Routes taken and length of stay after hospital admission with COVID-19: Results and statistical challenges

Centre for Statistical Methodology seminar

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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Different investigation types

I. **Description**

II. **Prediction**

III. **Causality and explanation**

Hernan, Hsu, Healy. A second chance to get causal inference right: a classification of data science tasks. Chance 2019; 32:42-49.

Different investigation types

I. **Description**

Today!

II. **Prediction**

Elizabeth Williamson, CSM seminar, 2nd December

Predicting risk of COVID-19 mortality in the general population

III. **Causality and explanation**

Karla Diaz-Ordaz, Ruth Keogh, CSM seminar, 9th December

Emulating target trials to estimate the effects of dynamic ventilation strategies for patients hospitalised with Covid-19

Hernan, Hsu, Healy. A second chance to get causal inference right: a classification of data science tasks. Chance 2019; 32:42-49.

Data

International Severe Acute Respiratory and emerging Infections Consortium WHO Clinical Characterisation Protocol UK (ISARIC WHO CCP-UK)

- Established following the H1N1 pandemic (2009) and emergence of MERS (2012)
- Key component is the COVID19 Clinical Information Network (CO-CIN)

COVID19 Clinical Information Network (CO-CIN)

- clinical care data in near-real time from 260 hospitals
- patients admitted to hospital in England, Scotland, and Wales since January 2020
- >100,000 patients included

Docherty AB, Harrison EM, Green CA, et al. Features of 20,133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985. doi: https://doi.org/10.1136/bmj.m1985

Questions

1. What are the risks of ICU admission and death?
   - by sex, age, presence of comorbidities

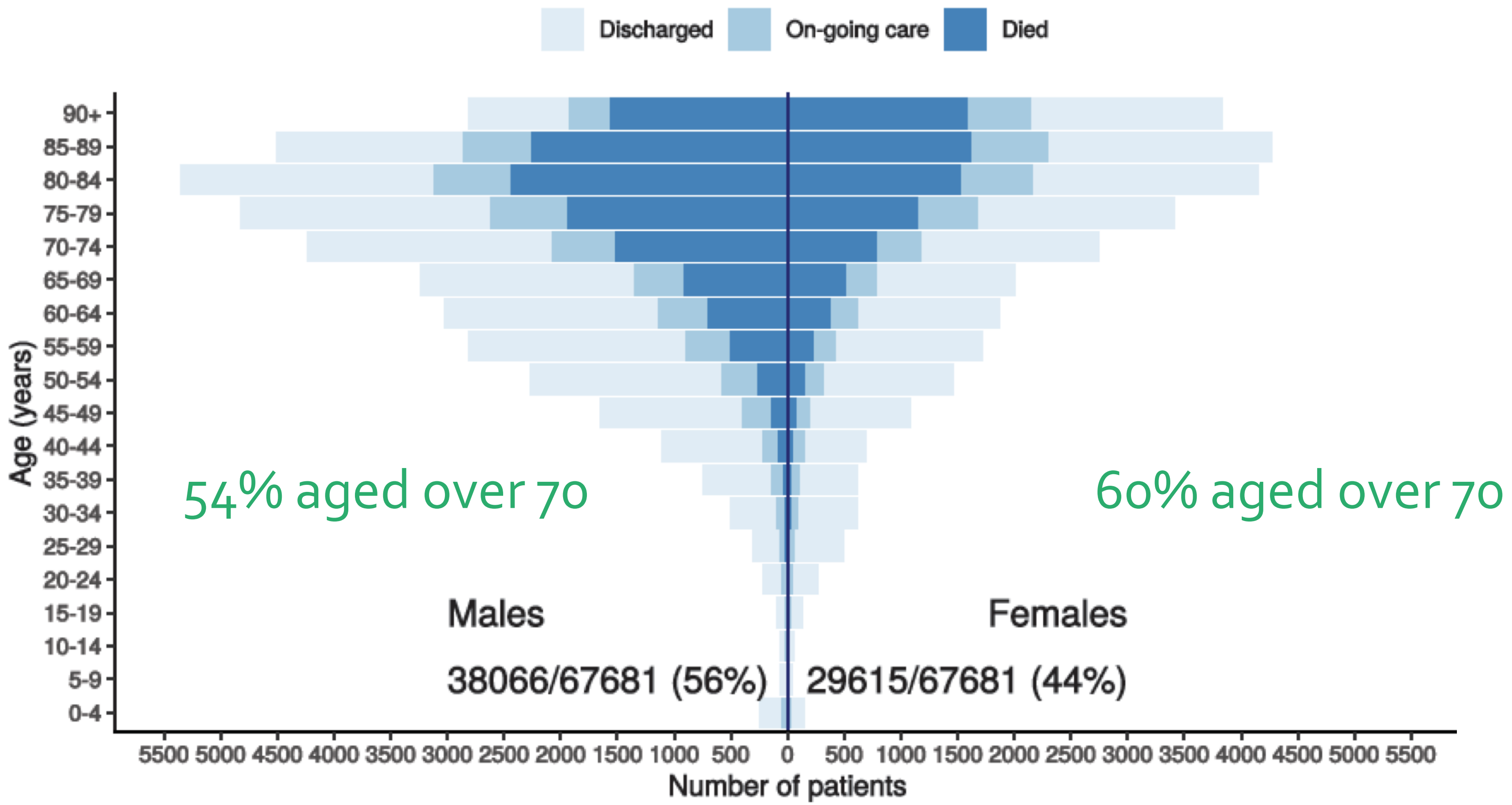
2. How do patients progress through their hospital stay?
   - by sex, age, presence of comorbidities

3. How long do people stay in the hospital ward and in ICU?

4. What are the risks of hospital admission?
   - by sex, age, presence of comorbidities

We undertook a descriptive analysis using CO-CIN data on 43256 people admitted to hospital between 11 March and 19 July with proven or high likelihood of SARS-Cov-2 infection

