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# Phenotypic clustering of patients hospitalized in intensive cardiac care units: Insights from the ADDICT-ICCU study

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**Keywords:**

Clustering analysis; Unsupervised machine learning; Cardiac intensive care unit  
Acute cardiac event; Heart failure

**Mots-clés :**

Analyse de regroupement ; Apprentissage automatique non supervisé ; Unité de soins intensifs cardiaques ; Événement cardiaque aigu, Insuffisance cardiaque

## 1. Abbreviations

ACS acute coronary syndromes

CAD coronary artery disease

CI confidence interval

HF heart failure

HFmEF heart failure with mid-range ejection fraction

HFpEF heart failure with preserved ejection fraction

HF<sub>r</sub>EF heart failure with reduced ejection fraction

ICCU intensive cardiac care unit

Kamila KAY-means for MIXed LARge data sets

LA left atrial

LV left ventricular

LVEF left ventricular ejection fraction

LVOT VTI left ventricular outflow tract velocity time integral

MAE major adverse event

MDMA 3,4-methylenedioxymethamphetamine

NSTEMI non-ST-segment elevation myocardial infarction

NT-proBNP N-terminal pro-B-type natriuretic peptide

OR odds ratio

PCI percutaneous coronary intervention

PG phenogroup

SD standard deviation

sPAP systolic pulmonary artery pressure

STEMI ST-segment elevation myocardial infarction

TAPSE tricuspid annular plane systolic excursion

# ABSTRACT

## ***Background.***

– Intensive cardiac care units (ICCUs) were created to manage ventricular arrhythmias after acute coronary syndromes, but have diversified to include a more heterogeneous population, the characteristics of which are not well depicted by conventional methods.

## ***Aims.***

– To identify ICCU patient subgroups by phenotypic unsupervised clustering integrating clinical, biological and echocardiographic data to reveal pathophysiological differences.

## ***Methods.***

– During 7–22 April 2021, we recruited all consecutive patients admitted to ICCUs in 39 centres. The primary outcome was in-hospital major adverse events (MAEs; death, resuscitated cardiac arrest or cardiogenic shock). A cluster analysis was performed using a Kamila algorithm.

## ***Results.***

– Of 1499 patients admitted to the ICCU (69.6% male, mean age  $63.3 \pm 14.9$  years), 67 (4.5%) experienced MAEs. Four phenogroups were identified: PG1 ( $n = 535$ ), typically patients with non-ST-segment elevation myocardial infarction; PG2 ( $n = 444$ ), younger smokers with ST-segment elevation myocardial infarction; PG3 ( $n = 273$ ), elderly patients with heart failure with preserved ejection fraction and conduction disturbances; PG4 ( $n = 247$ ), patients with acute heart failure with reduced ejection fraction. Compared to PG1, multivariable analysis revealed a higher risk of MAEs in PG2 (odds ratio [OR] 3.13, 95% confidence interval [CI] 1.16–10.0) and PG3 (OR 3.16, 95% CI 1.02– 10.8), with the highest risk in PG4 (OR 20.5, 95% CI 8.7–60.8) (all  $P < 0.05$ ).

## ***Conclusions.***

– Cluster analysis of clinical, biological and echocardiographic variables identified four phenogroups of patients admitted to the ICCU that were associated with distinct prognostic profiles.

## ***Trial registration.***

– ClinicalTrials.gov identifier: NCT05063097.

# RÉSUMÉ

## **Contexte.**

– Les unités de soins intensifs cardiaques (USIC) ont été initialement créées pour gérer les arythmies ventriculaires survenant après un syndrome coronaire aigu. Cependant, les USIC ont diversifié leur activité en incluant une population de plus en plus hétérogène, mais ses caractéristiques ne sont pas bien représentées par les méthodes conventionnelles.

## **OBJECTIFS.**

– Identifier les sous-groupes de patients par regroupement phénotypique non supervisé de type *clustering* intégrant des données cliniques, biologiques et échocardiographiques pour révéler les différences physiopathologiques sous-jacentes entre les différents sous-groupes de patients admis en USIC.

## **Méthodes.**

– Du 7 au 22 avril 2021, nous avons recruté tous les patients consécutifs admis en USIC dans 39 centres français. Le critère de jugement principal composite était les événements cardiaques indésirables majeurs (MAE) survenus à l'hôpital, définis par le décès toute cause, un arrêt cardiaque récupéré ou un choc cardiogénique. Une analyse groupée de type *clustering* a été réalisée à l'aide de l'algorithme Kamila.

## **Résultats.**

– Sur 1499 patients admis en USIC (69,6 % d'hommes, âge moyen  $63,3 \pm 14,9$  ans), 67 patients ont présenté un MAE (4,5 %). Quatre phénogroupes (PG) distincts ont été identifiés : PG1 ( $n = 535$ ), typiquement patients avec syndrome aigu sans élévation du ST ; PG2 ( $n = 444$ ), jeunes fumeurs avec syndrome aigu avec élévation du ST ; PG3 ( $n = 273$ ), patients âgés avec une insuffisance cardiaque à FEVG préservée et des troubles de la conduction ; et PG4 ( $n = 247$ ), patients avec une insuffisance cardiaque à FEVG réduite aiguë. En utilisant une analyse de régression, la survenue des MAE différait entre les quatre phénogroupes ( $P < 0,001$ ). Par rapport au PG1 de référence, l'analyse multivariée a révélé que le PG2 et le PG3 avaient un plus mauvais pronostic, et que le PG4 avait le pire pronostic en ce qui concerne la survenue de MAE (PG2 : OR 3,13, IC 95 % 1,16–10,0 ; PG3 : OR 3,16, IC 95 % 1,02–10,8 ; PG4 : OR 20,5, IC 95 % 8,7–60,8 ; tous  $P < 0,05$ ).

## **Conclusions.**

– L'analyse groupée de type « *clustering* » des variables cliniques, biologiques et échocardiographiques a identifié quatre phénogroupes de patients admis en USIC associés à des profils pronostiques distincts.

## 2. Background

Coronary care units originated in the 1960s with the aim of rapidly treating patients with dysrhythmias after acute myocardial infarction [1,2]. However, these have evolved and adopted a more comprehensive term, namely intensive cardiac care units (ICCUs), since they are no longer dedicated to ‘coronary’ issues [3,4]. Indeed, the heterogeneity of the admitted population has expanded to include older patients with miscellaneous cardiac diseases and patients with non-cardiac comorbidities [5]. For these reasons, the demand for cardiovascular critical care is increasing as the population ages and this is reflected in the trends in the use of critical care in general.

