Prediction of clinical events in acute myocarditis : Presentation of both regression analyse and bayesian analyse from the AMPHIBIA database

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Generalities

- **Inflammatory pathology of the myocardium without ischemic origin** :
  - inflammatory cell infiltrate:> 14 mononuclear leukocytes / mm^2 including> 7 LT / mm^2
  - myocytic necrosis

- Epidemiology :
  - incidence: 22 cases / 100,000 patient-years
  - median age 30-45 years, men 60-80%

- Polymorphism: etiologies, clinical presentations, prognosis

- **Diagnostic :**
  - Gold standard = Endomyocardial biospy
  - Shift to cardiac MRI over the past 20 years

Nosology

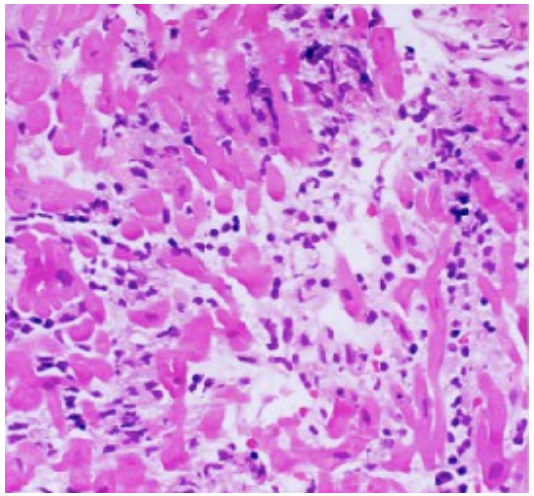
Histology

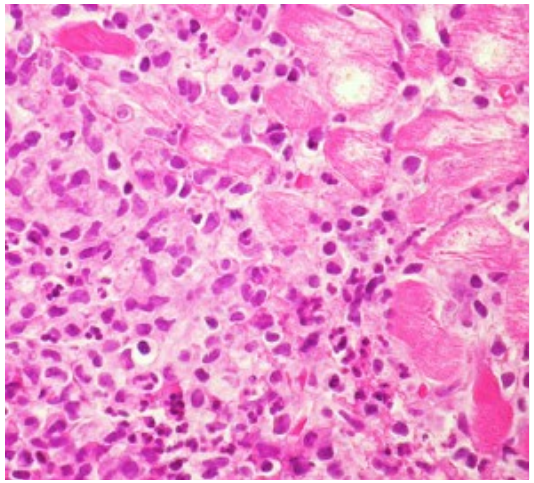
Lymphocytic

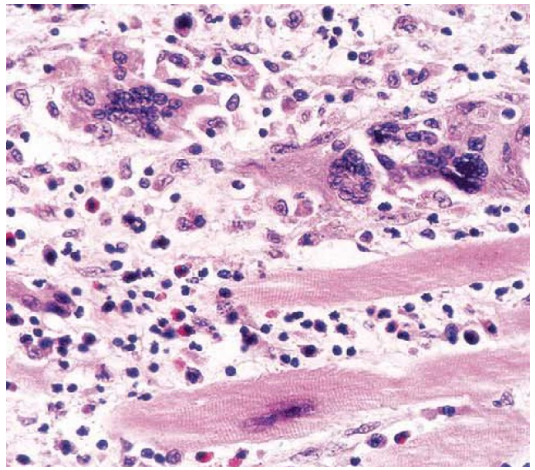
Eosinophils

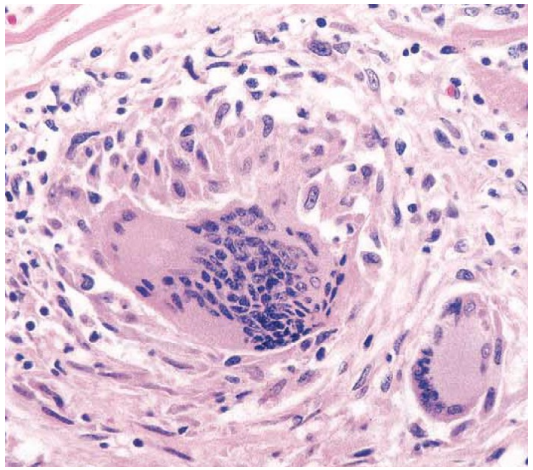
Giant cells

Granulomatous









Nosology

Histology

- Lymphocytic
- Eosinophils
- Giant cells
- Granulomatous

Etiology

Virus

- Entérovirus (Coxsakievirus)
- Adénovirus
- Herpes virus (HHV6, EBV, CMV)
- Parvovirus B19
- Hépatite C
- Grippe A et B
- VIH

Parasitoses

- Larva migrans
- Schistosoma

Bactéries

- Mycoplasme pneumonie
- Mycobactérie
- Streptocoque
- Borelia
- Brucella

Champignons

- Aspergillus
- Candida
- Cryptococcoque
- Histioplasma

Protozoaire

- Trypanosoma cruzi (Maladie de Chagas)

Toxiques

- Anthracyclines
- Cocaïne
- Amphétamine

Hypersensibilité

- Céphalosporines
- Digoxine
- Diurétiques
- Dobutamine
- Antidépresseurs tricycliques

Immunologiques

- Granulomatose éosinophilique avec polyangéite
- MICI
- Myocardite à cellule géantes
- Sarcoïdose
- Lupus
- Myosite

