WEBVTT

1 00:00:00.000 --> 00:00:04.900 (presenter faintly speaking continues)

2 00:00:04.900 --> 00:00:07.333 <v Presenter>Dr. Roychoudhury,</v>

3 00:00:07.333 --> 00:00:12.000 (presenter faintly speaking continues)

4 00:00:26.353 --> 00:00:28.407 research institute (indistinct).

5 00:00:30.330 --> 00:00:33.898 He had 15 years of extensive experience.

6 00:00:33.898 --> 00:00:38.565 (presenter faintly speaking continues)

7 00:00:43.050 --> 00:00:44.750 Model based projects (indistinct).

8 00:00:47.250 --> 00:00:50.501 He served as the (indistinct) co-chair

9 00:00:50.501 --> 00:00:54.629 (faintly speaking) workshop.

10 00:00:54.629 --> 00:00:55.950 (presenter faintly speaking)

11 00:00:55.950 --> 00:00:58.917 And he's serving as co-chair for DIA, FDA,

12 00:00:58.917 --> 00:01:02.584 biostatistics (indistinct).

13 00:01:03.636 --> 00:01:06.860 Dr. Roychoudhury was exacted to be a panel

14 00:01:06.860 --> 00:01:09.724 of the American (indistinct) Association.

15 00:01:09.724 --> 00:01:10.908 (presenter faintly speaking)

16 00:01:10.908 --> 00:01:15.019 the country (indistinct),

17 00:01:15.019 --> 00:01:20.019 international (indistinct) society in 2019.

18 00:01:20.416 --> 00:01:23.225 So let's welcome Dr. Roychoudhury.

19 00:01:23.225 --> 00:01:24.535 Now I'm yours.

20 00:01:24.535 --> 00:01:27.118 <v ->[Dr. Roychoudhury] Thank you.</v>

21 00:01:28.140 --> 00:01:30.401 Thanks a lot Dr. (indistinct) for the nice introduction.

22 00:01:30.401 --> 00:01:33.637 Can you all hear me well?

23 00:01:33.637 --> 00:01:37.657 And thank you for the opportunity to present here

24 00:01:37.657 --> 00:01:41.350 and having a chance to interact with all of you.

25 00:01:41.350 --> 00:01:44.880 So today, (faintly speaking) I'm gonna talk

26 00:01:44.880 --> 00:01:48.360 about a problem that is many

27 00:01:48.360 --> 00:01:51.570 of the recent drug development are facing,

28 00:01:51.570 --> 00:01:54.813 and we try to talk about better interpretation

29 00:01:54.813 --> 00:01:57.007 of clinical trial data,

30 00:01:57.007 --> 00:01:59.024 especially bringing the different perspective

31 00:01:59.024 --> 00:02:01.617 as some of you know and some of you don't.

32 00:02:01.617 --> 00:02:04.927 FDA actually specifically started

33 00:02:04.927 --> 00:02:07.890 a patient oriented drug development program,

34 00:02:07.890 --> 00:02:11.550 which kind of how to make the data more understandable

35 00:02:11.550 --> 00:02:13.950 to the patient, more reachable to the patient.

36 00:02:13.950 --> 00:02:17.030 So this was kind of on that theme mostly.

37 00:02:18.360 --> 00:02:21.031 Before I begin, just I wanted to mention

38 00:02:21.031 --> 00:02:24.515 the standard disclaimer, this my own view,

39 00:02:24.515 --> 00:02:27.900 and not necessarily reflect the view of the Pfizer.

40 00:02:29.700 --> 00:02:32.670 So I think many of you have work

41 00:02:32.670 --> 00:02:36.180 on survival analysis as a coursework

42 00:02:36.180 --> 00:02:40.710 or maybe analyzing trial data, research perspective.

43 00:02:40.710 --> 00:02:44.070 So often, in critical trial setting,

44 00:02:44.070 --> 00:02:46.710 we call that analysis over time to event data.

45 00:02:46.710 --> 00:02:51.172 Because we look into the data that up to time,

46 00:02:51.172 --> 00:02:54.390 so we analyze the time up to a certain event

47 00:02:54.390 --> 00:02:56.577 or sensor the data looked at.

48 00:02:56.577 --> 00:02:59.175 And the standard way of analyzing such data,

49 00:02:59.175 --> 00:03:01.320 these are the, more or less, a standard tool.

50 00:03:01.320 --> 00:03:04.161 I'm sure you all have done or are going to do

51 00:03:04.161 --> 00:03:07.083 in your courseworks, that looking into Kaplan marker

52 00:03:07.083 --> 00:03:09.887 which looks into the survival function,

53 00:03:09.887 --> 00:03:12.180 the effect over time.

54 00:03:12.180 --> 00:03:15.900 Log-rank test, which basically tests the difference

55 00:03:15.900 --> 00:03:18.690 between the two curve, that if the treatment is better

56 00:03:18.690 --> 00:03:22.407 than control or control is worse.

57 00:03:22.407 --> 00:03:25.830 And then last, to summarizing treatment of it, right?

58 00:03:25.830 --> 00:03:27.608 At the end of the day, we need to know

59 00:03:27.608 --> 00:03:29.213 how good is the treatment.

60 00:03:29.213 --> 00:03:32.360 And one way to say that was basically hazard ratio

61 00:03:32.360 --> 00:03:35.193 or something we call Cox regression.

62 00:03:36.584 --> 00:03:38.070 Now low-rank p val-

63 00:03:38.070 --> 00:03:41.077 These are very standard reporting techniques.

64 00:03:41.077 --> 00:03:44.520 Any time to event data, if you pick up any medical journals,

65 00:03:44.520 --> 00:03:47.520 are typically analyzed using three (indistinct).

66 00:03:47.520 --> 00:03:51.810 But the question was, and based on some examples done,

67 00:03:51.810 --> 00:03:54.960 we'll dive into the details as we go along.

68 00:03:54.960 --> 00:03:56.370 the question really came up,

69 00:03:56.370 --> 00:04:00.453 are these really good metrics to analyze the data?

70 00:04:02.940 --> 00:04:04.770 So just to give a quick introduction,

71 00:04:04.770 --> 00:04:06.420 I'm sure all of you know it very well.

72 00:04:06.420 --> 00:04:09.743 But just to understand the fundamental assumptions,

73 00:04:09.743 --> 00:04:13.098 what the Cox regression means.

74 00:04:13.098 --> 00:04:16.590 So Cox regression and hazard ratio are the very,

75 00:04:16.590 --> 00:04:17.931 very popular method.

76 00:04:17.931 --> 00:04:20.430 And it started, basically introduced

77 00:04:20.430 --> 00:04:25.430 by Dr. DR Cox in 1972, one of the brilliant statistician.

78 00:04:26.250 --> 00:04:28.890 And it's closely related to mathematically

79 00:04:28.890 --> 00:04:30.060 with the log-rank test,

80 00:04:30.060 --> 00:04:32.670 which actually kind of increases its popularity.

81 00:04:32.670 --> 00:04:34.753 There mathematically, the score function,

82 00:04:34.753 --> 00:04:39.690 the score test for Cox regression is equal value

83 00:04:39.690 --> 00:04:42.553 to the log-rank test under two sample case.

84 00:04:44.237 --> 00:04:46.260 But it has an assumption also.

85 00:04:46.260 --> 00:04:49.920 It assumes that the treatment effect basically is constant

86 00:04:49.920 --> 00:04:53.370 over time, so it emerges at the beginning of the trial

87 00:04:53.370 --> 00:04:56.163 and it remain kind of a constant over time.

88 00:04:57.510 --> 00:05:00.560 Which is a problem when this is not true,

89 00:05:00.560 --> 00:05:02.550 because not all drugs work the same way.

90 00:05:02.550 --> 00:05:05.344 Sometimes, maybe some patient get benefited

91 00:05:05.344 --> 00:05:09.720 after getting treated for longer time.

92 00:05:09.720 --> 00:05:13.244 On such case, such a measure has a ratio,

93 00:05:13.244 --> 00:05:16.380 start to lack its interpretation.

94 00:05:16.380 --> 00:05:18.030 And also there is some problem

95 00:05:18.030 --> 00:05:20.193 regarding causal inference perspective.

96 00:05:22.410 --> 00:05:24.711 Let's look into two examples, two, three examples,

97 00:05:24.711 --> 00:05:26.760 real life examples, and try to understand

98 00:05:26.760 --> 00:05:28.230 where the problem was.

99 00:05:28.230 --> 00:05:30.930 So first, let's start with more simpler

100 00:05:30.930 --> 00:05:33.930 when treatment effect emerges at the beginning

101 00:05:33.930 --> 00:05:37.770 and remained at that (indistinct) over the trial.

102 00:05:37.770 --> 00:05:39.177 So the trial on...

103 00:05:39.177 --> 00:05:40.650 And they're all real trials,

104 00:05:40.650 --> 00:05:44.040 and I added the references in case you want

105 00:05:44.040 --> 00:05:45.240 to look into later.

106 00:05:45.240 --> 00:05:48.008 The one on the left is basically a trial

107 00:05:48.008 --> 00:05:51.437 for non-small cell lung cancer where gemcitabine

108 00:05:51.437 --> 00:05:55.260 and gemcitabine plus erlotinib combination has been

109 00:05:55.260 --> 00:05:57.930 looked into, which is showed the blue curve.

110 00:05:57.930 --> 00:06:00.630 There is experimental combination drug,

111 00:06:00.630 --> 00:06:02.520 which shows superiority

112 00:06:02.520 --> 00:06:06.150 over the standard of care, gemcitabine.

113 00:06:06.150 --> 00:06:09.120 The one on the right is basically

114 00:06:09.120 --> 00:06:12.087 on refractory multiple myeloma disease,

115 00:06:12.087 --> 00:06:14.550 which is a very fatal disease.

116 00:06:14.550 --> 00:06:16.740 And they're basically triple combo,

117 00:06:16.740 --> 00:06:19.290 so kRd is a triple combination drug,

118 00:06:19.290 --> 00:06:22.290 where Rd is basically a double combination drug.

119 00:06:22.290 --> 00:06:24.124 I'm not going into the details of that.

120 00:06:24.124 --> 00:06:26.850 Looking into basically kRd,

121 00:06:26.850 --> 00:06:29.700 was the experimental drug of this showing the superiority?

122 00:06:29.700 --> 00:06:32.670 In both cases, the proportionality has assumption,

123 00:06:32.670 --> 00:06:35.243 looks valid, because the effects started and it continued.