Recently, expert groups from international professional societies have identified a need for ICCUs to adapt to this evolving landscape of cardiac critical care and called for additional research to quantitatively characterize the demographics, diagnoses, management and outcomes in contemporary ICCUs to guide such a redesign [4,6,7]. However, and as mentioned above, the epidemiological features and prognostic profiles of patients hospitalized for acute cardiac events in ICCUs are heterogeneous, particularly in terms of age, distribution of traditional risk factors and comorbidities.

Answering this issue with traditional statistical analyses appears to be challenging since they are built on a priori hypotheses. On the contrary, cluster analysis using unsupervised algorithms provides new perspectives for accurate phenotyping in heterogeneous populations such as patients with heart failure (HF) [8] or coronary artery disease (CAD) [9,10].

Therefore, we hypothesized that a clustering approach could highlight different phenogroups with specific clinical and prognostic profiles in patients hospitalized in ICCUs. The study aimed to:

- identify phenogroups among consecutive patients hospitalized in ICCUs using an unsupervised clustering approach based on clinical, biological and echocardiographic data;
- describe their clinical profiles;
- compare intra-hospital outcomes in the different phenogroups.

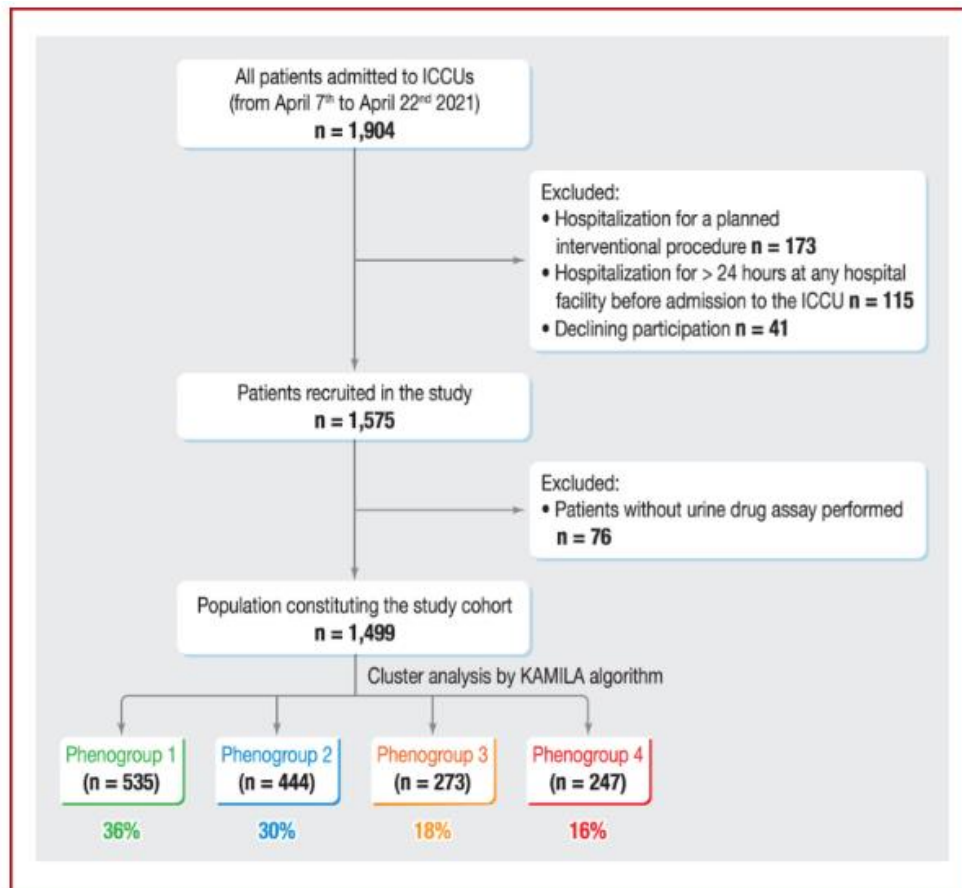
## 3. Methods

### 3.1. Study population

Details about the design of the Addiction in Intensive Cardiac Care Units (ADDICT-ICCU) study have previously been published [11]. Briefly, the ADDICT-ICCU study is a multicentre, prospective, observational study of all consecutive patients aged  $\geq 18$  years admitted to ICCUs for 2 weeks in April 2021 in 39 centers across France (Table A.2) [12]. The main exclusion criterion was hospitalization for a planned interventional procedure in order to focus the analysis on patients evaluated in an emergency setting for an acute cardiovascular event. Full inclusion and exclusion criteria are presented in Table A.3. The methodology for the collection of baseline characteristics is detailed in Text A.1. The main admission diagnosis was adjudicated by two independent experts at the end of the

hospitalization following the guidelines in each center (Text A.2 and Table A.4). The treatment of each patient was at the discretion of the treating physicians following the current European Society of Cardiology guidelines.

The study was registered at ClinicalTrials.gov (NCT05063097) and approved by the Committee for the Protection of Human Subjects, Île-de-France-7, France. The study was evaluated and approved by the local ethics committee of our institutions and conducted in accordance with the 1964 Declaration of Helsinki. All patients enrolled in this study were required to understand and give their consent for participation. This study followed the STROBE reporting guidelines for cohort studies.



**Fig. 1.** Study flowchart. ICCU: intensive cardiac care unit; Kamila: KAY-means for MIXed LARge data sets.

### 3.2. Clinical outcomes

The primary outcome was in-hospital major adverse events (MAEs), including in-hospital death, resuscitated cardiac arrest (severe ventricular arrhythmia requiring defibrillation or intravenous anti-arrhythmic agents) or cardiogenic shock requiring medical or mechanical haemodynamic support [13]. All events, including the in-hospital MAEs, were adjudicated by an independent committee of experts who reviewed anonymized medical documents according to standardized definitions [14].



