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PAGE
Population Approach Group Europe

Longitudinal biomarkers predicting death of hospitalized patients for SARS-COV-2 infection: a joint analysis with competing risks

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30/06/2022

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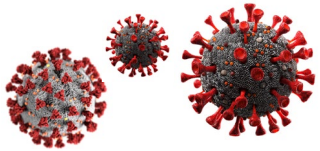
Context



Start of the COVID-19 pandemic

Thousands of cases

Saturation of intensive care units and emergency departments

- **Personalized predictions** of the survival of hospitalized patients for SARS-COV-2 infection can be useful:
  - To streamline therapeutic alternatives (escalation or limitation of care)
  - To improve hospital organization (beds, staff…) and forecast needs

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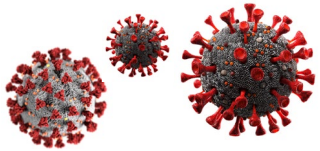

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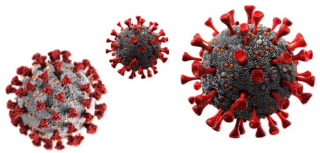
- Since 2020, prognostic **scores**[1,2,3] have been developed using clinical characteristics available at hospital admission

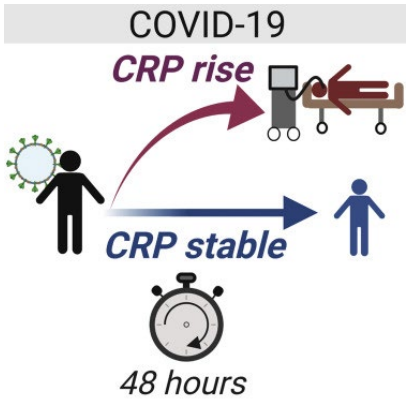
4C-score[1] includes baseline characteristics (age, gender, comorbidities) and baseline biomarker measurement (admission CRP, urea,…)

1- Knight et al., *BMJ*, 2020
2- Myrstad et al., *Scand J Trauma Resusc Emerg Med*, 2020
3- Liang et al., *JAMA Intern Med,* 2020

Context



- **Clinical studies** described association between prognosis and baseline biomarker measurements[4,5,6], or biomarkers changes between different days[7,8,9]



Mueller et al. Inflammatory Biomarker Trends Predict Respiratory Decline in COVID-19 Patients, Cells Reports Medicine, 2020

4- Zhang et al., J Thromb Haemost, 2020
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6- Tjendra et al. *Arch Pathol Lab Med,* 2020
7- Li et al., *Intern Emerg Med,* 2021
8- Lavillegrand et al. *Ann Intensive Care*, 2021
9- Mueller et al. *Cell reports Medicine*, 2020

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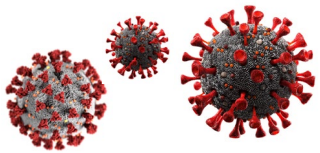

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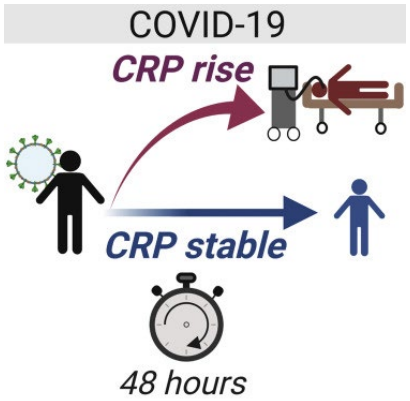

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- None of them consider **the full** follow-up of biological information until clinical outcome

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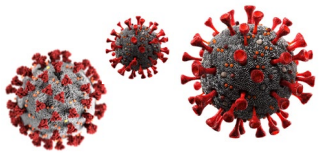

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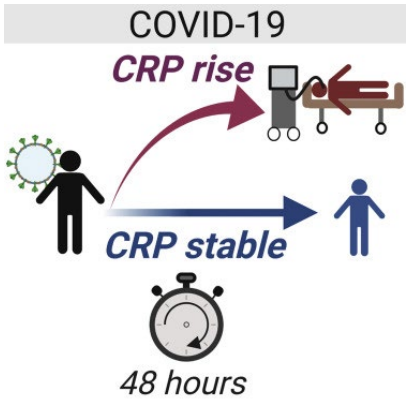

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Objectives:

- To build a multivariable joint model with several biomarkers most associated with the risks of in-hospital death / discharge from hospital
- To assess the added value of considering results of biological exams during stay compared to only baseline (admission) information

4- Zhang et al., J Thromb Haemost, 2020
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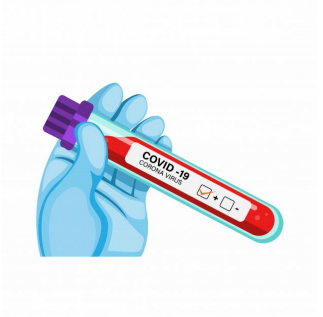


Patients

- Retrospective cohort (RisCOV, PI: Pr Xavier Lescure)
  - 327 patients
  - 59 biomarkers

- Patients hospitalized during the **first wave of COVID-19 pandemic** (January to July 2020) in the Infectious and Tropical Disease Department of Bichat AP-HP (Paris, France)

- An extraction of the AP-HP data warehouse provided all the results of **available biological exams** during hospital stay until day 30

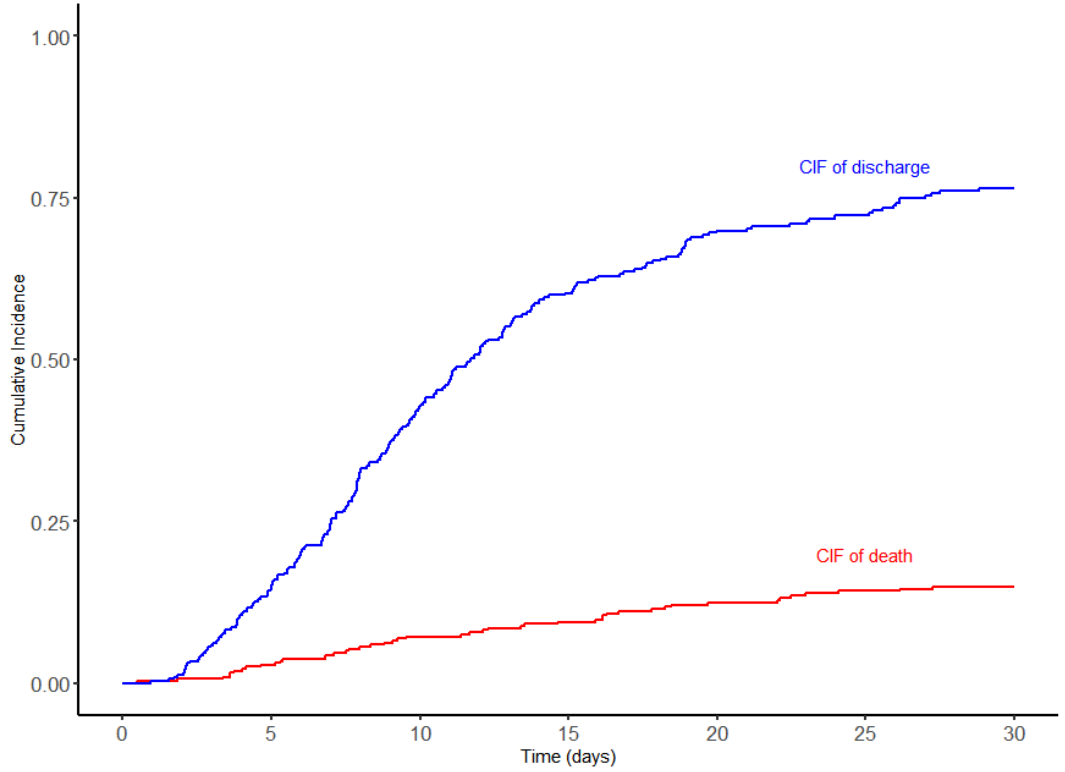
- Manual data collection for **clinical variables** and outcomes at day 30

