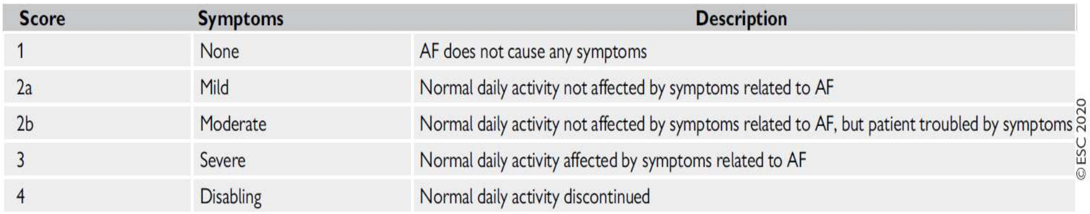
- Substrate severity, including comorbidities and structural changes, such as age and atrial fibrosis.

Given the high level of complexity in NVAF patients, the ESC Guidelines also recommend the Atrial Fibrillation Better Care (ABC) pathway for management. This approach has been shown to reduce mortality, stroke, major bleeding, cardiovascular events, and hospitalization, while also helping contain healthcare costs. The ABC pathway involves the assessment and management of three key domains:

- Anticoagulation/Avoid stroke, targeting anticoagulant therapy to reduce stroke risk.
- Better symptom control, addressing rhythm and rate control to alleviate NVAF-related symptoms.
- Cardiovascular risk factors and concomitant diseases, focusing on treatment of cardiovascular risk factors and comorbidities to reduce atrial remodeling, the development of NVAF, stroke risk, and symptom severity.

In summary, while the critically ill patient is complex, NVAF patients are similarly complex. Consequently, a critically ill patient with NVAF faces both the challenges of acute critical illness and the additional burden of the arrhythmia, resulting in an even higher level of clinical complexity.

Table 3: EHRA score in accordance with the 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (Hindricks et al., 2021).



Score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

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Six symptoms, including palpitations, fatigue, dizziness, dyspnoea, chest pain, and anxiety during AF, are evaluated with regard to how it affects the patient’s daily activity, ranging from none to symptom frequency or severity that leads to a discontinuation of daily activities.

2.3 Atrial fibrillation in critically ill patients

AF is the most common arrhythmia in critically ill patients: approximately one-third of patients in ICU have a pre-existing diagnosis of NVAF or develop new-onset NVAF during their ICU stay. The incidence of NVAF in ICU patients ranges from 4.5% to 15%, with considerable variability depending on the population studied (Bosch et al., 2018; Nelson et al., 2021).

Pre-existing NVAF follows the prevalence observed in the general population, affecting around 9% of critically ill patients, particularly elderly individuals with chronic conditions who are at higher risk of critical illness. New-onset NVAF, however, can be triggered by accelerated atrial remodeling and arrhythmogenic triggers that emerge during acute critical illness. Its prevalence ranges from 5% to 46%, representing approximately 52% of all atrial arrhythmias in ICU patients (Falsetti et al., 2020).

The high prevalence of NVAF in critical care settings is partly explained by the frequent coexistence of chronic conditions associated with AF, such as hypertension, myocardial ischemia, or chronic lung disease. Furthermore, critical illnesses predominantly affect adults over 65 years, coinciding with the age-related increase in NVAF risk observed in the general population.

Given the high frequency of NVAF in critically ill patients, the American Association for Thoracic Surgery recommends continuous ECG monitoring for patients undergoing procedures with high (> 15%) or intermediate (5–15%) risk of NVAF, or for patients with additional stroke risk factors (CHA_2DS_2-VASc ≥ 2) or a history of pre-existing or paroxysmal NVAF (Boriani et al., 2019).

Several acute conditions in ICU are associated with NVAF, including:

- Sepsis: incidence varies with severity 8–10% in sepsis, 6–22% in severe sepsis, and 23–44% in septic shock; 10% of these cases are new-onset NVAF.
- Acute respiratory failure: is associated to several acute diseases, as acute heart failure, and worsens the prognosis of each critical illness. It is commono among patients with a worse haemodynamic profile, as the ones with NVAF.
- Acute kidney injury, with pre-existing renal dysfunction increasing the risk of arrhythmias during acute illness.

- Acute brain injury, particularly when involving the hypothalamus, insula, or brainstem; NVAF occurs in 25% of patients without cardiac dysfunction, 28% in stroke patients, and 37.5% in subarachnoid hemorrhage.
- Malignancies, particularly with chemotherapy agents such as anthracyclines, melphalan, and interleukin-2.
- Trauma and burns, with NVAF incidence ranging from 4.3–14.8% in trauma and 3.2% in burn patients.
- Surgical procedures, including both cardiac and non-cardiac surgery; post-operative NVAF ranges from 0.3–26% for non-cardiac surgery (higher in thoracic procedures) and 30–50% for cardiac surgery. Atrial arrhythmias usually develop 2–3 days post-operatively (Boriani et al., 2019).

In the general population, AF develops through two sequential mechanisms: a substrate (atrial remodeling, fibrosis, or electrical remodeling) and an arrhythmogenic trigger. Substrate formation is driven by factors such as chronic heart failure, hypertension, valvular heart disease, myocardial infarction, inflammation, renin–angiotensin system activation, and oxidative stress. Tachycardia-induced electrical remodeling and ion channel alterations further contribute. Common triggers include electrolyte disturbances (hypokalemia, hypomagnesemia), hypovolemia, and autonomic dysfunction, leading to ectopic atrial foci, self-sustaining action potentials, or re-entry circuits.

In critically ill patients, the mechanisms are more complex. Pre-existing NVAF is often associated with chronic degenerative causes, whereas new-onset NVAF is primarily linked to the acute illness itself. Classical risk factors, including advanced age, hypertension, ischemic heart disease, heart failure, and valvular disease, remain relevant, but additional acute triggers must be considered, such as electrolyte imbalances, hypoxemia, adrenergic overstimulation, progressive autonomic dysfunction, systemic inflammation, sepsis, and shock. Acute illness accelerates cardiac remodeling and fibrosis, rapidly creating a substrate susceptible to arrhythmia. For example, brain injury or increased intracranial pressure may trigger NVAF via catecholamine surges (Boriani et al., 2019).

Inflammation, independent of infection, also plays a critical role through infiltration of inflammatory cells and oxidative damage to atrial myocytes, explaining associations with obesity and sepsis. Elevated inflammatory markers correlate with higher NVAF risk, and anti-inflammatory agents (e.g., glucocorticoids, statins) may reduce incidence, although further studies are needed. Other predisposing factors in critically ill patients include vasopressor use and fluid-electrolyte imbalances; catecholamines such as dopamine and epinephrine exert chronotropic effects that increase ectopic atrial impulses.

Echocardiographic atrial enlargement is more commonly associated with new-onset NVAF, suggesting that pressure or volume overload may contribute. Clinical prediction tools, such as that developed by Klouwenberg et al., assess risk in septic ICU patients based on age, obesity, immunosuppression, inflammation markers, shock, renal dysfunction, potassium levels, oxygen fraction, and length of stay (Klein Klouwenberg et al., 2017).

In trauma or burn patients, fluid resuscitation, catecholamine use, sepsis, and renal dysfunction collectively trigger systemic inflammation, predisposing to NVAF. Post-cardiac surgery, NVAF risk increases with age (especially > 55 years), surgical complexity, preoperative CHA_2DS_2-VASc score, severe obesity, β-blocker or antiplatelet therapy, and renal dysfunction. Notably, β-blockers may be associated with a rebound effect if temporarily discontinued (Boriani et al., 2019).

2.4 Thromboembolic and hemorrhagic risk in critically ill patients with AF

Thromboembolic risk in critically ill patients with AF

As in the general population, the presence of NVAF in critically ill patients is associated with an increased thromboembolic risk. This risk can be conceptualized through Virchow's triad, which includes hypercoagulability, vascular abnormalities, and altered blood flow (Ding, 2021).

Critically ill patients with NVAF exhibit a hypercoagulable state and reduced fibrinolysis due to heightened activation of the hemostatic process. Hypocontractility of the atria reduces local endothelial stress, increasing the expression of plasminogen activator inhibitor-1. Additionally, NVAF-related inflammation enhances endothelial adhesion molecule expression and promotes endothelial cell detachment, exposing tissue factor. These factors, combined with increased platelet activation, facilitate thrombus formation (Ding, 2021).

