



An overview of regression approaches for the competing risks data



Oksana Mykhailova and Julia Ditkovska,
Quartesian Clinical Research, Kyiv, Ukraine

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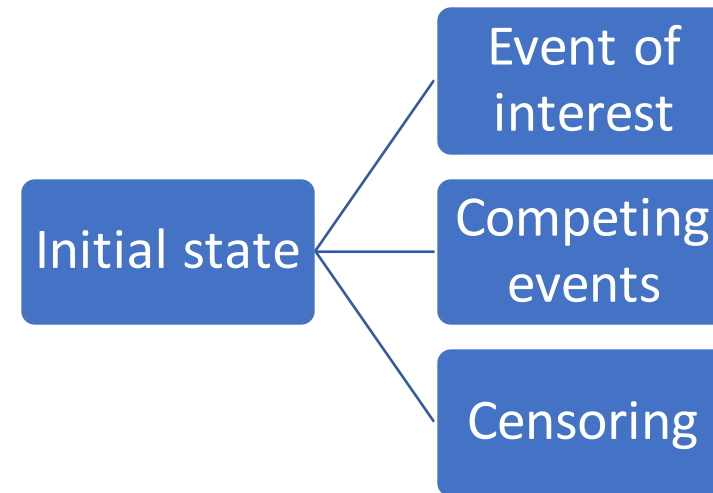
Quick Introduction to Survival Analysis

- Investigate the occurrence of the event of interest and time from the beginning observation period to it.
- In case of missing data, censoring is used.
- Censoring should be non-informative.
- Answer to the question “*What is the proportion of the population which will survive past a certain time?*”



Competing Risk – What is it?

- Competing risk means that more than one mutually exclusive event can occur with the patient.
- Competing risks use when the occurrence of one event prevents the occurrence of other events.
- Considering competing risks as censoring events can violate the assumption that censoring should be non-informative.
- Allow to model survival probabilities for events given competing events.
- Across the presentation competing risks will be presented as a bivariate random variable (T, C) , where C – random variable corresponding the type of event, T – type to event.



Important Measures in Competing Risk Setting

Cumulative Incidence Function (CIF)

The probability that an event of type k takes place at time t or earlier.

Cause-Specific Hazard Rate

The probability of an event of type k happened in a narrow time interval provided that any events did not occur before time t .

Sub-distribution Hazard Rate (by Fine and Gray)

The probability of an event of type k happened in a narrow time interval (provided that the event did not occur, or has a competing event before time t).



Cause-Specific vs Sub-distribution Hazard

Time	0	1	2	3	4
Participants with event of interest		2		3	2
Participants with competing event		2	3	2	
Sub-distribution hazard for event of interest	$\frac{0}{20}$	$\frac{2}{20}$	$\frac{0}{18}$	$\frac{3}{18} = 0.17$	$\frac{2}{15} = 0.13$
Cause-specific hazard for event of interest	$\frac{0}{20}$	$\frac{2}{20}$	$\frac{0}{16}$	$\frac{3}{13} = 0.23$	$\frac{2}{8} = 0.25$



