

# Clinical Epidemiology 5

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## Frequency and Prognosis

Written by: Jennifer Bryan, MD, MA, FRCP

With course and slide contributions by:

Drs. Cheryl Hunchak, Lisa Puchalski-Ritchie, Nazanin

Meshkat, Anne Aspler

University of Toronto, Division of Emergency Medicine



Global Health  
Emergency Medicine

# Please also note:

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The information in this presentation and the video recording is up to date as of the date it was recorded (June 2, 2020).

It has not been updated to include any subsequent advances in practice, and the information presented in this video does not replace hospital, health centre, or governmental guidelines.



# Disclosure Statement

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I have not received any financial or in-kind support from any commercial organization and have no conflicts of interest to declare.



# Course objectives

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- To gain competence in critical appraisal
- To find ways to keep up to date with medical literature
- To develop a basic approach to asking research questions, designing research studies and interpreting basic biostatistics
- To gain competence in the application of evidence-based emergency medicine to bedside patient care



# Course introduction

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- Nine sessions, all in R1 year
- Interactive, depends on your participation



# Course outline

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1. Introduction
2. Knowledge curation in the 21st century
3. Validity, Reliability, Bias And Chance, Introduction To Study Design
4. Diagnosis and Treatment
- 5. Frequency and Prognosis**
6. Risk
7. Introduction to biostatistics
8. Systematic Review, Meta-Analysis and Journal Club
9. Special study designs



# Suggested reading

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Fletcher RH, Fletcher SW. Clinical Epidemiology: The Essentials. 4th Ed. Chapters 4 and 7



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0:03 / 22:09



Clin epi 5 sneak peak for TAAAC-EM

Unlisted



# Outline of today's session

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- Prevalence
- Incidence
- Stratification
- Standardization
- Prognostic factors vs risk factors
- Clinical course vs. natural history
- Prognostic study designs
- Survival analysis and Kaplan Meier curves



# Review of previous sessions

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Yesterday you performed a procedure using ketamine for procedural sedation. Your patient developed laryngospasm. You're interested in doing a literature search to see how common that is. How might you structure your question?



# Review of previous sessions

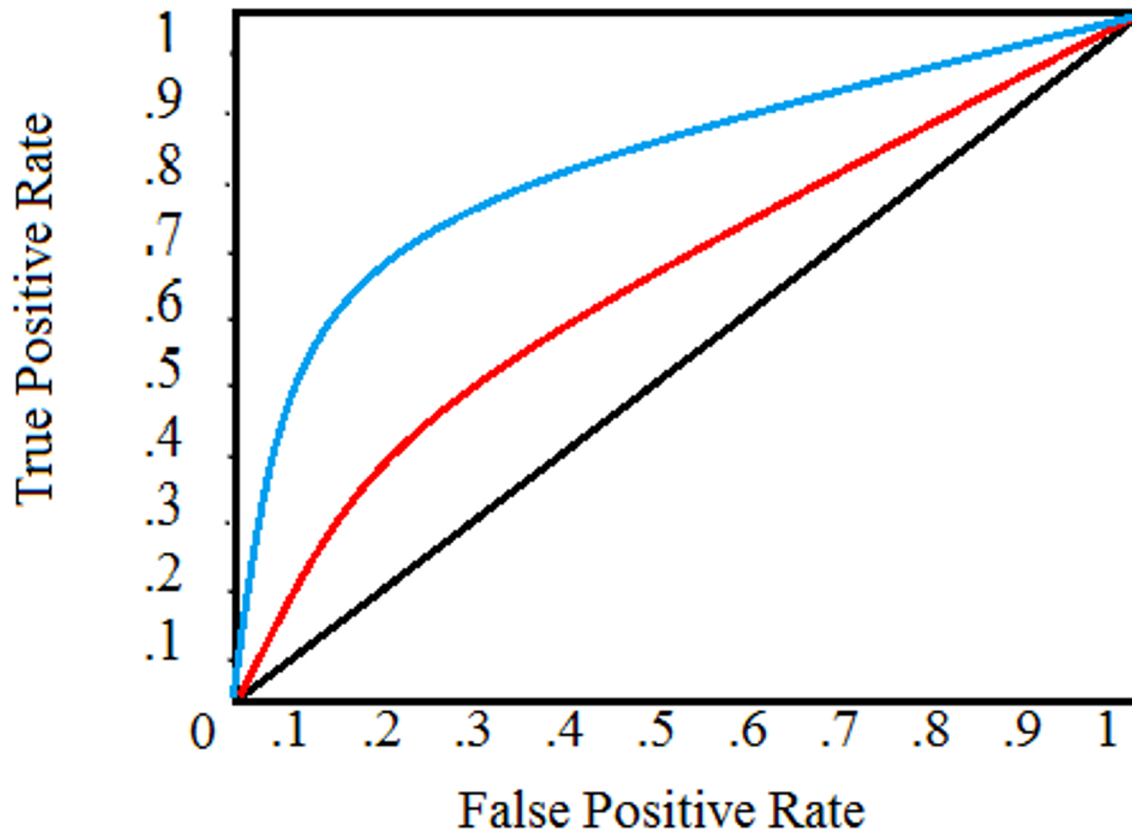
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- What is an example of a high specificity test?
- What is an example of a low specificity test?



# Review of previous sessions

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# Review of previous sessions

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What are limitations of RCTs?



Wang, Yeming, et al. "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial." *The Lancet* (2020).

We did a randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China. Eligible patients were adults (aged  $\geq 18$  years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Primary analysis was done in the intention-to-treat (ITT) population and safety analysis was done in all patients who started their assigned treatment. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04257656), NCT04257656.

Wang, Yeming, et al. "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial." *The Lancet* (2020).

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# Disease frequency: Prevalence and Incidence





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**Probabilities** of disease,  
improvement, deterioration, cure,  
side effects and death form the  
basis for answering most clinical  
questions