Several pro-thrombotic markers are implicated in this process, including platelet factor, von Willebrand factor, fibrinogen, β-thromboglobulin, and D-dimer. Abnormal elevations in these markers are more pronounced in patients with NVAF and stroke compared to those with stroke and sinus rhythm. Notably, D-dimer levels have been identified as independent predictors of left atrial appendage thrombi. Comorbidities further amplify this hypercoagulable state, increasing thrombotic risk.

Structural atrial changes, such as fibrosis and endothelial dysfunction, not only contribute to NVAF development but also provide an optimal substrate for thrombus formation. Atrial remodeling creates areas of stasis that favor thrombus generation and subsequent embolization.

Hemodynamic alterations further increase thrombotic risk. Atrial dilation, ineffective atrial systole, and rapid ventricular response reduce atrial blood flow velocity and cardiac output, exacerbating stasis. Atrial size, indexed to body surface area, is an independent predictor of stroke, highlighting the significance of structural remodeling in thrombogenesis (Watson et al., 2009).

In the context of acute cardioversion, thromboembolic risk is linked to pre-existing atrial thrombi, transient mechanical dysfunction following rhythm restoration, atrial stunning, and temporary pro-thrombotic states.

Hemorrhagic risk in critically ill patients with AF

Critically ill patients with NVAF are also at increased bleeding risk, particularly if receiving anticoagulation prior to ICU admission for NVAF or other comorbidities. Bleeding risk varies with anticoagulant type: for instance, MB rates per year in landmark trials are approximately 2.0% with apixaban (ARISTOTLE), 2.7% with dabigatran 110 mg, 3.1% with dabigatran 150 mg (RE-LY), 2.9% with rivaroxaban (ROCKET-AF), and 2.2–3.5% with warfarin (Lip et al., 2011).

Critical illness and simultaneous increase in thromboembolic and hemorrhagic risk

Critical illness itself increases both thromboembolic and hemorrhagic risk due to systemic inflammation, organ dysfunction, and treatment interventions, creating an imbalance between pro-thrombotic and hemorrhagic pathways. A recent study from Gamst et al. shows that thromboembolic risk in critically ill NVAF patients remains elevated even after adjusting for CHA_2DS_2-VASc score variables, emphasizing that NVAF independently contributes to thrombotic risk in this population.

In conclusion, critically ill patients with NVAF have a baseline thromboembolic risk related to atrial fibrillation, which is further augmented by acute illness, therapeutic interventions, organ dysfunction, and systemic inflammation, while simultaneously facing an increased hemorrhagic risk due to anticoagulation and the critical condition itself (Falsetti et al., 2021).

2.5 Risk scores: how useful in predicting acute events and guide terapeutic management?

Anticoagulation, essential for mitigating AF-related stroke risk, is currently recommended as the first-line treatment for most individuals. The decision to initiate anticoagulation should be guided by an accurate assessment of thromboembolic and bleeding risks, primarily utilizing the CHA_2DS_2-VASc and HAS-BLED scoring systems. Precise risk stratification according to these validated tools is a fundamental component emphasized by all major international guidelines governing the routine AF management. The widespread adoption of these scoring systems among outpatient populations underscores their validity and utility in clinical decision-making (Falsetti et al., 2020).

Despite this indication, among critically-ill patients anticoagulation has not been associated with reduced stroke rates, but with a raised major bleeding risk: in fact, real-world studies observed that this treatment is not routinely scheduled by intensivists in critically-ill subjects co-affected by AF. One of the major limitations to the benefits of full anticoagulation in this setting is the lack of accuracy of the currently used thromboembolic and haemorrhagic risk scores. In fact, albeit deemed useful for predicting in-hospital events in critically ill patients by some authors, several studies indicate these tools have limited accuracy in predicting their respective outcomes in this specific category of subjects. This highlights the need for improved risk-stratification methods to better identify the subjects at risk of adverse events.

Among the known limitations of the classical risk stratification, it is worth noting that CHA_2DS_2-VASc and HAS-BLED are designed to predict 1-year outcomes and were not initially intended to predict in-hospital events. Moreover, critical illness is characterised by coagulation abnormalities and reduced platelet counts and function. Critically ill patients are commonly older, burdened by several comorbidities and often chronically treated with antiaggregant and anticoagulant drugs. All these elements represent potentially confounding factors that are not accounted for in the items of classical risk stratification methods. This results in reduced ability of the scores to accurately predict their respective outcomes in this specific group.

Advances in diagnostics and treatments have increased lifespan, leading to a larger elderly population with many comorbidities, a trend projected to continue in the next years. Ageing itself is associated with repeated hospitalisations. With AF being common, multi-morbid patients affected by this arrhythmia are more frequent and often develop acute diseases. Therefore, finding innovative solutions to improve the stratification of cardioembolic and haemorrhagic risk is crucial to guide a tailored therapeutic approach during their hospitalisation (Bailly et al., 2018).

2.6 The need of new risk-prediction models: the AFICILL studies

Since several studies have already shown that classical risk scores, such as $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED, are not useful for thromboembolic and hemorrhagic risk stratification in critically ill patients with AF, most research in this field is now focusing on accounting for the complexity of these patients and on managing such complexity through the adoption of advanced statistical methods. Among these, topological data analysis (TDA) and machine learning (ML) are particularly noteworthy, as they are capable of capturing relationships among multiple variables within large and complex datasets.

In a recent pilot study, AFICILL 1.0 (Atrial Fibrillation In Critically ILL patients 1.0) (Falsetti et al., 2021), our group demonstrated the potential applicability of TDA- and ML-based models in critically ill patients with pre-existing NVAF (pNVAF). In this study, we enrolled all consecutive critically ill patients admitted to our Emergency Medicine Department (ED) in Ancona who were affected by pNVAF. We selected subjects in this pNVAF category because it was associated with the greatest therapeutic management complexity.

Patients with VAF typically exhibit a markedly elevated risk of thrombosis and should remain on anticoagulant therapy even during critical illness, when the risk of hemorrhage is increased.

Also new-onset NVAF increases thrombotic risk both in the short- and in the long-term, however this form is difficult to identify outside the ICU, often occurring as brief episodes that spontaneously revert to sinus rhythm. Moreover, since most of the patients with new-onset NVAF are submitted to cardioversion or undergo to spontaneous sinus rythm restoration, the choice to anticoagulate the patient can be done once the critical illness is resolved and when the thrombotic and haemorragic risk become assessable with the conventional risk scores, as CHA_2DS_2-VASc and HAS-BLED.

Conversely, significant uncertainty remains regarding the therapeutic management of pNVAF, particularly regarding the indication for anticoagulation: these patients are already treated before admission, and there is large uncertainty on how should they be managed during a critical illness. In this phase, the choice to mantain, start or stop the previous anticoagulation and the selection of the most appropriate anticoagulant drug should be tailored according to individual patients' characteristics, starting from the critical illness that led to admission but also considering comorbidities and polypharmacotherapy, thus increasing the degree of decision-making complexity.

In this initial study, the AFICILL 1.0, we observed that, in critically ill patients with pNVAF, advanced models yielded better performance than classical risk scores in predicting therapeutic failure (defined as death or transfer to the ICU), as well as in predicting stroke/TIA and MB because these models were able to consider the individual patient's characteristics. However, the limited number of patients and the retrospective nature of this study limited the generalizability of the results.

3. AIMS

With this work, we aimed to:

- Corroborate our previous observations, confirming that the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED risk scores exhibit limited predictive accuracy for stroke/TIA and MB in an expanded cohort of critically ill patients with pNVAF.
- Assess whether our recently developed ML and TDA-based algorithms maintain their superior performance over traditional risk scoring systems in predicting the occurrence of stroke/TIA, and MB within a larger cohort of critically ill patients with pNVAF.
- Assess the accuracy of our ML and TDA-based system to predict therapeutic failure, defined as the composite of death and ICU transfer, considering AF-related outcomes, specifically stroke/TIA and MB.

