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CIRO+, center of expertise for chronic organ failure

Clustering of comorbidities and implications for secundary care

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disclosures

None relevant to this paper


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Clusters of COPD patients with comorbidities:

Agenda

1) Epidemiology and impact of comorbidities in COPD

2) Gaps in current understanding of comorbidities in COPD

3) CIRO Comorbidity (CIROCO) Study

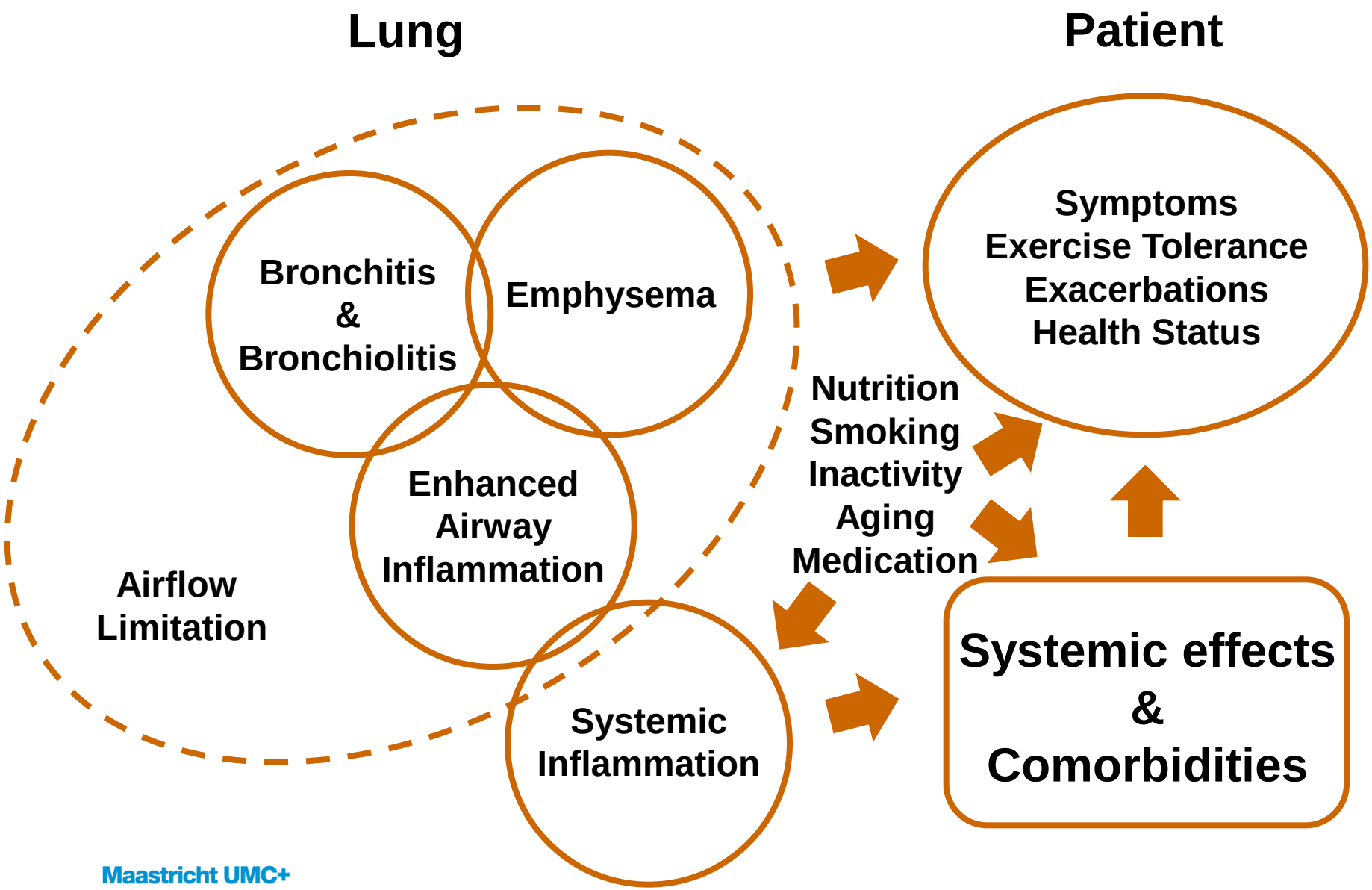
4) Conclusions and implications

Updated definition of COPD

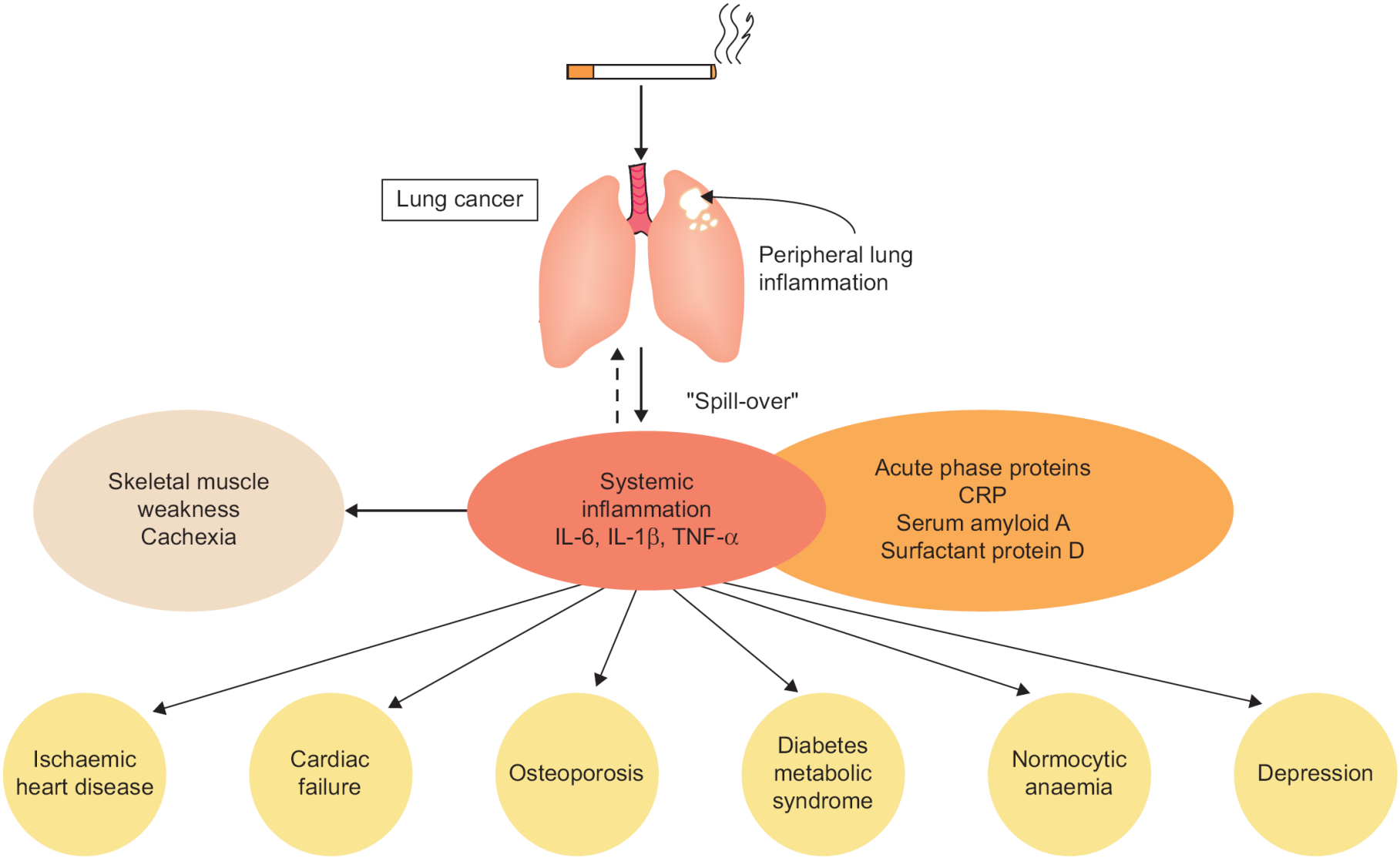
Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and *comorbidities* contribute to the overall severity in individual patients