Outcomes

- **Time to in-hospital death** (event of interest)
- **Time to discharge from hospital** (competing event)

Survival data

Cumulative incidence functions (CIF) for in-hospital death and discharge from hospital



Nb deaths	0	9	23	30	39	44	46
Nb discharges	0	48	137	191	220	227	238
Nb censoring	0	4	12	14	16	19	20
Nb at risk	327	266	155	92	52	37	23

$N = 327$ patients

Median follow-up time : 7.7 days

30 days after admission	
Deaths – Number (%)	46 (14%)
Discharges – Number (%)	238 (73%)
Censoring – Number (%)	43 (13%)
Hospital transfer	20 (6%)
Still hospitalized at D30	23 (7%)

Biomarker data

$N = 327$
$K = 59$

MARKER	UNIT	N*	n **
Complete blood count			
Erytrocytes	x10^12/L	326	6.6
Mean corpsular volume (MCV)	fL	326	6.6
Hemoglobin	g/dL	326	6.6
Hematocrit	%	326	6.6
Reticulocytes	x10^9/L	170	4.4
Leukocytes	x10^9/L	326	6.6
Basophil polynuclear cells	x10^9/L	322	6.4
Eosinophil polynuclear cells	x10^9/L	322	6.5
Neutrophil polynuclear cells	x10^9/L	326	6.5
Immatures granulocytes ratio	%	139	3.7
Lymphocytes	x10^9/L	326	6.5
Monocytes	x10^9/L	326	6.5
Platelets	x10^9/L	326	6.6
Coagulation			
Prothrombin Ratio (PR)	%	303	4.9
Activated partial tromboplastin time (aPTT)		297	4.6
Activated facteur II	%	153	4.5
Activated facteur V	%	155	4.5
Fibrinogen	g/L	294	4.4
Fibrin monomers	µg/mL	112	5.3
D-Dimers	ng/mL	218	3.9
Pulmonary functions			
Arterial pH		246	8.3
pO2a	mm Hg	246	8.3
pCO2a	mm Hg	246	8.3
Arterial lactate	mmol/L	231	8.1
Oxyhemoglobin ratio	%	245	8.0
Blood kidney functions/cellular lysis			
Natremia	mmol/L	327	7.1
Kalemia	mmol/L	325	7.1
Chloremia	mmol/L	300	5.7
Calcemia	mmol/L	315	5.3
Phosphates	mmol/L	281	4.9
Magnesium	mmol/L	260	5.2
Anion gap	mmol/L	280	4.8
Bicarbonates	mmol/L	295	5.7
Uremia	mmol/L	325	6.9
Protidemia	g/L	290	5.6
Creatininemia	µmol/L	327	6.5
Lactate dehydrogenase (LDH)	U/L	297	4.2
Creatine phosphokinase (CPK)	U/L	309	4.3
Alkaline phosphatases	U/L	313	5.3
Urine kidney functions			
Natriuresis	mmol/L	132	3.0
Kaliuresis	mmol/L	132	3.0
Urinary chloride	mmol/L	62	3.6
Proteinuria	g/L	109	2.9
Urinary urea	mmol/L	119	3.0
Creatinyuria	mmol/L	134	3.0
Glycosuria	mmol/L	76	3.2
Liver/pancreatic functions			
Alamine amino transferase (ALAT)	U/L	321	5.6
Aspartate amino transferase (ASAT)	U/L	321	5.6
Gamma GT	U/L	314	5.1
Total bilirubin	µmol/L	322	5.5
Lipasemia	U/L	158	4.3
Albuminemia	g/L	295	3.8
Markers of inflammation			
C-reactiv protein (CRP)	mg/L	318	5.5
Procalcitonin (PCT)	µg/L	229	4.0
Orosomucoid	g/L	101	4.2
Ferritin	µg/L	214	3.3
Haptoglobin	g/L	116	4.7
Cardiac markers			
Ultrasensitive troponin I	µg/L	253	3.6
NT pro-BNP	ng/L	262	3.5

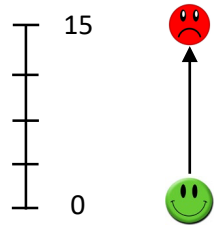
* : Number of patients with at least one observation between admission and day 30

** : mean number of observations for the patients having at least one between admission and day 30

4C-Score[1] at hospital admission (baseline)

Components of the 4C-Score

Age, years	< 50					0	✓
	$50 - 59$					+2	
	$60 - 69$					+4	
	$70 - 79$					+6	
	≥ 80					+7	
Sex at birth	**Female**		0		Male	+1	✓
Number of commorbidities Comorbidities include chronic cardiac disease, chronic respiratory disease (excluding asthma), chronic renal disease, mild to severe liver disease, dementia, chronic neurological conditions, connective tissue disease, diabetes mellitus, HIV or AIDS and malignancy.	**0**	0	**1**	+1	≥ 2	+2	✓
Respiratory rate, breaths/min	< 20	0	$20 - 29$	+1	≥ 30	+2	✗
Peripheral oxygen saturation on room air	$\geq 92\%$		0		$< 92\%$	+2	✗
Glasgow Coma Scale	**15**		0		< 15	+2	✗
Urea (mmoL/L) at admission	< 7	0	$7 - 14$	+1	> 14	+3	✓
C-reactive protein (mg/L) at admisson	< 50	0	$50 - 100$	+1	≥ 100	+2	✓



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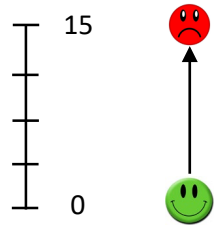

Number of patients	**N = 327**
Age – Number (%)	
< 50	73 (22)
[50-59[	74 (23)
[60-69[	71 (22)
[70-79[	62 (19)
≥ 80	47 (14)
Gender - Male – Number (%)	198 (61)
Number of commorbidities – Number (%)	
0	139 (43)
1	93 (28)
≥ 2	95 (29)
Urea (mmol/L) – med $[Q_1, Q_3]$	5.6 [4.1 – 8.1]
CRP (mg/L) – med $[Q_1, Q_3]$	67.5 [30.3 – 120.8]
Score – med $[Q_1, Q_3]$	6 [4 – 9]

1- Knight et al., *BMJ*, 2020

Univariable joint models

$y_{ijk} = \boldsymbol{m(\psi_{ik}, t_{ijk})} + g[m(\psi_{ik}, t_{ijk}), \sigma_k]\varepsilon_{ij}$ ⟶ Mixed-effects model

y_{ijk}: obs of marker k in patient i at time t_{ijk}
med_k: median(y_{ijk})

