iame UMR 1137
Infection • Antimicrobials • Modelling • Evolution

OUTCOME RÉA

Sepsis cluster analysis

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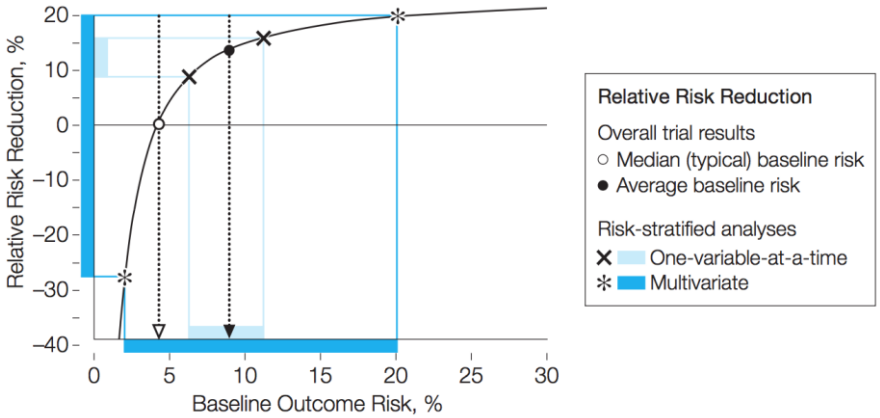
Jeudi 16 mai 2018

Problematic

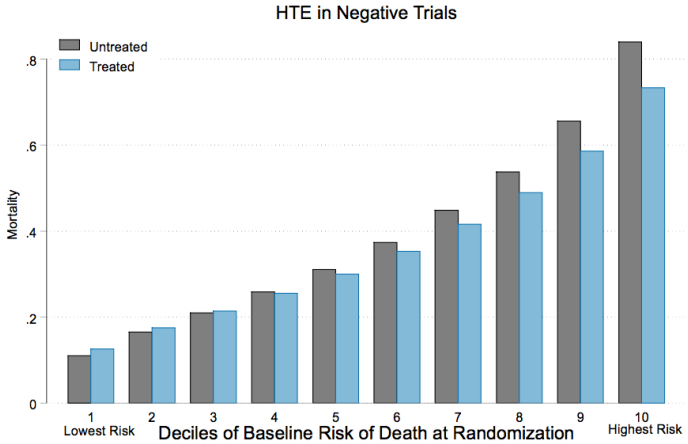
« One of the great disappointments during the past 30 years has been the failure to convert advances in our understanding of the underlying biologic features of sepsis into effective new therapies. »

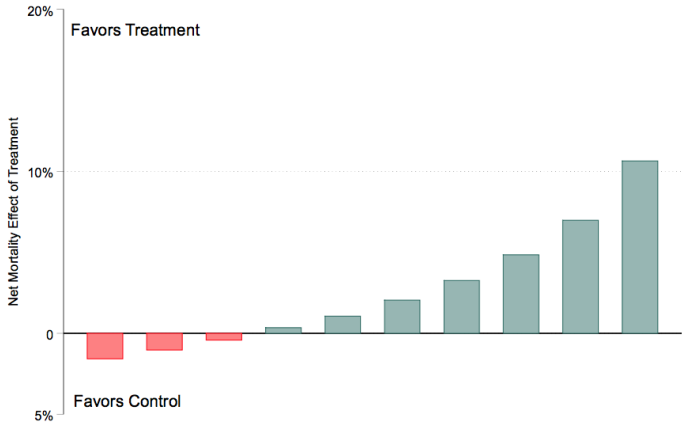
D. Angus - NEJM - 2013

Heterogeneity of treatement reponse



D.M. Kent - JAMA - 2007





T.J. Iwashyna - AJRCM - 2015

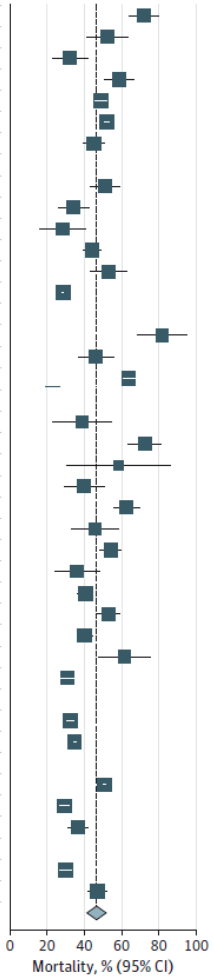
Sepsis and Septic Shock (Sepsis-3)

Box 3. New Terms and Definitions

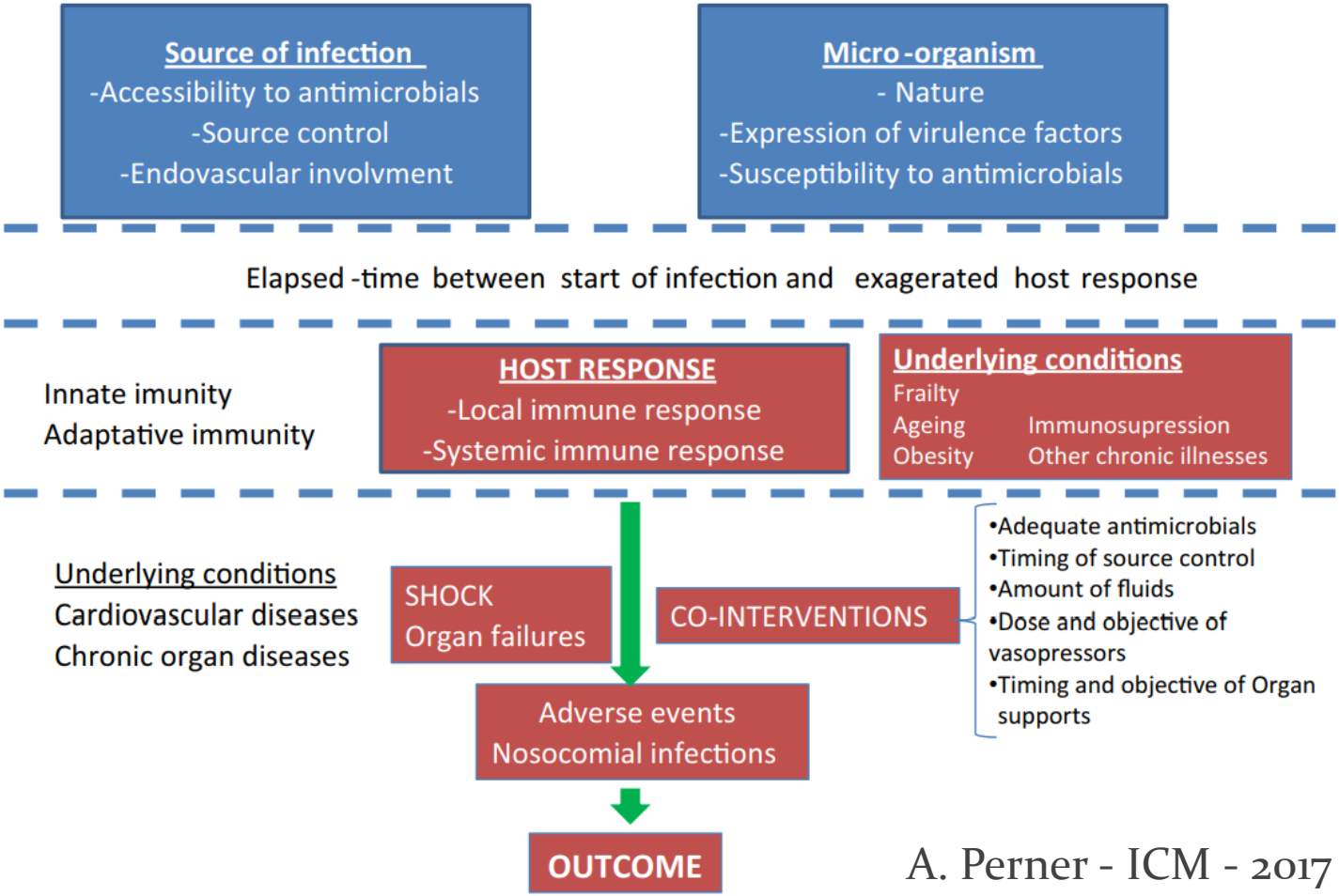
- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

M. Singer - JAMA – 2016
M. Shankar - JAMA - 2016

Source	Septic Shock Deaths, No.	Patients With Septic Shock, No.
Consensus Definition		
Degoricija et al,[46] 2006	90	125
Angkasekwinai et al,[38] 2007	41	78
Nesseler et al,[27] 2013	30	93
Sakr et al,[25] 2013	85	145
Goncalves-Pereira et al,[23] 2014	418	856
Leligdowicz et al,[5] 2014	4146	7974
Ortiz et al,[19] 2014	144	319
Hypotension		
Laupland et al,[47] 2004	81	159
Gaspraovic et al,[45] 2006	44	129
Shapiro et al,[44] 2006	15	53
Povoa et al,[35] 2009	202	458
Klein Klowenberg et al,[7] 2012	52	98
Kaukonen et al,[22] 2014	14 609	51 079
Hypotension + Perfusion Abnormalities and/or Vasopressor Therapy		
Rangel-Frausto et al,[56] 1995	51	110
Salvo et al,[55] 1995	27	33
Alberti et al,[52] 2002	752	1180
Hypotension or Vasopressor Therapy		
Dahmash et al,[59] 1993	14	36
McLauchlan et al,[58] 1995	73	101
Pittet et al,[57] 1995	7	12
Schoenberg et al,[53] 1998	32	80
Engel et al,[42] 2007	119	190
Esteban et al,[41] 2007	27	59
Khwannimit and Bhuayanontachai,[37] 2009	164	303
Moore et al,[33] 2011	22	61
Zahar et al,[30] 2011 (community)	215	530
Zahar et al,[30] 2011 (ICU)	123	232
Zahar et al,[30] 2011 (nosocomial)	233	580
Klein Klowenberg et al,[7] 2012	29	47
Park et al,[28] 2012	228	740
Hypotension or Serum Lactate Any Value or Vasopressor Therapy		
Liu et al,[21] 2014	827	2536
SSC database,[16] 2016[b]	6556	18 840
***International Classification of Diseases* Codes**		
Annane et al,[51] 2003	13 269	26 172
Flaatten,[50] 2004	457	1562
Whittaker et al,[24] 2013	117	321
Serum Lactate Level >4 mmol/L		
Levy et al,[6] 2010	242	811
Phua et al,[32] 2011	219	466
Overall (I^2 = 99.5%; P = .000)		



Sources of heterogeneity in sepsis



A. Perner - ICM - 2017

Cluster Analysis

Cluster Analysis

Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program

Wendy C. Moore[1,2], Deborah A. Meyers[1,2], Sally E. Wenzel[2], W. Gerald Teague[2], Huashi Li[1], Xingnan Li[1], Ralph D'Agostino, Jr.[3], Mario Castro[2], Douglas Curran-Everett[2], Anne M. Fitzpatrick[2], Benjamin Gaston[2], Nizar N. Jarjour[2], Ronald Sorkness[2], William J. Calhoun[2], Kian Fan Chung[2], Suzy A. A. Comhair[2], Raed A. Dweik[2], Elliot Israel[2], Stephen P. Peters[1,2], William W. Busse[2], Serpil C. Erzurum[2], and Eugene R. Bleecker[1,2], for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program[2]*