Vestbo et al, Am J Respir Crit Care Med 2013

COPD as a heterogenous and multi-component disease



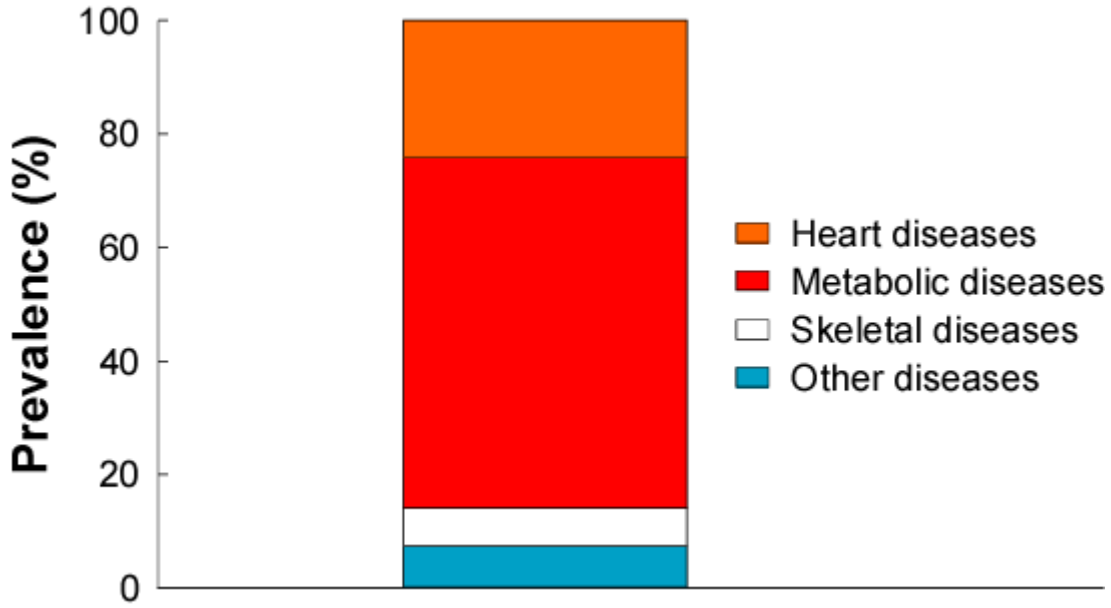
Systemic inflammation and comorbidities in COPD?



Barnes & Fabbri, Eur Respir J 2009

Comorbidities in COPD patients undergoing pulmonary rehabilitation

51% of the patients reported at least one chronic comorbidity



Crisafulli et al, Thorax 2008

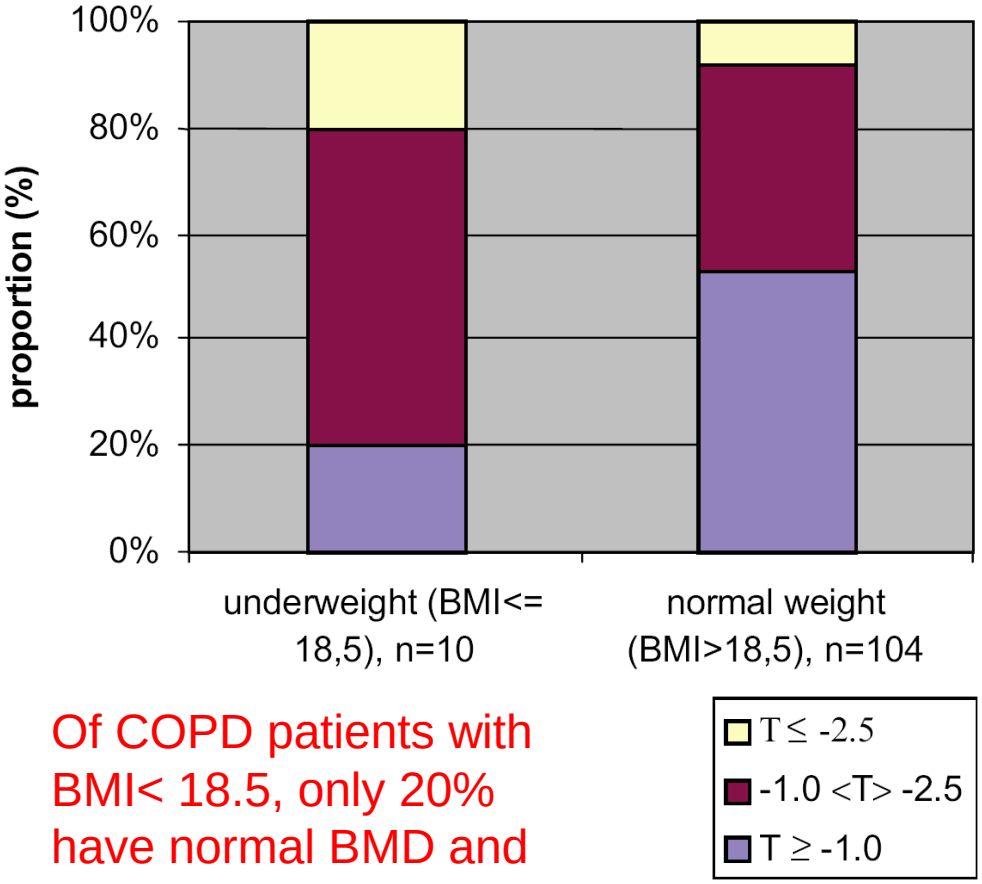
Comorbidity	Prevalence in COPD (%)	Ref.
Osteoporosis/osteopenia	50–70	[77–78]
Hypertension	40–60	[10,12,13]
Gastro-esophageal reflux disease	30–60	[12,88]
Skeletal muscle dysfunction	32	[74]
Depression	25	[82]
Ischemic heart disease	10–23	[12,18,26]
Previous myocardial infarction	4–23	[12,18,26]
Anemia	17	[68]
Diabetes	12–13	[10,17]
Previous stroke	10–14	[12,13,17]
Arrhythmia	6–14	[6,51]
Chronic renal failure	6–11	[12,26]
Congestive heart failure	5–7	[11,13]
Obstructive sleep apnea	1–4	[86]

COPD: Chronic obstructive pulmonary disease.

Many sekfreported and/or objectivated comorbidities co-occur in COPD!

Associations between comorbidities in COPD

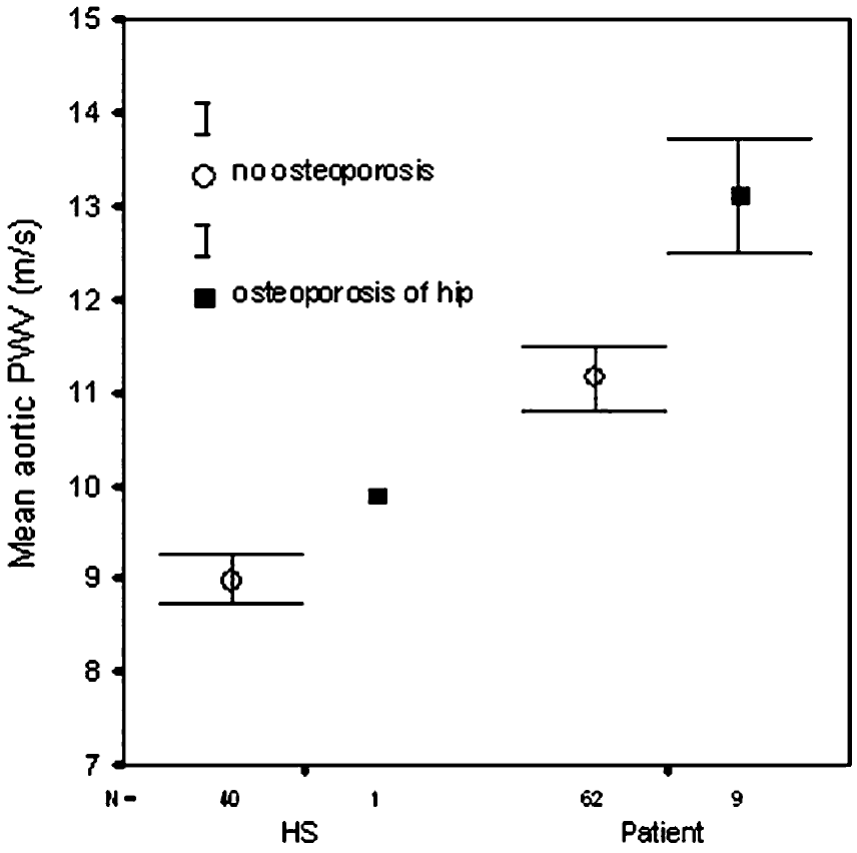
BMI - Osteoporosis



Of COPD patients with BMI< 18.5, only 20% have normal BMD and 20% have osteoporosis

