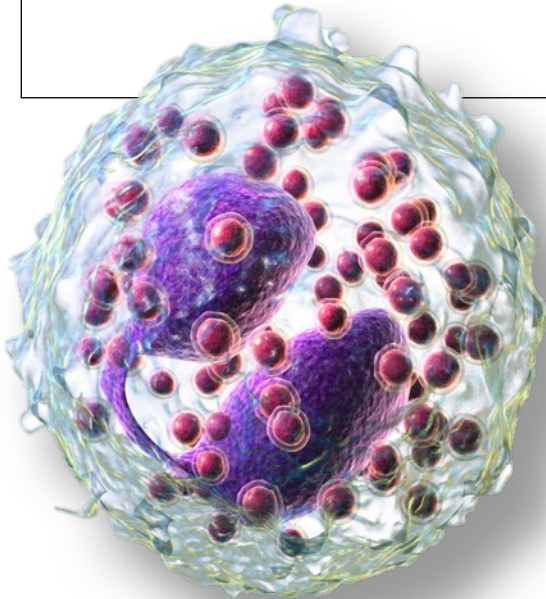


How to manage pleural eosinophilia ?

When should idiopathic pleural eosinophilic syndrome be considered ?



Dr CARADEC Emmanuella

No conflict of interest

A multi-faceted pathology

Eosinophilic pleural effusions (EPE) : Eosinophil count ≥ 10 % in the pleural fluid

Rare but not exceptional : prevalence 6-9 %

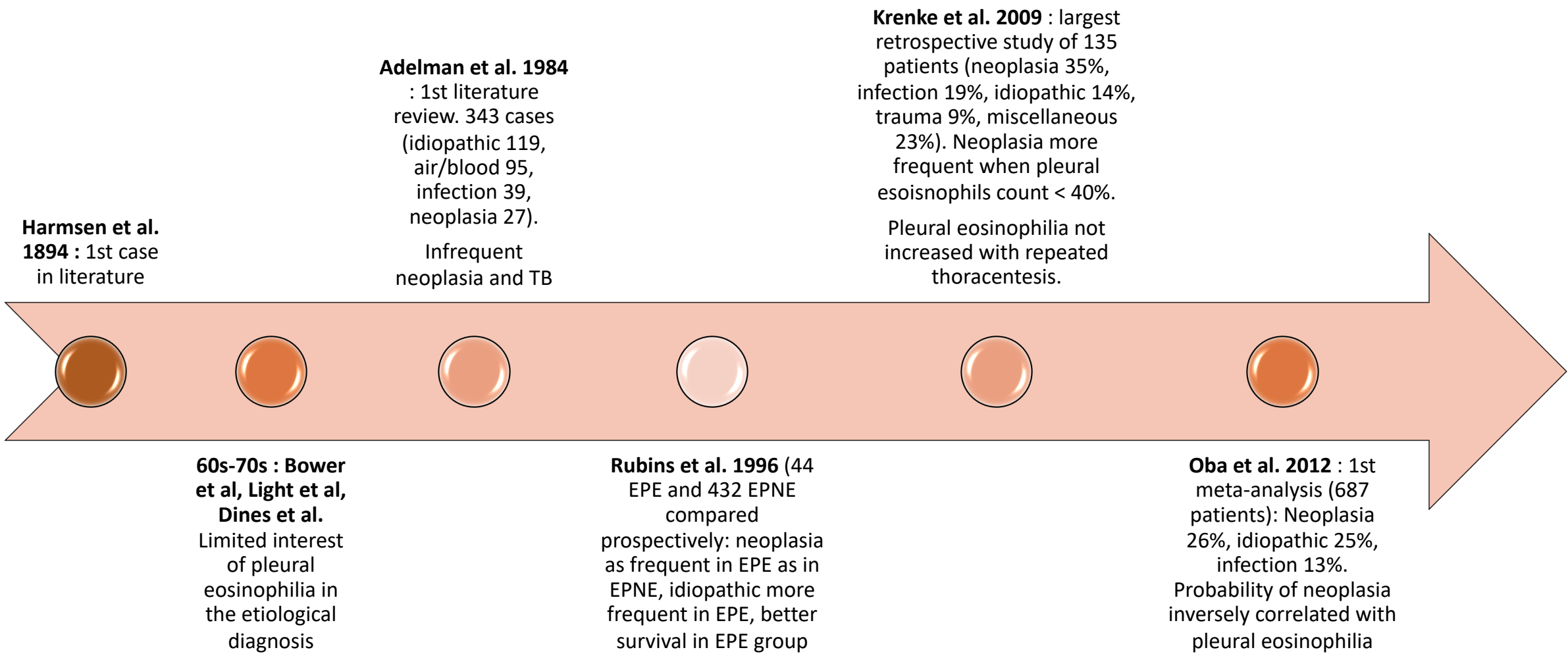
Wide variety of pathophysiologies and etiologies :

- Obvious : pneumothorax, hemothorax, trauma ...
- Frequent : neoplasia
- **BUT** > 25% undiagnosed or classified as « idiopathic »



Diagnostic difficulty in current practice
Inexperienced practitioners

An under studied pathology



Blood eosinophilia, pleural eosinophilia and etiology of EPE : what are the links?

Almost no data ...

- Except for malignant EPE : ↘ probability of neoplasia when pleural eosinophilia ↗ (threshold 30-40%)
- No demonstrated correlation between pleural and blood eosinophilia (*trend observed in study of Krenke and al : weak correlation $r=0.28$; $p=0.05$*)

No studies on the correlation between pleural/blood eosinophilia and non-malignant EPE

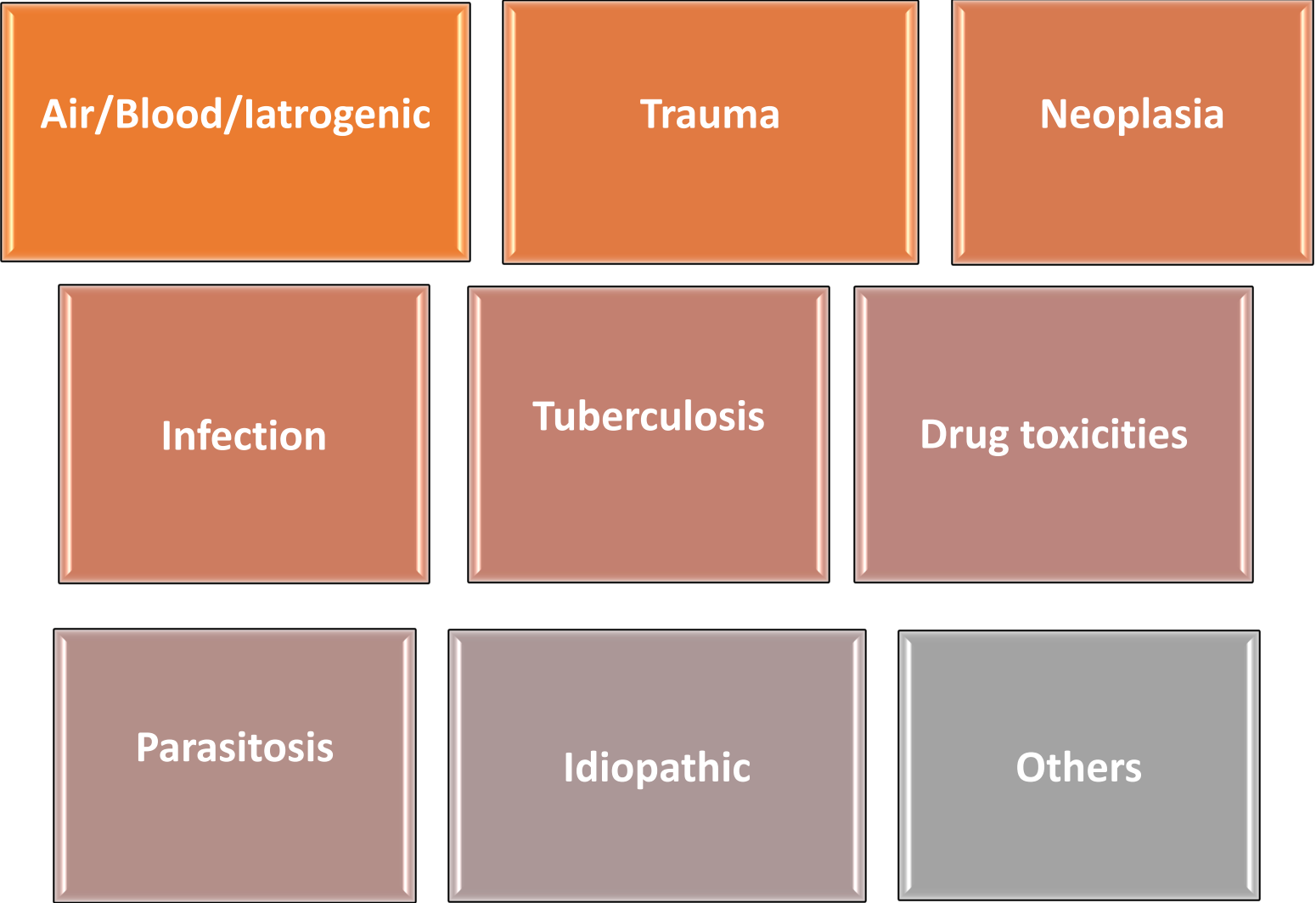
PleurEo : multicenter retrospective cohort

