Measures of comorbidity

Development and applications

Marcus Westerberg

Department of surgical sciences

Uppsala University

FMS spring meeting

2023-03-30

About me

Background

2012 Umeå ➡ Uppsala

2012-2015 BSc Mathematics

Department of Mathematics, Uppsala University

2015-2017 MSc Mathematics

Department of Mathematics, Uppsala University

2017-2022 PhD Applied Mathematics and Statistics, Centre for Interdisciplinary Mathematics (CIM)

Department of Mathematics and Department of Surgical Sciences, Uppsala University

Rolf Larsson, Pär Stattin, Hans Garmo

Thesis

Prostate cancer incidence, treatment and mortality:

Empirical longitudinal register-based studies and methods for handling missing data

Interests

Prostate cancer, colorectal cancer (SCREESCO, 20% PostDoc at KI)

Survival analysis, longitudinal studies, missing data, comorbidity,…

Undertreatment of prostate cancer

Radical treatment: radical prostatectomy (surgery) or radiotherapy

- beneficial for men with advanced prostate cancer
- **guidelines:** should be considered if life expectancy ≥ 5 years

Swedish study (2015): use of radical treatment was

- lower in older men with no comorbidity
- than in younger men with some comorbidity

} similar life expectancy based on age and CCI

Bratt O, et al. Undertreatment of men in their seventies with high-risk nonmetastatic prostate cancer. *European urology*, 2015, 68.1: 53-58.

Question: Could undertreatment be explained by additional unmeasured comorbidity?

Outline

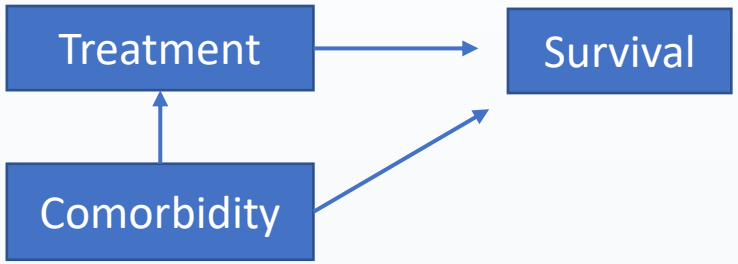
1. Some existing measures of comorbidity
2. Development of a *multidimensional* comorbidity index (under review)
3. Two applications (work in progress)
4. Discussion

What is comorbidity?

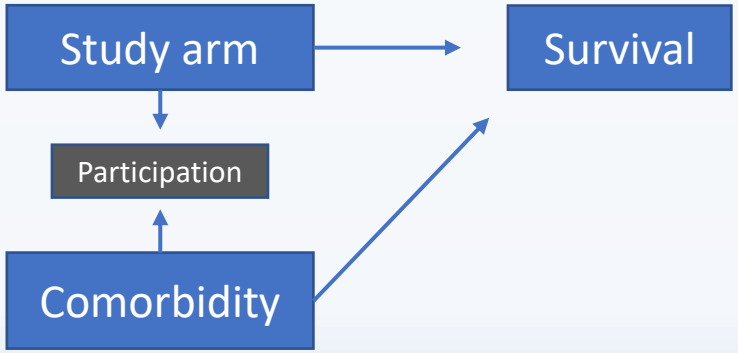
Combination of all other conditions

Use in epidemiology

- Description of cohort characteristics
- Adjustment for confounding



- Handle treatment selection or study participation



- Prediction of survival and life-expectancy

Comorbidity measure

One or more variables that may describe comorbidity

Example: Performance status (ECOG-PS)

Scale 0-4

0 = fully active, 4 = completely disabled

Charlson index (CCI), 1987

Charlson, ME, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases*, 1987, 40.5: 373-383.

Development

559 medical patients admitted during one month in 1984 to New York Hospital

1-year mortality

Validation

- 685 patients with breast cancer at Yale New Haven Hospital 1962 to 1969
- Censoring at cancer deaths
- Cox PH model

Results

Point system 0, 1, 2, 3,…

Discriminates risk of death

Validation: 86% with CCI = 0

”Swedish” Charlson index, 2021

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

METHODOLOGY

Adaptation of the Charlson Comorbidity Index for Register-Based Research in Sweden

This article was published in the following Dove Press journal:
Clinical Epidemiology

Jonas F Ludvigsson,[1–4] Peter Appelros,[5] Johan Askling,[6,7] Liisa Byberg,[8] Juan-Jesus Carrero,[1] Anna Mia Ekström,[9,10] Magnus Ekström,[11] Karin Ekström Smedby,[6] Hannes Hagström,[12–14] Stefan James,[15,16] Bengt Järvholm,[17] Karl Michaelsson,[8] Nancy L Pedersen,[18] Helene Sundelin,[19,20] Kristina Sundquist,[21] Johan Sundström[22–24]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [2]Department of Pediatrics, Orebro University Hospital, Orebro, Sweden; [3]Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK; [4]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA; [5]University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro SE-701 82, Sweden; [6]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [7]Rheumatology, Theme Inflammation and Infection, Karolinska University Hospital, Stockholm, Sweden; [8]Department of Surgical Sciences, Uppsala

Purpose: Comorbidity indices are often used to measure comorbidities in register-based research. We aimed to adapt the Charlson comorbidity index (CCI) to a Swedish setting.

Methods: Four versions of the CCI were compared and evaluated by disease-specific experts.

Results: We created a cohesive coding system for CCI to 1) harmonize the content between different international classification of disease codes (ICD-7,8,9,10), 2) delete incorrect codes, 3) enhance the distinction between mild, moderate or severe disease (and between diabetes with and without end-organ damage), 4) minimize duplication of codes, and 5) briefly explain the meaning of individual codes in writing.

Conclusion: This work may provide an integrated and efficient coding algorithm for CCI to be used in medical register-based research in Sweden.