Subdistribution parametrization

$\lambda_{1ik}(t) = h_{1k} \times \exp(\boldsymbol{\alpha_{1k}} \times [\boldsymbol{m(\psi_{ik}, t)} - med_k] + \beta_{1k} \times Score_i)$ ⟶ instantaneous risk of in-hospital death

$\lambda_{2ik}(t) = h_{2k} \times \exp(\boldsymbol{\alpha_{2k}} \times [\boldsymbol{m(\psi_{ik}, t)} - med_k] + \beta_{2k} \times Score_i)$ ⟶ instantaneous risk of discharge from hospital

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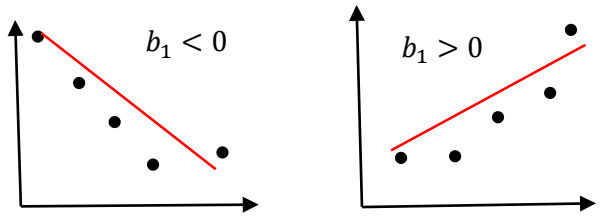
Linear

$$\boldsymbol{m(\psi_{ik}, t_{ijk})} = b_{0ik} + b_{1ik} \times t_{ijk}$$



$$b_{0ik} = \mu_{0k} + \eta_{b_{0ik}}$$
$$b_{1ik} = \mu_{1k} + \eta_{b_{1ik}}$$
$$b_{2ik} = \mu_{2k} + \eta_{b_{2ik}}$$
$$a_{ik} = \mu_{ak} \times e^{\eta^{a_{ik}}}$$

Random effects

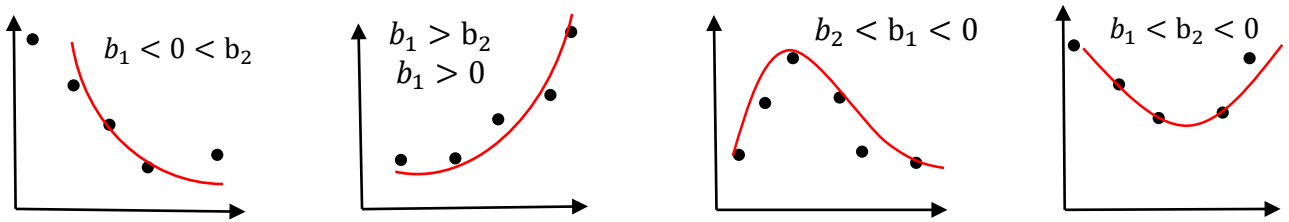
$$\eta_{.ik} \sim \mathcal{N}(0, \omega_{.ik})$$

$$\varepsilon_{ij} \sim \mathcal{N}(0,1)$$

Residual error

Nonlinear

$$\boldsymbol{m(\psi_{ik}, t_{ijk})} = b_{0ik} + a_{ik} \times [\exp(b_{1ik} \times t_{ijk}) - \exp(b_{2ik} \times t_{ijk})]$$



Univariable joint models

Model assignement and quality control

1

Linear modeling

Combined error function $\left(g\left[m\left(\psi_{ik}, t_{ijk}\right), \sigma_k\right] = \left[\sigma_{ak} + \sigma_{bk} \times m\left(\psi_{ik}, t_{ijk}\right)\right]\right)$

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Error model selection

- constant error
- proportional error
- combined error

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$< 10^{-4}$

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BIC criteria

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- constant error → $\widehat{err}_k = \frac{\hat{\sigma}_{ak}}{med_k}$
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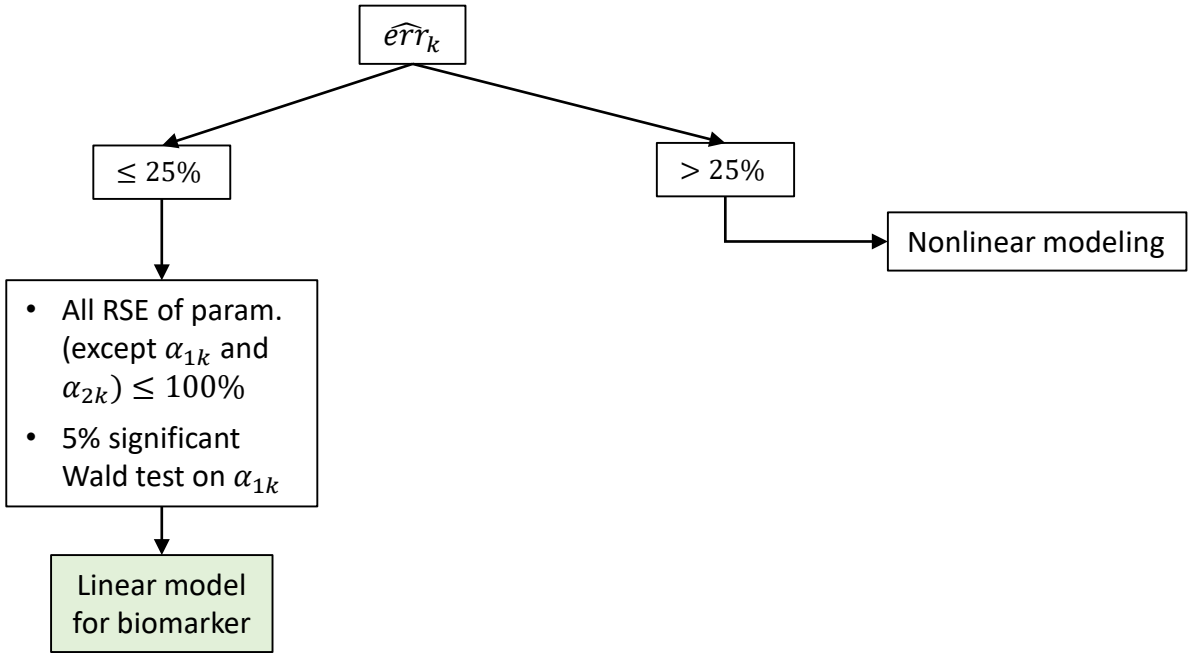