**Table 1**  
Baseline characteristics stratified by phenogroup.

	All patients (n = 1499)	Phenogroup 1 (n = 535)	Phenogroup 2 (n = 444)	Phenogroup 3 (n = 273)	Phenogroup 4 (n = 247)	P
<b>Demographic data</b>						
Age (years)	63.3 ± 14.9	66.3 ± 10.5	50.0 ± 13.3	74.7 ± 9.3	68.0 ± 13.9	<0.001
Male	1043 (69.6)	388 (72.5)	315 (70.9)	168 (61.5)	172 (69.6)	0.003
Body mass index (kg/m <sup>2</sup> )	27.3 ± 5.4	27.8 ± 5.2	26.3 ± 5.0	28.4 ± 6.4	26.6 ± 5.3	<0.001
<b>Cardiovascular risk factors</b>						
Diabetes mellitus	326 (21.7)	106 (19.8)	24 (5.4)	133 (48.7)	63 (25.5)	<0.001
Hypertension	795 (53.0)	351 (65.6)	57 (12.8)	236 (86.4)	151 (61.1)	<0.001
Dyslipidaemia	582 (38.8)	246 (46.0)	60 (13.5)	178 (65.2)	98 (39.7)	<0.001
Current/former smoker	380 (25.4)	84 (15.7)	222 (50.0)	13 (4.8)	61 (24.7)	<0.001
Family history of CAD	247 (16.5)	115 (21.5)	83 (18.7)	30 (11.0)	19 (7.7)	<0.001
<b>Drug and substance consumption</b>						
Illicit drug use	161 (10.7)	22 (4.1)	107 (24.1)	8 (2.9)	24 (9.7)	<0.001
Alcohol use at least once a week	799 (53.3)	334 (62.4)	241 (54.3)	109 (39.9)	115 (46.6)	<0.001
Carbon monoxide level (ppm)	4.90 ± 4.75	4.26 ± 3.67	6.70 ± 6.13	3.44 ± 2.75	4.68 ± 4.78	<0.001
<b>Medical history of cardiovascular disease</b>						
Known myocardial infarction	234 (15.6)	76 (14.2)	31 (7.0)	70 (25.6)	57 (23.1)	<0.001
Previous PCI	482 (32.2)	231 (43.2)	173 (39.0)	43 (15.8)	35 (14.2)	<0.001
Previous coronary artery bypass grafting	51 (3.4)	12 (2.2)	2 (0.5)	18 (6.6)	19 (7.7)	<0.001
Stroke	3 (0.2)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.4)	0.503
<b>Known chronic kidney disease</b>						
Low or absence (GFR > 60 mL/min/1.73 m <sup>2</sup> )	13 (0.9)	4 (0.7)	3 (0.7)	4 (1.5)	2 (0.8)	<0.001
Moderate (GFR 30–60 mL/min/1.73 m <sup>2</sup> )	93 (6.2)	10 (1.9)	7 (1.6)	45 (16.5)	31 (12.6)	<0.001
Severe (GFR < 30 mL/min/1.73 m <sup>2</sup> )	49 (3.3)	2 (0.4)	2 (0.5)	28 (10.3)	17 (6.9)	<0.001
History of HF hospitalization	88 (5.9)	8 (1.5)	5 (1.1)	33 (12.1)	42 (17.0)	<0.001
Known LVEF < 50%	102 (6.8)	11 (2.1)	12 (2.7)	32 (11.7)	47 (19.0)	<0.001
History of atrial fibrillation	175 (11.7)	28 (5.2)	11 (2.5)	67 (24.5)	69 (27.9)	<0.001
<b>Medical history of non-cardiovascular disease</b>						
Active cancer	61 (4.1)	15 (2.8)	6 (1.4)	26 (9.5)	14 (5.7)	<0.001
Human immunodeficiency virus	13 (0.9)	2 (0.4)	7 (1.6)	0 (0.0)	4 (1.6)	0.030
Chronic obstructive pulmonary disease	67 (4.5)	17 (3.2)	10 (2.3)	19 (7.0)	21 (8.5)	<0.001
Psychiatric history	156 (10.4)	59 (11.0)	39 (8.8)	29 (10.6)	29 (11.7)	0.57
<b>Chronic medications</b>						
Anticoagulant/antiplatelet aggregation	661 (44.1)	215 (40.2)	76 (17.1)	206 (75.5)	164 (66.4)	<0.001
Antihypertensive	816 (54.4)	327 (61.1)	96 (21.6)	232 (85.0)	161 (65.2)	<0.001
Statins	502 (33.5)	195 (36.4)	47 (10.6)	163 (59.7)	97 (39.3)	<0.001
<b>Clinical parameters at admission</b>						
Systolic blood pressure (mmHg)	136 ± 27	147 ± 23	122 ± 20	140 ± 26	134 ± 31	<0.001
Diastolic blood pressure (mmHg)	79 ± 17	84 ± 15	77 ± 15	70 ± 14	84 ± 21	<0.001
Pulse blood pressure (mmHg)	57.2 ± 21.6	62.8 ± 20.0	45.8 ± 14.1	70.8 ± 22.8	50.5 ± 21.8	<0.001
Heart rate (bpm)	83 ± 24	78 ± 20	83 ± 21	72 ± 21	103 ± 27	<0.001
Oxygen saturation (%)	97 ± 5	98 ± 2	97 ± 8	97 ± 3	96 ± 4	0.026
<b>Killip class</b>						
I	1245 (83.1)	514 (96.1)	430 (96.8)	208 (76.2)	93 (37.7)	<0.001
II	169 (11.3)	12 (2.2)	10 (2.3)	48 (17.6)	99 (40.1)	<0.001
≥ III	85 (5.7)	9 (1.7)	4 (0.9)	17 (6.2)	55 (22.3)	<0.001
Clinical right HF	133 (8.9)	4 (0.7)	4 (0.9)	38 (13.9)	87 (35.2)	<0.001
<b>Biological parameters at admission</b>						
Haemoglobin (g/L)	136 ± 19	143 ± 14	142 ± 16	117 ± 18	129 ± 21	<0.001
Creatinine (μmol/L)	96.4 ± 69.1	81.9 ± 28.0	76.0 ± 28.0	138 ± 118	118 ± 83.4	<0.001
High-sensitivity cardiac troponin peak (IU)	12,000 ± 34,118	11,593 ± 31,717	20,595 ± 47,840	4303 ± 11,811	5938 ± 19,819	<0.001
NT-proBNP (ng/L)	700 (169–2675)	342 (72–777)	573 (189–1177)	845 (210–3402)	1450 (722–9706)	<0.001
<b>Echocardiographic data</b>						
LVEF (%)	52.0 ± 13.1	56.7 ± 8.9	53.6 ± 10.6	54.7 ± 11.1	36.1 ± 14.8	<0.001
LV end-diastolic volume (mL/m <sup>2</sup> )	109 ± 43	100 ± 34	103 ± 34	111 ± 42	139 ± 60	<0.001
LA volume (mL)	48.5 ± 25.0	43.5 ± 22.6	41.2 ± 14.9	52.1 ± 25.6	68.6 ± 31.5	<0.001
LA dilatation	265 (17.7)	33 (6.2)	39 (8.8)	64 (23.4)	129 (52.2)	<0.001
E/A ratio (cm/s)	1.13 ± 0.52	0.96 ± 0.34	1.08 ± 0.36	1.13 ± 0.44	1.56 ± 0.82	<0.001
E/e' ratio (cm/s)	9.0 ± 3.4	8.3 ± 2.5	7.6 ± 2.4	10.5 ± 3.6	11.4 ± 4.6	<0.001
RV dilatation	103 (6.9)	18 (3.4)	21 (4.7)	15 (5.5)	49 (19.8)	<0.001
LVOT VTI (cm)	19 ± 5	20 ± 4	19 ± 4	22 ± 6	15 ± 5	<0.001
sPAP (mmHg)	35 ± 12	31 ± 8	32 ± 10	38 ± 10	46 ± 14	<0.001
TAPSE (mm)	20.9 ± 4.2	21.5 ± 3.9	21.5 ± 3.9	21.4 ± 4.0	17.6 ± 4.3	<0.001
<b>Admission diagnosis</b>						
NSTEMI	438 (29.2)	241 (45.0)	76 (17.1)	87 (31.9)	34 (13.8)	<0.001
STEMI	334 (22.3)	115 (21.5)	176 (39.6)	24 (8.8)	19 (7.7)	<0.001
Acute heart failure	211 (14.1)	4 (0.7)	4 (0.9)	56 (20.5)	147 (59.5)	<0.001
HFREF (LVEF ≤ 40%)	107 (7.1)	0 (0.0)	2 (0.5)	6 (2.2)	99 (40.1)	<0.001
HFmEF (41% ≤ LVEF ≤ 49%)	26 (1.7)	1 (0.2)	0 (0.0)	6 (2.2)	19 (7.7)	<0.001
HFpEF (LVEF ≥ 50%)	78 (5.2)	3 (0.6)	2 (0.5)	44 (16.1)	29 (11.7)	<0.001
Unexplained chest pain	102 (6.8)	56 (10.50)	34 (7.7)	12 (4.4)	0 (0.0)	<0.001
Conduction disturbances	83 (5.5)	18 (3.4)	5 (1.1)	58 (21.2)	2 (0.8)	<0.001
Pericarditis or myocarditis	73 (4.9)	10 (1.9)	47 (10.6)	9 (3.3)	7 (2.8)	<0.001
Pulmonary embolism	46 (3.1)	17 (3.2)	16 (3.6)	3 (1.1)	10 (4.0)	<0.001
Coronary spasm, aortic coronary dissection	41 (2.7)	13 (2.4)	23 (5.2)	1 (0.4)	4 (1.6)	<0.001
dissection, Takotsubo syndrome or spontaneous						
Ventricular arrhythmia	34 (2.3)	10 (1.9)	11 (2.5)	7 (2.6)	6 (2.4)	<0.001
Other	77 (5.1)	23 (4.3)	32 (7.2)	12 (4.4)	10 (4.0)	<0.001
<b>Outcomes</b>						
MAE	67 (4.5)	5 (0.9)	13 (2.9)	8 (2.9)	41 (16.6)	<0.001
Death	27 (1.8)	2 (0.4)	3 (0.7)	5 (1.8)	17 (6.9)	<0.001
Hospitalization duration (days)	7.5 ± 21.0	6.7 ± 22.9	6.4 ± 20.1	7.2 ± 16.4	11.6 ± 22.5	0.008
Hospitalization duration in ICCU (days)	2.9 ± 4.2	2.4 ± 2.1	2.6 ± 3.3	3.2 ± 6.2	4.5 ± 5.8	<0.001
<b>Location after ICCU hospitalization</b>						
Home (discharge)	1127 (75.2)	439 (82.1)	369 (83.1)	180 (65.9)	139 (56.3)	<0.001
Conventional cardiology	188 (12.5)	59 (11.0)	40 (9.0)	49 (17.9)	40 (16.2)	<0.001
Cardiovascular surgery	35 (2.3)	14 (2.6)	7 (1.6)	7 (2.6)	7 (2.8)	<0.001
Non-cardiovascular intensive care	10 (0.7)	3 (0.6)	4 (0.9)	0 (0.0)	3 (1.2)	<0.001
Other	122 (8.1)	11 (2.1)	23 (5.2)	36 (13.2)	52 (21.1)	<0.001

