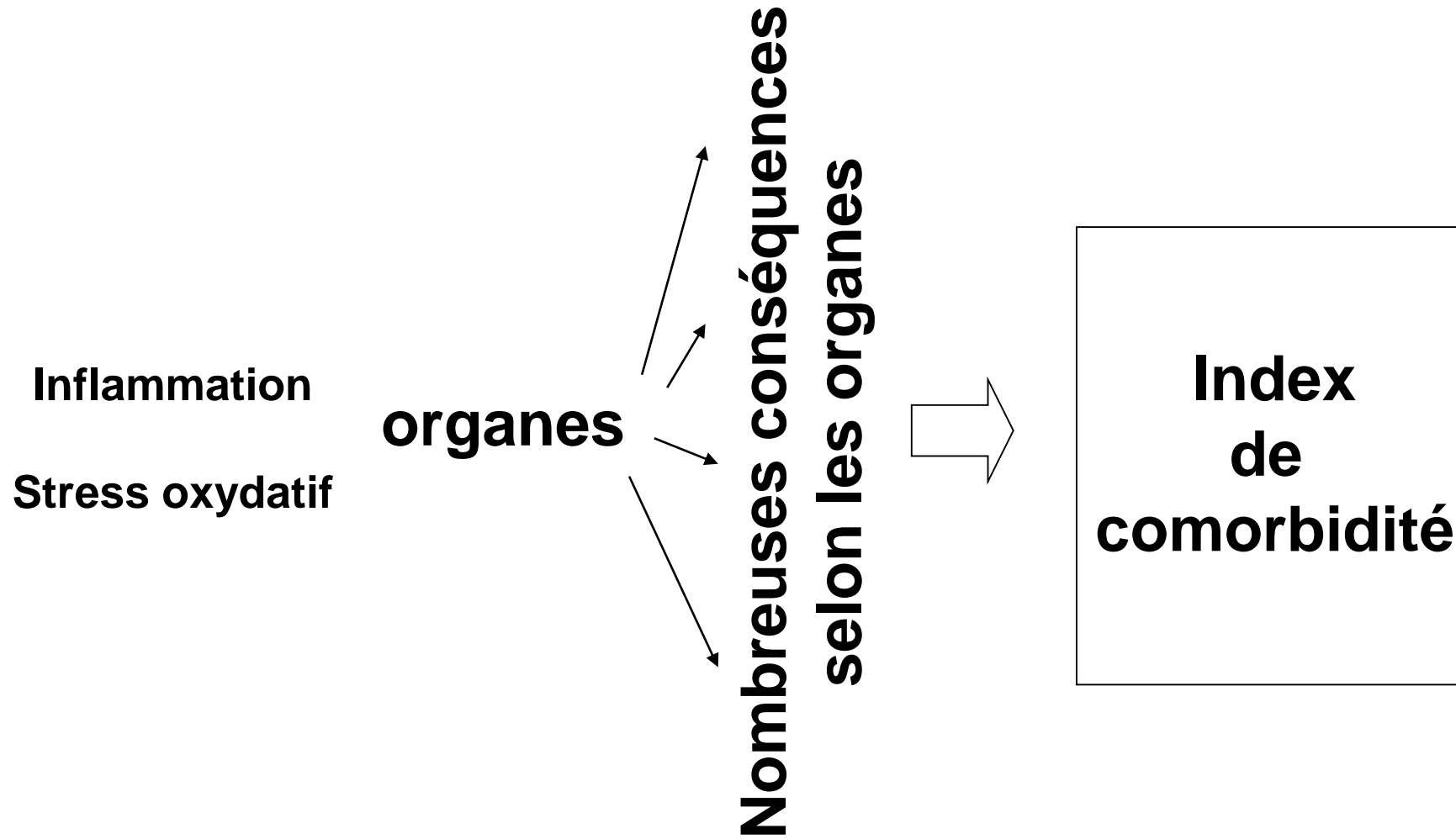


# Comorbidités et toxicités

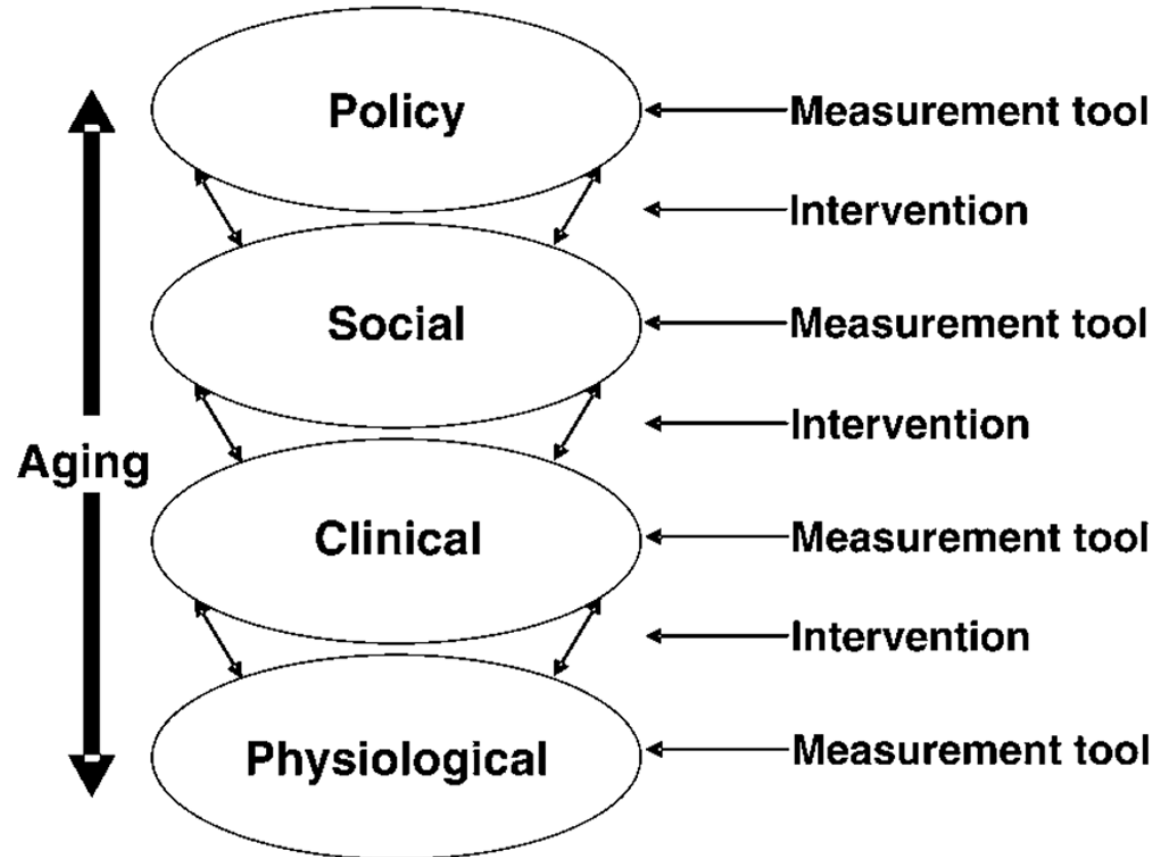
Pr Laure de Decker  
Université/CHU Nantes

# Les différents modèles



# Modèle de Mandelblatt

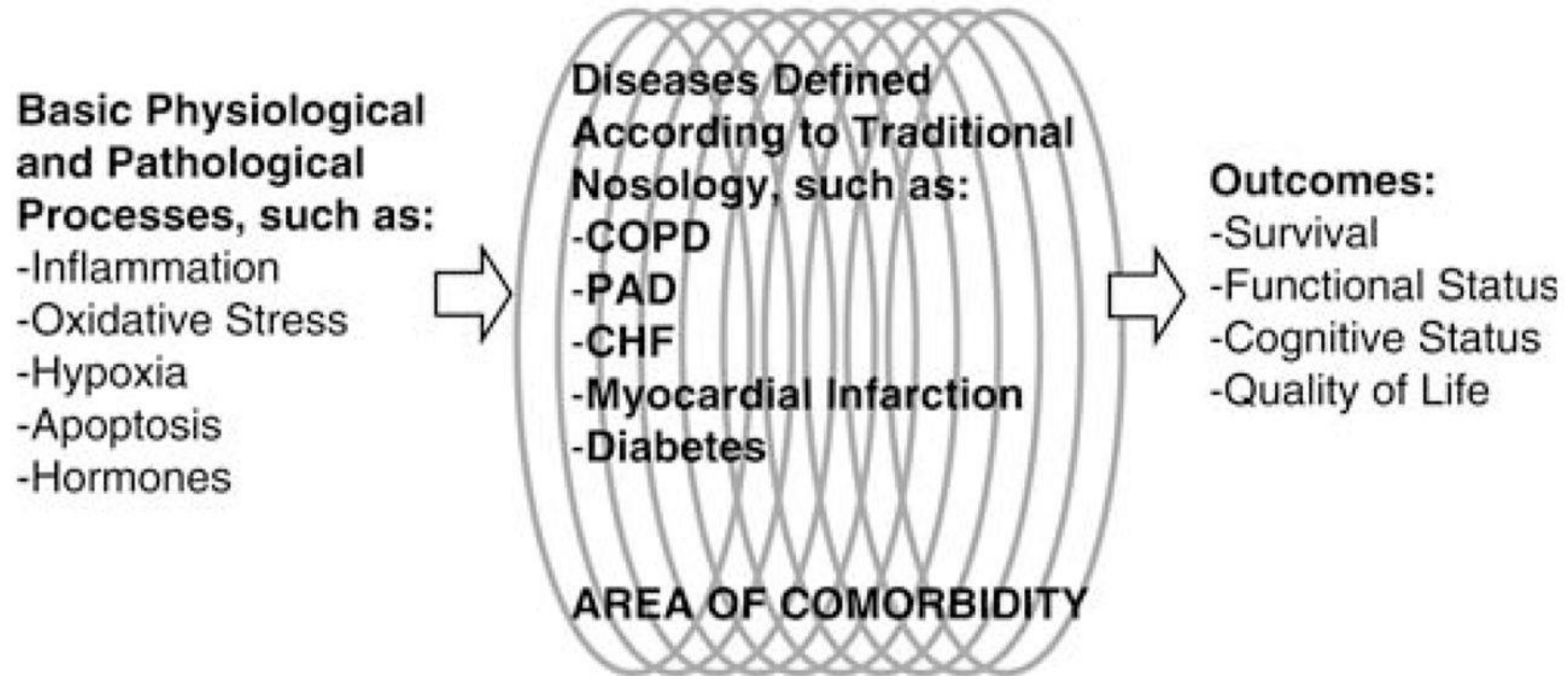
## Impact of Disease Burden



*Outcomes: Health Service Use, Disability, Survival, Quality of Life*

# Modèle de Ferruci

Comorbidity as an Interface Between  
Basic Pathology and Health-Related Outcomes