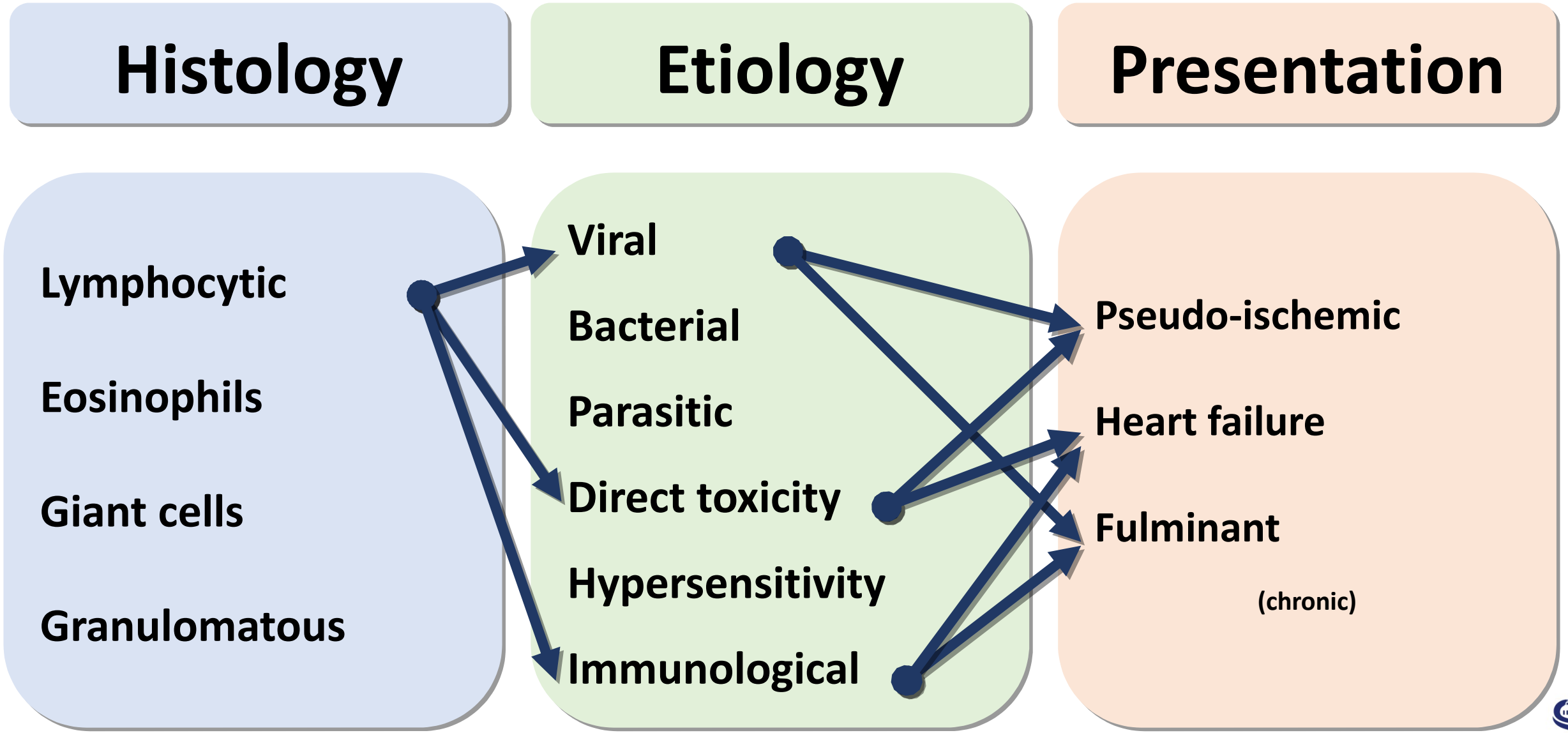
- Vaccination COVID19
- ICI

Nosology

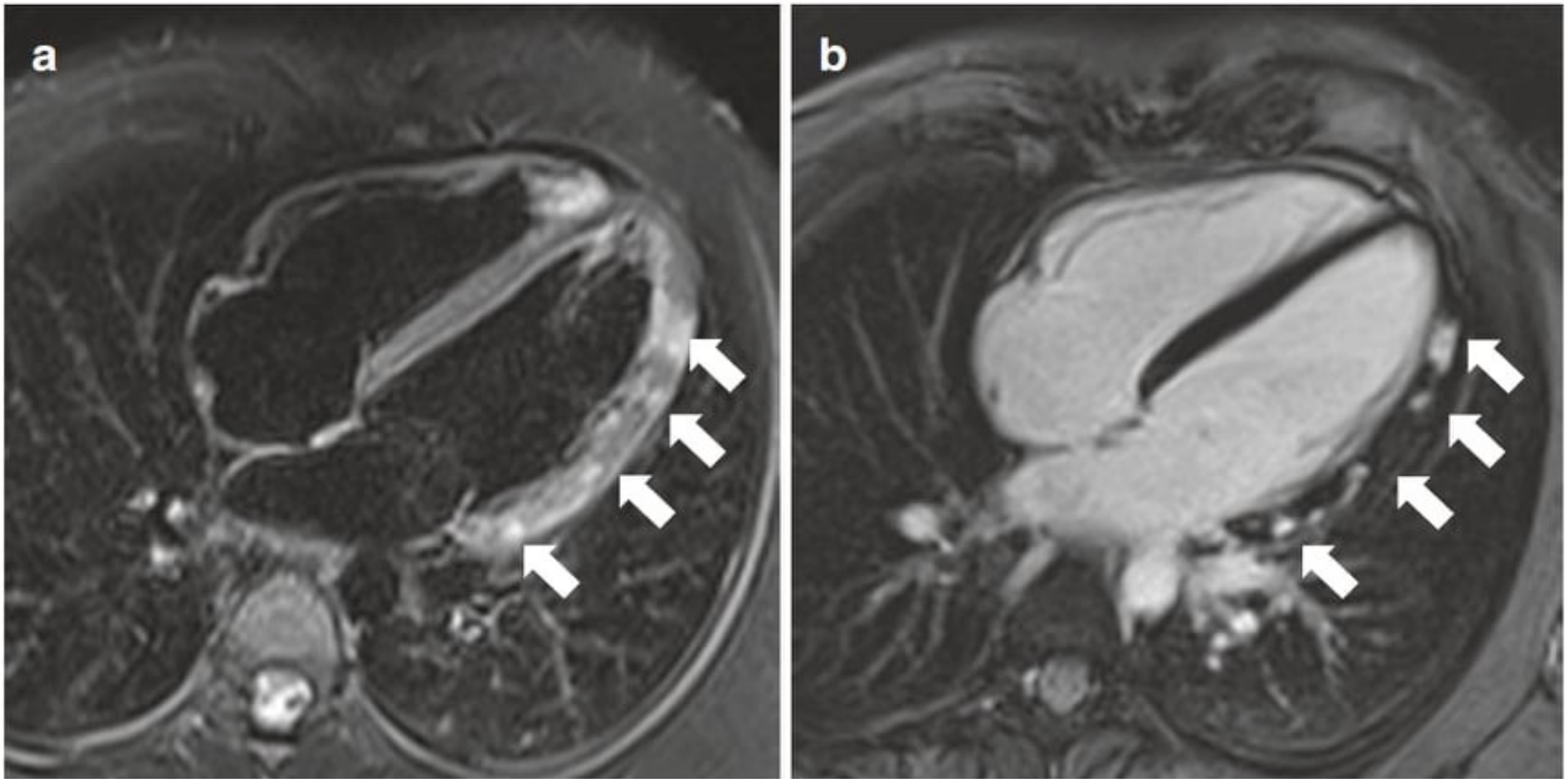
Acute myocardite

- Pseudo-ischemic
  Normal LVEF
- Left ventricle
  Dysfonction
  Heart Failure
- Fulminant
  Full atrioventricular block
  Malignant arrhythmia

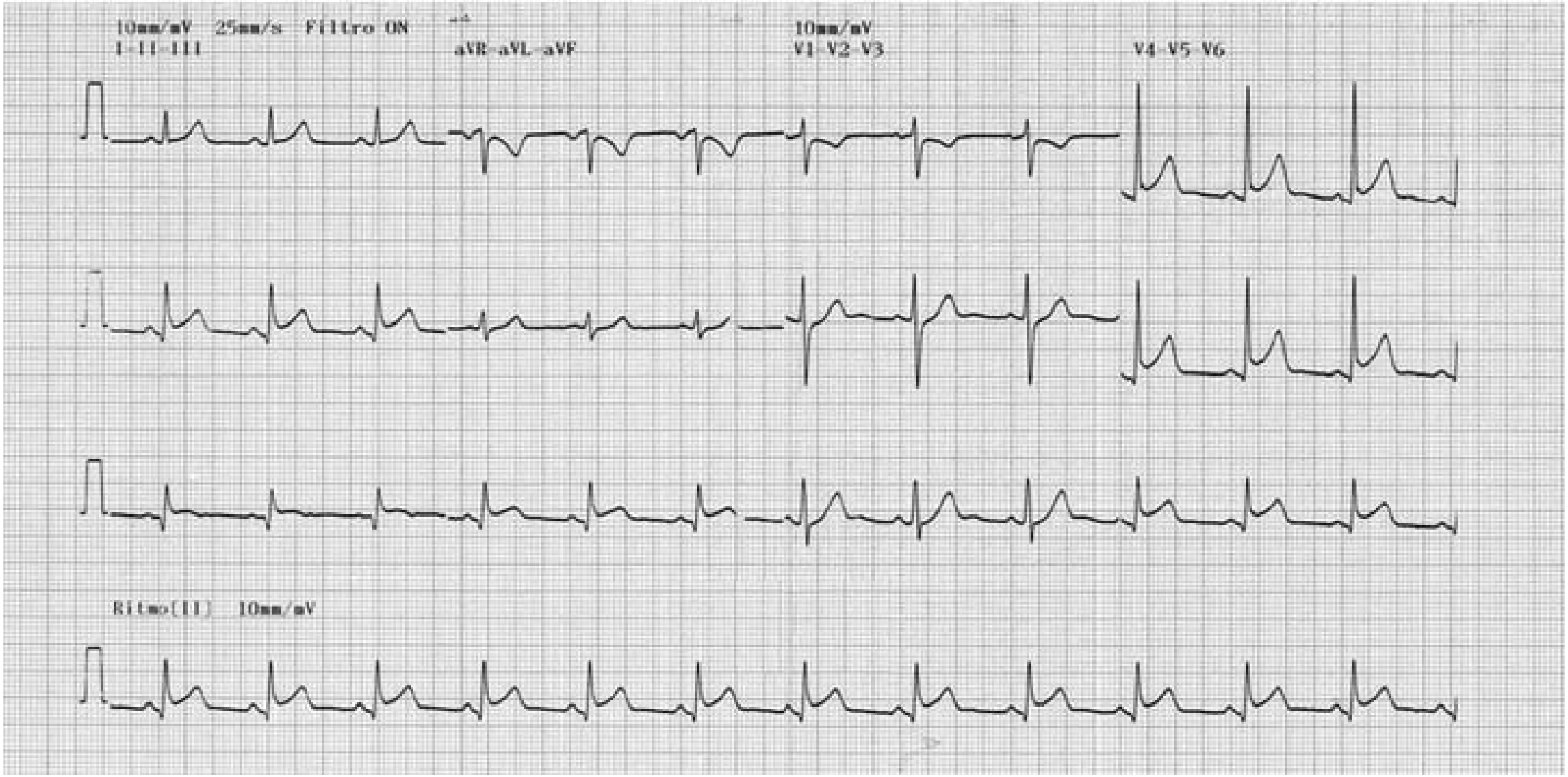
Nosologie


Histology
Etiology
Presentation
Lymphocytic
Eosinophils
Giant cells
Granulomatous
Viral
Bacterial
Parasitic
Direct toxicity
Hypersensitivity
Immunological
Pseudo-ischemic
Heart failure
Fulminant
(chronic)

Diagnostic - Imaging



Diagnostic - Electrocardiogram

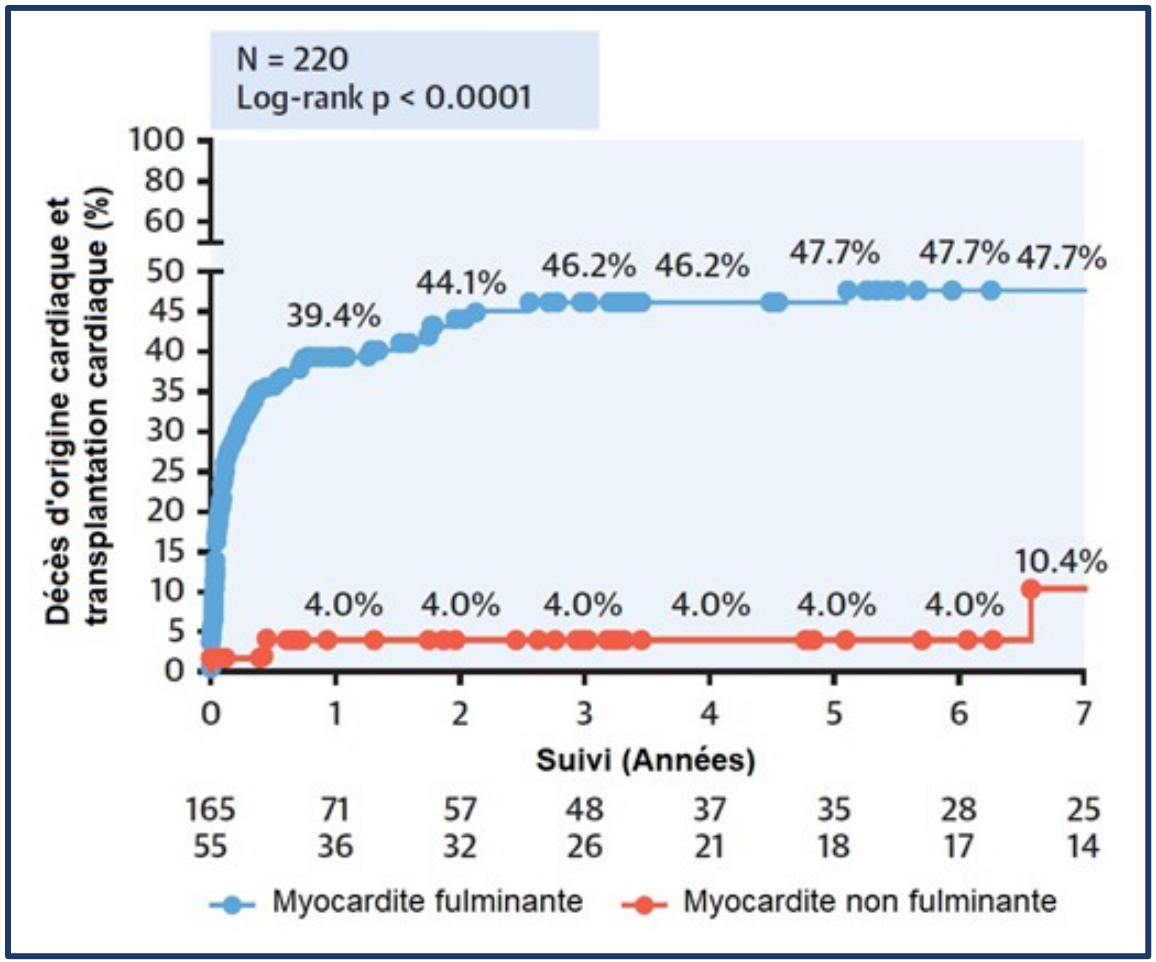


Treatments

- Antivirals
- Antibiotics
- Immunosuppressors
- NSAIDs
- Mecanical support
- Heart transplant