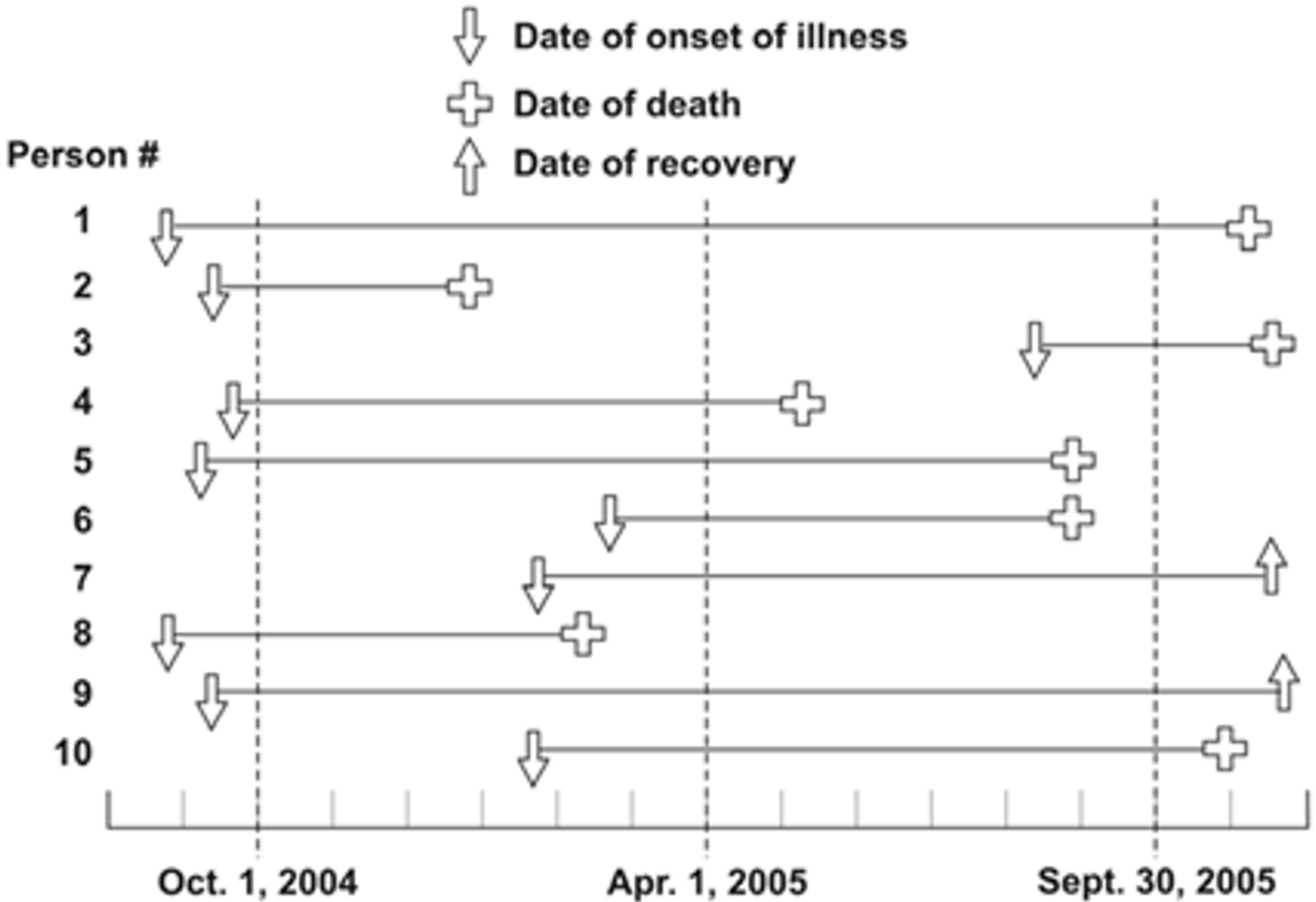


# Prevalence and Incidence

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- Ways of describing disease in a population
- Numerator = cases
- Denominator = population



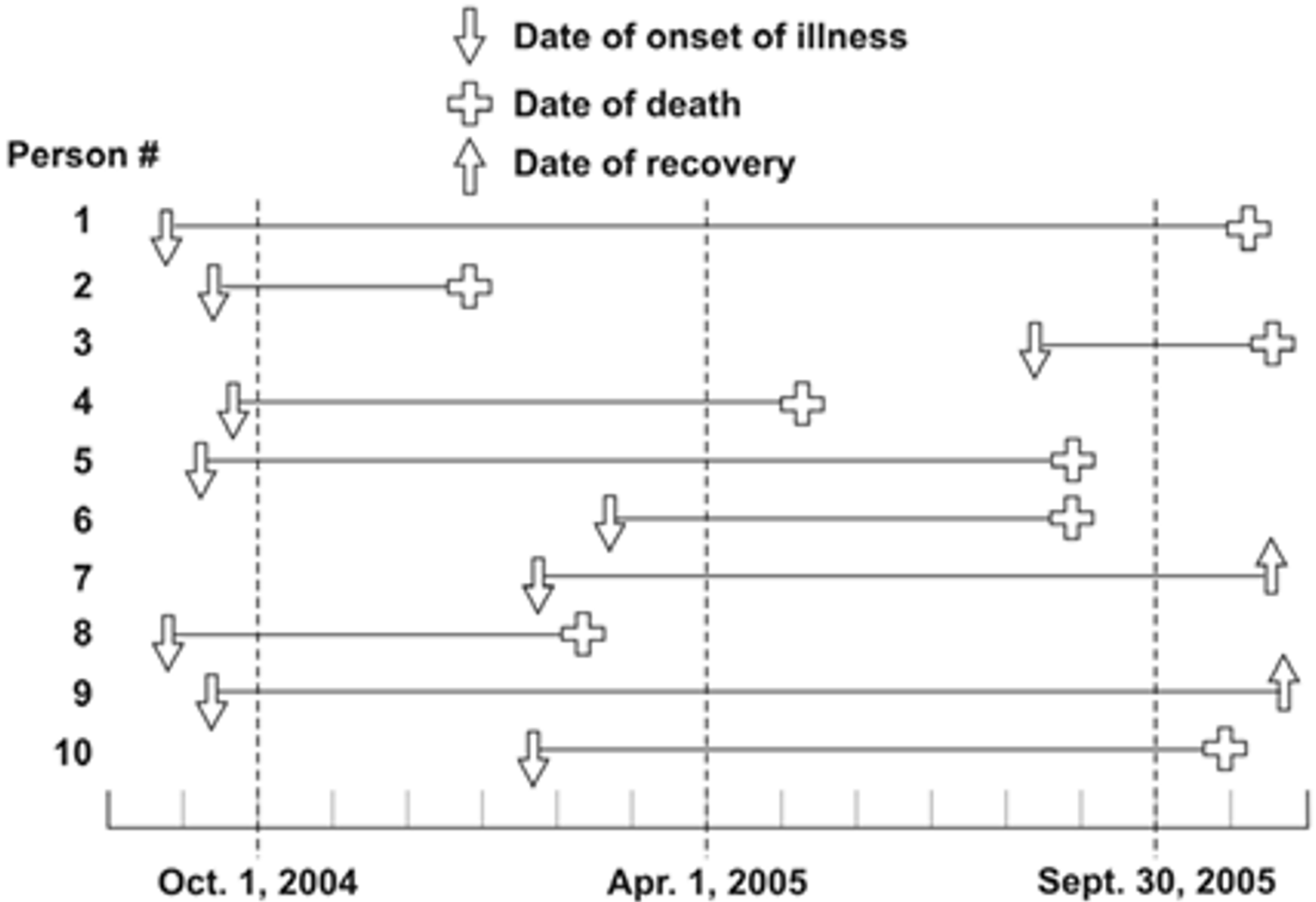


# Prevalence

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- Proportion at a certain time
- Numerator = cases
- Denominator = population





# How to study prevalence

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## Cross-sectional studies

- Also known as prevalence studies
- Observational (non-experimental)
- A single point in time (or a narrow time period)



# Prevalence of hypertension

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Tesfaye, Fikru, Peter Byass, and Stig Wall. "Population based prevalence of high blood pressure among adults in Addis Ababa: uncovering a silent epidemic." *BMC cardiovascular disorders* 9.1 (2009): 39.

Estimates from sample of 3713 adults in Addis Ababa: 31.5% of men and 28.9% of women had hypertension

Hypertension defined as: “systolic blood pressure (SBP)  $\geq$  140 mmHg (millimetres of mercury) or diastolic blood pressure (DBP)  $\geq$  90 mmHg or reported use of anti-hypertensive medication”



# What can change prevalence?

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- What if one year later another study was published and found rates of hypertension of 20% for men, 15% for women?





# What can change prevalence?

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- Actual change in disease rate
- Difference in sampling
- Definition
- Availability and use of testing
- Test sensitivity
- Population changes (migration, deaths)

