The Global PBC Study Group

EASL, Vienna 2015

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Background

Since 1990 standard treatment of Primary Biliary Cirrhosis (PBC): Ursodeoxycholic acid (UDCA)

- Response to UDCA is for some patients suboptimal
- Continued need for new therapeutic options in PBC

Entering a new era with new treatment options for PBC

Trial setting

- Choice of endpoint
- Meet criteria of regulatory requirements
- Identification of a surrogate endpoint

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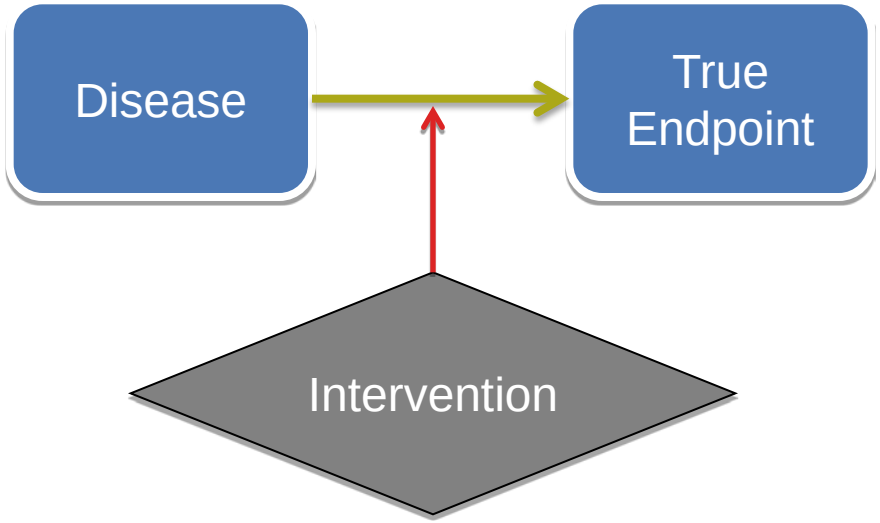
True endpoint problematic in PBC



PBC: Slowly progressive, chronic and rare disease

most patients present with early disease

➔ trials 8 – 10 years

Can we use surrogate endpoints?

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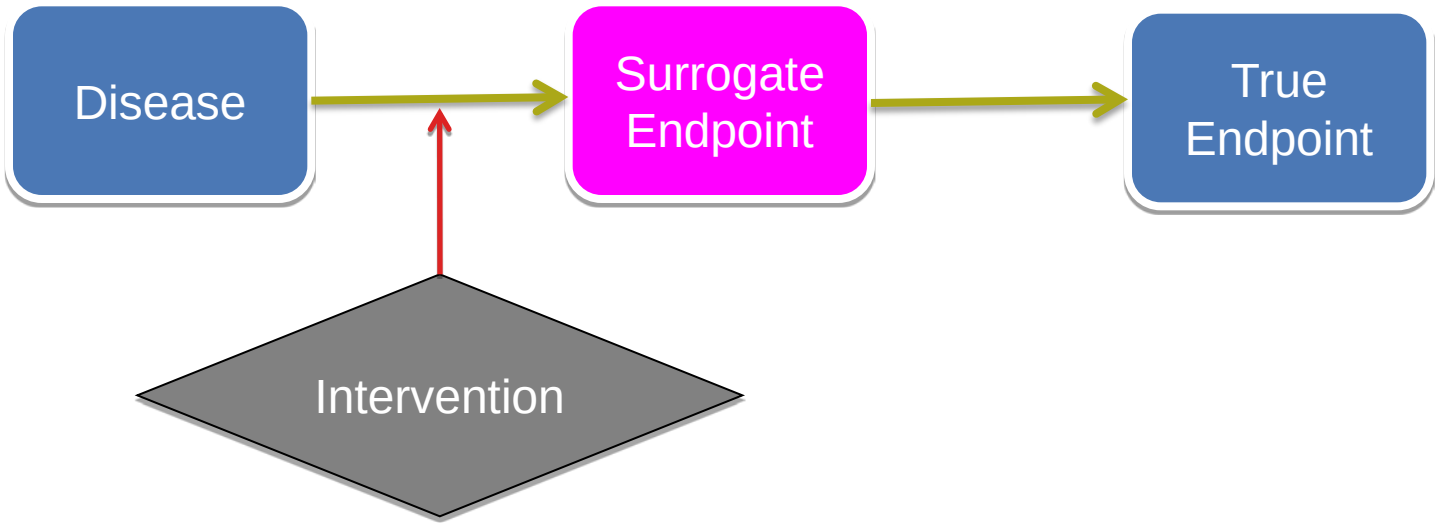
Requirements of a surrogate endpoint

- A validated substitute for the true endpoint
- Changes observed in the surrogate endpoint is expected to reflect changes in the true endpoint



Prentice, Stat in Med; 1989

Response Criteria in UDCA treated PBC

Criteria *Author*	Endpoint criteria	Endpoint	Reference
Barcelona *Parès*	ALP 40% decrease or normalization	Ltx-free survival	Gastroenterology 2006
Paris I *Corpechot*	ALP < 3 x ULN and AST < 2 x ULN and bilirubin < 1 mg/dl	Ltx-free survival	Hepatology 2008
Paris II *Corpechot*	ALP < 1.5 x ULN and AST < 1.5 x ULN and bilirubin < 1 mg/dl	Ltx-free survival, HCC ascites, variceal bleeding, encephalopathy,	J Hepatol 2011
Rotterdam *Kuiper*	Normalization of bilirubin and albumin	Ltx-free survival	Gastroenterology 2009
Toronto *Kumagi*	ALP < 1.67 X ULN	Histology	Am J Gastroenterol 2010
Toronto *Kumagi*	ALP < 1.67 x ULN and normal biirubin	Ltx-free survival	Hepatology 2010
Mayo *Mohma*	ALP < 1.67 x ULN and biirubin < 1 mg/dl	Ltx-free survival	Liv International 2010

Why chase the search of a surrogate endpoint in PBC?

- Time: a new intervention is quicker available on the market
- Care: the benefit/damage of an intervention is observed quicker
- Benefit for design of a new trial
  - Influence on sample-size calculation
  - Shorten duration of study
  - Influence of recruitment and participation enthusiasm
  - Reduced costs
- Benefit on long-term individual use:
  - Prediction models
  - Stopping rules

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What Makes a Good Surrogate Endpoint?

- Easy to measure
- Preferably non-invasive
- Progression of the surrogate endpoint precedes clinical symptoms
- Assessed within a short timeframe
- Epidemiology/clincal studies demonstrates that surrogate endpoints is linked to clinical outcomes
- Clinical trials demonstrate that treatment effects on the surrogate endpoint correspond to effects on the clinical outcome

Boissel JP et al. Eur J Clin Pharm 1992;43:235-44
Espeland MA et al. Current controlled trials in Cardiovascular Med 2005;6:3-6

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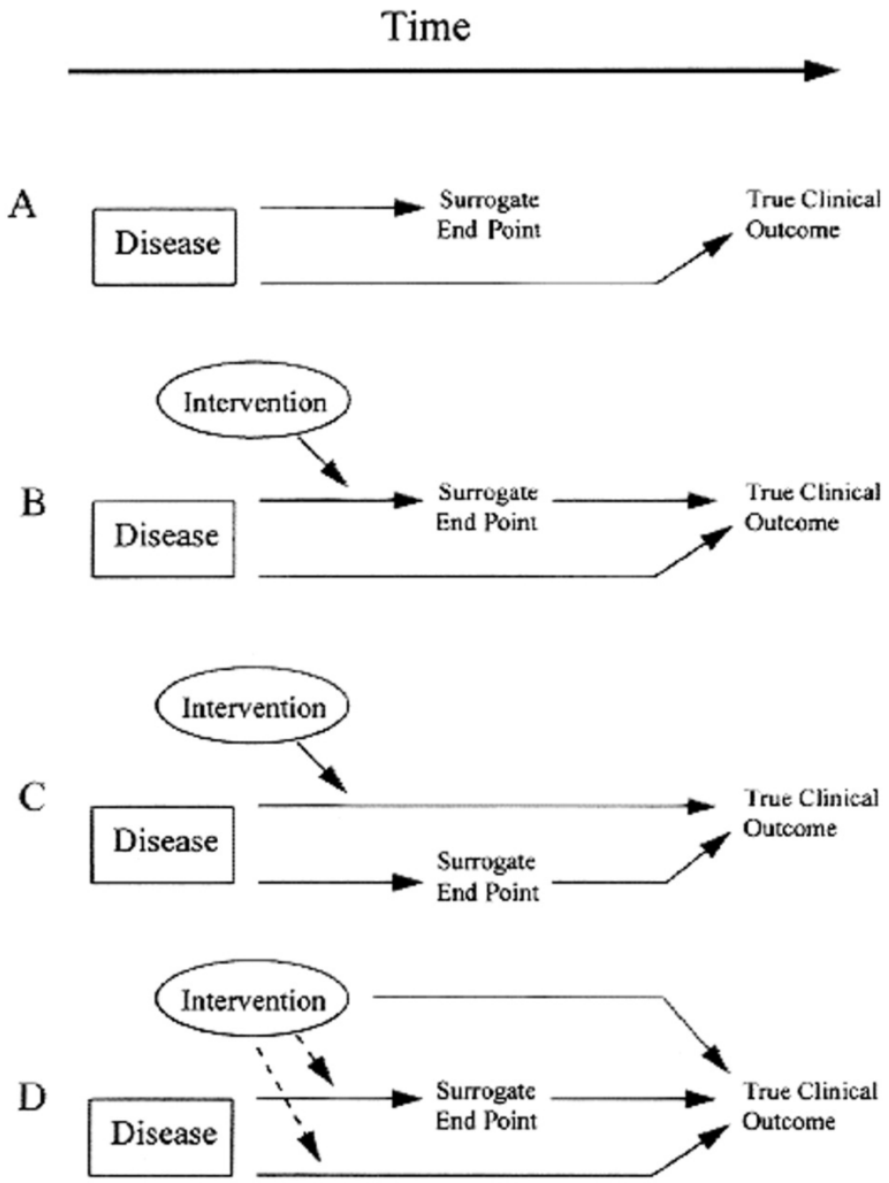
“A correlate does not a surrogate make”



Flemming Ann Intern Med. 1996

Reasons for failure of surrogate endpoints:

A. The surrogate is not in causal pathway of the disease

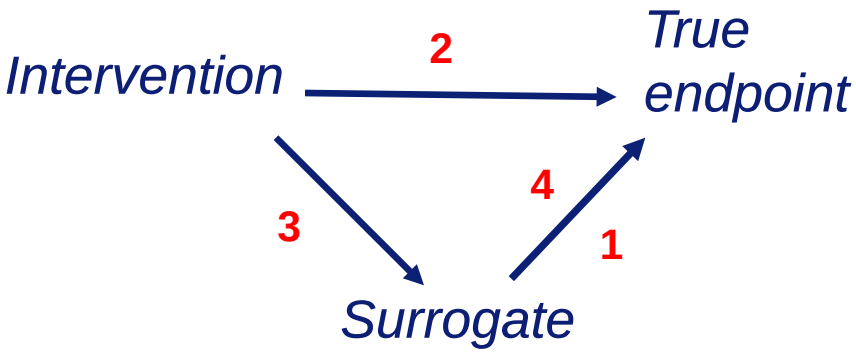
B. Of several causal pathways of disease the intervantion only affects the pathway mediated through the surrogate

C. The surrogate is not in the pathway of the intervention’s effect

D. The intervention has meachanisms of action independent of the disease process

- adverse drug reaction

How do you prove surrogacy?