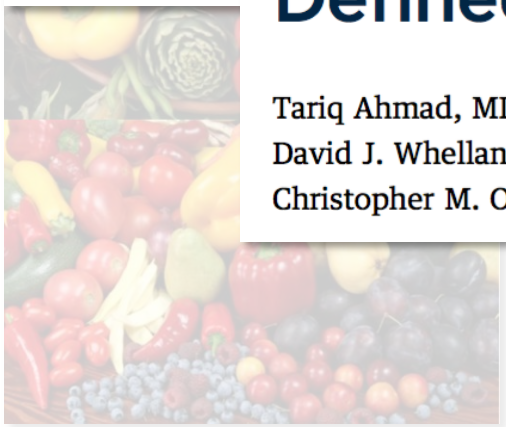
Cluster Analysis

Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program

Wendy C. Moore
Ralph D'Agostino
Nizar N. Jarjour[2]
Elliot Israel[2], Ste
for the National

Clinical Implications of Chronic Heart Failure Phenotypes Defined by Cluster Analysis

Tariq Ahmad, MD, MPH,*† Michael J. Pencina, PhD,† Phillip J. Schulte, PhD,† Emily O'Brien, PhD,† David J. Whellan, MD,‡ Ileana L. Piña, MD, MPH,§ Dalane W. Kitzman, MD,‖ Kerry L. Lee, PhD,† Christopher M. O'Connor, MD,*† G. Michael Felker, MD, MHS*†



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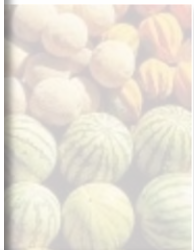


Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials

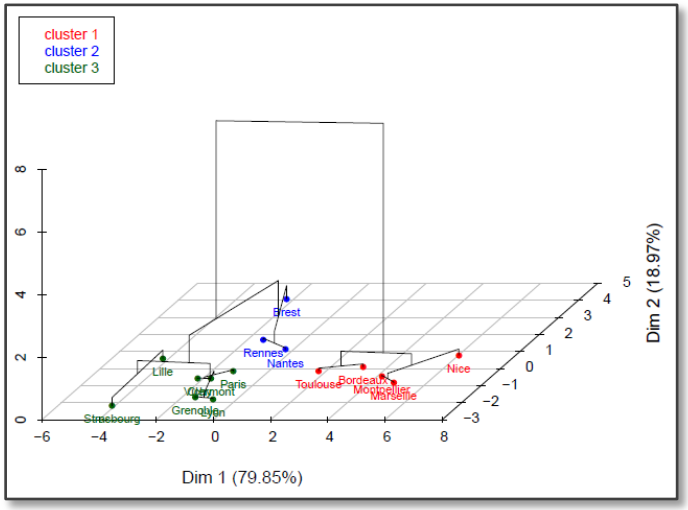
Carolyn S Calfee, Kevin Delucchi, Polly E Parsons, B Taylor Thompson, Lorraine B Ware, Michael A Matthay, and the NHLBI ARDS Network

Cluster Analysis

1st step: Multiple correspondence analysis
Ascending hierachical clustering analysis

2nd step: Cluster description with odd ratio
Outcomes

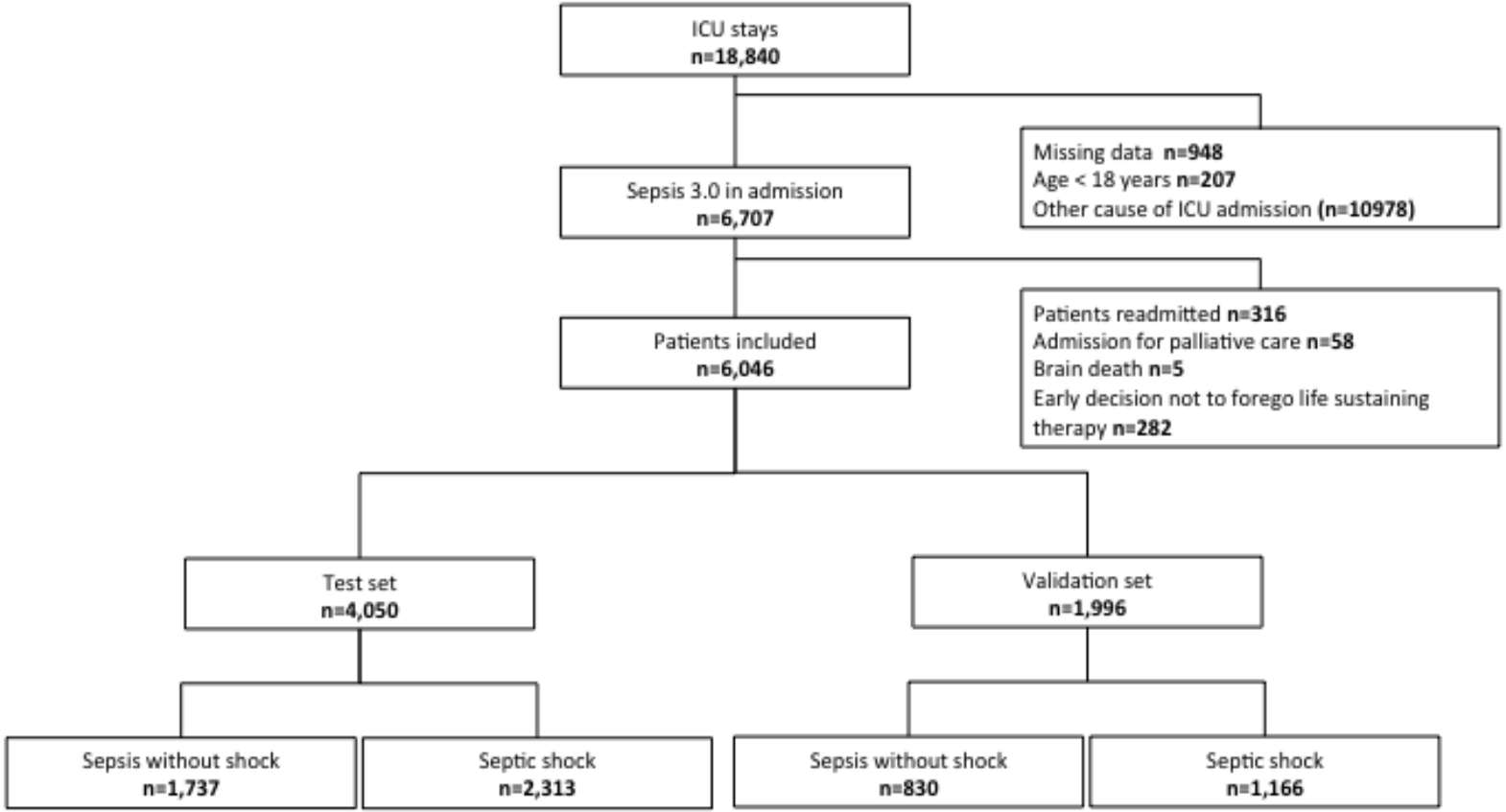
3th step: Validation



Cluster Analysis

Underlying conditions	Source & Micro-organism	Host reponse	Organ failures
Age	Medical admission	Myocardial dysfunction	Hemodynamic failure
Sex	Unscheduledsurgery	Cardiac arrest befor admission	Neurologic failure
Weight	Scheduledsurgery	Hyperglycemia	Renal failure
Malnutrition	Infection site	Hypoglycemia	Coagulation failure
Alcohol abuse	Infection micro-organisms	New atrial fibrillation	Liver failure
Not complicated diabetes	Bacteremia	Recurent atrial fibrialation	Blood lactate level
Complicated diabetes	Nosocomial	Respiratory rate	
Chronic heart failure	MDRO	Blood pressure	
Chronic kidney disease		Sodium blood level	
Liver cirrhosis		Potassium blood level	
COPD		Hematocric	
Solide tumor		Prothrombine tiem	
Hematological malignacy		Leucocyte	
HIV/AIDS/Transplant		Fluid replacement >50ml/kg	
Chronic steroid therapy			
Charlson score			

Methods

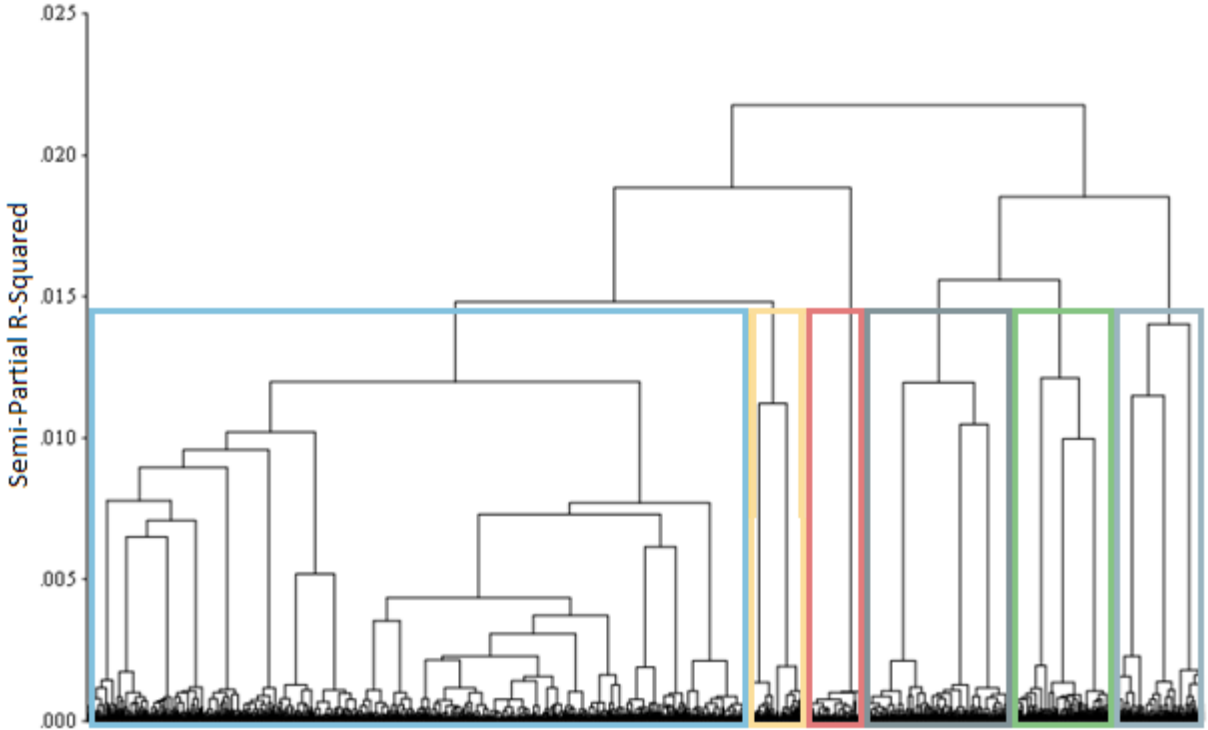


Results

Variable	Total n=6,046
Age, median [IQR]	65.1 [52.7-76.2]
Male, n (%)	3763 (62%)
Septic shock, n (%)	3479 (58%)
Admission category, n (%)	
- Medical	4848 (80%)
- Unscheduled surgery	943 (16%)
- Scheduled surgery	255 (4%)
In the first two days of ICU stay:	
- SOFA score, median [IQR]	6 [4-9]
- SAPSS II score, median [IQR]	46 [34-60]
- Mechanical ventilation, n (%)	3552 (59%)
- Renal replacement therapy, n (%)	635 (11%)
Mortality at 28 days	1442 (24%)
Mortality at 1 years	2097 (35%)