Keywords: Charlson comorbidity score, comorbidity, disease, epidemiology, public health, Sweden

Adapted CCI

- Based on ICD codes from the Patient Register

1 point

- Myocardial infarction
- Congestive heart failure
- Peripheral vascular disease
- Dementia
- Cerebrovascular disease
- Chronic lung disease
- Connective tissue disease
- Ulcer
- Chronic liver disease
- Diabetes

2 points

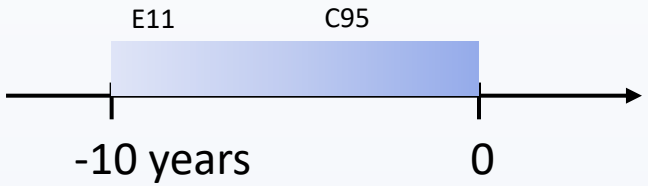
- Hemiplegia
- Moderate or severe kidney disease
- Diabetes with end-organ damage
- Tumor
- Leukemia
- Lymphoma

3 points

- Moderate or severe liver disease

6 points

- Tumor metastasis or AIDS



Ludvigsson JF, et al. Adaptation of the Charlson Comorbidity Index for Register-Based Research in Sweden. Clinical epidemiology. 2021;13:21-41.

Strengths and limitations with CCI

- Simple, transparent

- Selection of comorbidity categories may exclude important information
- Definitions and weights may be outdated (AIDS – 6 points)
- Better: use the individual disease categories?
- Most have CCI 0

CCI	
0	66%
1	14%
2	12%
3+	8%

ICD codes - hospitalization or specialist out-patient care

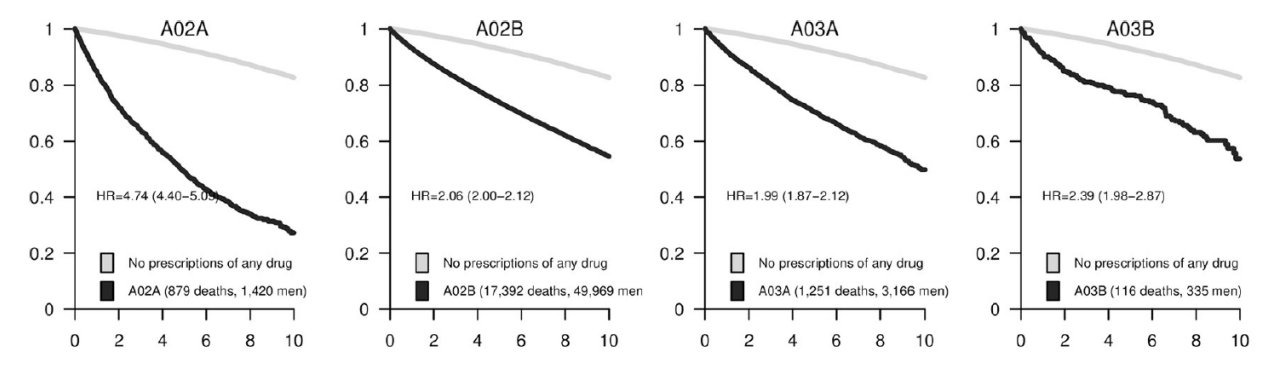
ATC codes - primary care

A Drug Comorbidity Index (DCI), 2021

Drug prescriptions can predict mortality

Gedeborg R, et al. Prescription-based prediction of baseline mortality risk among older men. PLoS ONE 2020; 15(10): e0241439.

ATC-group A: Antacids



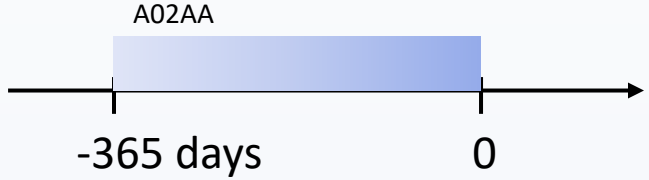
Development in men and validation in women, and vice versa

	C-index
DCI:	0.73 in men 0.76 in women
CCI:	0.67 in men 0.69 in women

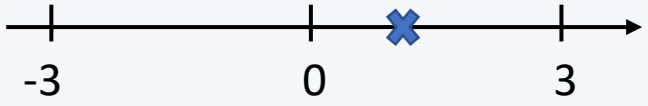
DCI improved prediction of survival in addition to age and CCI

Gedeborg R, et al. An Aggregated Comorbidity Measure Based on History of Filled Drug Prescriptions: Development and Evaluation in Two Separate Cohorts. *Epidemiology*. 2021;32(4):607-615.

- Prescribed Drug Register (ATC codes)
- Each selected ATC code is given a specific weight/point



All ATC codes → Just above 100 codes in the final DCI



A DCI for men with CRPC, 2021

Fallara G et al. A drug comorbidity index to predict mortality in men with castration resistant prostate cancer. *PLoS One*. 2021;16(7):e0255239. Published 2021 Jul 28.