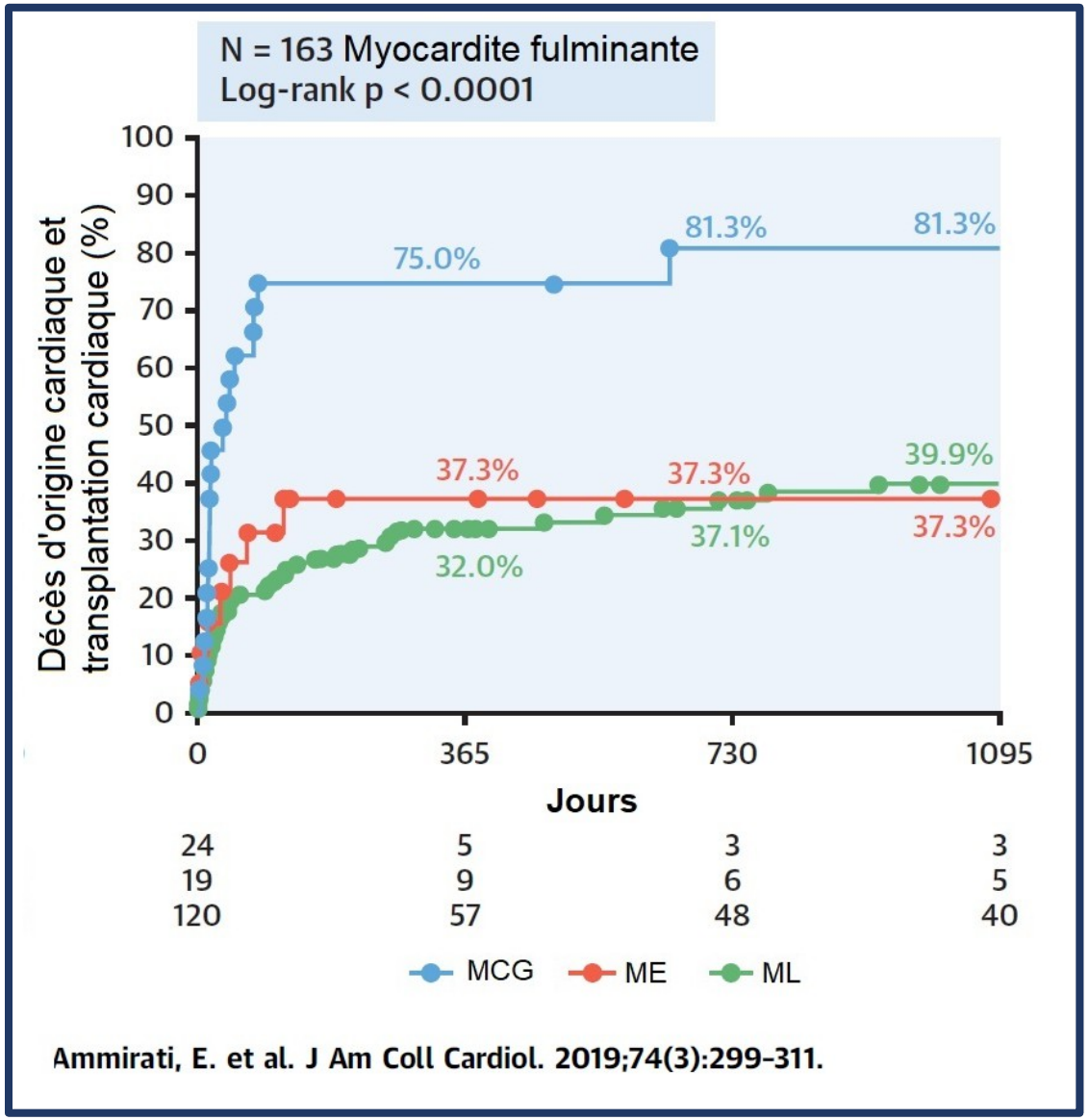
- NSAIDs
- B-blockers
- Ras-Blockers
- Sport Stopping
- Colchicine

Pronostic- Fulminant form



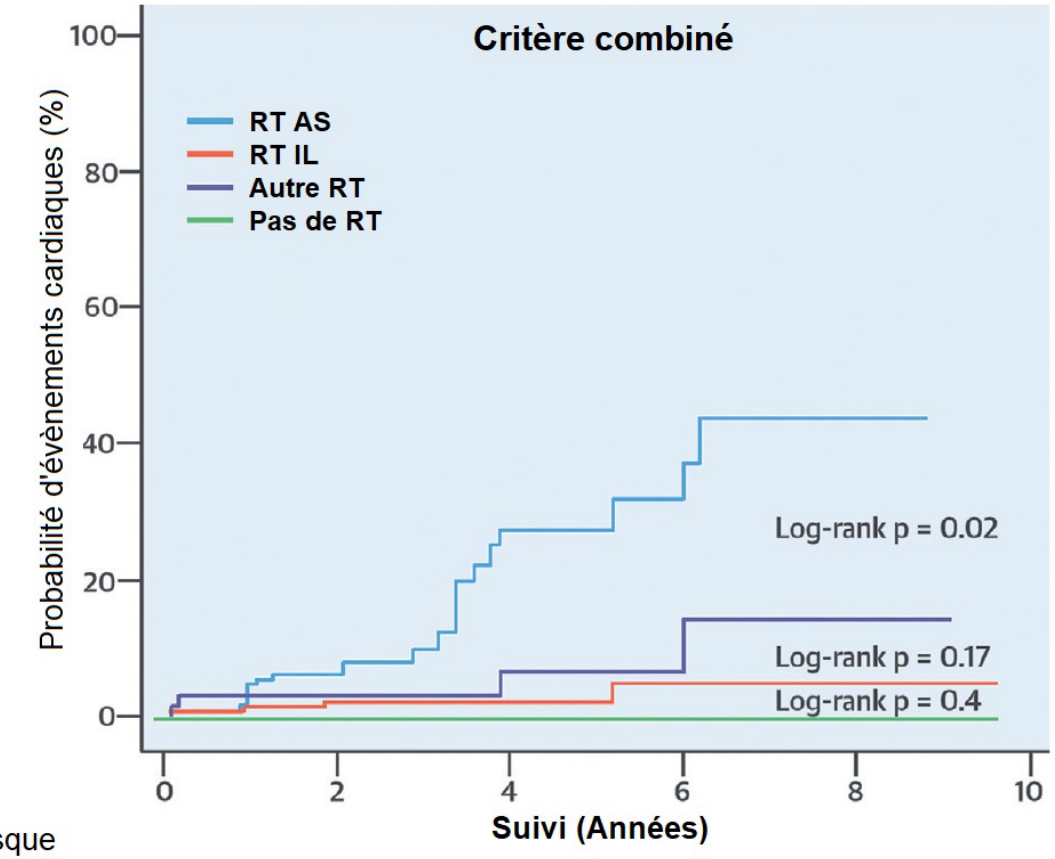
Ammirati, E. et al J Am Coll Cardiol. 2019;74(3):299-311

Pronostic – Histologic form



Ammirati, E. et al. J Am Coll Cardiol. 2019;74(3):299-311.

Pronostic – Medical imaging



A risque

RT AS	135	60	27	11	1	0
RT IL	154	92	52	21	6	0
Autre RT	59	44	24	11	6	0
Pas de RT	26	19	7	1	1	0

Aquaro, G.D. et al. J Am Coll Cardiol. 2017;70(16):1977-87.

Prognosis challenges

Histology

Fulminant – Left ventricle Dysfonction

MRI

Risk stratification

Goals

Develop a tool for stratifying the risk of serious events from the admission data of patients with acute myocarditis in the AMPHIBIA registry.

Bayesian approach

Regression approach

1 Introduction

2 method

3 Results

4 Discussion

5 Conclusion

Population – AMPHIBIA

Acute myocarditis: evaluation of prognosis and clinical, biological, radiological, immunological and histological characteristics

Hospitalization for acute myocarditis at the Heart Institute between 2008-2019

Data recovery from the medical file

Clinical, biological, radiological, histological, immunological

Medical file

Followup

Standardized telephone questionnary

Vital status: file, doctor or civil status

Inclusion criteria

<u>An acute clinical presentation</u>

- Chest pain
- Dyspnea, fatigue, heart failure
- Palpitations, syncop, sudden death
- Unexplained cardiogenic shock

<u>A diagnostic criterion</u>

- New electrical anomaly
- Troponin elevation
- New functional and structural anomaly

Clinically suspected myocarditis

MRI

<u>Edema</u>

T2 hypersignal
Or
Native T2 elevation

<u>Non-ischemic myocardial damage</u>

Late enhancement
Or
Native T1 elevation or ECV

Biopsy

Inflammatory cell infiltrate

+-Necrosis

Exclusion criterion

Confusing cardiac cause

- Severe valve disease
- Complex congenital heart disease
- History of heart transplant
- Coronary artery disease explaining the clinical presentation

Composite outcome

Death from any cause

Temporary circulatory assistance (ECMO-VA or Impella®)

Heart transplant

Two models

BAYESIAN

Data processing → 200 variables → 50 variables

Discretization → Threshold of interest or R-Genopt

Learning the model → Markov Blanket Algorithm

REGRESSION

50 variables → Odds Ratios → 27 variables → Step by step backward regression

↓

Multivariate model of 7 variables

1 Introduction

2 Méhods

3 **Results**

4 Discussion

5 Conclusion

Population characteristics

	Population totale (n=359)	Absence d'évènement (n=292)	Evènement (n=67)	p value
Suivi, années	**4.1 (1.7–6.6)**	**4.3 (2.2-6.7)**	**2.4 (0.1-5.9)**	**0,001**
Age, années	**36.8 ± 15.2**	**35.3 ± 14.4**	**43.7 ± 16.5**	**<0.001**
Sexe masculin	**262 (73)**	**229 (78)**	**33 (49)**	**<0.001**
Durée d'hospitalisation, jours	7 (5-15)	6 (4-10)	15 (27-50)	**<0.001**
Facteurs de risques CV				
Hypertension	30 (8.4)	23 (7.9)	7 (10)	0.49
Diabète	6 (1.7)	6 (2.1)	0 (0)	0.6
Tabagisme actif	124 (35)	111 (38)	13 (19)	**<0.01**
Dyslipidémie	24 (6.7)	19 (6.5)	5 (7.5)	0.79
Hérédité coronaire	24 (6.7)	22 (7.5)	2 (3)	0.28
Obésité (IMC>30)	43(12)	34 (12)	9 (14)	0.67
Antécédents cardiologiques				
Péricardite	9 (2.5)	9 (3.1)	0 (0)	0.22
Myocardite	**20 (5.6)**	**274 (94)**	**65 (97)**	**0.39**
Insuffisance cardiaque	**8 (2.2)**	**4 (1.4)**	**4 (6)**	**0.043**