4. PATIENTS AND METHODS

4.1 Selected timeframe and methodology of data collection

The AFICILL 2.0 (Atrial Fibrillation In Critically ILL patients 2.0) is a real-world retrospective study performed on a cohort not primarily designed for research purposes. It includes all the critically-ill patients with pNVAF, admitted to the medical stepdown unit (SDU) of the Internal and Sub-intensive Medicine Department at the Azienda Ospedaliero-Universitaria delle Marche, Ancona. Aim of the AFICILL 2.0 was to extend the number of cases and validate the ML classifiers obtained in our previous study performed in a smaller cohort (Falsetti et al., 2021). We considered all subjects with the above-mentioned features over a 10-year period, from January 1, 2002, to December 31, 2012. We selected this period to optimise data collection and obtain a more homogeneous population, particularly in terms of antithrombotic therapy: in fact, the 2010 ESC guidelines did not consider direct oral anticoagulants, that were introduced only in the 2012 update of the same guidelines (Camm et al., 2012). Thus, by avoiding patients hospitalized from 2012 onwards, we excluded those treated with new oral anticoagulants, obtaining a study population with the same thromboembolic and haemorrhagic risk profile. Since January 1, 2002, the SDU has been equipped with an electronic medical record system (eMRS) for inpatient management. All diagnoses documented within the eMRS for each patient were coded in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The full dataset was obtained by querying the eMRS and selecting all patients discharged with a diagnosis of pNVAF (ICD-9-CM: 427.3).

4.2 Inclusion and exclusion criteria

From the obtained dataset, we applied the following exclusion criteria: (i) patients under 18 years of age (ii) patients with valvular atrial fibrillation, defined as the presence of prosthetic mitral valve or moderate-to-severe mitral stenosis (iii) patients with new-onset atrial fibrillation, defined as an acute arrhythmic event arising during the hospitalization without a history of paroxysmal atrial fibrillation (iv) non critically-ill patients, particularly (v) those admitted for a planned cardioversion procedure for AF rhythm control and (vi) patients admitted for trauma, since the thrombotic and haemorrhagic risk profile of this group is completely different from the standard NVAF management, (vii) subjects admitted for surgical diseases.

We included all critically ill patients from the original dataset, irrespective of comorbidities, who were receiving multiple home pharmacological treatments and admitted for acute events requiring intermediate levels of care. These interventions encompassed continuous electrocardiographic monitoring, inotropic or vasopressor support, non-invasive ventilation, and renal replacement therapy, without the need for invasive ventilation or intensive care unit admission. The SDU was specialized in managing the following acute illnesses, alone or in combination: acute heart failure (AHF), acute respiratory failure (ARF), acute coronary syndrome (ACS), acute kidney injury (AKI), septic shock (SS) and cardiogenic shock (CS), infections (INF) and haemorrhagic shock (HS) (Falsetti et al., 2021).

Due to the common complexity of the critically ill subjects, we excluded patients discharged with syncope or major trauma diagnoses alone. However, since these manifestations were commonly associated with other acute diseases as previously listed, we considered syncope (SYN) and minor trauma (MT) only as complicating conditions of the above-mentioned pathologies.

4.3 Collected variables

The complete AFICILL dataset comprises 46 clinical and instrumental variables. To validate our models, we considered only the 31 most relevant clinical and demographic variables, with particular regard to the features selected by TDA and used by the ML models in our first study (Falsetti et al., 2021). Specifically, we obtained for each patient: (i) demographic characteristics (age, sex); (ii) patients' comorbidities (chronic obstructive pulmonary disease, COPD; hypertension, HYP; chronic heart failure, CHF; coronary artery disease, CAD; mild mitral valve disease, MMVD;

previous Stroke/TIA, PST; chronic kidney disease, CKD; mild-moderate aortic valve disease, MMAVD; previous gastrointestinal bleeding, PGIB; labile time in therapeutic range, l-TTR); (iii) chronic home treatments performed before admission, with particular regard to anticoagulant drugs (anticoagulant at admission use, ACAU: low-molecular-weight heparin, LMWH; oral anticoagulant durgs: vitamin K antagonists, VKA as Warfarin or Acenocumarol), antiplatelet drugs (aspirin or clopidogrel use, APAU), angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARB); (iv) one or more than one admission diagnoses (ACS, CS, HS, SS, ARF, INF, AHF, AKI); (v) common complicating conditions (SYN, MT); (vi) clinical events occurring from ED admission to hospital discharge (cardioembolic stroke/TIA; major bleeding, MB; in-hospital death; ICU transfer); (vii) drug treatments and procedures performed during hospitalization (amine, propafenone or flecainide, amiodarone, diuretics and electric cardioversion, ECV); (viii) admission vital parameters (systolic blood pressure, SBP; diastolic blood pressure, DBP).

4.4 Definitions of considered diseases

Due to the retrospective nature of the cohort, the attending physician assigned each diagnosis according to the following criteria, which were current at the moment of the patients' admission:

- Patients' comorbidities:
    - COPD: "A disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. It's a preventable and treatable disease with some significant extrapulmonary effects" ("Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary Updated 2003," 2004; Hurst & Wedzicha, 2007).
    - HYP: "A SBP $\geq$ 140 mmHg and/or a DBP $\geq$ 90 mmHg, based on the average of two or more properly measured, seated BP readings on each of two or more

office visits" or a subject undergoing to anti-hypertensive treatment before hospital admission (Giles et al., 2005; Lenfant et al., 2003).

- CHF: "A syndrome in which patients have symptoms of heart failure (typically breathlessness or fatigue, at rest or during exertion, or ankle swelling) and objective evidence of cardiac dysfunction at rest (systolic and/or diastolic), preferably documented by echocardiography" (Swedberg et al., 2005).
- CAD: "Coronary artery disease is defined as the presence of atherosclerotic plaques in the epicardial coronary arteries, leading to impaired myocardial perfusion either at rest or during stress, and manifesting clinically as stable angina or acute coronary syndromes" ("Guidelines on the Management of Stable Angina Pectoris: Executive Summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology," 2006).
- MMVD: "Mild mitral valve disease (mild mitral regurgitation) is characterized by a small, centrally directed color-Doppler jet (jet area $< \sim 4$ cm^2 or $< \sim 20\%$ of left-atrial area), a narrow vena contracta (< 0.3 cm), absence of significant flow–convergence, and no or minimal enlargement of left atrium or left ventricle. When quantitative Doppler (or PISA) data are available, regurgitant volume is < 30 mL/beat and effective regurgitant orifice area (EROA) is < 0.20 cm^2" (Bonow et al., 2006).
- PST:
  - Cardioembolic stroke: According to the 2002-2007 WHO definition, this event was assigned in the case of a "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin" (Sacco et al., 2013).
  - Cardioembolic TIA: According to the 2002-2007 WHO definition, this event was assigned as "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with clinical symptoms lasting less than 24 hours, and without evidence of acute infarction" (Coupland et al., 2017).

- CKD: “Kidney damage (structural or functional abnormalities), with or without decreased glomerular filtration rate (GFR), lasting for 3 months or more; or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for ≥ 3 months, with or without evidence of kidney damage” (Levey et al., 2005).
- MMAVD: “Peak aortic jet velocity: < 3.0 m/s (roughly corresponds to mean gradient < 20 mmHg). Mean transvalvular pressure gradient: < 20 mmHg. Aortic valve area (continuity equation): generally > 1.5 cm^2 (note: some laboratories used > 1.0–1.5 cm^2 to distinguish moderate vs. mild” (Bonow et al., 2006).
- PGIB: “A history that was positive at the moment of admission for gastric or intestinal bleeding for any cause. “Gastrointestinal bleeding (GI bleeding) is any hemorrhage originating from the lumen of the gastrointestinal tract. Clinically and anatomically it is classified as: (i) Upper gastrointestinal bleeding (UGIB): bleeding originating proximal to the ligament of Treitz (esophagus, stomach, or duodenum). Typical presentations are hematemesis and/or melena (“Non-Variceal Upper Gastrointestinal Haemorrhage: Guidelines,” 2002). (ii) Lower gastrointestinal bleeding (LGIB): bleeding originating distal to the ligament of Treitz (small bowel distal to the ligament, colon, rectum, anus). Typical presentation is hematochezia (bright red or maroon blood per rectum) but presentations can overlap depending on bleed volume and transit time” (Barnert & Messmann, 2009).
- l-TTR: “labile TTR (or labile INR) refers to unstable anticoagulation control characterized by wide fluctuations of INR over time and a significant proportion of time spent outside the therapeutic range, yielding a low overall Time in Therapeutic Range (e.g. TTR $< 60\%$)”. This definition reflects current clinical usage since the 2000s. Notably during the period under consideration, specifically the interval in which patients were hospitalised, the thresholds considered “acceptable” for TTR often varied (often with average TTRs around 55-65%), and at the time there was no international document or guideline that formally defined “labile TTR” as a clinical entity with a pre-established and universally adopted threshold.