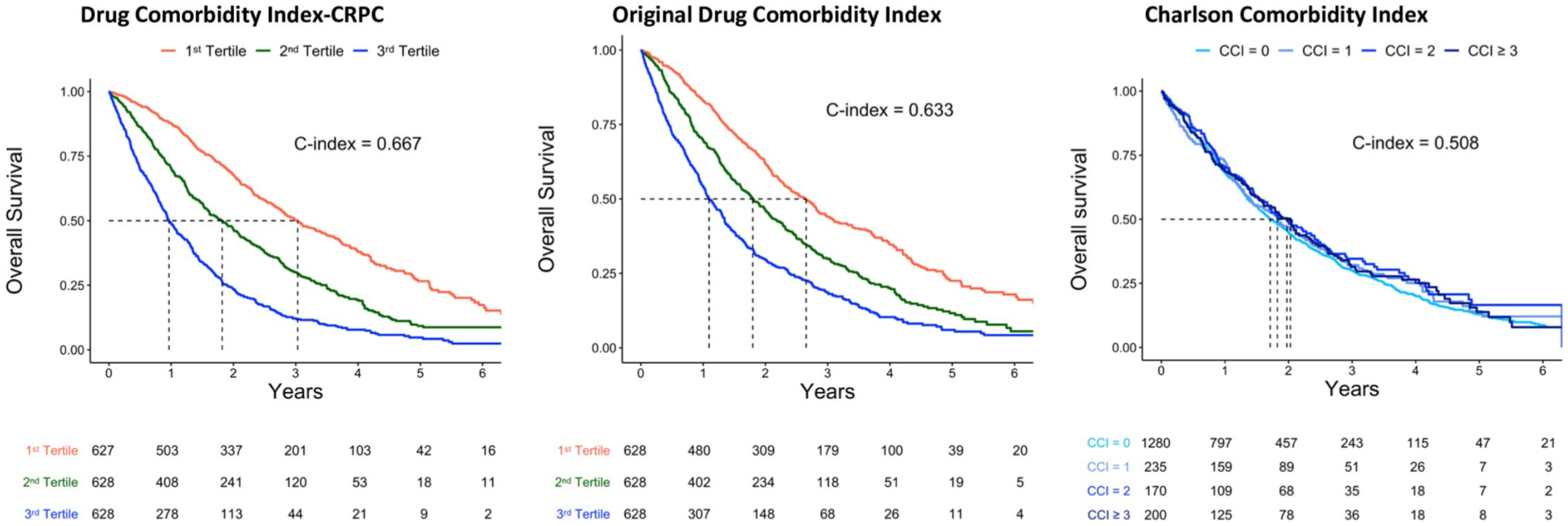


Fig 1. Overall survival for 1885 men with castration resistant prostate cancer (CRPC), stratified in tertiles of the Drug Comorbidity Index developed for CRPC (DCI-CRPC), the original DCI, and the Charlson Comorbidity Index.

A limitation with CCI and DCI

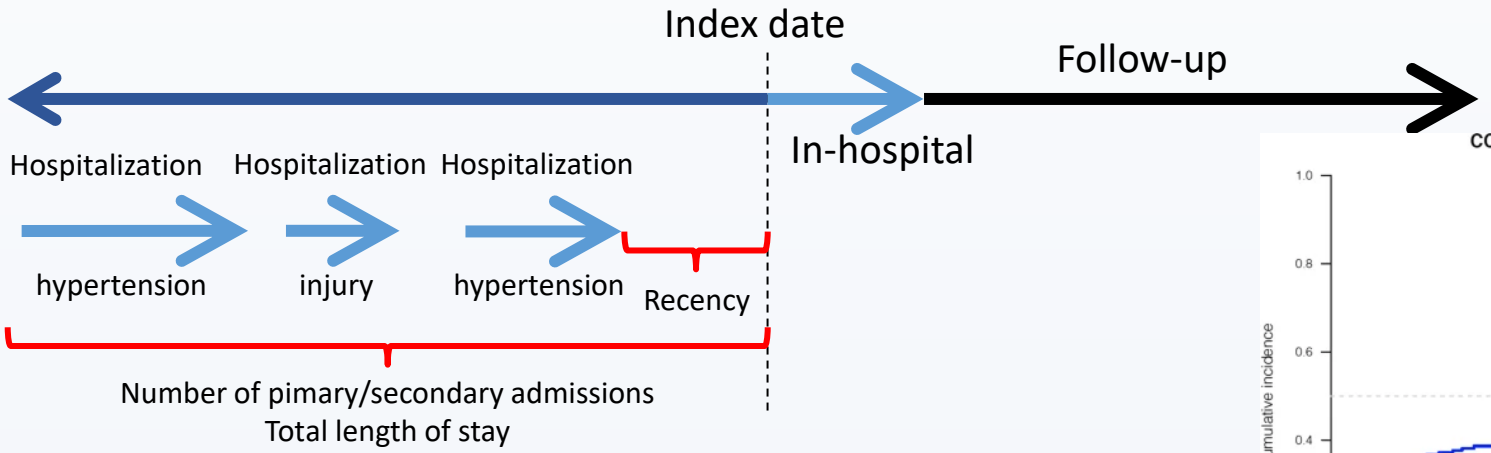
Do not account for additional dimensions, e.g. frequency, recency and duration of hospitalization!

Swedish study of patients at intensive care units (2022)

Aronsson Dannewitz A, et al. Optimized diagnosis-based comorbidity measures for all-cause mortality prediction in a national population-based ICU population. *Crit Care*. 2022;26(1):306.

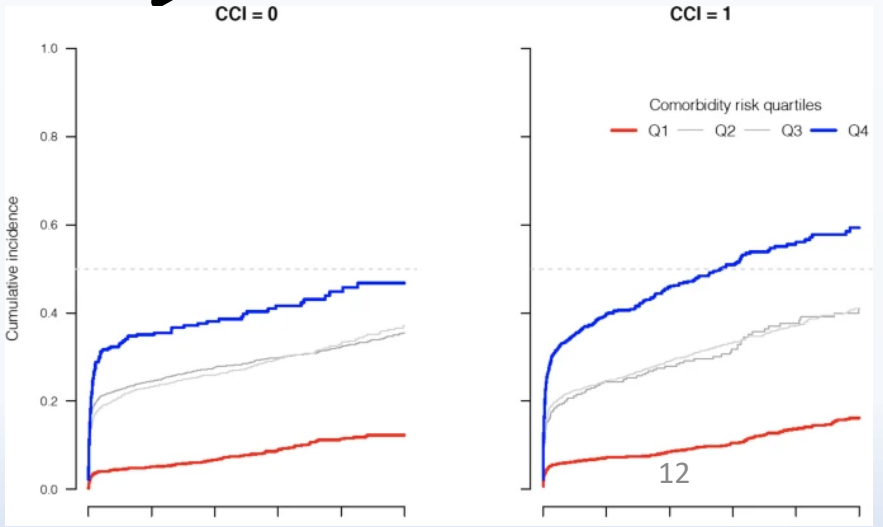
- Data from the Swedish Intensive Care Registry
- 36 different comorbidity categories (infectious disease, hypertension, injury,…)