Prove association between

1. Surrogate and True endpoint
2. Intervention and True endpoint
3. Intervention and surrogate endpoint

and

4. Prove Intervention is no longer significant if also Surrogate endpoint included for analysis of True endpoint

- Use meta-analysis of both endpoints in clinical trial settings of multiple related drugs
- Need in-depth understanding of disease process and mechanism of action of the intervention
- Approval EMEA and FDA

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Prentice, Stat in Med; 1989

4-level hierarchy for endpoints

Level 1

a true clinical efficacy measure

Level 2

a validated surrogate

likely appropriate primary endpoints in definitive or registration clinical trials

Level 3

a non-validated surrogate, yet one established to be “reasonably likely to predict clinical benefit”

might be considered as primary endpoints in clinical trials

Level 4

a correlate that is a measure of biological activity, but not yet established to be at a higher level

Fleming TR. Surrogate endpoints and FDA’s accelerated approval process. Health Affairs. 2005;24:67–78
Fleming TR, Powers, JH. Biomarkers and Surrogate Endpoints In Clinical Trials Stat Med 2012;31:2973-84

Philosophy

Joined forces

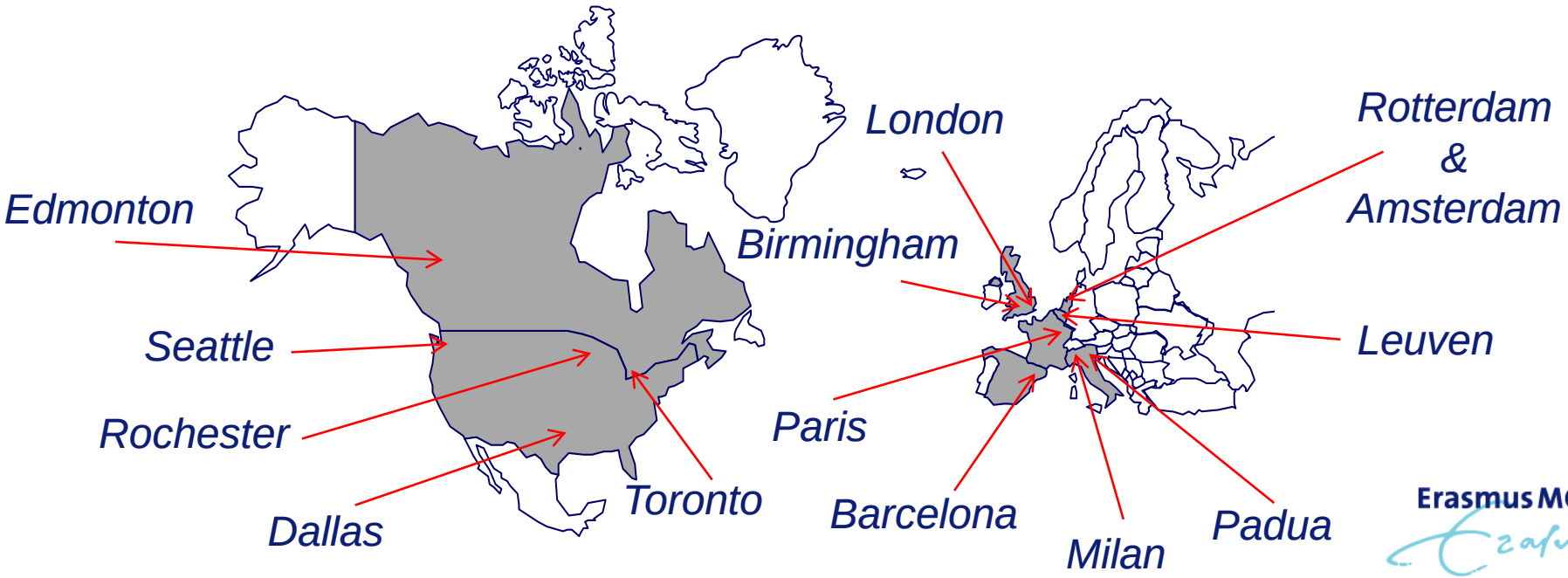
Joined forces

First “meeting” in 2011 in Berlin at EASL

Proposal: Meta-analysis of individual patient data

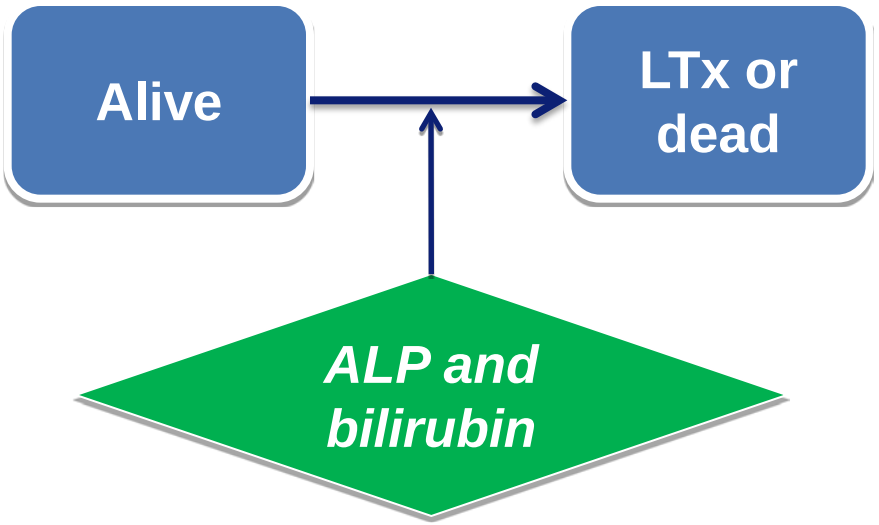
Long-term follow-up cohorts from 15 North American & European liver centres

Clinical data of PBC patients: treated and untreated



Aim

Determine the prognostic significance of ALP and bilirubin, as appropriate surrogate endpoints, in relation to transplant-free survival



Invitation to participate

Face-to-face meeting during every AASLD and EASL

Correspondence

- Protocol
- Consortium Agreement
- Case Record Form – electronic and paper
- Letter of expected inclusion

Site Visits (1-3 weeks visits)

- Update, help
- Construction of a total database
- Collection of data for specific projects

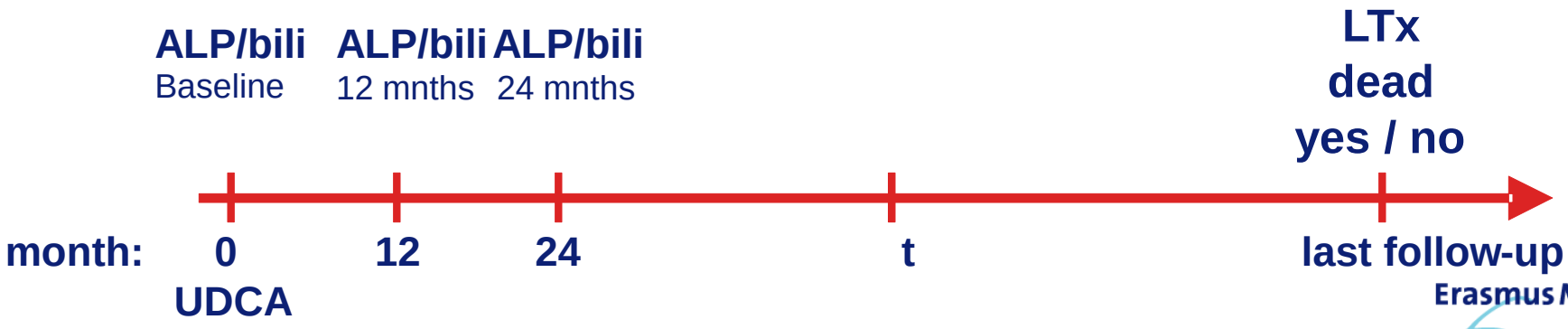
Data collection: individual patient data

True endpoints

- Liver transplantation (LTx)
- Death

Surrogate endpoints at baseline, **1 year** and 2 year of follow up:

- ALP, grid of cut off points (1.0, 1.1, …, **1.67**, …, 3.0 xULN)
- Total bilirubin



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CRF

SUMMARY CASE RECORD FORM

Study ID _____ Date of first visit (baseline) ___ / ___ / _____

Baseline patient information

General		PBC related information	
Date of birth	_____ / _____ / _____	Date of PBC diagnosis	___ / ___ / _____
Gender	male / female	AMA positive	Yes / No
Nationality	_____	Diagnostic liver biopsy*	Yes / No ___ / ___ / _____
Ethnicity	caucausian / african american /	if yes: stage**	I / II / III / IV
	asian / other: _____	Mayo Risk Score	_____
Weight	_____ (kg)	Child-Pugh Score***	_____ points
Alcohol	Yes / No _____ (units/day)	A-I overlap syndrome	Yes / No
Smoking	Previous / Current / No	Other major diseases (affecting 5yr life expectancy)	
UDCA therapy	Yes / No	_____	
Dose (mg/kg)	_____ (mg/kg)	Co-existing liver diseases (alcoholic, hepatitis B or C)	
Start date therapy	_____ / _____ / _____	_____	

PBC related information

Inducement for diagnosis fatigue / pruritus / lab (for _____) / other _____

* Within one year of inclusion date or earlier biopsy showing cirrhosis

** According to Ludwig classification

*** If cirrhosis is present

Folluw up period

First event of

Ascites	__ / __ / _____	No	Unknown
Variceal bleeding	__ / __ / _____	No	Unknown
Encephalopathy			
HCC	__ / __ / _____	No	Unknown
Cirrhosis	__ / __ / _____	No	Unknown
SBP	__ / __ / _____	No	Unknown

Use of medication (≥ 6 months)

Prednisone	Yes / No	__ / __ / _____	to	__ / __ / _____
Azathioprine	Yes / No	__ / __ / _____	to	__ / __ / _____
Budesonide	Yes / No	__ / __ / _____	to	__ / __ / _____
Methotrexate	Yes / No	__ / __ / _____	to	__ / __ / _____
Bezofibrates	Yes / No	__ / __ / _____	to	__ / __ / _____

SUMMARY CASE RECORD FORM

Months from baseline	Units Used	Normal range	0	6	12	24	36
Date			__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____
Bilirubin							
Albumin							
ALP							
AST							
ALT							
GGT							
Cholesterol							
IgM							
IgG							
Trombocytes							
Platelets							
PT							
Change UDCA dose or start							
other PBC therapy	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____

Months from baseline	48	60	72	84	96	108	120
	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____
Bilirubin							
Albumin							
ALP							
AST							
ALT							
GGT							
Cholesterol							
IgM							
IgG							
Trombocytes							
Platelets							
PT							
Change UDCA dose or start							
other PBC therapy	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____	__ / __ / ____

End of Follow Up

Steering Committee
Who

Rotterdam: BE Hansen & HR van Buuren

Birmingham: GM Hirschfield

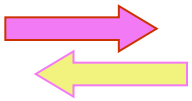
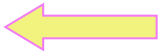
Rochester: KD Lindor