# Modèles de L. Fried

## Modèle classique

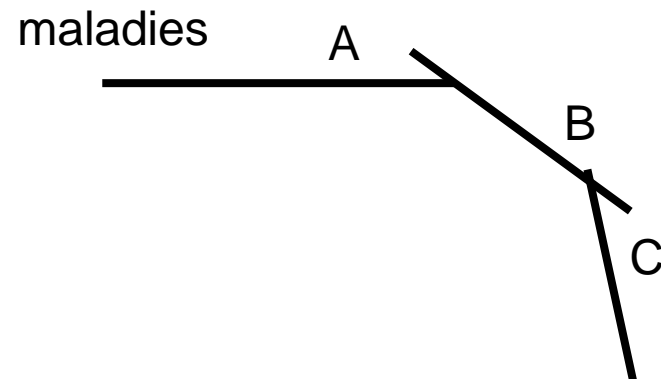
Symptôme → Maladie

## Modèle d'attribution

Attribution à une pathologie chronique

Problème non reconnu d'expression récente

## Modèle de comorbidité synergique



## Modèle de l'événement révélateur

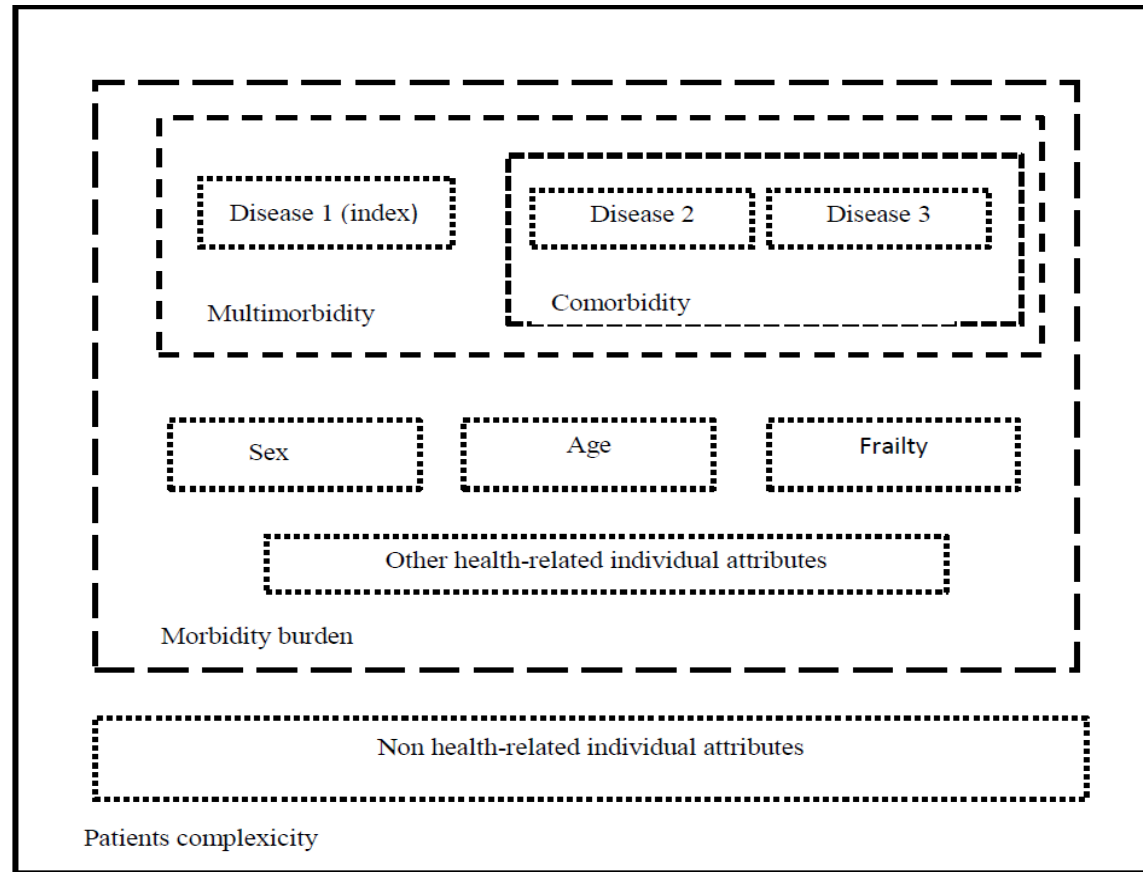
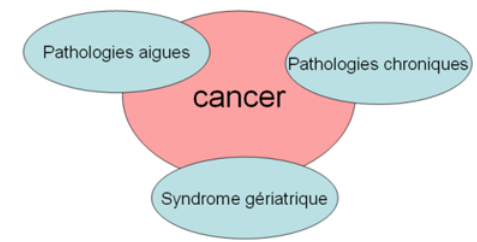
EVENEMENT

Affection compensée non reconnue

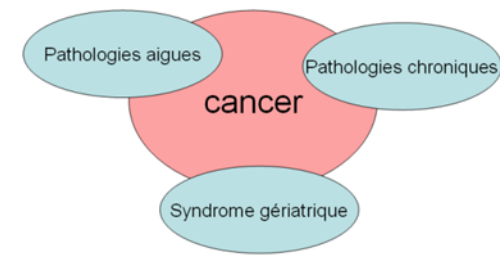


Affection décompensée reconnue

# La définition



La complexité d'un individu d'après le schéma issu de l'étude de Valderas.