Data are expressed as mean ± standard deviation, median (interquartile range) or number (%). CAD: coronary artery disease; GFR: glomerular filtration rate; HF: heart failure; HFmEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFREF: heart failure with reduced ejection fraction; ICCU: intensive cardiac care unit; LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; LVOT VTI: left ventricular outflow tract velocity time integral; MAE: major adverse event; NSTEMI: non ST-segment elevation myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCI: percutaneous coronary intervention; sPAP: systolic pulmonary artery pressure; STEMI: ST-segment elevation myocardial infarction; TAPSE: tricuspid annular plane systolic excursion.

### 3.3. Cluster analysis

A total of 55 clinical characteristics, including biological and echocardiographic data, were collected. The absence of collinearity between these 55 baseline variables was previously verified using the variance inflation factor and Pairwise correlation for numeric and categorical predictors (collinear R package). After the exclusion of collinear variables, 29 variables were selected for the clustering model and the definition of phenogroups: age, gender, body mass index, hypertension, dyslipidaemia, diabetes mellitus, known CAD, systolic blood pressure, diastolic blood pressure, heart rate, Killip class, haemoglobin, creatinine, peak troponin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), presence of left atrial (LA) dilatation defined by indexed LA end-diastolic volume  $\geq 34$  mL/m<sup>2</sup> [15], presence of left ventricular (LV) dilatation defined by indexed LV end-diastolic volume  $\geq 61$  mL/m<sup>2</sup> for women and  $\geq 74$  mL/m<sup>2</sup> for men [15], E/A ratio, E/e' ratio, LV outflow tract velocity time integral (LVOT VTI), tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (sPAP), right HF clinical sign, alcohol consumption, current or former smoker, level of carbon monoxide, illicit drug use and the final cardiovascular diagnosis. Due to a similar number of continuous and categorical variables, we used a clustering algorithm for mixed data. Because our data did not follow the normal-multinomial hypothesis, the use of the KAy-means for MIXed LArge data sets (Kamila) and K-prototypes algorithms are more efficient in the context of heterogeneous mixed data [16]. Based on statistical assessment, the Kamila algorithm (Kamila R package) performed better than K-prototypes (clustMixType R package, Text A.3). Using the prediction strength method [17], the optimal number of clusters to have relevant subgroups was 4 (Text A.3).

### 3.4. Statistical analysis

Descriptive results are presented as percentages for categorical data and mean  $\pm$  standard deviation (SD) or median (interquartile range) for continuous variables, depending on the normality of their distribution as assessed through graphical methods and the Shapiro-Wilk test for normality. Comparisons between clusters were analyzed by analysis of variance or Kruskal-Wallis test for numeric and chi-square test or Fisher exact test, as appropriate. The contribution of the variables to the construction of each phenogroup was evaluated by v-test, based on the measurement of the distance between the intra-class value and the overall value (tdisplay R package). A logistic regression analysis was used to assess the prognostic significance of each phenogroup. A two-tailed P-value  $< 0.05$  was considered statistically significant. Statistical analysis and clustering were performed using R software, version 4.1.1 (R Project for Statistical Computing).