Barcelona: A Parés

Paris: C Corpechot

Toronto: HLA Janssen

Steering Committee Tasks

Investigator		Steering Committee
proposal of new study question		Steering Committee must approve
submit a (summary) protocol to the Steering Committee		approval is valid for 3 months
investigator first author of manuscript		approval of author list approval of scientific content

Philosophy

To qualify for authorship: Contributions should be in at least three areas:

- Conception and design
- Entering a sufficient number of evaluable patients
- Generating laboratory data from patient materials
- Analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Publication rules

General papers:

papers on full series of patients, addressing major goals of the study

Local papers:

papers initiated by any member of the GLOBAL PBC STUDY GROUP with focus on a specific question on a defined subset of samples

Publication rules
Authorship rules for general papers:

- 2 to 5 authors who did the work
- One representative per clinical center in order of decreasing number of patients
- One representative of the coordination center
- 1 to 5 senior authors: i.e. partners who led the work, participated in design and organization, and in the writing of the article
- Followed by

'for the GLOBAL PBC STUDY GROUP'

Publication rules
Authorship rules for local papers:

- The authors who did the work

  In the clinical center that specifically recruited patients for this paper
- Followed by

  'for the GLOBAL PBC STUDY GROUP'

- No 'clinical list' and no authors who are not directly related to the work must appear

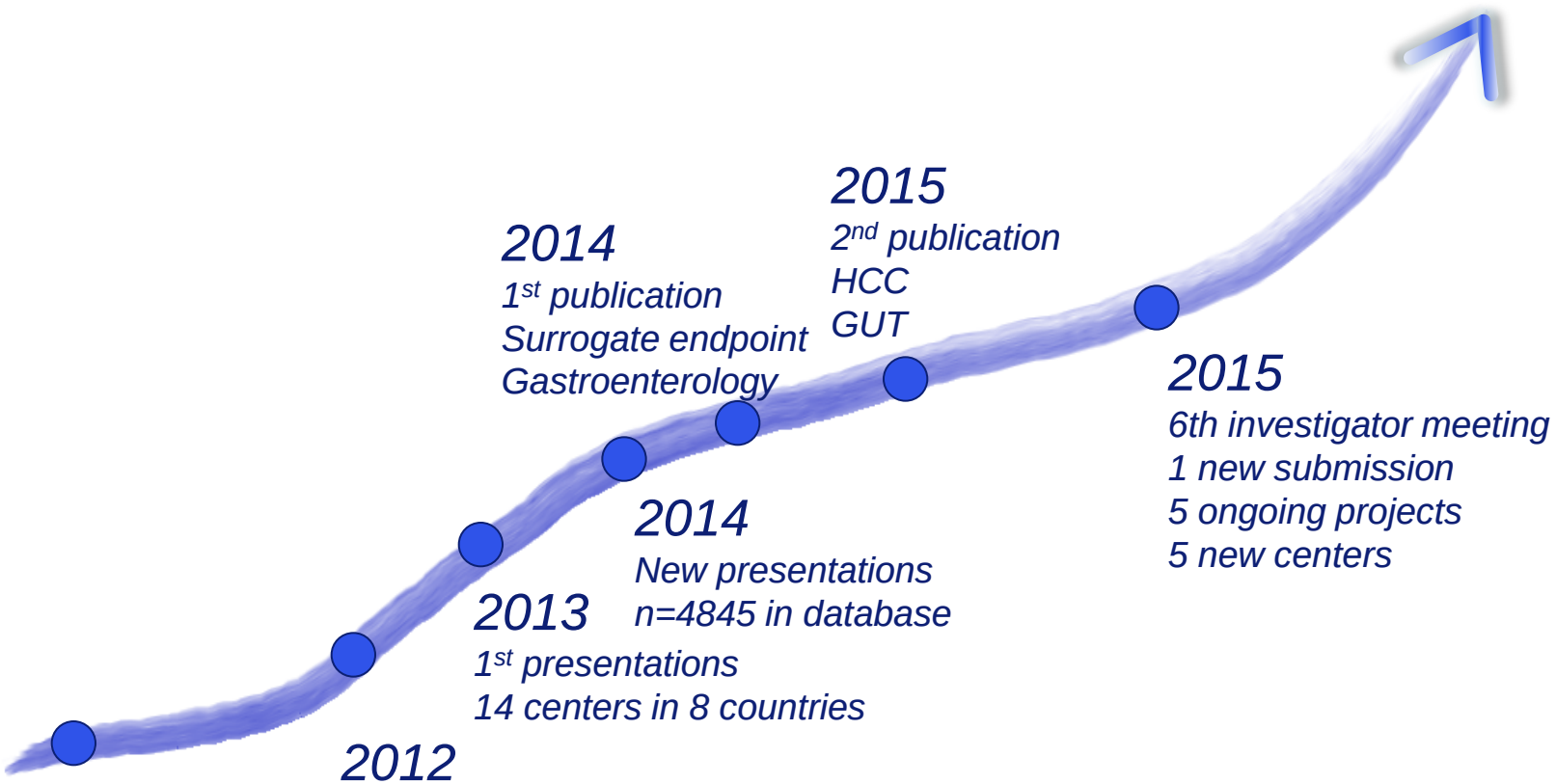
Data Ownership = ALL

Data stored in Rotterdam

If research question:

Data can be requested (after approval by Steering Committee) - visit to Rotterdam to run analysis

Continuous growth



AASLD 2013, Washington

PR and Communication

The Global PBC in the Yalung Ri (5630 m; Nepal)

Investigator Meetings: 2x yearly

Scientific Output:

- Presentations at EASL, AASLD, mono-thematic conferences, local
- Manuscripts

Email/Skype/TC contact: short lines

Logo

Grant applications

Newsletters

Website: under construction

Risk Score Calculator: submitted

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Challenges

- Financial support
  - Unrestricted grants from pharmaceutical industry
  - Application for official grants (EASL, …)
- Inclusion of new centers
- Ensuring high quality of data

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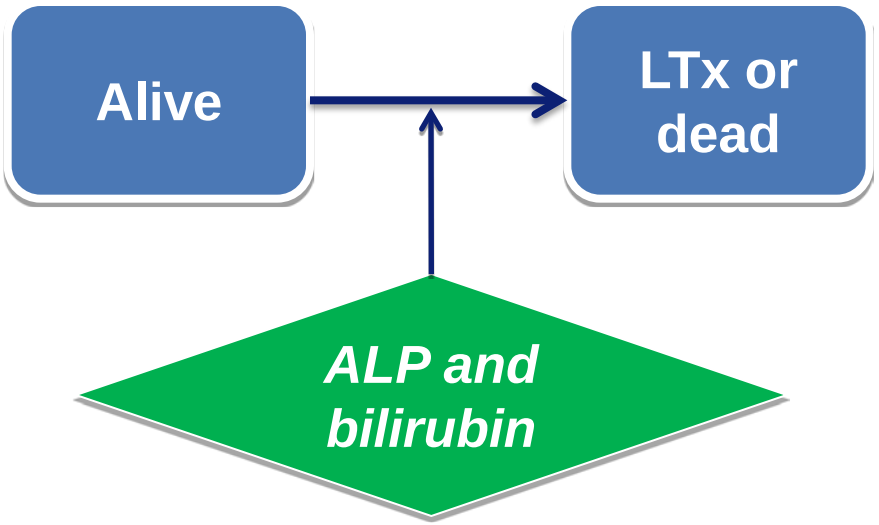
Global PBC projects

• Surrogate markers	*published*
• HCC	*published*
• Risk calculator	*submitted*
• Age and gender effects	*manuscript in preparation*
• Decompensation	*data collection running*
• Young Age	*data collection running*
• Liver transplantation	*data collection running*
• Dynamic prediction model	*analysis ongoing*
• …..	

Aim

Determine the prognostic significance of ALP and bilirubin, as appropriate surrogate endpoints, in relation to transplant-free survival



Potential surrogate markers in PBC

→ do changes reliably predict long-term outcome?

- liver histology
- liver imaging
- Fibroscan / Fibrotest e.s.o.
- Mayo / MELD score
- laboratory tests

Liver biochemical tests as surrogate endpoints

bilirubin, alkaline phosphatase,
gamma-gt, ASAT, ALAT,
albumin, PT/INR

- cheap
- non-invasive
- uniformly available
- changes observed within short time-frame

Serum bilirubin: a prognostic factor in primary biliary cirrhosis

Shapiro JM, Smith H, Schaffner F. Gut, 1979,20,137-140

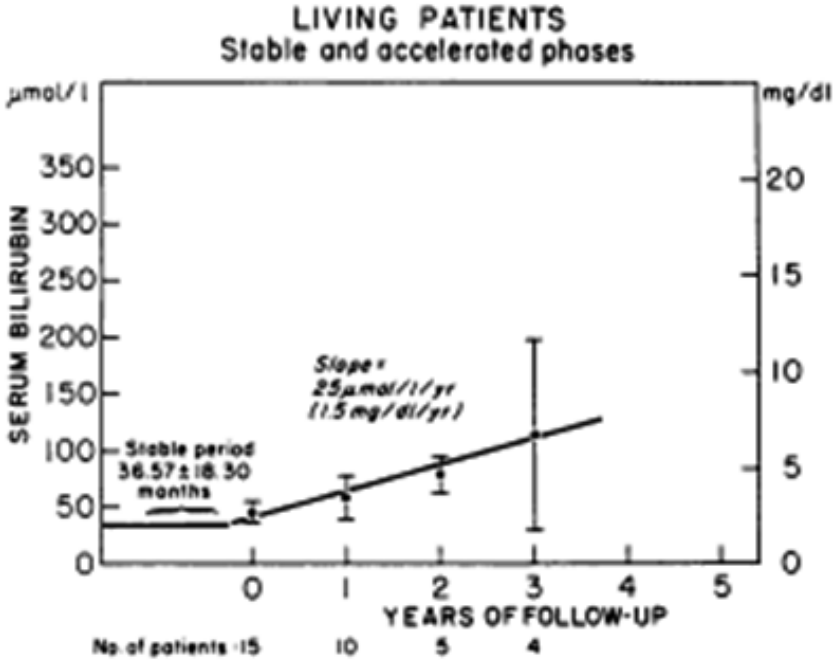


Fig. 1 *Serum bilirubin versus time for the 15 living patients who have had two consecutive serum bilirubin values greater than 34 μmol/l (2·0 mg/dl). The initial horizontal line shows the stable period before this change in serum bilirubin (averaging three years). The diagonal line denotes the linear rate of rise over time after the change in serum bilirubin. Results for each value are expressed ± SEM.*