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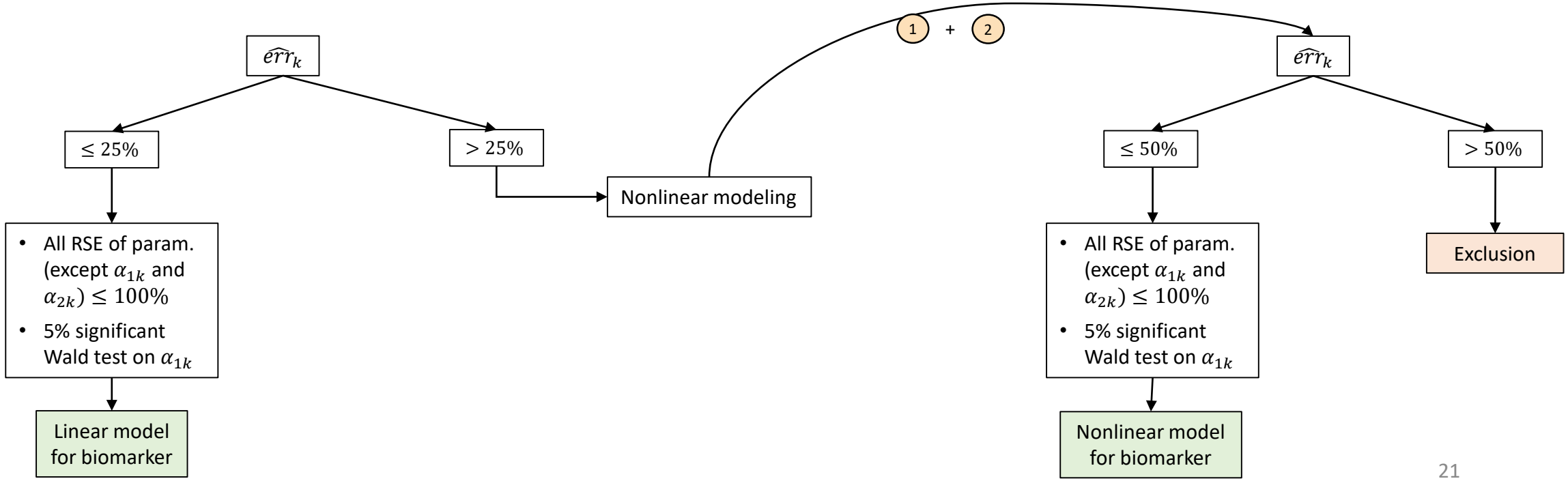
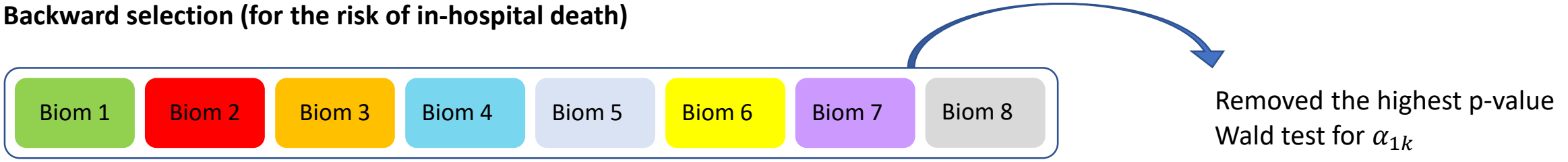


Multivariable analysis

Biomarkers selected at the previous step are grouped following the initial classification

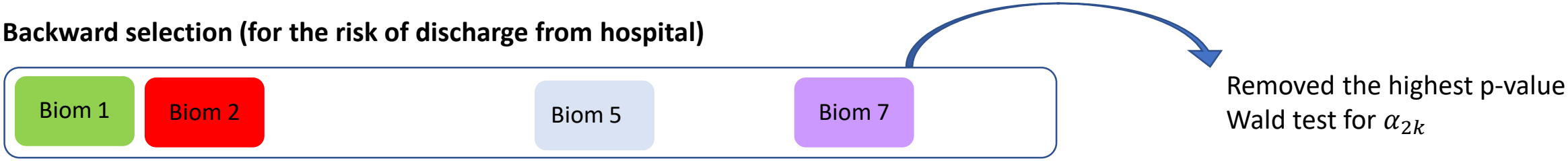
For each group, the biomarker with the **most significant** p-value for $\boldsymbol{\alpha_{1k}}$ is considered for the multivariable analysis

Backward selection (for the risk of in-hospital death)



Stop when all p-values for $\alpha_{1k} < \mathbf{5}\%$

Backward selection (for the risk of discharge from hospital)



Stop when all p-values for $\alpha_{2k} < \mathbf{5}\%$

Statistical methods

Model estimation

- Estimation by maximization of the likelihood (SAEM algorithm, Monolix 2018R2)

Individual predictions

- Derivation of dynamic predictions[10,11] given 3 landmark times: D3, D6, D9
- Performances assessment using time-dependant AUC[12] and comparison with the baseline model

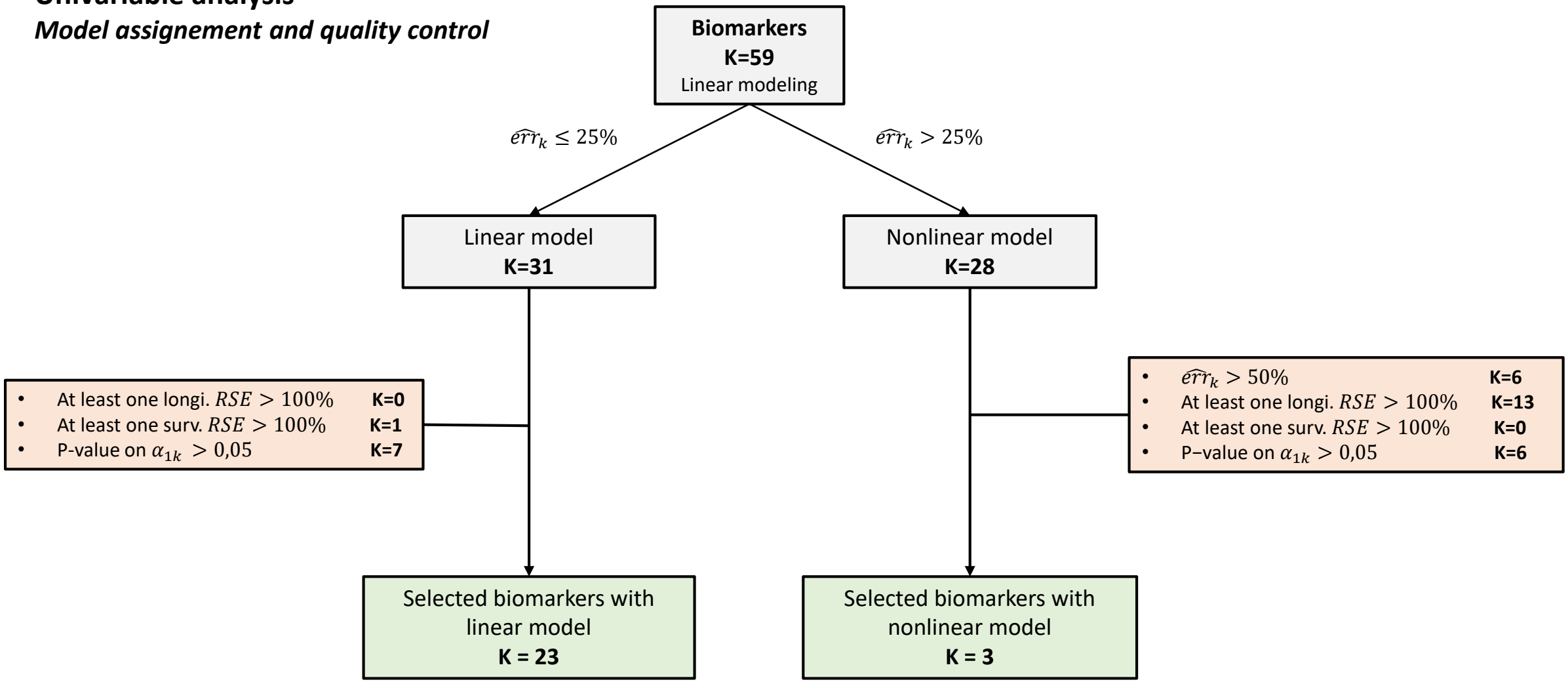
Baseline model

$$\lambda_{1i}(t) = h_1 \times \exp(\beta_1 \times Score_i) \longleftarrow \text{Subdistribution hazard for in-hospital death}$$
$$\lambda_{2i}(t) = h_2 \times \exp(\beta_2 \times Score_i) \longleftarrow \text{Subdistribution hazard for discharge from hospital}$$