124 00:06:37.290 --> 00:06:39.236 But that's not all always the case.

125 00:06:39.236 --> 00:06:41.569 Here are the very few, very recent examples,

126 00:06:41.569 --> 00:06:46.350 especially if you are looking into the newspapers as well.

127 00:06:46.350 --> 00:06:49.011 And I think two years or three years back,

128 00:06:49.011 --> 00:06:52.290 the person from MD Anderson actually got the Nobel Prize

129 00:06:52.290 --> 00:06:54.030 for looking into the immunotherapy,

130 00:06:54.030 --> 00:06:57.270 one of the fundamental research from that area.

131 00:06:57.270 --> 00:07:00.930 So when it does this particular type of therapy,

132 00:07:00.930 --> 00:07:05.220 basically putting people immune system,

133 00:07:05.220 --> 00:07:08.070 basically and they kind of train them

134 00:07:08.070 --> 00:07:09.753 to fight against their cancer.

135 00:07:10.650 --> 00:07:15.030 And CheckMate 141, which is squamous cell carcinoma

136 00:07:15.030 --> 00:07:16.047 on head and neck,

137 00:07:16.047 --> 00:07:18.705 and nivolumab is one of the immunotherapies

138 00:07:18.705 --> 00:07:21.593 of the first (indistinct) cluster for their client.

139 00:07:21.593 --> 00:07:25.530 When they looked into the actual treatment effect,

140 00:07:25.530 --> 00:07:27.120 started to emerge pretty late.

141 00:07:27.120 --> 00:07:30.930 So that means it take the time for the immune system

142 00:07:30.930 --> 00:07:32.073 to actually work.

143 00:07:33.000 --> 00:07:34.860 And then the question is,

144 00:07:34.860 --> 00:07:37.530 the treatment effect is no more constant, right?

145 00:07:37.530 --> 00:07:40.140 Immunity is at three month.

146 00:07:40.140 --> 00:07:43.179 It's even more problematic coming into the example

147 00:07:43.179 --> 00:07:47.310 in IM211 trial, which is urothelial carcinoma

148 00:07:47.310 --> 00:07:49.770 and well atezolizumab, a compound,

149 00:07:49.770 --> 00:07:54.155 and Roche was actually looking into against chemotherapy.

150 00:07:54.155 --> 00:07:57.690 The compound was detrimental at the beginning

151 00:07:57.690 --> 00:08:00.540 and slightly at least compared to the standard of care,

152 00:08:00.540 --> 00:08:03.660 the chemotherapy that how the people are treated.

153 00:08:03.660 --> 00:08:06.003 And then it showed benefit, definitely.

154 00:08:07.680 --> 00:08:10.200 But there is something more interesting in the second ex-

155 00:08:10.200 --> 00:08:12.750 I will concentrate and each of them are interesting,

156 00:08:12.750 --> 00:08:15.420 each of them have a story of its own.

157 00:08:15.420 --> 00:08:18.501 But I just focus on this IM211 trial

158 00:08:18.501 --> 00:08:21.750 to bring in the patient perspective a little bit.

159 00:08:21.750 --> 00:08:25.020 So if you look into this trial, of course the trial

160 00:08:25.020 --> 00:08:27.810 doesn't have a significant amount, right?

161 00:08:27.810 --> 00:08:31.320 The log-rank test, which tested the superiority

162 00:08:31.320 --> 00:08:35.277 of the curve basically said it's nonsignificant.

163 00:08:35.277 --> 00:08:37.710 But if you actually wanna look

164 00:08:37.710 --> 00:08:41.595 into this survival curve a little bit more details,

165 00:08:41.595 --> 00:08:45.510 one can see the survival effect is really emerging

166 00:08:45.510 --> 00:08:48.526 and once it gets into the 18 month,

167 00:08:48.526 --> 00:08:51.551 it started to be pretty significant.

168 00:08:51.551 --> 00:08:52.860 You come in carcinoma.

169 00:08:52.860 --> 00:08:57.150 So this is kind of an 8% survival benefit is for this class

170 00:08:57.150 --> 00:09:00.960 of patient is quite a meaningful benefit on that context.

171 00:09:00.960 --> 00:09:05.854 So the question is, are we evaluating this drug correctly

172 00:09:05.854 --> 00:09:09.270 by these two standard metrics like Cox, hazard ratio,

173 00:09:09.270 --> 00:09:11.843 which doesn't look good here, 0.9, close to one.

174 00:09:11.843 --> 00:09:14.280 So it has a ratio less than one

175 00:09:14.280 --> 00:09:16.770 because we are comparing treatment versus control.

176 00:09:16.770 --> 00:09:18.870 Less than one means treatment is better

177 00:09:18.870 --> 00:09:21.511 and bigger than one means treatment is worse.

178 00:09:21.511 --> 00:09:25.290 So basically doesn't really reflect these angles.

179 00:09:25.290 --> 00:09:28.740 And also, if you look into the hazard function plots

180 00:09:28.740 --> 00:09:29.940 or hazard ratio plots,

181 00:09:29.940 --> 00:09:33.339 you can quickly see they're not constant over time.

182 00:09:33.339 --> 00:09:38.339 They're actually emerging or varying there.

183 00:09:41.310 --> 00:09:43.500 I mean, there was been a working group,

184 00:09:43.500 --> 00:09:46.290 there has been a number of workshop here,

185 00:09:46.290 --> 00:09:49.590 and even FBA and other regulators got interested.

186 00:09:49.590 --> 00:09:53.190 There has been a lot of discussions started in 2016

187 00:09:53.190 --> 00:09:56.168 when nivolumab, the first class

188 00:09:56.168 --> 00:10:00.780 of immunotherapy compound came in in a development phase.

189 00:10:00.780 --> 00:10:02.460 And there has been a lot of research.

190 00:10:02.460 --> 00:10:04.500 People were looking into different tests, okay,

191 00:10:04.500 --> 00:10:08.730 log-rank is not good, because it is most powerful test

192 00:10:08.730 --> 00:10:11.250 under proportionality hazard assumption.

193 00:10:11.250 --> 00:10:14.250 We don't have it, especially for situation like this,

194 00:10:14.250 --> 00:10:16.133 CheckMate or IM211 trial;

195 00:10:17.000 --> 00:10:18.913 or we should do some other test.

196 00:10:18.913 --> 00:10:21.060 This is not powerful, some better test.

197 00:10:21.060 --> 00:10:24.330 So there has been a zoo of tests being came in.

198 00:10:24.330 --> 00:10:26.478 You may have heard about some of them weighted,

199 00:10:26.478 --> 00:10:29.040 so instead of log-rank test, weighted log-rank test

200 00:10:29.040 --> 00:10:33.040 where we selectively weight that separate areas

201 00:10:33.040 --> 00:10:35.403 of the Kaplan-Meier curve.

202 00:10:35.403 --> 00:10:38.350 Then some a little bit more robust, like Max-Combo,

203 00:10:38.350 --> 00:10:41.700 weighted Kaplan-Meier test, restricted mean survival time,

204 00:10:41.700 --> 00:10:43.320 and there are many, many.

205 00:10:43.320 --> 00:10:45.480 I mean, and they try to look into

206 00:10:45.480 --> 00:10:47.070 how to handle different potential.

207 00:10:47.070 --> 00:10:49.116 Because one thing we need to understand,

208 00:10:49.116 --> 00:10:53.730 proportional hazard is a very specific character.

209 00:10:53.730 --> 00:10:55.167 When we say proportional hazard

210 00:10:55.167 --> 00:10:58.710 that these two hazard plots are (indistinct).

211 00:10:58.710 --> 00:11:00.848 But once we set non-proportional hazard,

212 00:11:00.848 --> 00:11:03.540 there could be many, many possibilities.

213 00:11:03.540 --> 00:11:07.807 Drugs can be crossed, drugs can separate the link.

214 00:11:07.807 --> 00:11:10.530 Drugs can first separate and then emerge back.

215 00:11:10.530 --> 00:11:13.050 So it's a no more unique (indistinct).

216 00:11:13.050 --> 00:11:16.396 So we need a set of methodology that's sort of robust

217 00:11:16.396 --> 00:11:19.683 across this different class of alternatives.

218 00:11:20.700 --> 00:11:25.260 But the problem is even having a P value,

219 00:11:25.260 --> 00:11:28.235 suppose once we call about, okay, there's a good test

220 00:11:28.235 --> 00:11:31.317 and we got a good P value for such a curve.

221 00:11:31.317 --> 00:11:34.706 But one can say, oh how can a P value is meaningful?

222 00:11:34.706 --> 00:11:38.970 The beginning of the curve, the patients are getting worse.

223 00:11:38.970 --> 00:11:41.553 Is a P value really meaningful in this context?

224 00:11:43.200 --> 00:11:47.296 So rejecting the null is really a less informative.

225 00:11:47.296 --> 00:11:49.590 You need to know more information

226 00:11:49.590 --> 00:11:52.910 to understand these kind parts of compounds better.

227 00:11:54.262 --> 00:11:56.040 And that's also been looked into.

228 00:11:56.040 --> 00:12:00.000 There are multiple, multiple things has been looked into

229 00:12:00.000 --> 00:12:04.540 with simulation, with datas, lot of meta analysis

230 00:12:05.550 --> 00:12:08.220 with different data looking into the percentile, right?

231 00:12:08.220 --> 00:12:09.247 I mean one part of we're looking,

232 00:12:09.247 --> 00:12:12.624 why don't we look into the ratio of the median

233 00:12:12.624 --> 00:12:14.220 of the compound?

234 00:12:14.220 --> 00:12:17.220 Or we look into the (indistinct) time or percentile, right?

235 00:12:17.220 --> 00:12:19.290 Things are separating at percentile.

236 00:12:19.290 --> 00:12:21.174 Maybe we can look into percentile

237 00:12:21.174 --> 00:12:24.363 over the time ratios of those.

238 00:12:25.200 --> 00:12:27.810 Then milestone survival and coming into a moment,

239 00:12:27.810 --> 00:12:31.440 which is a sort of a very meaningful

240 00:12:31.440 --> 00:12:33.736 to a patient's restricted means survival.

241 00:12:33.736 --> 00:12:37.683 Basically you average over the area under the curve,

242 00:12:39.037 --> 00:12:42.196 which it has a ratio, because we are doing with a test,

243 00:12:42.196 --> 00:12:44.873 a dual estimator of that is weighted hazard ratio,

244 00:12:44.873 --> 00:12:46.487 piecewise hazard ratio.