Definitions



Results

- Summary score performed better than CCI for predicting mortality
- Separation of risk of death within strata of age and CCI

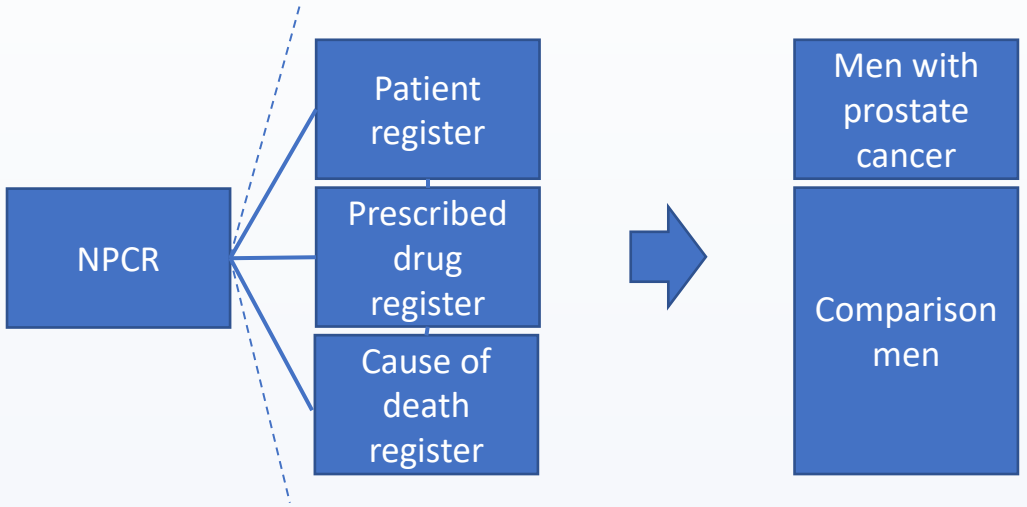


Development of the MDCI

Multidimensional Diagnosis-based Comorbidity Index

Development of the MDCI

Data: All men in Prostate Cancer data Base Sweden version 5 (PCBaSe 5) diagnosed 2008-2014



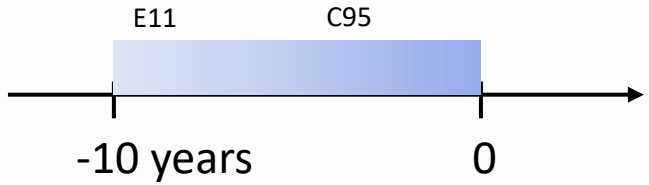
- Random sample from the Swedish male population
- 5 men identified at date of diagnosis for each case
- Without prostate cancer diagnosis at index date
- Matched by age, county of residence

- **Development cohort**: comparison men with index date between 2008 and 2013 (N=286,688)
- **Validation cohort 1:** comparison men with an index date in 2014 (N=54,539)
- **Validation cohort 2:** all prostate cancer cases diagnosed between 2008 and 2014 (N=68,357)

Development of the MDCI (short version)

The Patient Register

All ICD-10 codes (10,000 unique codes)



Data cleaning (explained soon)

➡ *Cleaned and processed codes*

Predictors

Occurrence: primary *or* secondary diagnosis within 10 years

Recency: primary diagnosis within 90, 180 and 365 days

Frequency: primary diagnosis at ≥2, ≥3, or ≥4 unique dates

Duration: number of days (≥7, ≥14) hospitalized with primary diagnosis

= 10 predictors per code

MDCI: Code structure and use

The character positions in a code indicate disease subcategories

I7: *Diseases of arteries, arterioles and capillaries*

I73: *Other peripheral vascular diseases*

I731: *Thromboangiitis obliterans*

I739: *Peripheral vascular disease unspecified*

I738: *Other specified diseases of peripheral vessels*

I738A: *Acrocyanosis*

I738B: *Acroparesthesia*

MDCI: Code processing

Extracted: unique registrations (ID + code + date)
Created: 4 versions of the Patient Register