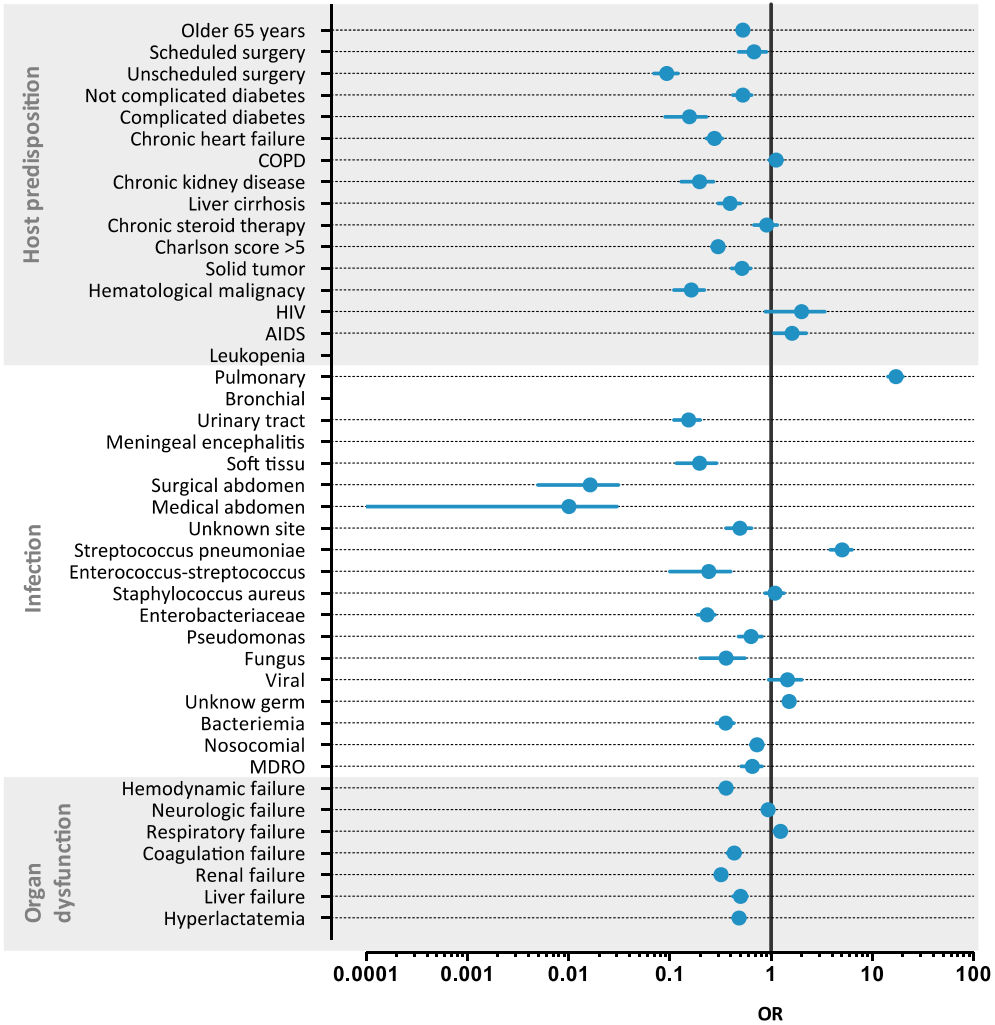
-> All Sepsis 3,0

Results



-> Test set (n=4050)

Results

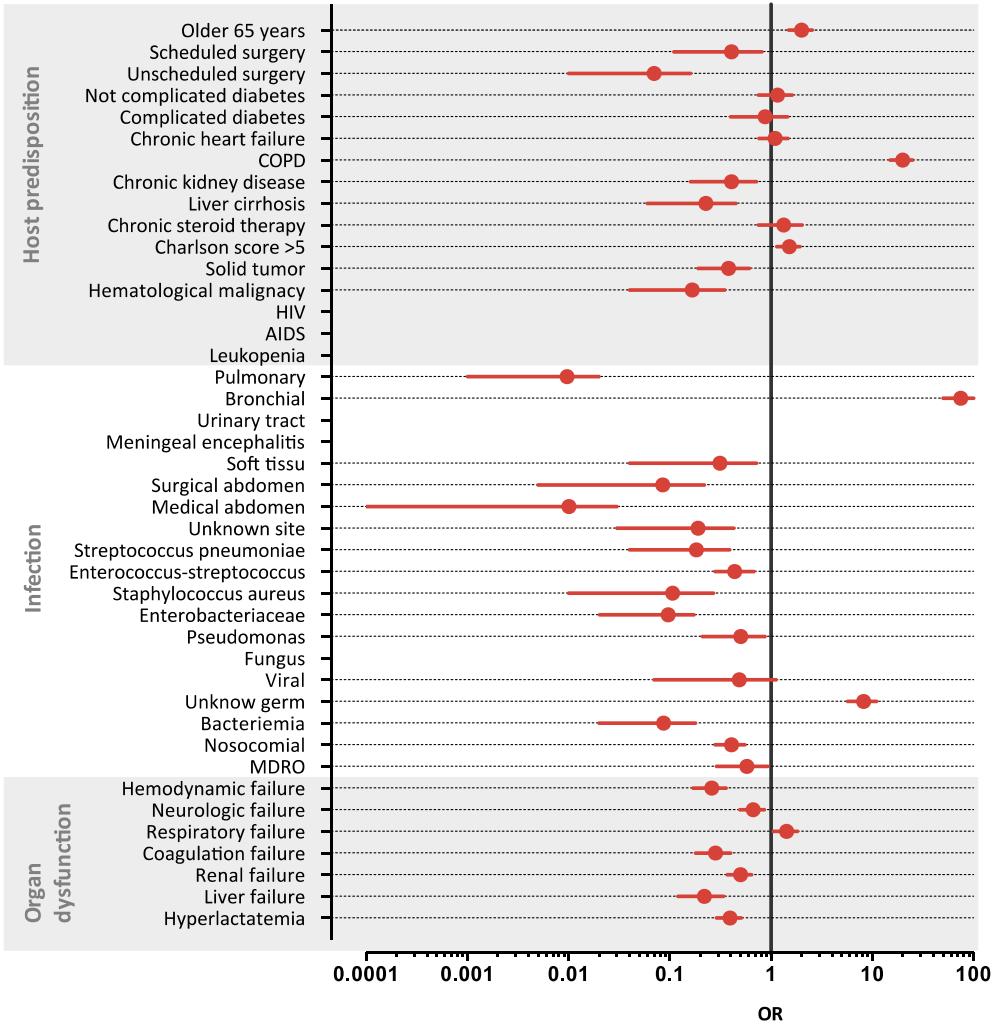


Pulmonary sepsis

n= 1,603 (40%)

- Age ≤ 65 years
- Charlson score ≤ 5
- Lung infection
- *S. Pneumoniae* and unknown germs

Results

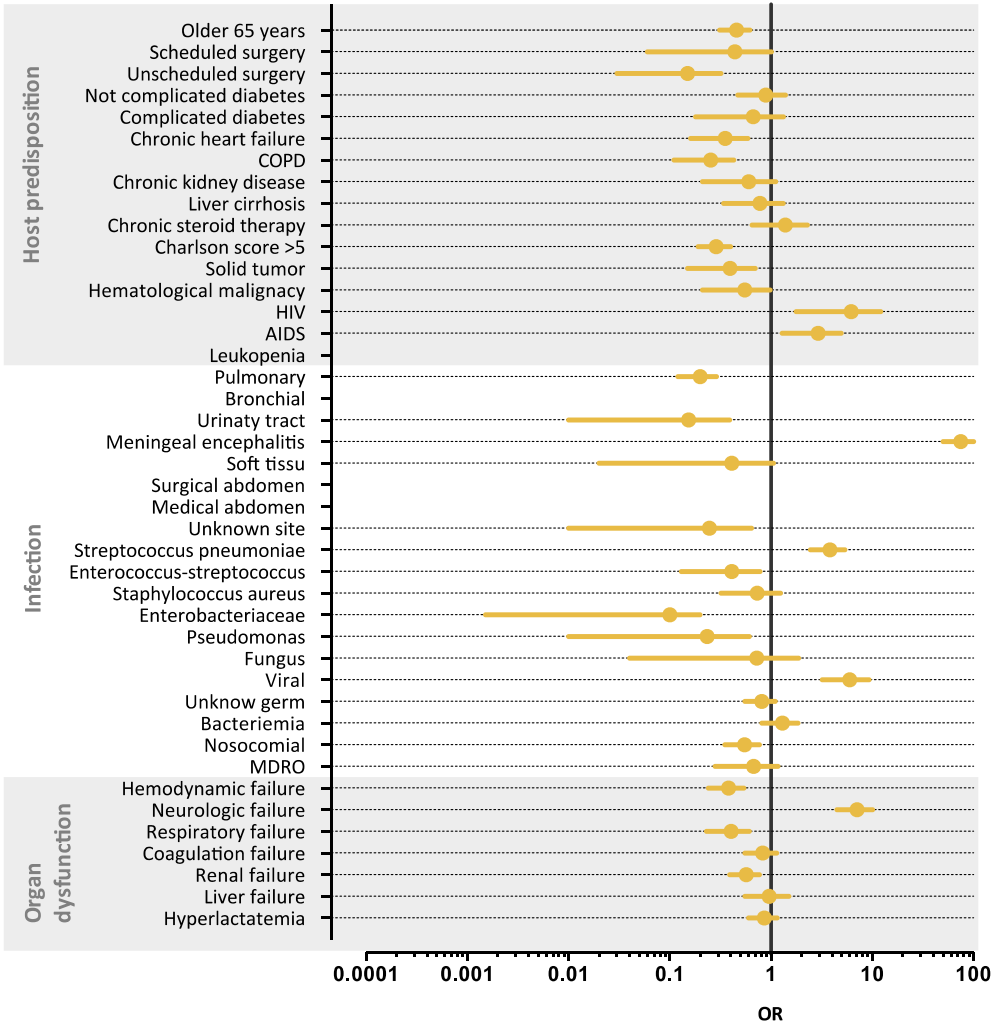


COPD Exacerbation

n= 243 (6%)

- Age > 65 years
- COPD
- Charlson score > 5
- Bronchial infection
- Unknown germs
- Low rate of organ failure