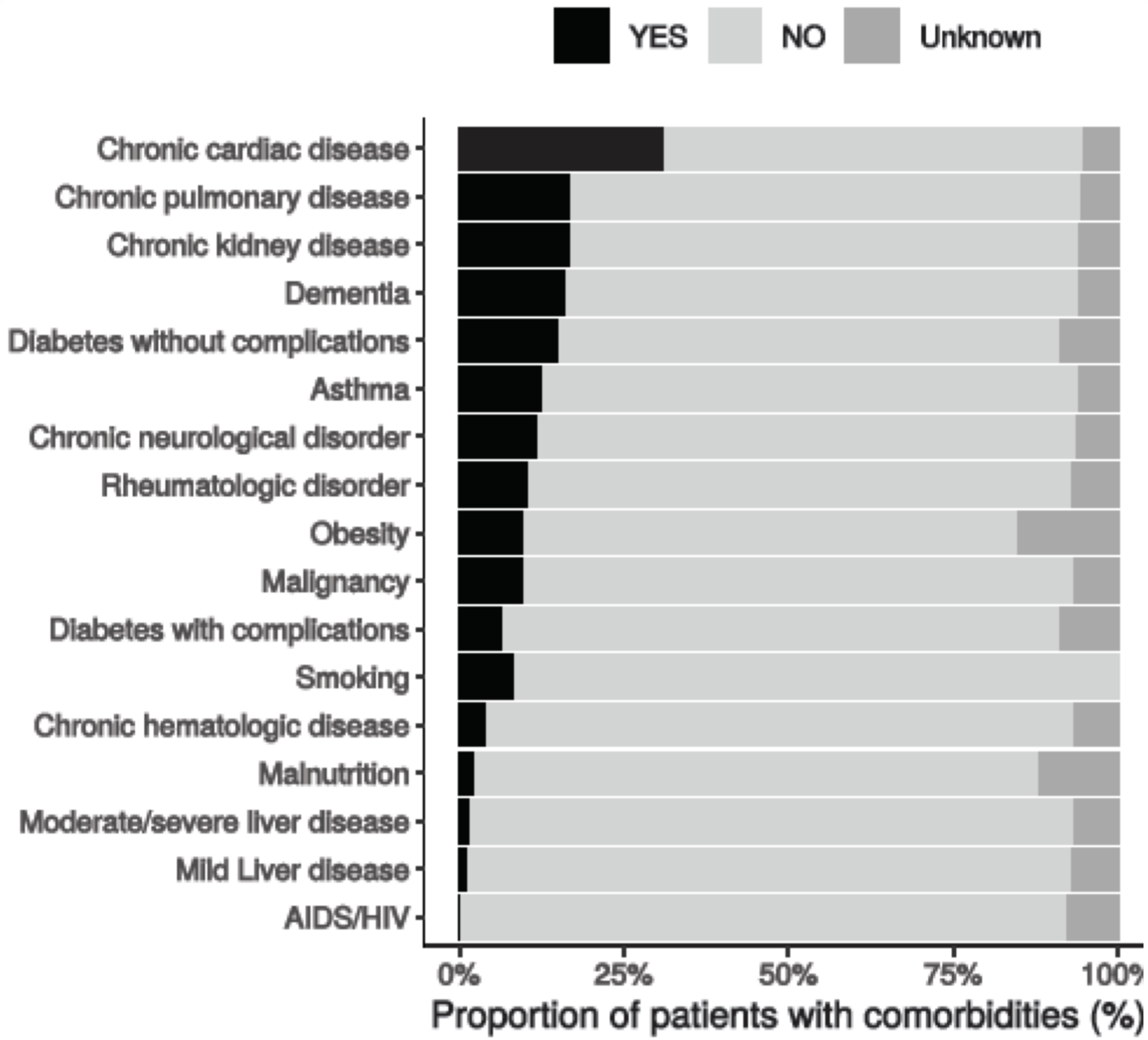
CO-CIN data characteristics



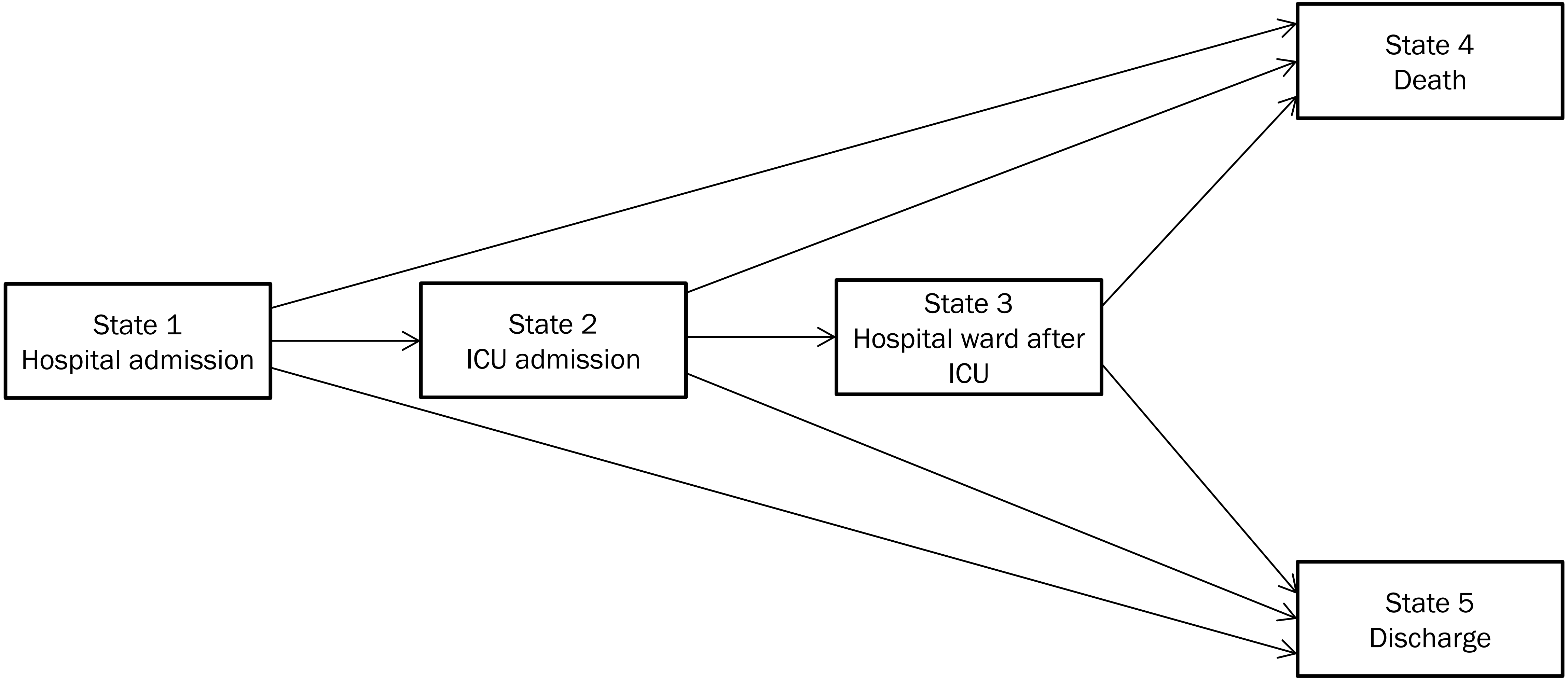
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/907617/s0652-dynamic-co-cin-report-sage-48.pdf