Two characters

I73 → I7
I731 → I7
I738 → I7

Three characters

I73 → I73
I731 → I73
I738 → I73

Four characters

I73 → I739 (unspecified)
I731 → I731
I738 → I738

Five characters

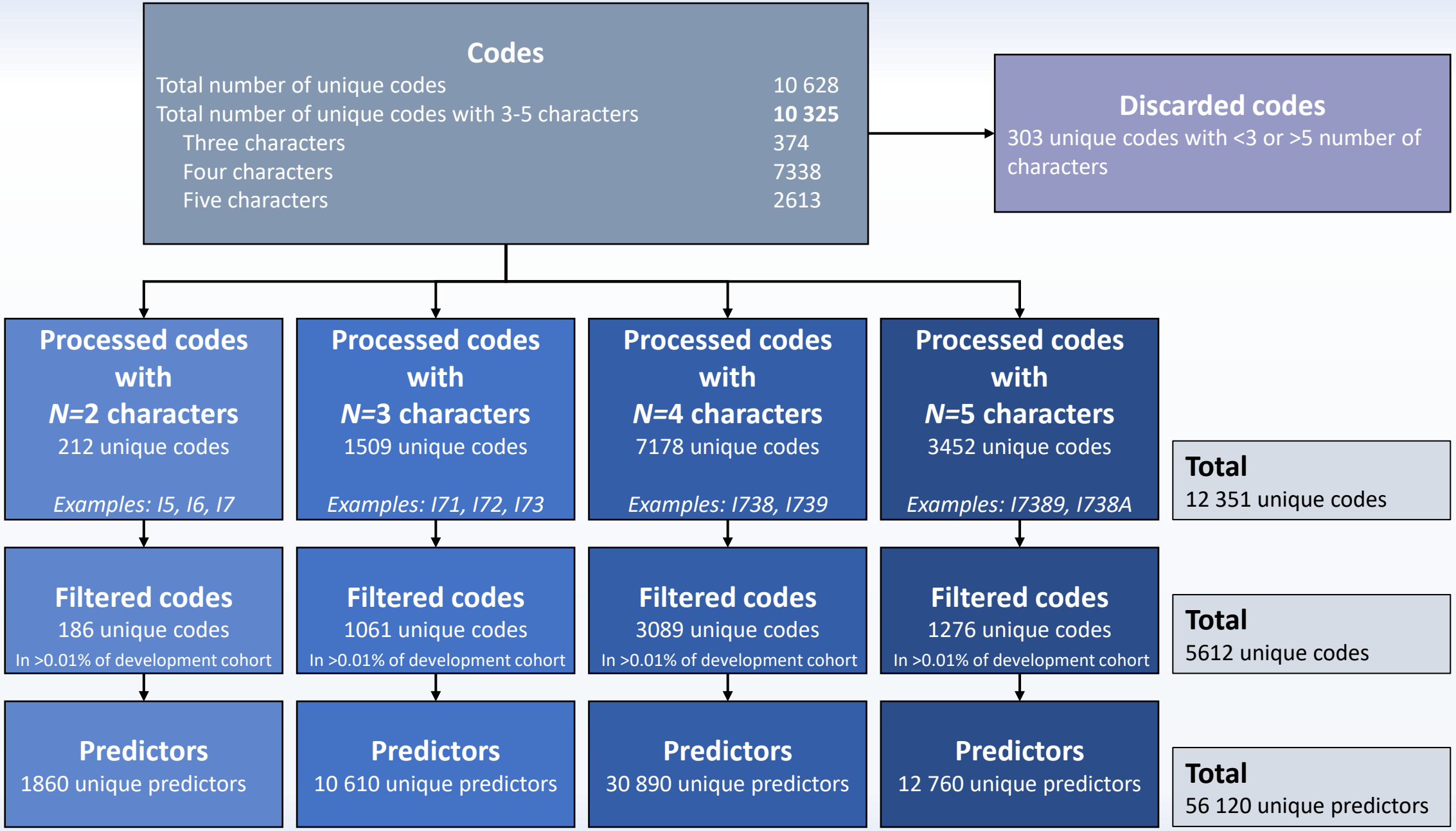
I73 → I7399
I731 → I7319
I7381 → I7381

I738 → I73899
I7381 → I7381

Scenario A

I738 → ⛔ I73899

Scenario B


Codes
Total number of unique codes 10 628
Total number of unique codes with 3-5 characters 10 325
Three characters 374
Four characters 7338
Five characters 2613
Discarded codes
303 unique codes with <3 or >5 number of characters
Processed codes with N=2 characters
212 unique codes
Examples: I5, I6, I7
Processed codes with N=3 characters
1509 unique codes
Examples: I71, I72, I73
Processed codes with N=4 characters
7178 unique codes
Examples: I738, I739
Processed codes with N=5 characters
3452 unique codes
Examples: I7389, I738A
Total
12 351 unique codes
Filtered codes
186 unique codes
In >0.01% of development cohort
Filtered codes
1061 unique codes
In >0.01% of development cohort
Filtered codes
3089 unique codes
In >0.01% of development cohort
Filtered codes
1276 unique codes
In >0.01% of development cohort
Total
5612 unique codes
Predictors
1860 unique predictors
Predictors
10 610 unique predictors
Predictors
30 890 unique predictors
Predictors
12 760 unique predictors
Total
56 120 unique predictors

Multidimensional Diagnosis-based Comorbidity Index (MDCI)

Outcome: death by any cause within 10 years from index date

Model selection: regularized Cox regression (elastic net)