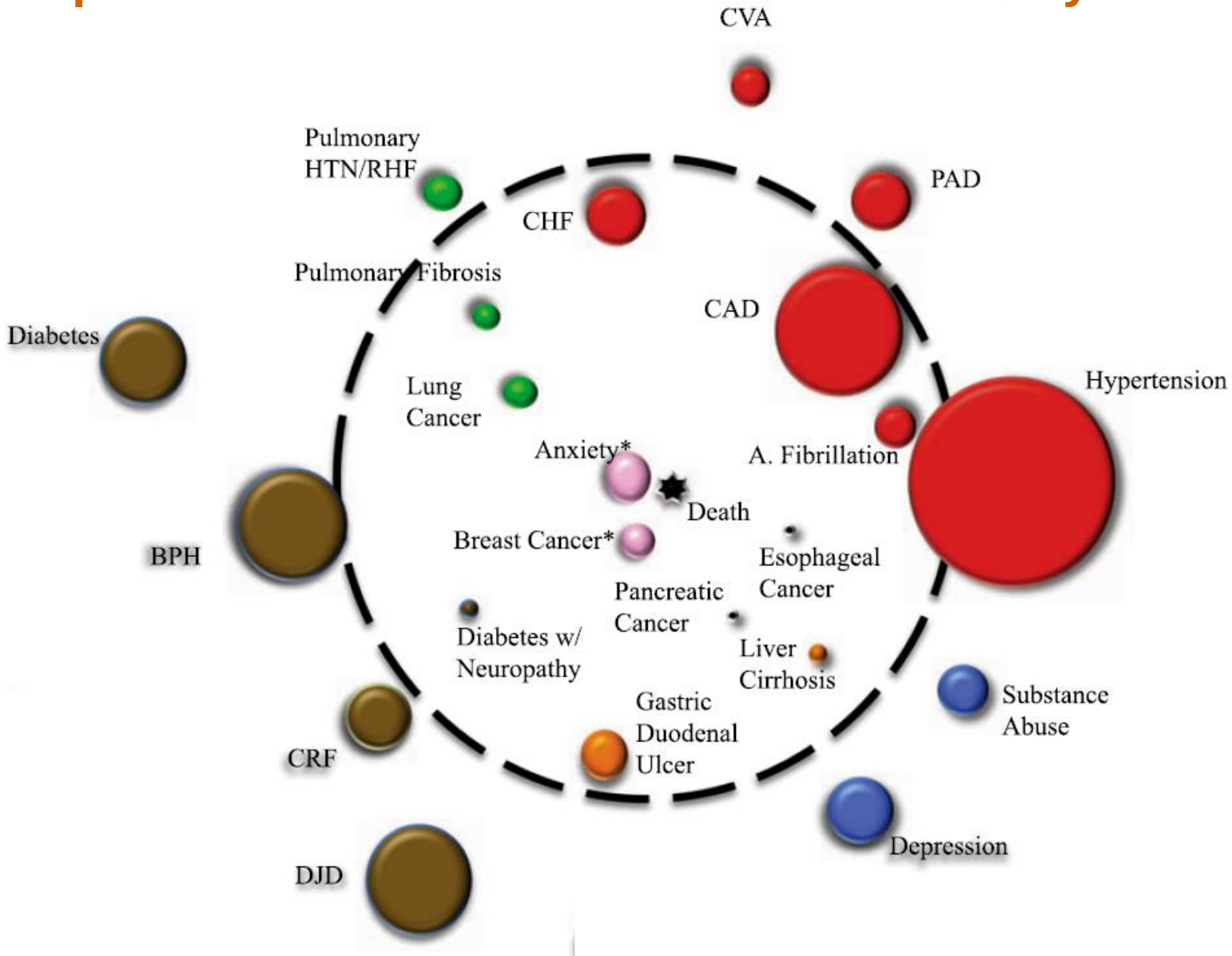
Vrieze et al, Osteoporosis Int 2007

Osteoporosis – Arterial Stiffness



Sabit et al, Am J Respir Crit Care Med 2007

Impact of various comorbidities on mortality in COPD



Divo et al, Am J Respir Crit Care Med 2012

Summarized

- Cardiovascular, metabolic, musculoskeletal and psychological conditions are commonly seen in patients with COPD
- The Global initiative for Obstructive Lung Disease (GOLD) now emphasizes that comorbidities may contribute to disease severity in individual patients
- Most co-morbidities have been studied individually, while combinations are most probably common
- Most studies used self-reported co-morbidity data and comorbidities are underassessed and underdiagnosed in COPD.
- Role of systemic inflammation in comorbidities?

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Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with Chronic Obstructive Pulmonary Disease

Lowie E. G. W. Vanfleteren[1,2], Martijn A. Spruit[1], Miriam Groenen[1], Swetlana Gaffron[3], Vanessa P. M. van Empel[1,4], Piet L. B. Bruijnzeel[5], Erica P. A. Rutten[1], Jos Op 't Roodt[6], Emiel F. M. Wouters[1,2], and Frits M. E. Franssen[1,2]

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Aims of the study

1) To study the frequencies of 13 clinically relevant and objectively identified (instead of selfreported) comorbidities in 213 patients with COPD

2) To investigate the clustering of these comorbidities

3) To explore differences in clinical characteristics and systemic inflammatory status between clusters of comorbidities

Vanfleteren et al, Am J Respir Crit Care Med 2013

Methodology

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Inclusion criteria :

* Patients with COPD referred for pulmonary rehabilitation at CIRO+
* Age between 40-80 years
* Post-bronchodilator FEV_1/FVC < 70%
* Post-bronchodilator FEV_1 < 80%
* Smoking history ≥ 10 pack years

Exclusion criteria:

* Other significant respiratory disease
* Previous lung surgery
* Significant inflammatory disease
* Acute myocardial infarction within the last six months
* Malignancy in the previous 5 years
* Exacerbation in the last 4 weeks
•Chronic use of systemic corticosteroid therapy (>10 mg prednisolone)

Comprehensive 4 day's assessment by multidisciplinary staff!

Vanfleteren et al, Am J Respir Crit Care Med 2013

Measurements

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Routine assessment of integrated health status:
Medical history and examination
Lung function
Blood gases
Body composition, using DEXA scan

Exercise capacity:
6MWD

Questionnaires:
HADS, MRC, SGRQ

Cardiovascular disease:
Carotid intima media thickness, using ultrasound
Electrocardiogram, cardiac infarction injury score

Laboratory:
Blood hematology and chemistry
Inflammatory status (CRP, IL-6, IL-8, leukocytes, TNF-R1, TNF-R2)

Vanfleteren et al, Am J Respir Crit Care Med 2013

Self-reported versus objectively diagnosed comorbidities

Subjects with ECG-changes compatible with **myocardial infarction** were only in 21% diagnosed with myocardial infarction. But only 22% of subjects reporting myocardial infarction also had compatible ECG changes.

Of the 110 subjects with elevated fasting glycemia, only 8 reported **diabetes** (7%). 8 of 11 (73%) subjects with diabetes still had elevated fasting glycemia, despite treatment.

The 2 patients reporting **chronic kidney disease** were correctly classified, but the other 40 patients classified with KDOQI stage 3 and higher CKD did not report chronic renal disease.

Of the 98 subjects with **hypertension**, 44 (45%) were treated with any antihypertensive medication. (ACE, ARB, Calciumblockers, Betablockers or diuretics). On the other hand, 44 of 86 (51%) subjects treated with antihypertensive medication still had elevated RR

24 of 74 (32%) subjects with **dyslipidemia** receive statins. On the other hand 24 of 56 (43%) subjects receiving statins had dyslipidemia

Self-reported versus objectively diagnosed comorbidities

MI's missed or reported but not on ECG

Over 50% had ↑ FBG but reported no DM

Most renal failures (EGFR<30!) not reported

Last than half not treated for significant hypertension

Most patients with dyslipidemia not treated with statins

Most patients on statins had no dyslipidemia

Even patients referred from specialist centers (no direct referrals from GP's) were poorly treated for comorbidities!