Population characteristics

	Population totale (n=359)	Absence d'évènement (n=292)	Evènement (n=67)	p value
Antécédents médicaux				
Asthme	15 (4.2)	11 (3.8)	4 (6)	0.49
Maladie auto-immune ou inflammatoire	**37 (10)**	**25 (8.6)**	**12 (18)**	**0.023**
Cancer actif	**10 (2.8)**	**4 (1.4)**	**6 (9)**	**<0.01**
VIH	5 (1.4)	4 (1.4)	1 (1.5)	1
Insuffisance rénale sévère (clairance <30ml/min)	5 (1.4)	3 (1)	2 (3)	0.12
Traitements				
Chimiothérapies	**10 (2.8)**	**7 (2.4)**	**3 (4.5)**	**0.4**
ICI	**3 (0.8)**	**0 (0)**	**3 (4.5)**	**<0.01**
Immunosuppresseurs	4 (1.1)	3 (1)	1 (1.5)	0.56
AINS	19 (5.3)	15 (5.1)	4 (6)	0.76
Corticoïdes	16 (4.5)	11 (3.8)	5 (7.5)	0.19
B-bloquants	15 (4.2)	6 (2.1)	9 (13)	**<0.001**
IEC/ARA II	21 (5.8)	14 (4.8)	7 (10)	0.086

Population characteristics

	Données	Population totale	Absence d'évènement	Evènement	p value
Prodromes	**359**	**243 (67.7)**	**201 (69)**	**42 (63)**	**0.33**
Fièvre		116 (32.3)	97 (33)	19 (28)	0.44
Symptômes des voies aériennes supérieures		122 (34.0)	104 (36)	18 (27)	0.17
Symptômes gastro-intestinaux		79 (22)	58 (20)	21 (31)	**0.041**
Symptômes cardio-vasculaires					
Délai de consultation, jours		1 (0-3)	1 (0-2.5)	2 (0-5)	0.097
Douleur thoracique		**285 (79)**	**254 (87)**	**31 (46)**	**<0.001**
Dyspnée		**93 (26)**	**58 (20)**	**35 (52)**	**<0.001**
Palpitations		21 (5.8)	13 (4.5)	8 (12)	**0.037**
Malaise		**29 (8.1)**	**14 (4.8)**	**15 (22)**	**<0.001**
Constantes à l'admission					
Température supérieure à 38°C	314	45 (14.3)	27 (10)	18 (34)	**<0.01**
Pression artérielle systolique	356	119 ± 2 1	122 ±19.5	106 ± 24.2	**<0.001**
Fréquence cardiaque	357	89 ± 27	85.3 ± 22.8	105 ± 36.4	**<0.001**

Population characteristics

	Données	Population totale	Absence d'évènement	Evènement	p value
Complications à l'admission (<24h)	359				
Insuffisance cardiaque congestive		**24 (6.7)**	**18 (6.2)**	**6 (9)**	**0.42**
Choc cardiogénique		**47 (13.1)**	**9 (3.1)**	**38 (57)**	**0.001**
ACR rythmique		**14 (3.9)**	**8 (2.7)**	**6 (9)**	**0.029**
TV sans ACR		**3 (0.8)**	**2 (0.7)**	**1 (1.5)**	**0.46**
Tamponnade drainée		2 (0.6)	2 (0.7)	0 (0)	1
ECG à l'admission	359				
Anormal		**265 (74)**	**214 (73)**	**51 (76)**	**0.63**
Tachycardie supra-ventriculaire		4 (1.1)	3 (1)	1 (1.5)	0.56
BAV de haut grade		**10 (2.8)**	**4 (1.4)**	**6 (9)**	**<0.01**
Tachycardie ventriculaire		5 (1.4)	3 (1)	2 (3)	0.49
Bloc de branche gauche complet		5 (1.4)	3 (1)	2 (3)	0.23
Bloc de branche droit complet		**11 (3.1)**	**4 (1.4)**	**7 (10)**	**<0.01**
Sus-décalage du ST		**164 (45.7)**	**145 (50)**	**19 (28)**	**<0.01**
Sous-décalage du ST ou anomalie de l'onde T		52 (14.5)	38 (13)	14 (21)	0.098

Population characteristics

	Données	Population totale	Absence d'évènement	Evènement	p value
ETT à l'admission					
DTDVGi, mm/m2	303	26.9 ± 3.80	26.6 ± 3.62	29.0 ± 4.48	**<0.01**
FEVG, %	**359**	**55 (42-60)**	**50 (58-61)**	**30 (15-40)**	**<0.001**
Dysfonction VG (FEVG<50%)	359	114 (31.8)	59 (20)	55 (82)	<0.001
Dysfonction ventriculaire droite	341	33 (9.7)	12 (4.1)	21 (41)	**<0.001**
Epanchement péricardique	354	88 (24.9)	58 (20)	30 (48)	**<0.001**
FEVG à la sortie; %	341	57 ± 9.32	58 ± 7.80	50.9 ± 14.2	<0.01
Dysfonction VG à la sortie	**341**	**48 (14.1)**	**32 (11)**	**16 (33)**	**<0.001**
IRM cardiaque		338	292 (100)	46 (69)	**<0.001**
Délai de réalisation, jours	338	5.6 ± 6.1	4.8 ± 5	11.1 ± 8.9	**<0.001**
VTDVGi, mm/m2	301	84.9 ± 18.4	84.6 ± 17.7	86.5 ± 22.6	0.62
FEVG, %		51 (48-55)	56 (49-61)	50 (34-58)	**<0.01**
Dysfonction VG (FEVG <50%)	**338**	**97 (28.7)**	**74 (25)**	**23 (50)**	**<0.001**
Œdème (T2 STIR ou cartographie T2)	338	337 (99.7)	292 (100)	45 (98)	0.14
Présence d'un RT	**338**	**314 (92.9)**	**276 (95)**	**38 (83)**	**<0.01**
Extension du RT	268	4 (2-7)	4 (2-7)	3 (2-5)	0.13
Elévation du T1 natif	132	132 (100)	25 (100)	107 (100)	1
Epanchement péricardique	338	129 (38.2)	108 (37)	21 (46)	0.26

Population characteristics

	Données	Population totale	Absence d'évènement	Evènement	p value
Biologie					
Créatinine, µmol/L	359	85 ± 77	80.5 ± 81	104 ± 57.9	**<0.01**
Taux de prothrombine, %	338	83.3 ± 16.5	85.6 ± 14.4	73.5 ± 21.3	**<0.001**
CRP, mg/L	331	61.8 ± 82.5	58.4 ± 79	78.4 ± 97.0	0.15
NT-proBNP, pg/mL	**241**	**3585 ± 7423**	**1872 ± 5121**	**10849 ± 10686**	**<0.001**
Troponine initiale (N fois la normale)	**354**	**104 ± 413**	**65.2 ± 104**	**286 ± 938**	**0.067**
Leucocytes/mm3	356	10767 ± 11122	10117 ± 9351	13622 ± 16630	0.1
Lymphocytes /mm3	253	1780 ± 101	1841 ± 992	1540 ± 1070	0.073
Histologie : Type de myocardite					1
Nombre disponible		26	1	25	
Lymphocytaire		17 (65)	1 (100)	16 (64)	
Eosinophiles		3 (12)	0 (0)	3 (12)	
Granulomateuse		1 (3.8)	0 (0)	1 (4)	
Cellules géantes		5 (19)	0 (0)	5 (20)	
Exploration coronaire	**359**	**208 (58)**	**162 (55)**	**46 (69)**	**0.049**
Coronarographie		189 (53)	145 (50)	44 (66)	**0.018**
Coroscanner		21 (5.8)	18 (6.2)	3 (4.5)	0.78
Exploration coronaire réalisée normale	208	205 (99)	160 (99)	45 (98)	0.55

Cardiological events

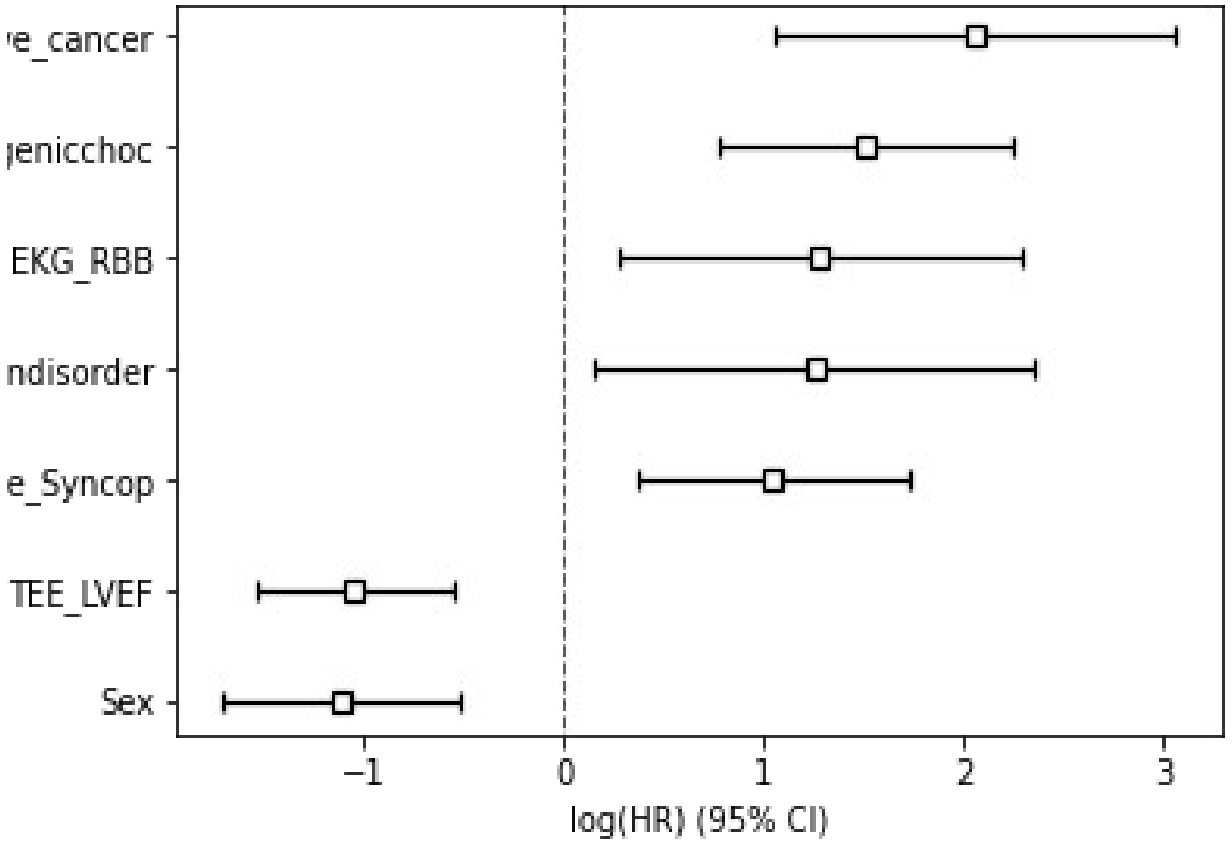
ALL	Population (n=359)
Composite outcome	**67 (18.7)**
Temporary mechanical support	**54 (15)**
Death	**31 (8.6)**
Cardiological death	21 (5.8)
Heart transplant	**6 (1.7)**