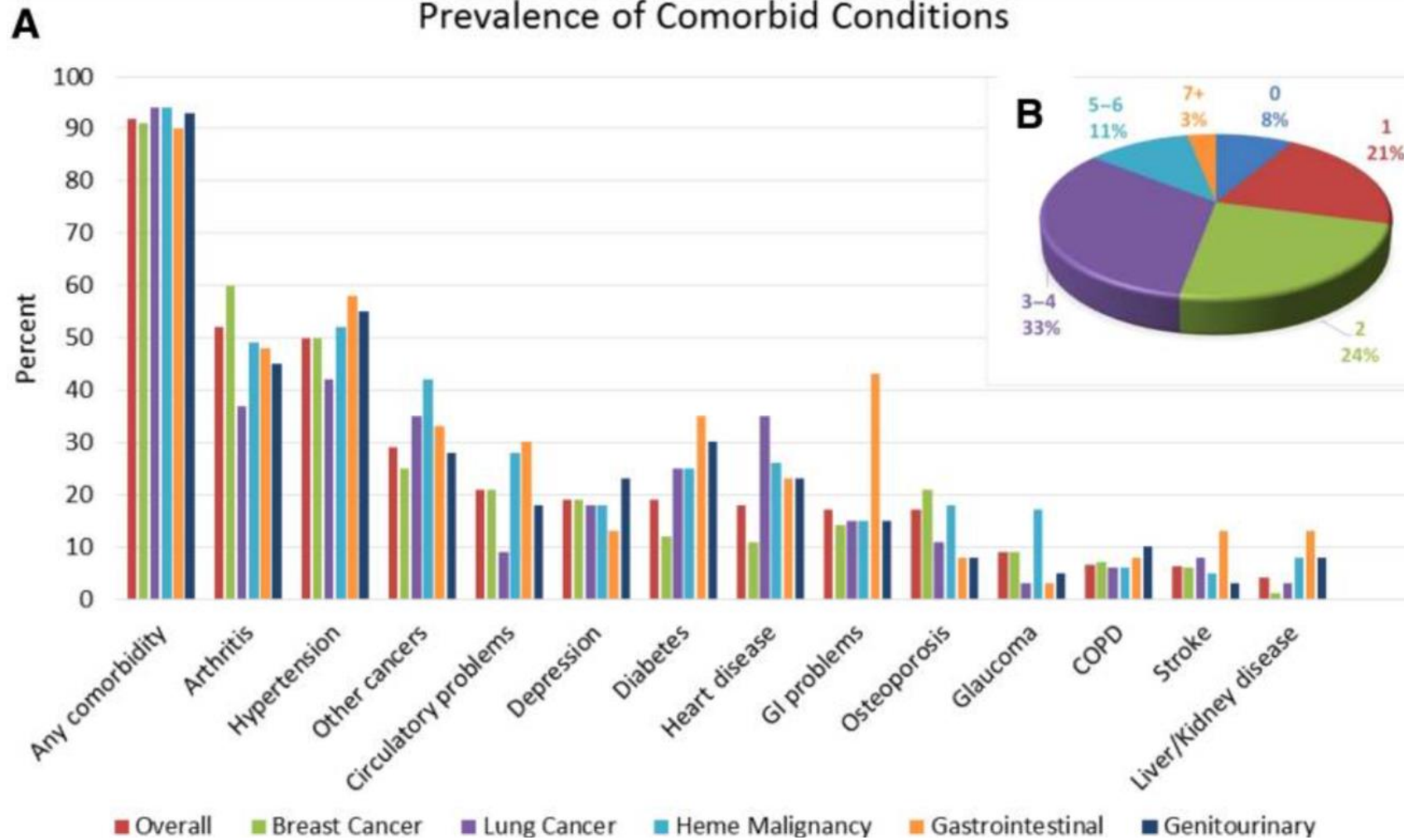
# Echelles de mesures

- Échelles pondérant un cumul de comorbidités s'intéressant au fardeau de comorbidité : la Cumulative Illness Rating Scale (CIRS), la Geriatric Index of Comorbidity (GIC), l'index de Charlson, l'indice de Kaplan-Feinstein et l'Index of Coexistent Diseases (ICED).
- Évaluation d'une comorbidité spécifique et son association avec une pathologie index(cancer)



Echelle	Variabilité intra-classe	Reproductibilité	Champs de validation
CIRS	0,78-0,95	0,76	-Chirurgie -Cancer de la personne âgée -Personnes âgées institutionnalisées
Kaplan-Feinstein		0,82	-Diabète -Cancer du poumon -Cancer de la prostate
Charlson	0,86-0,92	0,74-0,94	-Médecine interne -Cancer du poumon - Cancer du sein
Index of Coexistent Diseases	0,93		-Cancer du sein -Cancer de la prostate -Hémodialysé -Prothèse de hanche -RTUP -Colostomisé -IDM -Pontage coronarien

Comorbidités rencontrées chez les patients ayant un cancer



Williams GR, Deal AM, Lund JL et al. Oncologist. 2018 Apr;23(4):433-439.