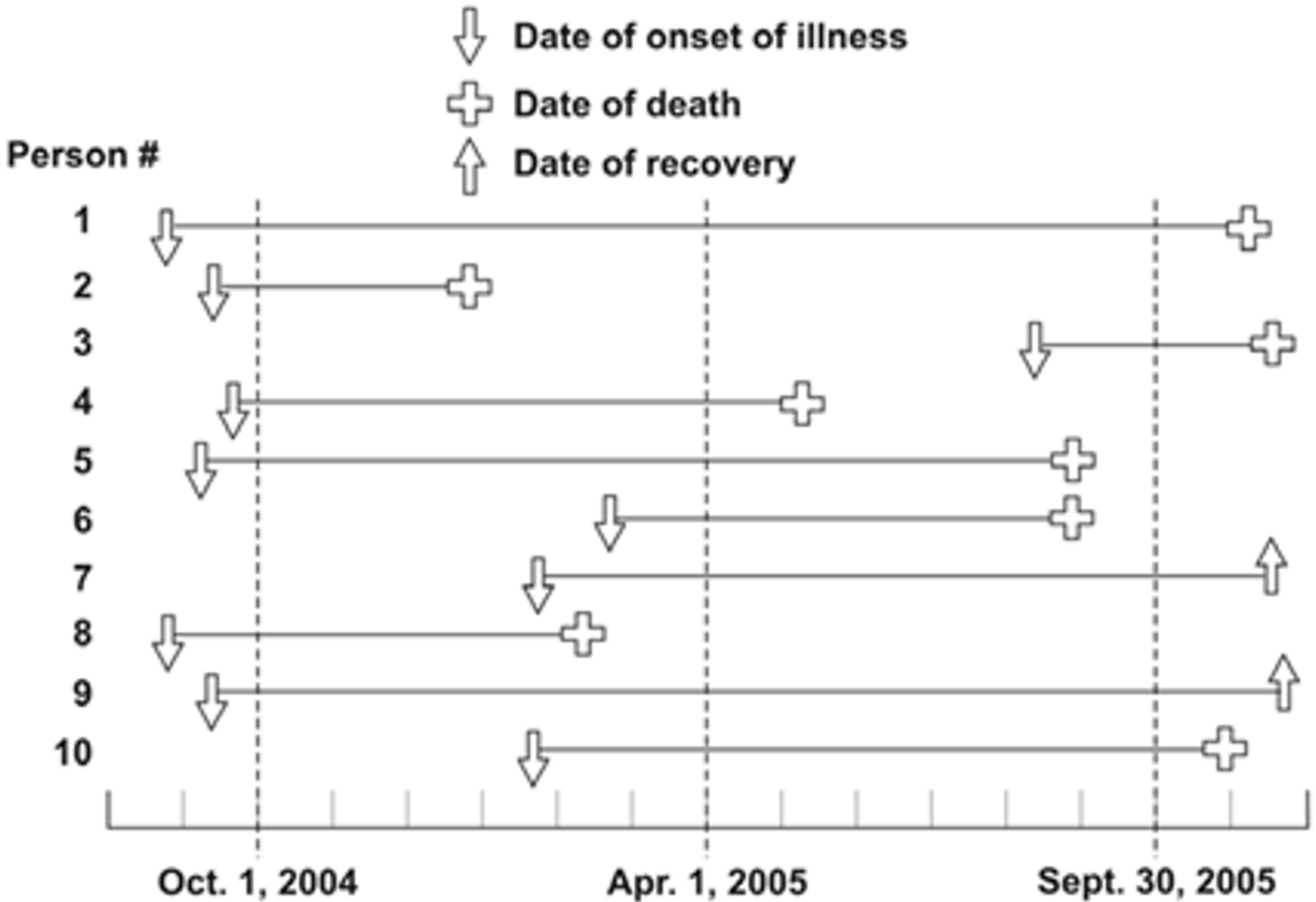


# Incidence

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- The occurrence of disease **over time**
- Numerator= number of new cases over time
- Denominator= population at risk





# How to study incidence

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- Cohort studies
  - Sample identified by exposure and followed for an outcome of interest



# Incidence: population at risk

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- Cumulative incidence
  - Stable population
- Incidence density
  - Dynamic population
  - Person-time (often person-years)



# Person-time (person-years, person-months)

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- E.g., Following patients for complications of ciprofloxacin in young adults, a patient followed for one year contributes 1 person-year, while one for ten years contributes 10 person-years
- If each patient had 1 complication, then the incidence density would be 2 complications per 11 person-years.



Bezabhe, Woldesellassie M., et al. "Adverse drug reactions and clinical outcomes in patients initiated on antiretroviral therapy: a prospective cohort study from Ethiopia." *Drug safety* 38.7 (2015): 629-639.

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- What is the incidence and nature of ADRs with ART
- Prospective cohort study
- Incidence of ADR 14.8/100 person-months



# Relationship between incidence and prevalence

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# Prevalence and Incidence

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- What is the difference between the prevalence of HIV in Addis in 2017 being 1% and the incidence of HIV in Addis in 2017 being 1%

(fictional incidence, in reality it's about 0.24/1000:

<https://www.unaids.org/en/regionscountries/countries/ethiopia>)



# Prevalence and Incidence

---

- What is the difference between the prevalence of HIV in Addis in 2017 being 1% and the incidence of HIV in Addis in 2017 being 1%
- What if the prevalence of HIV was 3% five years ago?



# What can change prevalence?

---

- Actual change in disease rate
- Difference in sampling
- Definition
- Availability and use of testing
- Test sensitivity
- Population changes (migration, deaths)



# Prevalence and Incidence

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- What is the difference between the prevalence of HIV in Addis in 2017 being 1% and the incidence of HIV in Addis in 2017 being 1%
- What if the prevalence of HIV was 3% five years ago?
- What if the incidence of HIV was 3% five years ago?



# Prevalence and Incidence

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- How does duration of disease impact prevalence?
- HIV?
- Penetrating myocardial injury?



# Prevalence and Incidence

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- How does duration of disease impact prevalence?
- $\text{Prevalence} \approx \text{incidence} \times \text{average disease duration}$  (if steady state)
- e.g., if the annual incidence of asthma is 3/1000 and the prevalence is 30/1000, what is the average disease duration?



# Interpreting Measures of Disease Frequency

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- Stratification
- Standardization



# Interpreting Measures of Disease Frequency

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- Direct comparison often misleading
- For example:
  - Crude death rates for all ages for 1995-1997
  - Mexico 4.7/1000 population
  - United States 8.7/1000 population
- Should people from the U.S. move to Mexico?





# Interpreting Measures of Disease Frequency

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- Direct comparison often misleading
- For example:
  - Crude death rates for all ages for 1995-1997
  - Mexico 4.7/1000 population
  - United States 8.7/1000 population
- We also know that the life expectancy at birth is higher in the United States
  - US 76.1 years, Mexico 71.6 years (1998)



# Interpreting Measures of Disease Frequency

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- Direct comparison often misleading
- For example:
  - Crude death rates for all ages for 1995-1997
  - Mexico 4.7/1000 population
  - United States 8.7/1000 population
- Are there other possible explanations?



# Interpreting Measures of Disease Frequency

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- Stratification
  - Break population into meaningful strata (groups)
  - Calculate and present rates within strata
  - Allows for visual comparison and standardization



# Stratification Example

(Pan American Health Organization: [https://www.paho.org/English/SHA/be\\_v23n3-standardization.htm](https://www.paho.org/English/SHA/be_v23n3-standardization.htm))

Age	Age specific mortality rate per 100,000 population 1995-1997	
	Mexico (2)	United States (3)
<1	1693.2	737.8
1-4	112.5	38.5
5-14	36.2	21.7
15-24	102.9	90.3
25-44	209.6	176.4
45-64	841.1	702.3
65+	4967.4	5062.6



# Stratification

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- Allows you to compare strata, and may point out important patterns and potential targets for intervention
  - i.e., High peri-natal/infant mortality may suggest need for improved access to skilled birth attendants
  - In this case, Mexican death rates are higher at all ages (but more than double US rates for age 4 and under)



# Standardization

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- Adjusting rates based on strata of known or hypothesized risk factors, most commonly age for mortality
- Allows for meaningful comparison between and within countries, regions, or hospitals, over time



# Standardization Example

(Pan American Health Organization: [https://www.paho.org/English/SHA/be\\_v23n3-standardization.htm](https://www.paho.org/English/SHA/be_v23n3-standardization.htm))

		Age specific mortality rate per 100,000 population 1995-1997		Expected # of Deaths	
Age	Standard population (1)	Mexico (2)	United States (3)	Mexico (1) x (2) /100000	United States (1) x(3) /100000
<1	2400	1693.2	737.8	41	18
1-4	9600	112.5	38.5	11	4
5-14	19000	36.2	21.7	7	4
15-24	17000	102.9	90.3	17	15
25-44	26000	209.6	176.4	55	46
45-64	19000	841.1	702.3	160	133
65+	7000	4967.4	5062.6	348	354
	100000			639	574