Intra-hospitaliers	Population (n =359)
Evènement composite	**55 (15.3)**
Assistance circulatoire temporaire	**54 (15)**
ECMO-VA	53 (14.8)
Contre pulsion	28 (7.8)
Impella	5 (1.4)
Délai d'implantation, jours	1 (0-3)
Taux d'implantation à J0 (n=55)	22 (40)
Durée d'assistance, jours	8.5 (6-21.5)
Décès	**18 (5)**
Décès d'origine cardiaque	17 (4.7)
Transplantation cardiaque	**5 (1.4)**

Extra-hospitaliers	Population (n=338)
Evènement composite	**14 (4.1)**
Assistance circulatoire temporaire	0 (0)
Décès	**13 (3.8)**
Décès d'origine cardiaque	5 (1.5)
Transplantation cardiaque	**1 (0.3)**

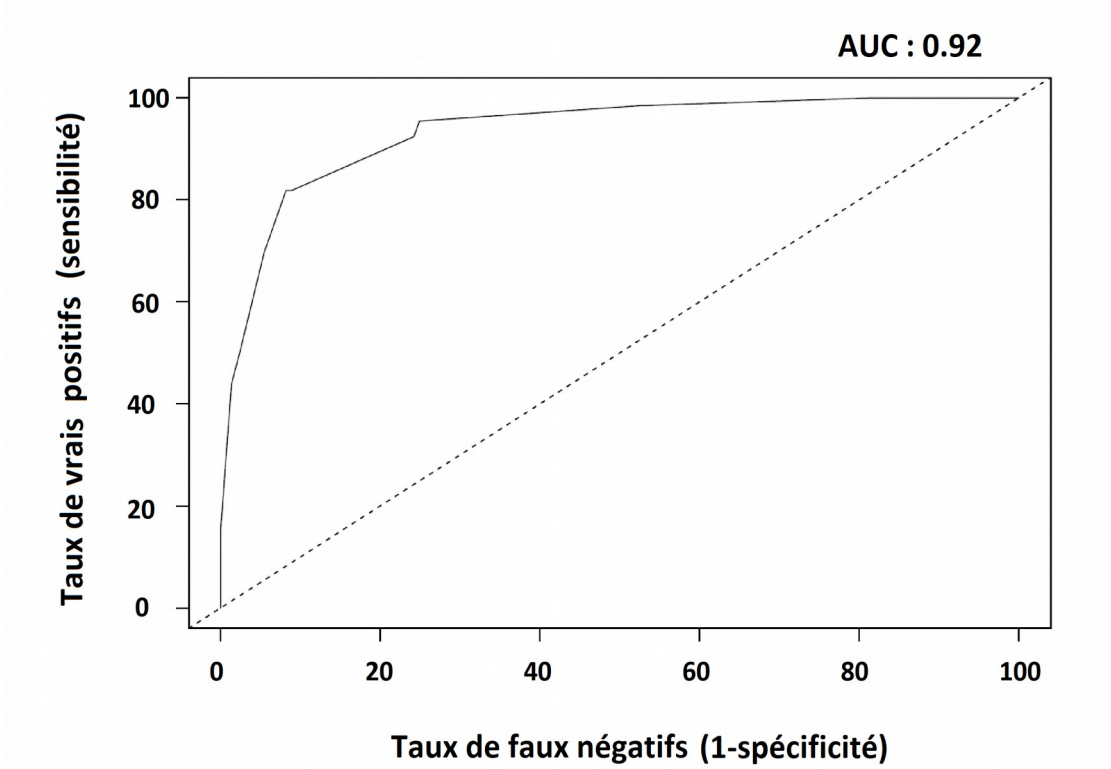
Regression model

Variables	Analyse univariée	
	HR (IC 95%)	P value
Sexe Féminin	**5.75 (2.82-11.70)**	**<0.001**
Age	1.54 (1.23-1.94)	**0.005**
Antécédents		
Tabagisme actif	0.43 (0.23-0.78)	**<0.001**
Maladie auto-immune ou inflammatoire	2.03 (1.09-3.80)	**0.026**
Cancer actif	**3.72 (1.61-8.63)**	**<0.001**
Insuffisance cardiaque	3.25 (1.18-8.63)	**<0.01**
Symptôme cardio-vasculaire		
Douleur thoracique	0.17 (0.11-0.28)	**<0.001**
Dyspnée	3.67 (2.28-5.96)	**<0.001**
Malaise	**5.47 (2.46-12 .16)**	**<0.001**
Complications à l'admission		
Choc cardiogénique	**19.61 (11.97-32.14)**	**<0.001**
ACR rythmique	2.991 (1.292-6.923)	**0.011**
Constantes		
Pression artérielle systolique	0.59 (0.46-0.75)	**<0.001**
Fréquence cardiaque	1.80 (1.41-2.94)	**<0.001**
Electrocardiogramme		
Bloc de branche droit complet	**5.4 (2.45-11.9)**	**<0.001**
Bloc auriculo-ventriculaire complet	**4.49 (1.93-10.4)**	**<0.001**
Sus-décalage du ST	0.44 (0.26-0.75)	**<0.001**
Echocardiographie		
FEVG (diminution)	**5.58 (3.66-8.51)**	**<0.001**
Dysfonction ventriculaire droite	9.10 (5.18-15.7)	**<0.001**
Biologie		
Créatinine	1.82 (1.43-2.32)	**<0.001**
NT-proBNP	4.23 (2.84-6.29)	**<0.001**
Troponine	1.34 (1.08-1.67)	**<0.01**
Leucocytes	1.37 (1.12-1.75)	**<0.01**
Hémoglobine	0.70 (0.57-0.088)	**<0.01**
Taux de prothrombine	0.67 (0.53-0.86)	**<0.01**



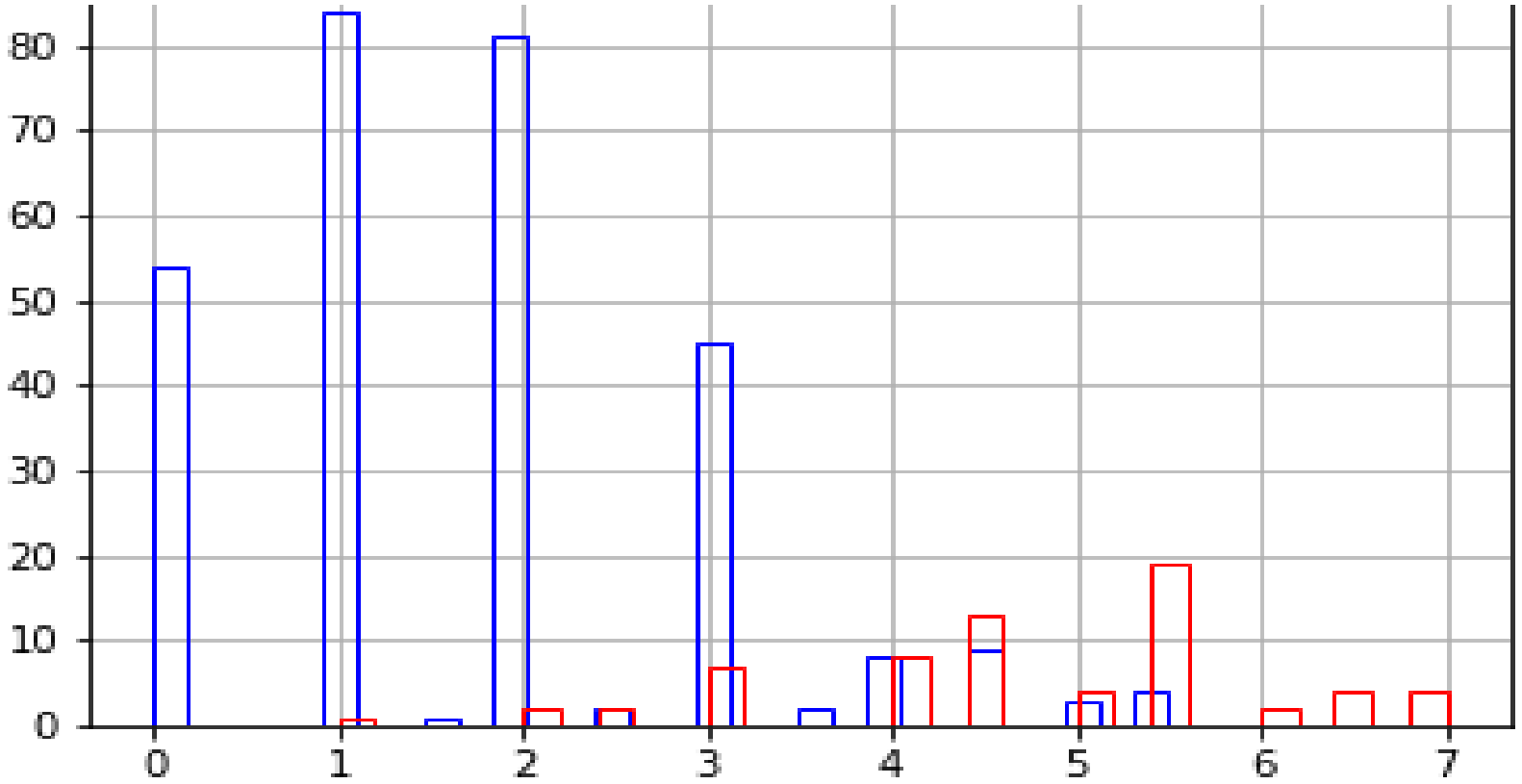
Regression model

Variable	Points
Femme	1
Cancer actif	2
Syncope	1
Choc cardiogénique	1.5
LVEF	
LVEF > 60%	0
56% ≤ LVEF ≤ 60%	1
42% ≤LVEF ≤ 55%	2
LVEF< 42%	3
Complete right bundle branch block	1.5
Complete atrioventricular block	1.5
TOTAL	**11**