## 4. Results

### 4.1. Patient characteristics

During 7–22 April 2021, according to the local admission register of each center, 1904 patients were admitted to ICCUs in the 39 participating centers. After exclusions, 1499 constituted our study cohort for analysis (Fig. 1). The reasons for failure to perform a urine drug assay are presented in Text A.4. Among the included 1499 patients (mean age  $63.3 \pm 14.9$  years, 69.6% male), 21.7% had diabetes mellitus, 53.0% had hypertension, 38.8% had dyslipidaemia, and 25.4% were current/former smokers (Table 1).

Regarding cardiovascular morbidities, 36.0% of the study population had known CAD, and 5.2% had known cardiomyopathy. Concerning the main admission diagnosis, 772 patients (51.5%) had an acute coronary syndrome (ACS) (438 non-ST-segment elevation myocardial infarction [NSTEMI] and 334 ST-segment elevation myocardial infarction [STEMI]), 211 (14.1%) acute HF, 83 (5.5%) severe cardiac conduction abnormalities, 98 (6.5%) arrhythmia, 46 (3.1%) pulmonary embolism, 73 (4.9%) myocarditis or pericarditis, 16 (1.1%) Takotsubo syndrome, 12 (0.8%) coronary spasm, 7 (0.5%) aortic dissection, 6 (0.4%) spontaneous coronary dissection, 102 (6.8%) chest pain without an identified cardiovascular cause, and 77 (5.1%) other cardiovascular or non-cardiovascular diagnoses. Among the 1499 patients screened with a urine drug assay, 161 (10.7%) had a positive urine test for at least one illicit drug, including 136 (9.1%) for cannabis, 32 (2.1%) for heroin or other opioids, 25 (1.7%) for cocaine, 10 (0.7%) for amphetamines and nine (0.6%) for 3,4-methylenedioxymethamphetamine (MDMA). The mean  $\pm$  SD duration of ICCU hospitalization was  $5 \pm 3$  days.

#### **4.2. Clinical, biological, and echocardiographic characteristics of each phenogroup**

The 29 clinical, biological, and echocardiographic input variables had different contributions in defining the phenogroups (Fig. 2). Clustering using Kamila algorithm established 4 phenogroups (Fig. 3) with significant differences in their clinical characteristics (Fig. A.1). Online Video 1 presents the four phenogroups according to the first three principal components in clustering assessed on three axes.

Phenogroup (PG) 1 (n = 535; 35.7%) had the highest proportion of patients with NSTEMI (45.0%), and patients were more likely to be men (72.5%), with a history of previous percutaneous coronary intervention (43.2%) compared with other PGs (Table 1). Regarding biological data, PG1 had the lowest NT-proBNP level (342 [72–777] ng/L). On echocardiography, PG1 had the highest LVEF value ( $56.7\% \pm 8.9$ ), the lowest LV end-diastolic volume ( $100 \pm 34$  mL/m<sup>2</sup>), and the lowest RV dilatation rate (3.4%). It also had the shortest hospitalization duration in the ICCU ( $2.4 \pm 2.1$  days) and a high discharge rate (82.1%).

PG 2 (n = 444; 29.6%) included the youngest patients ( $50.0 \pm 13.3$  years), had the highest proportions of patients with STEMI (39.6%), smokers (50.0%) and illicit drug use (24.1%) (Table 1). Apart from smoking, PG2 had the lowest proportions of traditional risk factors (diabetes mellitus 5.4%, hypertension 12.8%, dyslipidaemia 13.5%). Patients in PG2 had, on average, preserved LVEF ( $53.6\% \pm 10.6$ ). Regarding outcomes, PG2 had the shortest hospitalization duration ( $6.4 \pm 20.1$  days) with the highest ICCU discharge rate (83.1%).

PG 3 (n = 273; 18.2%) included the oldest patients ( $74.7 \pm 9.3$  years; Fig. A.2) and had the highest proportions of women (38.5%), acute HFpEF (16.1%) and conduction disturbances (21.2%). PG3 had the highest proportions of diabetes mellitus (48.7%), hypertension (86.4%), and dyslipidaemia (65.2%), the highest body mass index ( $28.4 \pm 6.4$  kg/m<sup>2</sup>; Fig. A.2) but a lower rate of smoking (4.8%). PG3 exhibited the highest proportion of extra-cardiac comorbidities including: anaemia (haemoglobin  $11.7 \pm 1.8$  g/dL), chronic kidney disease (creatinine  $138 \pm 118$  mol/L; Fig. A.2) and active cancer (9.5%). Regarding biomarkers, PG3 had a high (but not the highest) NT-proBNP level (845 [210–3402] ng/L). Patients in PG3 were more likely to have LV filling pressure increases but, on average, preserved LVEF

(54.7%  $\pm$  11.1). Notably, PG3 presented a lower ICCU discharge rate (65.9%) and a longer hospitalization length in ICCU (3.2  $\pm$  6.2 days).

PG 4 (n = 247; 16.5%) had the highest proportion of patients with acute HFrEF (40.1%), the highest heart rate (103  $\pm$  27 bpm; Fig. A.2) and the highest proportion of Killip class  $\geq$  III patients (22.3%). Regarding biomarkers, PG4 had the highest median NT-proBNP level (1450 [722–9706] ng/L). Patients in PG4 had the lowest LVEF (36.1%  $\pm$  14.8) and the most severe cardiac dysfunction (highest LV end-diastolic volume [139  $\pm$  60 mL/m<sup>2</sup> ] and LA dilatation rate [52.2%]) corresponding to the highest proportion of patients with elevated LV filling pressures, the highest RV dilatation rate (19.8%), the highest sPAP value (46  $\pm$  14 mmHg) and the lowest LVOT VTI (15  $\pm$  5 cm) as markers of cardiac output (Fig. A.2). Regarding out-comes, PG4 presented the longest hospitalization duration in the ICCU (4.5  $\pm$  5.8 days) with the lowest ICCU discharge rate (56.3%) and the longest length of stay in hospital (11.6  $\pm$  22.5 days)

### 4.3. Association of phenogroups with outcomes

During hospitalization, there were 67 in-hospital MAEs (4.5%), including 27 (1.8%) in-hospital deaths, 13 (0.9%) cardiac arrest events and 27 (1.8%) cardiogenic shocks requiring medical and/or mechanical haemodynamic support. The in-hospital MAE rate was higher for PG4 compared to the other phenogroups (P < 0.001). Using regression analysis, the occurrence of MAE differed among the four phenogroups (P < 0.001). Compared to PG1 as the reference, PG2 (odds ratio [OR] 3.13, 95% confidence interval [CI] 1.16–10.0; P = 0.024), PG3 (OR 3.16, 95% CI 1.02–10.8; P = 0.046) and PG4 (OR 20.5, 95% CI 8.70–60.8; P < 0.001) were associated with a higher risk of MAE (Table 2).