- 209 patients included between January 2015 and April 2020



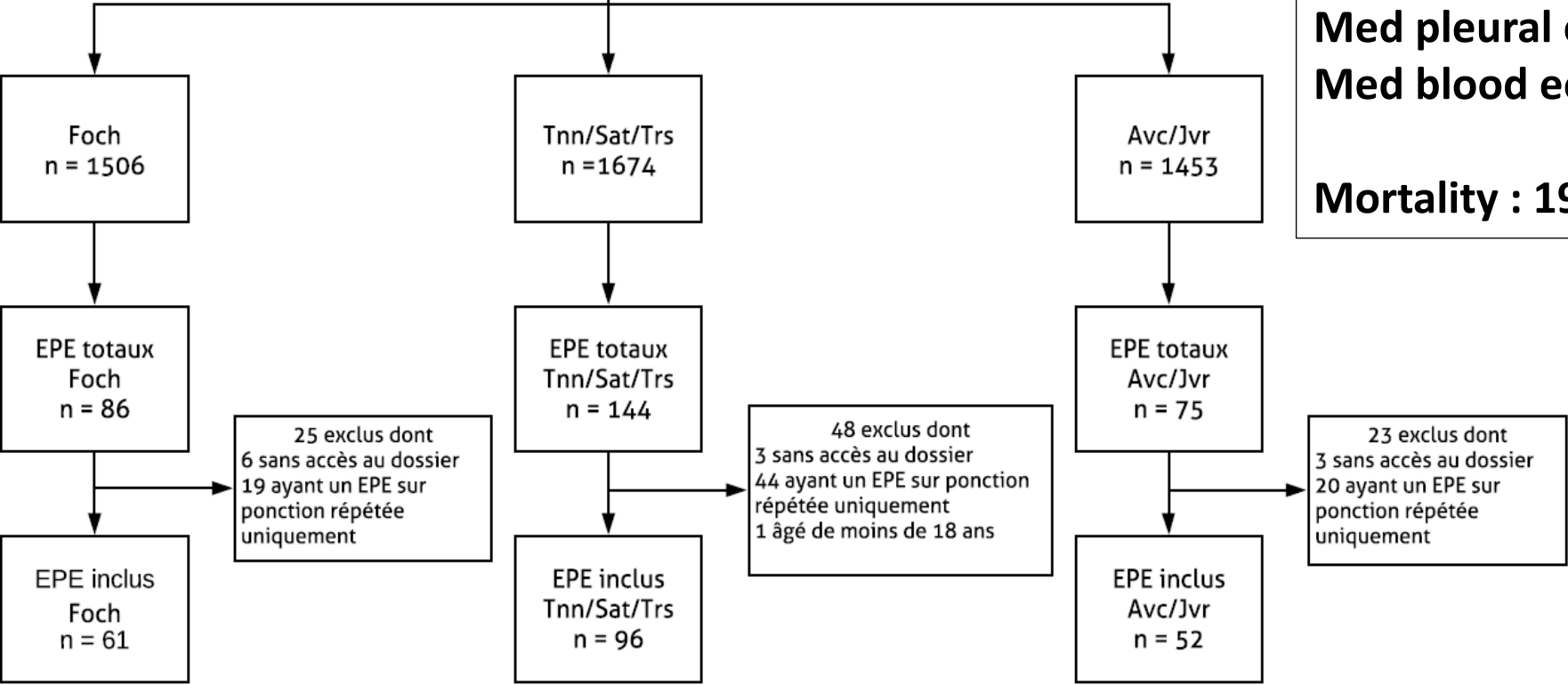
- Inclusion criteria : ≥ 18 yrs, at least 10% of pleural eosinophils on a first thoracentesis
- 1st aim : Compare the characteristics and etiologies of EPE according to their level of blood eosinophilia (*arbitrary threshold 0.5 G/L*)
- 2nd aim : Establish algorithm to help with the etiological diagnosis of EPE

PleurEo : etiological classification



PleurEo : flow chart

Ponctions pleurales
n = 4633



Prevalence EPE : 6,58%

Male : 68%
Med age : 53 yrs [34.0; 69.0]

Med pleural eosino = 29% [16.0; 58.0]
Med blood eosino = 0.37 G/L [0.20; 0.60]

Mortality : 19%

Etiological distribution of EPE

Air/Blood/Iatrogenic

Etiologies	N (%)
Air /Blood	53 (25,4)
Neoplasia	42 (20,1)
Infections	26 (12,4)
Iatrogenic	22 (10,5)
Drug toxicities	13 (6,2)
Idiopathic	12 (5,7)
Miscellaneous	11 (5,3)
Trauma	8 (3,8)
Parasitosis	7 (3,3)
Other organs (<i>heart, kidneys, liver, pancreas</i>)	7 (3,3)
Tuberculosis	6 (2,9)
Pulmonary embolism	1 (0,48)
Autoimmune diseases	1 (0,48)

→ Lung ++, breast, mesothelioma ...

→ NSAIDs, antibiotics, imatinib, fenofibrate ...

→ Asbestosis, IgG4 Related Disease, Auto inflammatory diseases, Post radiation, Crohn, Castelman, LAM, Aspergillated bronchogenic cyst