CO-CIN data characteristics

- 80% of patients had at least one comorbidity
- Many patients with multiple comorbidities



Multi-state model



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4. What are the risks of hospital admission?
   - by sex, age, presence of comorbidities

We undertook a descriptive analysis using CO-CIN data on 43256 people admitted to hospital between 11 March and 19 July with proven or high likelihood of SARS-Cov-2 infection

1. What are the risks of ICU admission and death?

Methods: risk of death

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Aim: to estimate risk of death by age group and sex

- For all individuals
- For individuals with each comorbidity individually
- For individuals with no comorbidities

Considerations

- Discharge from hospital is a competing event
- What about a standard survival analysis with 'censoring' at discharge – doesn't take into account that people discharged are no longer at risk of death in hospital

Methods

- Fine & Gray analysis for competing risks
- Each model includes age as a continuous variable modelled using a spline
- Results converted into cumulative incidences (aka 'risks')

Absolute risk of death: males

RESULTS OMITTED

Absolute risk of death: females

RESULTS OMITTED

Risk ratios for death: males

RESULTS OMITTED

Risk ratios for death: females

RESULTS OMITTED

Methods: risk of ICU admission

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Aim: to estimate risk of ICU admission by age group and sex

- For all individuals
- For individuals with each comorbidity individually
- For individuals with no comorbidities

Considerations

- Death and discharge from hospital are competing events

Methods

- Fine & Gray analysis for competing risks
- Each model includes age as a continuous variable modelled using a spline
- Results converted into cumulative incidences (aka 'risks') by age group

Absolute risk of ICU admission: males

RESULTS OMITTED

Absolute risk of ICU admission: females

RESULTS OMITTED

Risk ratios for ICU admission: males

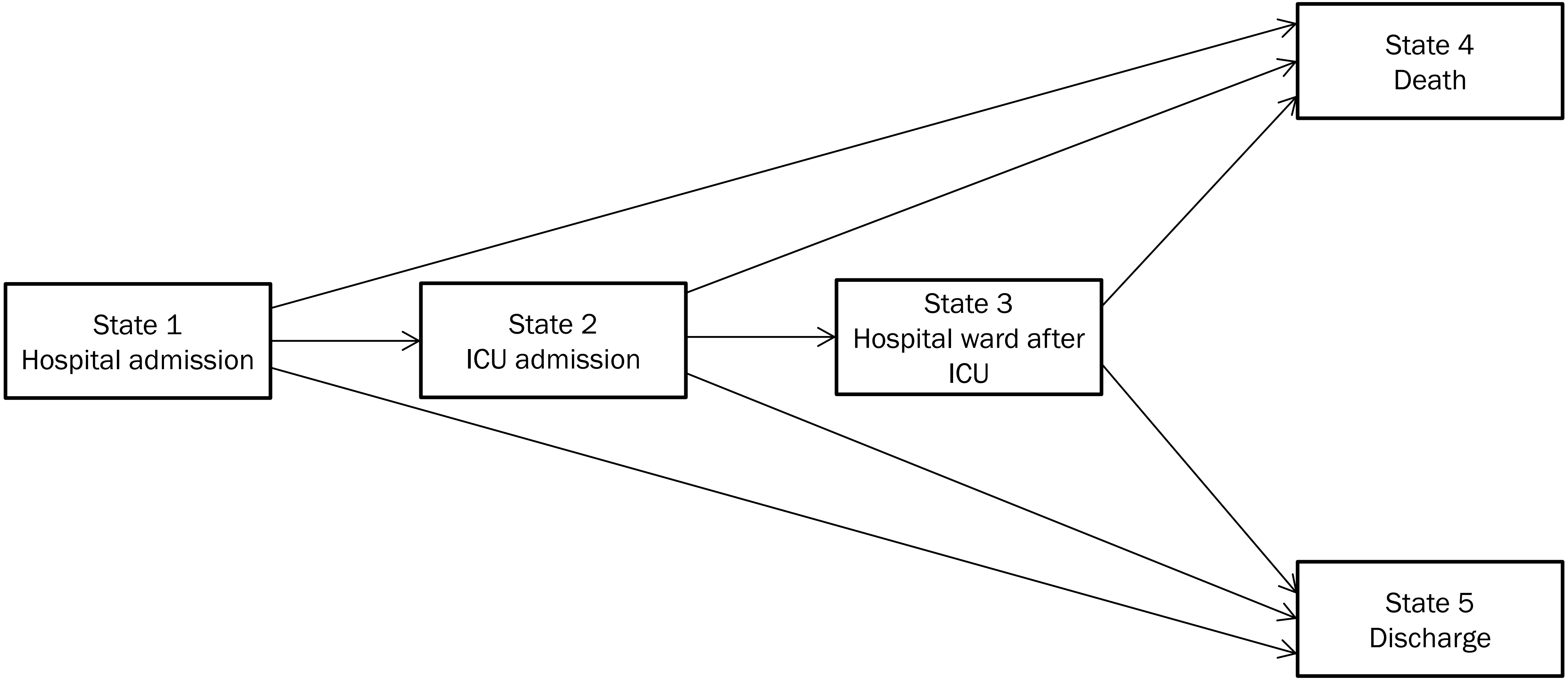
RESULTS OMITTED

Risk ratios for ICU admission: females

RESULTS OMITTED

2. How do patients progress through their hospital stay?

Multi-state model



Methods

Aim

to estimate the probability of being in a given state at a given day post-admission, by age and sex