# Complications post opératoires

Risk of surgical complication	Adj ORs of surgical complications compared with patients with CCI=0:
	Any comorbidity: 1.1 (95% CI: 0.91–1.4)
	Previous malignancy: 1.2 (95% CI: 0.7–2.1)
	CVD: 0.9 (95% CI: 0.5–1.5)
	COPD: 1.8 (95% CI: 0.7–4.7)
	Diabetes: 0.6 (95% CI: 0.1–1.4)
	Hypertension: 0.7 (95% CI: 0.4–1.4)
	DVT: 9.0 (95% CI: 1.1–27.9)

# Complications post opératoires

## Postoperative complications

Adj ORs of complications compared to those with CCI 0:

Any complications:

CCI 1: 1.38 (95% CI: 1.15–1.66)

CCI  $\geq$ 2: 1.83 (95% CI: 1.50–2.23)

Pulmonary complications:

CCI 1: 1.32 (95% CI: 1.10–1.59)

CCI  $\geq$ 2: 1.51 (95% CI: 1.25–1.83)

Cardiac complications:

CCI 1: 1.36 (95% CI: 1.11–1.66)

CCI  $\geq$ 2: 1.57 (95% CI: 1.28–1.93)

Non-cardiopulmonary complications:

CCI 1: 1.19 (95% CI: 0.95–1.52)

CCI  $\geq$ 2: 1.29 (95% CI: 1.02–1.65)

The odds of any complication are increased among patients with comorbidity who undergo surgery.

# Complications post opératoires

Geriatric Assessment as Predictor of Surgical Outcomes in Elderly Patients					
Reference	Age (years)	No. of Patients	Type of Surgery	Predictor	Outcome
Robinson et al <sup>20</sup>	68-80	110	Elective surgery requiring postoperative ICU admission	Impaired cognition, recent falls, lower albumin, greater anemia, functional dependence, and increased comorbidities	6-month postoperative mortality and postdischarge institutionalization
Robinson et al <sup>22</sup>	67-79	186	Elective surgery requiring postoperative ICU admission	Cognitive impairment	Increased postoperative complications, length of stay, and long-term mortality
Preoperative Assessment of Cancer in the Elderly (PACE) <sup>23</sup>	≥ 70	460	Cancer surgery for solid tumors	Disability, fatigue, and abnormal performance status	Postoperative complications
Dale et al <sup>24</sup>	80% were older than 60	76	Pancreaticoduodenectomy for pancreatic tumors	Fried's exhaustion	Major complications, longer hospital stay, and ICU admissions
Large et al <sup>25</sup>	≥ 65	49	Radical cystectomy for bladder cancer	Cognitive impairment and older age	Postcystectomy delirium
Fukuse et al <sup>26</sup>	60-84	120	Thoracic surgery, multiple causes	Functional dependency and cognitive impairment	Postoperative complications
Makary et al <sup>27</sup>	65-94	594	Multiple surgeries	Frailty	Postoperative complications, length of stay, and discharge to skilled nursing or assisted living facility
Kim et al <sup>28</sup>	≥ 65	141	Multiple surgeries	Functional dependency, poor nutrition, and cumulative impairment in geriatric assessment	In-hospital death, post-discharge institutionalization, adverse in-hospital events, and prolonged length of stay
Revenig et al <sup>21</sup>	19-86	189	Oncologic, urologic, and general surgery procedures	Intermediately frail or frail on the Hopkins Frailty Score	30-day postoperative complications
Huisman et al <sup>29</sup>	Older than 70	180	Elective surgery for solid tumors	Timed Up & Go test	30-day postoperative complications



# Morbi-mortalité post-opératoire

Calculateur du risque de complications en contexte chirurgical  
([www.riskcalculator.facs.org](http://www.riskcalculator.facs.org))