Regression model

Histogram of regression score for patients with and without Composite outcome



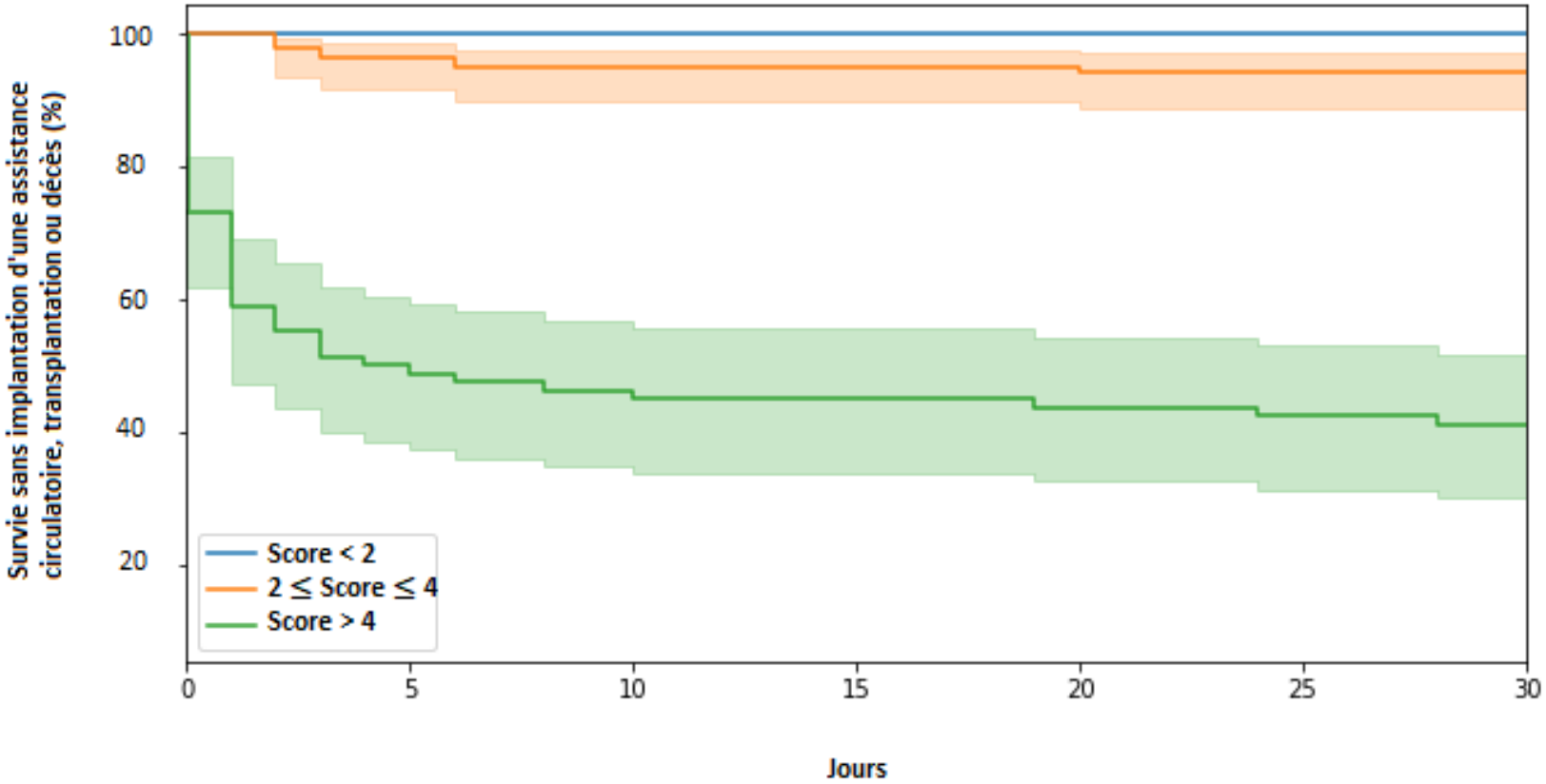
Regression model

Taux d'événements au long cours selon le niveau de risque prédit :

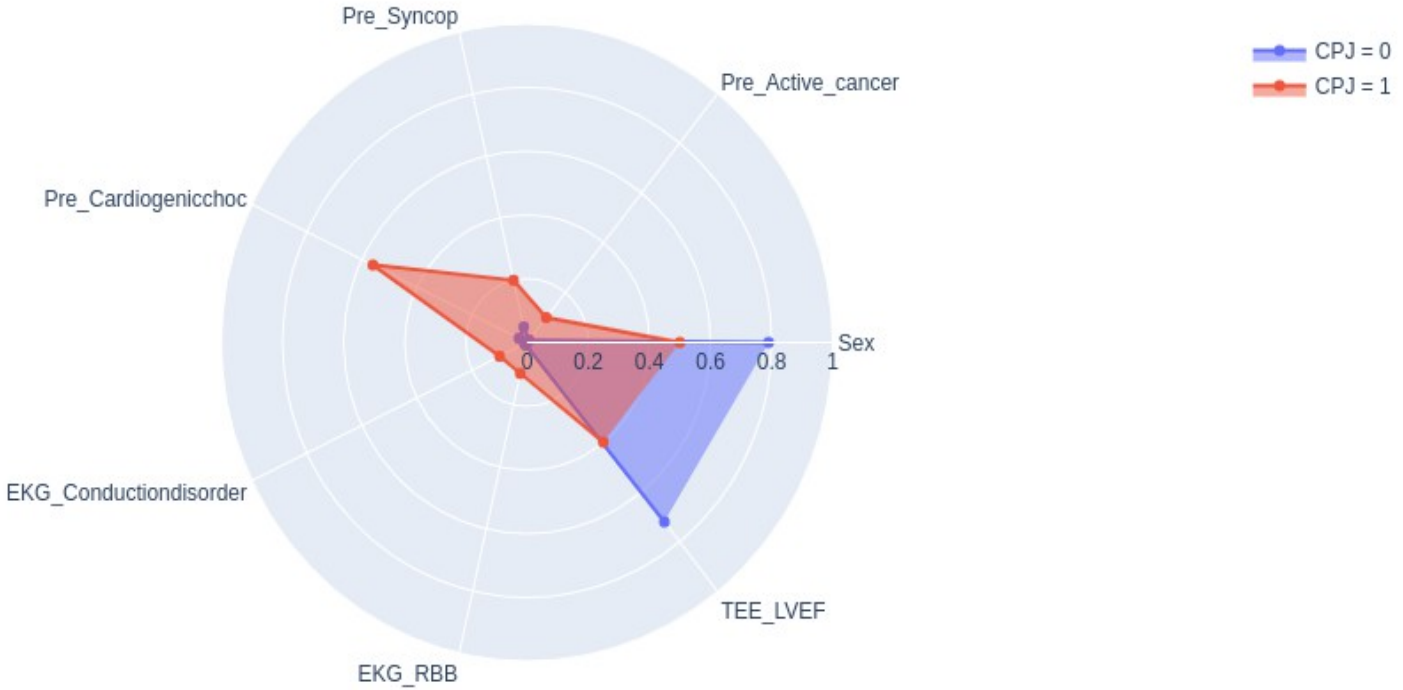
140 low risk patients (score < 2) = 0.7 % (IC 95% : 0-2.1%)

141 medium risk patients (score entre 2 ≤ Score < 4) = 26.2% (IC 95% : 15.5-26.8%)

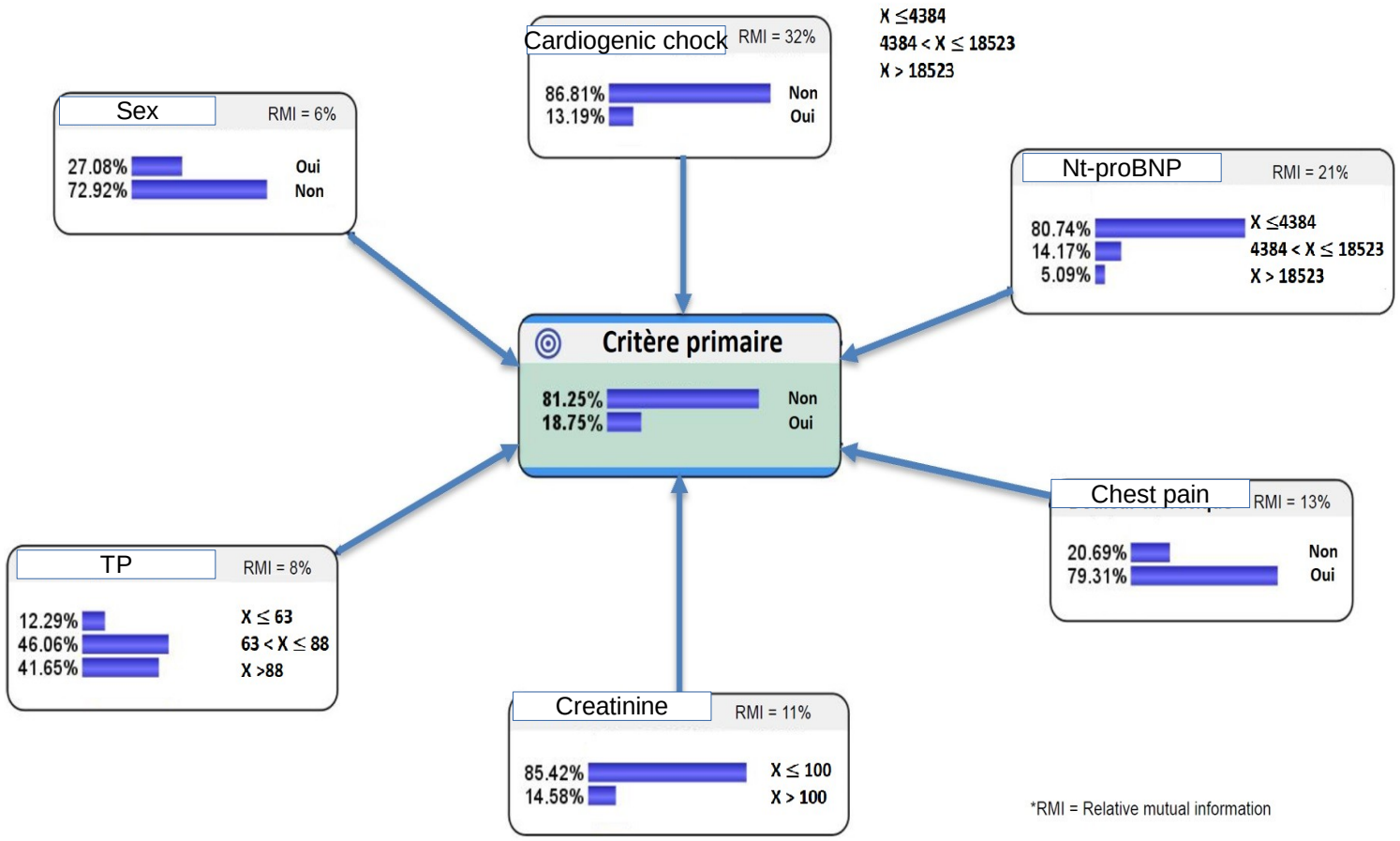
78 high risk patients (score ≥ à 4) = 69 % (IC 95% : 60-79.5%)