Methods

non-parametric multi-state modelling analysis by age group

Putter H et al. Tutorial in biostatistics: Competing risks and multi-state models. Statist. Med. 2007; 26:2389–2430.

mstate package in R

Multi-state model: males

Probability of being in a given state at x days after hospital admission

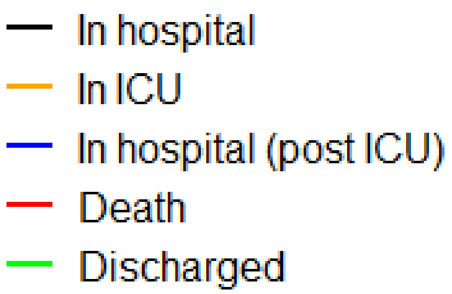
In hospital
In ICU
In hospital (post ICU)
Death
Discharged

RESULTS OMITTED

Multi-state model: females

Probability of being in a given state at x days after hospital admission

RESULTS OMITTED



3. How long do people stay in the hospital ward and in ICU?

Methods

- Some studies have used the observed distribution of time spent in different states, ignoring those who remain in hospital/were censored
- ....this gives biased estimates
- Expected length of stay can be estimated using the multi-state modelling analysis

Beyersmann J, Putter H. A note on computing average state occupation times. Demographic Research 2014; Volume 30: Article 62.

Expected length of stay

X_t: state of a patient at time t

$$\text{Expected time spent in state } k = \int_0^\infty \Pr(X_u = k)du$$

Expected length of stay

Males

Location	Expected length of stay in days (95% CI)
In hospital (pre-ICU)	RESULTS OMITTED
In ICU	
In the ward after ICU	

Females

Location	Expected length of stay in days (95% CI)
In hospital (pre-ICU)	RESULTS OMITTED
In ICU	
In the ward after ICU	

Older patients tended to spend more time in hospital, but less time in ICU (conditional on going to ICU)

Conditional length of stay

Question posed by LSHTM mathematical modelling team

What is the distribution of time spent in different states <u>conditional on what subsequently happens to the patient</u>?

e.g. Time spent in hospital in those who follow the pathways

Hospital → Death/Discharge

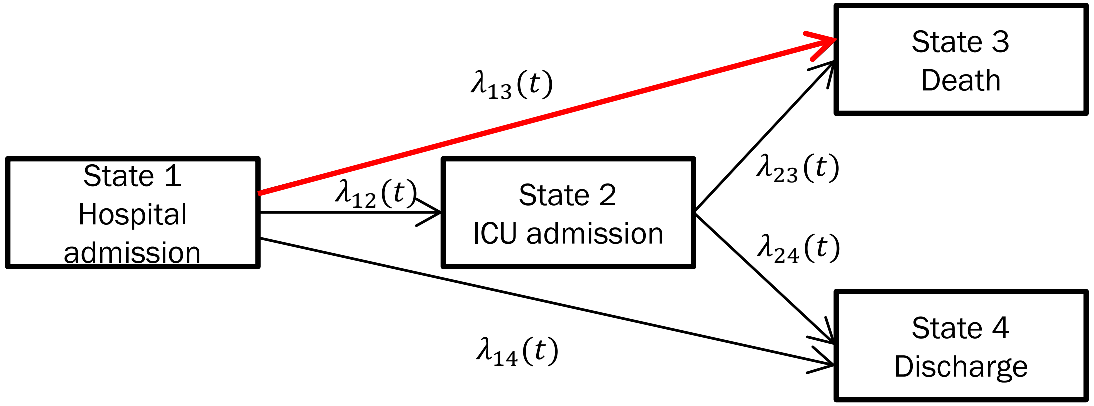
Hospital → ICU → Ward → Death/Discharge

- Usually we don't like to condition on things that happen in the future!
- For computational reasons simulated patients are assigned to a group that will follow a specific pathway

Conditional length of stay

Distribution of time spent in hospital among those who follow the path: Hospital → Death

T_2, T_3, T_4: random variables for times of transition to states 2,3,4



$$\Pr(T_3 = t \mid \underbrace{T_3 \leq T_4}_{\text{Death occurs before discharge}}, \underbrace{T_3 < T_2}_{\text{Death occurs before ICU}})$$

Conditional length of stay

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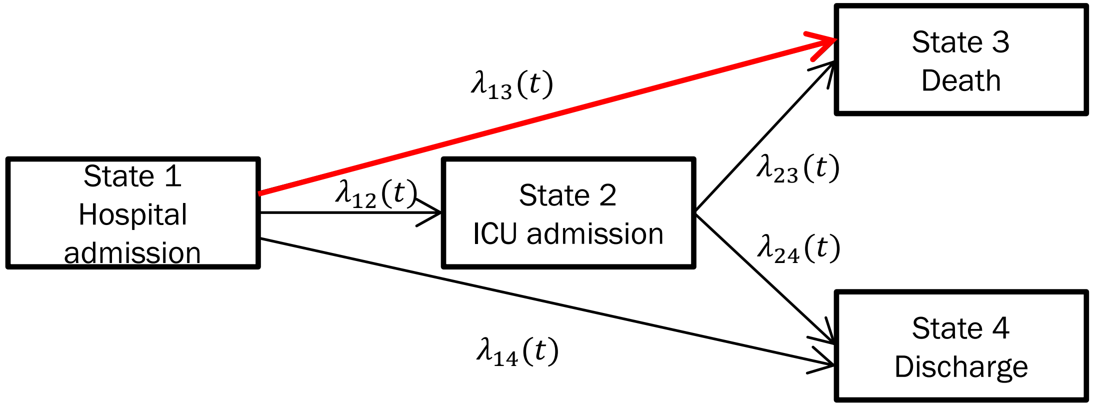
T_2, T_3, T_4: random variables for times of transition to states 2,3,4



$$\Pr(T_3 = t | \underbrace{T_3 \le T_4}_{\text{Death occurs before discharge}}, \underbrace{T_3 < T_2}_{\text{Death occurs before ICU}}) = \frac{\Pr(T_3 = t, T_3 \le T_4, T_3 < T_2)}{\int_0^\infty \Pr(T_3 = u, T_3 \le T_4, T_3 < T_2)du}$$