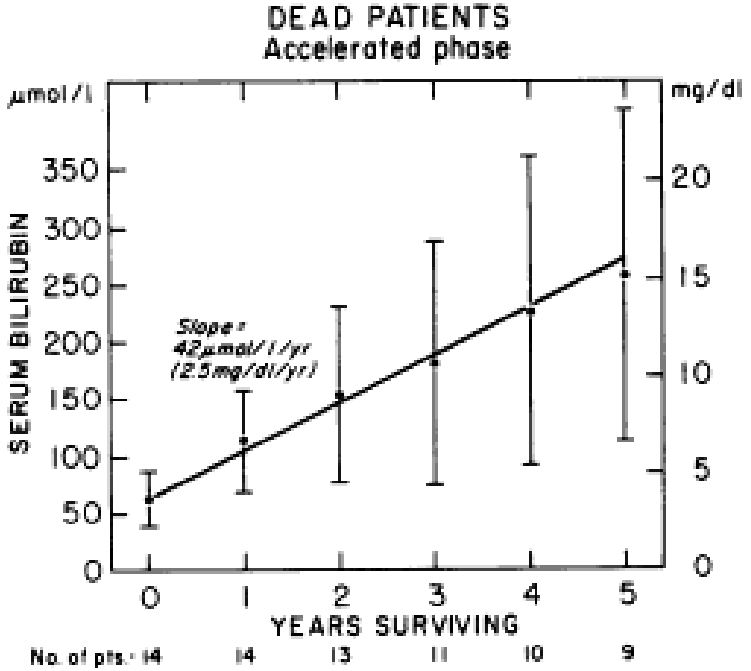


Fig. 2 *Serum bilirubin versus time in the 14 patients followed up until death. The line shows the approximate linear rate of rise of serum bilirubin after two consecutive previous values were both greater than 34 μmol/l (2·0 mg/dl). Please note the slope difference between Fig. 1 and 2. Results for each value are expressed ± SEM.*

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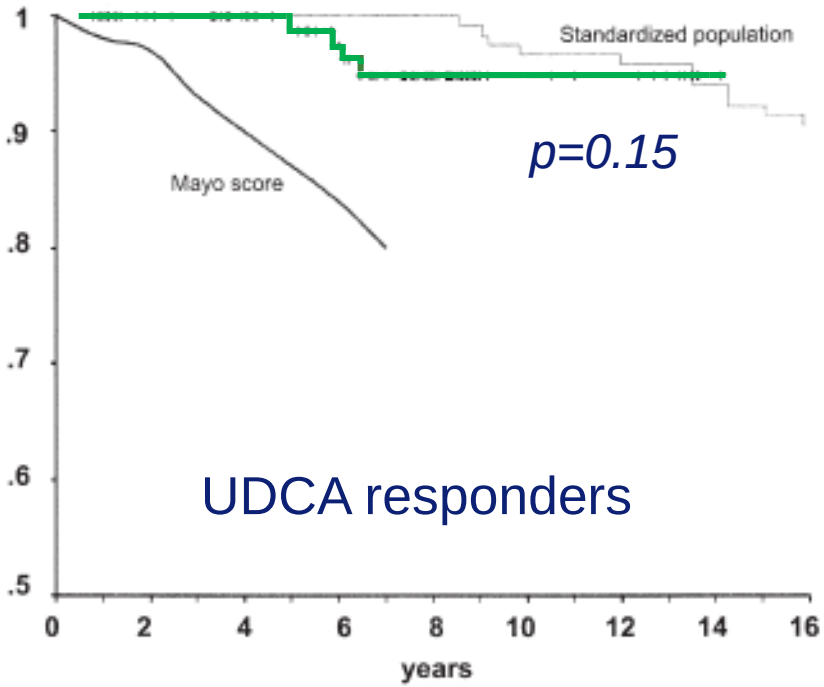
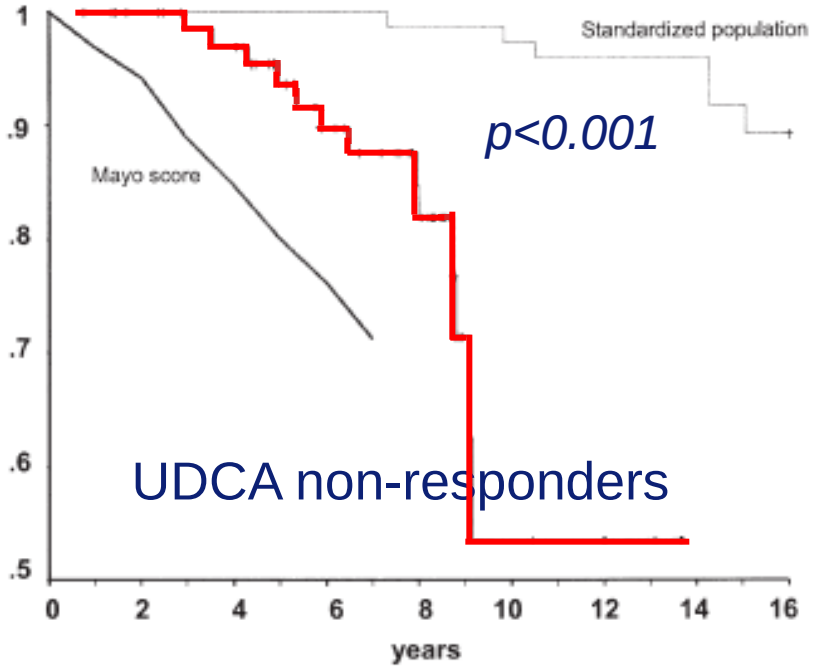
Biochemical response and prognosis

Pares definition for response:

ALP decrease > 40% OR normalization of ALP at 1 year





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Pares et al. Gastroenterology 2006;130:715-720

Bilirubin

Numerous studies showing prognostic significance of bilirubin

Bilirubin component of established prognostic models:

- Mayo model
- MELD score
- Child-Pugh score

Alkaline phosphatase

Key diagnostic variable

Mutiple studies indicating prognostic significance

Useful as surrogate endpoint?

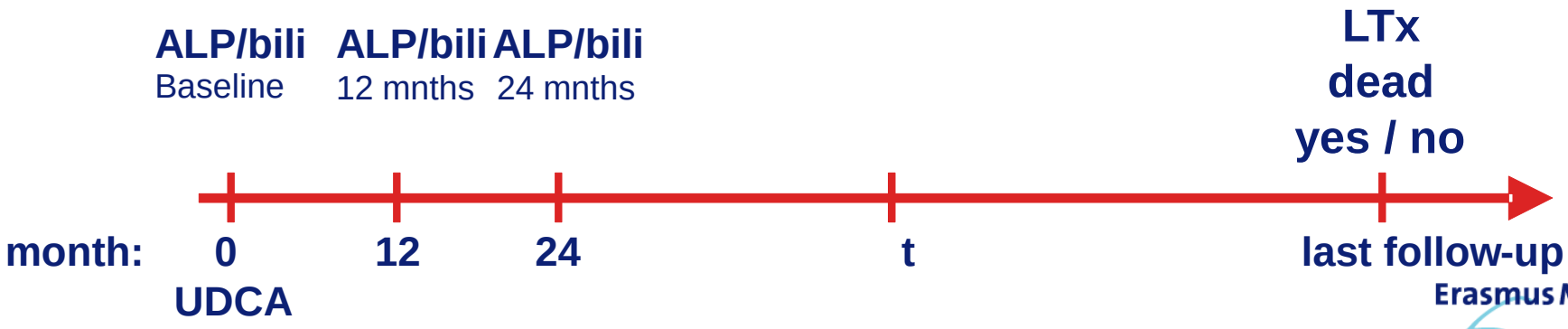
Methods

True endpoints

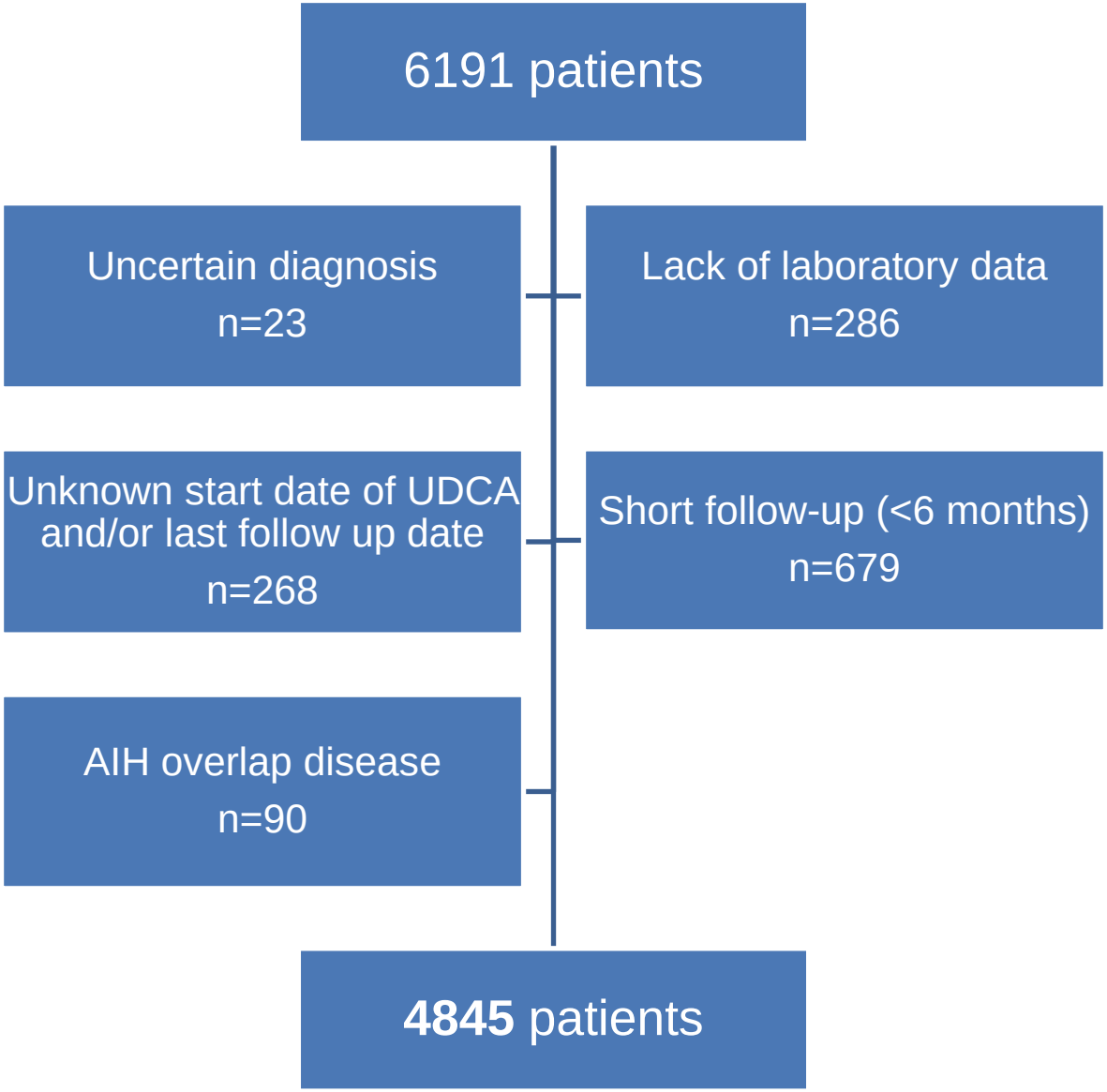
- Liver transplantation (LTx)
- Death

Surrogate endpoints at baseline, **1 year** and 2 year of follow up:

- ALP, grid of cut off points (1.0, 1.1, …, **1.67**, …, 3.0 xULN)
- Total bilirubin