10- Rizopoulos *Biometrics*, 2011
11- Desmée et al. *The AAPS Journal*, 2015
12- Blanche et al. *Biometrics*, 2015

Univariable analysis

Model assignement and quality control



Biomarkers selected for the multivariable analysis

Marqueur	N*	n**	α_1	RSE (α_1)	-log10 pvalue Wald test on α_1	model
Complete blood count						
Neutrophil polynuclear cells	**326**	**6.5**	**0.24**	**16.17**	**9.20**	**nonlin**
Platelets	326	6.6	-0.004	27.66	3.52	lin
Erythrocytes	326	6.6	-0.44	45.28	1.57	lin
Hemoglobin	326	6.6	-0.14	49.06	1.38	lin
Coagulation						
D-Dimers	**218**	**3.9**	**1.08**	**14.86**	**10.78**	**lin**
Activated facteur V	155	4.5	0.04	18.40	7.26	lin
Activated partial tromboplastin time (aPTT)	297	4.6	1.50	20.00	6.24	lin
Fibrinogen	294	4.4	0.70	22.10	5.22	lin
Activated facteur II	153	4.5	-0.02	45.62	1.55	lin
Pulmonary functions						
pHa	**246**	**8.3**	**-20.61**	**11.18**	**18.42**	**lin**
pCO2a	246	8.3	0.19	12.48	14.95	lin
Oxyhemoglobin ratio	245	8.0	-2.04	45.23	1.57	lin
Blood kidney functions/cellular lysis						
Lactate dehydrogenase (LDH)	**297**	**4.2**	**0.01**	**12.97**	**13.90**	**lin**
Uremia	325	6.9	0.07	18.11	7.48	nonlin
Kaliuresis	132	3.0	0.10	19.19	6.73	nonlin
Magnesium	260	5.2	6.65	23.96	4.52	lin
Calcemia	315	5.3	-6.00	25.27	4.12	lin
Creatininemia	327	6.5	0.003	32.27	2.71	lin
Phosphates	281	4.9	1.92	39.10	1.98	lin
Kalemia	325	7.1	0.99	44.01	1.64	lin
Urine kidney functions						
Liver/pancreatic functions						
Albuminemia	**295**	**3.8**	**-0.11**	**27.43**	**3.57**	**lin**
Lipasemia	158	4.3	0.88	17.22	8.19	lin
Markers of inflammation						
CRP	**318**	**5.5**	**1.25**	**17.63**	**7.85**	**lin**
Haptoglobin	116	4.7	0.42	19.03	6.83	lin
Orosomucoid	101	4.2	1.85	19.87	6.32	lin
Cardiac markers						
NT-proBNP	**262**	**3.5**	**0.48**	**23.01**	**4.86**	**lin**

* : Number of patients with at least one observation

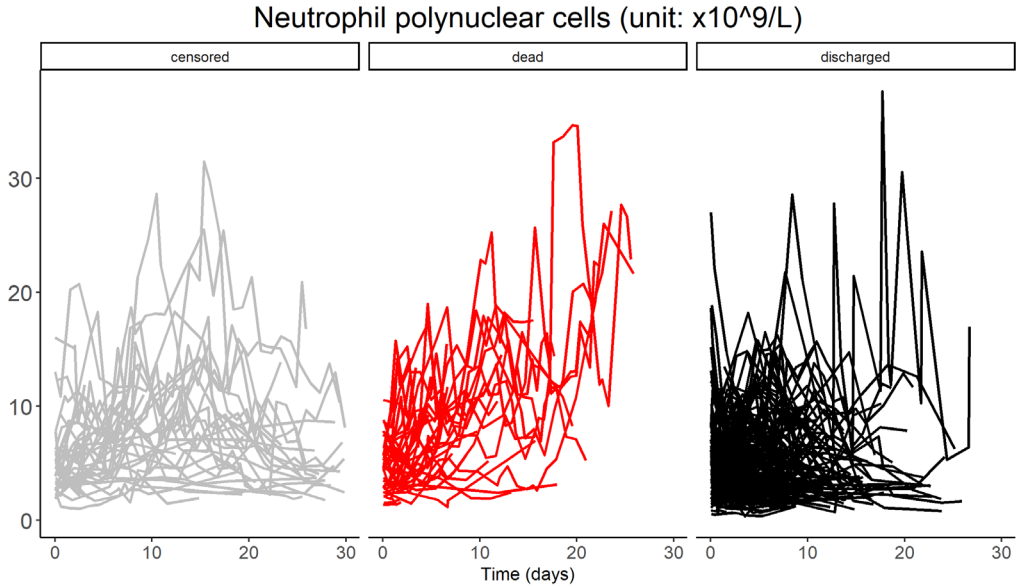
** : mean number of observations for the patients having at least one

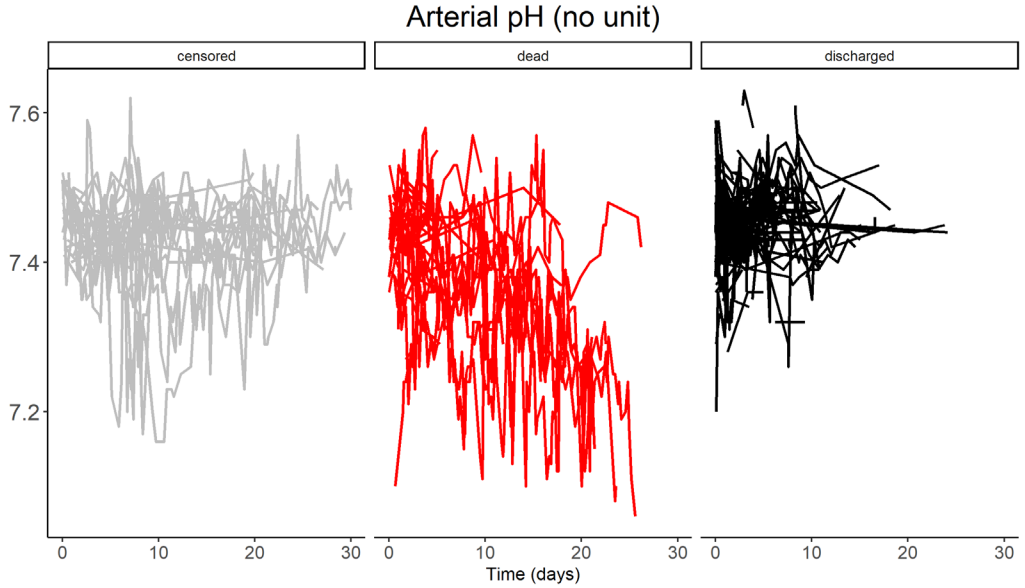
Parameter estimation (multivariable joint model)