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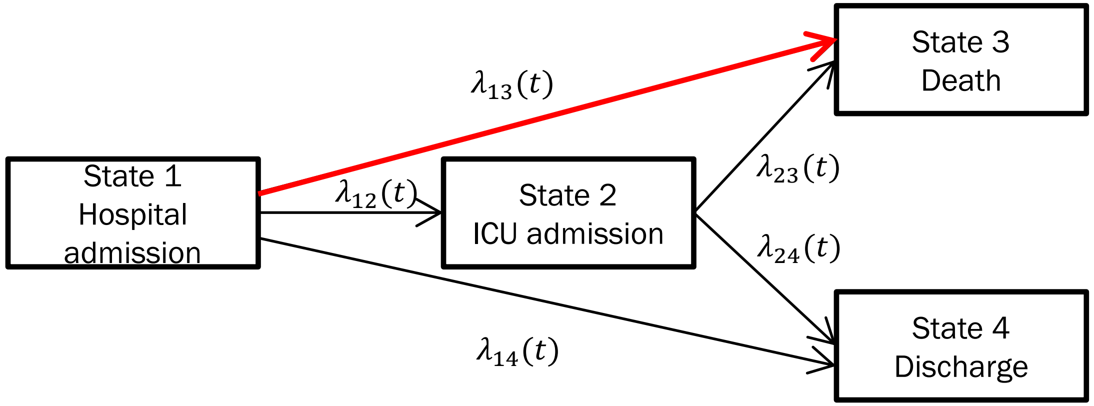

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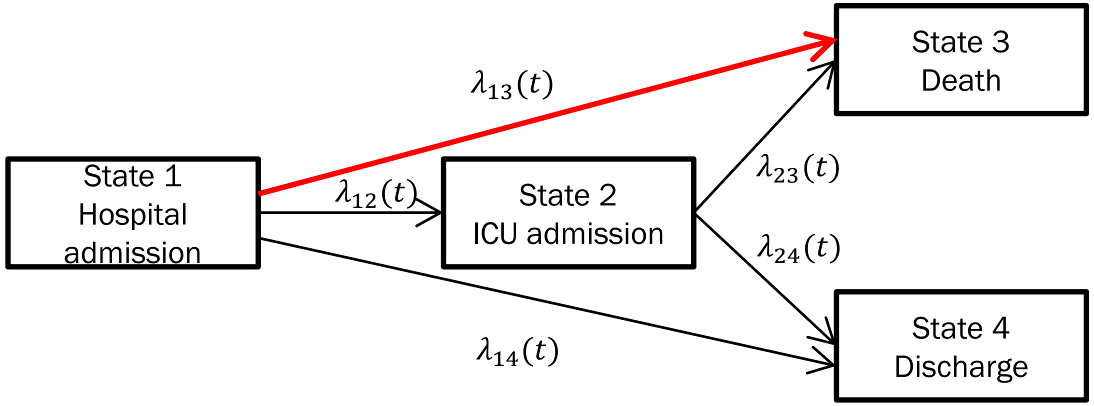


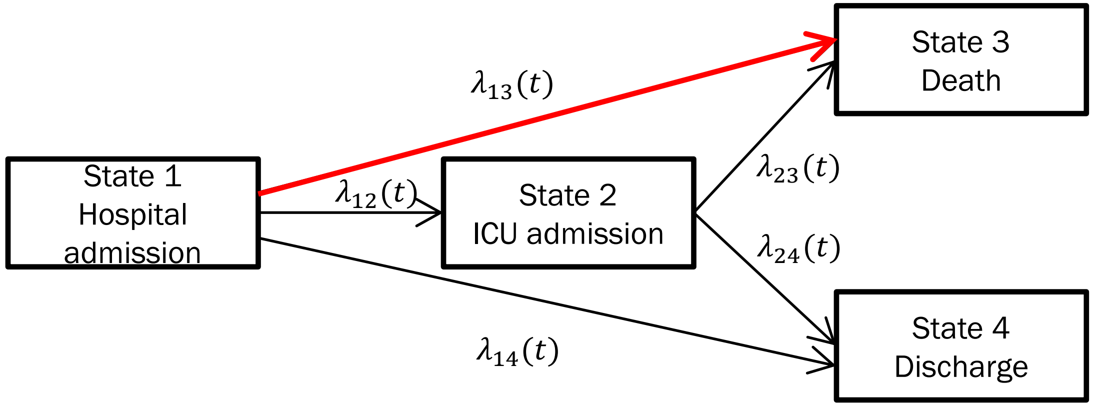
$$\Pr(T_3 = t | T_3 \le T_4, T_3 < T_2) = \frac{\Pr(T_3 = t, T_3 \le T_4, T_3 < T_2)}{\int_0^\infty \Pr(T_3 = u, T_3 \le T_4, T_3 < T_2)du}$$

$$\Pr(T_3 = t, T_3 \le T_4, T_3 < T_2) = \underbrace{\exp\left\{-\int_0^t (\lambda_{12}(v) + \lambda_{13}(v) + \lambda_{14}(v))dv\right\}}_{\text{Do not transition out of state 1 at any time up to time } t} \underbrace{\lambda_{13}(t)}_{\text{Die at time } t}$$

Conditional length of stay

Distribution of time spent in hospital among those who follow the path: Hospital → Death