**Procedure** 43632 - Gastrectomy, partial, distal, with gastrojejunostomy Clear

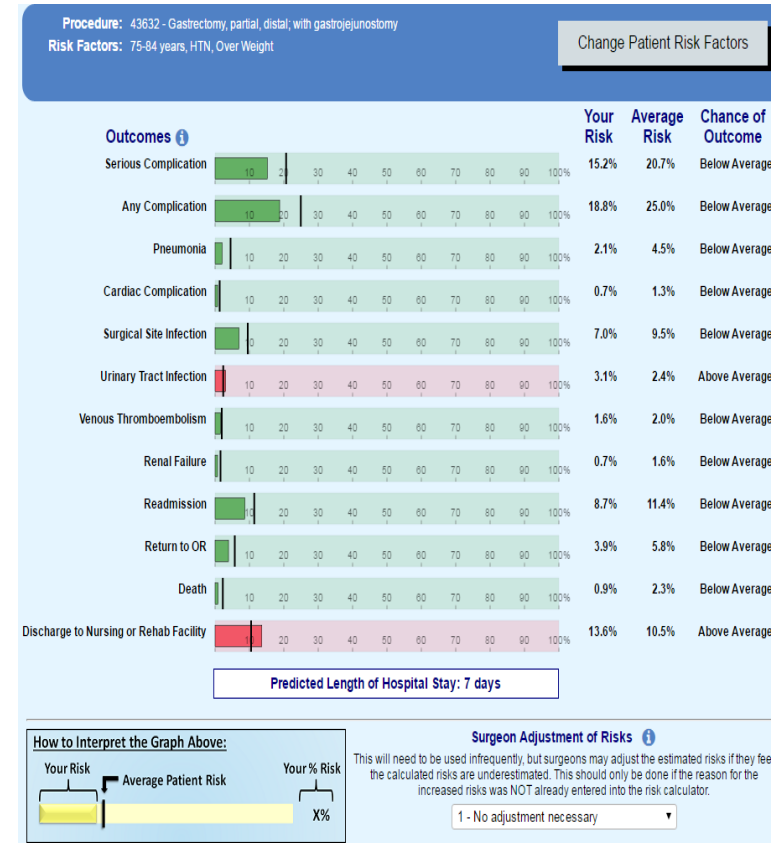
Begin by entering the procedure name or CPT code. One or more procedures will appear below the procedure box. You will need to click on the desired procedure to properly select it. You may also search using two words (or two partial words) by placing a "+" in between, for example: "cholecystectomy + cholangiography"

Reset All Selections

**Are there other potential appropriate treatment options?**  Other Surgical Options  Other Non-operative options  None

Please enter as much of the following information as you can to receive the best risk estimates.  
A rough estimate will still be generated if you cannot provide all of the information below.

<b>Age Group</b> 75-84 years	<b>Diabetes</b> No
<b>Sex</b> Male	<b>Hypertension requiring medication</b> Yes
<b>Functional Status</b> Independent	<b>Congestive Heart Failure in 30 days prior to surgery</b> No
<b>Emergency Case</b> No	<b>Dyspnea</b> No
<b>ASA Class</b> Mild systemic disease	<b>Current Smoker within 1 Year</b> No
<b>Steroid use for chronic condition</b> No	<b>History of Severe COPD</b> No
<b>Ascites within 30 days prior to surgery</b> No	<b>Dialysis</b> No
<b>Systemic Sepsis within 48 hours prior to surgery</b> None	<b>Acute Renal Failure</b> No
<b>Ventilator Dependent</b> No	<b>BMI Calculation:</b>
<b>Disseminated Cancer</b> No	Height: 70 in / 178 cm
	Weight: 178 lb / 80 kg



# Chimiothérapie CRASH/ CARG

CRASH (Chemotherapy Risk Age Scale for High Risk Patients) Scoring Analysis

Chemotherapy risk (see table)		
<b>Hematologic risk factors</b>		
Diastolic blood pressure (greater than 72 = 1)		
IADL (less than 26 = 1)		
LDH (greater than 459 = 2)*		
<b>Non-hematologic risk factors</b>		
ECOG PS (1-2 = 1; 3-4 = 2)		
MMS (less than 30 = 2)		
MNA (less than 28 = 2)		
<b>Heme score</b> (incl. chemo risk)		
<b>Non-heme score</b> (incl. chemo risk)		
<b>Combined score</b> (count chemo risk only once)		

**Individual risk**

Sample	CRASH score (points / % with severe toxicity)			
	Heme subscore	Non-Heme subscore	Combined score	Risk Category
Derivation (n=347)	0-1: 7%	0-2: 33%	0-3: 50%	Low Int-Low Int-High High
	2-3: 23%	3-4: 46%	4-6: 58%	
	4-5: 54%	5-6: 67%	7-9: 77%	
	Greater than 5: 100%	Greater than 6: 93%	Greater than 9: 79%	
Validation	0-1: 12%	0-2: 42%	0-3: 61%	
	2-3: 35%	3-4: 59%	4-6: 72%	
	4-5: 45%	5-6: 66%	7-9: 77%	
	Greater than 5: 50%	Greater than 6: 100%	Greater than 9: 100%	

Ref: Extermann et al., ASCO 2010

Estimation du risque de chimio-toxicité selon le score CARG (*the cancer and aging research group toxicity tool*) [30]

Variables	Points	Total	Risque estimé (%)
Âge ≥ 72 ans	2	0-5 (faible)	30
Cancer gastro-intestinal ou génito-urinaire	2	6-9 (modéré)	52
Chimiothérapie à dose standard	2	10-19 (élevé)	83
Polychimiothérapie	2		
Hémoglobine	3		
< 11 g/dL (homme)			
< 10 g/dL (femme)			
Clairance de la créatinine < 34 mL/min	3		
Altération de l'audition	2		
Au moins une chute dans les 6 derniers mois	3		
Aide dans la prise des médicaments	1		
Limitation à la marche	2		
Diminution parfois de l'activité sociale en raison de problèmes de santé (physiques ou émotionnels)	1		