- Admission diagnoses or complicating conditions:
  - ACS: “Acute Coronary Syndrome (ACS) designates a spectrum of clinical conditions caused by acute myocardial ischemia, typically arising from atherosclerotic plaque disruption (rupture or erosion), with subsequent thrombus formation leading to partial or complete coronary artery occlusion”(Diop & Aghababian, 2001). The syndrome includes the following entities: “Unstable Angina (UA) — ischemic symptoms (e.g. rest angina, new-onset or accelerating angina, angina at minimal exertion or at rest), in which myocardial necrosis does not occur: there is no persistent ST-segment elevation on ECG, and cardiac biomarkers of necrosis remain normal” (Braunwald et al., 2002). “Non-ST-elevation Myocardial Infarction (NSTEMI): similar clinical presentation (ischemic symptoms), usually with ECG changes such as ST-segment depression or T-wave inversion (or other non-ST-elevation changes) and positive serum markers of myocardial necrosis (troponin, CK-MB). This reflects myocardial injury without the classic ST-elevation pattern” (Anderson et al., 2007). “ST-elevation Myocardial Infarction (STEMI): myocardial infarction characterized by a persistent ST-segment elevation on ECG (or new left-bundle-branch block in some definitions) indicating acute transmural infarction, typically due to complete coronary occlusion. This was recognized as part of the ACS spectrum already in early 2000s, even if some guideline-documents focused on UA/NSTEMI” (Braunwald et al., 2002).
  - CS: “Cardiogenic shock is a state of circulatory failure due to primary cardiac pump dysfunction, resulting in markedly reduced cardiac output, systemic hypotension, impaired tissue perfusion, and consequent end-organ hypoxia/hypoperfusion” (Hollenberg et al., 1999).
  - HS: “Hemorrhagic shock is a form of circulatory shock characterized by a critically reduced intravascular blood volume due to acute bleeding, leading to inadequate tissue perfusion, reduced oxygen delivery, cellular hypoxia, end-organ dysfunction (or failure), and potentially death” (Gutierrez et al., 2004).

- SS: “Septic shock is defined as sepsis induced persistent arterial hypotension (or need for vasopressors) despite adequate fluid resuscitation, in the absence of other causes reflecting acute circulatory failure in the context of infection” (Levy et al., 2003).
- ARF: “Acute respiratory failure is broadly defined as a sudden (or rapid) inability of the respiratory system to maintain adequate gas exchange: to ensure sufficiently oxygenated arterial blood (and/or to eliminate carbon dioxide), leading to respiratory distress and often requiring ventilatory support (non-invasive or invasive)” (Forte et al., 2006).
- INF: “Infection is defined as the invasion of a host organism’s tissues by pathogenic or potentially pathogenic microorganisms (such as bacteria, viruses, fungi, protozoa or parasites), with their subsequent multiplication and establishment within the host, often accompanied by a host immune response and sometimes the production of toxins; this interaction may lead to cellular or tissue injury, clinical signs or symptoms (disease), or, in some cases, remain sub-clinical (colonization or asymptomatic infection)” (Calandra & Cohen, 2005).
- AHF: “Acute heart failure is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. It may occur with or without previous cardiac disease. Cardiac dysfunction can be related to systolic or diastolic dysfunction, abnormalities in cardiac rhythm, or a preload-afterload mismatch. It is often life-threatening and requires urgent treatment. AHF includes: De novo AHF: new onset AHF in a patient previously without known cardiac dysfunction. and acute decompensation of pre-existing CHF. Clinically, it may manifest with a variety of presentations, for example: acute pulmonary oedema, volume overload (congestion), acute dyspnea, orthopnea, fluid retention, and cardiogenic shock or hypertensive crisis, depending on the underlying cause” (“Executive Summary of the Guidelines on the Diagnosis and Treatment of Acute Heart Failure: The Task Force on Acute Heart Failure of the European Society of Cardiology,” 2005).
- AKI: “Acute renal failure is defined as an abrupt (within 24–48 hours) and sustained decline in kidney function, manifested by: increase in serum

creatinine (absolute or relative), and/or decrease in urine output (oliguria/anuria)" (Bellomo et al., 2004).

- SYN: "Syncope is a transient, self limited loss of consciousness, usually leading to falling. The onset is relatively rapid, and the mechanism is transient global cerebral hypoperfusion. Recovery is spontaneous, complete and usually prompt" (Brignole, 2001).
- MT: minor trauma is defined "as any combination of injuries resulting in an Injury Severity Score (ISS) less than 9" (Rapsang & Shyam, 2015).

4.5 Clinical risk stratification

For each subject, we performed a risk stratification of death, stroke/TIA risk and major bleeding risk using APACHE-II, $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores following their original definitions (Capuzzo et al., 2000; Friberg et al., 2012; Gage et al., 2004; Pisters et al., 2010). We calculated each score using the data obtained on the day of admission, and collected the results in our database.

4.6 Clinical Outcomes

The main outcome (MO) of the study was defined, as in our previous study, as the composite outcome of therapeutic failure (TF), defined as death or ICU transfer due to worsening clinical conditions.

We also defined the occurrence from admission in the ED to discharge stroke/TIA and MB as secondary outcomes. For each patient, we collected the occurrence of these two specific AF-related clinical events during hospitalisation, particularly (i) cardioembolic stroke and transient ischemic attack and (ii) MB according to the international society of haemostasis and thrombosis (ISTH) definition (Kaatz et al., 2015).

In this study, we defined the concurrent clinical events according to the definition that was current at the moment of the patients' admission:

- Cardioembolic stroke: According to the 2002-2007 WHO definition, this event was assigned in the case of a "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin" (Sacco et al., 2013).
- Cardioembolic TIA: According to the 2002-2007 WHO definition, this event was assigned as "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with clinical symptoms lasting less than 24 hours, and without evidence of acute infarction" (Coupland et al., 2017).
- MB: According to the ISTH "is defined as any bleeding that is fatal, and/or symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells" (SCHULMAN & KEARON, 2005).

4.7 Ethical issues

Our first study, the AFICILL 1.0, was approved by the institutional review board named CERM (Comitato Etico Regione Marche, Prot. 168/2018, 21 June 2018).

The present study, AFICILL 2.0, which extends the initial cohort, has been approved by the institutional review board named CET Marche (Comitato Etico Territoriale Marche, Prot. 164/2025, 19 June 2025). Written informed consent for the use of personal data was obtained from all enrolled subjects. Consent for the use of personal data from deceased patients or subjects unable to give consent was obtained from family members. All patients were treated in accordance with the clinical guidelines current at the time of hospital admission, by the attending physician.

4.8 Methodology for data analysis

The comprehensive AFICILL dataset consists of 46 clinical and instrumental variables evaluated during hospitalization for critical illness in patients with pNVAF. From this dataset, we extracted, utilizing TDA, 31 variables associated with the study outcomes.

The initial investigation (Falsetti et al., 2021) involved applying TDA to analyze three specific outcomes, MO, stroke/TIA, MB, using the Kepler Mapper algorithm. The Mapper method requires raw data (or samples), a clustering algorithm, specifically DBSCAN, which produces the number of clusters, and a filter function, termed the lens, computed on the members of each cluster, along with the percentage overlap among bins. For clarity, DBSCAN is an unsupervised clustering technique that groups data points in a metric space by identifying densely connected regions. The algorithm begins by selecting a sample and assigning it to the first cluster; subsequent iterations identify neighbouring points within a specified distance threshold and add them to the cluster. If no new neighbours are found, the algorithm proceeds by selecting another point to form a new cluster. The primary objective of the initial study was to evaluate the reliability of the CHA_2DS_2-VASc and HAS-BLED scores within this cohort, rather than to assess the accuracy of the clinicians' diagnoses of bleeding or thrombosis. These scores were employed as lenses in the construction of Mapper graphs, intended to reveal whether the dataset could be partitioned into distinct, independent subgroups (disconnected subgraphs), indicative of underlying clinical heterogeneity. To interpret the Mapper graphs, the lens values were cross-referenced with the binary outcomes (negative/positive). Results showed that patients with the lowest or highest score values generally aligned with their corresponding outcomes, negative or positive respectively, whereas individuals with intermediate scores exhibited inconsistent outcome predictions and potential misclassification. This suggests that intermediate score values represent ambiguous zones or "grey areas", necessitating further analysis to resolve underlying uncertainties. A more extensive description of this method can be retrieved in the original paper (Falsetti et al., 2021). The dataset was analyzed using TDA, and the pertinent topological features were compared through statistical testing. The results of these analyses informed the selection of relevant features.