Common Regression Approaches for Competing Risks Setting

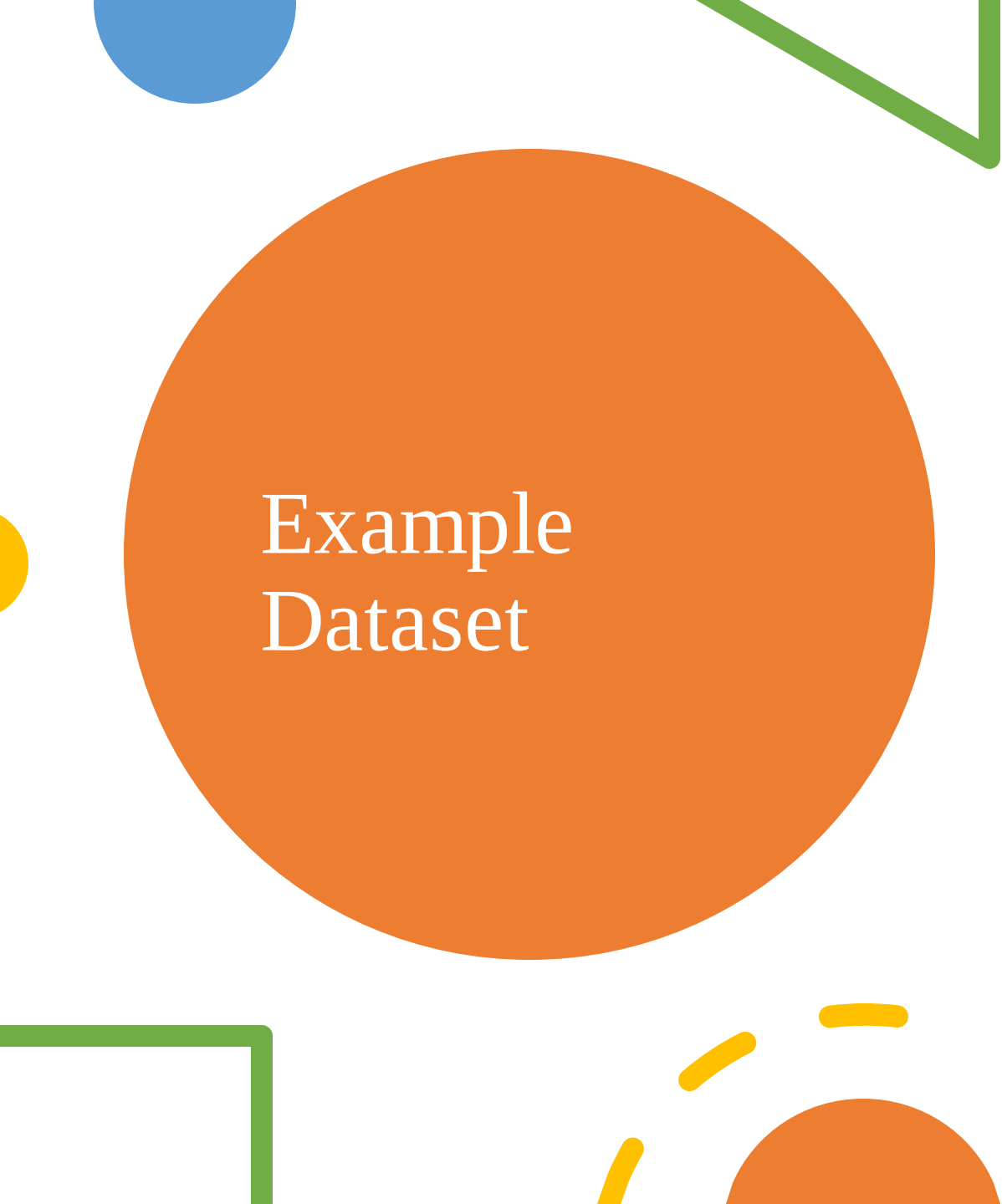
Cause-Specific Hazard Model

- Cox regression models apply for the event of interest
- Competing events are considered as censored observations

Sub-distribution Hazard Model

- Cox regression model applies for the sub-distribution instead of cause-specific hazard
- Treat covariates in the context of competing risks





Example Dataset

There is a Phase 3 oncology trial where new anti-cancer treatment compared with approved treatment. Our aim is compare time until progressive disease between two treatment groups.

Event of interest - Progressive disease

Competing event - Death

Example Dataset

Status:

- 0 – censor observation
- 1 – progressive disease
- 2 – death before the progressive disease

T – time until the event

Subject	Treatment	Age	Status	T
7770001	Approved Treatment	42	0	2081
7770002	Approved Treatment	69	0	1602
7770003	Approved Treatment	71	0	1496
7770004	Approved Treatment	73	0	1462
7770005	Approved Treatment	69	0	1433
7770006	Approved Treatment	50	0	1377
7770007	Approved Treatment	86	0	1330
7770008	Approved Treatment	30	0	996
7770009	Approved Treatment	51	0	226
7770010	Approved Treatment	85	0	1199
7770011	Approved Treatment	78	0	1111
7770012	Approved Treatment	76	0	530
7770013	Approved Treatment	35	0	1182
7770014	Approved Treatment	53	0	1167
7770015	Approved Treatment	66	2	418
7770016	Approved Treatment	68	1	383
7770017	Approved Treatment	82	2	276
7770018	Approved Treatment	32	1	104