Definitions of 13 comorbidities (1)

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Underweight: BMI < 21 kg·m^{-2} *(Celli et al., N Engl J Med 2004)*

Muscle wasting: FFMI < 16 kg·m^{-2} for men or < 15 kg·m^{-2} for women *(Schols et al., Am J Clin Nutr 2005)*

Obesity: BMI ≥ 30 kg·m^{-2} *(WHO)*

Renal failure: eGFR (Cockroft and Gault) < 60 ml·min^{-1} *(KDOQI, Am J Kidney Dis 2007)*

Osteoporosis: T-score < -2,5 on the local sites hip and lumbal spine or whole body *(Graat-Verboom et al., J. Osteoporos 2010)*

Anemia: Hemoglobin level <13 g·dL^{-1} (8,1 mmol/L) in men and <12 g·dL^{-1} (7,5 mmol/L) in women *(WHO)*

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Vanfleteren et al, Am J Respir Crit Care Med 2013

Definitions of 13 comorbidities (2)

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Hypertension:	Systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mm Hg (ESH/ESC, Blood Press 2007)
Atherosclerosis:	c-IMT > 0.9 mm (*ESH/ESC,Blood Press 2007)*
Myocardial infarction:	Cardiac infarction injury score (CIIS) ≥ 20 *(Rautaharju et al., Circulation 1981)*
Glucose-intolerance:	Fasting glucose > 5,6 mmol·L^{-1} *(ADA, Diabetes Care 2010)*
Dyslipidemia:	Triglyceride level > 1,7 mmol·L^{-1} or a HDL <1,03 mmol·L^{-1} in males or <1,29 mmol·L^{-1} in females. *(Alberti et al., Lancet 2005)*
Anxiety/depression:	Hospital Anxiety and Depression Scale (HADS) ≥ 10 *(Zigmond et al., Acta Psychiatr Scand 1983)*

Vanfleteren et al, Am J Respir Crit Care Med 2013

Statistics

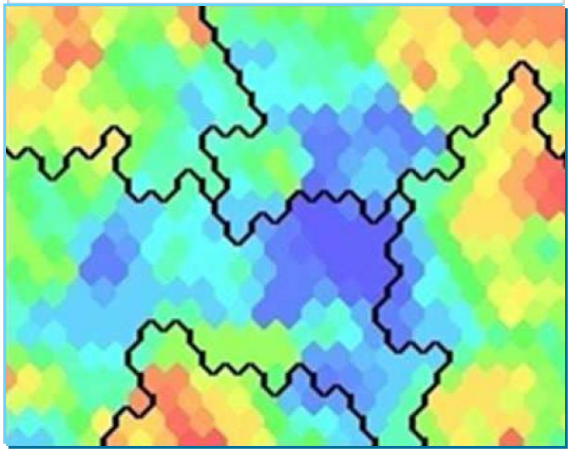
Viscovery® software

Identification of homogenous data groups

Ward hierarchical cluster analysis

Model based on:
Presence of comorbidities
Degrees of comorbidities

Self-organizing maps: non-linear representation of data distribution



Selforganizing maps?

An unbiassed approach, by creating a self-organizing map.

All subjects were placed on the map based based on their profile of comorbidities.

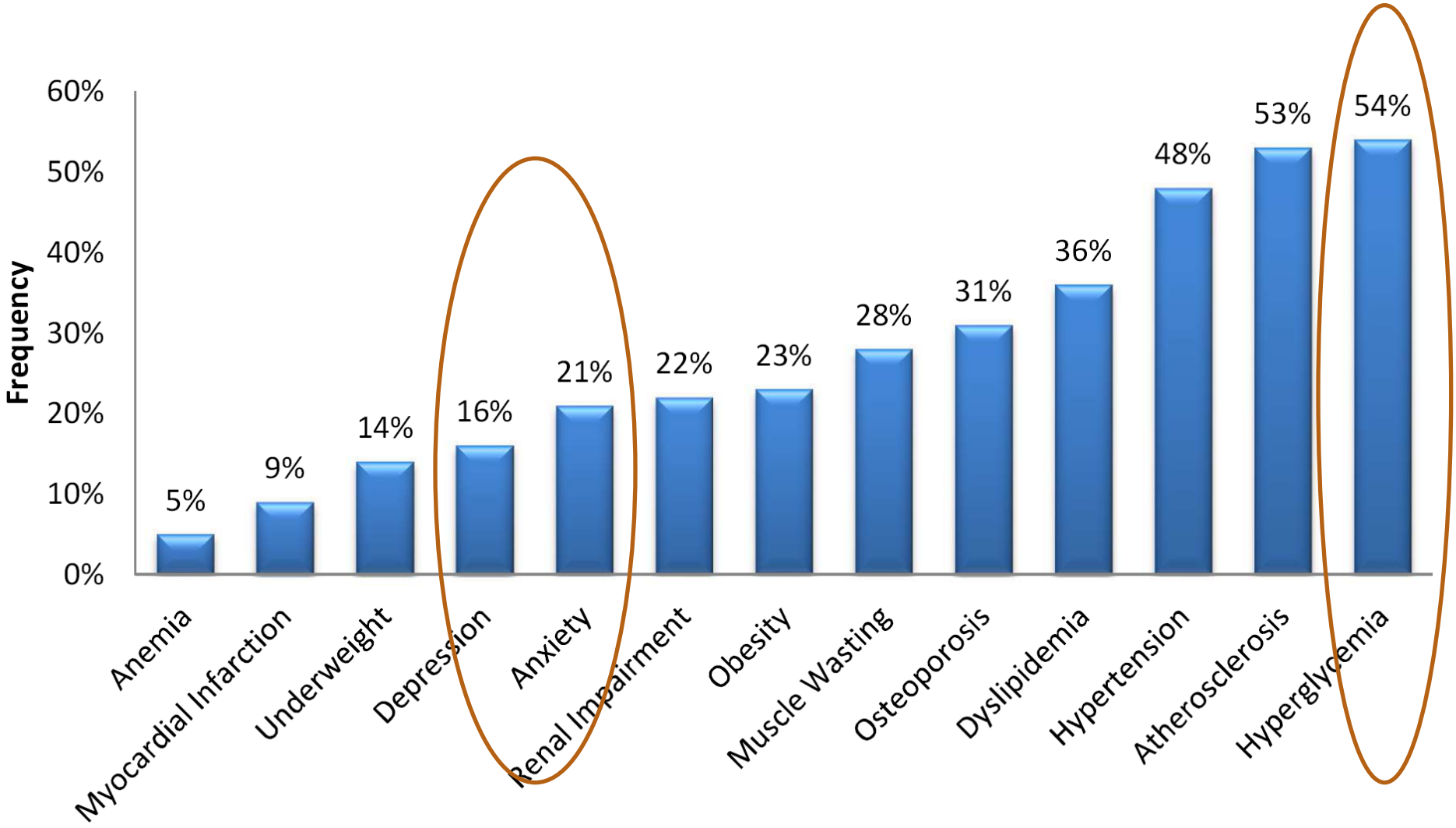
The more they do resemble to each other by having similar comorbidities the closer they are together. The more they differ the farther they are away from each other.

If we look at a different comorbidity they just wave another flag, a red one if they have the comorbidity and a blue one if they don’t.

Subjects characteristics (n = 213)

Age, years	63.6 ± 7.0
Male, %	59
BMI, $kg \cdot m^{-2}$	26.2 ± 5.1
FFMI, $kg \cdot m^{-2}$	17.0 ± 2.4
Current smoker, %	28
Packyears	46 ± 26
Long-term oxygen therapy, %	17
FEV_1, liters	1.4 ± 0.5
FEV_1, % predicted	51.2 ± 16.9
FEV_1/FVC	0.4 ± 0.1
ITGV, % predicted	148 ± 33
TLCO, % predicted	56 ± 17
6MWD, meters	470 ± 106
mMRC dyspnea grade	2.1 ± 1.1
SGRQ, total score	51.3 ± 17.5

