PERSUADE BC_OS_output

2021-03-15

Contents

[Link to PERSUADE GitHub page](#)

Kaplan-Meier
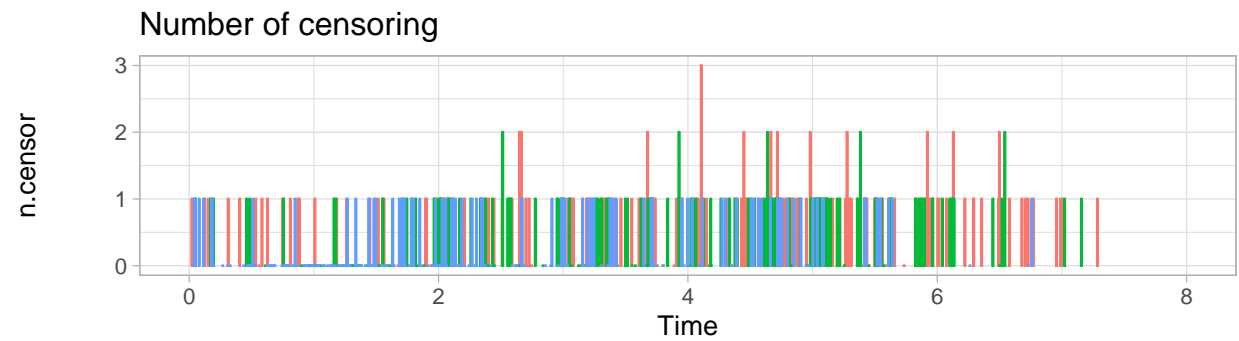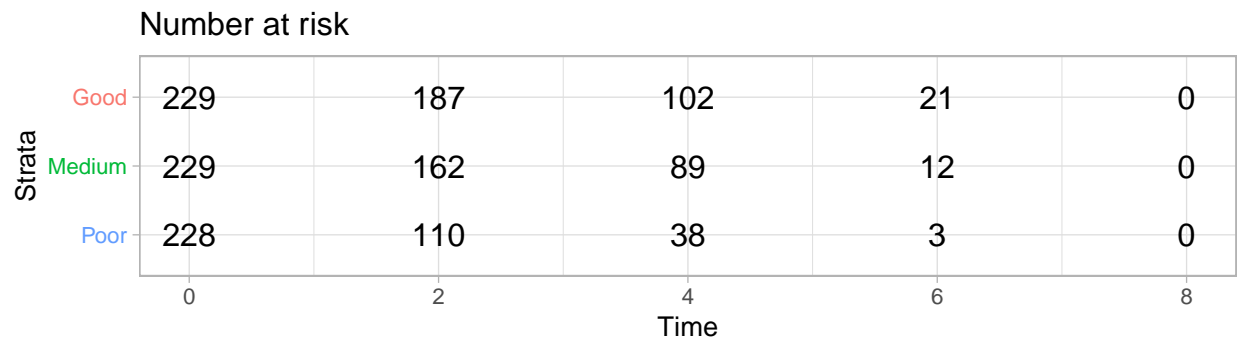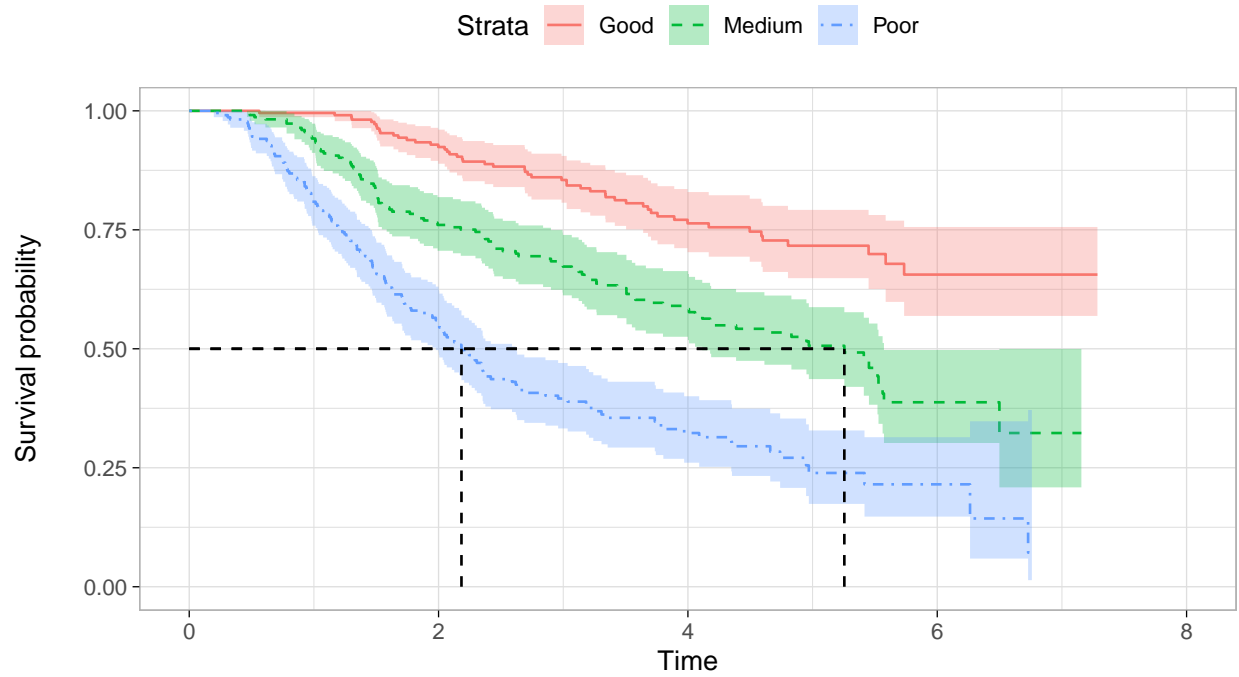
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group=Good	229	229	229	51	5.934330	0.1616003	NA	NA	NA
group=Medium	229	229	229	103	4.600852	0.1856699	5.254795	4.115068	5.572603
group=Poor	228	228	228	145	3.101736	0.1772520	2.183562	1.978082	2.619178