T_2, T_3, T_4: random variables for times of transition to states 2,3,4



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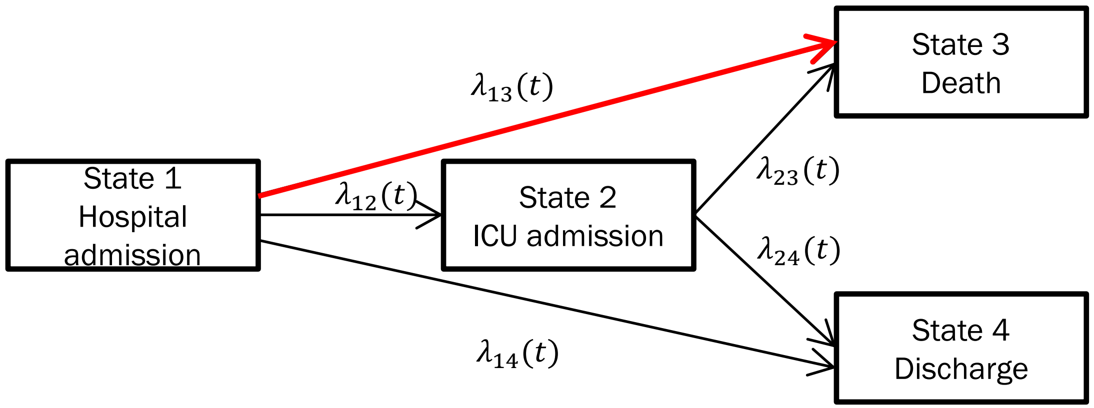
$$\Pr(T_3 = t, T_3 \le T_4, T_3 < T_2) = \exp\left\{-\int_0^t (\lambda_{12}(v) + \lambda_{13}(v) + \lambda_{14}(v))dv\right\}\lambda_{13}(t)$$

Non-parametric estimator $\prod_{u<t}\{1 - \hat{\lambda}_{12}(u) - \hat{\lambda}_{13}(u) - \hat{\lambda}_{14}(u)\}\,\hat{\lambda}_{13}(t)$

Conditional length of stay

Distribution of time spent in hospital among those who follow the path: Hospital → Death

T_2, T_3, T_4: random variables for times of transition to states 2,3,4



Unfortunately this method cannot be implemented in standard software, e.g. using the mstate package in R

$$\Pr(T_3 = t | T_3 \le T_4, T_3 < T_2) = \frac{\Pr(T_3 = t, T_3 \le T_4, T_3 < T_2)}{\int_0^\infty \Pr(T_3 = u, T_3 \le T_4, T_3 < T_2) du}$$

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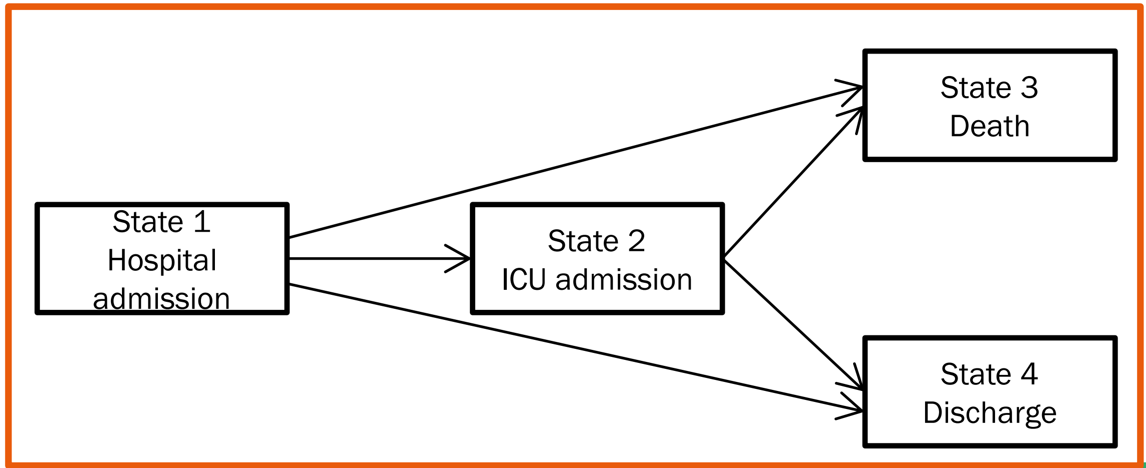
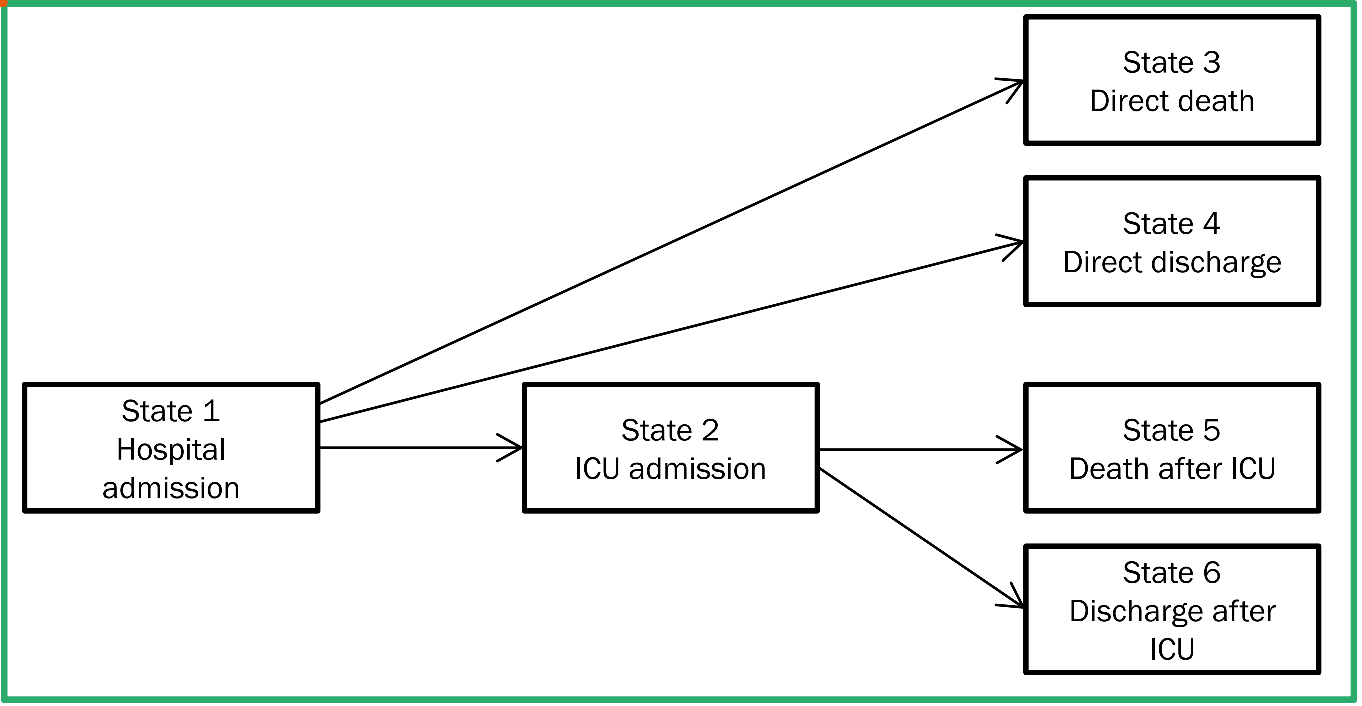
Alternative approach