In the first study, on the basis of the TDA results, three ML algorithms were developed: the first for stroke/TIA, considering both cardioembolic and non-cardioembolic ischemic stroke and TIA; the second for MB, including all non-traumatic major bleeding events according to ISTH criteria; and the third for MO, considering the composite outcome of death or transfer to the ICU.

To validate our three models (MO, stroke/TIA and MB), we selected and compared the 31 most pertinent clinical and demographic variables in both cohorts. Baseline differences between AFICILL 1.0 and AFICILL 2.0 cohort were assessed using t-tests for continuous variables and Fisher's Exact Test or Chi-Square Test for dichotomous and categorical variables. Each test evaluated the null hypothesis that the distributions of the variables were identical across both datasets.

Then, we further trained and tested the three ML models obtained with the original study with the new AFICILL 2.0 cohort, obtaining ROC curves to assess the accuracy of the models.

We also evaluated the predictive capabilities of various scoring systems for thromboembolic and bleeding risks, adopting ROC curve analysis. Specifically, the $CHADS_2$ and CHA_2DS_2-VASc scores were utilised to assess the likelihood of thromboembolic events, while the HAS-BLED score was applied to estimate bleeding risk. Additionally, the APACHE-II score was used to evaluate the risk of MO. We compared the accuracy of each score against the respective ML model. In particular, we compared the ROC curve of $CHADS_2$ and CHA_2DS_2-VASc with the stroke/TIA ML method, the ROC curve of HAS-BLED with the MB ML method and APACHE-II with the ML MO method. The comparisons of ROC curves were performed with the DeLong Method.

5. RESULTS

We obtained a total of 4196 patients admitted to our SDU with a diagnosis of pre-existing NVAF, comprising the AFICILL 1.0 (n=1705) and AFICILL 2.0 (n=2490) cohorts.

To obtain only medical, critically ill subjects from each group, we excluded patients undergoing elective cardioversion (n=242 from AFICILL 1.0 and n=60 from AFICILL 2.0) and patients with major trauma (n=137 from AFICILL 1.0 and n=328 from AFICILL 2.0), thus obtaining a final cohort of 3817 patients (n=1326 from AFICILL 1.0 and n=2105 from AFICILL 2.0). Baseline characteristics and differences between the first and second cohorts are summarised in Table 4.

Table 4: Baseline characteristics of the items of the AFICILL 1.0 and AFICILL 2.0 cohorts selected with TDA and adopted in the ML models.

Variable	**AFICILL 1.0 (n=1326)**	**AFICILL 2.0 (n=2105)**	**p**
Demographic characteristics			
Sex (n, %) [Female]	655 (49.3%)	1130 (53.7%)	0.9127
Age (mean, SD), years	77.1 ± 11.3	78.2 ± 8.6	<0.0001
Patients' comorbidities			
COPD (n, %)	302 (22.7%)	562 (26.7%)	0.296
HYP (n, %)	617 (46.5%)	1113 (52.9%)	0.7832
MMVD (n, %)	216 (16.3%)	483 (47.4%)	0.2659

CHF (n, %)	458 (34.5%)	704 (33.4%)	0.0818
Previous Stroke/TIA (n, %)	215 (16.2%)	134 (6.4%)	0.7690
CAD (n, %)	545 (41.0%)	564 (26.8%)	0.3131
MMAVD (n, %)	153 (11.5%)	379 (37.8%)	0.2417
PGB (n, %)	54 (4.1%)	171 (8.1%)	0.7722
Labile TTR (n, %)	51 (3.8%)	39 (1.9%)	0.2803
Treatments performed before admission			
Anticoagulants at Admission (n, %)	805 (60.6%)	1119 (61.0%)	0.2107
ASA or Clopidogrel Use (n, %)	519 (39.1%)	633 (30.1%)	0.8547
ACEi/ARB (n, %)	588 (44.3%)	672 (34.7%)	0.2061
Admission diagnoses			
SYN (n, %)	51 (3.8%)	131 (6.2%)	0.4254
ACS (n, %)	178 (13.4%)	164 (7.8%)	0.8883
CS (n, %)	34 (2.6%)	59 (2.8%)	1.0000
HS (n, %)	18 (1.4%)	28 (1.3%)	0.3203
SS (n, %)	136 (10.2%)	210 (10.0%)	0.3636
ARF (n, %)	273 (20.6%)	480 (22.8%)	0.752
INF (n, %)	226 (17.0%)	768 (36.5%)	0.1103

AHF (n, %)	597 (45.0%)	852 (40.5%)	0.0288
CKD (n, %)	219 (16.5%)	555 (26.4%)	0.5821
Admission vital parameters			
SBP (mean, SD), mmHg	128.7 ± 26.8	126.1 ± 22.8	<0.0001
DBP (mean, SD), mmHg	77.0 ± 16.0	0.1 ± 0.3	<0.0001
Drug treatments and procedures performed during hospitalization			
Amine (n, %)	346 (26.1%)	253 (12.6%)	0.3382
Propafenone/Flecainide (n, %)	152 (11.4%)	42 (2.1%)	0.2068
Electric Cardioversion (n, %)	168 (12.7%)	0 (0.0%)	0.6176
Amiodarone (n, %)	443 (33.4%)	656 (33.2%)	0.2087
Diuretics (n, %)	882 (66.4%)	1531 (78.8%)	0.2153
Clinical events occurring from ED admission to discharge			
Stroke/TIA (n, %)	199 (15.0%)	134 (6.4%)	<0.0001
MB (n, %)	140 (10.6%)	227 (10.8%)	0.3254
Main Outcome (n, %)	188 (14.1%)	314 (14.9%)	0.1934
In-hospital death (n, %)	152 (11.6%)	276 (13.1%)	0.0521
ICU Transfer (n, %)	36 (2.71%)	38 (1.8%)	0.2471

Of the 31 variables considered, 28 showed no statistically significant difference between the two datasets. Four variables differed significantly between AFICILL 1.0 and AFICILL 2.0. Specifically, we observed a statistically significant difference for age (77.1 ± 11.3 years in AFICILL 1.0 vs 78.2 ± 8.6 years in AFICILL 2.0, $p<0.0001$), SBP (128.7 ± 26.8 mmHg in AFICILL 1.0 vs 126.1 ± 22.8 mmHg in AFICILL 2.0, $p<0.0001$), DBP (77.0 ± 16.0 mmHg in AFICILL 1.0 vs 73.3 ± 12.6 mmHg in AFICILL 2.0, $p<0.0001$) and AHF (597 patients, 45.0% in AFICILL 1.0 vs 852 patients, 40.5% in AFICILL 2.0, $p=0.0289$). These differences, while statistically significant, are not extreme in scale and affect only a small subset of features.

Moreover, although statistically different, the differences are not clinically relevant, because the absolute variations in mean age (≈1.1 years), systolic and diastolic blood pressure (≈2.6 mmHg and ≈3.7 mmHg, respectively), and the prevalence of acute heart failure (≈4.5%) are too small to have a meaningful impact on patient management or outcomes in routine clinical practice. Despite minor differences in a few variables, the overall feature distribution between the two datasets is largely consistent.