# Standardization Example

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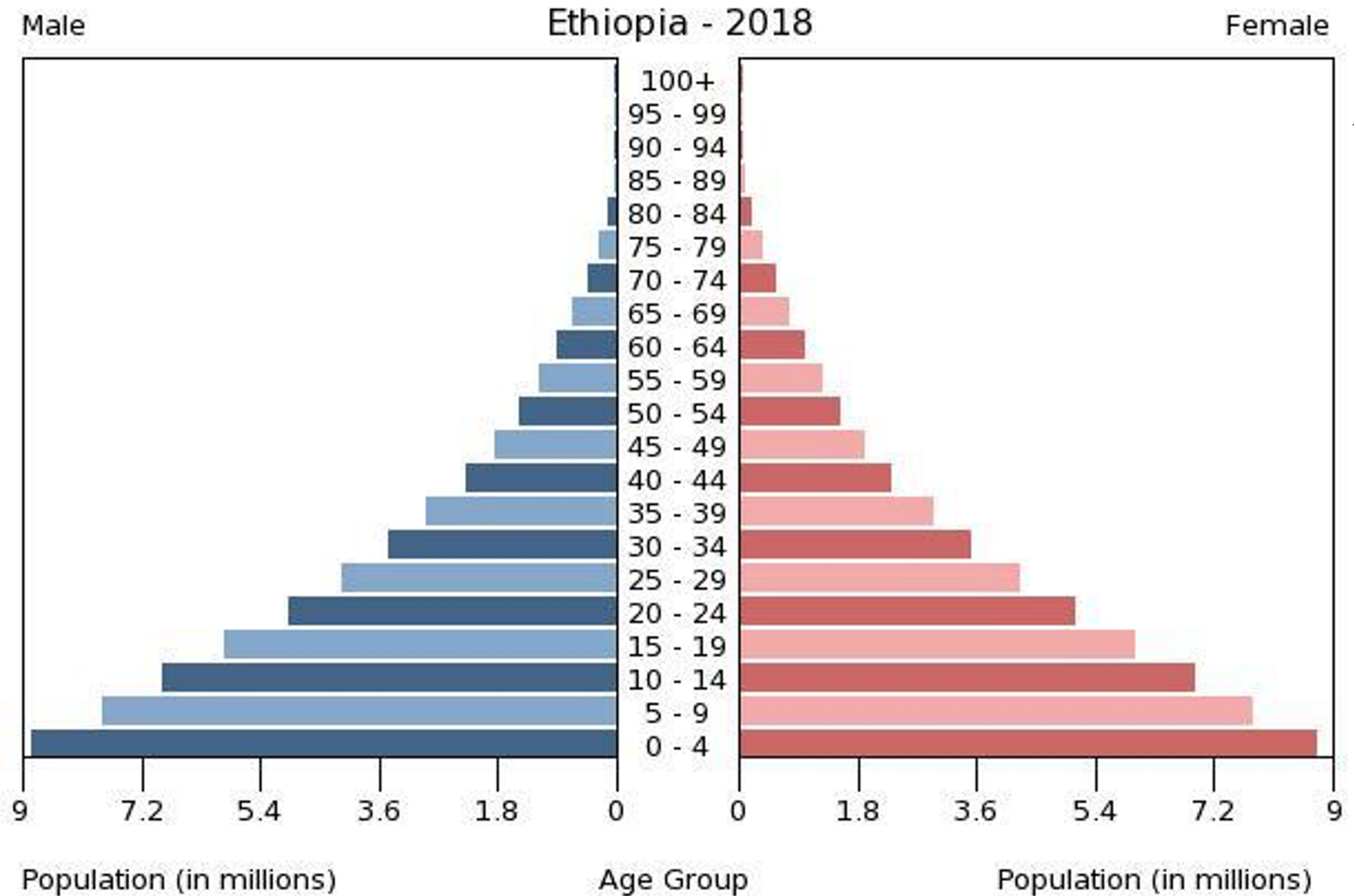
# Example: Comparing death rates

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- Standardization allows you to compare “apples to apples”
  - i.e., In this case, higher crude mortality in the US is shown to be due to a higher proportion of elderly



<https://www.cia.gov/library/publications/the-world-factbook/fields/341.html>



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Questions about prevalence and incidence, stratification and standardization?



# Prevalence and Incidence

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- Prevalence and incidence are both measures of disease frequency
- They are studied using different study designs
- Stratification and standardization allow for better accuracy in comparing disease frequency



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# Prognosis



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# Prognosis

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- Prognostic factors vs risk factors
- Clinical course vs. natural history
- Prognostic study designs
- Survival analysis



# Prognostic studies

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- The prediction of the course of disease





# Prognostic studies

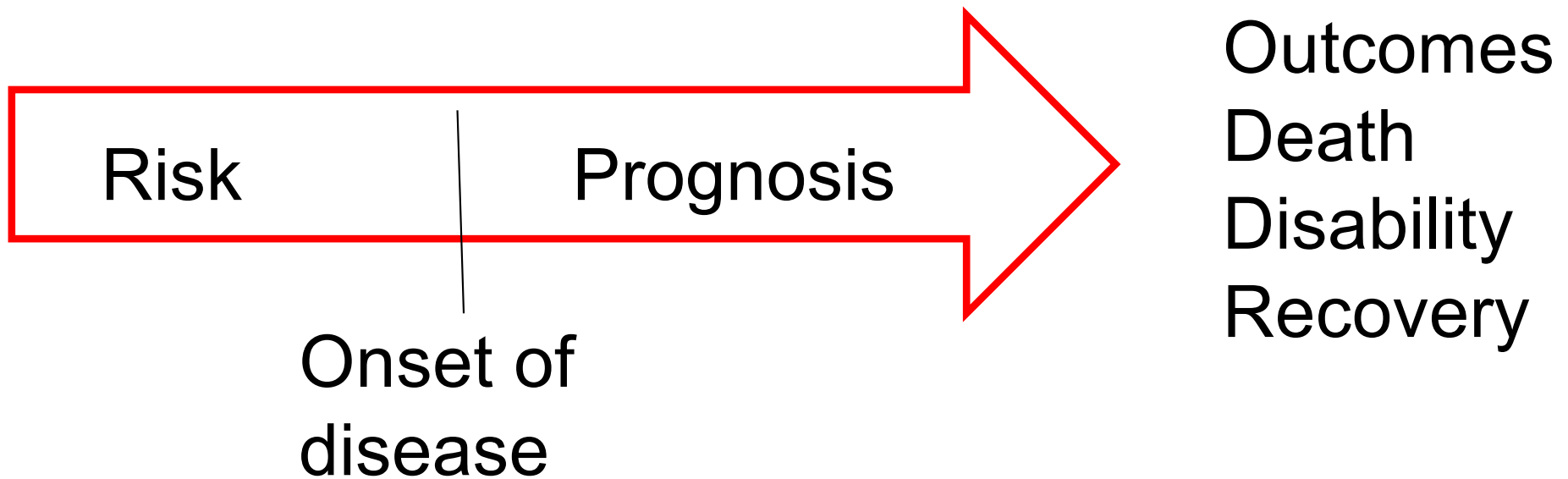
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- Prognostic factors vs. risk factors
- Risk factors: patients are well and we want to know the risk of disease onset
- Prognostic factors: patients have a disease and we want to know their likely outcome



# Prognostic studies

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# Studies of risk vs. studies of prognosis