# Toxicités médicamenteuses

**Table 4.** A multivariate model for predicting grade  $\geq 3$  chemotherapy-associated adverse events.

	aOR <sup>a</sup>	95%CI		P <sup>a</sup>
Type of cancer (reference: colorectal cancer)				
Gastrointestinal cancer (other than colorectal)	<b>3.7</b>	1.5	8.9	<b>.003</b>
Breast cancer	<b>7.1</b>	2.1	24.7	<b>.002</b>
Genitourinary tract cancer	<b>7.1</b>	2.5	19.8	<b>&lt;.001</b>
Other cancer	<b>7.6</b>	1.7	32.7	<b>.007</b>
ECOG PS (reference: PS 0)				
1-2	<b>2.4</b>	1.1	5.6	<b>.04</b>
3-4	<b>1.1</b>	0.3	3.6	<b>.88</b>
One or more grade 3 or 4 comorbidites (CIRS-G)	<b>3.7</b>	1.8	7.7	<b>&lt;.001</b>
BMI class (reference: 22-25 kg/m <sup>2</sup> )				
<22 kg/m <sup>2</sup>	<b>0.6</b>	0.2	1.5	<b>.24</b>
>25 kg/m <sup>2</sup>	<b>0.3</b>	0.1	0.8	<b>.01</b>
>30 kg/m <sup>2</sup>	<b>0.3</b>	0.1	0.8	<b>.02</b>
MAX2 index (reference: a index of 0)				
1	<b>2.4</b>	1.1	5.2	<b>.02</b>
2	<b>0.9</b>	0.3	2.6	<b>.78</b>
Area under curve [95%CI]	<b>0.78 [0.72-0.85]</b>			

Significant results are given in bold. The MAX2 score is an estimate of the frequency of severe adverse events for a given chemotherapy regimen.

<sup>a</sup>In a multivariate logistic regression for severe adverse events, adjusted for all the other variables in the table; Wald's test for P-value estimation.

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale-Geriatric; ECOG PS, Eastern Cooperative Oncology Group performance status.

Le type de cancer, l'indice de performance, les comorbidités, l'indice de masse corporelle et l'indice MAX2 étaient indépendamment associés à des toxicités de grades 3/4/5.

# Toxicités médicamenteuses

Receipt of chemotherapy  
Receipt of toxicity

Patients with severe comorbidity vs patients without severe comorbidity:

Mean number of chemotherapy cycles: 3.2 vs 3.5

Completed all four cycles: 65% vs 73%

Completed cycles without delay: 46% vs 59%

Dose reductions: 29% vs 35%

Second line systemic therapy: 27% vs 26%

RT: 35% vs 48%

Toxicity:

Grade 3–4 thrombocytopenia: 46% vs 36%

Thrombocytopenic bleedings: 3% vs 4%

Grade 3–4 neutropenia: 48% vs 42%

Neutropenic fevers: 12% vs 5%

Death from neutropenic infection: 3% vs 0%

Patients with comorbidity are less likely to complete all cycles of chemotherapy and have slightly more dose reductions. Thrombocytopenia and neutropenia are slightly more frequent among patients with comorbidity.

# Toxicités médicamenteuses

## Tous cancer

- CIRS>6; tox non hématologique

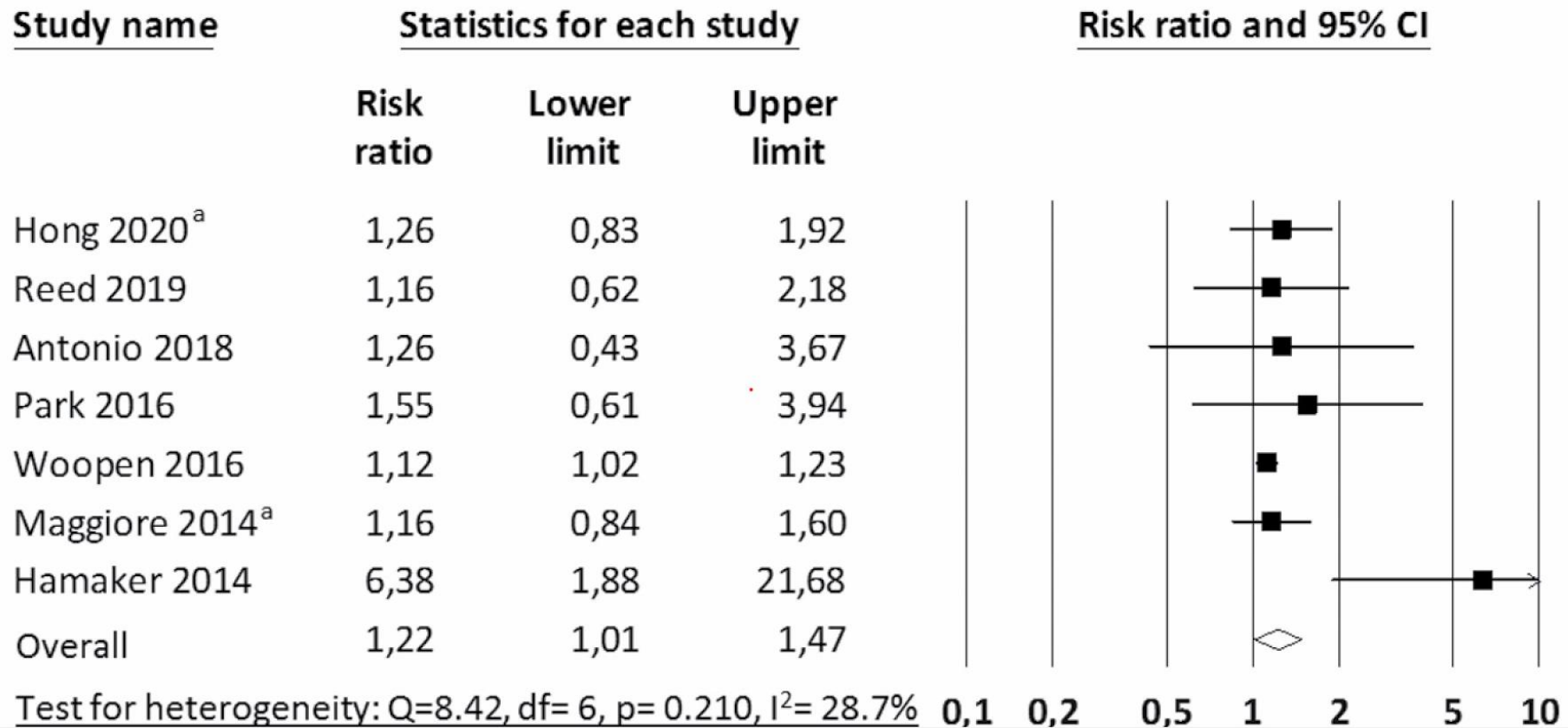
## Cancers spécifiques.....