245 00:12:46.487 --> 00:12:50.776 Cox model, now, the initial Cox model doesn't have

246 00:12:50.776 --> 00:12:52.640 a time component in it (indistinct).

247 00:12:52.640 --> 00:12:55.098 Only the time component is in the baseline hazard.

248 00:12:55.098 --> 00:12:58.267 We can introduce a time component into that

249 00:12:58.267 --> 00:13:02.836 to make sure the treatment effect is sort of time dependent.

250 00:13:02.836 --> 00:13:06.919 And then there are other things like net benefit.

251 00:13:07.879 --> 00:13:10.463 I won't dive every one of details,

252 00:13:10.463 --> 00:13:12.128 but I just wanted to mention that hazard,

253 00:13:12.128 --> 00:13:13.860 so weighted hazard ratio means hazard ratio,

254 00:13:13.860 --> 00:13:16.170 we were doing a Cox regression.

255 00:13:16.170 --> 00:13:19.620 We were looking into basically the regression coefficient

256 00:13:19.620 --> 00:13:21.043 corresponding to the treatment using

257 00:13:21.043 --> 00:13:22.980 a partial likelihood method.

258 00:13:22.980 --> 00:13:26.192 And now, the whole idea was similar to like testing

259 00:13:26.192 --> 00:13:28.290 where we are weighting different part

260 00:13:28.290 --> 00:13:31.164 of Kaplan-Meier differently, we weight different part

261 00:13:31.164 --> 00:13:33.447 of the partial likelihood differently.

262 00:13:33.447 --> 00:13:36.030 Or there are other type of weightings as well,

263 00:13:36.030 --> 00:13:37.620 like average weights and others.

264 00:13:37.620 --> 00:13:39.180 So basically, the whole idea was not

265 00:13:39.180 --> 00:13:40.941 to treat each event similar,

266 00:13:40.941 --> 00:13:44.220 but differently based on their interest.

267 00:13:44.220 --> 00:13:47.073 But that's the (indistinct) of course,

268 00:13:47.910 --> 00:13:49.680 treatment emerges at the end.

269 00:13:49.680 --> 00:13:52.320 We may be interested more towards the end,

270 00:13:52.320 --> 00:13:55.260 but it adds a subjective choice, right?

271 00:13:55.260 --> 00:14:00.260 And it's not very easy for non-clinicians

272 00:14:00.269 --> 00:14:03.543 to understand on that aspect.

273 00:14:06.420 --> 00:14:11.420 So now then, of course in 2005, people also talk quite a bit

274 00:14:11.700 --> 00:14:14.610 about piecewise hazard ratios

275 00:14:14.610 --> 00:14:17.730 and now still piecewise hazard is still very important.

276 00:14:17.730 --> 00:14:22.730 Like you divide the whole time axis into different intervals

277 00:14:23.220 --> 00:14:27.764 and you basically calculate local hazard ratios.

278 00:14:27.764 --> 00:14:29.700 Which is very meaning 'cause you can look

279 00:14:29.700 --> 00:14:32.040 into the first part when (indistinct) not separated.

280 00:14:32.040 --> 00:14:33.600 The hazard ratio's close to one,

281 00:14:33.600 --> 00:14:35.760 then the hazard ratio emerges.

282 00:14:35.760 --> 00:14:37.260 And there's a natural extension

283 00:14:37.260 --> 00:14:40.620 of that was basically using a regression using a time factor

284 00:14:40.620 --> 00:14:41.490 into the core value.

285 00:14:41.490 --> 00:14:46.490 But really, the power and the performance really depends

286 00:14:46.580 --> 00:14:51.360 on the function that you choose, which is, again,

287 00:14:51.360 --> 00:14:53.670 is difficult to interpret in a practical sense

288 00:14:53.670 --> 00:14:56.343 that if results really value on such a choice.

289 00:14:57.257 --> 00:15:00.144 But one thing was kinda after all,

290 00:15:00.144 --> 00:15:01.650 among all this discussion,

291 00:15:01.650 --> 00:15:03.870 one thing was when we talked to non-statisticians,

292 00:15:03.870 --> 00:15:07.050 specifically clinician, one thing was very clear,

293 00:15:07.050 --> 00:15:08.850 one measure we found.

294 00:15:08.850 --> 00:15:11.640 The measure is improvement in survival.

295 00:15:11.640 --> 00:15:15.090 That means they're very clear about certain metric

296 00:15:15.090 --> 00:15:17.760 that, okay, what is the survival gain at five year

297 00:15:17.760 --> 00:15:18.593 or eight year?

298 00:15:18.593 --> 00:15:21.180 Those metrics seems to be very intuitive,

299 00:15:21.180 --> 00:15:24.720 very clear to to non-statistician patient

300 00:15:24.720 --> 00:15:28.350 and all other stakeholders.

301 00:15:28.350 --> 00:15:31.498 But the only problem is at the beginning of the file,

302 00:15:31.498 --> 00:15:34.830 you just don't know when the curve is gonna be separate.

303 00:15:34.830 --> 00:15:36.090 You don't know that.

304 00:15:36.090 --> 00:15:38.460 So (indistinct) finds such point,

305 00:15:38.460 --> 00:15:40.443 can be very dangerous for you.

306 00:15:43.740 --> 00:15:45.630 The last measure I mentioned was this,

307 00:15:45.630 --> 00:15:47.400 been over and over discussed,

308 00:15:47.400 --> 00:15:50.062 which is called residual, meaning lifetime,

309 00:15:50.062 --> 00:15:53.334 basically (indistinct) lifetime,

310 00:15:53.334 --> 00:15:55.590 residual means survival time.

311 00:15:55.590 --> 00:15:57.600 Which has been over and over discussed recently

312 00:15:57.600 --> 00:16:00.469 in clinical literature, as well as in statistical,

313 00:16:00.469 --> 00:16:02.010 restricted mean people.

314 00:16:02.010 --> 00:16:03.493 When people looking into restricted mean,

315 00:16:03.493 --> 00:16:07.646 that means they're looking for supposed up to a time Tau.

316 00:16:07.646 --> 00:16:11.813 You cut the curve, you compare the area under the curve,

317 00:16:11.813 --> 00:16:13.496 which is in this block.

318 00:16:13.496 --> 00:16:16.050 And you see if you can look into the difference,

319 00:16:16.050 --> 00:16:17.486 you can look into the ratio,

320 00:16:17.486 --> 00:16:21.060 and try to see if the area under the curve is better

321 00:16:21.060 --> 00:16:21.893 on that context.

322 00:16:21.893 --> 00:16:24.060 But remember, the problem is here,

323 00:16:24.060 --> 00:16:26.425 the comparison also very much depends on the choice

324 00:16:26.425 --> 00:16:30.660 of the cutoff, where you choose it, basically.

325 00:16:30.660 --> 00:16:32.820 The Tau and risk of the censoring pattern

326 00:16:32.820 --> 00:16:35.402 of the Kaplan-Meier plays a very big role

327 00:16:35.402 --> 00:16:38.714 in such a such compass,

328 00:16:38.714 --> 00:16:42.650 especially in a setting for such metrics.

329 00:16:42.650 --> 00:16:45.900 Especially, it's very problematic

330 00:16:45.900 --> 00:16:49.110 when in a cancer setting like metastatic,

331 00:16:49.110 --> 00:16:50.400 the one I showed you earlier,

332 00:16:50.400 --> 00:16:53.520 because there is a, the disease is very fit on it,

333 00:16:53.520 --> 00:16:55.080 happens very quickly.

334 00:16:55.080 --> 00:16:56.820 Patient gets multiple therapies.

335 00:16:56.820 --> 00:16:59.192 So censoring patterns are much more aggressive,

336 00:16:59.192 --> 00:17:01.200 whereas there are other disease setting

337 00:17:01.200 --> 00:17:04.290 where RMST seems to be very meaningful.

338 00:17:04.290 --> 00:17:07.557 Because you get lot of follow up much more uniformly.

339 00:17:10.377 --> 00:17:13.050 Now the problem was, okay, all these measures differently.

340 00:17:13.050 --> 00:17:16.290 We apply, we get different results, we get, okay,

341 00:17:16.290 --> 00:17:18.090 one is good right here, right?

342 00:17:18.090 --> 00:17:20.340 We talked about IM211 at beginning.

343 00:17:20.340 --> 00:17:21.750 We saw survival benefit.

344 00:17:21.750 --> 00:17:24.090 We see that the survival benefit coming

345 00:17:24.090 --> 00:17:29.090 into the 12 month zone, but RMST was still showing, okay,

346 00:17:29.520 --> 00:17:31.743 there is no confirmation of such an effect.

347 00:17:33.780 --> 00:17:36.420 So there has been a interesting paper

348 00:17:36.420 --> 00:17:37.770 I came across last year.

349 00:17:37.770 --> 00:17:41.468 It was a patient voice survey in UK.

350 00:17:41.468 --> 00:17:45.072 They basically did a survey on patients

351 00:17:45.072 --> 00:17:48.510 as well as the health practitioners

352 00:17:48.510 --> 00:17:52.923 who are participating in the TACT trial.

353 00:17:52.923 --> 00:17:55.740 Taxotere is a adjuvant chemotherapy drug.

354 00:17:55.740 --> 00:17:57.003 It's a very big trial.

355 00:17:57.003 --> 00:18:01.115 And they surveyed that what patients really want,

356 00:18:01.115 --> 00:18:03.960 how they want the trial results are for.

357 00:18:03.960 --> 00:18:06.003 I mean, because at the end of the day,

358 00:18:06.870 --> 00:18:09.090 the doctors tried to discuss these results

359 00:18:09.090 --> 00:18:11.368 with the patient before they choose as a therapy.

360 00:18:11.368 --> 00:18:15.714 And then, it's not surprising that actually,

361 00:18:15.714 --> 00:18:19.470 it's coming in that the patients are really want

362 00:18:19.470 --> 00:18:21.983 to understand these results in a very simple term.

363 00:18:21.983 --> 00:18:23.190 I mean, it's not like,

364 00:18:23.190 --> 00:18:27.450 oh, your drug may not be decreased event rate,

365 00:18:27.450 --> 00:18:31.437 but it expected survival going to get really bigger.

366 00:18:31.437 --> 00:18:34.050 But that's not the question a patient is asking, right?

367 00:18:34.050 --> 00:18:36.828 I mean, it's not type of mindset a patient has.

368 00:18:36.828 --> 00:18:41.160 Then of course, the patients are one who have the results

369 00:18:41.160 --> 00:18:42.300 as soon as possible.