R package *glmnet*

$$\lambda\left[(1-\alpha)\sum_j \beta_j^2/2 + \alpha\sum_j |\beta|_j\right]$$

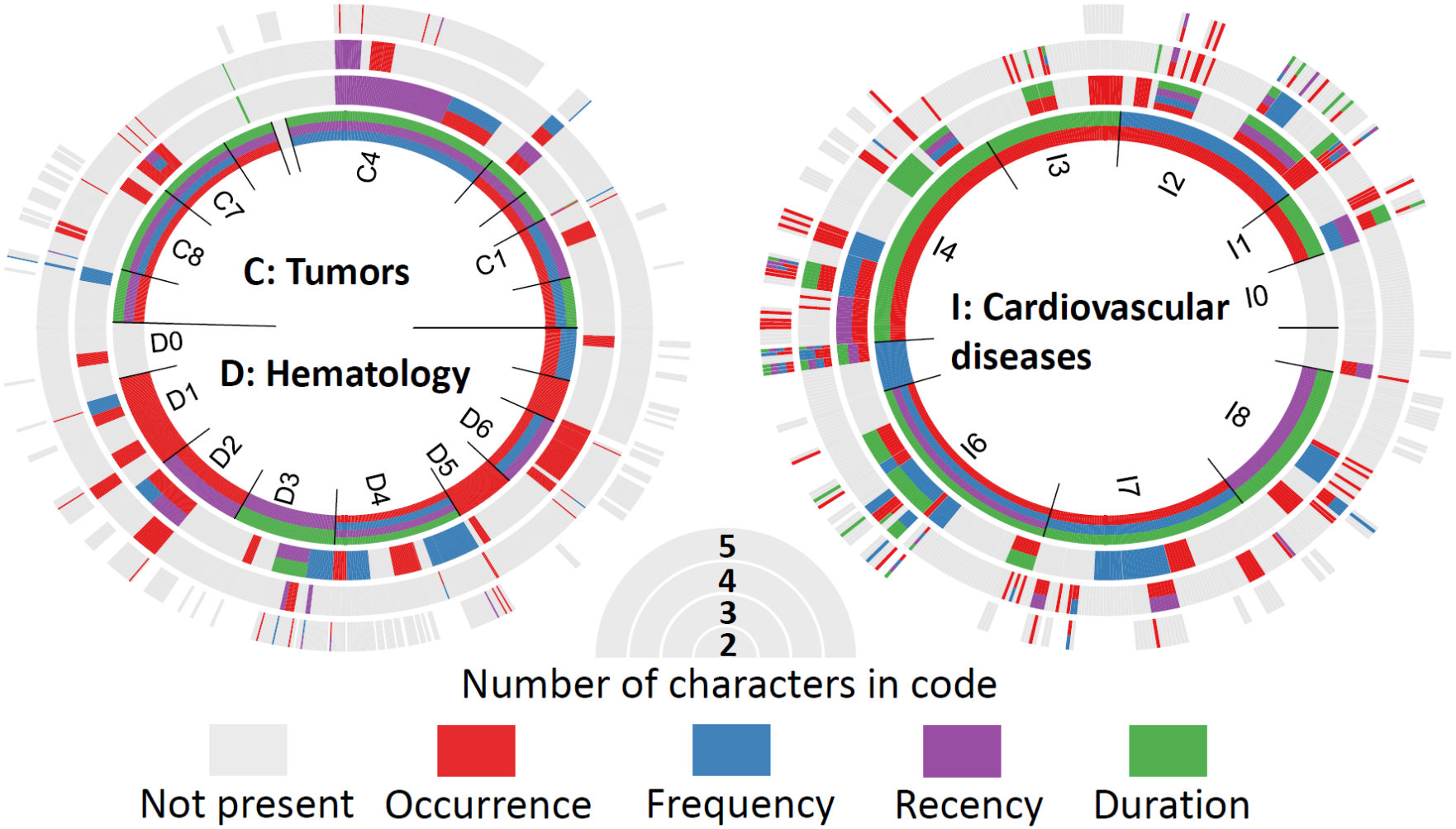
- α = 0.5
- 10-fold cross-validation
- Selected the λ with the largest C-index

Final model	
Unique codes	978
Predictors	1543

MDCI
= linear predictor
= sum of code-specific predictor x weight

Prognostic factors present in selected model

Occurrence: 870 (56%) Frequency: 261 (17%) Recency: 264 (17%) Duration:148 (10%)



Results: MDCI vs DCI vs CCI

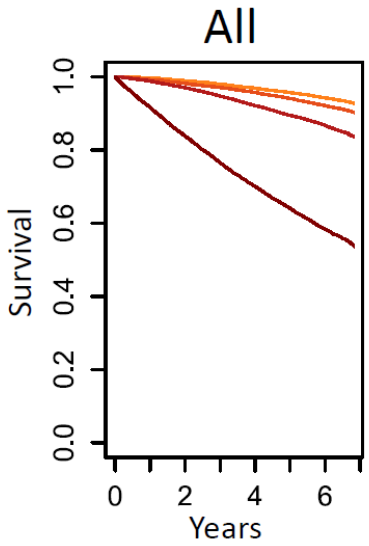
C-indices in the validation cohorts

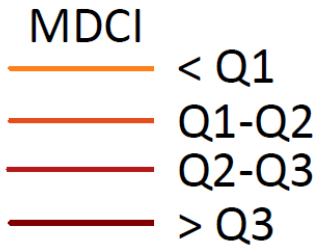
	Validation cohort of men **without** prostate cancer	Validation cohort of men **with** prostate cancer
1 year of follow-up		
MDCI	0.842	0.794
CCI	0.758	0.683
DCI	0.804	0.731

10 years of follow-up		
MDCI	0.757	0.702
CCI	0.688	0.628
DCI	0.732	0.666

MDCI vs DCI vs CCI

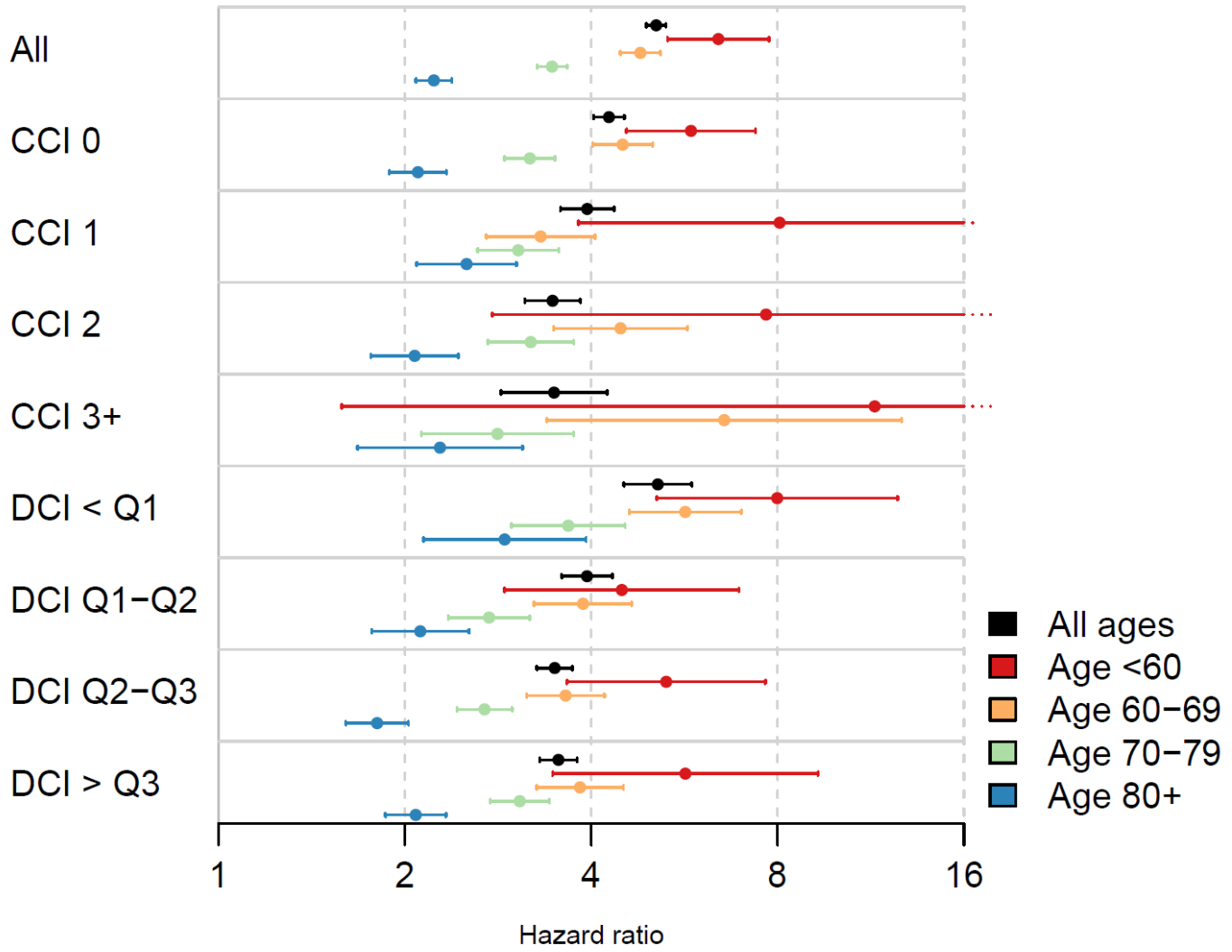
Survival in validation cohort 2 (men with prostate cancer)