Flowchart excluded patients



Clinical characteristics

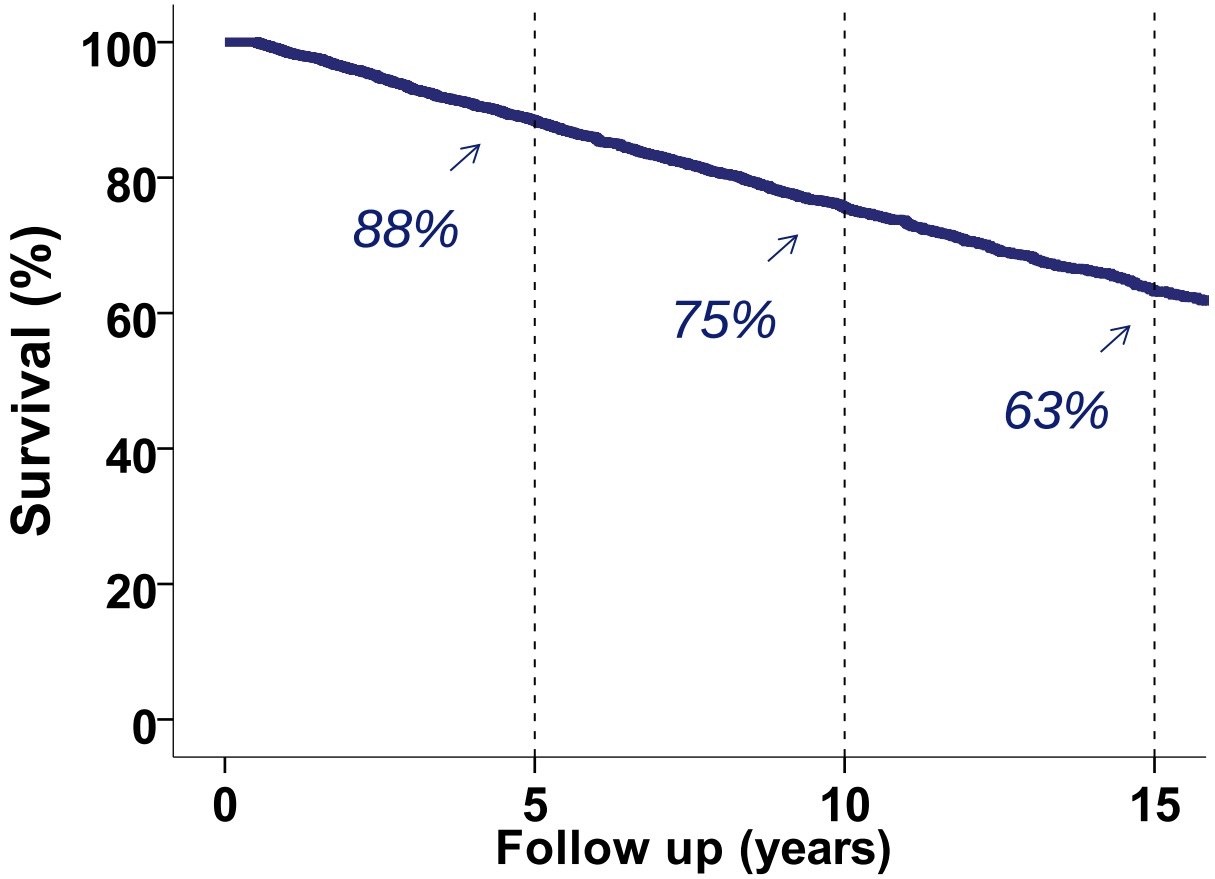
	Total group N=4845*	UDCA N=4119*	Non UDCA N=640*
Age (yr) *Mean (sd)*	53 (12)	52 (12)	56 (13)
Female *n (%)*	4348 (89.7%)	3706 (90.0%)	568 (88.8%)
Calendar time (yr) *Median (IQR)*	1998 *1991 – 2004*	1998 *1991 – 2003*	1999 *1989 – 2005*
Follow up (yr) *Median (IQR)*	7.3 (3.6 – 11.5)	7.7 (3.9 – 12.0)	5.3 (2.2 – 8.4)

**of 83 patients it is unknown whether they were using UDCA or not*

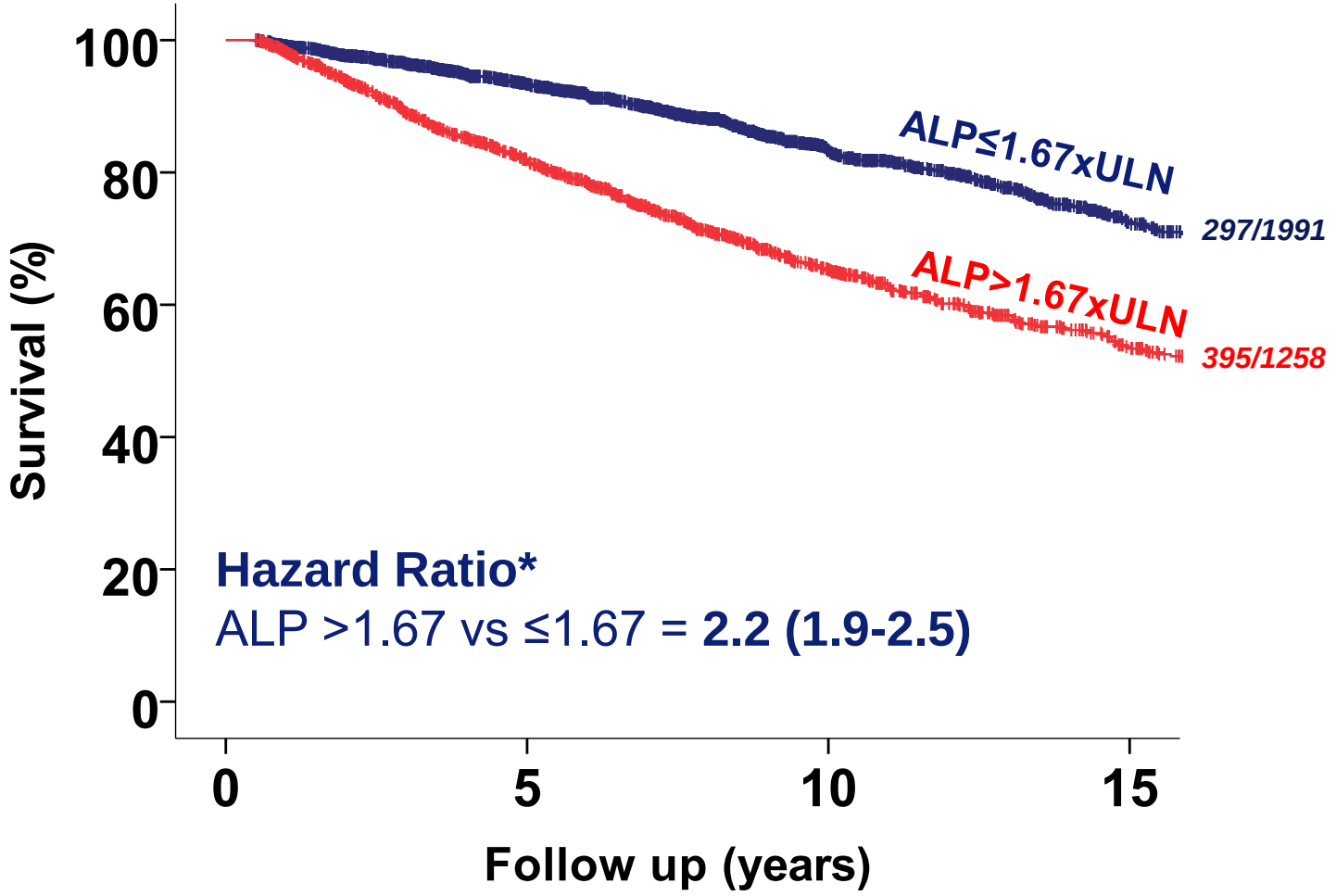
Clinical endpoints

	Total group N=4845	UDCA N=4119	Non UDCA N=640
Alive	3727 (76.9%)	3233 (78.5%)	441 (68.9%)
Death or liver transplantation	1118 (23.1%)	886 (21.5%)	199 (31.1%)
Death, all causes **-liver related**	729 (15.0%) 358 (7.4%)	566 (13.7%) 269 (6.5%)	139 (21.7%) 74 (11.6%)
Liver transplantation	389 (8.0%)	320 (7.8%)	60 (9.4%)

Transplantation-free survival



ALP values after 1 year of follow-up predict outcome



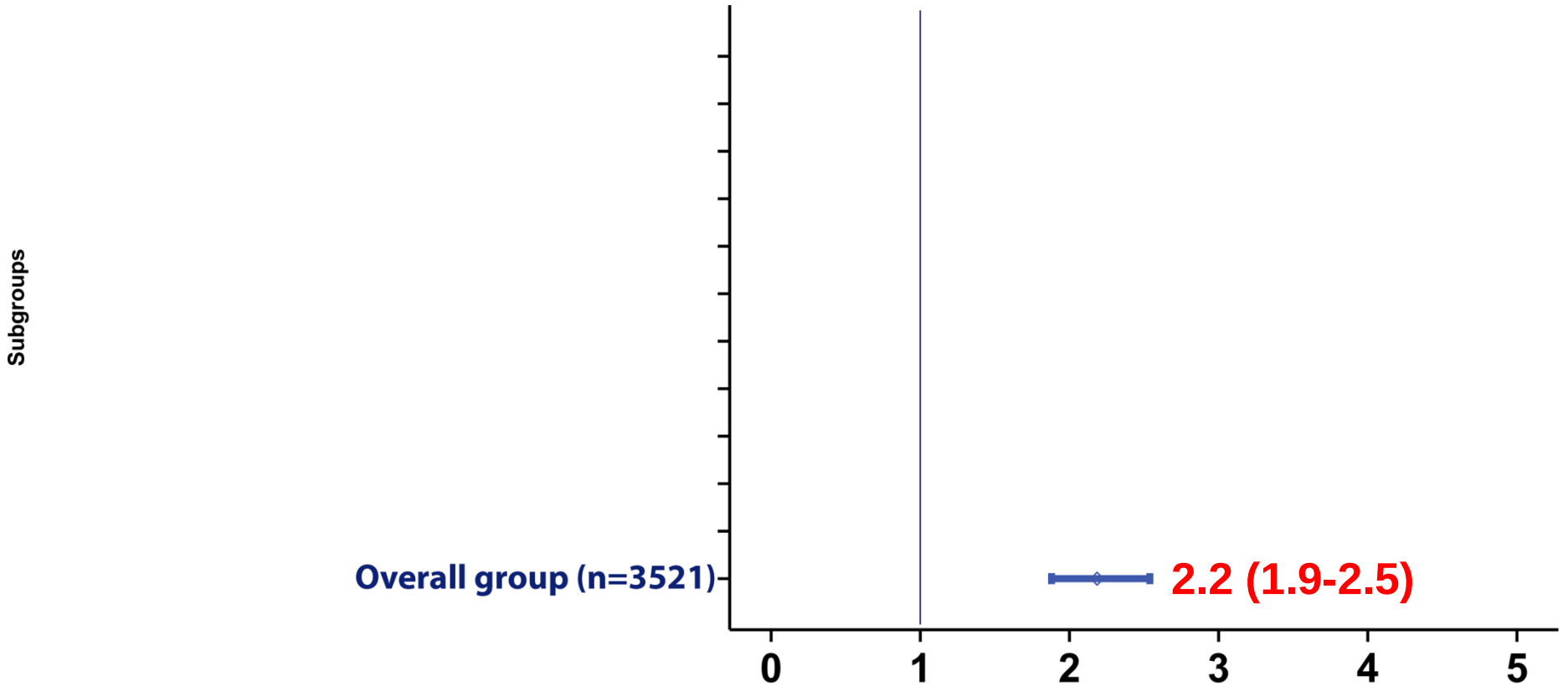
*adjusted for: centre, gender, age, year of diagnosis