370 00:18:42.300 --> 00:18:44.450 It's a very interesting article I suggest to read.

371 00:18:44.450 --> 00:18:46.427 It's a very fun reading article

372 00:18:46.427 --> 00:18:51.240 to look into the patient voice, how patient wanted...

373 00:18:51.240 --> 00:18:53.190 Because most of the time patients are not being

374 00:18:53.190 --> 00:18:55.736 always communicated about trial results

375 00:18:55.736 --> 00:18:57.584 and how they wanted.

376 00:18:57.584 --> 00:19:00.480 It came out to be very nicely in this,

377 00:19:00.480 --> 00:19:05.086 especially most of them actually want still comfortable

378 00:19:05.086 --> 00:19:08.760 to have the results from their nurse or doctors.

379 00:19:08.760 --> 00:19:10.950 Because they're more comfortable to discuss with them

380 00:19:10.950 --> 00:19:14.433 rather than having a big seminar or formal paper.

381 00:19:16.498 --> 00:19:20.850 But really, let's think about the patient perspective,

382 00:19:20.850 --> 00:19:22.485 what question they really ask.

383 00:19:22.485 --> 00:19:25.230 The question they really ask are these, right?

384 00:19:25.230 --> 00:19:28.731 I mean, if we put ourself onto that shoes,

385 00:19:28.731 --> 00:19:31.503 the question is does this drug really work?

386 00:19:32.490 --> 00:19:35.781 What are my chances that I will do better

387 00:19:35.781 --> 00:19:40.200 in terms of survival or in terms of painful quality

388 00:19:40.200 --> 00:19:44.883 of my life if on the new drug compared to no treatments?

389 00:19:45.882 --> 00:19:48.480 So these are the much more simple question.

390 00:19:48.480 --> 00:19:53.280 Unfortunately, many of the well known methods are unable

391 00:19:53.280 --> 00:19:56.910 to address because I mean, you can indirectly address

392 00:19:56.910 --> 00:20:01.060 those question or you may have the study shows you have

393 00:20:01.923 --> 00:20:04.110 a benefit of pharma.

394 00:20:04.110 --> 00:20:06.570 But that really doesn't answer the question

395 00:20:06.570 --> 00:20:08.253 from that patient perspective.

396 00:20:10.080 --> 00:20:12.240 Which actually motivates us a little bit,

397 00:20:12.240 --> 00:20:13.890 that can we dig in?

398 00:20:13.890 --> 00:20:17.190 Can we try to see if we can use

399 00:20:17.190 --> 00:20:19.571 our modern statistical analytic methods

400 00:20:19.571 --> 00:20:21.330 to address some of that question,

401 00:20:21.330 --> 00:20:24.120 especially from peer's perspective,

402 00:20:24.120 --> 00:20:27.393 from a kind of practitioner's perspective.

403 00:20:30.450 --> 00:20:34.080 So one of the thing that is more easier for anybody

404 00:20:34.080 --> 00:20:36.240 to understand the visual graphics, right?

405 00:20:36.240 --> 00:20:39.030 Kaplan-Meier plot is something which is more easy

406 00:20:39.030 --> 00:20:41.700 to comprehend compared to many other metrics.

407 00:20:41.700 --> 00:20:44.880 So that was kind of how our motivation (indistinct) became.

408 00:20:44.880 --> 00:20:47.188 And then the question is really,

409 00:20:47.188 --> 00:20:49.293 it's not like what trial shows.

410 00:20:49.293 --> 00:20:52.245 Now the question, if a new patient is entering the trial,

411 00:20:52.245 --> 00:20:56.790 can we predict their benefits based

412 00:20:56.790 --> 00:20:58.563 on the available data we have?

413 00:21:00.687 --> 00:21:02.430 And this could be an additional metrics.

414 00:21:02.430 --> 00:21:06.060 Of course we are not saying these metrics is gonna change

415 00:21:06.060 --> 00:21:07.890 the trial or the trial practice,

416 00:21:07.890 --> 00:21:09.990 but this is definitely another metric

417 00:21:09.990 --> 00:21:12.120 which can help patient much better

418 00:21:12.120 --> 00:21:13.803 for making their decisions.

419 00:21:15.660 --> 00:21:20.100 So what we introduced is basically this quantity

420 00:21:20.100 --> 00:21:23.763 which is called individual effect, Y minus X.

421 00:21:23.763 --> 00:21:25.290 What is Y?

422 00:21:25.290 --> 00:21:29.850 So Y is a survival time at the treatment arm.

423 00:21:29.850 --> 00:21:33.150 I'm just making simpler, instead of progression survival,

424 00:21:33.150 --> 00:21:34.920 let's have the conversation on survival,

425 00:21:34.920 --> 00:21:36.963 because it's just easier to understand.

426 00:21:37.830 --> 00:21:42.790 So Y is basically if a patient receives treatment

427 00:21:44.544 --> 00:21:49.358 and control, Y means their survival time in treatment

428 00:21:49.358 --> 00:21:52.830 and X is the survival time in control.

429 00:21:52.830 --> 00:21:56.461 But in a real trial, there was never been one patient

430 00:21:56.461 --> 00:21:59.280 who received both treatment and control.

431 00:21:59.280 --> 00:22:03.090 So this quantity is actually counterfactual.

432 00:22:03.090 --> 00:22:04.980 We cannot have that data.

433 00:22:04.980 --> 00:22:08.705 So we somehow have to predict this.

434 00:22:08.705 --> 00:22:10.740 So in order to do that,

435 00:22:10.740 --> 00:22:14.010 we first need to understand the marginal distribution

436 00:22:14.010 --> 00:22:15.450 of Y and X.

437 00:22:15.450 --> 00:22:17.610 And then also understand the need

438 00:22:17.610 --> 00:22:21.040 to take account the correlation in Y and X.

439 00:22:22.620 --> 00:22:24.925 Let's dive in what we need to do in this step,

440 00:22:24.925 --> 00:22:26.610 and I'll go into details of the statistics

441 00:22:26.610 --> 00:22:31.354 in next of my few slides, what technically it means.

442 00:22:31.354 --> 00:22:34.530 Basically, we are trying to find,

443 00:22:34.530 --> 00:22:36.444 so what we are trying to do,

444 00:22:36.444 --> 00:22:41.113 we are trying to find this predictive patient level effect

445 00:22:42.270 --> 00:22:44.160 of a drug.

446 00:22:44.160 --> 00:22:46.050 So what we need to have for that?

447 00:22:46.050 --> 00:22:48.870 We need to have a marginal distribution

448 00:22:48.870 --> 00:22:52.050 of survival for both,

449 00:22:52.050 --> 00:22:55.680 if a patient is independently goes to treatment

450 00:22:55.680 --> 00:22:57.420 or in control, basically.

451 00:22:57.420 --> 00:22:59.420 We need the marginal distribution first.

452 00:23:00.270 --> 00:23:03.739 Then we somehow need to calculate the difference

453 00:23:03.739 --> 00:23:06.960 by considering the association between them.

454 00:23:06.960 --> 00:23:10.833 Because Y and X are coming from a same patient.

455 00:23:13.230 --> 00:23:15.240 So first thing was interest,

456 00:23:15.240 --> 00:23:19.260 first thing was kind of how to do the marginal distribution

457 00:23:19.260 --> 00:23:20.093 of Y and X.

458 00:23:20.093 --> 00:23:22.350 That part is easier.

459 00:23:22.350 --> 00:23:25.293 That part is technically maybe intrigued, but easier.

460 00:23:26.562 --> 00:23:28.967 So suppose any trial data we have,

461 00:23:28.967 --> 00:23:31.320 we can have multiple trial data.

462 00:23:31.320 --> 00:23:34.590 We look into the treatment, and we look into the control.

463 00:23:34.590 --> 00:23:36.090 I just, for simplicity,

464 00:23:36.090 --> 00:23:39.771 suppose we have one one trial in our hand.

465 00:23:39.771 --> 00:23:40.604 And if there are multiple,

466 00:23:40.604 --> 00:23:42.780 we can definitely add more layers to that

467 00:23:42.780 --> 00:23:45.150 and adding trial specific event.

468 00:23:45.150 --> 00:23:46.629 So we can fit a...

469 00:23:46.629 --> 00:23:50.040 Piecewise exponential models are more,

470 00:23:50.040 --> 00:23:51.020 kind of a flexible model.

471 00:23:51.020 --> 00:23:52.650 So of course, one can use (indistinct),

472 00:23:52.650 --> 00:23:53.768 other parametric family.

473 00:23:53.768 --> 00:23:56.100 The reason we are moving into parametric

474 00:23:56.100 --> 00:23:57.990 because we wanted to extrapolate.

475 00:23:57.990 --> 00:24:00.930 We wanted to see the survival in the future.

476 00:24:00.930 --> 00:24:03.390 So that's why we chose basically

477 00:24:03.390 --> 00:24:07.676 piecewise exponential graph where each of the within,

478 00:24:07.676 --> 00:24:11.717 so the whole time axis is divided into different time span,

479 00:24:11.717 --> 00:24:14.790 different time points,

480 00:24:14.790 --> 00:24:18.450 and then we assume the hazard response within that.

481 00:24:18.450 --> 00:24:20.520 But just not, we don't assume any hazard ratio.

482 00:24:20.520 --> 00:24:22.830 We are (indistinct) treatment effect responsive.

483 00:24:22.830 --> 00:24:26.370 We are fitting this piecewise exponential separately

484 00:24:26.370 --> 00:24:28.860 for treatment and control, basically.

485 00:24:28.860 --> 00:24:30.960 So there is no proportional hazard option.

486 00:24:32.250 --> 00:24:35.430 And then here, we assume that alpha and beta (indistinct)

487 00:24:35.430 --> 00:24:38.250 and using the, basically, the gamma prior

488 00:24:38.250 --> 00:24:41.430 for each of the interval specific hazard.

489 00:24:41.430 --> 00:24:43.680 And we assume non-informative practice.

490 00:24:43.680 --> 00:24:45.360 Most often we only have the trial data,

491 00:24:45.360 --> 00:24:46.740 not much information,

492 00:24:46.740 --> 00:24:48.930 but if they have more information from early trials,

493 00:24:48.930 --> 00:24:51.150 you can use informatic (faintly speaking).

494 00:24:51.150 --> 00:24:53.667 But one of the major challenge always

495 00:24:53.667 --> 00:24:55.118 for piecewise exponential is

496 00:24:55.118 --> 00:24:57.993 how you choose cut points there.