Results

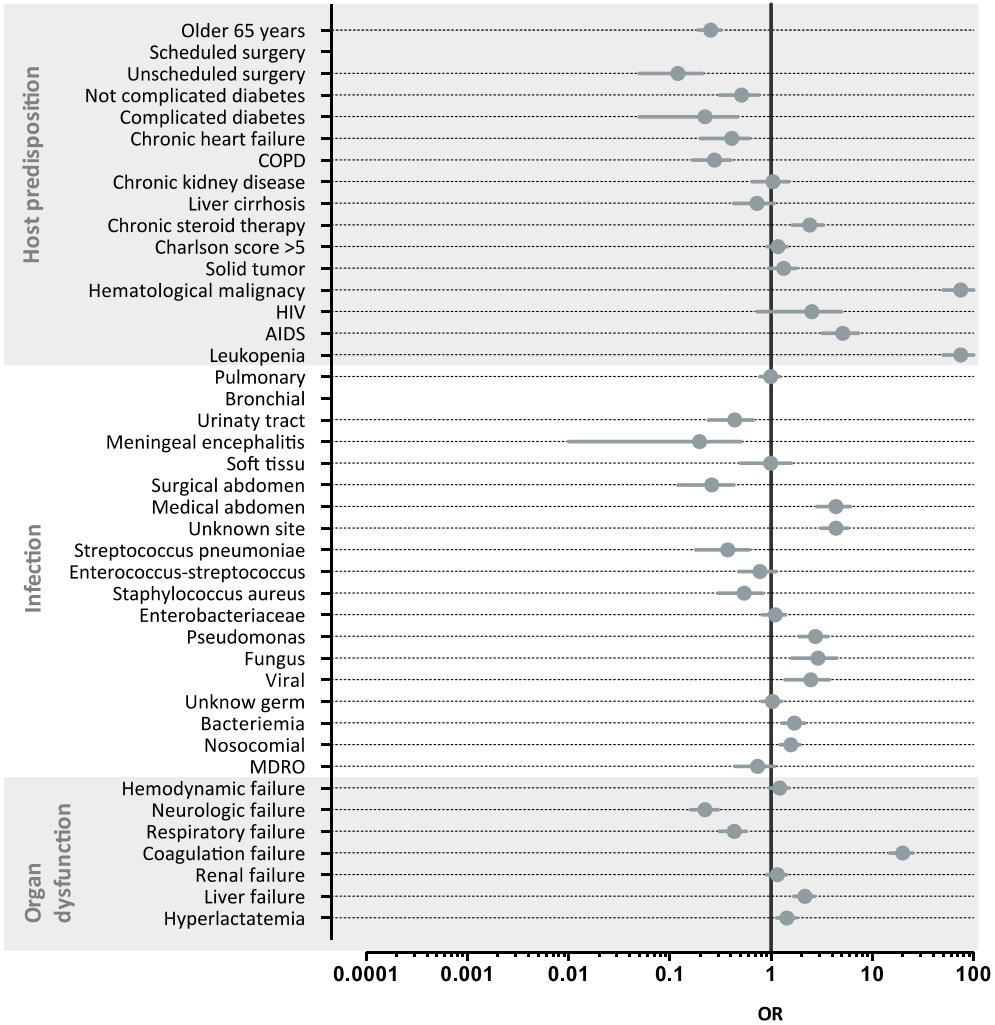


Meningo-encephalitis

n= 149 (4%)

- Age ≤ 65 years
- Charlson score ≤ 5
- HIV and AIDS
- Meningeal encephalitis
- *S. Pneumoniae* and viruse
- Neurological failure

Results

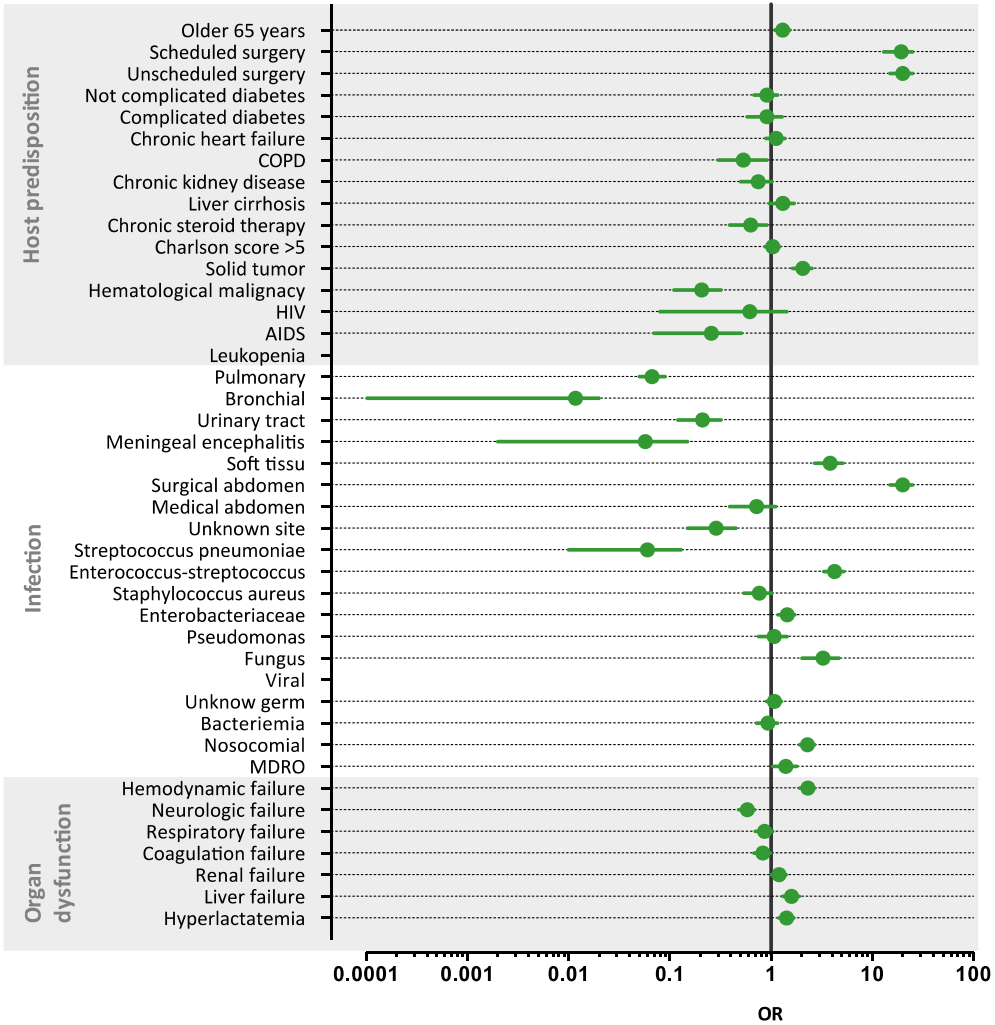


Immunocompromised patients

n= 338 (8%)

- Age ≤ 65 years
- Chronic steroid therapy, AIDS and hemotological malignancy
- Leukopenia
- Medical abdomen and unknown site of infection
- *Pseudomonas*, fungy and viruse
- Bacteriemia
- Nosocomial
- Coagulation and liver failure

Results

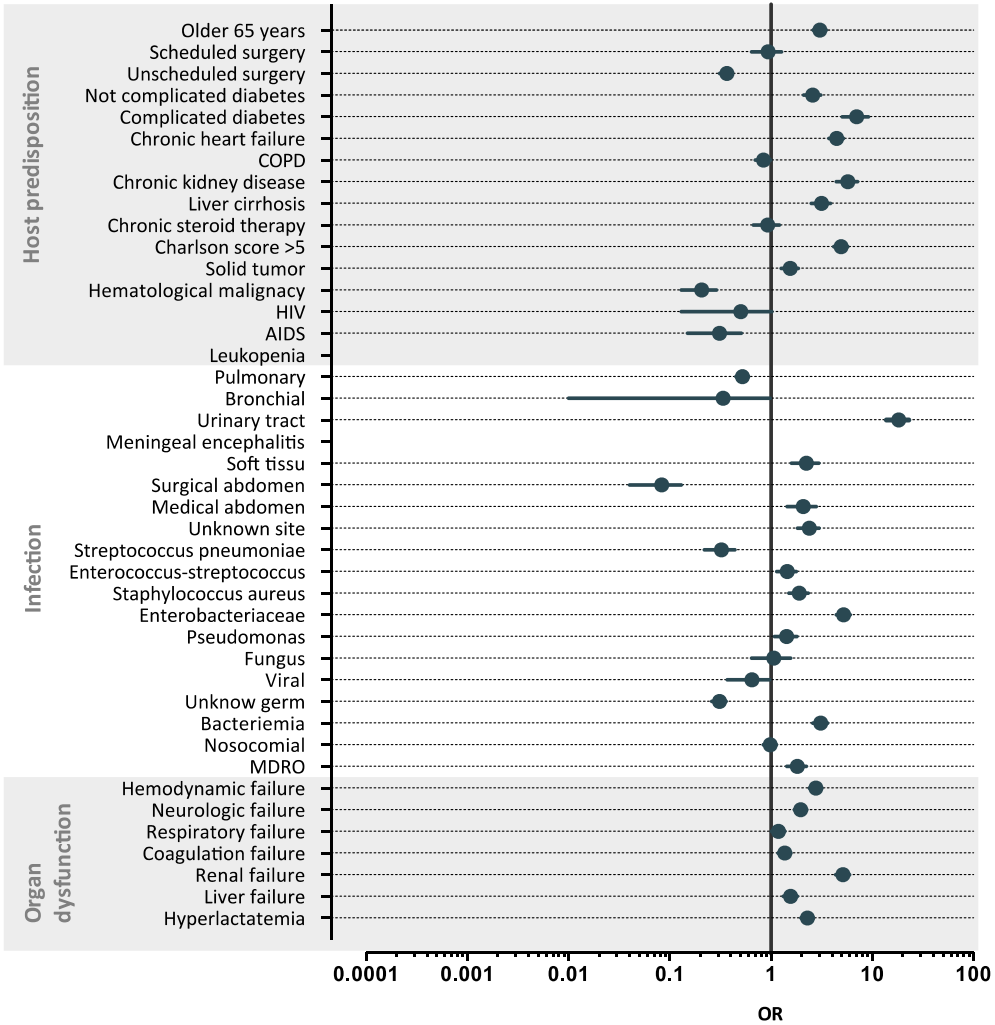


Surgical sepsis

n= 623 (15%)

- Age > 65 years
- Scheduled or unscheduled surgery
- Solid tumor
- Soft tissue and surgical abdomen
- Digestive germs and fungy
- Nosocomial
- Hemodynamic and liver failure