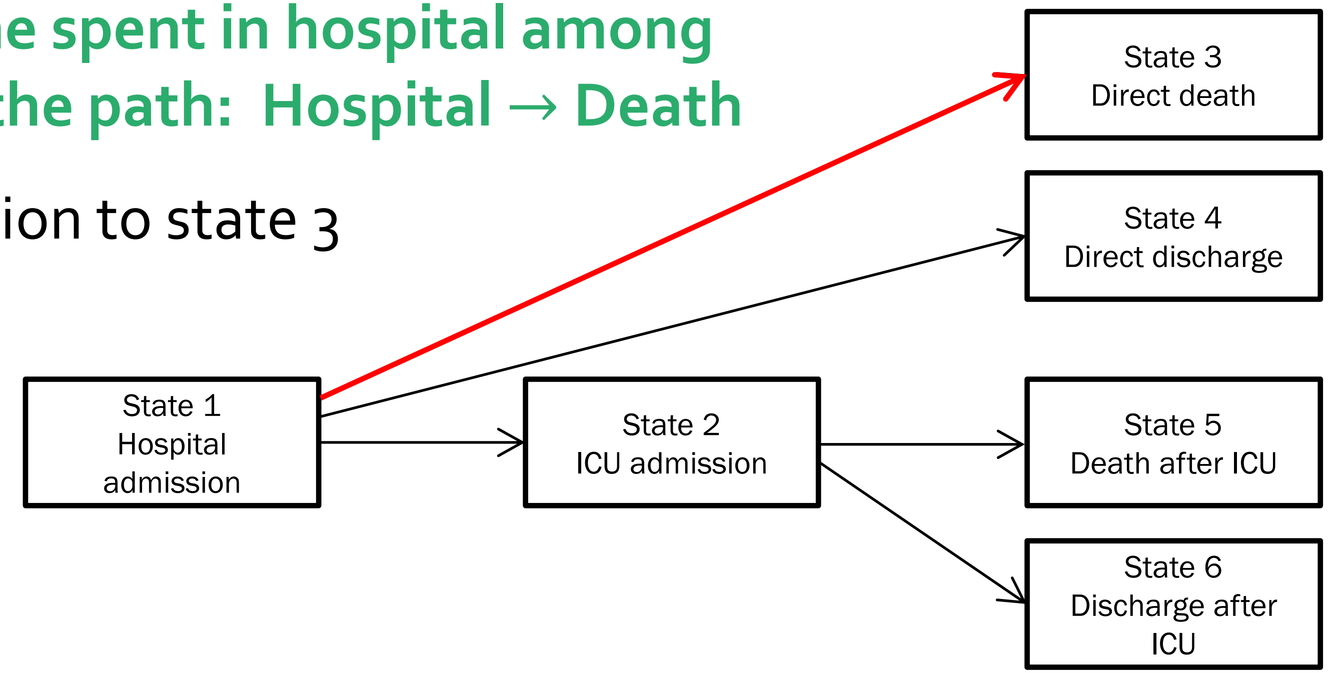
- Alternative way of thinking about the multi-state model
- Suggested by Hein Putter
- Enables the conditional length of stay distributions to be estimated using the output (with some effort!) from `mstate`



Alternative approach

Distribution of time spent in hospital among those who follow the path: Hospital → Death

T_3 : time of transition to state 3



$$\Pr\left(T_3 = t \middle| X_{\text{final}} = 3\right) = \Pr\left(T_3 \geq t \middle| X_{\text{final}} = 3\right) - \Pr\left(T_3 \geq t + 1 \middle| X_{\text{final}} = 3\right)$$

Alternative approach

Distribution of time spent in hospital among those who follow the path: Hospital → Death

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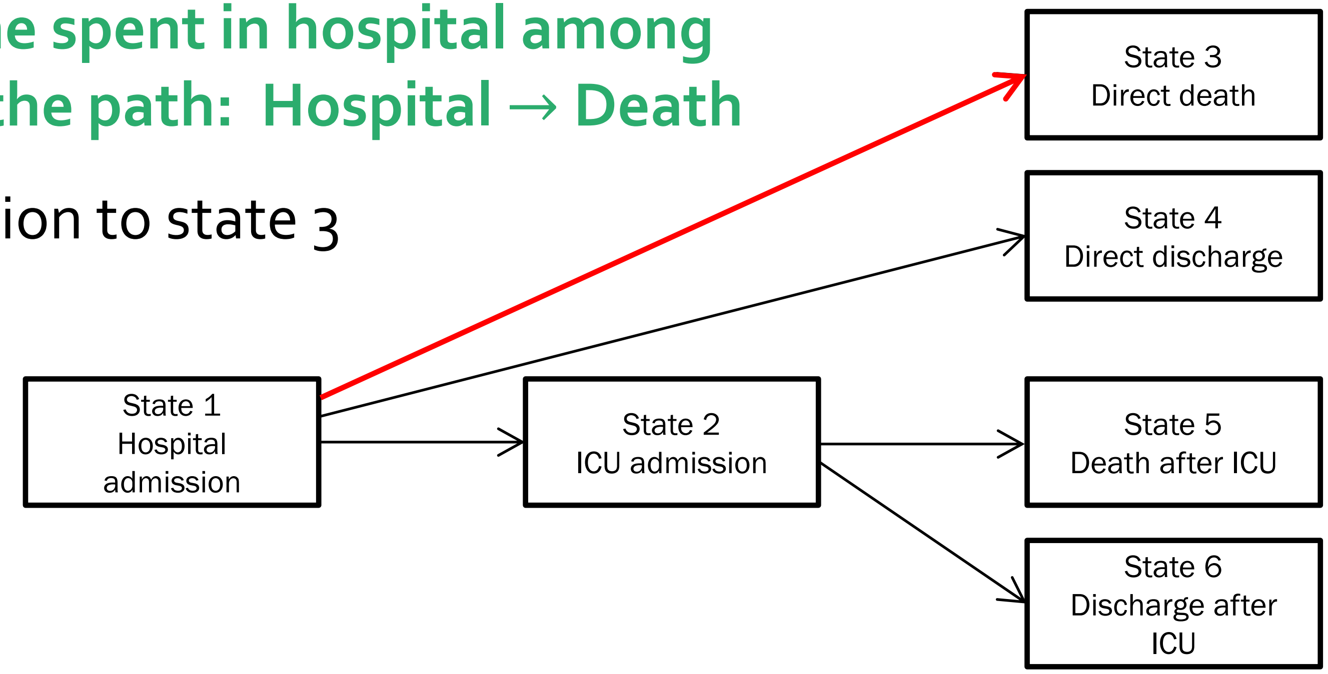