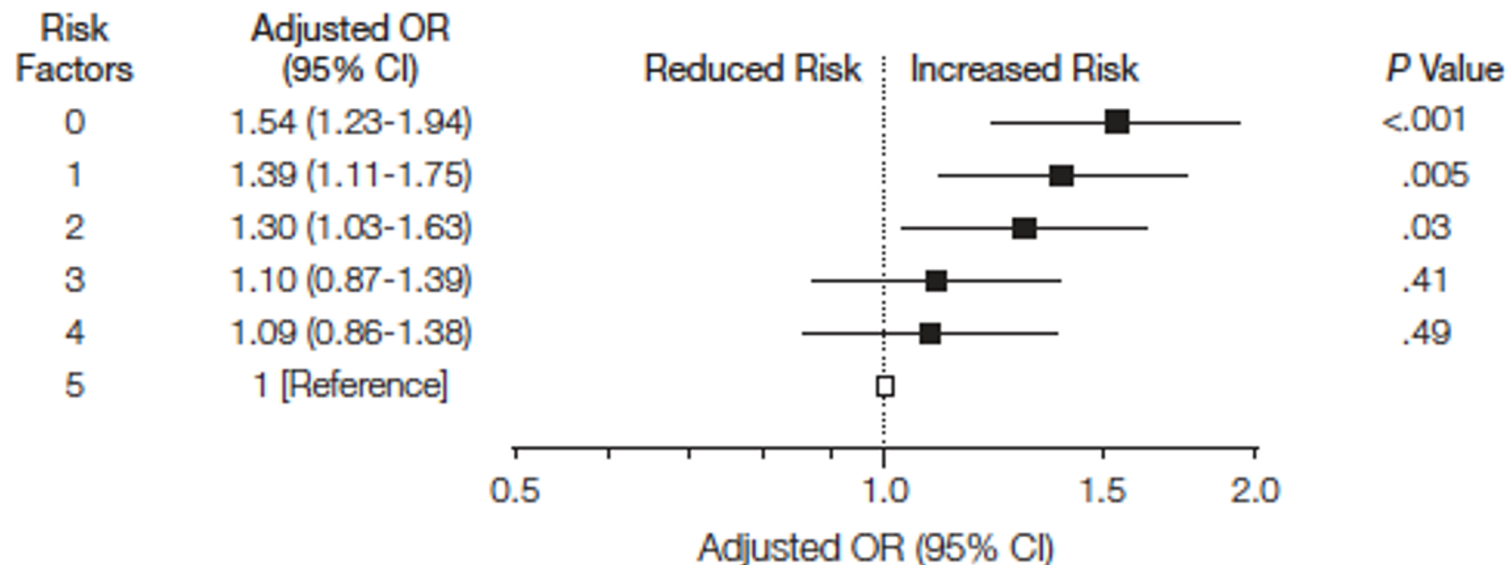
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<b><u>Risk</u></b>	<b><u>Prognosis</u></b>
Healthy people	Patients with a disease
Low probability events	Relatively frequent events
Different factors	Different factors



# Prognostic studies

**Figure 2.** Mortality Risk of Patients With and Without Cardiovascular Risk Factors and First Myocardial Infarction



Canto, John G., et al. "Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction." *JAMA* 306.19 (2011): 2120-2127.



# Prognostic studies

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- Key terms
  - Zero time, inception cohort
  - Follow-up period
  - Disease outcomes



# Prognostic studies

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- Clinical course vs. natural history



# Prognostic studies

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- Clinical course vs. natural history
- Infamous natural history study: “Tuskegee Study of Untreated Syphilis in the Negro Male.”



# Prognostic studies

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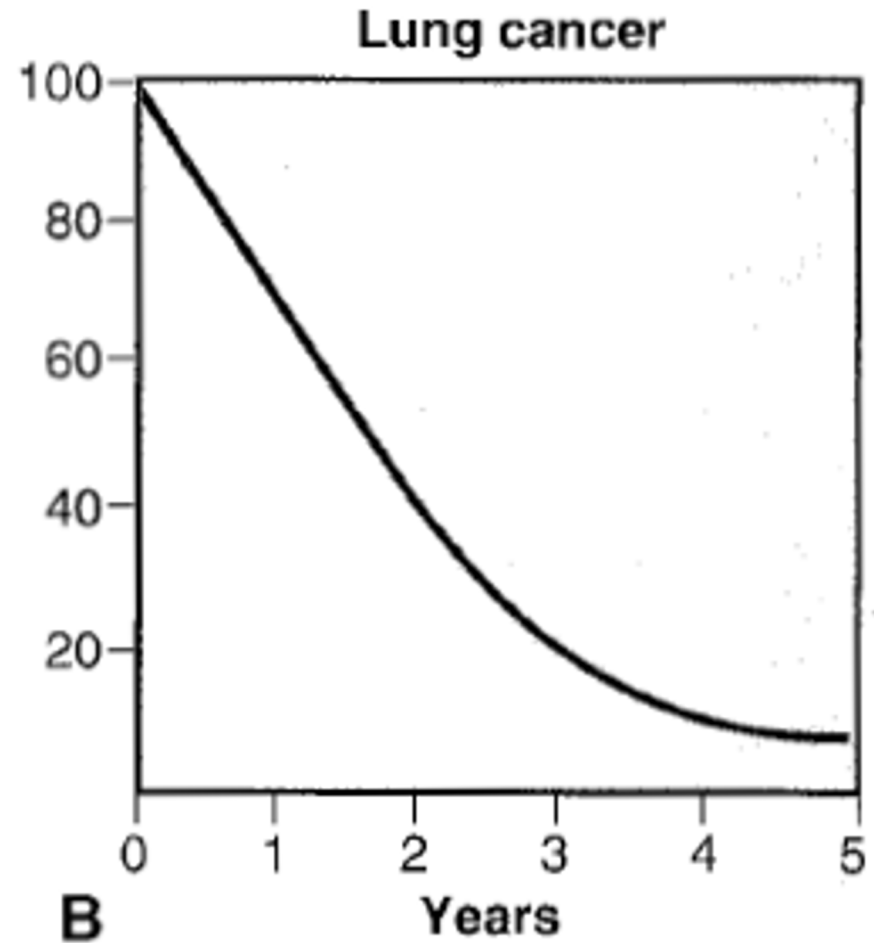
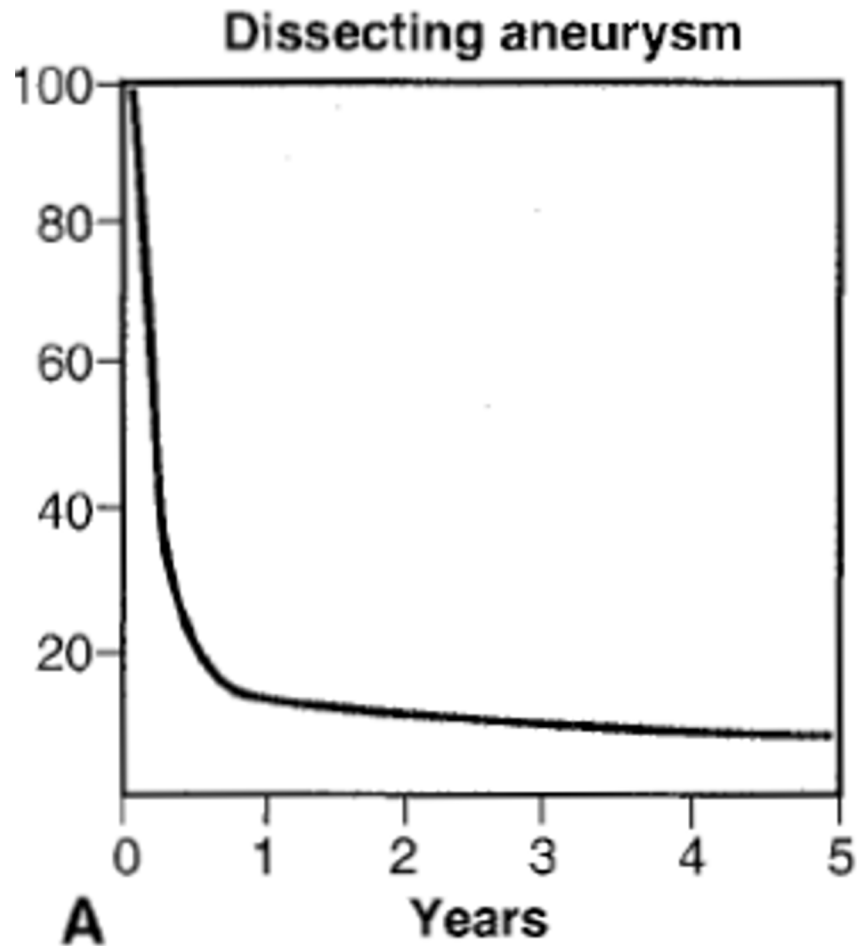
- Clinical course vs. natural history
- Infamous natural history study: “Tuskegee Study of Untreated Syphilis in the Negro Male.”
- 1932-1972
- Penicillin established as treatment in 1945