Results

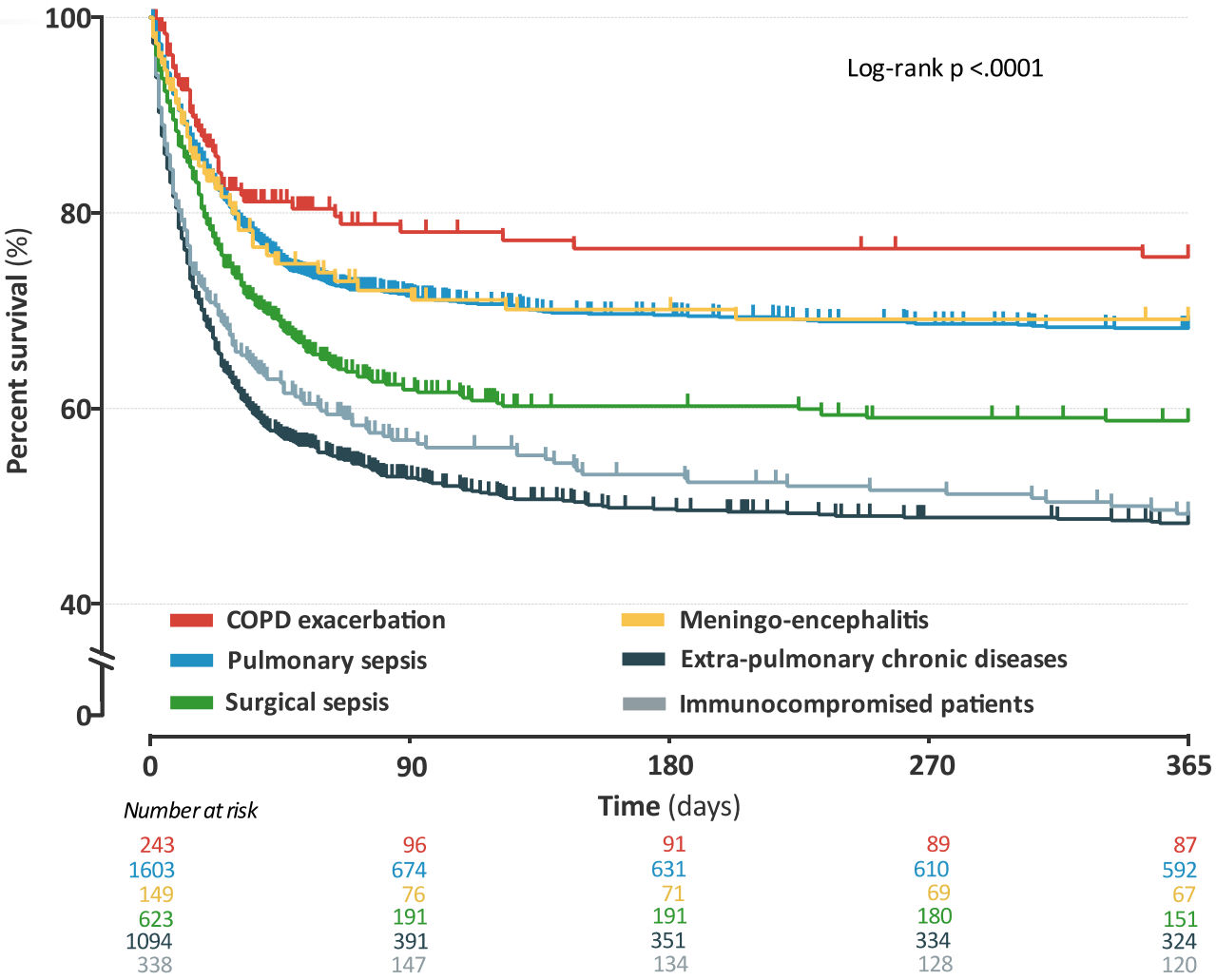


Extra-pulmonary chronic diseases

n= 1,094 (27%)

- Age > 65 years
- Multiple chronic diseases
- Charlson score > 5
- Urinary tract, soft tissue, medical abdomen and unknown site of infection
- *S. aureus* and digestive germs
- Bacteriemia
- MDRO
- Multiple organ failure

Results


Log-rank p <.0001
Percent survival (%)
100
80
60
40
0
COPD exacerbation
Pulmonary sepsis
Surgical sepsis
Meningo-encephalitis
Extra-pulmonary chronic diseases
Immunocompromised patients
0
90
180
270
365
Time (days)
Number at risk
243 96 91 89 87
1603 674 631 610 592
149 76 71 69 67
623 191 191 180 151
1094 391 351 334 324
338 147 134 128 120

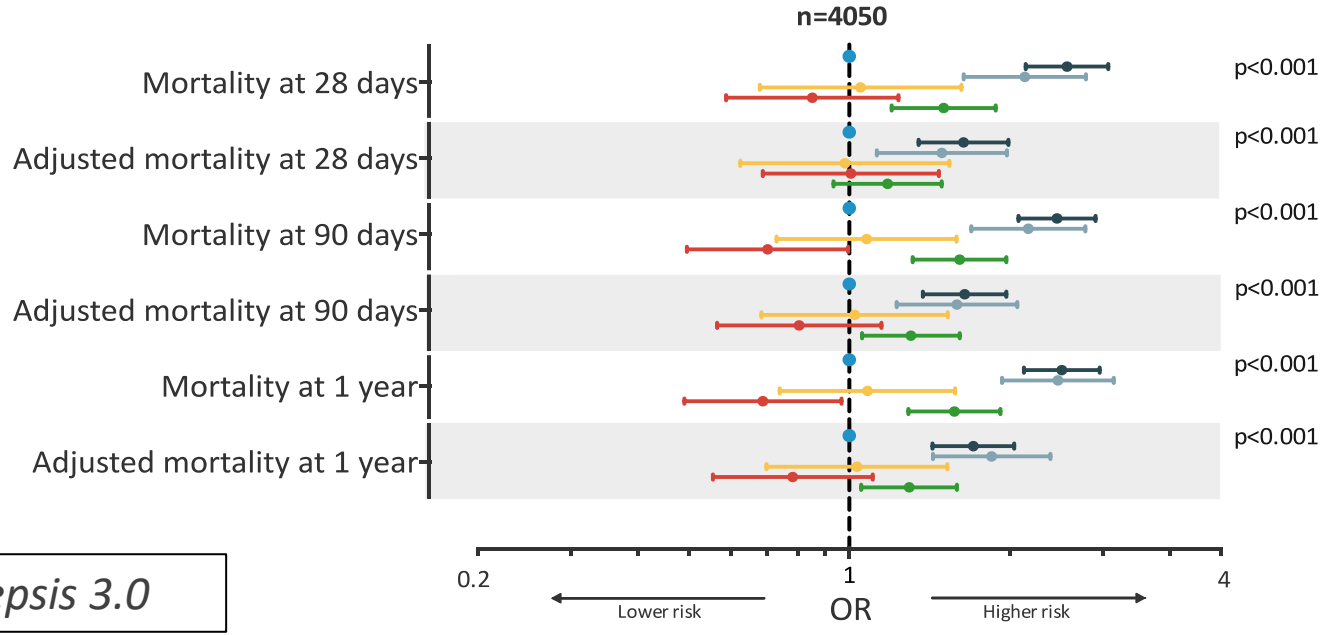
Outcomes

Variable	Pulmonary sepsis n=1,603	COPD exacerbation n=243	Surgical sepsis n=623	Meningo-encephalitis n=149	Immunocompromised patients n=338	Extra-respiratory chronic diseases n=1,094	*P*-Value
Baseline characteristics *							
Admission before 2008, n (%)	841 (52%)	135 (56%)	365 (59%)	79 (53%)	134 (40%)	454 (41%)	<.001
SOFA score at admission, median [IQR]	5 [3-7]	4 [2-6]	6 [4-9]	5 [3-8]	7 [5-10]	8 [5-11]	<.001
Septic shock, n (%)	714 (44%)	68 (28%)	470 (75%)	58 (39%)	204 (60%)	799 (73%)	<.001
Outcomes							
28-day mortality	279 (17%)	37 (15%)	150 (24%)	27 (18%)	105 (31%)	384 (35%)	<.001
90-day mortality	376 (23%)	42 (18%)	206 (33%)	37 (25%)	135 (40%)	470 (43%)	<.001
1-year mortality	406 (25%)	46 (19%)	217 (35%)	40 (27%)	154 (46%)	503 (46%)	<.001
ICU stay (days), median [IQR]	7 [4-15]	7 [4-12]	9 [5-18]	10 [5-16]	5 [3-12]	8 [4-15]	<.001
Hospital stay (days), median [IQR]	21 [11-38]	19 [12-31]	31 [17-54]	23 [15-41]	26 [12-43]	21 [11-38]	<.001
Ventilator-free days (days), median [IQR]	23 [6-28]	28 [16-28]	20 [1-26]	20 [3-28]	22.5 [3-28]	18 [1-28]	<.001
Catecholamine-free days (days), median [IQR]	28 [23-28]	28 [25-28]	25 [14-28]	28 [24-28]	26 [8-28]	24 [5-28]	<.001
Renal replacement therapy before 28-day, n(%)	364 (23%)	40 (16%)	236 (38%)	37 (25%)	152 (45%)	557 (51%)	<.001
Organ system failure-free days (days), median [IQR]	19 [1-24]	21 [10-24]	15 [0-23]	17 [1-23]	18 [0-24]	11 [0-22]	<.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; IQR = interquartile range
Free days were censored at 28 days; A ventilator-free day refer to a day without invasive or non-invasive mechanical ventilation or death; A catecholamine-free day refer to a day without to vasoactive or inotropic agent or death; An organ system failure-free day refer to a day without SOFA score upper zero or death;
P- values were obtained by Analysis of variance or Chi-2 test.