Subpopulations

- If ALP<1.67 and normal bilirubin is a surrogate endpoint it should work
  - for any subpopulation
  - at different follow-up times : t=0, 1yr, 2yr, …, 5yr

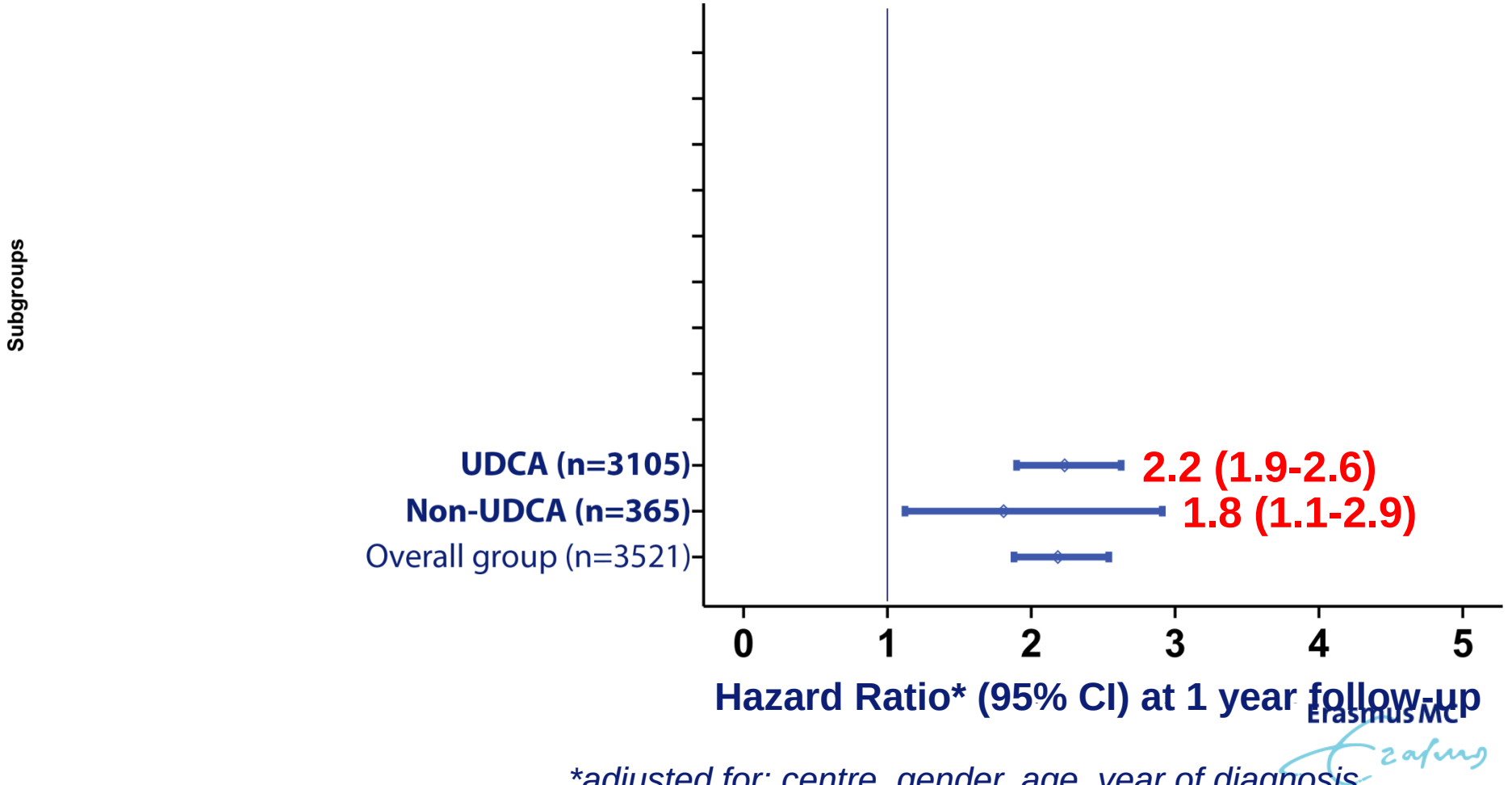
- Study Populations:
  - All, UDCA treated, no UDCA
  - Female/male
  - Age groups: <55 yr, <60 yr, <65 yr
  - Diagnose years: <1990, 1990-1999, >2000
  - Disease state: by bilirubin/alb, by biopsy

The effect of ALP>1.67xULN versus ALP≤1.67xULN in different subgroups



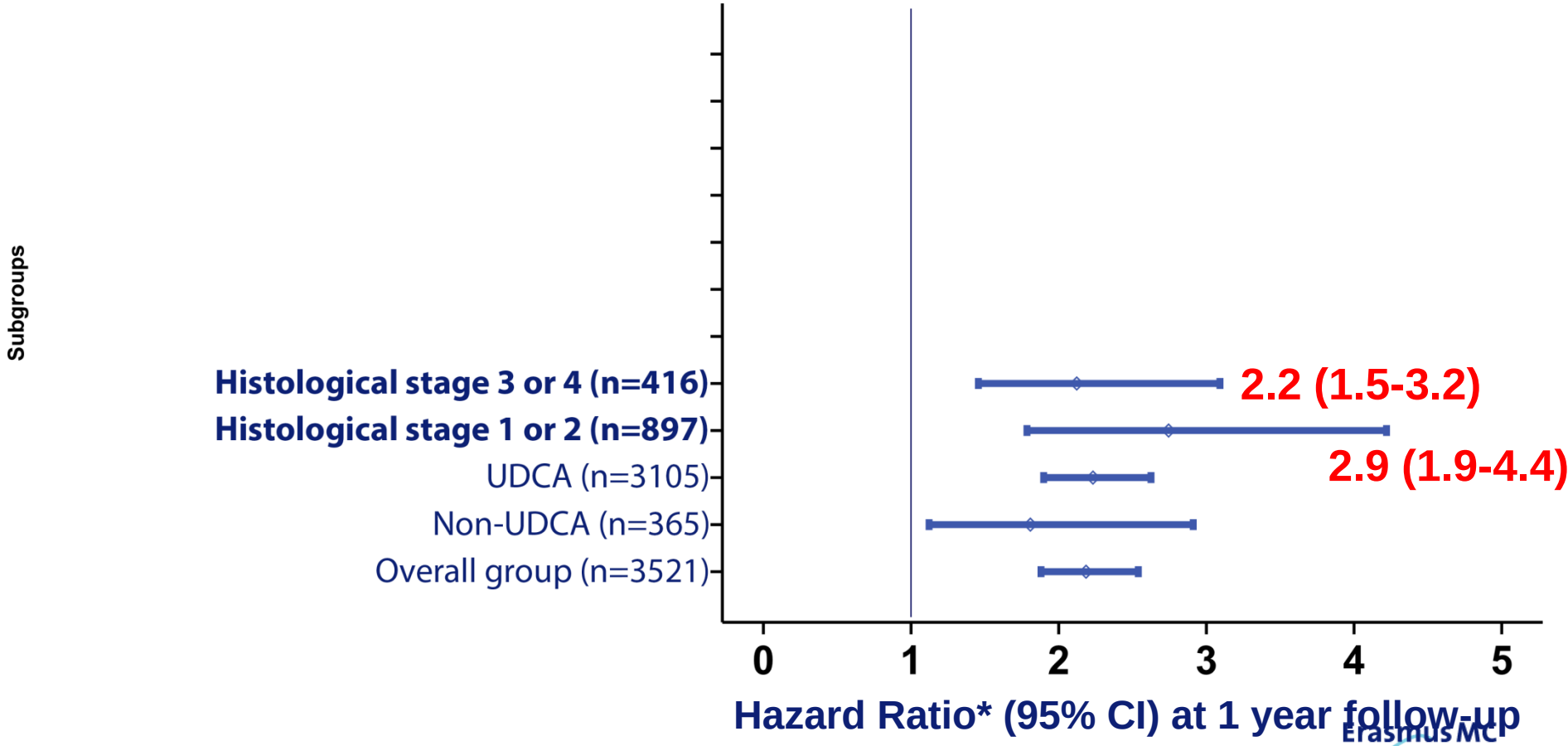
*adjusted for: centre, gender, age, year of diagnosis

ALP values predict outcome in both treated and untreated PBC patients



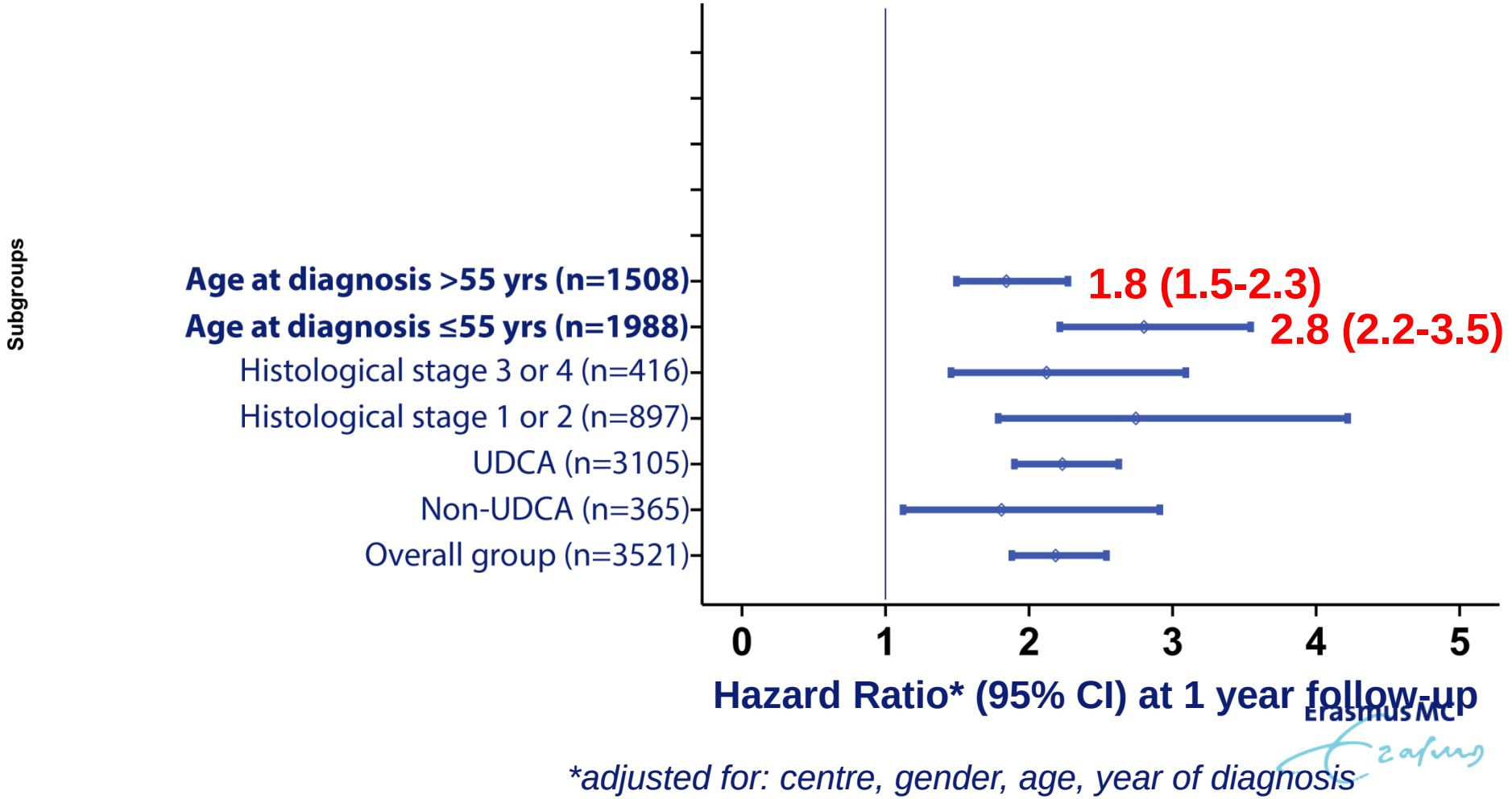
*adjusted for: centre, gender, age, year of diagnosis