- Cancer ovaire, Colorectal métastatique : pas toxicité augmentée
- Cancer colorectal, poumon, LLC : augmentations des complications globales
- En fonction des études : Sein

George M, Smith A, Sabesan S et al. *JMIR Cancer*. 2021 Oct 13;7(4):e26425.  
KH, Lee JJ, Kim J, Zhou JM et al. *J Geriatr Oncol*. 2019 Sep;10(5):733-741.  
Klepin HD, Pitcher BN, Ballman KV et al. *J Oncol Pract*. 2014 Sep;10(5):e285–92.  
Freyer G, Geay JF, Touzet S, et al. *Ann Oncol*. 2005 Nov;16(11):1795-800  
Marinello R, Marengo D, Roglia D, et al. *Arch Gerontol Geriatr*. 2009 Mar-Apr;48(2):222-6.  
Grønberg BH, Sundstrøm S, Kaasa S, et al. *Eur J Cancer*. 2010 Aug;46(12):2225-34.  
Jehn CF, Böning L, Kröning H, et al. *Eur J Cancer*. 2014 May;50(7):1269-75.  
Clough-Gorr KM, Stuck AE, Thwin SS, et al. *J Clin Oncol*. 2010 Jan 20;28(3):380-6.  
Jorgensen ML, Young JM, Dobbins TA, et al. *Med J Aust*. 2014 Apr 21;200(7):403-7.  
Goede V, Cramer P, Busch R et al. *Haematologica*. 2014 Jun 28;99(6):1095–100.

# Toxicités médicamenteuses

## G. Association of polypharmacy and treatment-related toxicity



# Radiothérapie

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## Recognizing Frailty in Radiation Oncology Clinical Practice: Current Evidence and Future Directions



Aideen Skelly, BSc (hons), and Anita O'Donovan, PhD

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The number of older adults presenting for radiation therapy is increasing, as many older adults may be excluded from receipt of surgery and chemotherapy due to multimorbidity or concerns about toxicity. For radiation oncologists, making decisions about appropriate treatment modalities for their older patients can be difficult. Comprehensive Geriatric Assessment (CGA) is recommended to aid the decision-making process in radiation oncology, in conjunction with the judicious use of frailty screening tools, which are the first step in identifying those who need a CGA. In this review, the current scientific evidence regarding screening tools and CGA will be appraised in the context of radiation oncology. Several screening tools that have been tested in radiation oncology are described, as well as how they have been combined (or not) with CGA. Current clinical practice is reviewed, and future directions for radiation oncology are discussed.

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Rien de spécifique

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## Predictors of Toxicity Among Older Adults with Cancer

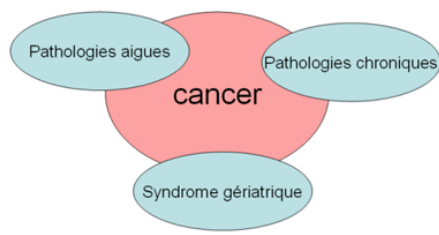


Martine Extermann, MD, PhD,\* Indrin J. Chetty, PhD,<sup>†</sup> Stephen L. Brown, MD,<sup>‡</sup>  
Mohammed Al-Jumayli, MD,\* and Benjamin Movsas, MD<sup>§</sup>

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An increasing number of cancer patients are of advanced age as the incidence of cancer increases with age. In this article, the clinical predictors of toxicity that may help in treatment selection are addressed, as well as mitigators of toxicity. The potential of artificial intelligence to enable further progress in the understanding of the interaction of age and tolerance to radiation is reviewed. The final section reviews the literature on patient-related outcomes for older patients.

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## Take home message

### Toxicités et Comorbidités

Nécessiter de les connaître, de les prévenir, de les traiter et de les intégrer dans le plan de soins et dans la recherche.