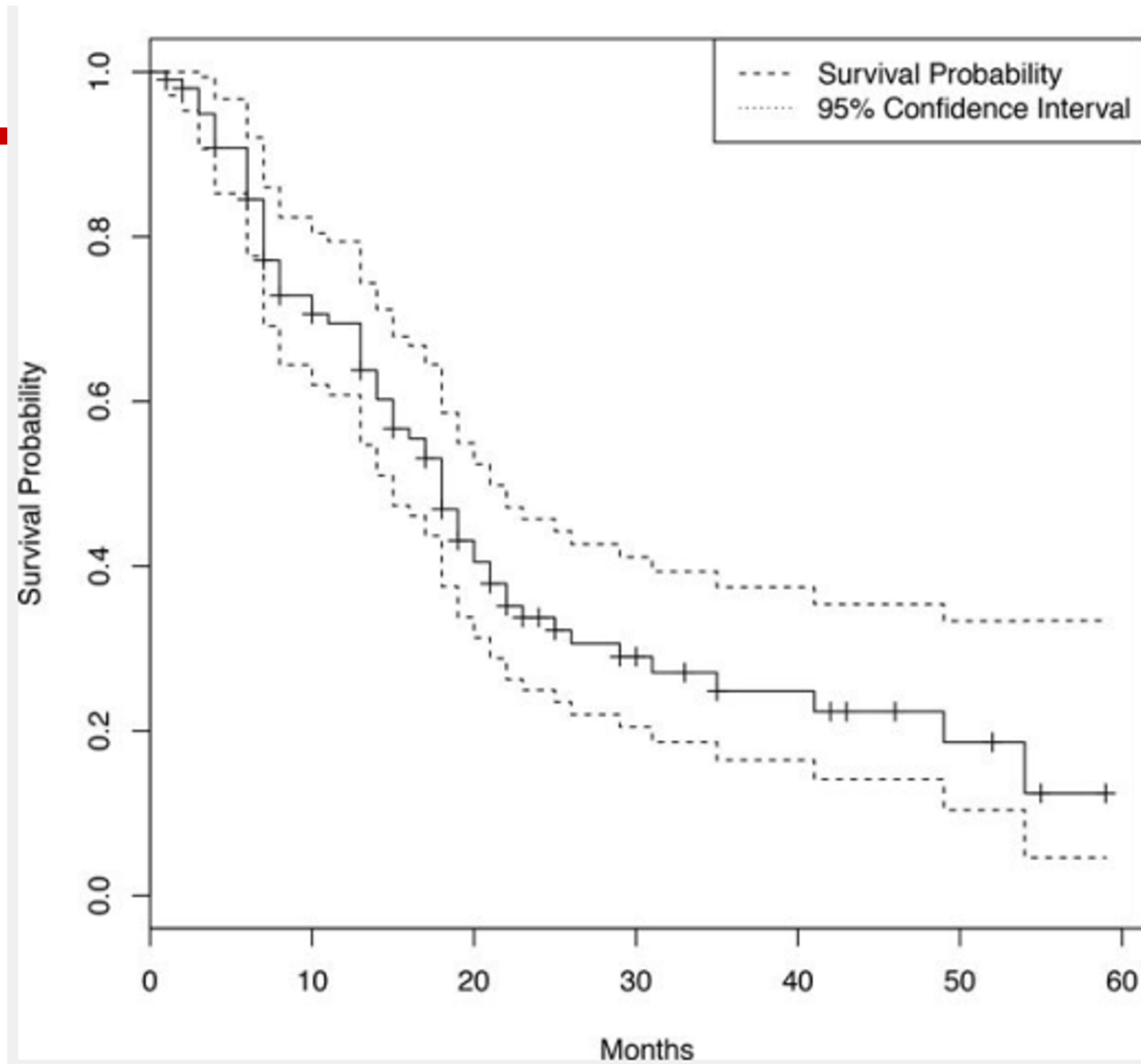


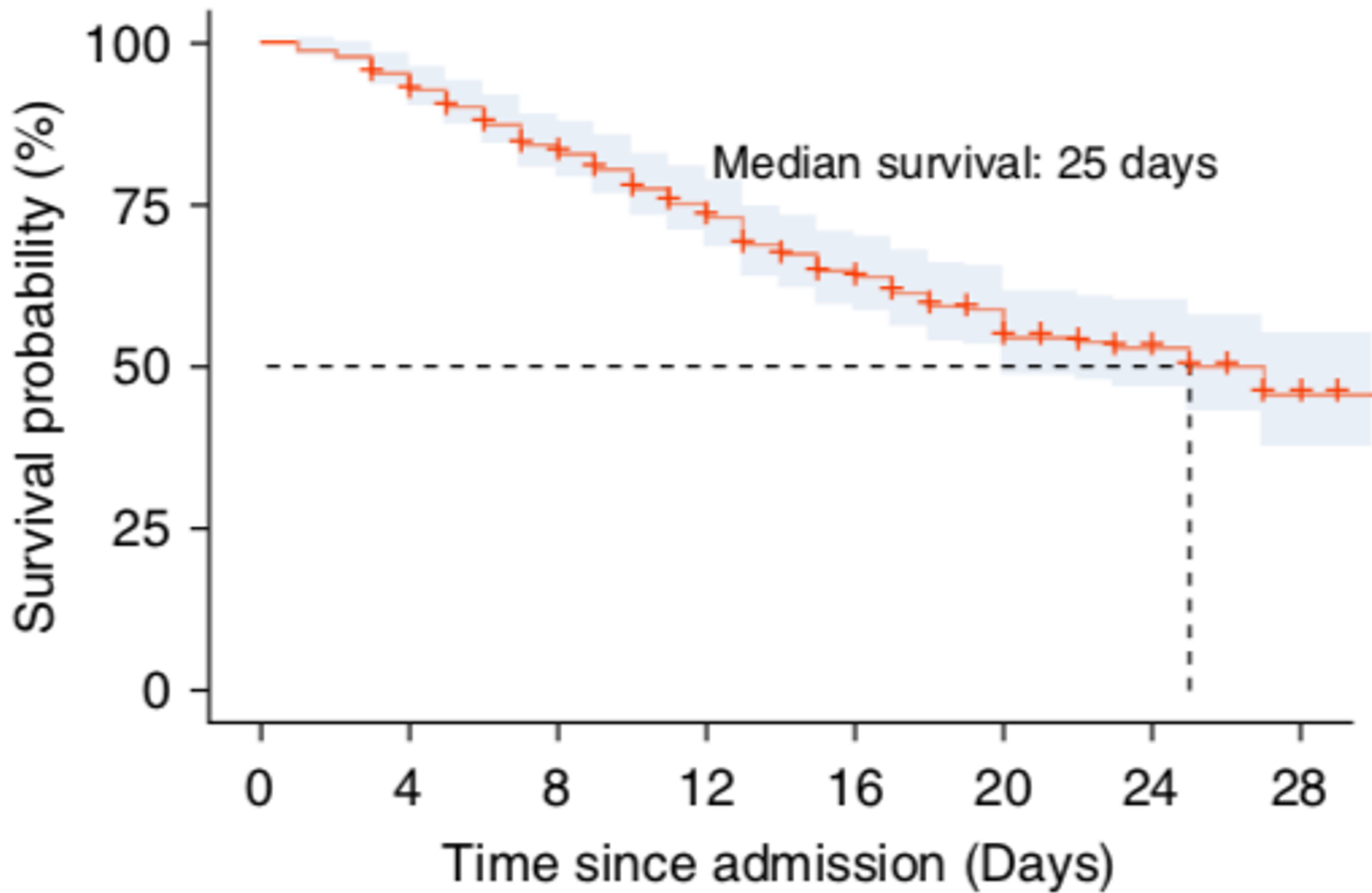
# Prognostic studies: survival

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# Prognostic studies: survival