Others

Blood eosinophilia < 0,5 G/L vs. ≥ 0,5 G/L

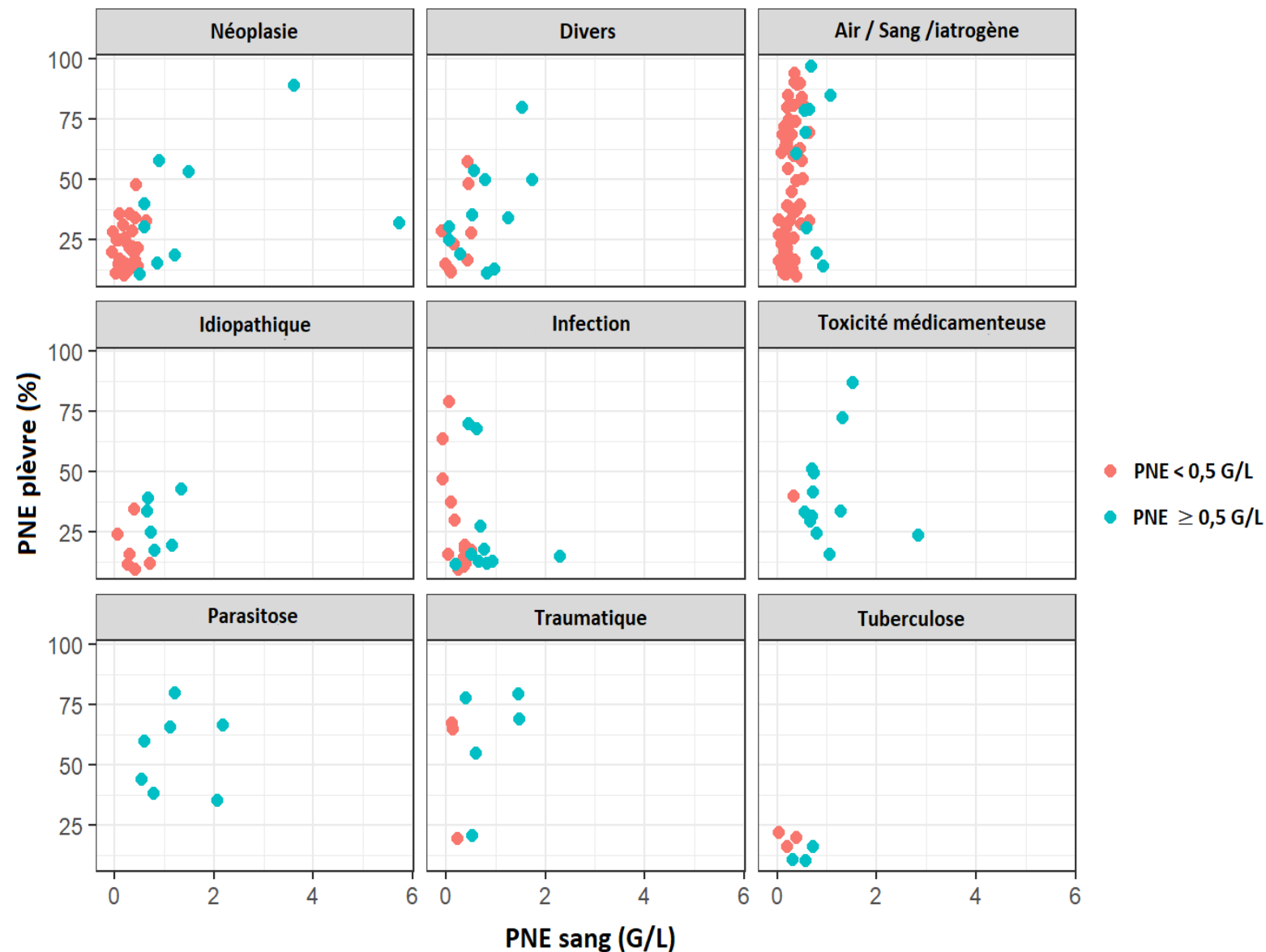
Variable	PNE < 0,5 (n = 137)	PNE ≥ 0,5 (n = 72)	Effe ctifs	p-value ¹
Age, années méd	51 [31; 66]	57 [41; 72]	209	0.026
Sexe masculin, n (%)	89 (65%)	53 (74%)	142	0.2
Tabagisme, n (%)	86 (63%)	47 (67%)	133	0,6
Sevré	40 (47%)	22 (47%)	62	0.97
Actif	46 (53%)	25 (53%)	71	-
Nbr PA, méd	20 [10; 40]	30 [11; 50]	126	0.14
Centre, n (%)				
Tenon	63 (46%)	16 (22%)	79	<0.01
Foch	36 (26%)	25 (35%)	61	-
Avicenne	28 (20%)	20 (28%)	48	-
Saint Antoine	10 (7.3%)	7 (9.7%)	17	-
Jean Verdier	0 (0%)	4 (5.6%)	4	-
Comorbidités, n (%)				
Respiratoires	68 (50%)	33 (46%)	101	0.7
Cardiovasculaires	45 (33%)	30 (42%)	75	0.3
Néoplasies	34 (25%)	9 (12%)	43	0.056
Maladies de système	4 (2.9%)	6 (8.3%)	10	0.10
Autres	43 (31%)	24 (33%)	67	0.9
Statut vital, n (%)				
Décédé	32 (23%)	7 (9.9%)	39	0.018
Vivant	105 (77%)	64 (90%)	169	-
Diagnostic étiologique, n (%)				
Air / sang / Iatrogène	66 (48%)	9 (12%)	75	<0.001
Néoplasie	33 (24%)	9 (12%)	42	-
Infection	16 (12%)	10 (14%)	26	-
Autres (divers, AI, EP, autres organes)	9 (6.6%)	11 (15%)	20	-
Toxicité médicamenteuse	1 (0.73%)	12 (17%)	13	-
Idiopathique	6 (4.4%)	6 (8.3%)	12	-
Traumatique	3 (2.2%)	5 (6.9%)	8	-
Parasitose	0 (0%)	7 (9.7%)	7	-
Tuberculose	3 (2.2%)	3 (4.2%)	6	-

Med : médiane ; PA : paquets années ; AI : auto immunitaire ; EP : embolie pulmonaire

¹ : tests statistiques utilisés : Chi2, Fischer, Wilcoxon

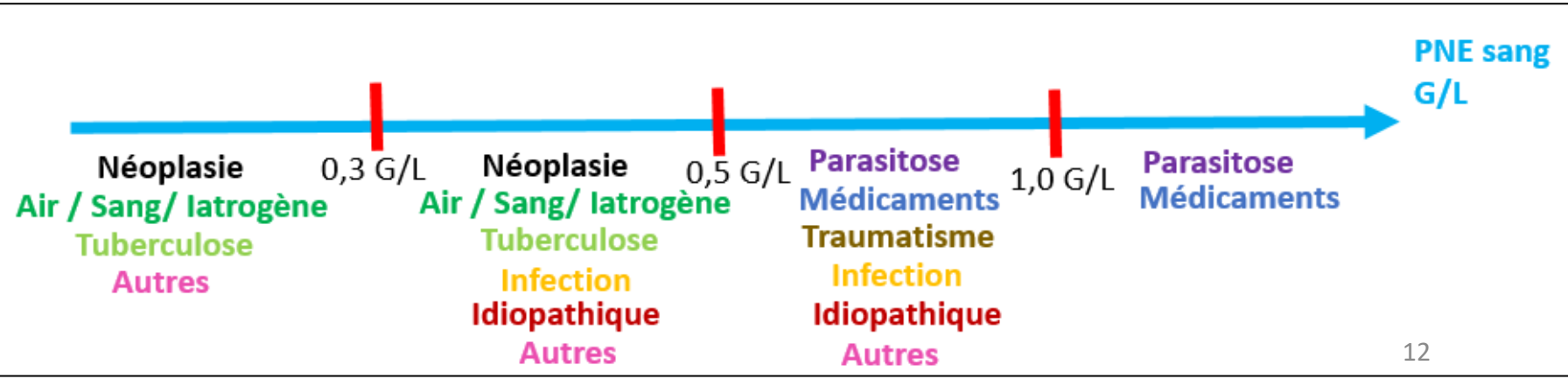
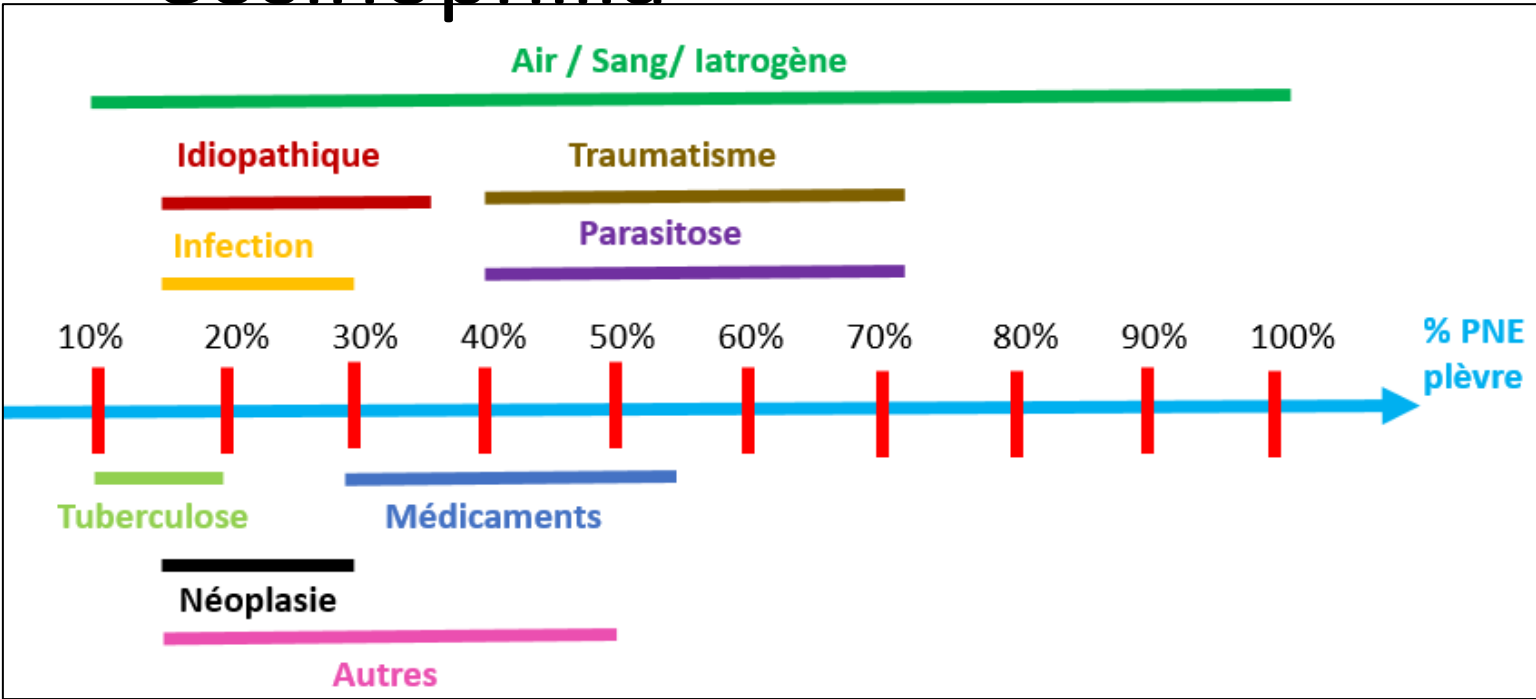
- **Significantly different etiologies (p<0.001)**
 - PNE < 0.5 G/L : air/blood/iatrogenic, neoplasia +++
 - PNE ≥ 0.5 G/L : trauma, drugs toxicities, parasitosis, others, idiopathic
 - Infections and tuberculosis equally frequent in the 2 grps
- **Mortality +++ when PNE < 0.5 G/L : 23% vs. 9.9% (p=0.018)**