Frequencies of objectively identified comorbidities



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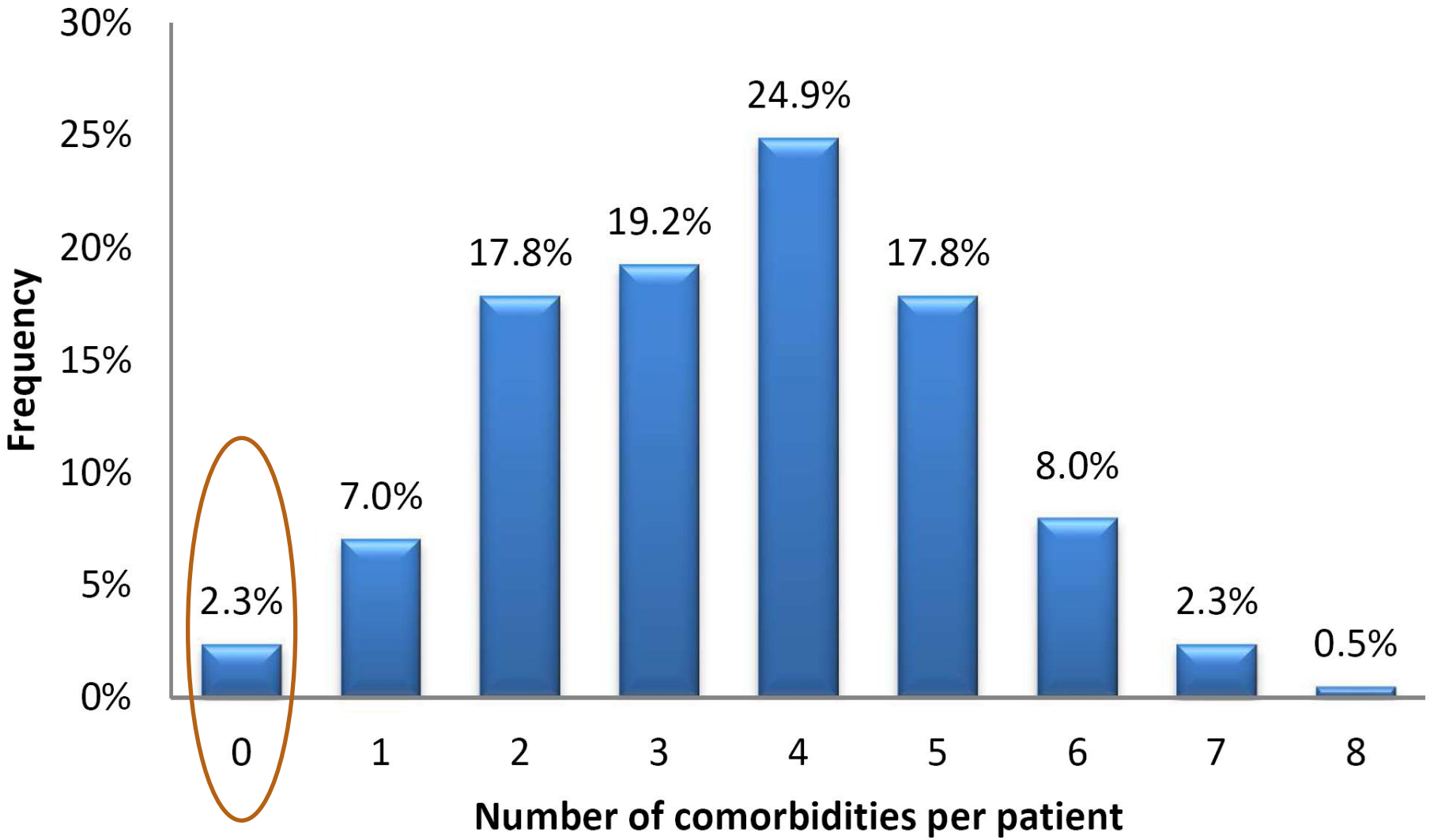
Number of objectively identified comorbidities



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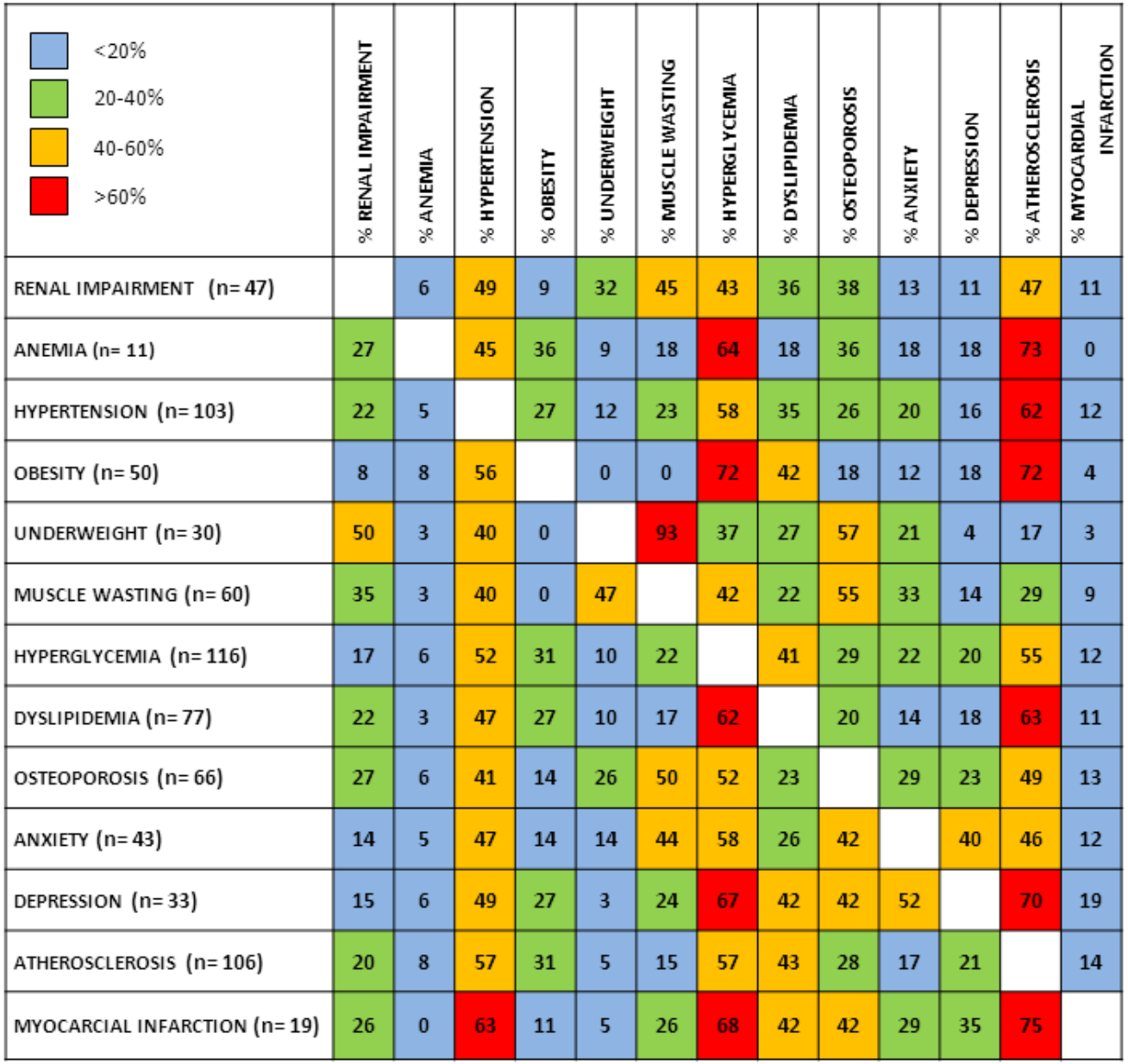
Coexistence of comorbidities



<20% 20-40% 40-60% >60%	% RENAL IMPAIRMENT	% ANEMIA	% HYPERTENSION	% OBESITY	% UNDERWEIGHT	% MUSCLE WASTING	% HYPERGLYCEMIA	% DYSLIPIDEMIA	% OSTEOPOROSIS	% ANXIETY	% DEPRESSION	% ATHEROSCLEROSIS	% MYOCARDIAL INFARCTION
RENAL IMPAIRMENT (n= 47)		6	49	9	32	45	43	36	38	13	11	47	11
ANEMIA (n= 11)	27		45	36	9	18	64	18	36	18	18	73	0
HYPERTENSION (n= 103)	22	5		27	12	23	58	35	26	20	16	62	12
OBESITY (n= 50)	8	8	56		0	0	72	42	18	12	18	72	4
UNDERWEIGHT (n= 30)	50	3	40	0		93	37	27	57	21	4	17	3
MUSCLE WASTING (n= 60)	35	3	40	0	47		42	22	55	33	14	29	9
HYPERGLYCEMIA (n= 116)	17	6	52	31	10	22		41	29	22	20	55	12
DYSLIPIDEMIA (n= 77)	22	3	47	27	10	17	62		20	14	18	63	11
OSTEOPOROSIS (n= 66)	27	6	41	14	26	50	52	23		29	23	49	13
ANXIETY (n= 43)	14	5	47	14	14	44	58	26	42		40	46	12
DEPRESSION (n= 33)	15	6	49	27	3	24	67	42	42	52		70	19
ATHEROSCLEROSIS (n= 106)	20	8	57	31	5	15	57	43	28	17	21		14
MYOCARCIAL INFARCTION (n= 19)	26	0	63	11	5	26	68	42	42	29	35	75	