497 00:24:59.070 --> 00:25:00.870 There's like the cut choice of cut points,

498 00:25:00.870 --> 00:25:02.670 people often do eyeballing, right?

499 00:25:02.670 --> 00:25:04.920 They look into the plot, eyeball the times,

500 00:25:04.920 --> 00:25:06.572 but those are mostly subjected.

501 00:25:06.572 --> 00:25:10.050 That means one prediction to another prediction,

502 00:25:10.050 --> 00:25:13.440 it can vary there, which is problematic.

503 00:25:13.440 --> 00:25:16.864 We need a a little bit more uniformal way

504 00:25:16.864 --> 00:25:18.543 of selecting these cut offs.

505 00:25:19.440 --> 00:25:22.097 The second more easier one can think, okay,

506 00:25:22.097 --> 00:25:24.477 I use the person notes there.

507 00:25:24.477 --> 00:25:27.479 But here the problem is when we fixed the personnel,

508 00:25:27.479 --> 00:25:30.180 maybe from one plot to another,

509 00:25:30.180 --> 00:25:32.520 there may be intervals which doesn't have much event.

510 00:25:32.520 --> 00:25:36.930 So (indistinct) may not be basically calculated

511 00:25:36.930 --> 00:25:38.553 in a right way.

512 00:25:39.900 --> 00:25:41.010 So not stairwise.

513 00:25:41.010 --> 00:25:43.623 There is no event within that interval.

514 00:25:44.550 --> 00:25:46.980 So what we did, we basically looked into

515 00:25:46.980 --> 00:25:49.950 a optimal cutoff points searching algorithm.

516 00:25:49.950 --> 00:25:53.820 So we basically first divided the cut,

517 00:25:53.820 --> 00:25:56.220 the axis based on the person health.

518 00:25:56.220 --> 00:25:57.840 So you have 10 intervals to...

519 00:25:57.840 --> 00:25:59.989 So basically, at most, 10 intervals.

520 00:25:59.989 --> 00:26:02.743 So then we consider all possible models.

521 00:26:02.743 --> 00:26:05.391 So one component, two component,

522 00:26:05.391 --> 00:26:07.800 to the power 10 component model.

523 00:26:07.800 --> 00:26:11.070 Of course, if some of intervals doesn't have very few event,

524 00:26:11.070 --> 00:26:12.390 we basically merge them

525 00:26:12.390 --> 00:26:14.550 so that you have a reasonable estimate

526 00:26:14.550 --> 00:26:16.587 for (indistinct) basically.

527 00:26:16.587 --> 00:26:19.530 And we chose the best model based on the DIC

528 00:26:19.530 --> 00:26:22.209 among those two to the power, N number of models.

529 00:26:22.209 --> 00:26:23.267 Of course, there's not always 10

530 00:26:23.267 --> 00:26:28.267 beause some of the intervals may be empty, so we plot them.

531 00:26:28.330 --> 00:26:32.130 And one can actually do a k-fold cross validation as well,

532 00:26:32.130 --> 00:26:35.460 which is we also looked into kind of a giving more

533 00:26:35.460 --> 00:26:36.480 or less similar result.

534 00:26:36.480 --> 00:26:38.217 But if you have a long term data,

535 00:26:38.217 --> 00:26:40.350 one can also do a k-fold validation

536 00:26:40.350 --> 00:26:42.780 in order to choose the hard points.

537 00:26:44.032 --> 00:26:46.949 Now the second part is prediction, right?

538 00:26:46.949 --> 00:26:50.887 So prediction, so what you got from the model now

539 00:26:50.887 --> 00:26:53.190 is that distribution of (indistinct).

540 00:26:53.190 --> 00:26:54.328 That's parameter.

541 00:26:54.328 --> 00:26:56.210 But when you go to prediction,

542 00:26:56.210 --> 00:26:58.380 we are talking about sampling space now.

543 00:26:58.380 --> 00:27:01.620 So we are talking about a new patient's survival time.

544 00:27:01.620 --> 00:27:06.620 So that needs to take account uncertainty of the new sample.

545 00:27:06.660 --> 00:27:09.480 That's the beauty of the Bayesian distribution,

546 00:27:09.480 --> 00:27:11.100 the posterior predictive distribution

547 00:27:11.100 --> 00:27:12.090 automatically does that.

548 00:27:12.090 --> 00:27:15.540 And the setting, the reason we took this setting,

549 00:27:15.540 --> 00:27:19.229 because the predictive posterior parameter distribution

550 00:27:19.229 --> 00:27:22.110 is again, a piecewise (indisitinct) distribution,

551 00:27:22.110 --> 00:27:23.700 which is basically closed form,

552 00:27:23.700 --> 00:27:26.820 that first hour computation quite a bit.

553 00:27:26.820 --> 00:27:29.580 And then we basically use, as I say,

554 00:27:29.580 --> 00:27:32.670 it's can easily done with this Beyesian computation.

555 00:27:32.670 --> 00:27:35.640 But if you want to do more complex model,

556 00:27:35.640 --> 00:27:37.500 we'll one, need to move into a little bit more

557 00:27:37.500 --> 00:27:41.643 MCMC algorithm or kind of writing and way of sampling it.

558 00:27:45.301 --> 00:27:48.450 Now the third aspect, which was actually the more,

559 00:27:48.450 --> 00:27:50.174 most interesting aspect.

560 00:27:50.174 --> 00:27:52.493 Now we got the marginal distribution.

561 00:27:52.493 --> 00:27:55.788 We predicted the marginal survival times.

562 00:27:55.788 --> 00:27:59.160 Now the question is, it's the same patient, right,

563 00:27:59.160 --> 00:28:00.090 we are talking.

564 00:28:00.090 --> 00:28:02.248 So they're correlated, X and Y.

565 00:28:02.248 --> 00:28:05.523 How we most are correlation structure, which is meaningful?

566 00:28:07.290 --> 00:28:10.791 Now that thing was actually the idea was came

567 00:28:10.791 --> 00:28:15.791 from a very old paper by Lehmann and Doksum in 1974,

568 00:28:16.104 --> 00:28:19.500 which we were looking for a scale shifting distribution

569 00:28:19.500 --> 00:28:21.210 I'm going into in a moment.

570 00:28:21.210 --> 00:28:24.446 Which actually brings up a very important property.

571 00:28:24.446 --> 00:28:26.790 And that property is very important

572 00:28:26.790 --> 00:28:30.257 because this methodology, it depends on that property.

573 00:28:30.257 --> 00:28:33.000 And we can talk about in the setting

574 00:28:33.000 --> 00:28:35.820 where you think this property is not true.

575 00:28:35.820 --> 00:28:38.580 So the property is basically a rank preserving property.

576 00:28:38.580 --> 00:28:42.410 What that means, that means if a two population,

577 00:28:42.410 --> 00:28:47.050 so if one fail earlier in control,

578 00:28:48.930 --> 00:28:50.837 they will fail also earlier in treatment.

579 00:28:50.837 --> 00:28:52.860 That's a rank preserving property.

580 00:28:52.860 --> 00:28:55.920 That's a very important property for this.

581 00:28:55.920 --> 00:28:57.930 But one can also question that, okay,

582 00:28:57.930 --> 00:29:00.060 for targeted therapy, that may not be true.

583 00:29:00.060 --> 00:29:03.328 Somebody with a biomarker that order may change, right?

584 00:29:03.328 --> 00:29:05.580 So we need to do appropriate adjustments

585 00:29:05.580 --> 00:29:07.080 to make that assumption.

586 00:29:07.080 --> 00:29:08.250 I'm going into that.

587 00:29:08.250 --> 00:29:10.700 That was one of the referee comments, by the way.

588 00:29:11.880 --> 00:29:13.080 But before going into that,

589 00:29:13.080 --> 00:29:15.000 this paper was really fascinating.

590 00:29:15.000 --> 00:29:18.637 I mean, it was very simple paper in actually 1974

591 00:29:20.069 --> 00:29:23.807 and also of statistics, very simply written paper.

592 00:29:23.807 --> 00:29:27.810 And what they were saying that they were looking

593 00:29:27.810 --> 00:29:32.760 into distance between two normal curves there.

594 00:29:32.760 --> 00:29:36.090 And the property they introduced was scale shifting,

595 00:29:36.090 --> 00:29:39.843 a shift function, which basically makes that,

596 00:29:40.992 --> 00:29:43.320 so your X and Y, what you just mentioned,

597 00:29:43.320 --> 00:29:45.450 we said X plus delta X,

598 00:29:45.450 --> 00:29:48.917 which is one can interpret as gain also,

599 00:29:48.917 --> 00:29:52.233 and Y kind of have a same distribution.

600 00:29:53.970 --> 00:29:55.782 That was the main property.

601 00:29:55.782 --> 00:30:00.210 But it's very, basically, that means you project this curve

602 00:30:00.210 --> 00:30:01.457 to other curve.

603 00:30:01.457 --> 00:30:03.543 There is a path to project all.

604 00:30:04.980 --> 00:30:06.713 And the solution of delta X is,

605 00:30:06.713 --> 00:30:10.050 I mean, what can easily cost start that it's not unique.

606 00:30:10.050 --> 00:30:13.770 But they actually, this is how they constructed it

607 00:30:13.770 --> 00:30:16.950 using the shift function.

608 00:30:16.950 --> 00:30:18.750 But what did that means for our case?

609 00:30:18.750 --> 00:30:20.310 Why we need that, right?

610 00:30:20.310 --> 00:30:22.890 So this means that, so if we,

611 00:30:22.890 --> 00:30:26.410 if I know marginally, the (indistinct) tells of X,

612 00:30:26.410 --> 00:30:29.940 I can project the same content into the Y distribution,

613 00:30:29.940 --> 00:30:32.340 that basically we'll coordinate ourselves.

614 00:30:32.340 --> 00:30:36.900 So that means if we build, if the ordering of X remain,

615 00:30:36.900 --> 00:30:38.430 ordering in Y will remain too.

616 00:30:38.430 --> 00:30:41.230 That is what the rank preservation property's coming in.

617 00:30:42.870 --> 00:30:44.897 I'm sorry, I'm going to revisit the...

618 00:30:44.897 --> 00:30:47.820 I mean, like I said, sometimes simple papers give you

619 00:30:47.820 --> 00:30:49.653 very nice ideas as I find.

620 00:30:50.607 --> 00:30:52.380 So now the job is simple, right?

621 00:30:52.380 --> 00:30:55.530 Now we have marginal distribution in hand.