Etiologies according to pleural and blood eosinophilia



- Composition of pleural fluid significantly different according to etiology especially for PNE ($p < 0.001$)
- Significantly different blood eosinophilia according to etiology ($p < 0.001$)

Etiologies according to pleural and blood eosinophilia



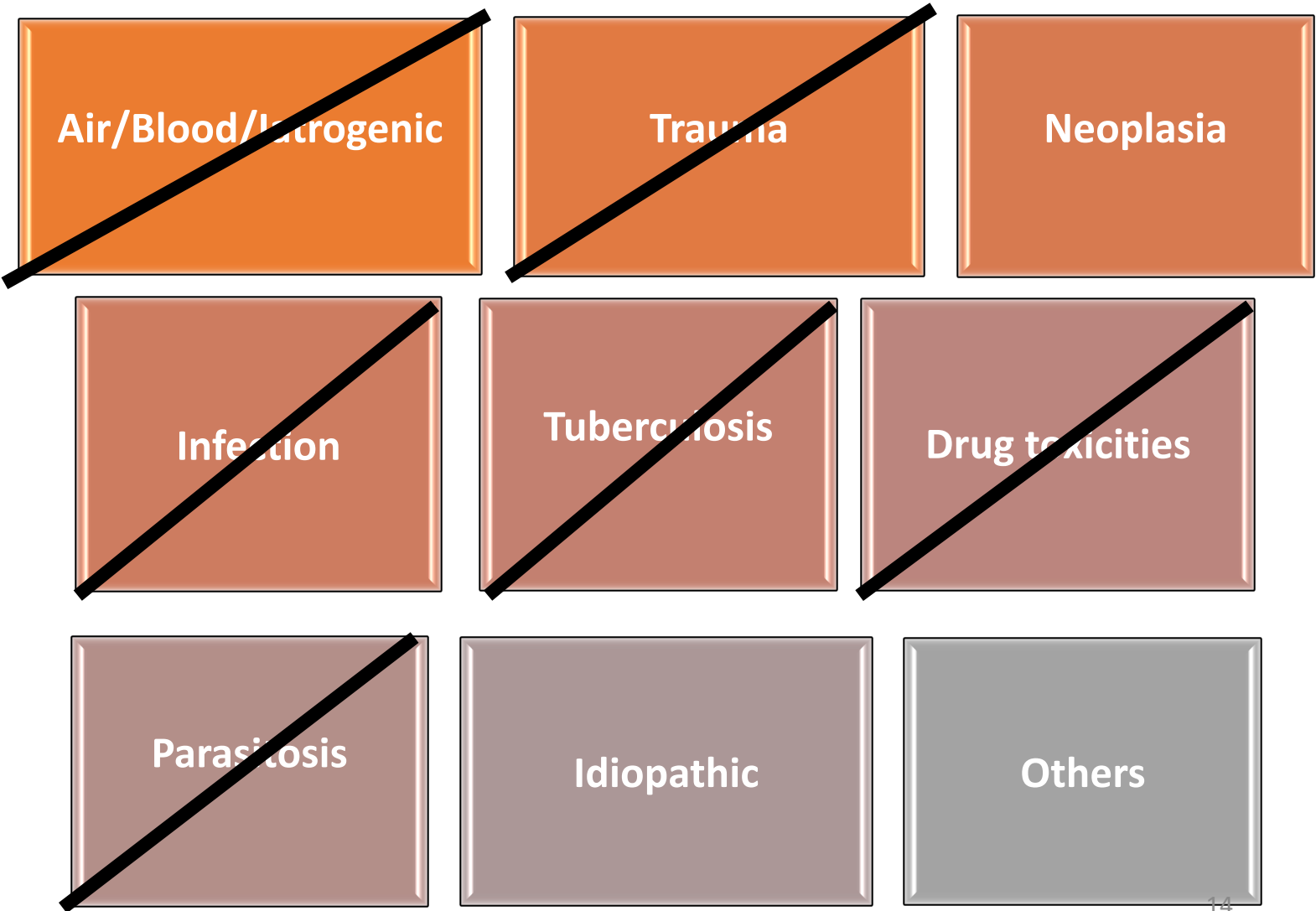
Etiological differences with the literature

Study	Total	Malig-nancy	Para-pneumonic effusion	TB	PE	Transu-date	CVD	Other	Idiopathic effusion	Air/blood
Bower [12], 1967	21	1 (5)	1 (5)	0	2 (10)	0	1 (5)	3 (14)	6 (29)	7 (33) ¹
Light et al. [24], 1973	8	1 (13)	2 (25)	0	0	0	0	2 (25)	2 (25)	1 (13) ²
Kokkola and Valta [13], 1974	78	6 (8)	3 (4)	14 (18)	0	0	8 (10)	1 (1)	44 (56)	2 (3)
Hirsch et al. [25], 1979	23	8 (35)	3 (13)	0	0	0	0	0	12 (52)	0
Pettersson and Riska [14], 1981	26	1 (4)	3 (12)	1 (4)	0	0	8 (31)	0	12 (46)	1 (4)
Mihailescu and Micu [15], 1985	11	3 (27)	1 (9)	5 (45)	0	1 (9)	0	1 (9)	0	0
Wysenbeek et al. [16], 1985	36	7 (19)	3 (8)	0	1 (3)	5 (14)	1 (3)	2 (6)	3 (8)	14 (39) ³
Kuhn et al. [17], 1989	22	5 (23)	1 (5)	1 (5)	1 (5)	3 (14)	1 (5)	0	2 (9)	8 (36) ⁴
Lakhotia et al. [18], 1989	18	1 (6)	4 (22)	0	0	1 (6)	0	0	12 (67)	excluded
Rubins and Rubins [6], 1996	44	10 (23)	4 (9)	0	0	9 (20)	0	3 (7)	11 (25)	7 (16)
Riantawan et al. [19], 1998	31	24 (77)	2 (6)	0	0	0	0	3 (10)	2 (6)	excluded
Martinez-Garcia et al. [5], 2000	45	11 (24)	15 (33)	7 (16)	1 (2)	4 (9)	0	0	7 (16)	excluded
Kalomenidis and Light [1], 2003	53	15 (28)	8 (15)	0	0	9 (17)	0	4 (8)	17 (32)	0
Matthai and Kini [20], 2003	26	4 (15)	7 (27)	5 (19)	0	3 (12)	0	6 (23)	1 (4)	0
Reechaipichitkul and Chuesakoolvanich [21], 2003	50	12 (24)	3 (6)	3 (6)	0	0	0	2 (4)	5 (10)	25 (50) ⁵
Ozkara et al. [22], 2007	60	22 (37)	3 (5)	6 (10)	3 (5)	2 (3)	2 (3)	3 (5)	18 (30)	1 (2)
Krenke et al. [23], 2009	135	47 (35)	23 (17)	3 (2)	3 (2)	7 (5)	2 (1)	10 (7)	19 (14)	21 (16)
Total	687	178 (26)	86 (13)	45 (7)	11 (2)	44 (6)	23 (3)	40 (6)	173 (25)	63 (13)
PleurEo	209	42 (20,1)	26 (12,4)	6 (2,9)	1 (0,48)	4 (1,9)	1 (0,48)	11 (5,3)	12 (5,7)	53 (25,4)