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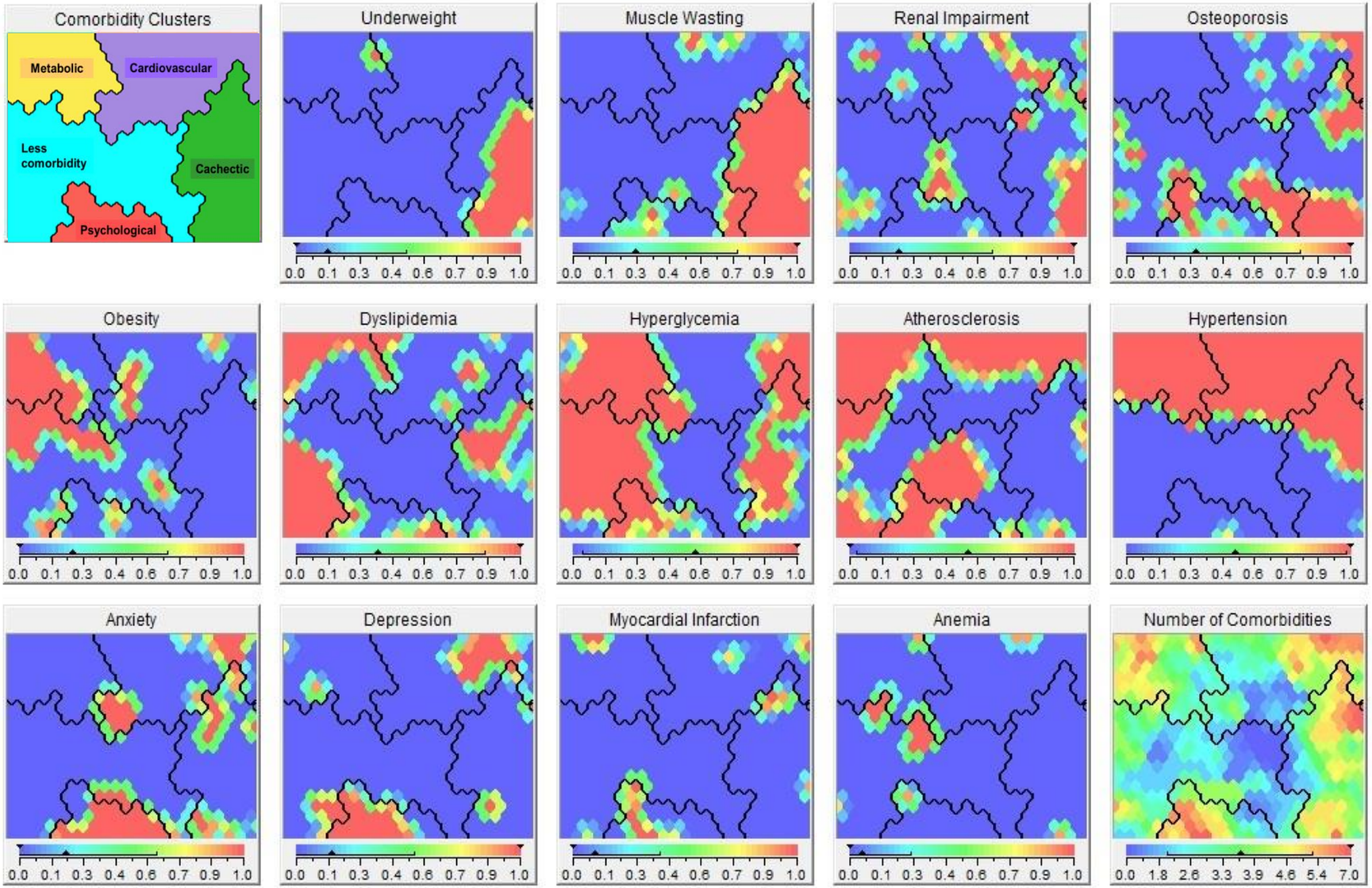

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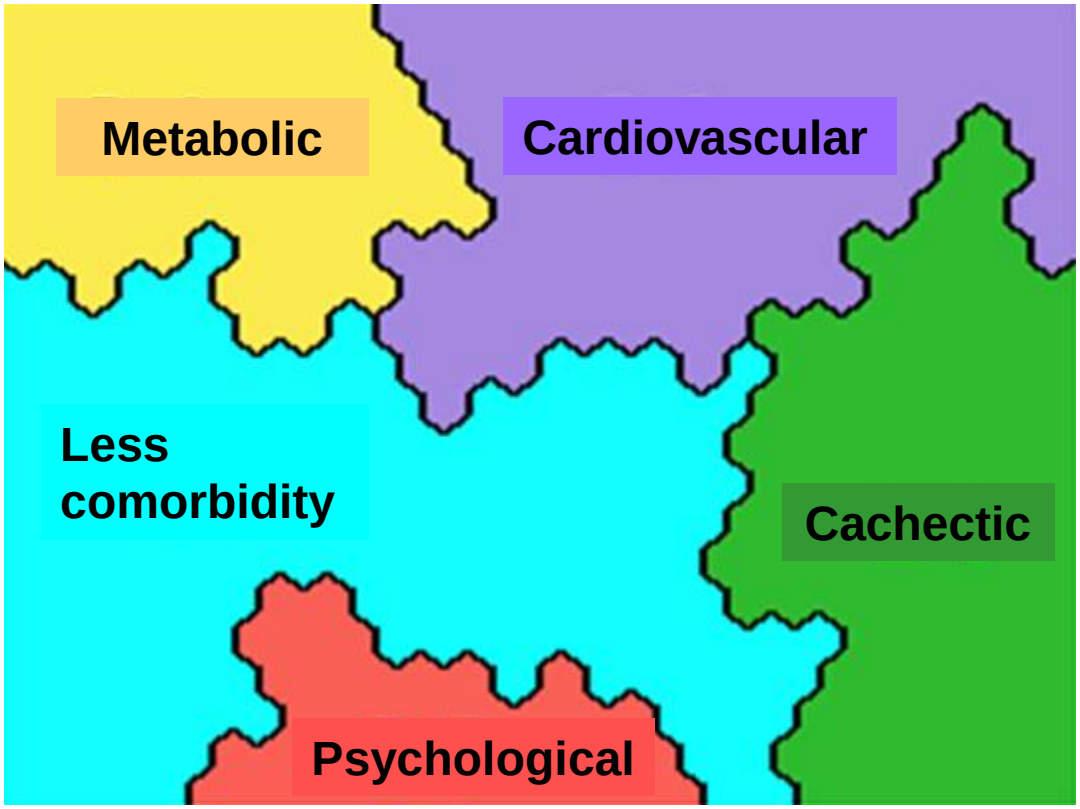
Identification of five comorbidy clusters



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Emerging clusters

- less comorbidity
- cardiovascular
- cachectic
- metabolic
- psychological

Characteristics of comorbidy clusters (1)

Comorbidities	CLUSTER 1 'less comorbidity'	CLUSTER 2 'cardio-vascular'	CLUSTER 3 'cachectic'	CLUSTER 4 'metabolic'	CLUSTER 5 'psychologic'
n	67	49	44	33	20
Number of Comorbidities	2.5 ± 1.4	3.8 ± 1.7	4.2 ± 1.4	4.4 ± 1.1	4.1 ± 1.8
Renal Impairment, %	16	24	45	9	5
Anemia, %	9	4	2	3	5
Hypertension, %	3	98	43	100	5
Obesity, %	30	14	0	61	15
Underweight, %	0	0	66	3	0
Muscle Wasting, %	12	10	98	0	20
Hyperglycemia, %	52	41	43	91	60
Dyslipidemia, %	42	16	25	67	40
Osteoporosis, %	27	37	52	0	35
Anxiety, %	5	28	26	0	84
Depression, %	6	23	7	6	68
Atherosclerosis, %	56	67	12	81	53
Myocardial Infarction, %	2	11	7	13	32

Light grey: less prevalent ; dark grey: more prevalent compared to the whole study sample