Summary of Example Dataset

Treatment	Status			Total
	0	1	2	
Approved Treatment	14	12	12	38
New Treatment	29	9	16	54
Total	43	21	28	92

Cause-Specific Hazard Model – 1st approach

The following SAS code uses PROC PHREG to fit cause-specific hazard regression model for the event of interest and provides hazard ratios for pairs of treatment group, where the event of interest is progressive disease, and covariates are Treatment and Age.

```
proc phreg data = example_data;  
  class Treatment / order = internal ref = first;  
  model T*Status(0,2) = Treatment Age;  
  hazardratio 'Cause-Specific Hazards' Treatment / diff=pairwise;  
run;
```



Cause-Specific Hazard Model – 1st approach

The main text outputs for the executed code from the previous slide.

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Treatment	1	4.6720	0.0307
Age	1	1.6580	0.1979

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Treatment New Treatment	1	-0.95851	0.44345	4.6720	0.0307
Age	1	-0.01699	0.01319	1.6580	0.1979

Cause-Specific Hazards: Hazard Ratios for Treatment			
Description	Point Estimate	95% Wald Confidence Limits	
Treatment Approved Treatment vs New Treatment	2.608	1.093	6.219
Treatment New Treatment vs Approved Treatment	0.383	0.161	0.915

Cause-Specific Hazard Model – 2nd approach

The following SAS code use PROC PHREG to fit cause-specific hazard regression model for all possible events (progressive disease and death) and plot predicted CIF for each treatment group at specified Age.

```
proc phreg data = example_data plots(overlay) = CIF;  
  class Treatment / order = internal ref = first;  
  model T*Status(0) = Treatment Age/ eventcode(COX) = 1;  
  baseline covariates=Risk out=out1 cif=_all_ / rowid = Treatment;  
run;
```

Cause-Specific Hazard Model – 2nd approach

The main text outputs for the executed code from the previous slide.