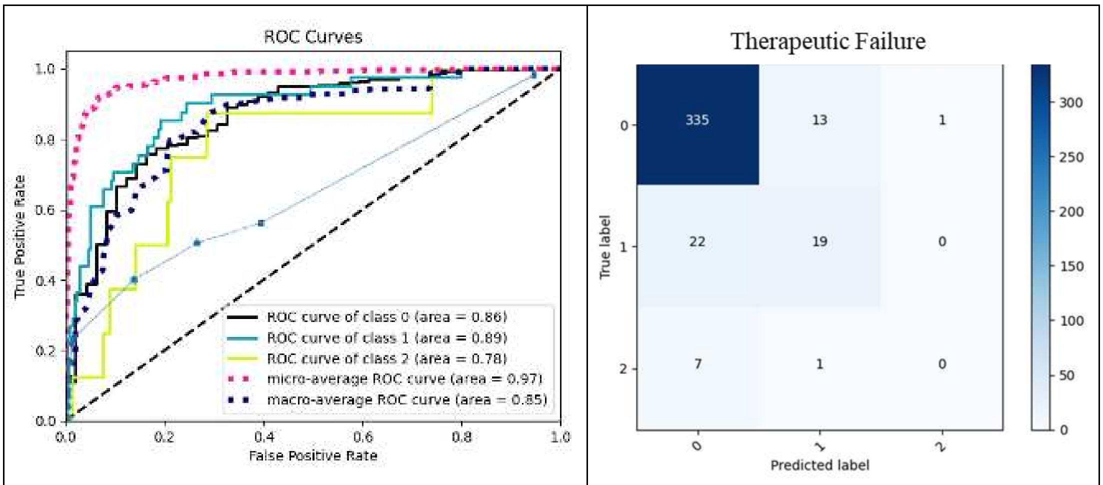
When assessing the outcomes, we observed no statistically significant differences in MO (188 patients, 14.1% in AFICILL 1.0 vs. 314 patients, 14.9% in AFICILL 2.0; $p = 0.1934$) or ICU transfer (36 patients, 2.7% in AFICILL 1.0 vs. 38 patients, 1.8% in AFICILL 2.0; $p = 0.2471$). For in-hospital death, the prevalence was numerically higher in AFICILL 2.0 (276 patients, 13.1%) than in AFICILL 1.0 (152 patients, 11.6%), with a borderline p-value ($p = 0.0521$), suggesting a possible trend that did not reach statistical significance. Overall, the two cohorts showed largely consistent outcome distributions, with only minor differences that are unlikely to be clinically meaningful. A highly significant difference in stroke/TIA prevalence was observed between the two cohorts (15.0% vs. 6.4%, $p < 0.0001$), indicating a markedly higher proportion of positive cases in the AFICILL 1.0 cohort. This difference was mainly due to a different adjudication of the stroke/TIA event: in the first study, we considered all the stroke/TIA, alone or in combination with systemic embolism, while in the second study we focused only on acute cerebral embolic events, removing vascular events or massive, systemic embolism associated with a high mortality. In a substudy of the AFICILL 1.0 cohort (Falsetti et al., 2020), when applying the same criteria used for AFICILL 2.0, we observed a markedly lower prevalence, similar to that observed in the AFICILL 2.0 cohort (110 subjects, 7.6%).

Thus, analysing the AFICILL 2.0 cohort as a validation set for the ML models generated with AFICILL 1.0, we can underline that: (i) the same feature set is available in both datasets; (ii) no data leakage is present (AFICILL 2.0 was not used during training); (iii) most variables are stable, ensuring compatibility with the model's assumptions and learned patterns. Therefore, AFICILL 2.0 can be deemed as suitable for external validation of the XGBoost model trained on AFICILL 1.0. This approach provides a robust test of the model's generalizability and performance in an independent cohort. Thus, we obtained substantial stability in the AUC of the three analysed ML algorithms, as shown in Table 5 and Figure 2. The statistical comparison is performed using an approximate version of the DeLong test based on the z-test.

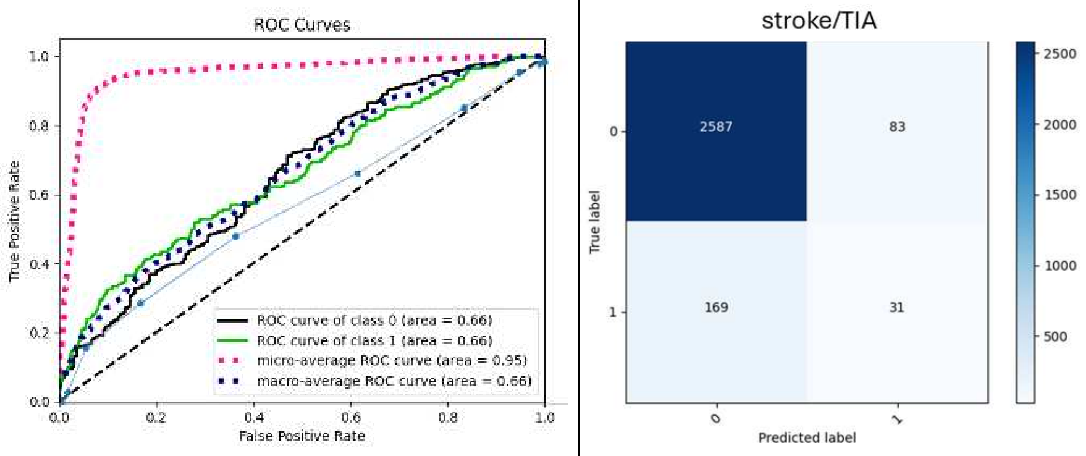
Table 5: Original models' performances and performances after validation.

Outcome	**AFICILL 1.0**	**AFICILL 2.0**	**z-score**	**p-value**
TF (AUC)	0.974	0.961	1.05	0.294
Stroke/TIA (AUC)	0.931	0.954	-1.82	0.069
MB (AUC)	0.930	0.973	-4.41	0.00001

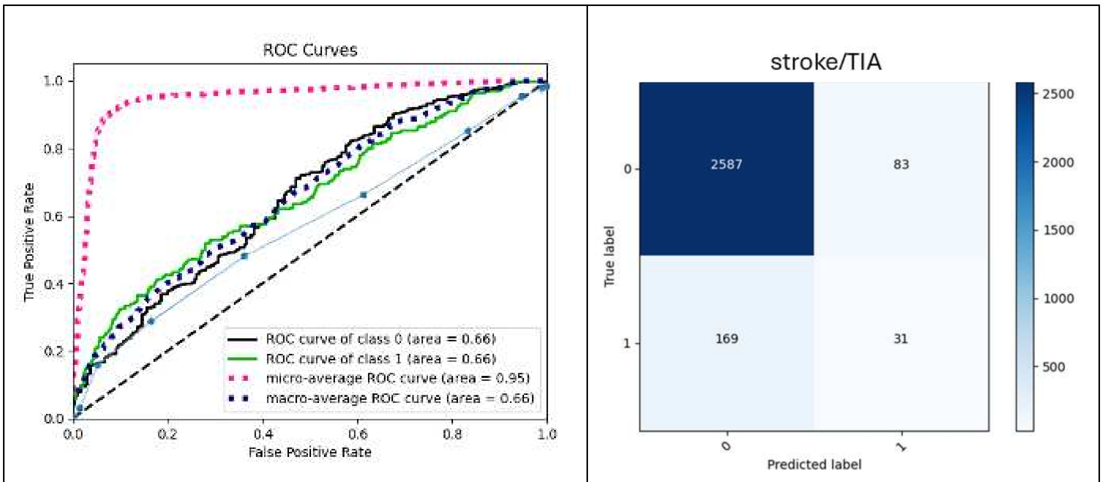
Figure 2: ROC curve analysis for ML performances on the AFICILL 2.0 cohort.