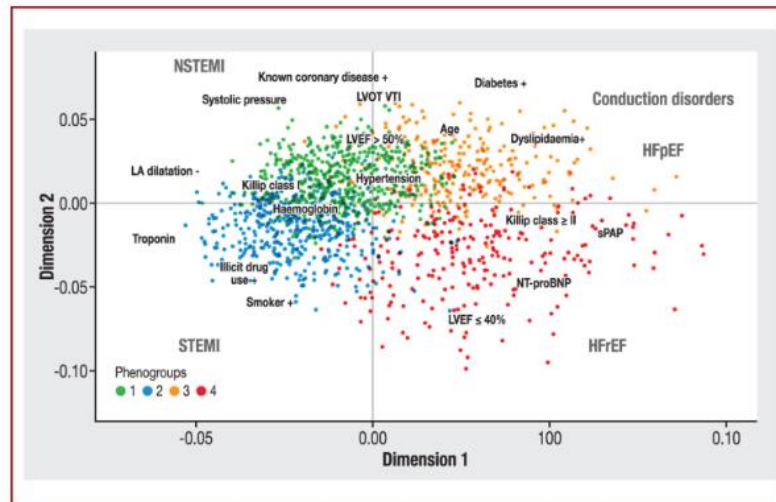
In multivariable regression analysis after adjustment using step- wise variable selection, PG2 and PG3 had a worse prognosis and PG4 had the worst prognosis regarding the occurrence of MAEs compared to PG1 (e.g. model 1: PG2: OR 3.14, 95%CI 1.11–10.3, P = 0.038; PG3: OR 3.18, 95% CI 1.02–10.9; P = 0.041; PG4: = 15.3, 95% CI, 5.75–49.1; P < 0.001; Table 2).

Using the Kruskal-Wallis test, the differences in ICCU hospitalization duration were significantly different from one phenogroup to another (P < 0.001). Indeed, the lowest mean hospitalization durations in the ICCU were for PG1 (2.4  $\pm$  2.1 days) and PG2 (2.6  $\pm$  3.3 days), while PG3 (3.2  $\pm$  6.2 days) and PG4 (4.5  $\pm$  5.8 days) had the highest mean hospitalization durations in ICCU.

## 5. Discussion

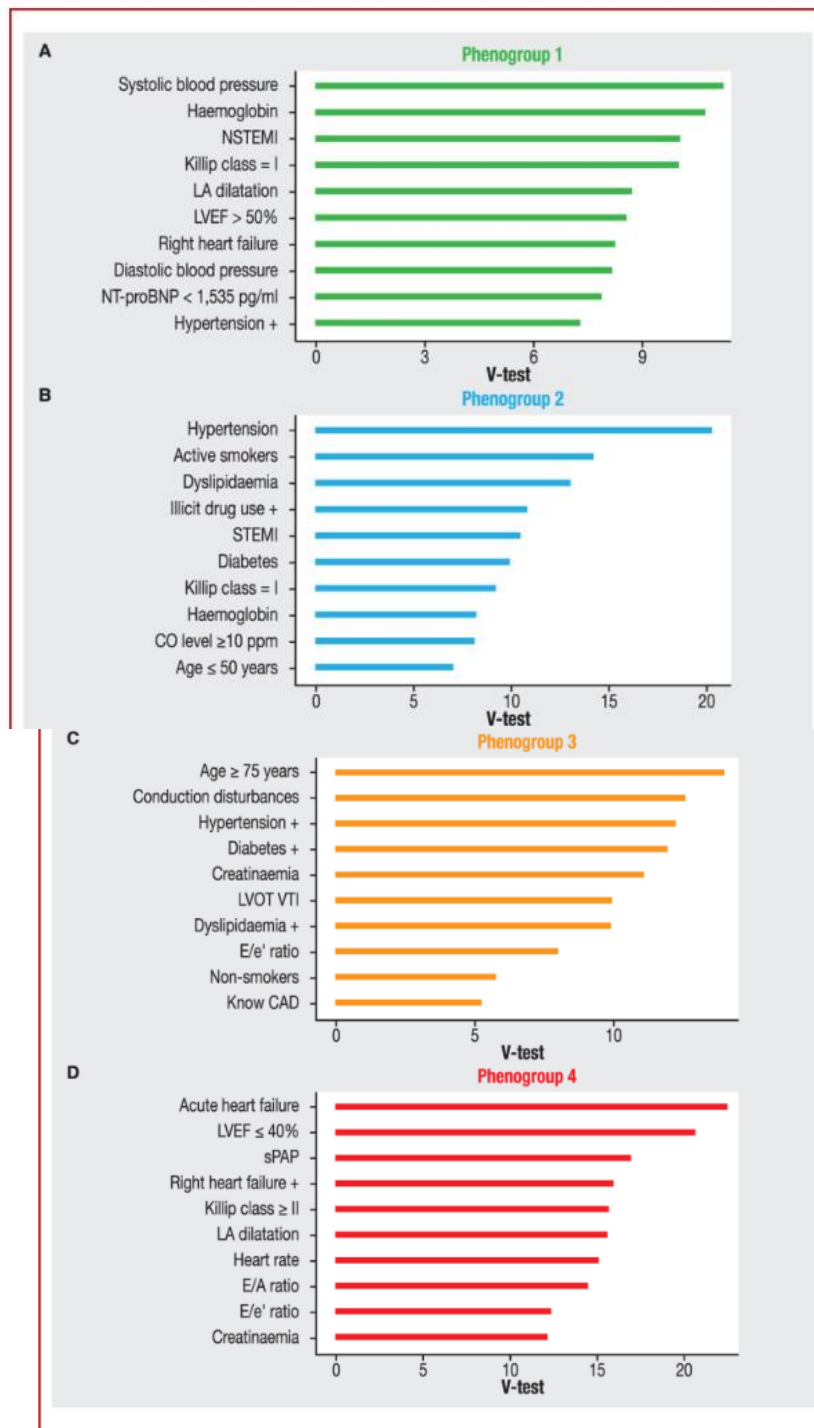
In this ancillary study of a cohort of consecutive patients hospitalized in an ICCU – from the ADDICT-ICCU study [12] – an unsupervised approach of clustering integrating clinical, biological and echocardiographic data identified four mutually exclusive phenogroups of patients. These phenogroups were associated with distinct clinical and prognostic profiles. PG1 mainly included males admitted for NSTEMI with no clinical or biological marker of HF, and the best LV structural and functional parameters on echocardiography. PG2 tended to include younger males who were often smokers and/or illicit drug users admitted for STEMI without other traditional risk factors. This phenogroup had the shortest hospitalization duration and the highest ICCU discharge rate. PG3 tended to include older women hospitalized for acute decompensated HFpEF or conduction disturbances with a metabolic

syndrome profile including cardiovascular risk factors except smoking and several non-cardiovascular comorbidities including anaemia, chronic kidney disease, and active cancer. PG4 tended to include patients hospitalized for acute decompensated HFrEF with severe clinical, biological, and echocardiographic markers of acute HF due to systolic LV dysfunction associated with LV dilatation. This phenogroup had the longest hospital and ICCU durations and the lowest ICCU discharge rate.