622 00:30:55.530 --> 00:30:57.060 We get the predictive distribution,

623 00:30:57.060 --> 00:30:59.700 how to predict the marginal, and now we know

624 00:30:59.700 --> 00:31:02.790 how to link them using the quantile function

625 00:31:02.790 --> 00:31:05.160 from one to another, how to project.

626 00:31:05.160 --> 00:31:06.186 So basically what we did,

627 00:31:06.186 --> 00:31:10.033 we simulated from this posterior distribution

628 00:31:10.033 --> 00:31:13.260 and then we simulated this uniform numbers.

629 00:31:13.260 --> 00:31:17.127 And then what we did in order to bring X and Y to related,

630 00:31:17.127 --> 00:31:19.620 we basically from same quantile,

631 00:31:19.620 --> 00:31:23.040 we obtained the X for given US,

632 00:31:23.040 --> 00:31:27.050 we obtained the quantile XS and YS for each case.

633 00:31:27.050 --> 00:31:28.740 So they're related by that way.

634 00:31:28.740 --> 00:31:31.320 We project it from X to Y

635 00:31:31.320 --> 00:31:34.573 and then that gives us a pair XS YS for them

636 00:31:34.573 --> 00:31:37.053 and we can make the distribution.

637 00:31:41.029 --> 00:31:43.920 But of course, this is questionable, right?

638 00:31:43.920 --> 00:31:46.470 I mean, we are saying the order remains,

639 00:31:46.470 --> 00:31:48.300 which is not always true.

640 00:31:48.300 --> 00:31:51.542 Suppose this is a very classic example

641 00:31:51.542 --> 00:31:53.823 from the nivolumab trial.

642 00:31:54.690 --> 00:31:58.110 So it's attacking the PD1 inhibitor.

643 00:31:58.110 --> 00:32:02.937 So people with PD1 expressed, it's supposed to work better.

644 00:32:02.937 --> 00:32:05.070 So if you pick two subject,

645 00:32:05.070 --> 00:32:07.918 one is PD1 expressed and PD1 expressed not,

646 00:32:07.918 --> 00:32:12.330 if in control, PD1 expressed one actually works worse

647 00:32:12.330 --> 00:32:15.360 than the PD1 non-expressed treatment that can reverse.

648 00:32:15.360 --> 00:32:19.174 Because PD1 is the line, the target of the truck.

649 00:32:19.174 --> 00:32:21.030 So on such a case,

650 00:32:21.030 --> 00:32:24.270 our solution is basically divide the groups

651 00:32:24.270 --> 00:32:26.430 into the homogenous biomarker class.

652 00:32:26.430 --> 00:32:28.260 And then, the (indistinct) still works.

653 00:32:28.260 --> 00:32:31.590 And that can be easily done adding it as a regression

654 00:32:31.590 --> 00:32:32.433 into the model.

655 00:32:35.459 --> 00:32:37.570 So then finally, we summarize this

656 00:32:41.576 --> 00:32:45.270 with a survival gain and out the loss of tests,

657 00:32:45.270 --> 00:32:48.267 I mean basically using the posterior, sorry,

658 00:32:48.267 --> 00:32:52.140 the predictive distribution of Y minus X.

659 00:32:52.140 --> 00:32:56.160 And then also, we summarized the median

660 00:32:56.160 --> 00:32:59.460 and the 95% prediction intervals.

661 00:32:59.460 --> 00:33:03.330 And also to us, the Kaplan-Meier plot is still important

662 00:33:03.330 --> 00:33:05.670 because that's where the whole story begin.

663 00:33:05.670 --> 00:33:09.240 That's the data which generates our marginal distribution

664 00:33:09.240 --> 00:33:10.260 where we actually...

665 00:33:10.260 --> 00:33:13.503 So we should compare that side by side on this.

666 00:33:15.840 --> 00:33:17.821 Let's see how this method works then.

667 00:33:17.821 --> 00:33:20.280 I mean, so we started, does it improves anything

668 00:33:20.280 --> 00:33:23.220 after all doing fancy things,

669 00:33:23.220 --> 00:33:26.850 make things complicated, making lot of mathematical names.

670 00:33:26.850 --> 00:33:28.407 Did you improve anything?

671 00:33:28.407 --> 00:33:32.160 So did you gain more insight into this?

672 00:33:32.160 --> 00:33:33.540 So let's go back to this trial

673 00:33:33.540 --> 00:33:36.615 where begin the urothelial cancer trial of atezolizumab,

674 00:33:36.615 --> 00:33:40.890 which is basically the low-rank test says

675 00:33:40.890 --> 00:33:42.140 it was basically...

676 00:33:43.338 --> 00:33:45.780 The survival curves are not separated.

677 00:33:45.780 --> 00:33:49.923 Basically significance that doesn't reach.

678 00:33:49.923 --> 00:33:53.880 The Cox has a ratio, upper bound is about one,

679 00:33:53.880 --> 00:33:55.770 even the median, because it's very interesting.

680 00:33:55.770 --> 00:33:58.890 Because the curve actually is separated after median.

681 00:33:58.890 --> 00:34:00.821 So even somebody looking into the median,

682 00:34:00.821 --> 00:34:04.620 the treatment is worse than that for the standard of care.

683 00:34:04.620 --> 00:34:07.920 So the question is really, how can we...

684 00:34:07.920 --> 00:34:10.950 But when we look into the survival differences,

685 00:34:10.950 --> 00:34:13.680 we see a significant survival gain by the patient

686 00:34:13.680 --> 00:34:16.283 who remain on the therapy for a longer time.

687 00:34:16.283 --> 00:34:21.283 But the question is, can we somehow communicate

688 00:34:23.700 --> 00:34:25.893 that better with this individual event?

689 00:34:29.190 --> 00:34:32.406 So the one on the left hand,

690 00:34:32.406 --> 00:34:37.140 one on the left side is basically the probability plot.

691 00:34:37.140 --> 00:34:39.930 So it is basically the first column.

692 00:34:39.930 --> 00:34:44.910 We looked into the gain of survival bigger than zero month,

693 00:34:44.910 --> 00:34:46.743 one month, two month, six month.

694 00:34:47.700 --> 00:34:51.009 And the plot on the right side is basically median

695 00:34:51.009 --> 00:34:52.920 and then predicted interval.

696 00:34:52.920 --> 00:34:57.920 So as you can see, there is an initial setback.

697 00:34:59.520 --> 00:35:03.030 There is a significant probability

698 00:35:03.030 --> 00:35:06.570 that atezolizumab can actually improve the survival

699 00:35:06.570 --> 00:35:07.530 in the problem.

700 00:35:07.530 --> 00:35:08.880 At least you have,

701 00:35:08.880 --> 00:35:10.920 if you're looking to this plot,

702 00:35:10.920 --> 00:35:13.500 the improvement of three month or higher,

703 00:35:13.500 --> 00:35:15.870 which is urothelial cancer is pretty good,

704 00:35:15.870 --> 00:35:17.910 you have 30 to 40% probability,

705 00:35:17.910 --> 00:35:20.340 which needs to be considered for these patient.

706 00:35:20.340 --> 00:35:21.480 Because they don't have,

707 00:35:21.480 --> 00:35:24.080 they only have chemotherapy as a treatment for that.

708 00:35:25.050 --> 00:35:27.900 The most interesting thing comes actually

709 00:35:27.900 --> 00:35:30.180 on the right hand side.

710 00:35:30.180 --> 00:35:33.930 If you look into that, the patient as we talked about,

711 00:35:33.930 --> 00:35:38.220 the benefit actually emerges as the patient went long term

712 00:35:38.220 --> 00:35:39.243 into the therapy.

713 00:35:41.010 --> 00:35:43.810 It start pretty much, much (faintly speaking) to others,

714 00:35:45.170 --> 00:35:46.753 compared to others.

715 00:35:49.380 --> 00:35:50.213 Let's look into another.

716 00:35:50.213 --> 00:35:51.900 So okay, non-proportional hazard,

717 00:35:51.900 --> 00:35:52.800 this may be useful.

718 00:35:52.800 --> 00:35:56.010 But can we still use that for proportional hazard?

719 00:35:56.010 --> 00:35:56.947 Do they have any value?

720 00:35:56.947 --> 00:35:59.159 Actually, do they add anything?

721 00:35:59.159 --> 00:36:02.432 'Cause they're log-rank has a ratio are more popular, right?

722 00:36:02.432 --> 00:36:03.810 Our argument is no,

723 00:36:03.810 --> 00:36:06.360 but maybe this measure can help you there too.

724 00:36:06.360 --> 00:36:09.000 So I go back to this lung cancer PA3 example

725 00:36:09.000 --> 00:36:12.600 of gemcitabine and gemcitabine plus erlotinib,

726 00:36:12.600 --> 00:36:14.361 which is statistically significant

727 00:36:14.361 --> 00:36:17.339 with a very marginal hazard ratio.

728 00:36:17.339 --> 00:36:19.719 But statistically significant

729 00:36:19.719 --> 00:36:23.678 and the media advantage was also not very good

730 00:36:23.678 --> 00:36:27.399 by only .3 months of advantage.

731 00:36:27.399 --> 00:36:29.250 The question is really,

732 00:36:29.250 --> 00:36:33.527 does the survival effect is meaningful in that way?

733 00:36:33.527 --> 00:36:34.360 Always.

734 00:36:36.665 --> 00:36:40.537 So again, we started to plot these two.

735 00:36:42.030 --> 00:36:45.490 So the one here is basically the plot

736 00:36:46.941 --> 00:36:50.610 for the survival gain, X minus Y, once again, control.

737 00:36:50.610 --> 00:36:52.980 Same patient treated in treatment

738 00:36:52.980 --> 00:36:55.140 versus same patient treated in control.

739 00:36:55.140 --> 00:36:56.516 What is the survival gain?

740 00:36:56.516 --> 00:37:00.957 And the one on the right is basically the median

741 00:37:00.957 --> 00:37:02.880 and the corresponding interval.

742 00:37:02.880 --> 00:37:04.609 As you can see here,

743 00:37:04.609 --> 00:37:07.783 especially the patient who discontinued

744 00:37:08.750 --> 00:37:12.270 or there are some questionable benefit on that question.

745 00:37:12.270 --> 00:37:14.430 So just having a proportional hazard

746 00:37:14.430 --> 00:37:19.031 and giving a hazard ratio may not be giving the full point

747 00:37:19.031 --> 00:37:20.187 that we are looking for.

748 00:37:20.187 --> 00:37:22.380 There may be some more to it,

749 00:37:22.380 --> 00:37:25.290 which can be further investigated.