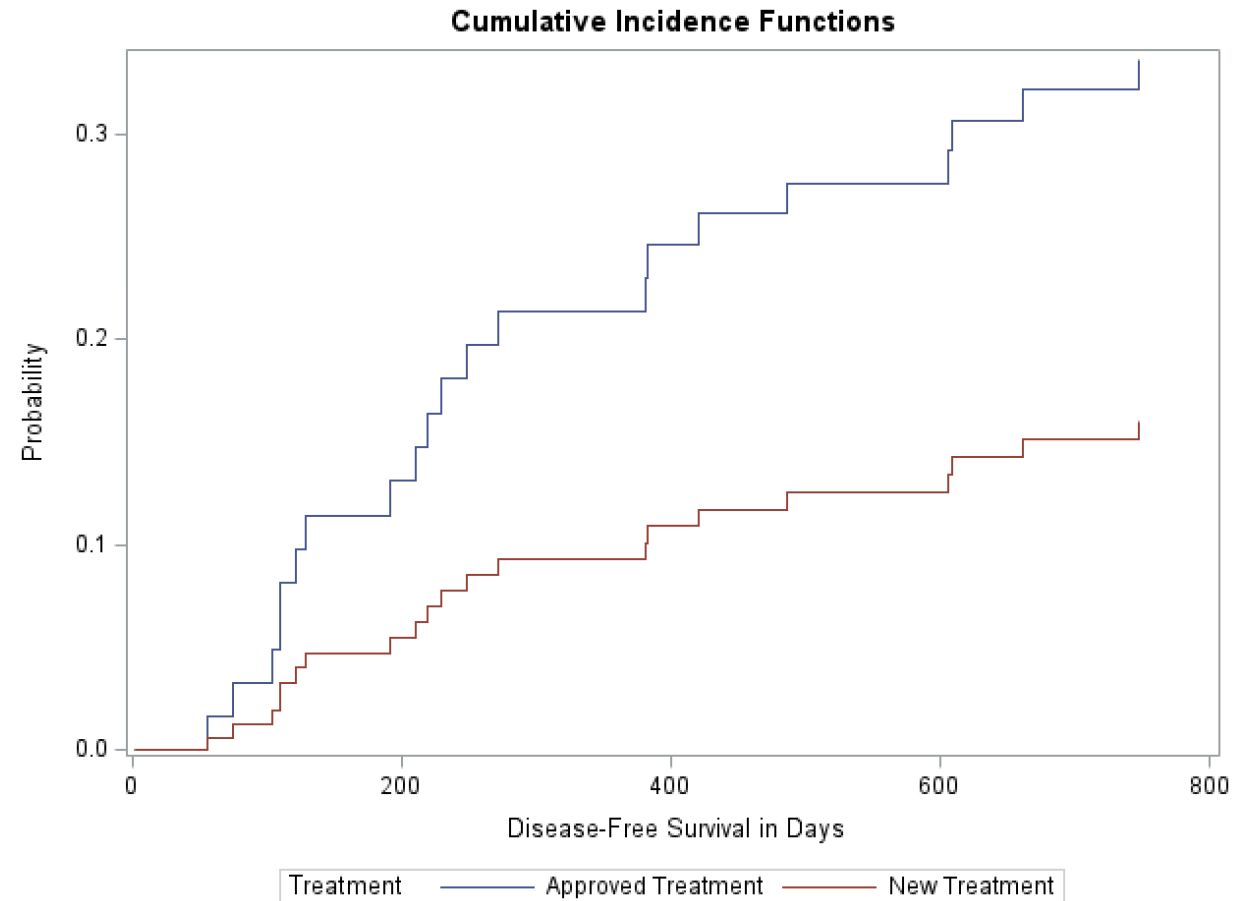
Status = 1

Type 3 Tests					
Effect	DF	Wald Chi-Square	Pr > ChiSq		
Treatment	1	4.6720	0.0307		
Age	1	1.6580	0.1979		
Analysis of Maximum Likelihood Estimates					
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Treatment New Treatment	1	-0.95851	0.44345	4.6720	0.0307
Age	1	-0.01699	0.01319	1.6580	0.1979
Analysis of Maximum Likelihood Estimates					
Parameter		Hazard Ratio	Label		
Treatment New Treatment		0.383	Treatment New Treatment		
Age		0.983			

Status = 2

Type 3 Tests					
Effect	DF	Wald Chi-Square	Pr > ChiSq		
Treatment	1	0.9168	0.3383		
Age	1	0.0749	0.7844		
Analysis of Maximum Likelihood Estimates					
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Treatment New Treatment	1	-0.37322	0.38978	0.9168	0.3383
Age	1	0.00313	0.01145	0.0749	0.7844
Analysis of Maximum Likelihood Estimates					
Parameter		Hazard Ratio	Label		
Treatment New Treatment		0.689	Treatment New Treatment		
Age		1.003			

CIF for each
Treatment Group at
Age = 60.7 (mean)



Sub-distribution Hazard Model by Fine and Gray

The following SAS code use PROC PHREG to fit sub-distribution hazard regression model for the event of interest and provides hazard ratios for pairs of treatment group, where the event of interest is progressive disease, and covariates are Treatment and Age.

```
proc phreg data = example_data;  
  class Treatment / order = internal ref = first;  
  model T*Status(0) = Treatment Age / eventcode = 1;  
  hazardratio 'Subdistribution Hazards' Treatment / diff=pairwise;  
run;
```



Sub-distribution Hazard Model by Fine and Gray

The main text outputs for the executed code from the previous slide.

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Treatment	1	3.7244	0.0536
Age	1	1.2934	0.2554

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Treatment New Treatment	1	-0.84096	0.43576	3.7244	0.0536
Age	1	-0.01472	0.01294	1.2934	0.2554

Subdistribution Hazards: Hazard Ratios for Treatment			
Description	Point Estimate	95% Wald Confidence Limits	
Treatment Approved Treatment vs New Treatment	2.319	0.987	5.447
Treatment New Treatment vs Approved Treatment	0.431	0.184	1.013

Comparing Cause-Specific and Sub-distribution Hazard Models

	Cause-Specific Hazard Model	Sub-distribution Hazard Model
Effect, Wald Chi-Square (p-value)		
Treatment	4.6720 (0.0307)	3.7244 (0.0536)
Age	1.6580 (0.1979)	1.2934 (0.2554)
Hazard Ration		
Treatment - New Treatment	0.383	0.431
Age	0.983	0.982