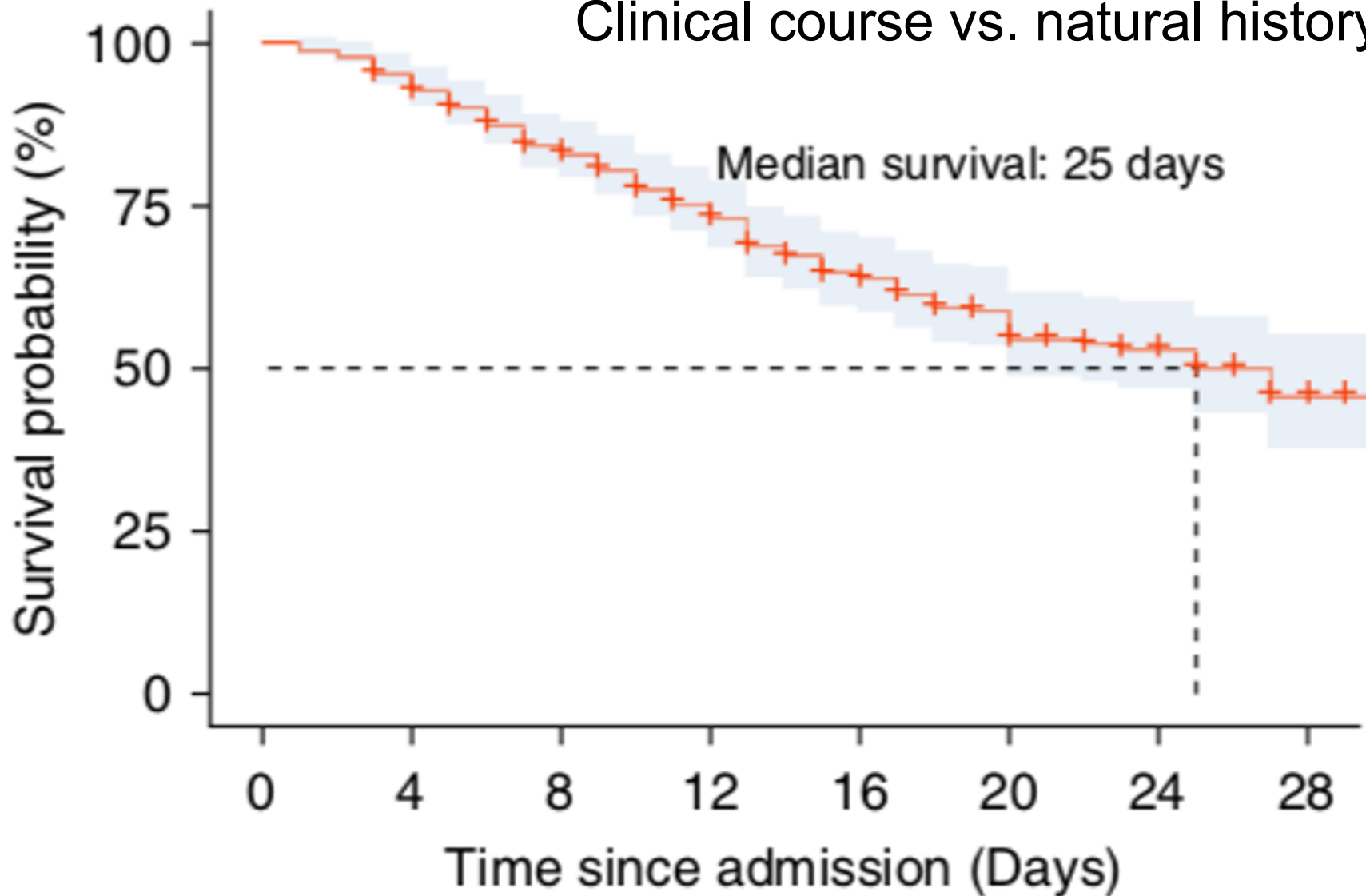
Wang, Yang, et al. "Clinical course and outcomes of 344 intensive care patients with COVID-19." *American Journal of Respiratory and Critical Care Medicine* (2020).

<https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0736LE>



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## Clinical course vs. natural history?

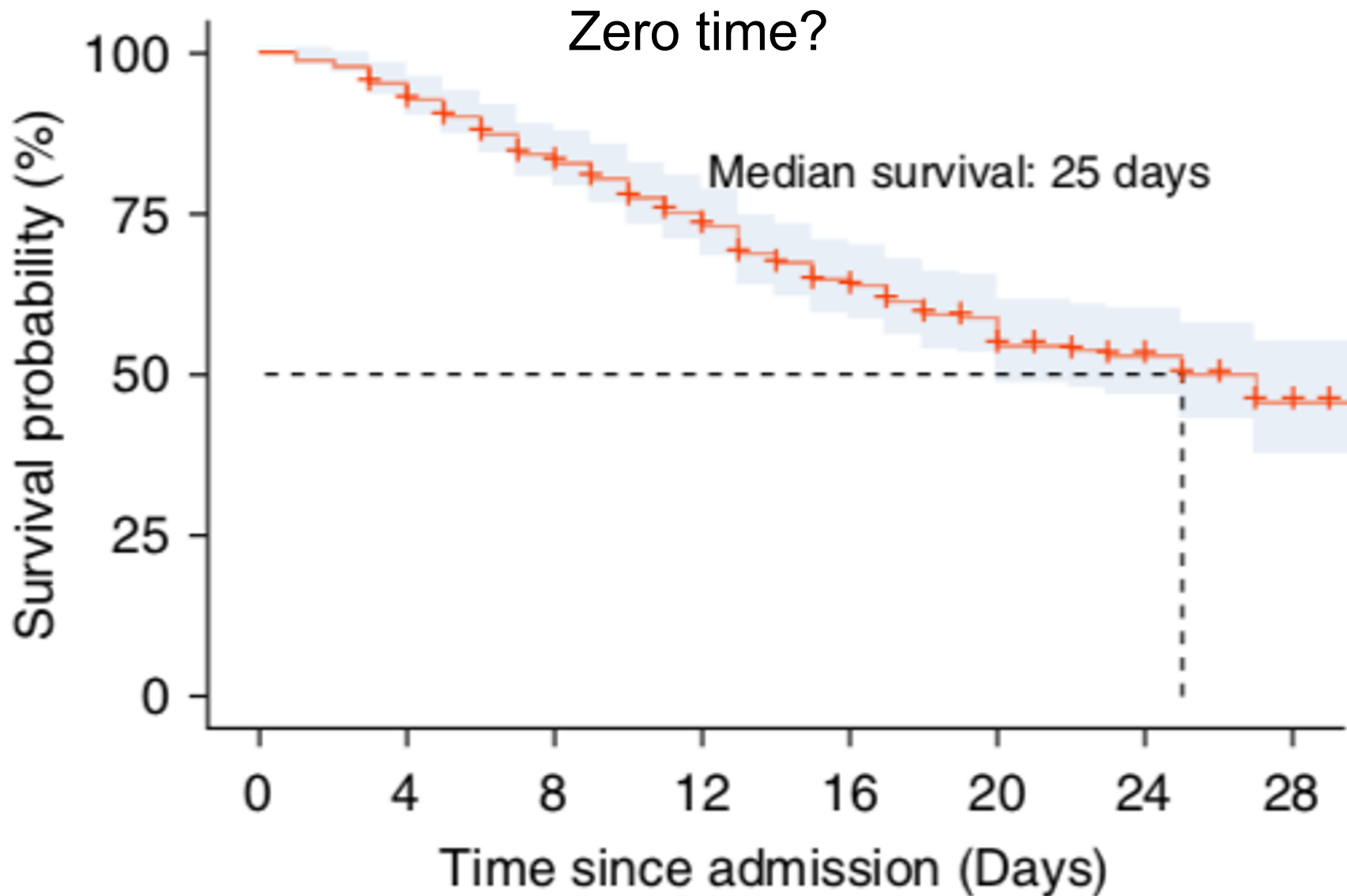


Wang, Yang, et al. "Clinical course and outcomes of 344 intensive care patients with COVID-19." *American Journal of Respiratory and Critical Care Medicine* ja (2020).