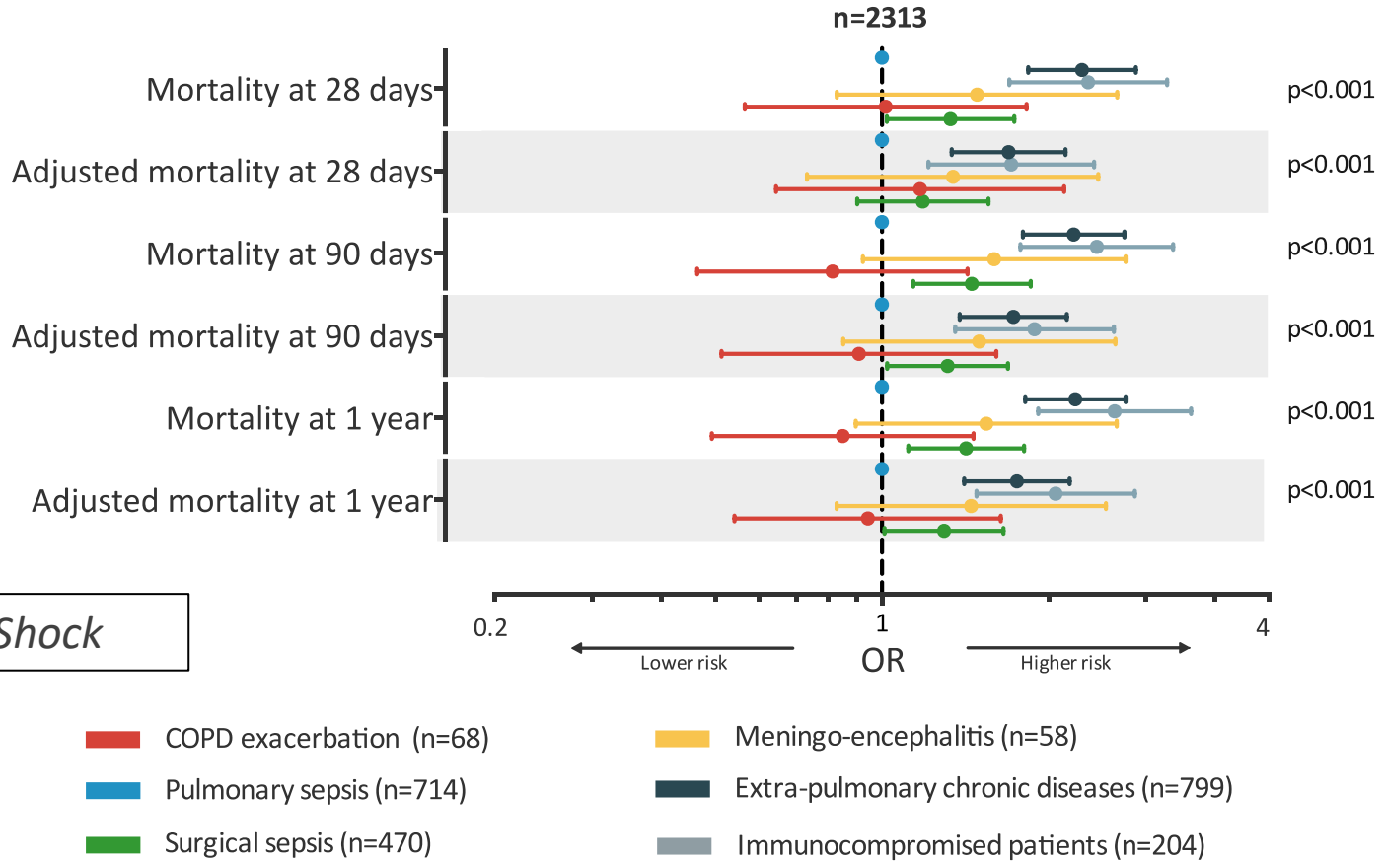
Results

Pulmonary sepsis	Extra-pulmonary chronic diseases	Immunocompromised patients	Meningo-encephalitis	COPD Exacerbation	Surgical sepsis
n=1,603 (40%) - Age ≤ 65 years - Charlson score ≤ 5 - Lung infection - *S. Pneumoniae* and unknown germs	**n=1,094 (27%)** - Age > 65 years - Multiple chronic diseases - Charlson score > 5 - Urinary tract, soft tissue, medical abdomen and unknown site of infection - *S. aureus* and digestive germs - Bacteriemia - MDRO - Multiple organ failure	**n=338 (8%)** - Age ≤ 65 years - Chronic steroid therapy, AIDS and hemotological malignancy - Leukopenia - Medical abdomen and unknown site of infection - *Pseudomonas*, fungy and viruse - Bacteriemia - Nosocomial - Coagulation and liver failure	**n=149 (4%)** - Age ≤ 65 years - Charlson score ≤ 5 - HIV and AIDS - Meningeal encephalitis - *S. Pneumoniae* and viruse - Neurological failure	**n=243 (6%)** - Age > 65 years - COPD - Charlson score > 5 - Bronchial infection - Unknown germs - Low rate of organ failure	**n=623 (15%)** - Age > 65 years - Scheduled or unscheduled surgery - Solid tumor - Soft tissue and surgical abdomen - Digestive germs and fungy - Nosocomial - Hemodynamic and liver failure



-> All Sepsis 3.0

Results



-> Septic Shock

Outomes

Variable	Pulmonary sepsis n=1,603	COPD exacerbation n=243	Surgical sepsis n=623	Meningo-encephalitis n=149	Immunocompromised patients n=338	Extra-respiratory chronic diseases n=1,094	*P*-Value
Baseline characteristics *							
Admission [illegible]	8 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<.001
SOFA score at admission, median [IQR]	5 [3-7]	4 [2-6]	6 [4-9]	5 [3-8]	7 [5-10]	8 [5-11]	<.001
Septic shock, n (%)	714 (44%)	68 (28%)	470 (75%)	58 (39%)	204 (60%)	798 (73%)	<.001
Outcomes							
28-day mortality	279 (17%)	37 (15%)	150 (24%)	27 (18%)	105 (31%)	384 (35%)	<.001
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ICU stay (days), median [IQR]	7 [4-15]	7 [4-12]	9 [5-18]	10 [5-16]	5 [3-12]	8 [4-15]	<.001
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Ventilator-free days (days), median [IQR]	23 [6-28]	28 [16-28]	20 [1-26]	20 [3-28]	22.5 [3-28]	18 [1-28]	<.001
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Renal replacement therapy before 28-day, n(%)	364 (23%)	40 (16%)	236 (38%)	37 (25%)	152 (45%)	557 (51%)	<.001
Organ system failure-free days (days), median [IQR]	19 [1-24]	21 [10-24]	15 [0-23]	17 [1-23]	18 [0-24]	11 [0-22]	<.001

How to assign a new patient into clusters with only available data at ICU admission ?

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; IQR = interquartile range
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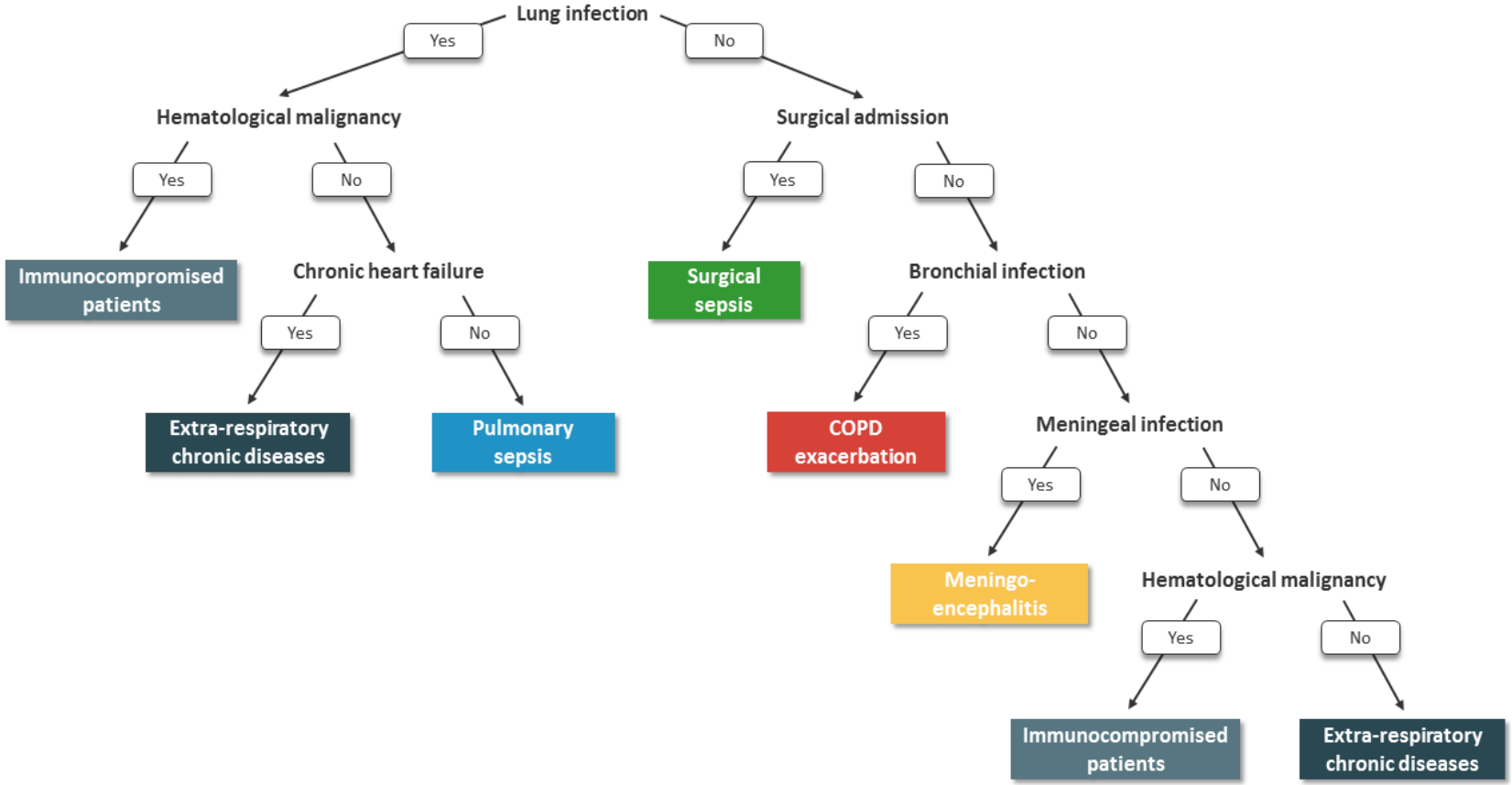
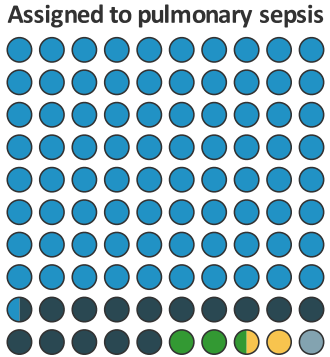
P- values were obtained by Analysis of variance or Chi-2 test.

Results

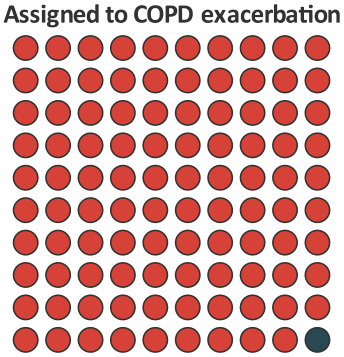


Algorithme de CART « Classification and Regression Trees »

Results

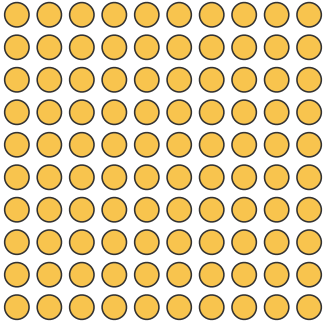


Right cluster: 81% (n=1231/1526)

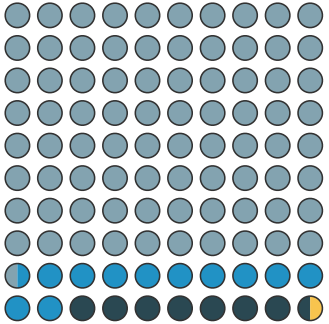


Right cluster: 99% (n=231/233)

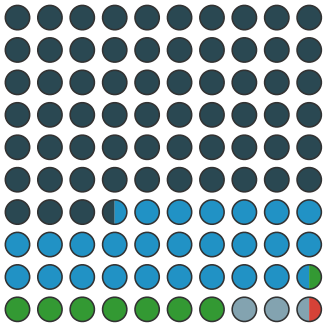
Right cluster: 78% (n=497/640)



Right cluster: 100% (n=118/118)



Right cluster: 80% (n=286/356)



Right cluster: 63% (n=746/1177)