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$$\Pr\left(T_3 \geq t \middle| X_{\text{final}} = 3\right) = \frac{\Pr\left(X_{\text{final}} = 3 \middle| T_3 \geq t\right) \Pr(T_3 \geq 3)}{\Pr(X_{\text{final}} = 3)}$$

Application in CO-CIN

Distribution of time spent in hospital

Hospital → Death/discharge

Hospital → ICU → Ward → Death/discharge

RESULTS OMITTED

4. What are the risks of hospital admission?

Question 4

Risks of hospitalisation with COVID-19 for individuals with vs without long term conditions

- asthma, cancer, diabetes, heart disease, lung disease, neurological condition, obesity, none
- by age category and sex

Recall we have access to the CO-CIN data on 43256 people admitted to hospital between 11 March and 19 July with proven or high likelihood of SARS-Cov-2 infection

Q4: Risks of hospitalisation

- we want probability (in the population, denoted by a super-index 0) of being a hospitalised case $D = 1$ given comorbidity G_j and age group A_k

$$P^0(D = 1|G_j = 1, A_k = 1)$$

- How to estimate something resembling original question using data from **hospitalised cases only**?

By Bayes' rule

$$= \frac{P^0(G_j = 1|D = 1, A_k = 1){\color{red}P^0(D = 1|A_k = 1)}}{{\color{blue}P^0(G_j = 1|A_k = 1)}}$$

can't estimate with our data

Can estimate from our data

- We need to either (a) get data for those terms, or (b) somehow, avoid them

Strategy

- To estimate $P^0(G_j = 1|A_k = 1)$ use Health Survey from England (HSE) 2019 data
- And we can get rid of $P^0(D = 1|A_k = 1)$ by changing estimand
- Note that the expression for hospitalisation risk in those without comorbidity G_j is

$$P^0(D = 1|G_j = 0, A_k = 1) = \frac{P^0(G_j = 0|D = 1, A_k = 1)P^0(D = 1|A_k = 1)}{P^0(G_j = 0|A_k = 1)}$$

- so that the red term does not appear in the risk ratio for being hospitalised

$$\frac{P^0(D = 1|G_j = 1, A_k = 1)}{P^0(D = 1|G_j = 0, A_k = 1)}$$

Risk ratios estimation

- Risk ratios:

the proportion of hospitalised people by age no longer appears!

$$\frac{\mathcal{P}^0(D=1|G_j=1,A_k=1)}{\mathcal{P}^0(D=1|G_j=0,A_k=1)} = \frac{\mathcal{P}^0(G_j=1|D=1,A_k=1)/\mathcal{P}^0(G_j=1|A_k=1)}{\underbrace{\mathcal{P}^0(G_j=0|D=1,A_k=1)}_{\text{estimated by observed proportions in case-only data}}/\underbrace{\mathcal{P}^0(G_j=0|A_k=1)}_{\text{estimated using HSE data}}}$$

- ONS 2020 population projections by age used to standardised HSE estimates
- This is known as "case-only" design (with associated analytical techniques) suggested in the 90s

Assumptions

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- Conditional on being in hospital with COVID-19, the age-sex specific risk ratios of having each comorbidity are the same in COCIN and the general UK population
- the age-sex specific risk ratios of having each comorbidity in the population was unchanged at the beginning of the epidemic, and thus can be estimated by the latest HSE data

- The comorbidities are measured in an equivalent way across HSE and COCIN
  - HSE obesity (BMI=30+) vs COCIN clinician-defined (possibly 40+)
  - HSE long-term conditions questionnaire used for cancer, heart, lung and neurological disease **only in those 16+ years old**

Relative risks of hospitalisation in Males over 50

RESULTS OMITTED

RR Hospitalisation with COVID in females over 50

RESULTS OMITTED

Discussion and Conclusions

Conclusions

- As has been noted before, age is the factor most strongly associated with higher mortality.
- By contrast, risk of ICU admission was higher in younger patients.
- We see there is strong effect modification by age on the "effect" of each comorbidity
- these "effects" are different for each of the outcomes considered:
    - mortality: RR for diabetes within age groups tended to be >1
    - ICU admission: Patients with comorbidities were also less likely to be admitted to ICU
    - hospital admission: most comorbidities resulted in RR >1 within age groups, except for obesity and asthma

Some Caveats

- There was some missing data on comorbidities. We performed a complete cases analysis
- The results have to be considered in the context of the small numbers for some comorbidities in the very elderly
- For the relative risks of hospitalisation, where we used HSE. A limitation is the differences in how the survey and the COCIN data collection measure the comorbidities of interest

The role of statistical methodology

The scientific questions were relatively straightforward…

- but the nature of the patients' outcomes meant that there is a need to deal with competing risks carefully
- it is not always straightforward to answer the questions with the data at hand. Estimating risk of hospitalisation using only hospital data is not possible, but statistical methods allowed us to estimate relative risks by using supplemental information
- the information needed for mathematical modelling is not always aligned to how we (statisticians) think about state transitions, and again, we needed to extend statistical methodology in order to estimate conditional length of stay

Acknowledgements

Prof Nick Jewell, LSHTM

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Data

- ISARIC COVID19 Clinical Information Network (CO-CIN)

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