**Fig. 2.** Characteristic plots of the four phenogroups. The over- or under-representation of a variable within a phenogroup was analysed by V-test within the clustering, based on the hypergeometric distribution. The value of the V-test score indicates over-representation of this variable in the applicable phenogroup. CAD: coronary artery disease; CO: carbon monoxide; LA: left atrial; LVEF: left ventricular ejection fraction; LVOT VTI: left ventricular outflow tract velocity time integral; NSTEMI: non ST-segment elevation myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; sPAP: systolic pulmonary artery pressure; STEMI: ST-segment elevation myocardial infarction.

These findings suggest that each phenogroup may represent a more homogeneous subset of patients with similar cardiovascular pathophysiology and in-hospital risk profiles. The characteristics of these four phenogroups may result in the identification of different populations hospitalized in the ICCU who have different management and intra-hospital pathways. The data suggest that patients admitted for ACS (PG1 and PG2) do not represent the most important burden for ICCUs in terms of prognosis and length of hospital stay compared to other patients (PG3 and PG4). These findings are in line with prior studies using the French nationwide administrative database for admissions in the ICCU [3,18]. Indeed, Roubille et al. have previously described that patients admitted for ACS were significantly younger (mean age 67 years), with better outcomes (in-hospital mortality 4.0%), and shorter in-hospital stays (mean 6.7 days) [3]. Moreover, although PG2 patients were predominantly male with the highest proportion of smokers and illicit drug users, their prognosis was similar to PG3 patients, which had the highest proportion of women with a metabolic syndrome profile including hypertension, diabetes, and dyslipidaemia [19], which are associated with several non-cardiovascular comorbidities [3,5]. Therefore, our study suggests that despite the importance of initial clinical parameters in current admission risk stratification for severity, age and non-cardiovascular comorbidities could be crucial to accurately stratify the risk of poorer outcomes and longer length of hospital stay in the ICCU.



**Fig. 3.** Cluster analysis. Biplot representation depicts the relationships between clinical characteristics (white boxes) and final cardiovascular diagnosis (black boxes) used for building phenogroups. Patients are displayed (dots) based on their individual characteristics. Results are projected onto the two first dimensions yielded by multiple correspondence analysis. Colors correspond to the very clear distinction of the four phenogroups from cluster analysis (Online Video 1). HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LA: left atrial; LVEF: left ventricular ejection fraction; LVOT VTI: left ventricular outflow tract velocity time integral; NSTEMI: non ST-segment elevation myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; sPAP: systolic pulmonary artery pressure; STEMI: ST-segment elevation myocardial infarction.



**Table 2**  
Association of phenogroups with adverse outcomes on regression analysis.

	No MAEs (n=1432)	MAEs (n=67)	Unadjusted		Model 1 <sup>a</sup>		Model 2 <sup>b</sup>	
			OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
PG1 (n=535)	530 (99.1)	5 (0.9)	Reference		Reference		Reference	
PG2 (n=444)	431 (97.1)	13 (2.9)	3.13 (1.16–10.0)	0.024	3.14 (1.11–10.3)	0.038	3.23 (1.11–10.9)	0.040
PG3 (n=273)	265 (97.1)	8 (2.9)	3.16 (1.02–10.8)	0.046	3.18 (1.02–10.9)	0.041	3.29 (1.05–11.3)	0.044
PG4 (n=247)	206 (83.4)	41 (16.6)	20.5 (8.70–60.8)	<0.001	15.3 (5.65–49.1)	<0.001	19.8 (7.4–63.4)	<0.001

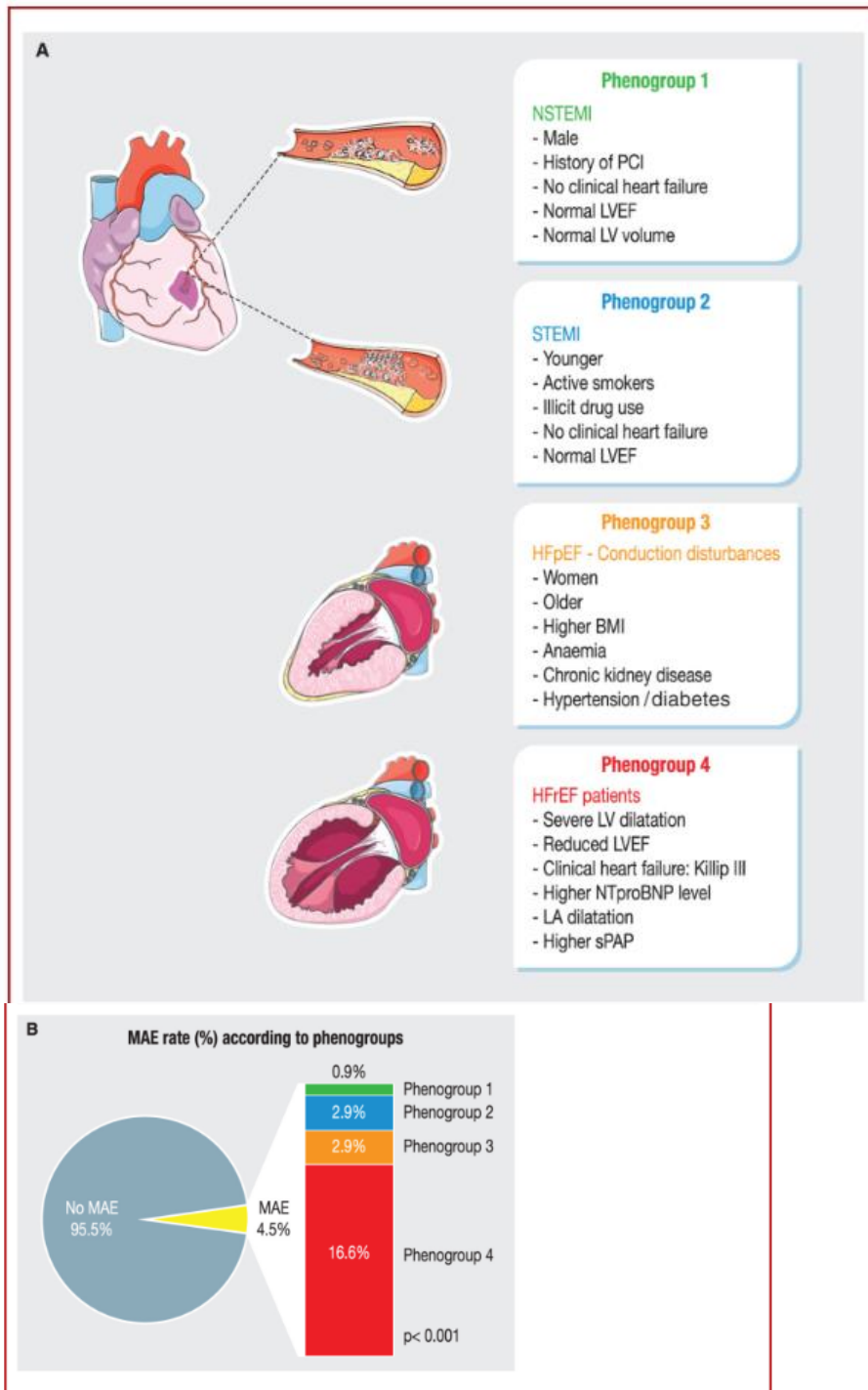
Data are expressed as number (% of PG group) unless otherwise indicated. CAD: coronary artery disease; CI: confidence interval; LVEF: left ventricular ejection fraction; MAE: major adverse event; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OR: odds ratio; PG: phenogroup.