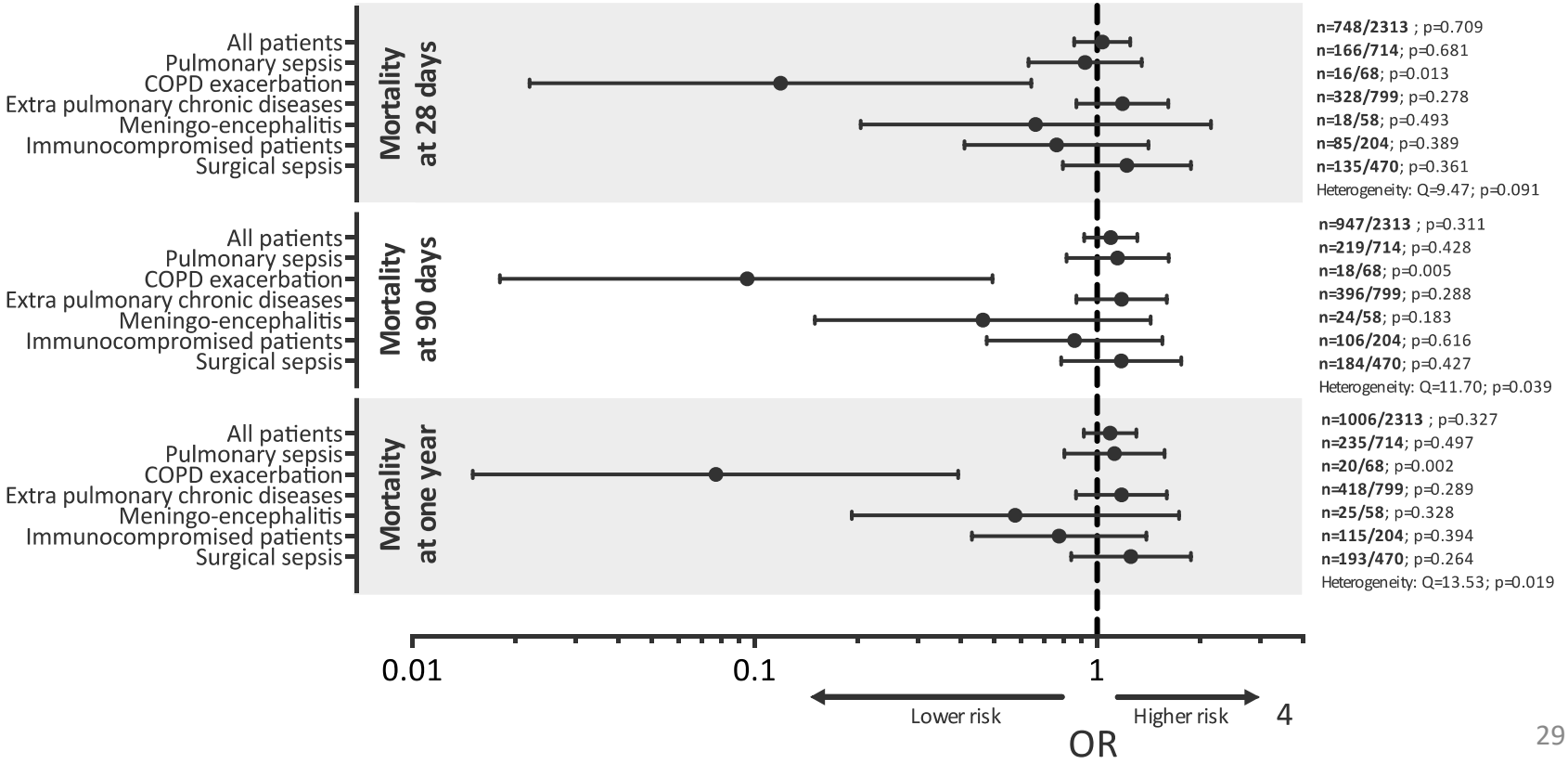
Reference cluster :

- COPD exacerbation
- Pulmonary sepsis
- Surgical sepsis
- Meningo-encephalitis
- Extra-pulmonary chronic diseases
- Immunocompromised patients

Binary tree performance evaluated in test set using percentage of patients assigned well

Response to specific therapy ?

Response to specific therapy ?



Conclusion

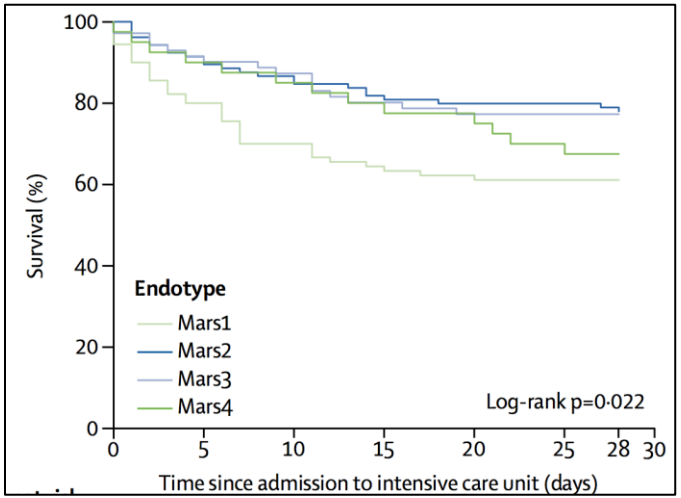
Avantage

- Large multicenter study
- Sepsis 3.0
- Easy to collect immeditly available variables
- Independent external validation

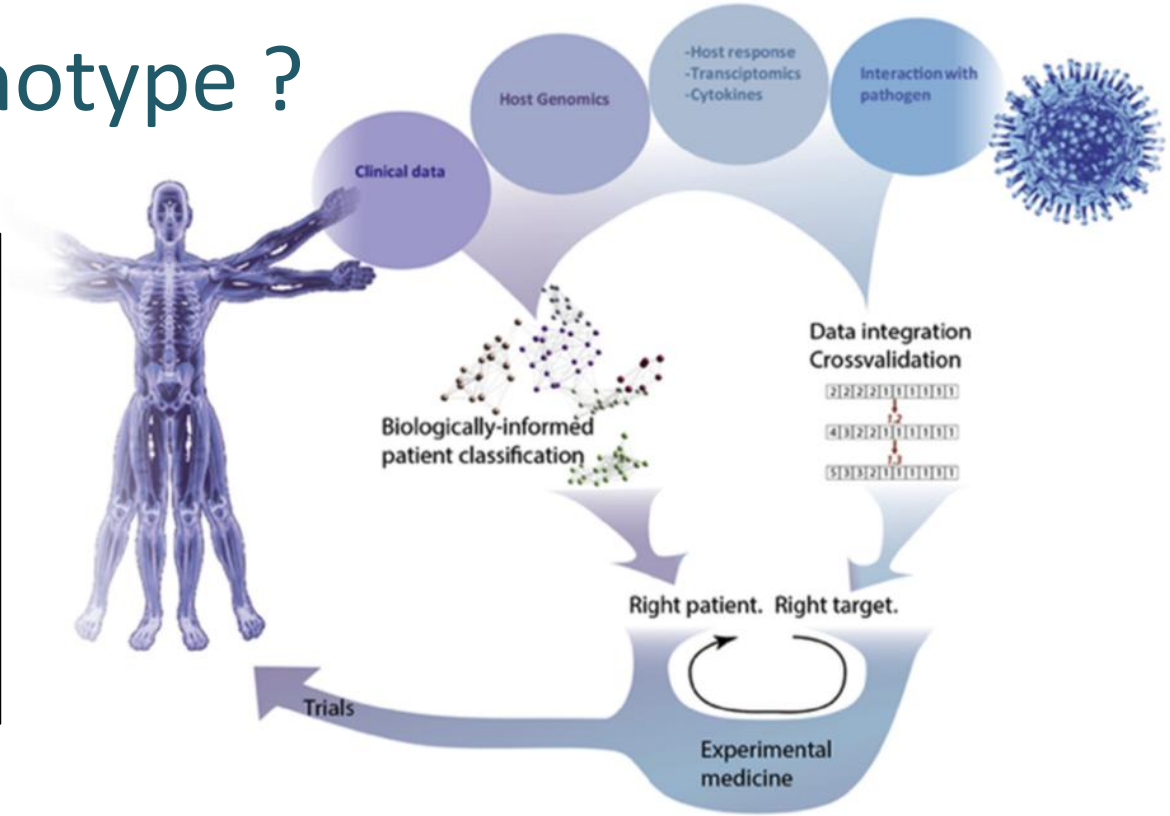
Limitation

- Lack of data about adaptative and innate immune system

Phenotype or Genotype ?



B.P. Scicluna - LRM - 2017



Summary of a systems medicine approach to infection. A wide range of data sources can be combined using various methods (see text) to achieve two fundamental goals – clinically-informative phenotyping of patients, and identification of therapeutic targets.

C.D. Russell – Current Opinion in Systems Biology - 2017

Conclusion

- 6 very different clusters identifiable with 6 discrimitating variables available at admission

- These clusters clearly differed in outcome

- Independent of gravity at admission

- Low impact of organ failure on characterization of clusters

- Consider these clusters in stratification or in selection criteria of population in clinical trials may reduce uncontrolled differences in patient’s outcome

Matériel et Méthodes

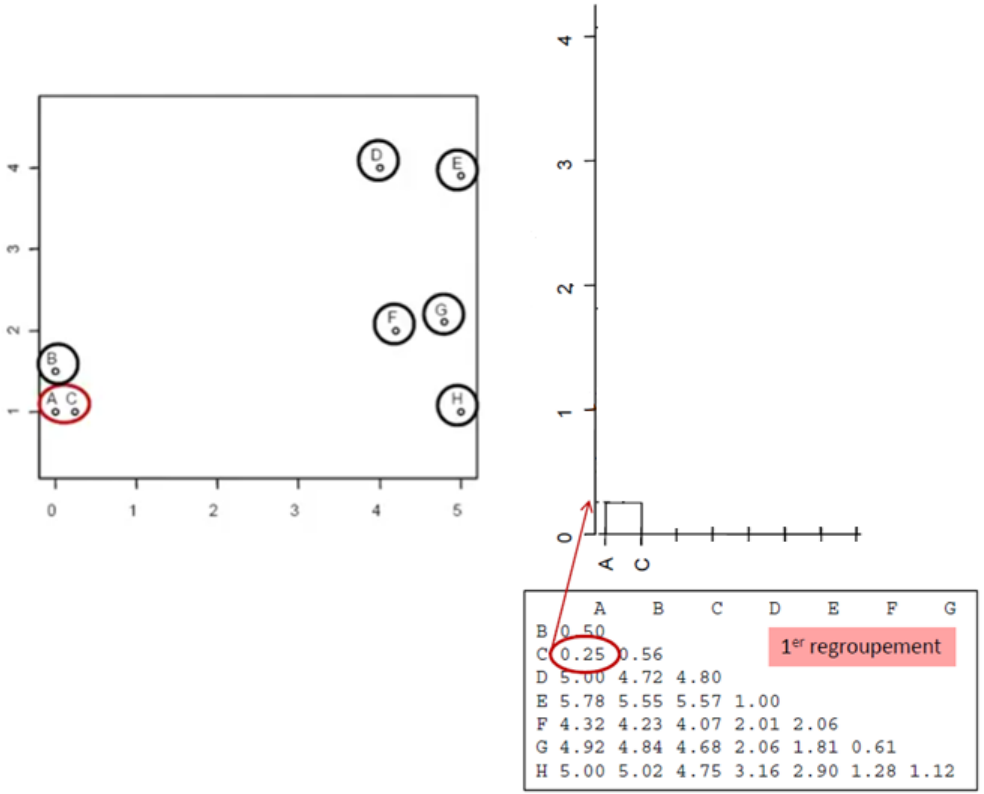
Classification hiérarchique ascendante

- Principe généraux
- Distances et Indices de similarité
- Choix du nombre de cluster
- Cas particulier des variables qualitatives
- Interprétation des classes