MDCI vs DCI vs CCI

1-year hazard ratio >Q3 vs <Q1 (reference)
in validation cohort 1 (comparison men)



Application 1

MDCI and DCI vs CCI

Adjustment for confounding

Adjustment for confounding

Background

- Radiotherapy (RT) and radical prostatectomy (RP) for nonmetastatic prostate cancer reduce mortality
- Comparable 10-year mortality in the ProtecT study

  Hamdy FC, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med. 2016;375:1415-24.

Real life: Older more fragile men with higher prostate cancer burden more often receive RT than RP

Material

All men in PCBaSe 5 diagnosed 2008-2019, ≤85 years old

PSA<20 ng/ml, Gleason sum 6-7, and T1c/T2 and no verified bone metastases

Initiated primary RT with curative intent (N=23,000) or

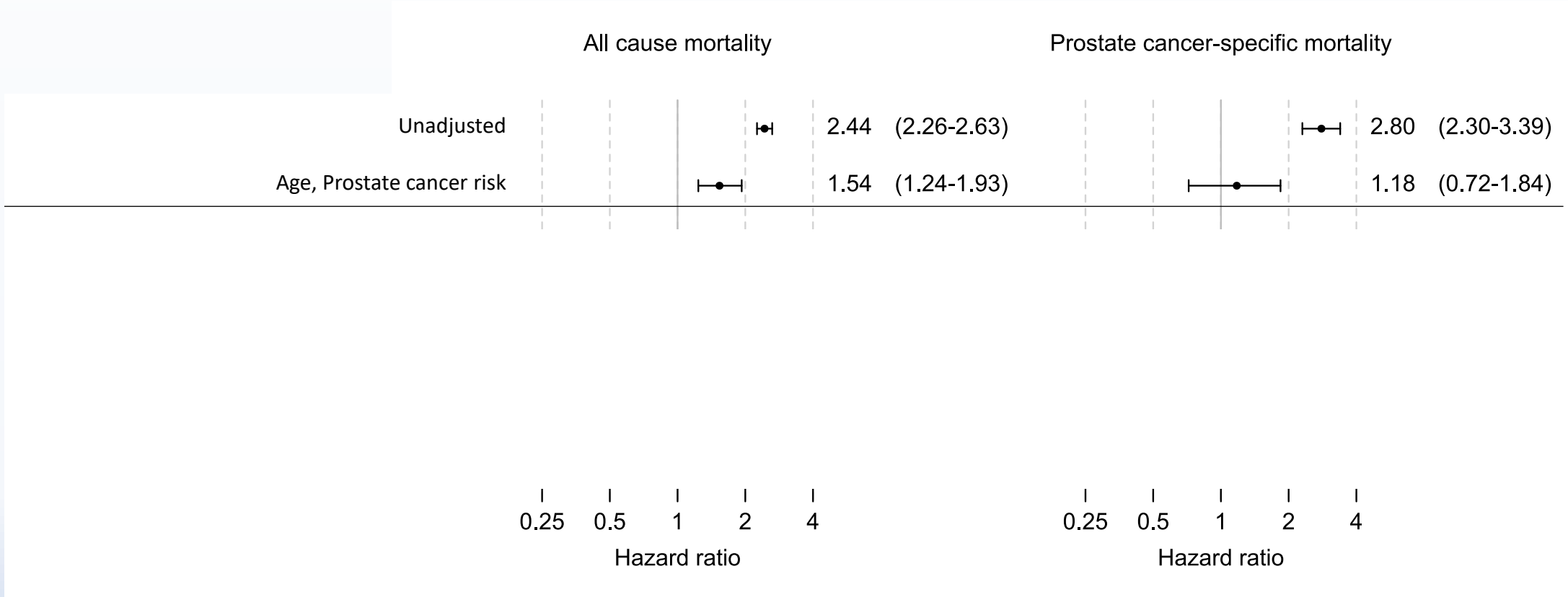
primary RP (N=10,000)

within one year of diagnosis

Adjustment for confounding

Unadjusted 10-year overall mortality	Unadjusted 10-year prostate cancer-specific mortality
RP: **9.5%**	**1.7%**
RT: **22.1%**	**5.0%**

10-year hazard ratio (RT/RP)



Application 2
Prediction of ECOG-PS

Prediction of ECOG-PS

Background

ECOG-PS often used for selection in RCTs (e.g. ECOG-PS 0-2)