Oba et al.The Prevalence and Diagnostic Significance of Eosinophilic Pleural Effusions: A Meta-Analysis and Systematic Review, Respiration. 2012¹³

How to manage pleural eosinophilia ?

- **1st step :**
Rule out obvious etiologies
- **2nd step :**
Parasitosis/Drug/Trauma: blood eosinophilia ≥ 0.5 G/L and pleural eosinophilia $\geq 30\%$
- **3rd step :**
Infections: Context and response to ATB, PNN pl +++, CRP
- **4th step :**
Tuberculosis: Low pleural and blood eosinophilia, Ly pl $> 3 \times$ PNE pl
- **5th step :**
Rest ? context, age, laterality, abundance, CRP... Interest of algorithms +++



Idiopathic pleural eosinophilic syndrome : does it exist ?

Unclear definition – 25% of EPE

“Idiopathic pleural effusion is evoked when no etiology is found after the clinical, biological and radiological assessment “

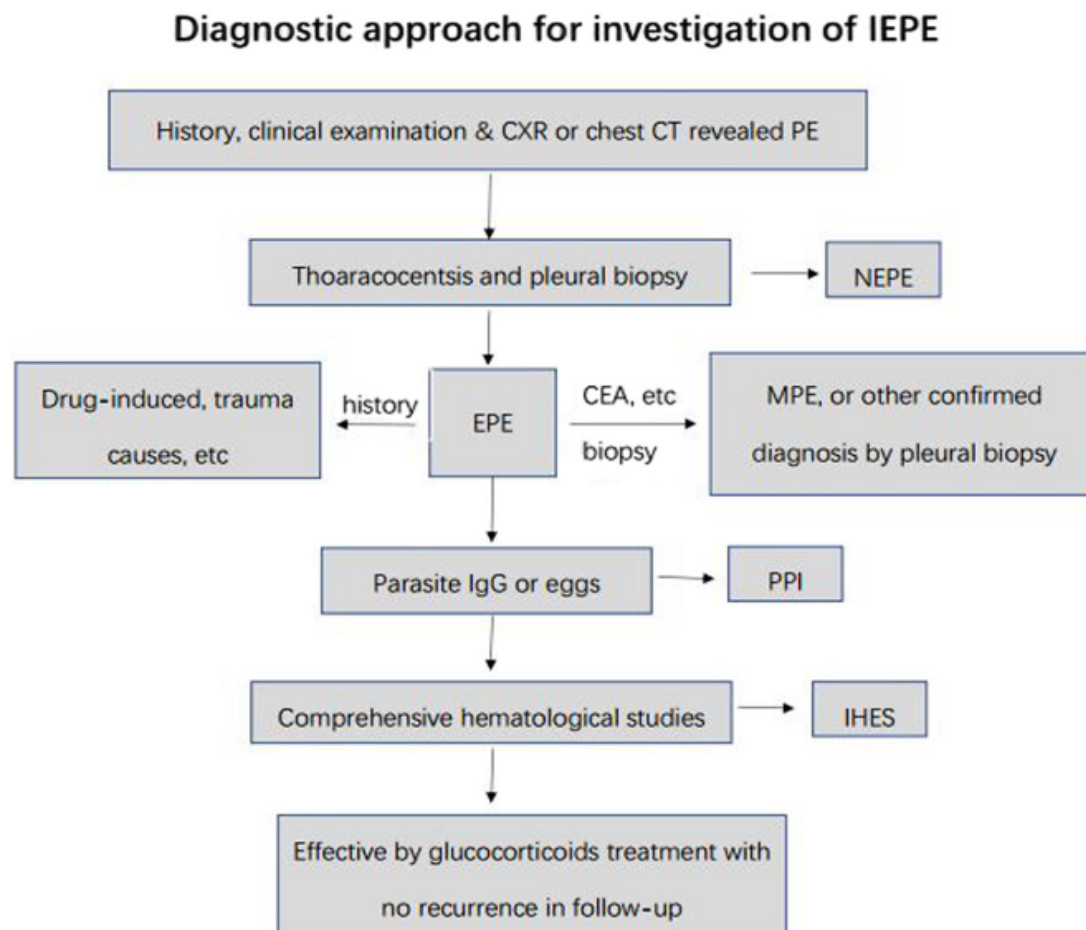
A variable minimum follow-up period is mentioned in some studies ranging from 6 to 36 months

Unsystematic thoracoscopy or pleuroscopy

Idiopathic pleural eosinophilic syndrome : does it exist ?

No	Chief complaint (duration)	Side of PE	Pathology of pleura biopsy	Treatment	Follow-up (mth)	Other organ involvement	Eos ($\times 10^9/L$)	Eos (%)	LDH (U/L)	Proteins (g/dl)
1	Fever, shortness of breath (20 d)	Bilateral	Eosinophilic infiltration	Glucocorticoid	9	lung	0.49	31	265	51.8
2	shortness of breath (2 mth)	Right	Eosinophilic infiltration	Glucocorticoid	15	N	2.16	20	338.5	52.6
3	Chest pain, shortness of breath (1 mth)	Bilateral	Lymphocytic infiltration	Glucocorticoid	12	Lung pericardium	0.6	22.5	209	49.7
4	Cough, shortness of breath (1 mth)	Bilateral	Noncaseating granulomas	Glucocorticoid	8	N	0.36	50.5	421.9	48.3
5	Shortness of breath (2.5 mth)	Bilateral	Lymphocytes infiltration	Glucocorticoid	16	N	0.71	14.3	89.8	37.5
6	Chest pain, shortness of breath (1 mth)	Left	Eosinophilic infiltration	Glucocorticoid	11	Lung	0.49	21	221.0	43.2
7	Cough, excessive sputum, shortness of breath (1 mth)	Bilateral	Eosinophilic infiltration	Glucocorticoid	10	N	0.64	19	189.4	39.8
8	Fever, shortness of breath (1 mth)	Left	Lymphocytic infiltration	Glucocorticoid	12	N	0.35	15.2	201.2	35.6
9	Cough, chest pain, shortness of breath (2 mth)	Bilateral	Eosiniphilic & lymphocytic infiltration	Glucocorticoid	11	Pericardium	0.42	21.2	234.4	43.2
10	Fever, cough (15 d)	Bilateral	Granulocytic & lymphocytic infiltration	Glucocorticoid	10	Lung	0.34	18.9	321.4	34.2
11	Shortness of breath (2 m)	Right	Eosinophilic infiltration	Glucocorticoid	11	N	0.84	12.4	214.5	32.8

Idiopathic pleural eosinophilic syndrome : does it exist ?