<sup>a</sup> Covariates in model 1 by stepwise variable selection with entry and exit criteria set at the  $P \leq 0.05$  level: age, male, heart rate, creatinine, NT-proBNP, and LVEF.

<sup>b</sup> Covariates in model 2 included known traditional prognosticators of intra-hospital severity: age, male, hypertension, known CAD and LVEF.

While ICCUs were historically created to manage ACS [1,2,4], the current study reports an ongoing shift in the patients treated in the ICCU towards a broader array of cardiovascular diseases with a significant overlay of non-cardiac organ dysfunction and comorbidities [5]. ACS represented just over half of the patients hospitalized in the ICCUs. This finding is consistent with prior European [3,18] and American [5] reports, in which 49% and 32%, respectively, of patients hospitalized in ICCU had ACS. Among this large proportion of patients hospitalized for a non-ACS event, the rate of patients admitted for acute HF has increased from 10% in 2014 [3,18] to 15–36% in more recent registries [5]. Concurrent with a decline in the proportion of admissions for ACS compared with historical patterns [1,2], the burden of HF on ICCU resources has increased. In line with recent data [5], despite ranking less than ACS in its contribution to the number of admissions, HF (including HFpEF and HFrEF) represented a much larger amount of total ICCU time (means of 7.2 and 11.6 days for PG3 and PG4 versus 6.7 and 6.4 days for PG1 and P2, respectively). Moreover, 474 patients (31.6%) had HF as a part of their presenting syndrome when considering the primary and secondary diagnoses. This prominence is consistent with the increasing prevalence of HF in the European population [20]. In parallel with this growing increase in HF, our study emphasizes the fact that the ICCU population has become older, with more comorbidities [5]. Consistently, PG4 presented the most important intra-hospital severity with the worst outcomes. The identification of subsets of patients with distinct clinical, intra-hospital burden profiles and outcomes may help guide future clinical trials, especially for patients with HF who require early optimization of treatments. Indeed, several studies have already highlighted the complexity of advanced ICCU care required for ever more comorbid patients admitted to contemporary ICCUs [5]. Therefore, all of these results suggest that acute HF has a very strong impact on the prognosis of patients hospitalized in the ICCU. In addition, we note that the mortality rate was higher compared to other registries describing patients with acute HF. This can be explained by a higher rate of de novo HF with reduced LVEF but also patients with ACS complicated by acute HF, which is known to have a poor prognosis in these high-risk patients.

ICCU are a major component of the French health system, representing about 1.5% of all admissions [3]. Considering that an important part of admissions in the emergency room are for cardiovascular disorders, this study reinforces the need for a close and interconnected management of emergency and cardiology departments with the ICCUs as the natural junction. Indeed, while recent decades have seen important progress in the management of patients with ACS (PG1 and PG2), the results of this study emphasize the need to optimize the in-hospital management of patients without ACS. Therefore, optimizing these older patients with more comorbidities admitted for HF (PG3 and PG4) could improve patient prognosis and reduce the length of in-hospital stays. Finally, the current study adds to previous studies demonstrating the evolving landscape of cardiac critical care [1,5,21], and is responsive to calls for additional research to fill important gaps in the evidence base.



**Central Illustration.** Clustering of four phenogroups with different prognostic profiles in the ICCU. A. Four mutually exclusive phenogroups as determined by clustering; B. MAE rate (defined by in-hospital death, resuscitated cardiac arrest or cardiogenic shock requiring medical or mechanical haemodynamic support) to the four phenogroups. BMI: body mass index; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICCU: intensive cardiac care unit; LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; MAE: major adverse event; NSTEMI: non ST-segment elevation myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCI: percutaneous coronary intervention; sPAP: systolic pulmonary artery pressure; STEMI: ST-segment elevation myocardial infarction.



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## **5.1. Study limitations**

This study has some limitations. Data were missing for, on average across variables, 2.5% of patients. However, this relatively low rate of missing data did not seem to necessitate the use of a missing data imputation method for the analyses. The exclusion of all patients hospitalized in the ICCU for a planned interventional procedure led to a risk of selection bias. However, excluding these patients concentrated the phenotypic analysis on patients with an acute cardiovascular event. Notably, we did not collect information to determine the type of myocardial infarction according to its international definition. Finally, data on the nationwide activity in ICCUs in France indicates an average ICCU admission rate of 45 patients per center over 15 days [18], so the theoretical recruitment would have been 1755 patients in 39 centers. Therefore, our recruitment of 1904 patients is consistent with systematic and consecutive selection. Although the current approach may represent a major shift from traditional studies, it is a novel attempt towards a more personalized approach to patients hospitalized in ICCU. Whether automated unsupervised phenogrouping of patients hospitalized in the ICCU may improve clinical decision-making should be further explored in prospective studies.

# **6. Conclusions**

Using an unsupervised cluster analysis in this prospective multicentre study of consecutive patients admitted to ICCUs from 39 centers for acute cardiac events, four different phenogroups of patients were identified and these were associated with distinct prognostic profiles. Further prospective studies should evaluate how these data using unsupervised phenogrouping could impact clinical decision-making and guide therapy (Central Illustration).

## **Authors' contributions**

Kenza Hamzi: analysis, interpretation of data and writing the manuscript. Emmanuel Gall: collection, analysis and interpretation of data. Eric Vicaud: study design, interpretation of data and verification of the underlying data. Jean-Guillaume Dillinger: study design, collection, analysis and interpretation of data. Patrick Henry: study design, collection, analysis and interpretation of data. Théo Pezel: study design, collection, analysis, interpretation of data, writing the report and decision to submit the paper for publication. All other authors: data collection and analysis.

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## Disclosure of interest

The authors declare that they have no competing interest

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