ALP values predict outcome in both early and late stage disease



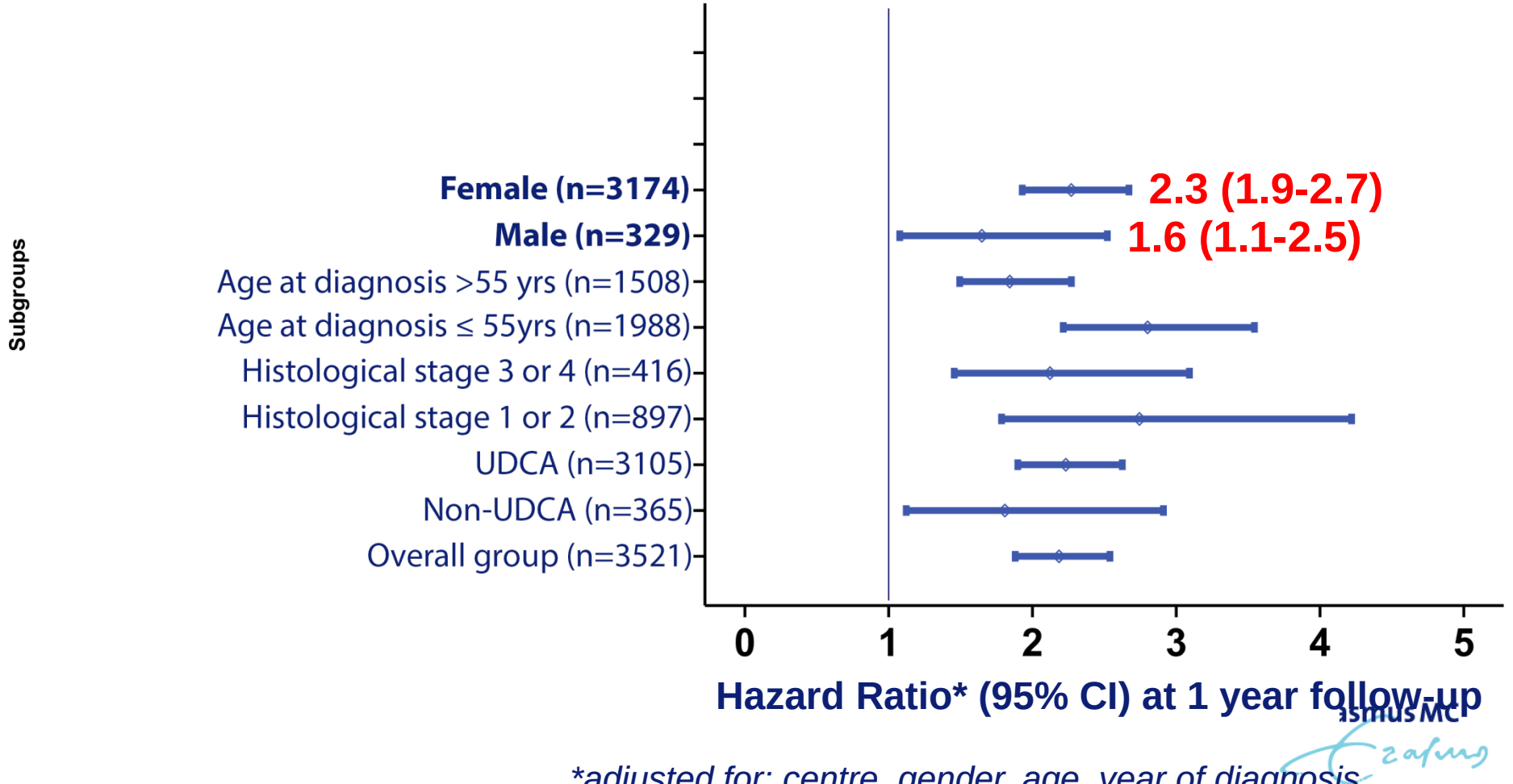
*adjusted for: centre, gender, age, year of diagnosis

ALP values predict outcome in both young and old patients at time of diagnosis



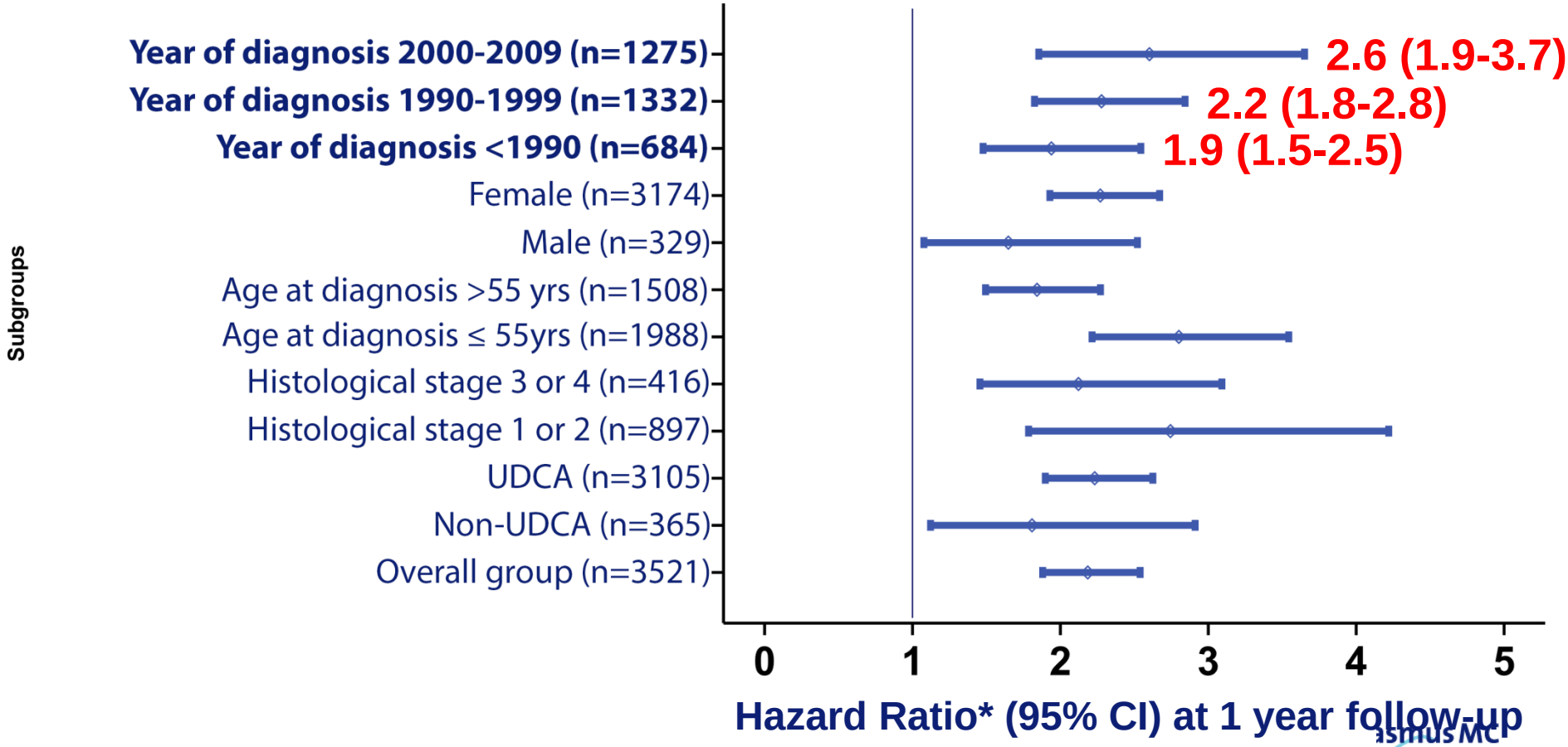
*adjusted for: centre, gender, age, year of diagnosis

ALP values predict outcome in both males and females



*adjusted for: centre, gender, age, year of diagnosis

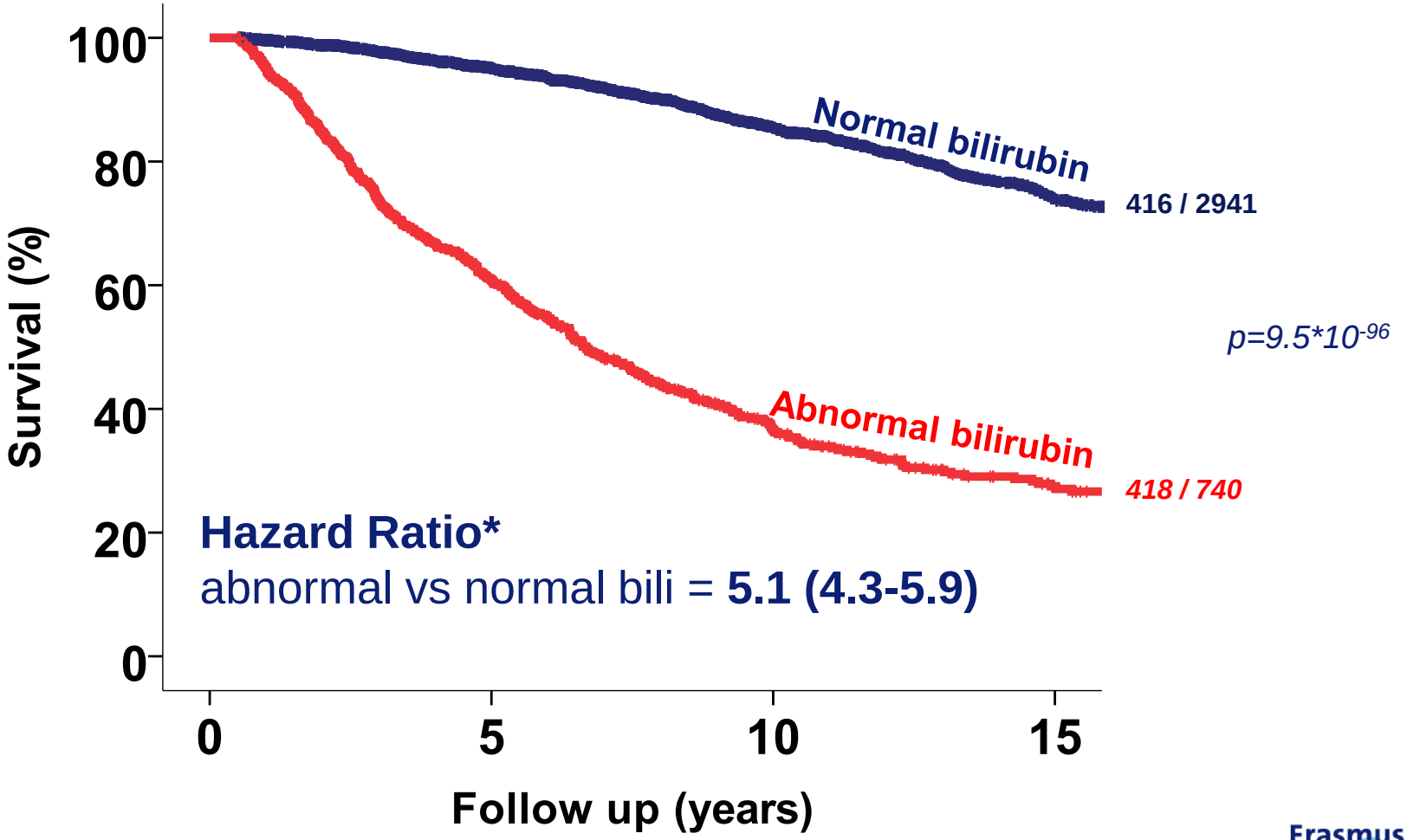
ALP values predict outcome regardless of year of diagnosis