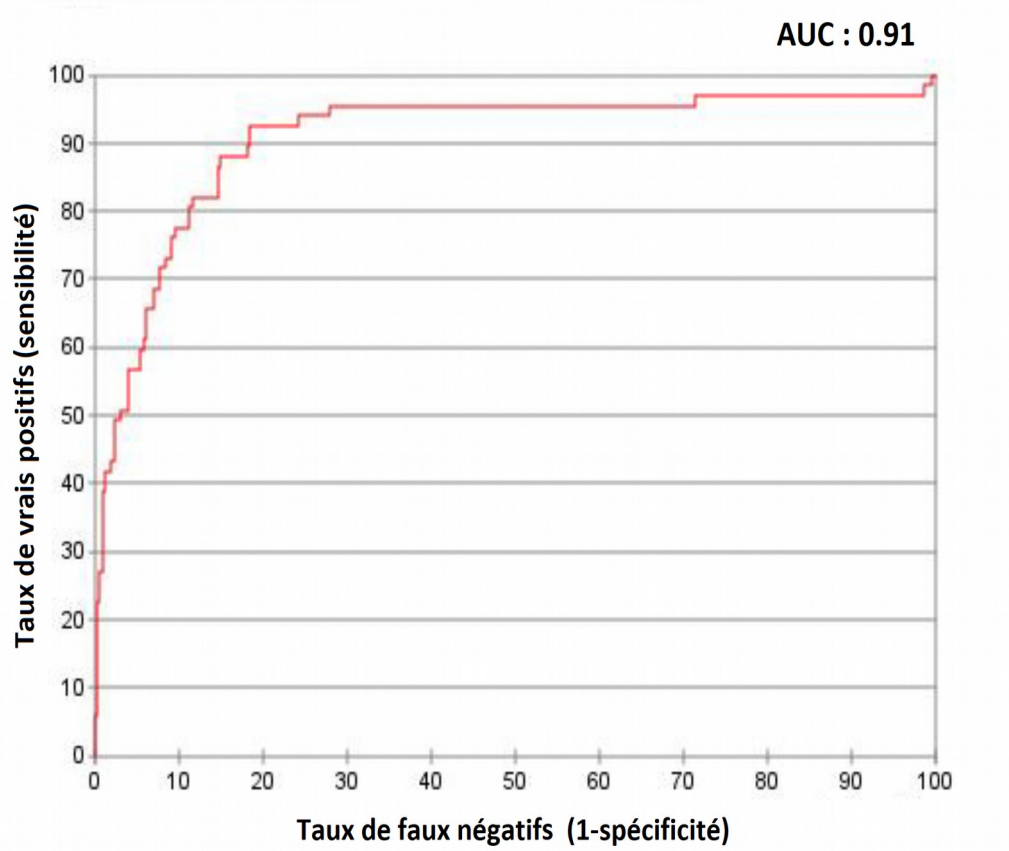


Regression model



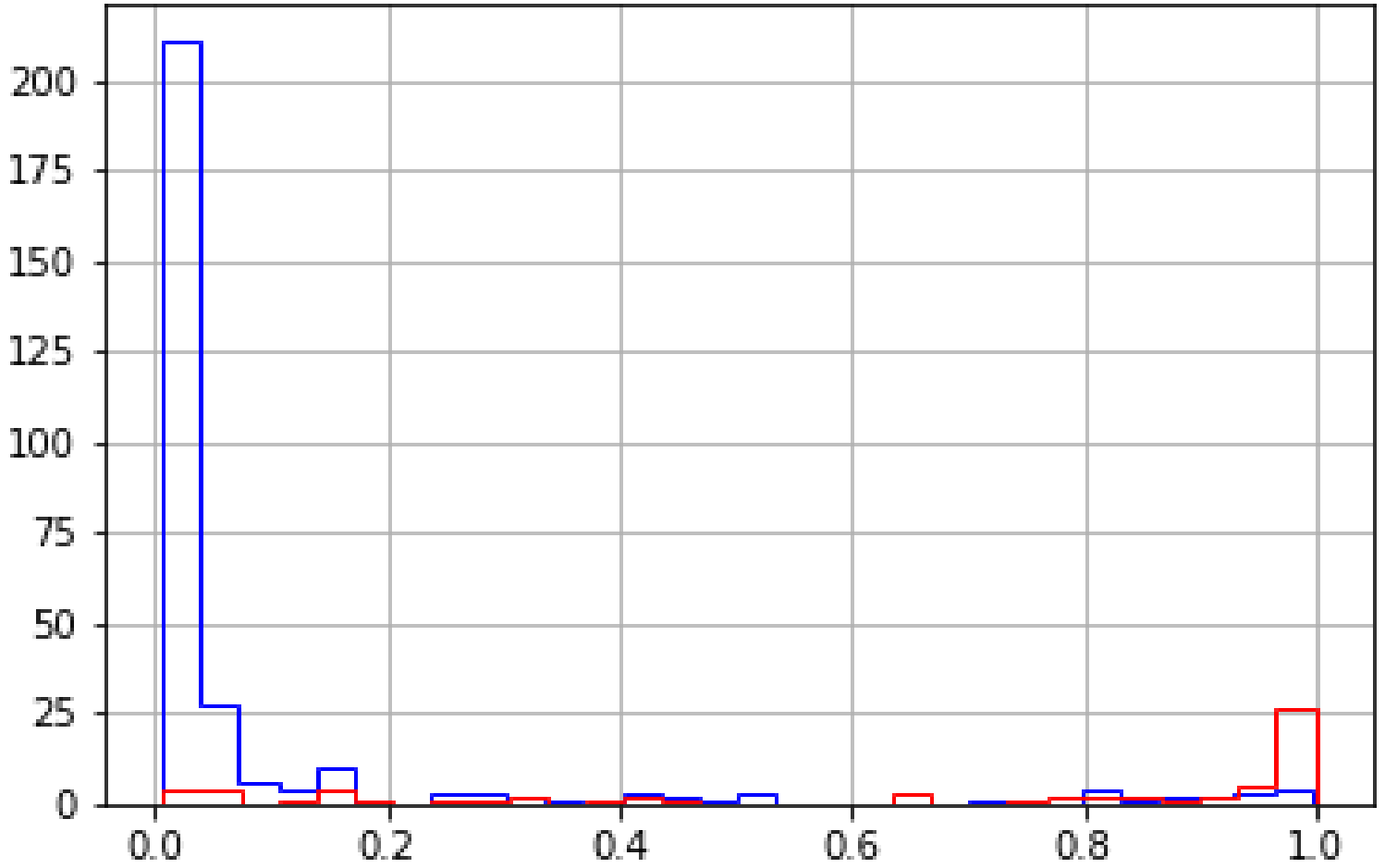
Bayesian model





Bayesian model

Histogram of Bayesian score for patients with and without PJC



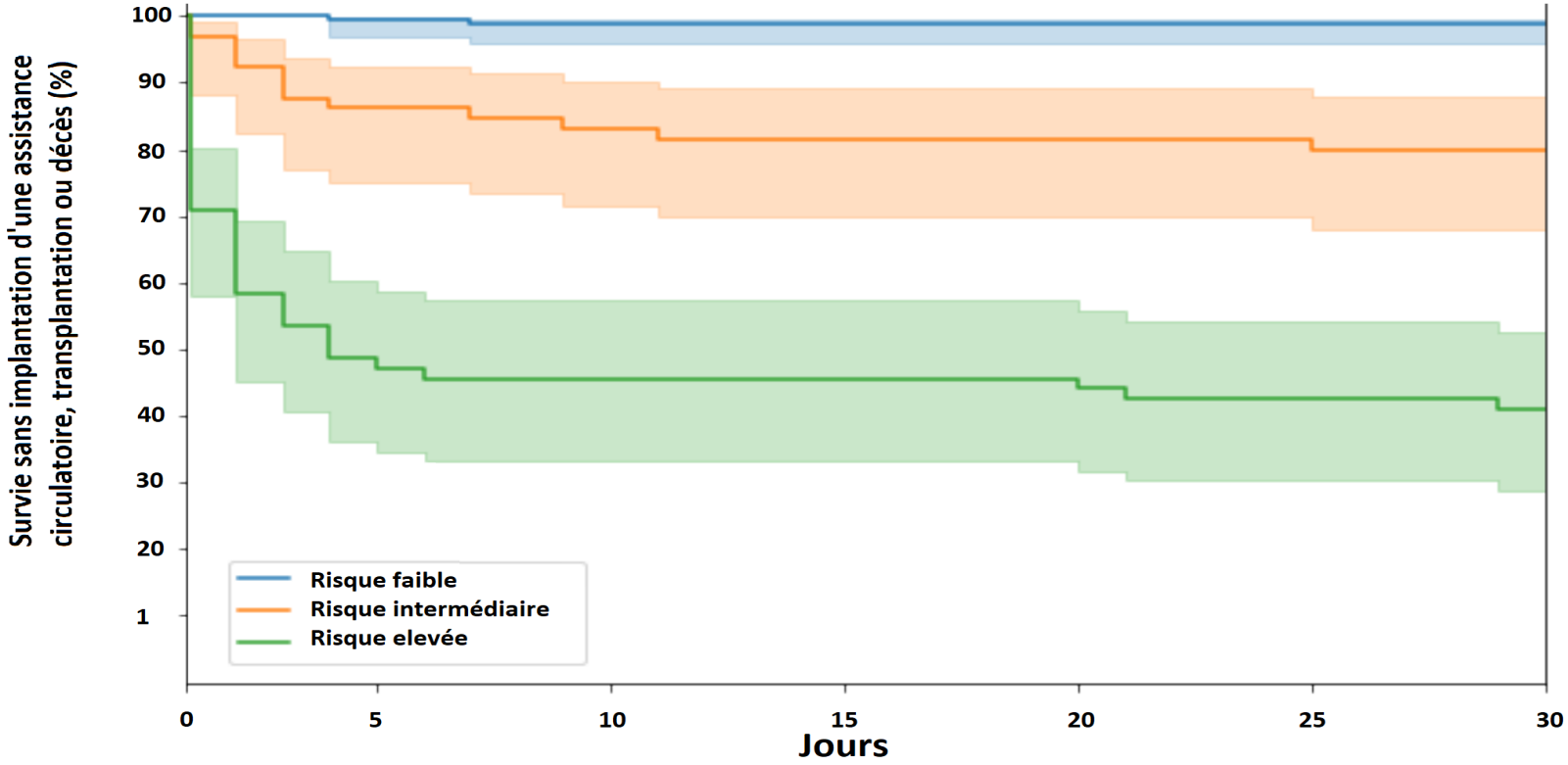
Bayesian model

Taux d'événements au long cours selon le niveau de risque prédit :

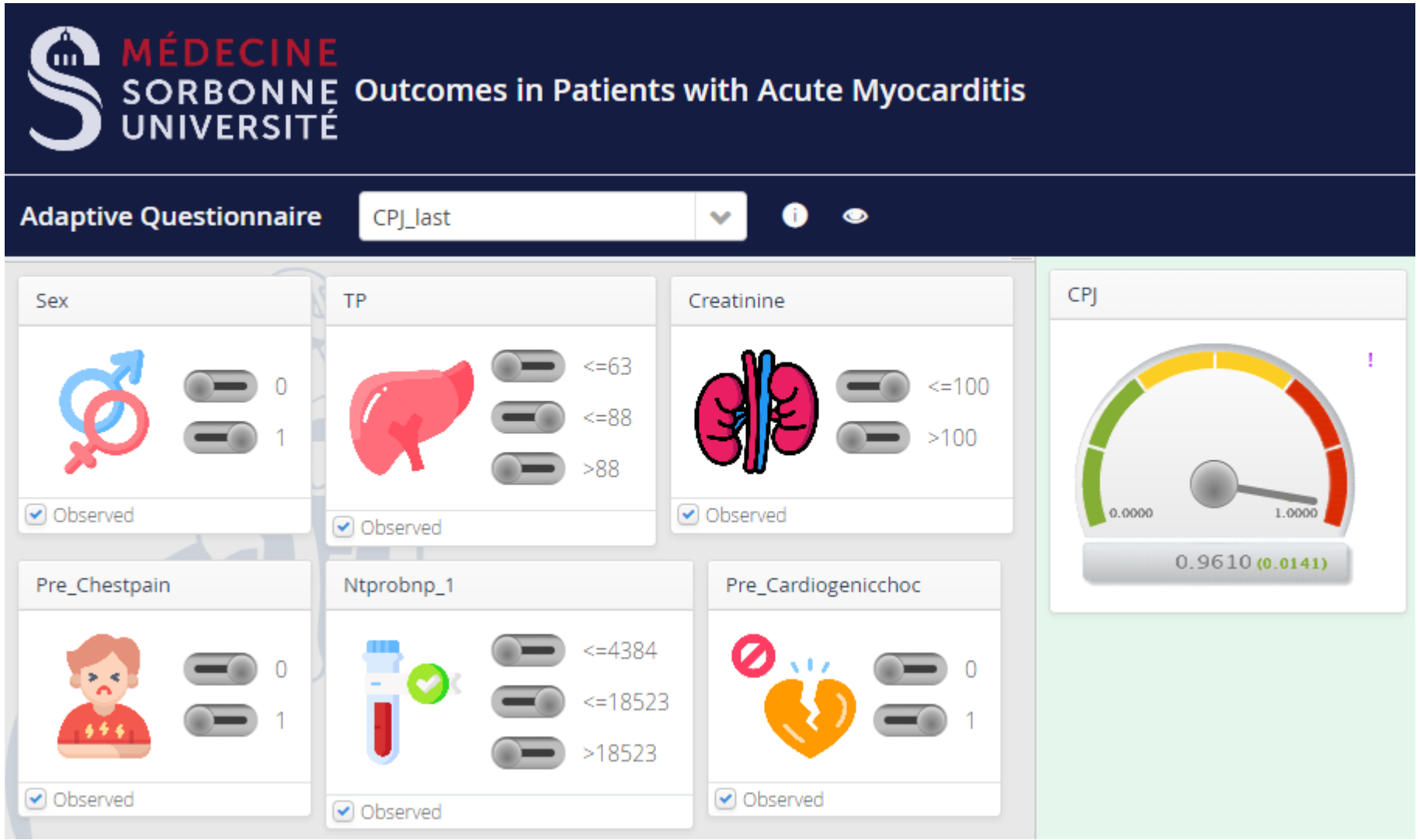
229 low risk patients (probabilité à moins de 5%) = 2.18% (IC 95% : 0.3-4.1%)

65 medium risk patients (probabilité entre 5 et 50%) = 7.6% (IC 95% : 3.4-12.2%)

65 high risk patients (probabilité supérieure à 50%) = 67.7% (IC 95% : 56.3-79.1%)



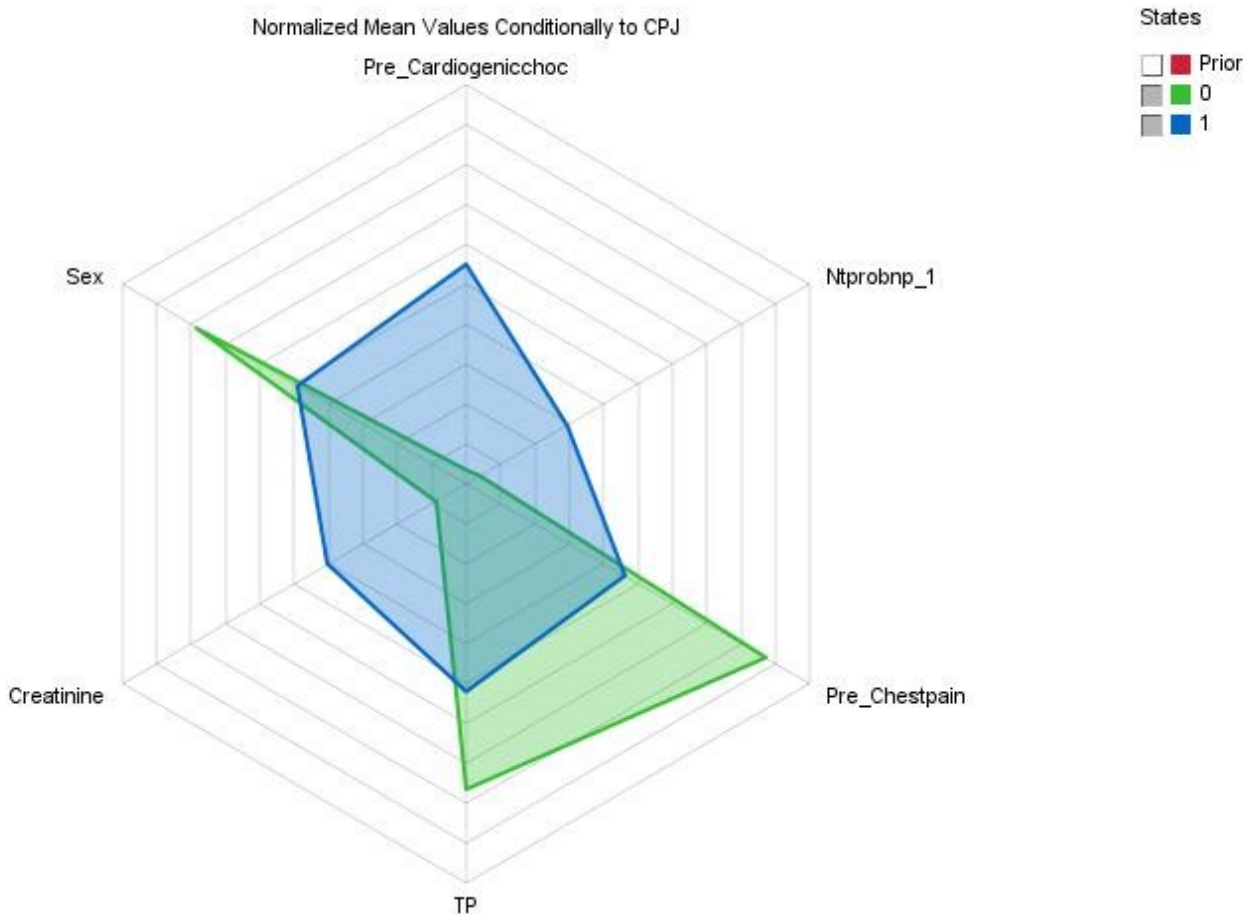
Bayesian model



https://simulator.bayesialab.com/#!questionnaire/145867270512

Bayesian model

Node:
Mean:



1 Introduction

2 Methods

3 Results

4 **Discussion**

5 Conclusion

Limits

- Monocentric
- 12-year period: diagnostic and therapeutic development
- Imputation of missing data
- External validation

Conclusion

- Both models are clinically insightfull
- They use differents variables
- The discretization is not the same
- The regression uses the Time to event
- Bayesian network is able to include variables with missing values
  - Further development

    Analyse combined predictions of the two models

    Adjust a bayesian network with variables selected by the regression

    External validation