Vanfleteren et al, Am J Respir Crit Care Med 2013

Characteristics of comorbidy clusters (2)

Clinical characteristics	CLUSTER 1 'less comorbidity'	CLUSTER 2 'cardio-vascular'	CLUSTER 3 'cachectic'	CLUSTER 4 'metabolic'	CLUSTER 5 'psychologic'
n	67	49	44	33	20
Age, years	62.1 ± 6.8	67.2 ± 5.8	62.5 ± 7.2	63.1 ± 7.3	62.8 ± 6.8
Male, %	60	65	43	79	45
mMRC dyspnea grade	1.99 ± 1.01	2.29 ± 1.21	1.73 ± 0.9	2.12 ± 1.11	2.84 ± 1.12
Current smoker, %	30	16	45	15	35
Packyears	44 ± 20	45 ± 26	49 ± 30	51 ± 34	42 ± 16
LTOT, %	13	18	18	15	25
6MWD, meter	474 ± 102	446 ± 133	496 ± 101	473 ± 91	459 ± 74
FEV1, % predicted	52.7 ± 17.4	50.9 ± 17.7	48.3 ± 16.3	54.2 ± 16	48.3 ± 15.4
ITGV, % predicted	143 ± 33	148 ± 29	166 ± 34	134 ± 33	146 ± 28
TLCO, % predicted	60 ± 16	57 ± 18	44 ± 13	60 ± 14	55 ± 14
SGRQ Total score	47.6 ± 15.3	56.5 ± 17.2	45.8 ± 19.4	49.9 ± 16.1	65.9 ± 12.5
SGRQ symptoms, score	49.1 ± 18.1	58.8 ± 20.7	55.5 ± 23.1	52.8 ± 20.2	69.9 ± 14.4
SGRQ activity, score	68.3 ± 20.2	70.2 ± 22.0	60.4 ± 24.9	66.4± 20.5	83.5 ± 13.9
SGRQ impact, score	36.3 ± 17.9	43.6 ± 21.2	35.1 ± 21.5	39.6 ± 18.1	52.6 ± 16.6

Light grey: less prevalent ; dark grey: more prevalent compared to the whole study sample

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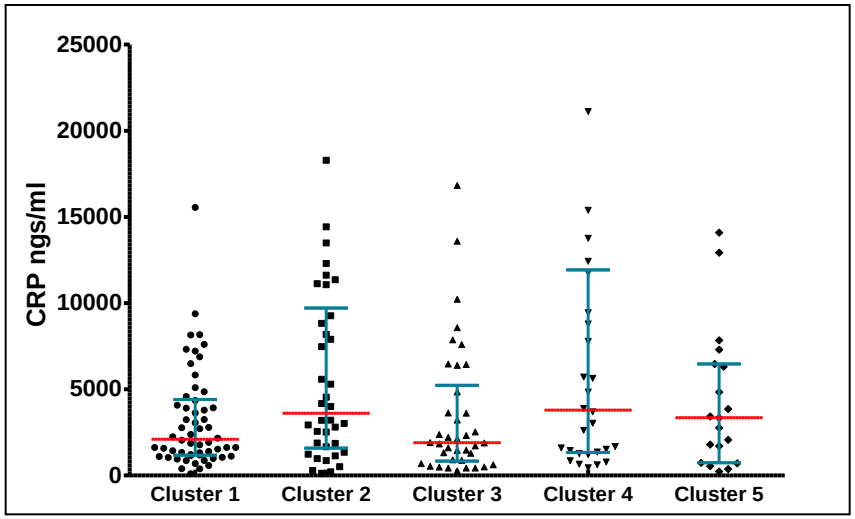
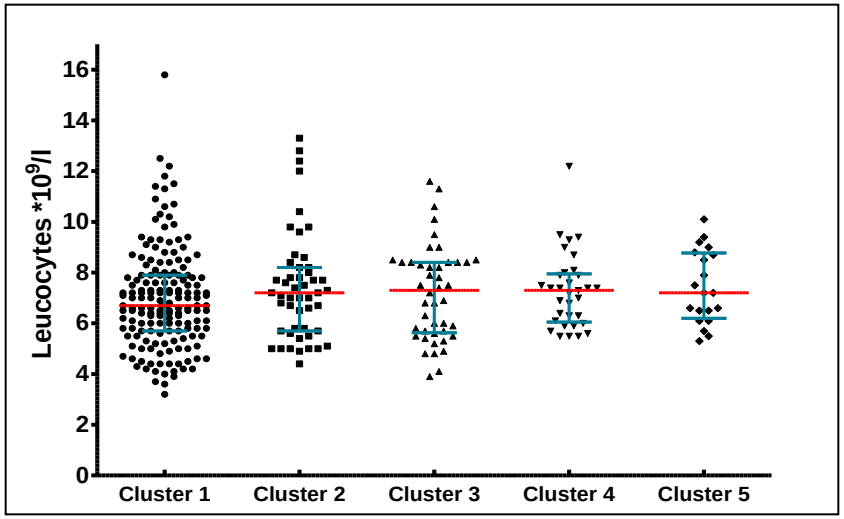
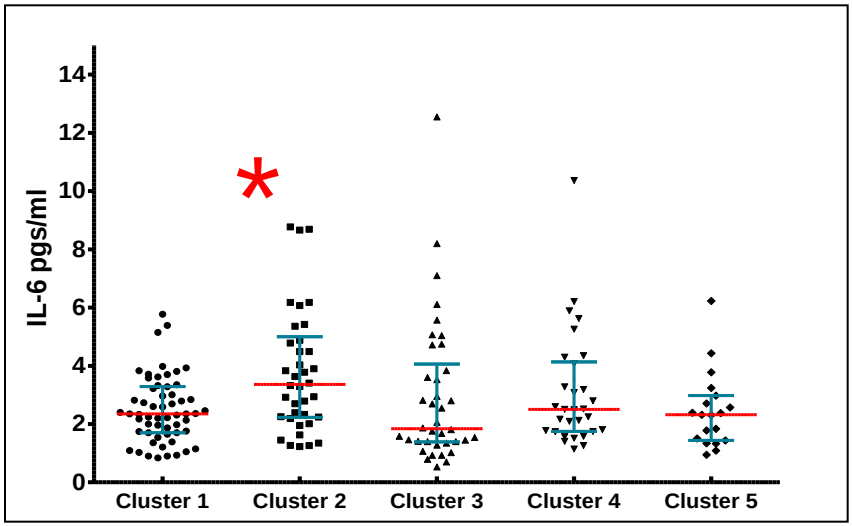
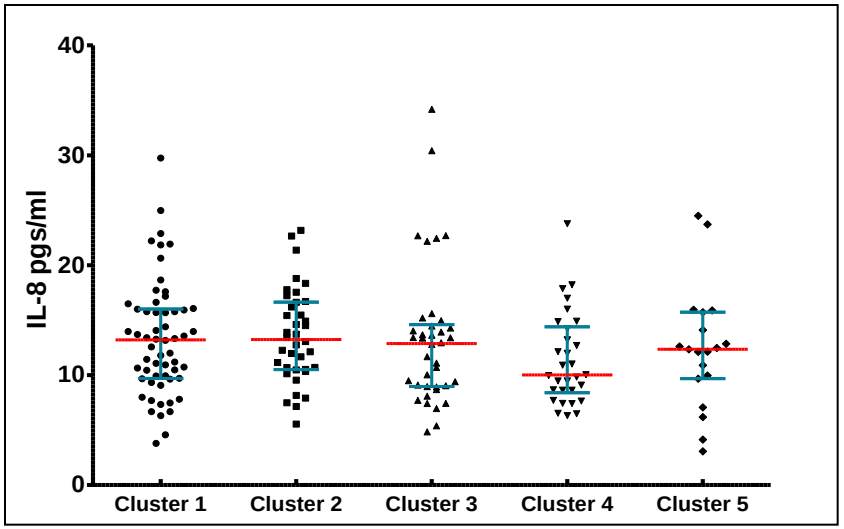
Plasma inflammatory markers for the 5 clusters