*adjusted for: centre, gender, age, year of diagnosis

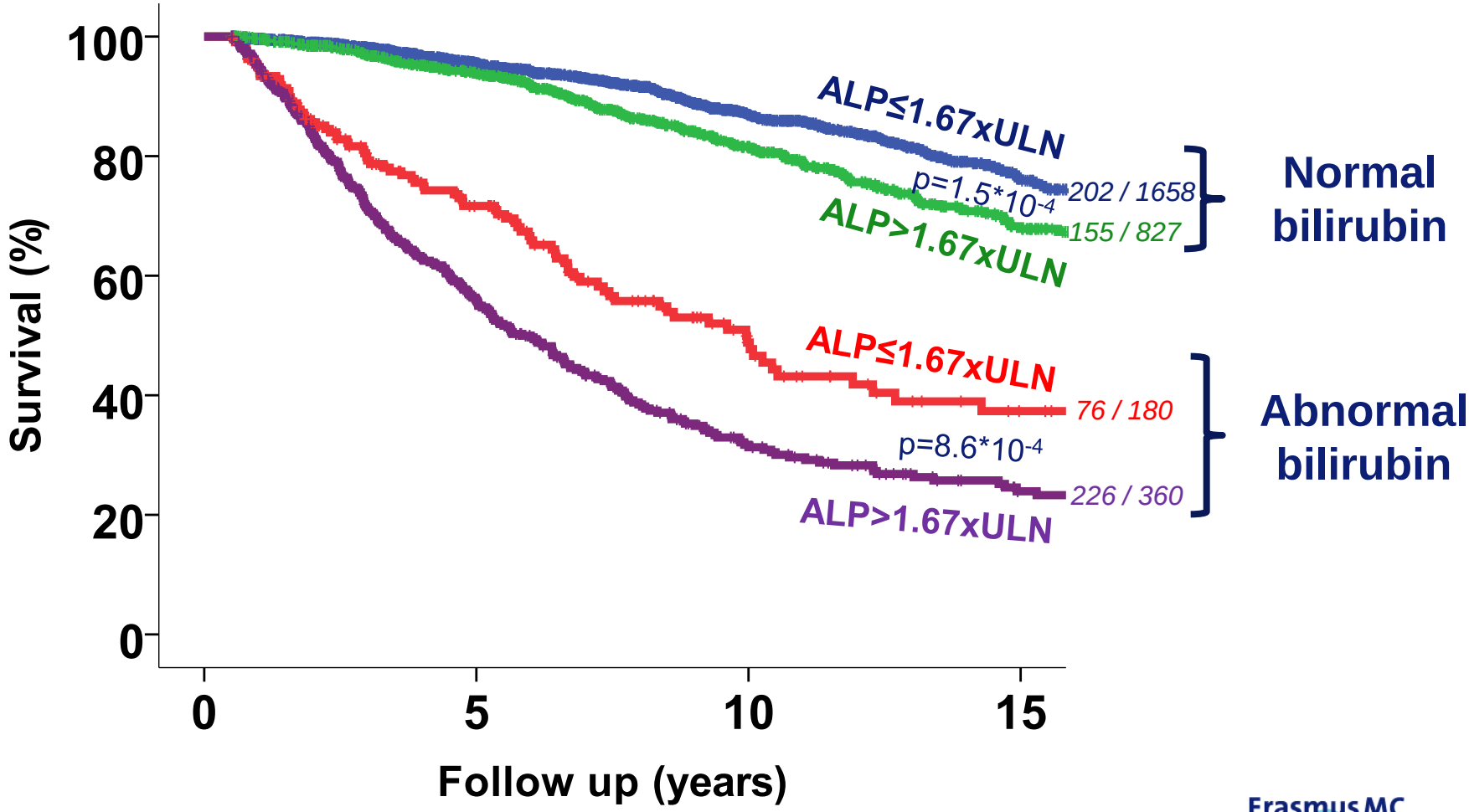
Lammers et al., Gastroenterology 2014

Abnormal bilirubin values are associated with worse transplant-free survival



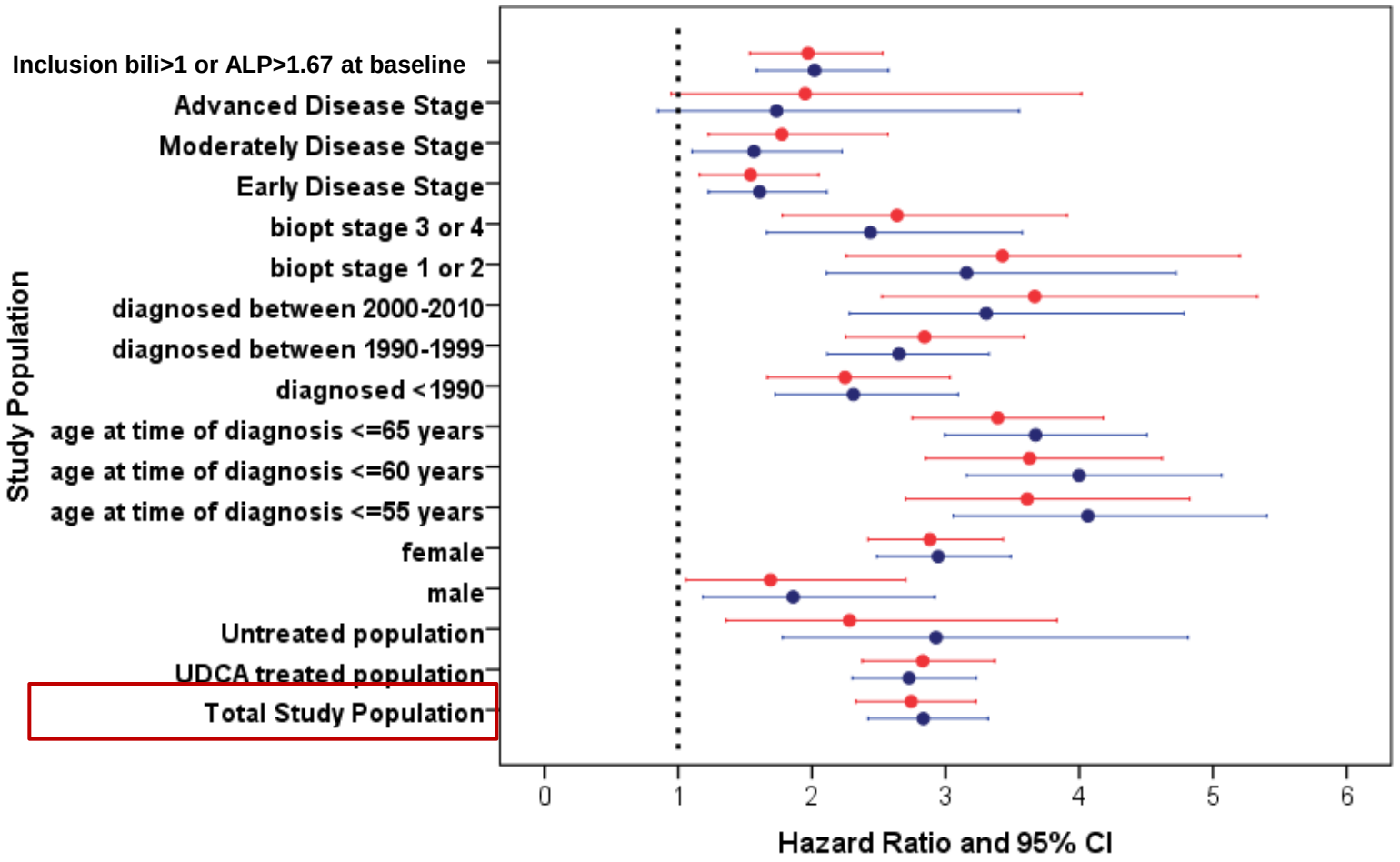
*adjusted for: centre, gender, age, year of diagnosis

ALP values have predictive significance in addition to bilirubin values



Lammers et al., Gastroenterology 2014

Hazard Ratio ALP>1.67 or bilirubin>1 versus ALP<1.67 and bilirubin normal at 1 year follow-up



- Crude HR, stratified on centre
- HR adjusted by age, sex, diagnose year stratified on centre

What Makes a Good Surrogate endpoint?

Bilirubin & alkaline phosp

- *Easy to measure* **+**
- *Preferably non-invasive* **+**
- *Progression of the surrogate endpoint* **+**

  precedes clinical symptoms
- *Assessed within a short timeframe* **+**
- *Epidemiology/clincal studies demonstrates* **+**

  that surrogate endpoints is linked to clinical outcomes
- *Clinical trials demonstrate that treatment* **+ / -**

  effects on the surrogate endpoint

  correspond to effects on the clinical outcome

Summary

- Alkaline phosphatase (ALP) and bilirubin values are correlated with transplant-free survival
- The combination of ALP and bilirubin is a stronger predictor of outcome than ALP or bilirubin alone
- The combination of ALP and bilirubin is a strong predictor
  - overall
  - in multiple subgroups
  - at multiple time points
  - throughout followup

  thus independent of subgroup and time, UDCA treated or untreated patients

Lammers et al., Gastroenterology 2014

Conclusion

Surrogate Endpoints in PBC Trials:
Are we there yet?

- Currently no validated surrogate endpoint (*level 2 evidence*) for true clinical endpoints in PBC *(unless we reconsider method to prove)*

- Biochemical variables alkaline phosphatase and bilirubin **seem reasonably likely to predict clinical risk** in both UDCA treated and untreated patients (**level 3 evidence**)

- Further validation of surrogate endpoints in other cohorts, in particular in patients treated with other drugs than UDCA, is necessary