750 00:37:25.290 --> 00:37:27.780 When it's prescribing a patient,

751 00:37:27.780 --> 00:37:29.875 maybe there are certain characteristics

752 00:37:29.875 --> 00:37:33.627 why the patients may be continuing early

753 00:37:33.627 --> 00:37:36.720 and some kind of (indistinct) and some kind of special...

754 00:37:36.720 --> 00:37:40.080 So those patient may not be the benefit is as good,

755 00:37:40.080 --> 00:37:43.143 as prominent as the patients who are long term treated.

756 00:37:46.410 --> 00:37:48.300 So we also investigate CM.

757 00:37:48.300 --> 00:37:50.640 I just don't want to show all the plot just not

758 00:37:50.640 --> 00:37:53.322 to bore anymore, but messages are very similar.

759 00:37:53.322 --> 00:37:56.970 We also look into CM141.

760 00:37:56.970 --> 00:37:59.010 We also look into that ASPIRE trial

761 00:37:59.010 --> 00:38:02.410 as I explained you earlier about multiple myeloma

762 00:38:03.467 --> 00:38:08.452 and the CheckMate141 is basically squamous cell carcinoma

763 00:38:08.452 --> 00:38:09.767 in head and neck.

764 00:38:09.767 --> 00:38:14.280 And we also looked into the CheckMate057 trial

765 00:38:14.280 --> 00:38:17.370 where there's a significant subgroup

766 00:38:17.370 --> 00:38:22.370 that means the one group with PDL-1 expressed

767 00:38:23.010 --> 00:38:24.777 has a significant survival.

768 00:38:24.777 --> 00:38:28.480 But PDL-1 non-expressed has no survival benefit

769 00:38:33.146 --> 00:38:35.970 with the (indistinct).

770 00:38:35.970 --> 00:38:38.010 So we looked into all these examples

771 00:38:38.010 --> 00:38:41.790 into the export data and our codes are also relevant

772 00:38:41.790 --> 00:38:44.190 in public if you want to play with that.

773 00:38:44.190 --> 00:38:46.020 Basically the message we got,

774 00:38:46.020 --> 00:38:49.320 so the one on here is that this table

775 00:38:49.320 --> 00:38:52.470 toward the mean survival gain,

776 00:38:52.470 --> 00:38:54.990 median survival gain, the predictor interval.

777 00:38:54.990 --> 00:38:57.450 And what is the chance that probability

778 00:38:57.450 --> 00:39:01.547 that Y, which means your time,

779 00:39:01.547 --> 00:39:05.380 if a subject is receiving treatment

780 00:39:05.380 --> 00:39:08.040 and X if a subject is receiving control,

781 00:39:08.040 --> 00:39:11.046 what's the time Y is bigger than X,

782 00:39:11.046 --> 00:39:15.360 is basically we started to see some interesting feature.

783 00:39:15.360 --> 00:39:19.200 It gives us much more quantification of benefit compared

784 00:39:19.200 --> 00:39:21.907 to our P value or a hazard ratio in that way.

785 00:39:21.907 --> 00:39:24.960 Of course there are uncertainties in all of them

786 00:39:24.960 --> 00:39:26.460 as well as the clear cases

787 00:39:26.460 --> 00:39:28.806 where we saw statistical significance.

788 00:39:28.806 --> 00:39:32.580 We see some uncertain situation, that patient may

789 00:39:32.580 --> 00:39:36.303 or may not be benefit in some cases.

790 00:39:37.253 --> 00:39:41.640 So the quick conclusion with the increasing complexity

791 00:39:41.640 --> 00:39:45.300 of the drug and the different complex pathways

792 00:39:45.300 --> 00:39:47.349 we are talking, it is very important.

793 00:39:47.349 --> 00:39:50.970 And different patterns of treatment effect,

794 00:39:50.970 --> 00:39:54.900 it's very important to have a simpler language

795 00:39:54.900 --> 00:39:55.733 with the patient.

796 00:39:55.733 --> 00:39:59.070 I mean, because we're all telling what they're answering

797 00:39:59.070 --> 00:40:00.885 their question at least directly.

798 00:40:00.885 --> 00:40:05.356 We find predicted individual effects sort of a step towards

799 00:40:05.356 --> 00:40:10.356 that, which answers the patient's question more clearly,

800 00:40:10.800 --> 00:40:12.415 kind of a clinically relevant.

801 00:40:12.415 --> 00:40:14.201 And also it step forward,

802 00:40:14.201 --> 00:40:19.201 and as well as it supports this 21st century cure act

803 00:40:19.221 --> 00:40:21.210 of patient centricity.

804 00:40:21.210 --> 00:40:26.060 Especially find very useful in where your standard is

805 00:40:26.060 --> 00:40:28.353 of proportional hazard fails.

806 00:40:31.110 --> 00:40:33.735 I just wanted to quickly thank my collaborators

807 00:40:33.735 --> 00:40:38.735 whom I collaborated with and here is outpatient

808 00:40:38.910 --> 00:40:40.860 along with the software is available

809 00:40:40.860 --> 00:40:42.657 in case you want to try out.

810 00:40:42.657 --> 00:40:44.527 And the references that I mentioned

811 00:40:44.527 --> 00:40:47.010 including actually the...

812 00:40:47.010 --> 00:40:49.980 I just wanted to always mention,

813 00:40:49.980 --> 00:40:54.030 if you are reading the famous Lehmann book,

814 00:40:54.030 --> 00:40:55.380 it's actually there as well.

815 00:40:55.380 --> 00:40:58.685 I just find out last night it's there as well.

816 00:40:58.685 --> 00:41:01.233 And not only (faintly speaking) statistics people.

817 00:41:02.941 --> 00:41:05.820 And I just want to thank you for your attention.

818 00:41:05.820 --> 00:41:06.653 Thank you.

819 00:41:17.667 --> 00:41:19.967 <v Presenter>Does anybody have any questions?</v>

820 00:41:22.200 --> 00:41:23.033 <v Attendee>Sure.</v>

821 00:41:23.033 --> 00:41:26.521 Is there a notion of why you get that kind of culling effect

822 00:41:26.521 --> 00:41:29.550 with the treatment groups you were showing

823 00:41:29.550 --> 00:41:31.380 in the survival curves that the,

824 00:41:31.380 --> 00:41:33.273 basically the treatment arm looked worse at first.

825 00:41:33.273 --> 00:41:36.777 <v ->[Dr. Roychoudhury] Yes, I think for a (indistinct),</v>

826 00:41:37.980 --> 00:41:41.850 I think there was a certain group biomarker.

827 00:41:41.850 --> 00:41:44.520 It's again, a heterogeneity of treatment effect.

828 00:41:44.520 --> 00:41:46.200 Certain biomarkers did, I mean,

829 00:41:46.200 --> 00:41:48.600 most of the non-proportional hazard are the same story.

830 00:41:48.600 --> 00:41:51.000 I mean, the certain groups didn't function well

831 00:41:51.000 --> 00:41:53.986 at the beginning until they basically received the treatment

832 00:41:53.986 --> 00:41:54.830 follow up as well.

833 00:41:54.830 --> 00:41:58.565 They actually worse, they were quite a bit.

834 00:41:58.565 --> 00:42:01.470 <v Presenter>Okay, so do you think it's a treatment effect,</v>

835 00:42:01.470 --> 00:42:03.998 not a property of the population that was in it?

836 00:42:03.998 --> 00:42:05.736 <v ->[Dr. Roychoudhury] I think it's, I mean,</v>

837 00:42:05.736 --> 00:42:09.290 it's more of a safety of words I guess I believe.

838 00:42:09.290 --> 00:42:13.485 But of course, it's a road we don't know all the details

839 00:42:13.485 --> 00:42:14.940 inside of it.

840 00:42:14.940 --> 00:42:17.490 But the compound, which is the results which is available

841 00:42:17.490 --> 00:42:20.100 in that paper, it seems like there is an effect

842 00:42:20.100 --> 00:42:22.909 where it's really detrimental, the treatment effect.

843 00:42:22.909 --> 00:42:25.826 (faintly speaking)

844 00:42:36.844 --> 00:42:39.003 <v Presenter>Any other questions?</v>

845 00:42:42.990 --> 00:42:44.740 All right, anything from Zoom land?

846 00:42:55.950 --> 00:42:58.203 <v Attendee>Yeah, I have a question.</v>

847 00:42:59.350 --> 00:43:03.200 So it's interesting to model non-proportional patterns,

848 00:43:03.200 --> 00:43:07.020 but I think maybe another interesting question

849 00:43:07.020 --> 00:43:09.676 is to why there was non-proportional pattern

850 00:43:09.676 --> 00:43:10.967 (faintly speaking), right?

851 00:43:10.967 --> 00:43:15.421 So maybe (faintly speaking).

852 00:43:15.421 --> 00:43:18.030 So say for example if we owe something

853 00:43:18.030 --> 00:43:20.901 like a random voice or like classification,

854 00:43:20.901 --> 00:43:22.770 (indistinct) then we'll be able

855 00:43:22.770 --> 00:43:26.610 to see each subgroup benefits from the treatment

856 00:43:26.610 --> 00:43:28.527 or like why this (faintly speaking)?

857 00:43:31.567 --> 00:43:33.930 (indistinct) comment something else,

858 00:43:33.930 --> 00:43:38.010 like the modeling, the causes or figuring out

859 00:43:38.010 --> 00:43:39.697 why there's non-proportional patterns.

860 00:43:39.697 --> 00:43:42.918 <v ->[Dr. Roychoudhury] Sure, I think what you just said,</v>

861 00:43:42.918 --> 00:43:46.963 that was basically the method, some of five star,

862 00:43:46.963 --> 00:43:50.223 some of the method that more people develop.

863 00:43:50.223 --> 00:43:52.200 (indistinct) and their group did.

864 00:43:52.200 --> 00:43:57.030 They basically looked into a elastic net

865 00:43:57.030 --> 00:44:00.885 to find out the sets were basically you have,

866 00:44:00.885 --> 00:44:03.058 which is heterogeneous.

867 00:44:03.058 --> 00:44:05.370 They divided the group,

868 00:44:05.370 --> 00:44:08.310 this heterogeneous clusters, basically, into that.

869 00:44:08.310 --> 00:44:11.432 And then tried to interpret treatment of problems.

870 00:44:11.432 --> 00:44:15.180 I mean, the major problem is sometimes

871 00:44:15.180 --> 00:44:18.367 those groupings are very hard to interpret.

872 00:44:18.367 --> 00:44:20.880 Because it's so much data driven, right?