<https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0736LE>



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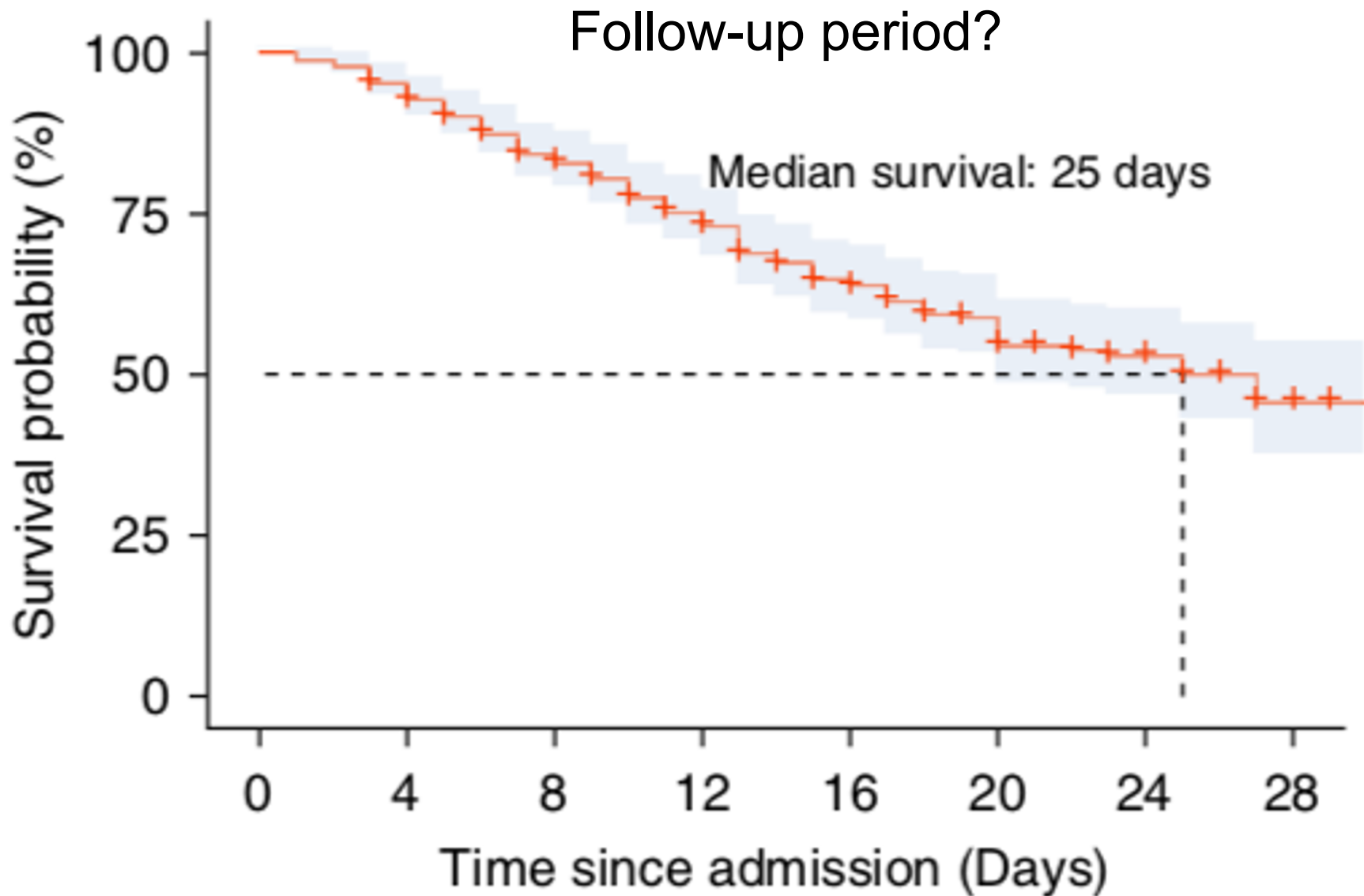


Wang, Yang, et al. "Clinical course and outcomes of 344 intensive care patients with COVID-19." *American Journal of Respiratory and Critical Care Medicine* ja (2020).

<https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0736LE>



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Wang, Yang, et al. "Clinical course and outcomes of 344 intensive care patients with COVID-19." *American Journal of Respiratory and Critical Care Medicine* ja (2020).

<https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0736LE>



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# Questions?

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# Summary

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- Frequency, prevalence
- Stratification, standardization
- Prognostic factors vs risk factors
- Clinical course vs. natural history
- Prognostic study designs
- Survival analysis





# General topic resources

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1. Fletcher RH & Fletcher SW. Clinical Epidemiology: The Essentials. 4th Ed. Chapter 4: Frequency Treatment and Chapter 7: Prognosis
2. AAU Health Sciences Library Institution Repository of Postgraduate Projects: <http://etd.aau.edu.et/handle/123456789/218>
3. CDC Principles of Epidemiology. <https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html>
4. UNAIDS: Ethiopia <https://www.unaids.org/en/regionscountries/countries/ethiopia>
5. PAHO: Standardization: A Classic Epidemiological Method for the Comparison of Rates
6. [https://www.paho.org/English/SHA/be\\_v23n3-standardization.htm](https://www.paho.org/English/SHA/be_v23n3-standardization.htm)
7. <https://www.cia.gov/library/publications/the-world-factbook/fields/341.html>
8. Alsan M, Wanamaker M, Hardeman RR. The Tuskegee study of untreated syphilis: A case study in peripheral trauma with implications for health professionals. Journal of general internal medicine. 2020 Jan 1;35(1):322-5. <https://link.springer.com/article/10.1007/s11606-019-05309-8> (related, movie Miss Evers' Boys, available for free on YouTube: <https://www.youtube.com/watch?v=nHP1p9bRQ3Q>)

Principles of Epidemiology in Public Health Practice, Third Edition

An Introduction to Applied Epidemiology and Biostatistics

Principles of Epidemiology in Public Health Practice, Third Edition

An Introduction to Applied Epidemiology and Biostatistics



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# Discussed papers

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1. Wang, Yang, et al. "Clinical course and outcomes of 344 intensive care patients with COVID-19." *American Journal of Respiratory and Critical Care Medicine* ja (2020).  
<https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0736LE>
2. Wang, Yeming, et al. "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial." *The Lancet* (2020).  
[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31022-9/fulltext?utm\\_source=yahoo&utm\\_medium=referral&utm\\_campaign=in-text-link](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext?utm_source=yahoo&utm_medium=referral&utm_campaign=in-text-link)
3. Tesfaye, Fikru, Peter Byass, and Stig Wall. "Population based prevalence of high blood pressure among adults in Addis Ababa: uncovering a silent epidemic." *BMC cardiovascular disorders* 9.1 (2009): 39.  
<https://link.springer.com/article/10.1186/1471-2261-9-39>
4. Bezabhe, Woldesellassie M., et al. "Adverse drug reactions and clinical outcomes in patients initiated on antiretroviral therapy: a prospective cohort study from Ethiopia." *Drug safety* 38.7 (2015): 629-639.  
<https://link.springer.com/article/10.1007/s40264-015-0295-7>
5. Canto, John G., et al. "Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction." *JAMA* 306.19 (2011): 2120-2127. <https://jamanetwork.com/journals/jama/article-abstract/1104631>
6. Gong H, Wu TT, Clarke EM. Pathway-gene identification for pancreatic cancer survival via doubly regularized Cox regression. In *BMC systems biology* 2014 Jan (Vol. 8, No. 1, p. S3). BioMed Central.  
<https://bmcsystbiol.biomedcentral.com/articles/10.1186/1752-0509-8-S1-S3>



# Additional examples

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Rheumatic heart disease prevalence in Ethiopia:

[https://journals.sagepub.com/doi/full/10.1177/2047487316687104?casa\\_token=Y0ma-VioKY8AAAAA%3AgOO5DPm0UGAoxcHggmn50WT2N6a5sD6-yusHFT9z0unL18cgAD1WGRRBTOF2OgUYL2MDTk4YOuzFw](https://journals.sagepub.com/doi/full/10.1177/2047487316687104?casa_token=Y0ma-VioKY8AAAAA%3AgOO5DPm0UGAoxcHggmn50WT2N6a5sD6-yusHFT9z0unL18cgAD1WGRRBTOF2OgUYL2MDTk4YOuzFw)

Incidence, prevalence + age standardization: Malaria in Ethiopia

<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-017-1919-4>

Incidence TB among PWHIV Addis:

<https://www.sciencedirect.com/science/article/pii/S1201971220301120>

Italy coronavirus case fatality by age: <https://www.statista.com/statistics/1106372/coronavirus-death-rate-by-age-group-italy/>