Summary

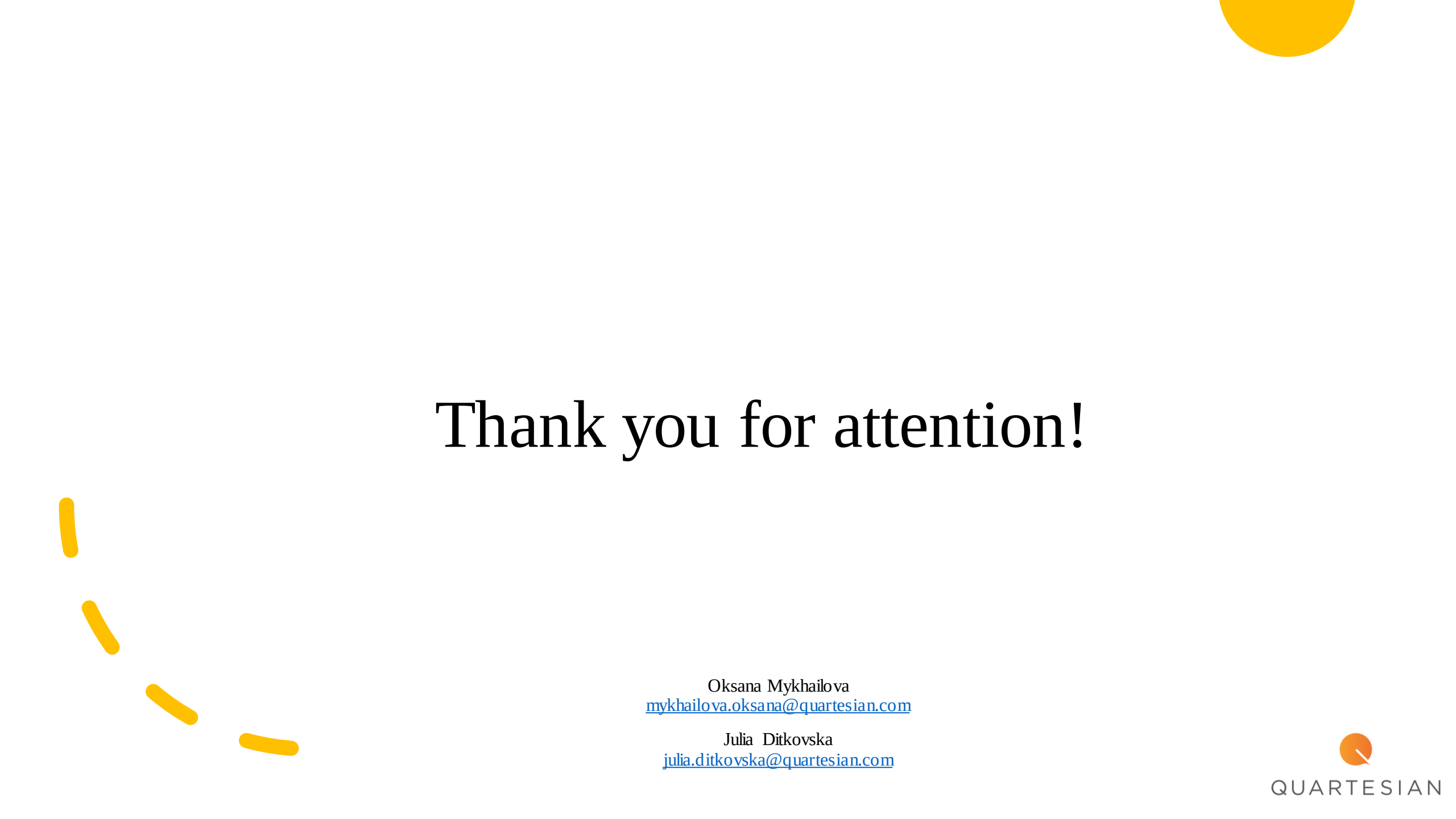
Competing risk analysis is considering when the patient is at risk of more than one mutually exclusive event.

The competing risk setting is closer to reality world than classical survival analysis.

Regression model assess the association between baseline covariates with outcome.

There are two methods to perform competing risk regression models in SAS: Cause-Specific or Sub-distributional Hazard Models.





Thank you for attention!

Oksana Mykhailova
mykhailova.oksana@quartesian.com

Julia Ditkovska
julia.ditkovska@quartesian.com