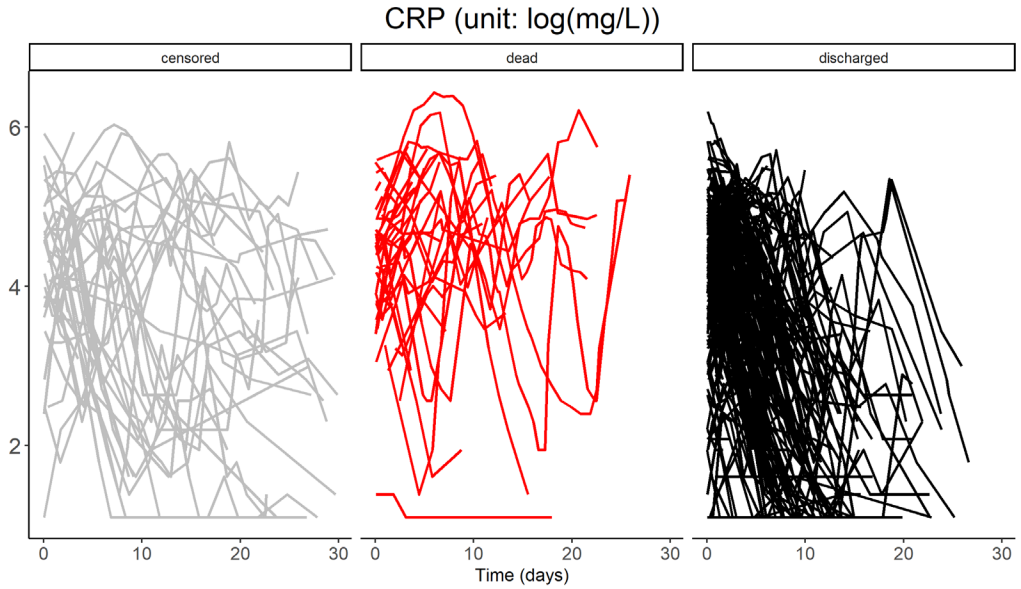
Parameter	Value	R.S.E.(%)
Longitudinal submodel		
Neutrophils		
μ_{0n} (G.L^{-1})	4.59	3.6
μ_{1n} (d^{-1})	-0.15	16.0
μ_{2n} (d^{-1})	-0.16	10.0
μ_{an} (G. L^{-1})	5.30	29.8
ω_{0n} (G.L^{-1})	2.10	7.1
ω_{1n} (d^{-1})	0.13	13.0
ω_{2n} (d^{-1})	0.076	24.2
ω_{an} (G.L^{-1})	0.83	24.8
σ_{bn}	0.32	2.2
pH		
μ_{0p}	7.44	0.05
μ_{1p} (d^{-1})	0.0027	29.1
ω_{0p}	0.039	7.1
ω_{1p} (d^{-1})	0.0053	11.6
σ_{ap}	0.055	1.7
CRP		
μ_{0c} (mg.L^{-1})	4.18	1.5
μ_{1c} (mg. L^{-1}. d^{-1})	-0.16	7.3
ω_{0c} (mg.L^{-1})	0.93	5.2
ω_{1c} (mg. L^{-1}. d^{-1})	0.15	7.4
σ_{ac} (mg. L^{-1})	0.71	2.1

Parameter	Value	R.S.E.(%)	p-value
Survival submodel			
Death			
h_1 (d^{-1})	0.00037	65.3	
α_{1n} (L×10^{-9})	**0.14**	**24.2**	$< 10^{-5}$
α_{1p}	**-11.4**	**24.9**	$< 10^{-5}$
α_{1c} (L.mg^{-1})	**0.63**	**34.7**	0.004
β_1	**0.33**	**18.1**	$< 10^{-5}$
Discharge			
h_2 (d^{-1})	0.014	51.4	
α_{2n} (L×10^{-9})	**-0.14**	**39.1**	**0.01**
α_{2p}	**25.2**	**25.2**	$< 10^{-5}$
α_{2c} (L.mg^{-1})	**-1.09**	**16.2**	$< 10^{-5}$
β_2	**-0.12**	**27.3**	0.0002

Longitudinal evolution of the selected biomarkers







Individual predictions (baseline model)

Parameter estimates

Parameter	Estimate	SE	RSE (%)	P-value
Death				
h_1	0.0003	0.00016	53	
β_1	0.357	0.05	14	$< 10^{-12}$
Discharge				
h_2	0.129	0.016	13	
β_2	-0.143	0.02	13	$< 10^{-12}$

$$\exp(\hat{\beta}_1) = \mathbf{1.43}\ (95\%\ \text{CI} = [\mathbf{1.30}\ ;\mathbf{1.58}])$$

$$\exp(\hat{\beta}_2) = \mathbf{0.87}\ (95\%\ \text{CI} = [\mathbf{0.83}\ ;\mathbf{0.90}])$$

Patient A

- Baseline score = 8
- Discharged at day 24

Survival prediction at day 30:

$0.90\ (95\%\ \text{CI}\ [0.87,0.93])$

Patient B

- Baseline score = 6
- Dead at day 22

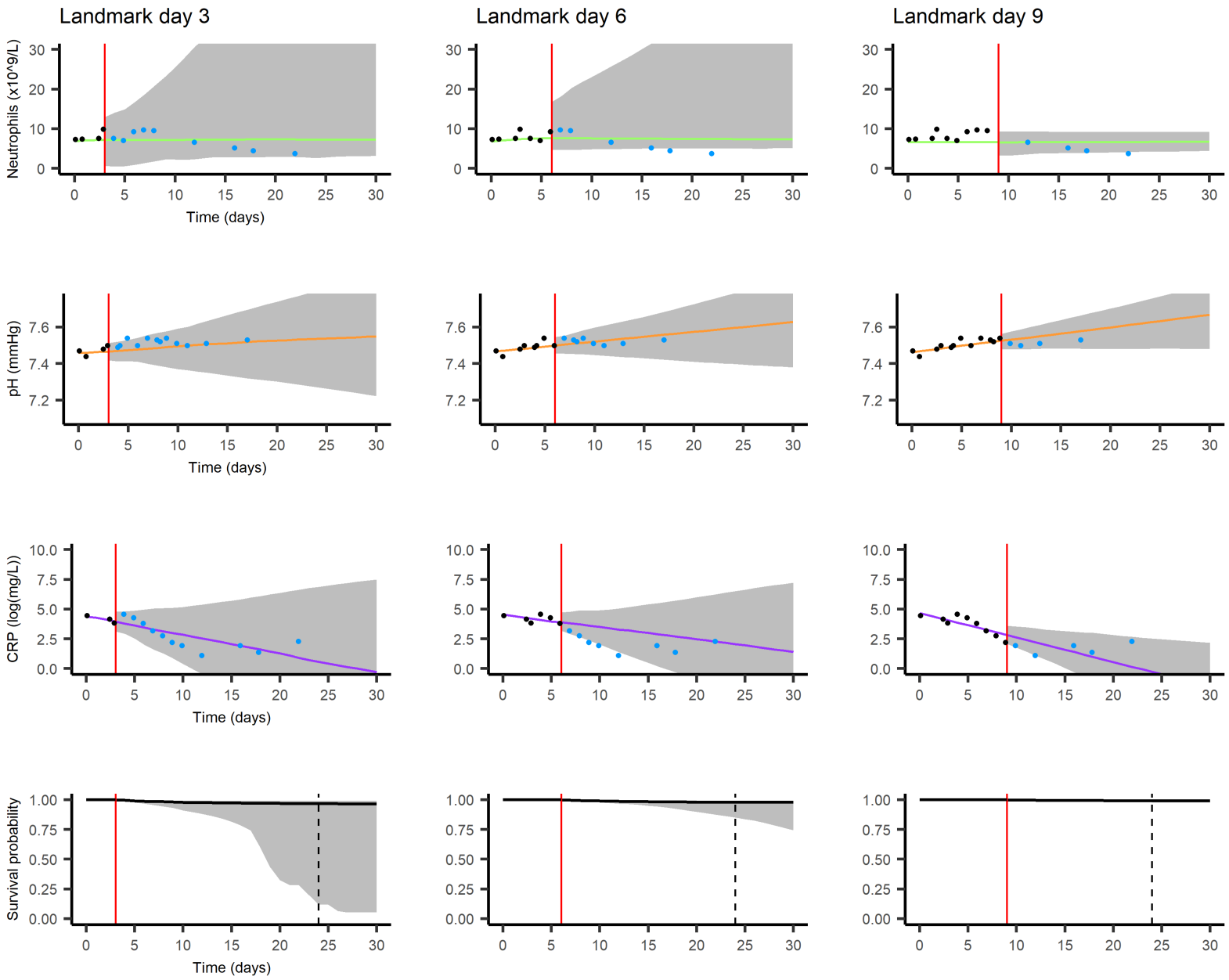
Survival prediction at day 30:

$0.95\ (95\%\ \text{CI}\ [0.93,0.97])$

Individual *dynamic predictions*

Patient A, baseline score = 8, discharged at day 24

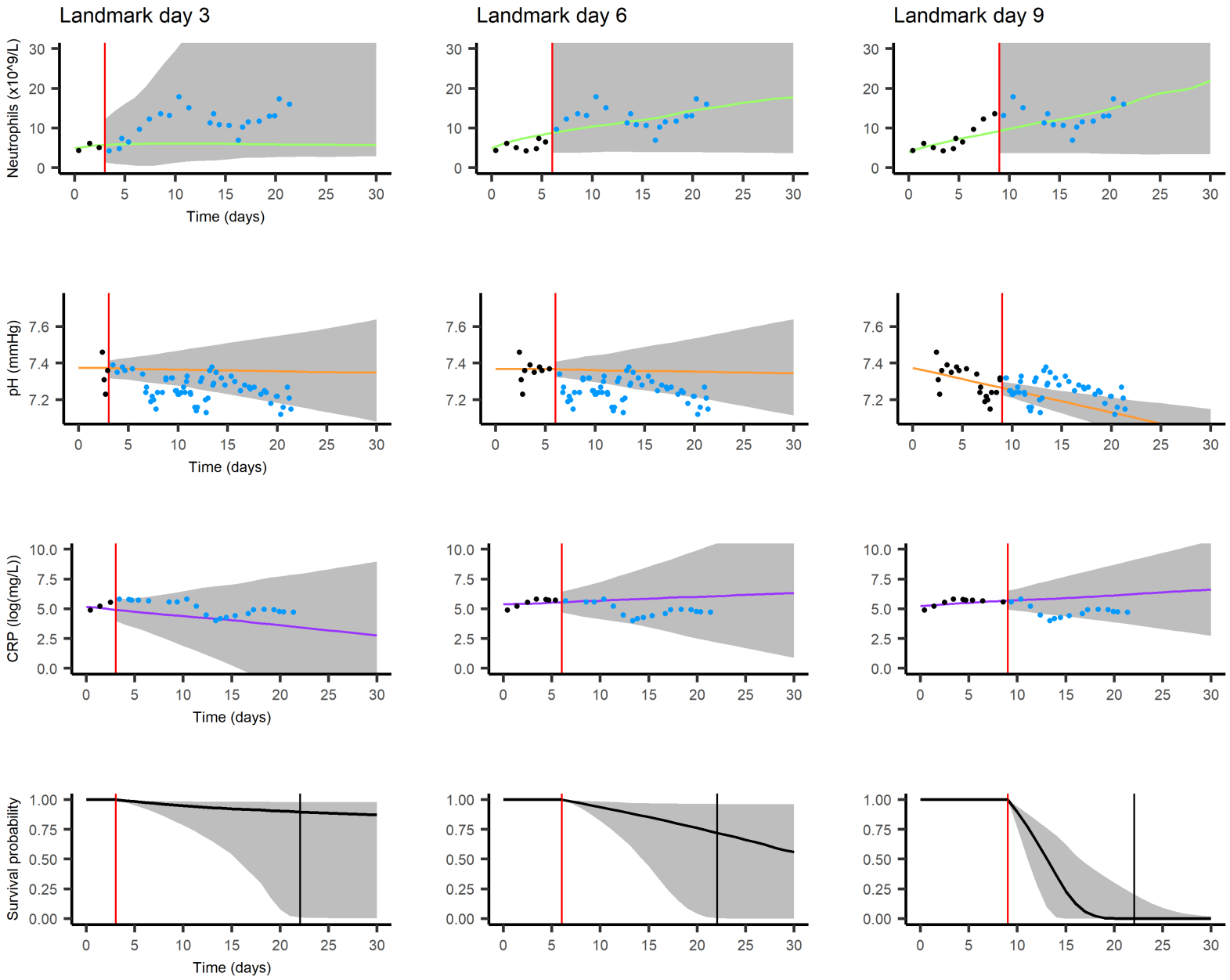
- landmark time
- future marker value
- observed marker value
- predicted pH value
- predicted CRP value
- predicted neutrophil value
- predicted survival
- death
- discharge
- 95% prediction interval



Individual dynamic predictions

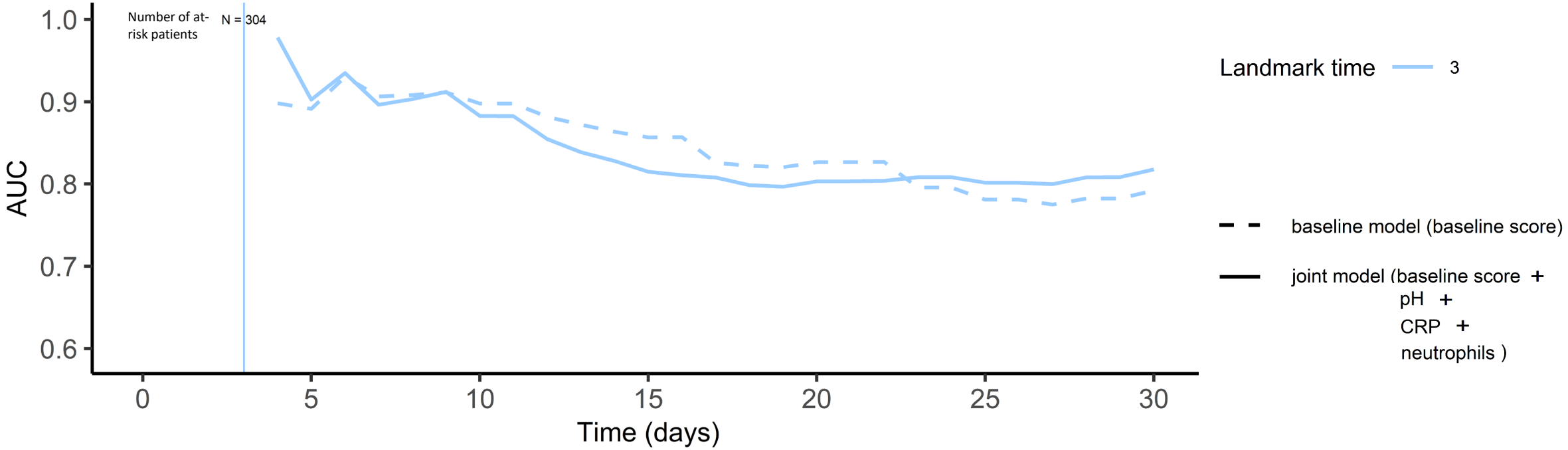
Patient B, baseline score = 6, dead at day 22