Abbreviations: IEPE, idiopathic eosinophilic effusion; CXR, chest X-ray; PE, pleural effusion; NEPE, non-EPE; CEA, carcinoembryonic antigen; MPE, malignant pleural effusion; PPI, pleural parasitic infestation; IHES, idiopathic hyper eosinophilic syndrome.

Luo et al - Diagnostic procedure for idiopathic eosinophilic pleural effusion: a single-center experience - BMC Pulmonary Medicine - 2020

Idiopathic pleural eosinophilic syndrome : mandatory pleuroscopy ?

Patients	Age	Follow-up (months)	Neutrophils %	Eosinophils %	Lymphocytes %	Macroscopic	Microscopic
1	35	102	8.8	59	22	PP, PT	DEI
2	39	96	21	15	54	PP, PT	DEI
3	41	72	10	48	34	PP, PT	DEI
4	59	90	38	10	52	PP, PT	DEI
5	84	48	15	10	60	DN	NCG
6	91	24	2.7	16	81	PP, PT	DEI
7	44	27	30	11	45	DN	NCG
8	38	72	15	23	61	PP, PT	DEI
9	69	24	18	45	35	PP, PT	DEI
10	57	26	5	40	45	PP, PT	DEI
Median	50.5	60	15	19	48.5		

-PP, pleural plaques; PT, pleural thickening; DEI, diffuse eosinophilic inflammation; DN, diffuse nodule; NCG, non-caseating granulomas.



Proposal to replace the term idiopathic EPE by indeterminate EPE before pleuroscopy

PleurEo : idiopathic EPE (23 cases)

- Initially only 12 out of 209 patients
- After warehouse analysis without time limits at Foch, addition of 11 IEPEs, **i.e. a total of 23 patients**
- Baseline characteristics similar to the other two cohorts of IEPE
- At least 12 month follow-up period
- ¾ thoracoscopy

Variable	Médiane [Q25-75]	Effectifs, n (%)
Age	50.0 [34.5; 66.0]	23
Sexe masculin		18 (78%)
Tabagisme		16 (69,6%)
Comorbidités		8 (34,8%)
Aucune		15 (65,2%)
Respiratoires		7 (30,4%)
Cardiovasculaires		7 (30,4%)
Néoplasies		2 (8,7%)
Maladies systémiques		1 (4,35%)
Autres		8 (34,8%)
Terrain atopique		4 (17,4%)
Statut vital		
Décédé		3 (13%)
Vivant		20 (87%)
Latéralité		
Unilatéral		15 (65%)
Bilatéral		8 (35%)
Abondance		
Faible		5 (22%)
Moyenne		15 (65%)
Grande		3 (13%)
PNE pl %	29.0 [21.0; 39.5]	23
Lymphocytes pl %	42.0 [25.0; 51.0]	23
PNN pl %	5.00 [1.00; 7.00]	23
Autres cellules pl %	21 [12; 26]	23
GB/mm3	2900 [500 ;4700]	23
GR/mm3	3200 [1040 ;11542]	23
Protéines pleural (g/L)	50 [45,3 ;56]	23
LDH pleural (U/L)	493 [263 ;576]	23
PNE s (G/L)	0.750 [0.525; 1.05]	23
CRP (mg/L)	21.7 [16.6; 77.5]	23
LDH (U/L)	240 [167 ;281]	23
BNP (ng/ml)	22 [11 ;181]	23
Gammaglobulines (g/L)	13,1 [11,7 ;14,8]	23
Épanchement péricardique		2 (8,7%)
Evolution sous traitement		
Pas de récidence		12 (52%)
Récidive après disparition		6 (26%)
Persistance sous traitement		3 (13%)
Pas de données		2 (8,7%)
PEC chirurgicale		17 (74%)

PleurEo : idiopathic EPE vs. rest of EPE (23 vs. 131) (except Air/Blood/Iatrogenic)

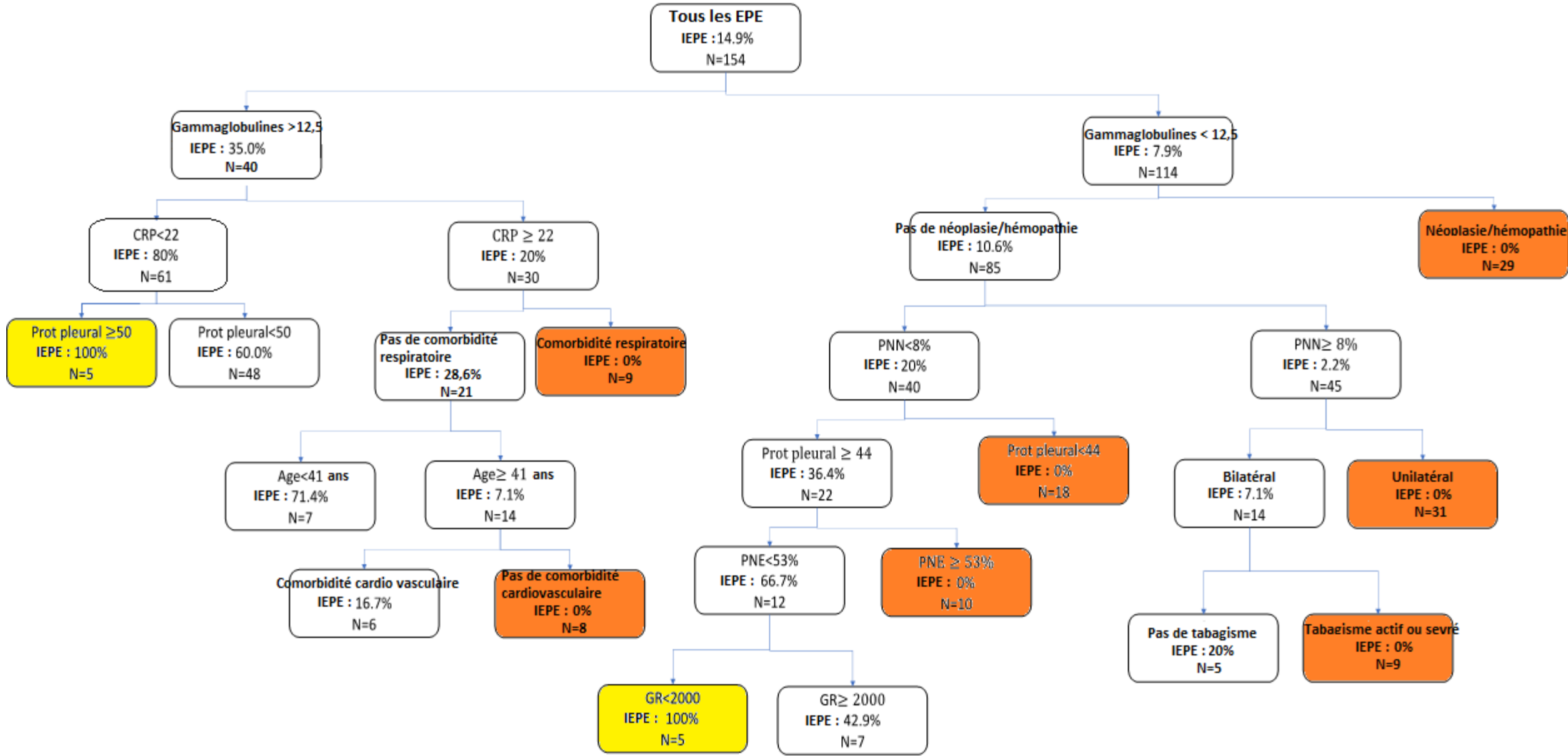
Determination of the thresholds of the univariate continuous variables with p value <0.20

Parameters	Threshold	P value	AUC
Protides pl	47.0	<0.001	0.722
PNN pl	9.0	0.019	0.618
Lymphocytes pl	25.0	0.111	0.614
BNP	22.0	0.046	0.667
LDH s	285.73	0.024	0.648
Gammaglobuline	12.578	0.009	0.732
CRP	35.0	0.120	0.634
Age	52.0	0.032	0.634

Multiple logistic regression with forward-backward model, all variables with p<0.20 were included in the model.