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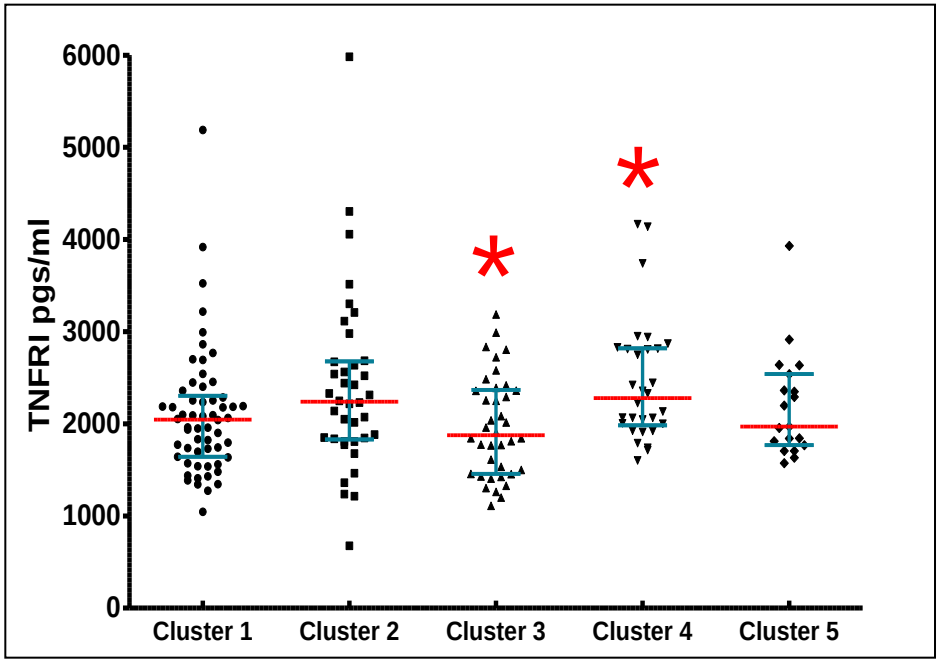

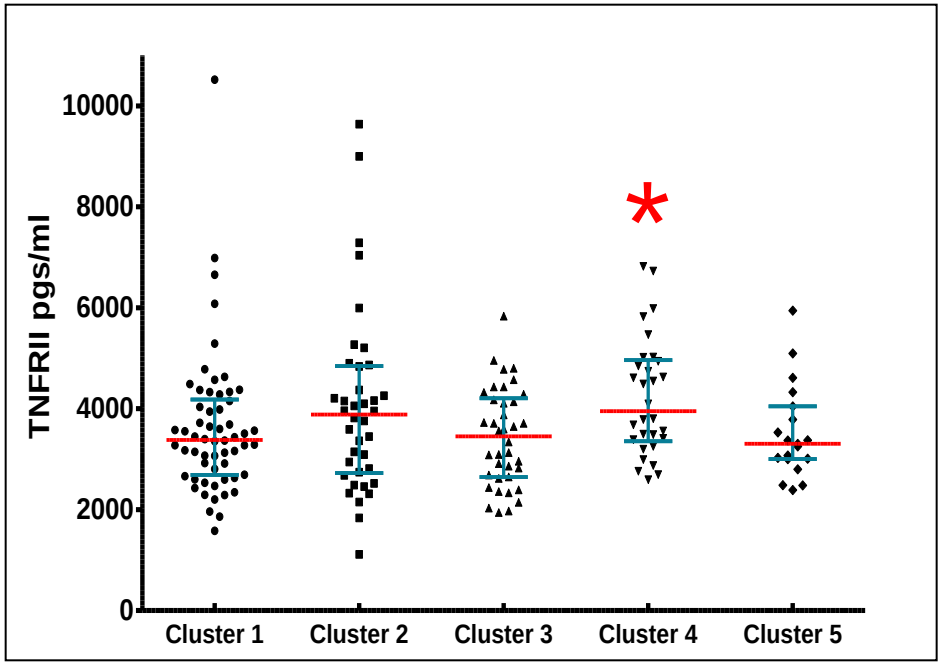

	CLUSTER 1 'less comorbidity'	CLUSTER 2 'cardio-vascular'	CLUSTER 3 'cachectic'	CLUSTER 4 'metabolic'	CLUSTER 5 'psychologic'
CRP, ngs/ml	2286 (844, 6188)	3380 (947, 12062)	2005 (677, 5938)	3860 (1073, 13886)	2519 (767, 8283)
IL-6, pgs/ml	2.4 (1.3, 4.3)	3.4 (1.8, 6.6)	2.2 (1.1, 4.7)	2.7 (1.6, 4.5)	2.2 (1.3, 3.6)
IL-8, pgs/ml	12.3 (8.2, 18.6)	12.9 (9.3, 17.9)	12.1 (7.8, 18.7)	10.8 (7.6, 15.2)	11.1 (6.6, 18.7)
TNF-R1, pgs/ml	2013 (1508, 2689)	2229 (1513, 3285)	1896 (1434, 2505)	2377 (1850, 3055)	2133 (1685, 2699)
TNF-R2, pgs/ml	3417 (2454, 4758)	3698 (2399, 5701)	3302 (2478, 4401)	4080 (3115, 5344)	3419 (2675, 4371)
Leucocytes *10^9/L	7.3 (5.6, 9.5)	7.1 (5.5, 9.4)	7.0 (5.3, 9.1)	7.2 (5.9, 8.7)	7.3 (6.0, 8.9)

Vanfleteren et al, Am J Respir Crit Care Med 2013

Conclusions of clustering comorbidities in COPD

1) In a cohort of moderate to severe patients with COPD, 97% of patients had one or more of the thirteen selected clinically relevant comorbidities, most of those underreported and/or undertreated
2) Five clusters of clinically important and objectively diagnosed comorbidities were identified using Viscovery® analysis
    1) Less
    2) Cardiovascular
    3) Cachectic
    4) Metabolic
    5) psychologic
3) Clusters cannot be discriminated based on severity of airflow limitation or functional performance, but markedly differ in terms of health status
4) Inflammatory markers were mostly comparable between clusters

Clusters of COPD patients based on comorbidities: **Implications**

1. **Implications for physicians and patients**
   - **Awareness amongst physicians**
   - **may contribute to the development of new chronic disease management guidelines**

2. Implications for future studies
   - Validation of these comorbidity clusters in other cohorts, both COPD and non-COPD,
   - Unravel the complex interactions between systemic inflammation, life style factors and comorbidities in COPD

3. Implications for pulmonary rehabilitation?

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Clusters of COPD patients based on comorbidities: Implications

1. Implications for physicians and patients
   - awareness amongst physicians and
   - may contribute to the development of new chronic disease management guidelines

2. Implications for future studies
   - Validation of these comorbidity clusters in other cohorts, both COPD and non-COPD,
   - Unravel the complex interactions between systemic inflammation, life style factors and comorbidities in COPD

3. **Implications for pulmonary rehabilitation?**

PR outcomes for each comorbidity cluster

Variable	Sample	Pre (mean ± SD)	Mean change (95% CI)
6MWT, m	Cluster 1 (n=55)	479 ± 94	31 (16, 46)
	Cluster 2 (n=43)	455 ± 127	28 (11, 45)
	Cluster 3 (n=39)	500 ± 103	27 (10, 44)
	Cluster 4 (n=31)	475 ± 87	22 (2, 42)
	Cluster 5 (n=19)	459 ± 76	55 (37, 72)
CWRT, s	Cluster 1 (n=53)	373 ± 297	226 (146, 306)
	Cluster 2 (n=39)	349 ± 257	184 (102, 266)
	Cluster 3 (n=35)	280 ± 166	150 (30, 269)
	Cluster 4 (n=29)	368 ± 229	235 (103, 367)
	Cluster 5 (n=18)	389 ± 317	217 (47, 388)
SGRQ total, score	Cluster 1 (n=41)	48.5 ± 15.5	-1.8 (-5.6, 1.9)
	Cluster 2 (n=30)	55.3 ± 18.7	-4.9 (-8.4, -1.4)
	Cluster 3 (n=38)	45.4 ± 19.8	-1.6 (-6.2, 3.1)
	Cluster 4 (n=27)	49.0 ± 16.7	-6.9 (-11.4, -2.3)
	Cluster 5 (n=15)	67.4 ± 12.2	-9.1 (-17.6, -0.7)

Mesquita, Vanfleteren et al. 2015

Comorbidity and rehabilitation: Suggestions to move forward

- COPD patients in rehabilitation programs are almost by definition multimorbid
- To learn more how comorbidities affect rehabilitation
  - Collect and report data about comorbidities (objectified!) and treat!
  - Take comorbidities into account in planning intervention
  - Consider multiple dimensions of multimorbidity

One size fits all

Baseline intake and assessments