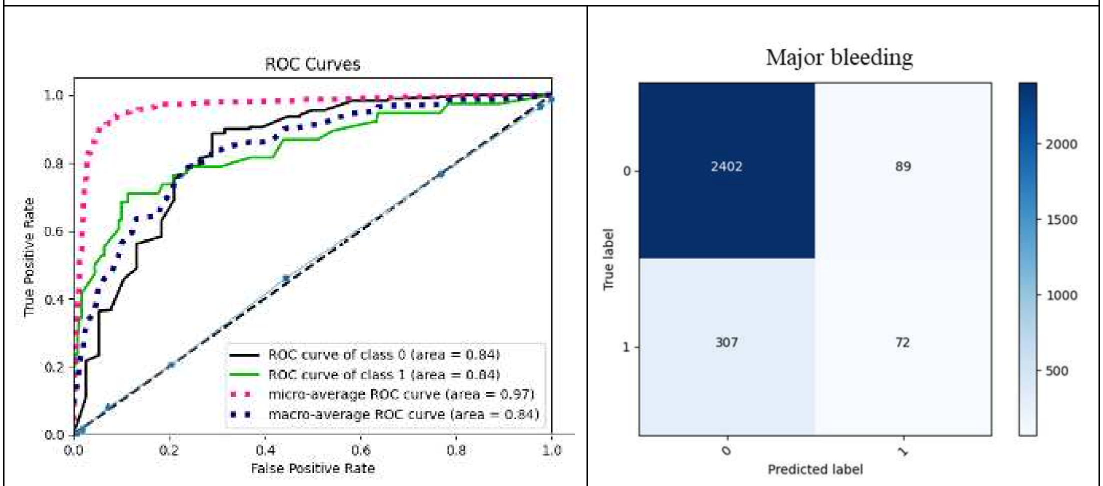
Panel A: Validation of ROC curve analysis for therapeutic failure for the ML algorithm. The sky-blue line represents the APACHE-II score with AUC = 0.6397



Panel B: Validation of ROC curve analysis for stroke/TIA for the ML algorithm. The sky-blue line represents the CHADS$_2$ score with AUC = 0.5775



Panel C: Validation of ROC curve analysis for stroke/TIA for the ML algorithm. The sky-blue line represents the CHA_2DS_2-VASC score with AUC = 0.5793



Panel D: Validation of ROC curve analysis for major bleeding for the ML algorithm. The sky-blue line represents the HAS-BLED score with AUC = 0.5089

Across all outcomes, we observed that ML models outperformed classical models in predicting them:

- Main Outcome: we tested the ROC curve analysis of the composite outcome on APACHE-II Score. Comparing the performances of APACHE-II against the ML classifier, we obtained a statistically significant difference (AUC APACHE-II: 0.6397; 95%CI 0.6064-0.6729; AUC ML: 0.96; 95%CI 94.6-97.2; $p<0.0001$, Figure 2, Panel A).
- Cardioembolic Stroke/TIA: the occurrence of stroke/TIA was not predicted correctly by both $CHADS_2$ and CHA_2DS_2-VASc. The ML prediction model overperformed the classical approach (AUC CHADS2: 0.5775; 95%CI: 0.5332-0.6218; $p<0.0001$; AUC CHA2DS2-VASc: 0.5793; 95%CI: 0.5357-0.6228; AUC ML: 0.95; 95%CI 94.3- 96.6; $p<0.0001$, Figure 2, Panel B and Panel C).
- Major Bleeding: the occurrence of MB was not predicted correctly by HAS-BLED score. The ML prediction model overperformed the classical approach (AUC HAS-BLED: 0.5089 95%CI 0.4786, 0.5392; AUC ML; 0.973 95%CI 95.5–98.1; $p<0.0001$, Figure 2, Panel D).

The statistical comparison was performed using a two-sided z-test of AUCs. The extremely low p-values obtained (< 0.0001 in all comparisons) indicate that the differences in AUC between classical risk scores and ML models are not due to chance. ML classifiers have a substantially superior discriminative ability compared with traditional scores. The magnitude of the AUC differences (e.g., 0.64 versus 0.96 for MO, 0.58 versus 0.95 for stroke/TIA, and 0.51 versus 0.97 for MB) further underscores that the gain is not only statistically significant but also clinically meaningful: the ML models approach near-perfect discrimination, while classical scores remain only slightly better than random guessing (AUC ≈ 0.5–0.6). Thus, these results highlight that ML approaches can capture outcome-relevant information far beyond what conventional risk scores provide.

6. DISCUSSION

6.1 Description of the population and severity assessment

The population examined in our study consists of elderly and frail patients with multimorbidity, typically presenting with two or more chronic conditions and frequently receiving multiple pharmacological treatments. These individuals present to the ED with an acute medical issue that further increases their clinical complexity and leads to admission to the SDU.

In addition, the patients in our cohort suffer from pNVAF. Anticoagulant therapy is a key component in the management of NVAF and plays a crucial role in improving both prognosis and survival. Critically ill, multimorbid patients with pNVAF who require hospitalisation are at increased risk of both thromboembolic and haemorrhagic events due to the interplay between acute illness, underlying arrhythmia, comorbidities, and polypharmacy. Consequently, their diagnostic and therapeutic management is particularly challenging. Notably, the current literature still lacks robust, evidence-based guidelines for optimal antithrombotic management in this patient population (Cook et al., 2008).

6.2 The role of ischemic risk assessment

Patients with pNVAF are at a heightened risk of thromboembolic events, particularly in the context of acute illness (Bikdeli et al., 2021). Currently, there is a lack of definitive guidelines regarding optimal anticoagulation strategies for critically ill patients with pNVAF. Notably, full anticoagulation with low-molecular-weight heparin has been linked to an increased MB risk, and with a non-significant in-hospital stroke/TIA incidence reduction. A recent sub-analysis of the AFICILL 1.0 study, limited to subjects with cardioembolic stroke, showed that a very low CHA_2DS_2-VASc score identified those at very low risk of ischemic events who might not require treatment despite their critical illness (Falsetti et al., 2020). However, these observations still require longitudinal data, and need further validation. Our observations, however, do not support the use of the $CHADS_2$ or CHA_2DS_2-VASc scores in guiding decisions regarding the initiation of systemic anticoagulation among patients with pNVAF during a critical illness. Our ML model for cardioembolic stroke mantained a stable accuracy in predicting the events between the two cohorts, showing its robustness in a larger cohort (Vitali et al., 2019).

6.3 The role of haemorragic risk assessment

Patients with pNVAF, who are at a substantially higher risk of cardioembolic events than the general population, are frequently treated with anticoagulant therapy. However, the use of these agents is inherently associated with an increased risk of bleeding complications.

In the patients examined, the individual risk of bleeding is increased due to several factors that can occur in the acute phase of a disease. In particular, stress ulcers, consumption of coagulation factors and reduced platelet count are common events in critically ill patients admitted to intensive and semi-intensive care units. Furthermore, the acute phase of some diseases requires the use of anticoagulants or antiplatelet drugs, which can exponentially increase the risk of bleeding.

Predicting the risk of bleeding is therefore essential in these patients but, despite this important need, in our cohort the HAS-BLED score did not show any accuracy in discriminating patients who had experienced major bleeding during hospitalisation, suggesting no role for this score in patients with a critical illness. Surprisingly, our ML model showed a significant improvement in predicting the MB events between the two cohorts, probably related to an improved training of the model (Cook et al., 2001; Falsetti et al., 2021; Subat et al., 2019).

6.4 Comment on ML and TDA techniques

With this paper we aimed to improve events prediction with new TDA and ML methods. These models have the ability to analyse a greater number of characteristics than those contained in the $CHADS_2$ and CHA_2DS_2VASc scores. $CHADS_2$ takes into account: congestive HF, HYP, age ≥ 75 years, diabetes mellitus, history of previous stroke or TIA. CHA_2DS_2VASc takes into account: congestive HF, HYP, age ≥ 75 years (2 points), diabetes mellitus, history of previous stroke or TIA, vascular disease, age 65-74 years (1 point), sex (1 point for women), as shown in Table 1 (Lip et al., 2010).

TDA and ML allow the patient's cardiovascular risk to be calculated by taking into account more items than those used by the two classic risk scores. Our approach has shown the better performance of these new methods compared to the $CHADS_2$ and CHA_2DS_2VASc scores, in predicting stroke/TIA in this larger cohort of critical patients with pNVAF. It is likely that the ability of TDA and ML to analyse more patient data than the classic scores allows them to obtain a more accurate predictive result that fully considers the complexity of these critically ill and multimorbid patients. In particular, some characteristics that could have a significant impact on the prediction of stroke/TIA that are not included in the scores but are taken into consideration by the TDA and ML are: diagnosis at the time of admission (e.g. AHF, ACS), physiological parameters (e.g. SBP, DBP) and therapeutic management during hospitalisation. Other elements calculated by the new methods that have been shown to play an important role in calculating the risk of acute cardioembolic events are comorbidities such as chronic lung and kidney diseases. It should be noted that both COPD and CKD have already been identified as additional risk factors for stroke/TIA during AF but, despite their high prevalence, they are not included in commonly used risk scores. Finally, the anticoagulant approach prior to hospitalisation has also been shown to be a determining factor in the level of cardioembolic risk in this specific category of patients. It must be underlined that our ML/TDA method to assess cardioembolic stroke/TIA adopted the $CHADS_2$ or the CHA_2DS_2-VASc scores as “lenses” for the Mapper algorythm (Falsetti et al., 2021). This concept must be underlined, since the methods adopted in AFICILL 1.0 and 2.0 do not aim to replace these score, but to extend them with more data and more effective statistical methods.