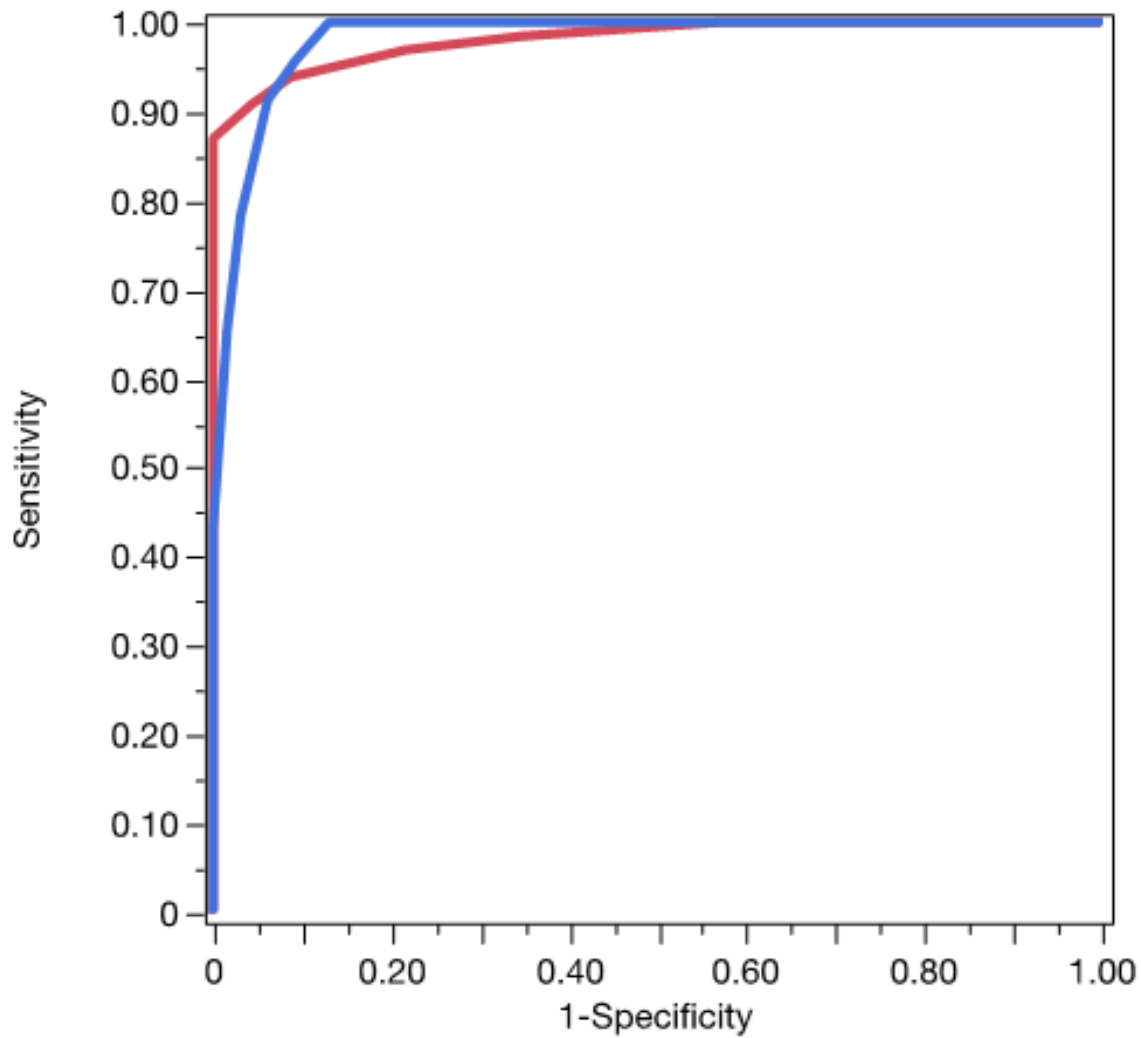
Parameters	OR 95% CI	P value
Age > 52 ans	0.32 [0.11 – 0.94]	0.039
CRP > 35 mg/l	0.26 [0.09 – 0.77]	0.015
LDH s > 285.73 U/l	0.07 [0.02 – 0.54]	0.011
Lymphocytes pl > 25.0 %	4.42 [1.28 – 15.29]	0.019
PNN pl > 9.0 %	0.18 [0.05 – 0.65]	0.009