Population

Variables utilisées dans la classification

Classification hiérarchique ascendante (1)

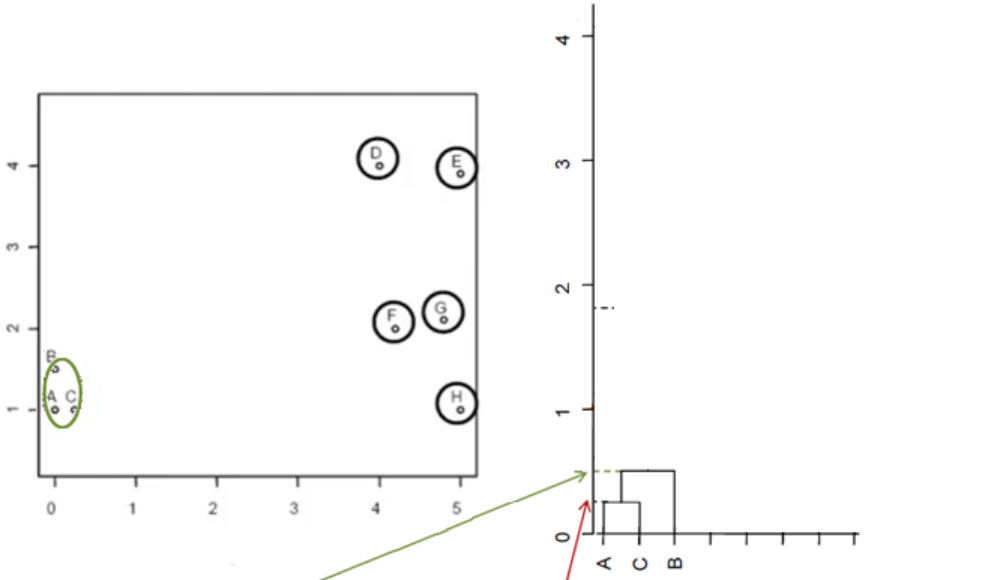


	A	B	C	D	E	F	G
B	0.50						
C	0.25	0.56					
D	5.00	4.72	4.80				
E	5.78	5.55	5.57	1.00			
F	4.32	4.23	4.07	2.01	2.06		
G	4.92	4.84	4.68	2.06	1.81	0.61	
H	5.00	5.02	4.75	3.16	2.90	1.28	1.12

1er regroupement

F.Husson

Classification hiérarchique ascendante (2)



	AC	B	D	E	F
B	0.50				
D	4.80	4.72			
E	5.57	5.55	1.00		
F	4.07	4.23	2.01	2.06	
G	4.68	4.84	2.06	1.81	0.61
H	4.75	5.02	3.16	2.90	1.28	1.12

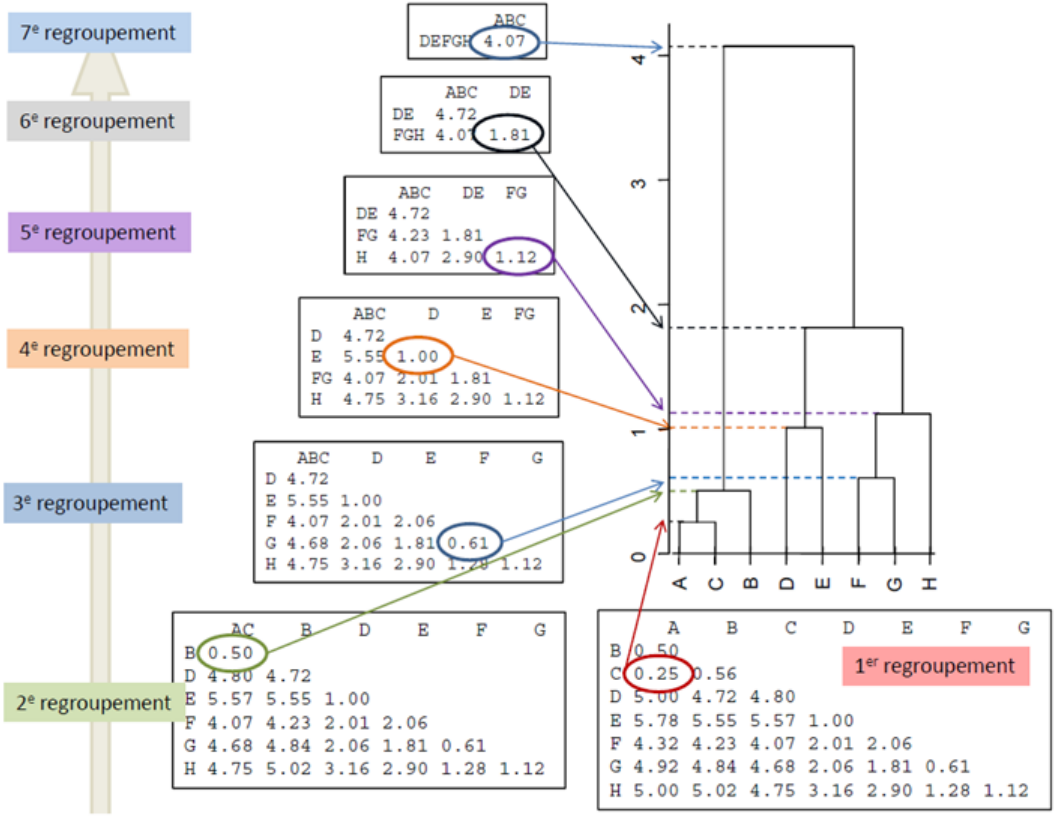
2e regroupement

	A	B	C	D	E	F
B	0.50					
C	0.25	0.56				
D	5.00	4.72	4.80			
E	5.78	5.55	5.57	1.00		
F	4.32	4.23	4.07	2.01	2.06	
G	4.92	4.84	4.68	2.06	1.81	0.61
H	5.00	5.02	4.75	3.16	2.90	1.28	1.12

1er regroupement

F.Husson

Classification hiérarchique ascendante (3)



F.Husson

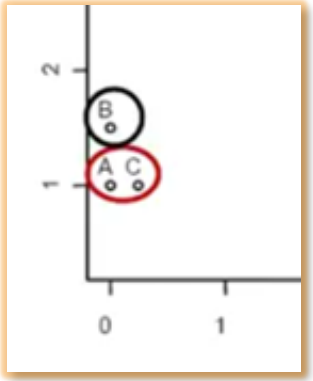
Distance et indice de similarité

Ressemblance entre individus:

- Distance euclidienne
- Indice de Jaccard
- .....

Ressemblance entre groupes d'individus:

- Saut minimum (la plus petite distance)
- Saut maximum (la plus grande distance)
- Distance moyenne
- Indice de Ward



Méthode de Ward

Méthode de Ward

- A chaque étape : regroupe les individus/groupes qui minimise la diminution de la variabilité interclasse
- Basée sur le théorème de Huygens :

(Variabilité Totale = Variabilité InterClasse + Variabilité IntraClasse)

- Nécessite des distances euclidiennes

Avantage:

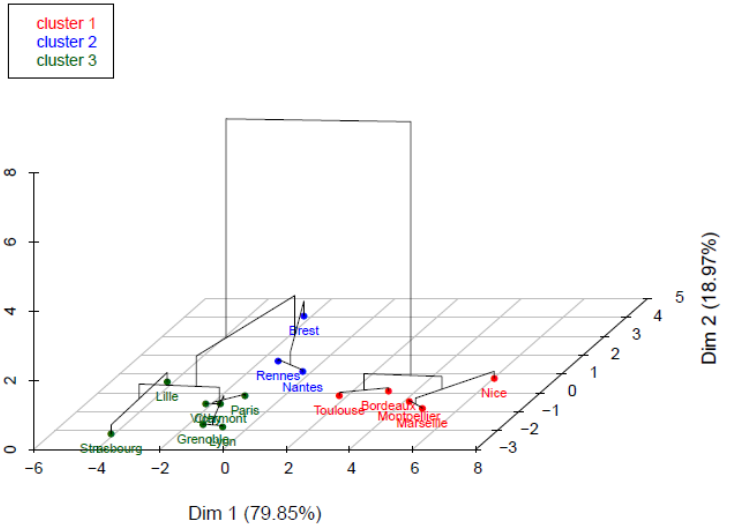
- Regroupe les objets de faibles poids
- Moins sensible au bruit

R. Griffiths – Journal of Documentation - 1984

Gestion des variables catégorielles

1er temps: Analyse en composantes multiples

2nd temps: Classification Hiérarchique Ascendante sur les coordonnées des dimensions de l'Analyse en composantes multiples



Package FactomineR

Gestion des variables qualitatives

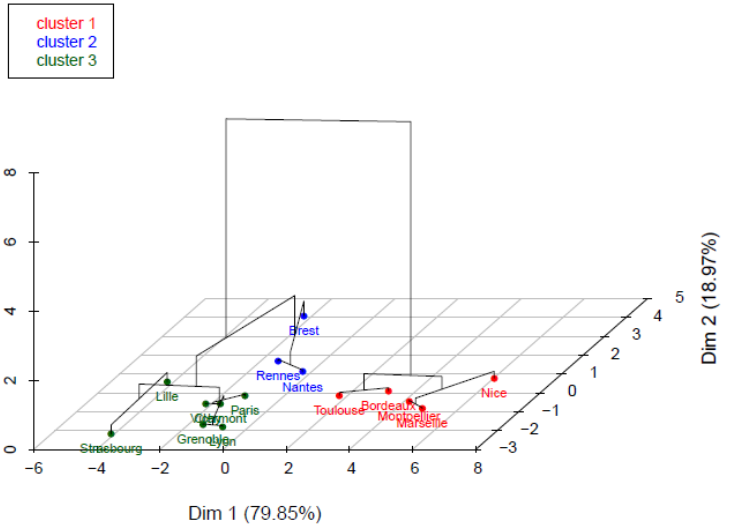
Avantage:

Limite le temps de calcul

Concentre l'information sur les premières dimensions

Représentation des arbres et des classes sur un plan factoriel

Possible si les deux méthodes utilisent des distances euclidiennes

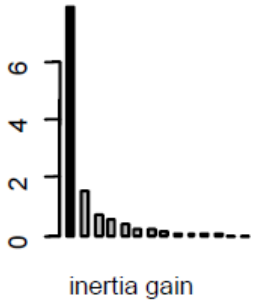


Package FactomineR

Choix des classes:

Démarche descendante:

Gain d'inertie



Nombres Cluster / Individus

Allure générale de l'arbre

Interprétabilité des classes