Regarding the prediction of bleeding risk, our study demonstrates the superiority of TDA and ML over the HAS-BLED score in critically ill patients with pNVAF. The HAS-BLED score takes the following items into consideration: HYP (uncontrolled high blood pressure, usually systolic > 160 mmHg), abnormal kidney or liver function, stroke (history of previous stroke), bleeding (history of major bleeding or predisposition to bleeding, e.g. anaemia), labile INR that is unstable or high international normalised ratio (INR), or time in therapeutic range < 60% (relevant to patients on Warfarin), elderly (age ≥ 65 years), drugs (use of medications that increase bleeding risk, e.g. antiplatelets, Non-Steroidal Anti-Inflammatory Drugs or NSAIDs) or excessive alcohol intake, as shown in Table 2.

Our study showed that in critically ill patients with pNVAF, HAS-BLED characteristics such as age, anaemia, previous gastrointestinal bleeding, low TTR and use of antiplatelet drugs are those most associated with MB. This confirms the predictive validity of using these items even in critically ill patients hospitalised for acute conditions. The newly developed methods have enabled the estimation of bleeding risk while simultaneously incorporating additional characteristics that have been shown to enhance the validity of risk prediction. Among these, relevant factors are: comorbid conditions, indicators specific to critical illness, such as acute events leading to hospitalization, physiological parameters at the time of admission, and ongoing anticoagulant therapy. It must be underlined that our ML/TDA method to assess haemorragic risk adopted the HAS-BLED score as a “lens” for the Mapper algorythm (Falsetti et al., 2021). This concept must be underlined, since the methods adopted in AFICILL 1.0 and 2.0 do not aim to replace these score, but to extend them with more data and more effective statistical methods.

Our method also enabled the development of an accurate prediction model for MO, incorporating both general and NVAF-specific factors, as cardioembolic stroke/TIA and MB. Notably, these two items exerted a decisive influence on MO, underscoring the urgent need for dedicated models capable of accurately predicting thromboembolic and haemorrhagic events in this setting. Such models are essential for improving clinical management and reducing in-hospital mortality.

6.5 Potential evolutions of the method

In recent years, several research efforts have aimed to develop novel risk scores capable of predicting thromboembolic and haemorrhagic events in patients with AF with greater accuracy than $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED. However, in all cases, the predictive performance of these scores proved suboptimal when applied outside their original derivation cohorts. A systematic review demonstrated that these newer models exhibited predictive abilities comparable to those of the traditional risk scores, irrespective of the larger number of variables included or the use of differential weighting.

An effective clinical score reflects an optimal balance between evidence, practicality, and robustness. The findings presented in this study indicate that more advanced analytical strategies can contribute to the development of more effective predictive models. ML techniques enable the evaluation of a greater number of patient characteristics than traditional scoring systems, thereby offering a more accurate and comprehensive risk assessment. Moreover, recent advances in computational performance allow ML algorithms to process increasingly large amounts of information with greater speed. The ability to obtain rapid risk-prediction outputs will be essential for implementing this approach in settings such as ED, SDUs, and ICUs, where prompt decision-making is critical to daily clinical practice.

The dissemination of electronic medical records, into which patient data can be systematically integrated, will be of fundamental importance. These computerised records can be used by the ML system to immediately obtain data and quickly perform predictive computations. This would enable clinicians to obtain immediate estimates of both thrombotic and haemorrhagic risk for the patient under evaluation. Moreover, the widespread use of mobile applications among healthcare professionals could further enhance the accessibility and applicability of these methods. Nonetheless, it is essential to underscore that predictive models are intended to support and inform clinical decision-making, rather than replace clinical judgement (Borre et al., 2018; Proietti et al., 2018).

7. STUDY LIMITATIONS

The principal limitation of this work lies in its study design, which is a retrospective observational analysis conducted on a cohort not previously identified for a scientific research purpose. Certain variable, such as the time elapsed since the diagnosis of AF, were not available and should be considered in future integrations of the model. More extensive, multicentre, prospective external validations will be necessary to confirm our results and make the new TDA and ML methods safely and generally applicable to all real-life settings.

Secondly, only vitamin K antagonists were used as oral anticoagulants in the cohort of patients analysed, as the time frame within which the patients were recruited predates the marketing of new oral anticoagulants (NOACs) in Italy, which began in 2013 (Abrignani et al., 2022). It is likely that the introduction of NOACs has reduced the risk of bleeding in these patients, but in any case, some difficulties in choosing the most appropriate therapy would continue to persist, which justifies and promotes the idea of extending the study to also analyse this population of patients treated with more modern therapies. We also assessed adherence to current anticoagulant therapy guidelines in a retrospective cohort, when the current reference guidelines had not yet been published, although this was done purely for exploratory purposes, allowing us to project the current guideline recommendations onto our cohort. Although these limitations must be taken into account when extending our results to the overall population with AF, the evidence we have provided has important implications for the clinical management of patients with AF admitted to the ED and ICU.

Moreover, we did not consider the newer CHA_2DS_2-VA score, which is now suggested by guidelines, since this score was not current at the moment of the study and was not used to guide anticoagulant therapy in the considered timeframe (Van Gelder et al., 2024).

Another critical aspect concerns the rapid and dynamic evolution of thrombotic and haemorrhagic risk in critically ill patients. As their clinical condition changes, continuous reassessment becomes essential. Accordingly, validation should be conducted using a dynamically updated, daily dataset incorporating patients' physiological parameters, laboratory and instrumental findings, as well as the therapies and procedures administered. Such an approach would enable real-time risk estimation, providing clinicians with frequent and timely updates on fluctuations in patients' thrombotic and haemorrhagic risk.

Another limit is associated to a different definition of stroke/TIA between the cohorts. In the AFICILL 2.0 we considered only the ones with cardioembolic origin, while in the first cohort we adopted a less strict criterion. Despite this difference, we did not observe any improvement in stroke/TIA prediction between AFICILL 1.0 and AFICILL 2.0 adopting $CHADS_2$ and CHA_2DS_2-VASc, and the quality of the prediction of the ML model did not change, underlying the robustness of the method.

A further limitation of the study arises from the current technological, ethical, and regulatory constraints associated with the implementation of ML in real-world clinical settings. Many EDs, SDUs, and ICUs are still not equipped with electronic or computerised medical records, which are essential for the rapid data acquisition required by ML systems. Moreover, the computational processes involved in analysing large volumes of patient-specific data are not yet capable of generating predictions with sufficient speed to match the rapid decision-making workflow that characterises clinical practice in these settings. Conversely the substantial investments and rapid advancements in ML computational infrastructure, suggest that systems capable of performing large-scale calculations and generating predictions in a timeframe compatible with the fast-paced workflow of these clinical settings, may become available in the near future. Regarding the ethical and regulatory challenges associated with implementing ML systems in real-world medical practice, multiple initiatives are currently underway to address these concerns. For instance, the European Commission has outlined a set of seven requirement, encompassing both ethical principles and technical guideline, that aim to facilitate the translation of artificial intelligence technologies into practical, clinically applicable tools (Hickman & Petrin, 2021).

8. CONCLUSIONS

This study, conducted in a larger cohort of critically ill patients with pNVAF, corroborates the findings of our previous analysis in a smaller cohort. As already observed in our first study, we confirm the poor performance of the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED risk scores in predicting stroke/TIA and MB, respectively, in this specific patient group.

Both our ML and TDA-based algorithms preserved superior performance in predicting stroke/TIA and MB when compared with traditional risk scores in this patient population.

Furthermore, our results confirm the accuracy of these methods in predicting the primary outcome, defined as the composite of death and ICU transfer.

Our findings lay the groundwork for the design of subsequent prospective, multicentric studies. This research would be helpful to further validate our data, making the new ML methods applicable in the everyday clinical practice, improving the antithrombotic management of critically ill patients with pNVAF. A potential improvement of our methods could be the sequential assessment of the risk by connecting the ML algorithms with a continuous source of data, as an electronic medical record. This would improve the speed and consistency of the risk assessment, particularly in response to variations in clinical conditions. This could allow these methods to be highly effective in the ED, SDU, and ICU, where the haemorrhagic and thrombotic risk is expected to change daily, and the promptness of action plays an essential role in the diagnostic-therapeutic management of patients.

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