Often not measured/recorded in quality registers

Material

- All men in PCBaSe 5 diagnosed with prostate cancer
- Registered in the Patient-overview Prostate Cancer (PPC/IPÖ)
- All unique dates of contacts (in-person or by telephone) between 2014 and 2020
- With recorded ECOG-PS

Methods

Outcome:
ECOG-PS 0-2 (positive) vs 3-4 (negative)

Predictors
Age, CCI, DCI, MDCI

Models**:** logistic regression (GAM, *mgcv*)

ROC curves

Bootstrap 95% CIs (B=2000)

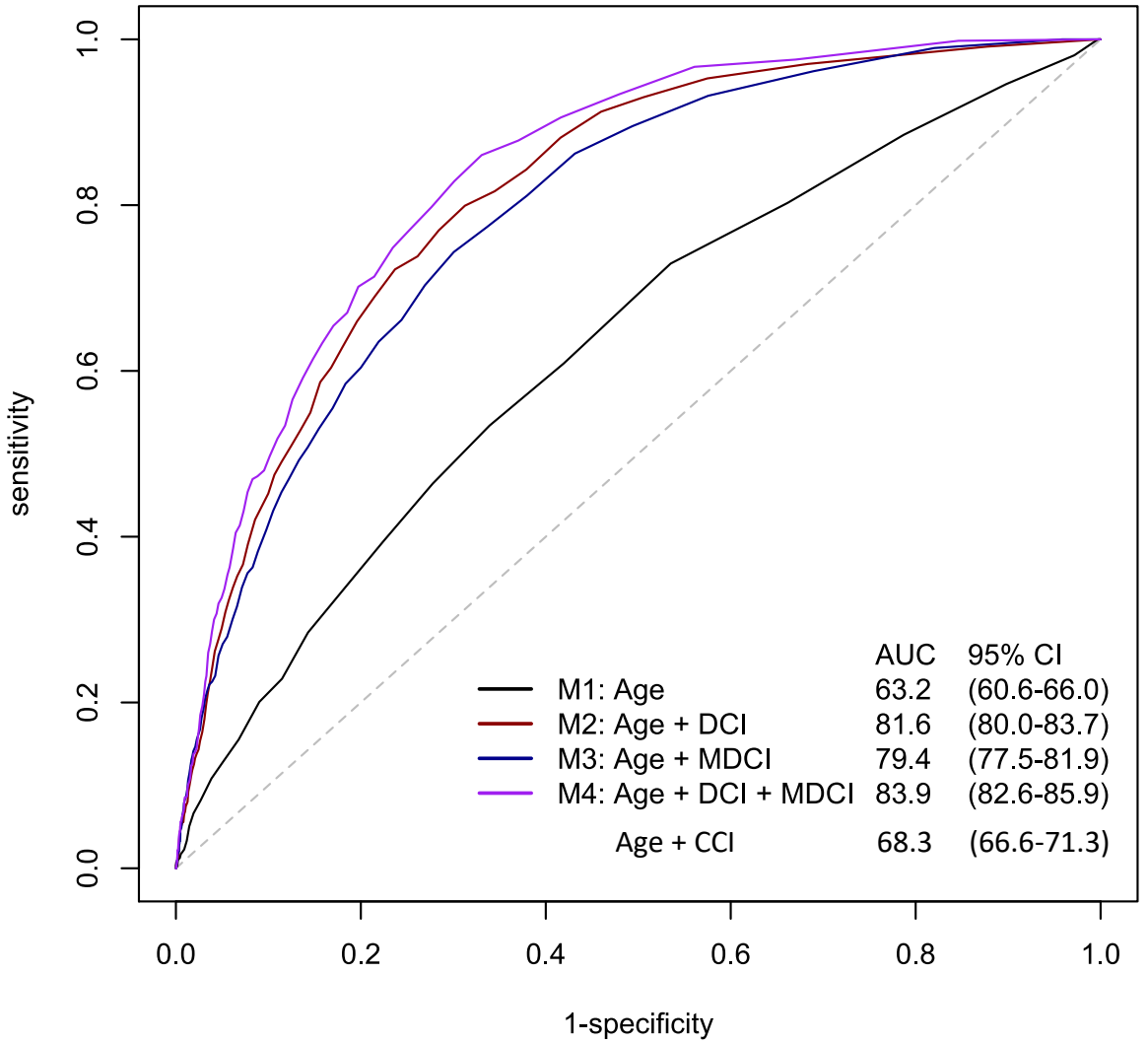
Prediction of ECOG-PS

Population and results

3752 eligible individuals
12,057 contacts/visits

ECOG-PS 0:	N=5708
ECOG-PS 1:	N=3997
ECOG-PS 2:	N=1779
ECOG-PS 3-4:	N=573 (5%)

Complementary analyses
ECOG-PS 0-1 vs 2-4
ECOG-PS 0 vs 1-4



Discussion

Use of administrative databases (coverage, coding errors)

Generalizability of the DCI and MDCI

- Women and younger age groups
- General population, other health care systems
- Temporal and regional variations
- New diagnoses, changing risk of death
- New developments in treatments and use
  - new medicines and changes in use
- No claim to be valid in other settings/countries and over time
  - derive specific weights if possible
- Hospital medications?

Summary

- DCI and MDCI improve prediction of mortality
  - beyond age and CCI
- DCI+MDCI can increase granularity in estimation of baseline mortality risk:
  - seem to capture some wider aspects of ”frailty”
- Useful to consider additional dimensions (recency,…)
- CCI may not be sufficient for confounding adjustment
- Age + MDCI + DCI are predictive of performance status

Acknowledgements

Hans Garmo

Sandra Irenaeus

Rolf Gedeborg

Pär Stattin

NPCR

Funding: Swedish Cancer Society, Region Uppsala

Contact

Marcus Westerberg

marcus.westerberg@uu.se

Department of surgical sciences, Uppsala University