PleurEo : Decision Tree Model for idiopathic EPE

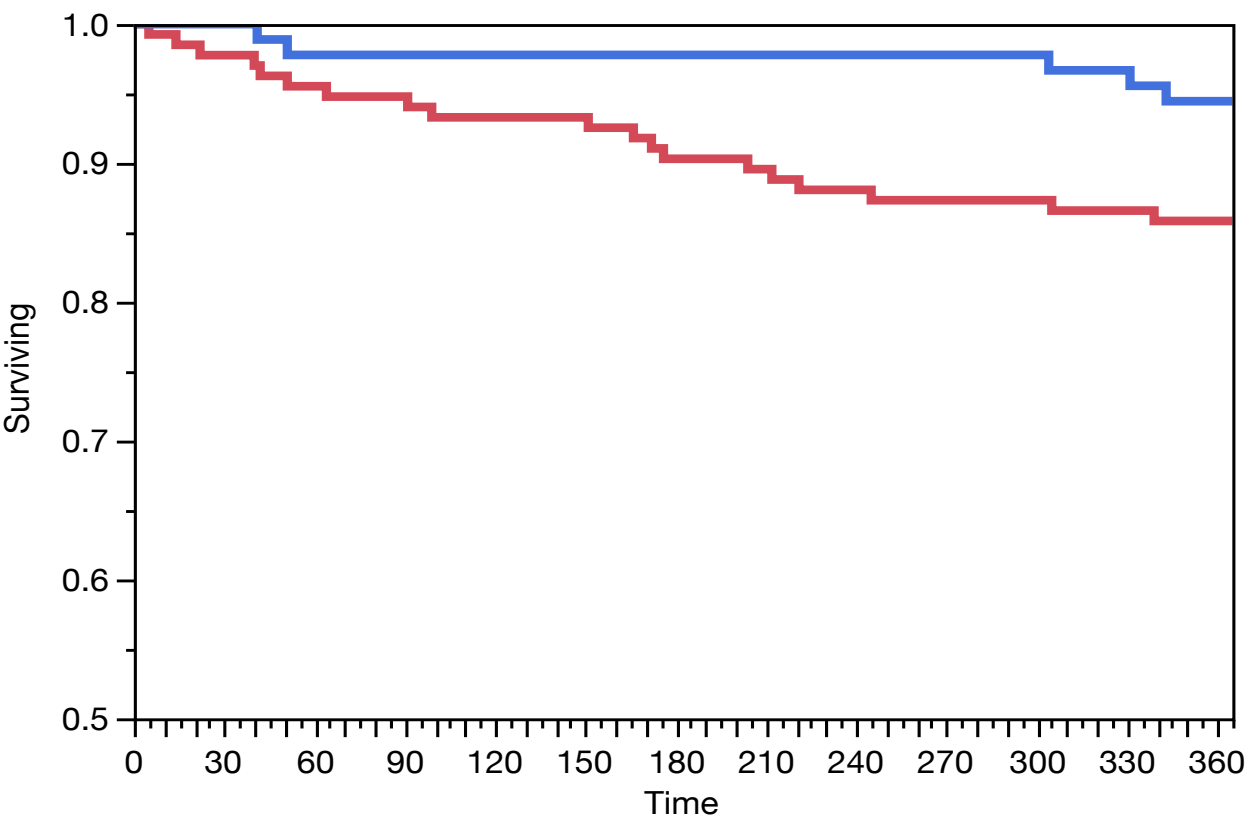


PleurEo : Decision Tree Model for idiopathic EPE

5 k-fold cross validation
 $R^2=0.692$
 $AUC=0.981$
 $Se=78.3\%$
 $Sp=96.9\%$

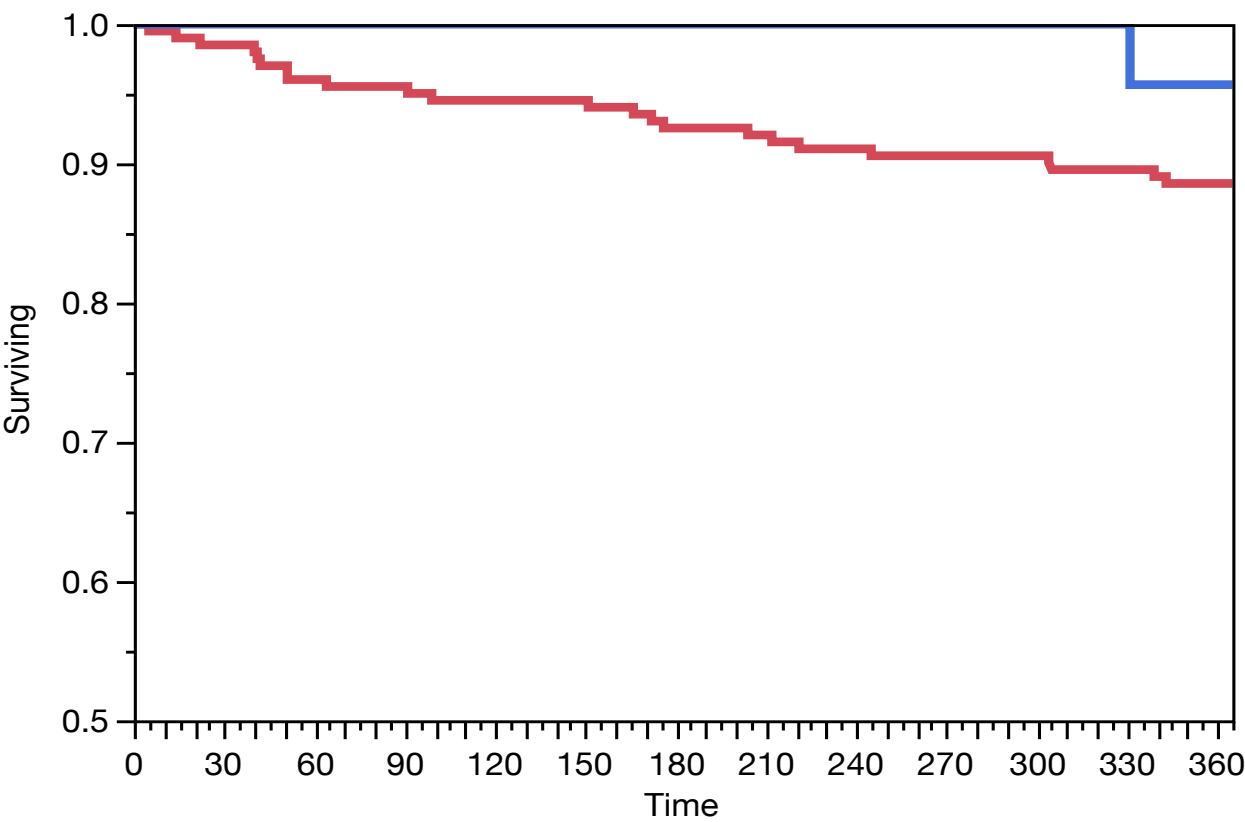


PleurEo : Survival analysis PNE < 0,5 G/L vs. ≥ 0,5 G/L



- Analysis on 224 patients (90 with PNE blood ≥ 0,5 G/L and 134 with PNE blood < 0,5 G/L, Missing data, N=5)
- **Log rank test, p=0.037**
- PNE blood < 0,5 G/L : survival rate at one year=85.6 [79.8 – 91.8]
- PNE blood ≥ 0,5 G/L : survival rate at one year=94.4 [89.6 – 99.3]

PleurEo : Survival analysis IEPE vs. rest of EPE



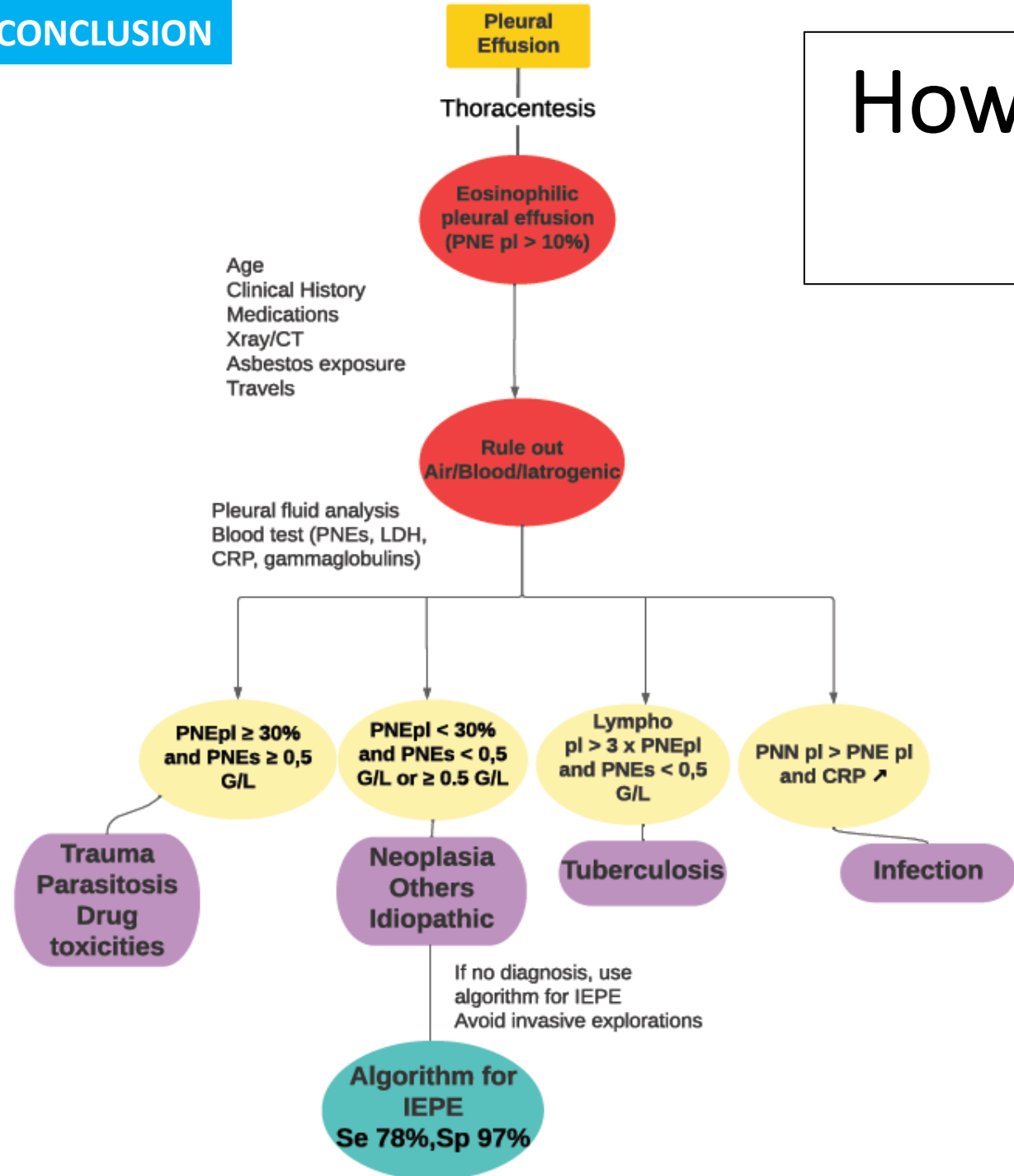
- Analysis on 224 patients (23 with IEPE and 201 with other pathologies, Missing data, N=5)
- **Log rank test, $p=0.295$**
- Other pathologies : survival rate at one year=88.6 [84.1 – 93.0]
- IEPE : survival rate at one year=95.7 [86.6 – 104.7]

Study limitations

Missing data (retrospective)

Selection bias : 3 large centers all including thoracic surgery, pulmonology and oncology departments

How to manage pleural eosinophilia ?



Use of algorithms can avoid unnecessary invasive explorations especially for IEPE

Thank you for your attention