- landmark time
- future marker value
- observed marker value
- predicted pH value
- predicted CRP value
- predicted neutrophil value
- predicted survival
- death
- discharge
- 95% prediction interval



Prediction performances

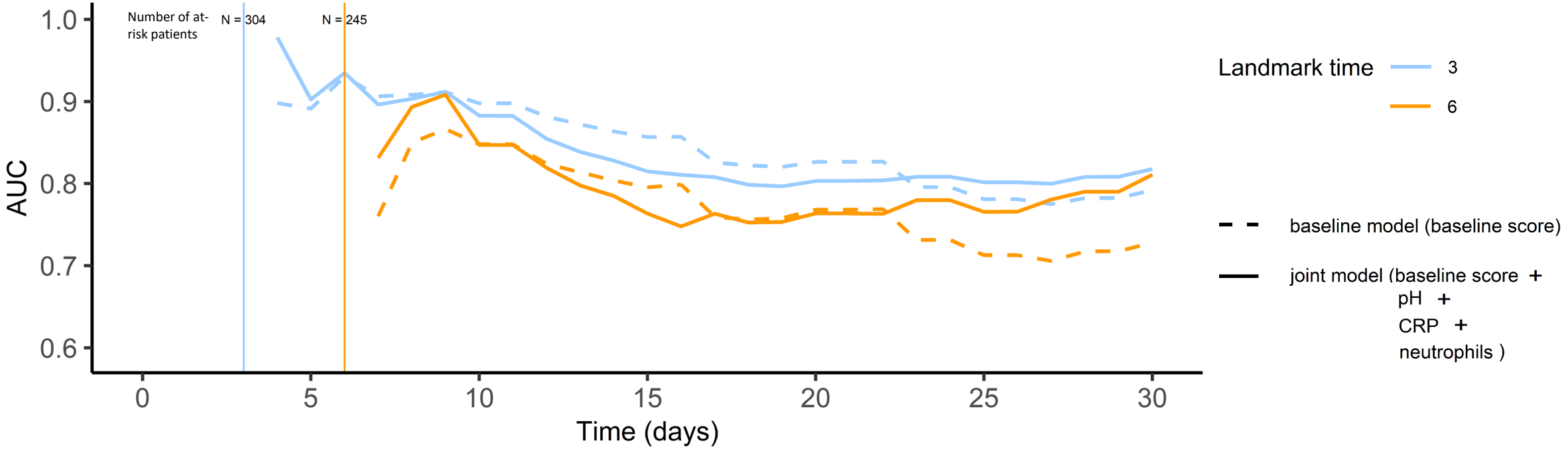
Time-dependant AUC for baseline and multivariable joint model



Horizon time = 30	Landmark day 3
AUC [95% CI] – baseline model	0.79 [0.72,0.86]
AUC [95% CI] – joint model	0.82 [0.75,0.89]
p-value	0.37

Prediction performances

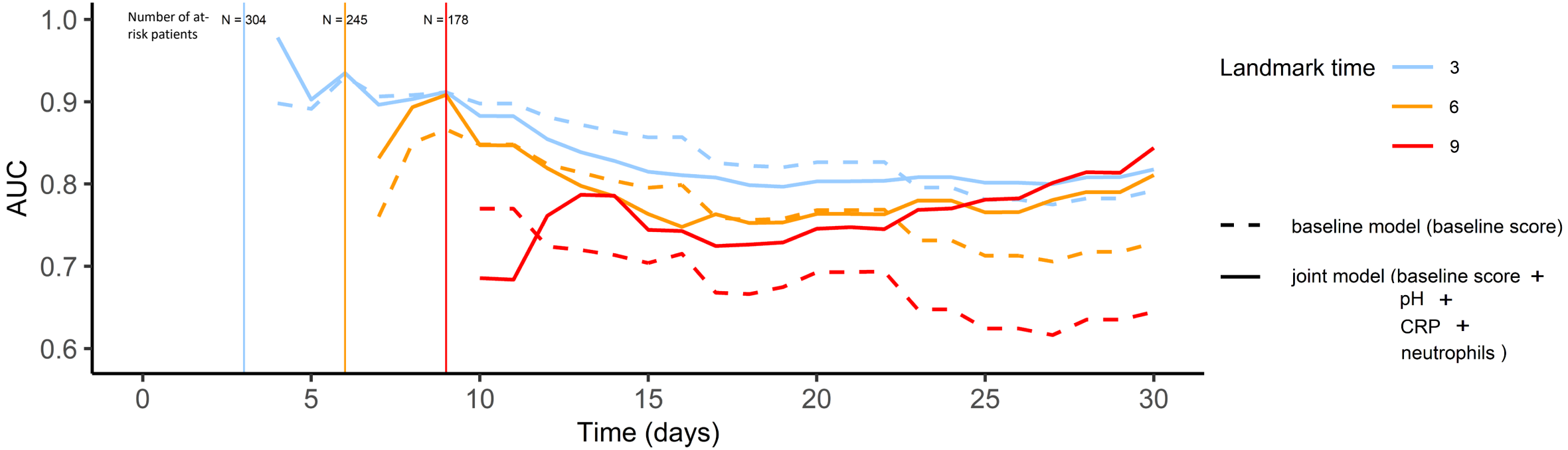
Time-dependant AUC for baseline and multivariable joint model



Horizon time = 30	Landmark day 3	Landmark day 6
AUC [95% CI] – baseline model	0.79 [0.72,0.86]	**0.73** [0.65,0.81]
AUC [95% CI] – joint model	0.82 [0.75,0.89]	**0.81** [0.73,0.89]
p-value	0.37	**0.04**

Prediction performances

Time-dependant AUC for baseline and multivariable joint model



Horizon time = 30	Landmark day 3	Landmark day 6	Landmark day 9
AUC [95% CI] – baseline model	0.79 [0.72,0.86]	**0.73** [0.65,0.81]	**0.64** [0.55,0.74]
AUC [95% CI] – joint model	0.82 [0.75,0.89]	**0.81** [0.73,0.89]	**0.84** [0.75,0.93]
p-value	0.37	**0.04**	**$<10^{-5}$**

Discussion

- We showed the added-value of **longitudinal biological follow-up** and the joint modelling approach for improving prognosis predictions.

- The originality of the work relies on:
  - the statistical approach combining multiple longitudinal models jointly estimated with a parametric subdistribution model
  - the use of real-life hospital data to collect massive data on biological examinations

- Such a tool could help clinicians in **complex decisions** such as therapeutic escalation or limitation of care (which arise during the follow-up and not at admission)

Discussion

- We showed the added-value of **longitudinal biological follow-up** and the joint modelling approach for improving prognosis predictions.

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  - the statistical approach combining multiple longitudinal models jointly estimated with a parametric subdistribution model
  - the use of real-life hospital data to collect massive data on biological examinations

- Such a tool could help clinicians in **complex decisions** such as therapeutic escalation or limitation of care (which arise during the follow-up and not at admission)

Limits

- No correlation was tested between parameters

- Performances should be evaluated on an external data set

- In high dimension, stepwise/backward selection on regression models have been shown to be outperformed by penalized regression methods[13,14]

Perspective: a **LASSO penalization[13]** implementation

13- Tibshirani, *Journal of the Royal Statistical Society,* 1996
14- Ribbing, *J Pharmacokinet Pharmacodyn,* 2007

Thank you for your attention!

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