873 00:44:20.880 --> 00:44:24.750 And secondly, specify such a method as an analysis

874 00:44:24.750 --> 00:44:26.700 and this is a great method to exploration.

875 00:44:26.700 --> 00:44:27.750 I fully agree.

876 00:44:27.750 --> 00:44:28.923 But if you think about a drug

877 00:44:28.923 --> 00:44:31.740 and kind of a reporting of a drug,

878 00:44:31.740 --> 00:44:34.380 that could be a very risky method to do.

879 00:44:34.380 --> 00:44:37.320 But definitely, they are thinking down on that avenue.

880 00:44:37.320 --> 00:44:39.390 The only reason I think the five star was

881 00:44:39.390 --> 00:44:42.780 a very interesting idea, the only problem really came

882 00:44:42.780 --> 00:44:45.343 in is the estimation of treatment effect

883 00:44:45.343 --> 00:44:46.240 at the end of the day.

884 00:44:46.240 --> 00:44:49.046 Because now, you have a selection, right?

885 00:44:49.046 --> 00:44:53.820 Now you have to have the selection probability incorporated

886 00:44:53.820 --> 00:44:55.910 into the treatment effect.

887 00:44:55.910 --> 00:44:59.070 Some clusters are so small when you put the adjustment

888 00:44:59.070 --> 00:45:01.230 to the selection probability,

889 00:45:01.230 --> 00:45:04.443 it's not very intuitive to non-status station anymore.

890 00:45:05.492 --> 00:45:06.870 But it's been done.

891 00:45:06.870 --> 00:45:08.460 I mean, there are an example,

892 00:45:08.460 --> 00:45:09.960 I think in (indistinct) medicine,

893 00:45:09.960 --> 00:45:12.520 if you search by five star, you can see that.

894 00:45:12.520 --> 00:45:15.746 I think that the major got hit by the interpretation

895 00:45:15.746 --> 00:45:17.321 of the treatment effect.

896 00:45:17.321 --> 00:45:19.233 But you know what they did?

897 00:45:19.233 --> 00:45:22.440 They actually fit a parametric...

898 00:45:22.440 --> 00:45:23.850 First, they did three things.

899 00:45:23.850 --> 00:45:25.530 They looked into each set,

900 00:45:25.530 --> 00:45:28.380 because those population are homogenous.

901 00:45:28.380 --> 00:45:30.867 So they fit the Cox regression model there.

902 00:45:30.867 --> 00:45:33.813 And also they looked into a parametric regression model.

903 00:45:34.710 --> 00:45:36.848 But the only problem is,

904 00:45:36.848 --> 00:45:41.580 as soon as you adjust for your selection probabilities,

905 00:45:41.580 --> 00:45:44.494 if you have a huge effect, right?

906 00:45:44.494 --> 00:45:49.353 The selection probability somehow do a tool on that,

907 00:45:50.490 --> 00:45:54.390 which is clinicians don't find very intuitive, that case.

908 00:45:54.390 --> 00:45:56.063 Because at the end of our regular...

909 00:45:56.063 --> 00:45:59.009 I mean, how do you put such a thing on a drug level?

910 00:45:59.009 --> 00:46:01.110 That is a problem.

911 00:46:01.110 --> 00:46:03.600 But I think such a thing should be done for our...

912 00:46:03.600 --> 00:46:06.502 If we have already face data, we should explore this.

913 00:46:06.502 --> 00:46:10.497 I really think that should be the case.

914 00:46:23.907 --> 00:46:27.120 <v Presenter>Okay, so we don't have any questions.</v>

915 00:46:27.120 --> 00:46:28.733 Let's thanks again.

916 00:46:28.733 --> 00:46:32.370 <v Attendee>Yeah, I have one, just one quick question.</v>

917 00:46:32.370 --> 00:46:35.370 When you're predicting your why,

918 00:46:35.370 --> 00:46:39.613 why not augment that data with publicly available data

919 00:46:39.613 --> 00:46:43.175 based on features like comorbidity, age,

920 00:46:43.175 --> 00:46:48.175 some of the known predictors in terms of survival rates?

921 00:46:48.565 --> 00:46:50.633 <v ->[Dr. Roychoudhury] Absolutely, absolutely.</v>

922 00:46:52.051 --> 00:46:54.294 Sorry, I skipped that.

923 00:46:54.294 --> 00:46:56.544 But that's a great question.

924 00:46:56.544 --> 00:46:59.006 Actually, if we see that, I just wanted to go...

925 00:46:59.006 --> 00:47:01.042 We actually said if you have such a thing,

926 00:47:01.042 --> 00:47:03.997 we just convert this into a regression.

927 00:47:03.997 --> 00:47:05.310 So you can actually,

928 00:47:05.310 --> 00:47:07.981 instead of having just a unstructured model here,

929 00:47:07.981 --> 00:47:10.260 we can actually plug in all the rigorous (indistinct).

930 00:47:10.260 --> 00:47:13.040 But of course then, you don't have (indistinct)

931 00:47:13.040 --> 00:47:14.430 in your family anymore.

932 00:47:14.430 --> 00:47:15.990 It'll be conditionally extensive.

933 00:47:15.990 --> 00:47:18.390 But that's a very easy extension of this.

934 00:47:18.390 --> 00:47:20.411 Yes, absolutely.

935 00:47:20.411 --> 00:47:21.393 Absolutely.

936 00:47:26.970 --> 00:47:30.990 We actually did that for, sorry.

937 00:47:30.990 --> 00:47:33.443 We actually did that for this example

938 00:47:33.443 --> 00:47:36.840 where there's heterogeneous effect by the biomarker.

939 00:47:36.840 --> 00:47:39.660 You basically fill in the regression,

940 00:47:39.660 --> 00:47:41.970 and that's how we operate.

941 00:47:41.970 --> 00:47:42.870 Sorry, I interrupted.

942 00:47:42.870 --> 00:47:44.550 Somebody was...

943 00:47:44.550 --> 00:47:45.893 <v Attendee>Great, thank you.</v>

944 00:47:46.918 --> 00:47:49.500 <v Attendee>Oh, I have another question.</v>

945 00:47:49.500 --> 00:47:51.150 So when you tell the patients

946 00:47:51.150 --> 00:47:54.384 about their predictive treatment effects,

947 00:47:54.384 --> 00:47:59.384 if that affects I'd say how patients attach

948 00:48:02.160 --> 00:48:04.713 to the assigned treatment,

949 00:48:07.020 --> 00:48:11.970 that some way actually affects how you estimate your,

950 00:48:13.563 --> 00:48:18.240 for example, the first step for the estimates.

951 00:48:18.240 --> 00:48:23.240 And does that actually affect the way how you...

952 00:48:24.180 --> 00:48:25.800 Because I think estimation

953 00:48:25.800 --> 00:48:30.480 and also the following steps are actually the different,

954 00:48:30.480 --> 00:48:33.120 for example, the purpose of clinical trial

955 00:48:33.120 --> 00:48:34.560 will be estimation.

956 00:48:34.560 --> 00:48:37.517 But the purpose of, like say telling patients

957 00:48:37.517 --> 00:48:39.847 the individual treatment effects,

958 00:48:39.847 --> 00:48:42.769 a predicted individual treatment effects will be

959 00:48:42.769 --> 00:48:44.250 like a different purpose.

960 00:48:44.250 --> 00:48:47.310 It's not really the estimation for the clinical trial.

961 00:48:47.310 --> 00:48:51.690 Those two can become comfort when you, for example,

962 00:48:51.690 --> 00:48:54.272 using a patient algorithm to update your,

963 00:48:54.272 --> 00:48:57.570 like say marginal distribution.

964 00:48:57.570 --> 00:49:01.800 And then the next step is telling like say patients

965 00:49:01.800 --> 00:49:04.230 about prediction.

966 00:49:04.230 --> 00:49:06.480 And for new patients coming in,

967 00:49:06.480 --> 00:49:11.480 you do the marginal distribution estimation again.

968 00:49:13.260 --> 00:49:16.560 And does that actually pose a little bit of a problem

969 00:49:16.560 --> 00:49:20.130 when prediction actually change people's mind

970 00:49:20.130 --> 00:49:23.970 about their, like say how they attach

971 00:49:23.970 --> 00:49:25.117 to the assigned treatment?

972 00:49:25.117 --> 00:49:28.496 <v ->[Dr. Roychoudhury] Yeah, I think yeah.</v>

973 00:49:28.496 --> 00:49:29.967 That's a very valid question.

974 00:49:29.967 --> 00:49:33.180 I think that's the main reason we needed

975 00:49:33.180 --> 00:49:34.440 this algorithm, right?

976 00:49:34.440 --> 00:49:36.688 And we did not stop just marginally.

977 00:49:36.688 --> 00:49:40.830 But if you look into the new data that's coming in,

978 00:49:40.830 --> 00:49:42.330 of course we need to be careful

979 00:49:42.330 --> 00:49:45.603 because that's not coming from a clinical trial data.

980 00:49:47.410 --> 00:49:49.350 And this one is a more simplified

981 00:49:49.350 --> 00:49:51.750 because the third step was calculated

982 00:49:51.750 --> 00:49:53.400 from clinical trial data,

983 00:49:53.400 --> 00:49:54.870 which is a randomized study.

984 00:49:54.870 --> 00:49:57.480 But if you add more observational data to it,

985 00:49:57.480 --> 00:49:58.313 if I understand how they're touched

986 00:49:58.313 --> 00:50:01.410 and we continue to update that,

987 00:50:01.410 --> 00:50:02.850 it just need to be more careful

988 00:50:02.850 --> 00:50:07.314 about using two different quality of data in that way.

989 00:50:07.314 --> 00:50:08.864 Does that answer your question?

990 00:50:10.590 --> 00:50:11.963 <v Attendee>Sure, thank you.</v>

991 00:50:15.240 --> 00:50:19.031 <v Presenter>Okay, so we are running out of time,</v>

992 00:50:19.031 --> 00:50:22.308 so let's thanks Dr. Roychoudhury again.

993 00:50:22.308 --> 00:50:23.558 Wonderful talk.

994 00:50:24.447 --> 00:50:27.030 <v ->[Dr. Roychoudhury] Thank you.</v>

995 00:50:27.912 --> 00:50:30.713 <v Presenter>Please make sure you sign</v>

996 00:50:30.713 --> 00:50:32.551 the admit sheet.

997 00:50:32.551 --> 00:50:36.634 (attendees chattering continues)

998 00:50:52.896 --> 00:50:56.979 (attendees chattering continues)