Proportional hazards assumption

Should stratified parametric survival models be used?

To inform the decision whether stratified or non-stratified models should be used. One should assess whether the proportional hazard (PH) assumption holds. The PH assumption entails that the ratio of the hazards of two groups is constant over time. When the PH assumption holds, one may fit non-stratified (parametric) survival models, meaning that a single (parametric) survival model can be fitted to all groups with the group effect(s) included as a covariate of the model. When the PH assumption does not hold it is advised to fit separate (parametric) survival models to the different groups. Finally, proportional hazards is only relevant for exponential, Weibull, and Gompertz models. Log-logistic and log normal models since these are accelerated failure time models and, by definition, do not consider hazards to be proportional over time. Group (treatment) effect can of course be modelled as a covariate when using these models. For more information, please refer to the NICE TSD 14.

The figures below allow to examine whether the PH assumption holds. Figure A shows the relation between the natural logarithm of time (x-axis) and the natural logarithm of the cumulative hazard (y-axis). The lines in the figure representing the different groups. An indication that the PH assumption holds is when these lines are parallel. Figures B and C represent the scaled Schoenfeld residual plots. In those plots, the relation of time (x-axis) and the residuals of each observed events (y-axis) is plotted. For the PH assumption to hold, there should be not apparent relations between these residuals and time. To investigate this, a smoothed spline has been plotted (cyan). Once this smoothed line systematically deviates from a straight line with intercept 0, one can consider that the PH assumption is violated, because it indicates a relation between the coefficient (or group variable in this case) and time. This is demonstrated in the paper from Grambsch and Therneau, Biometrika, Volume 81, Issue 3, September 1994, Pages 515–526.

Another indication that the PH assumption does not hold is when the lines from different groups Kaplan-Meier plot (previous page) cross each other.

Interpretation in this case: Based on Figure A, one could argue that the PH assumption holds since the different lines look quite parallel to each other. However, when inspecting Figures B and C, one can see that the hazard first decreases and then increases over time (in both Figures). This indicates that the PH assumption probably does not hold.

CAUTION: An indication that the PH assumption holds during the observed period of time does not indicate that it holds after the observation period (during the extrapolation).

A: LN(cumulative hazard)
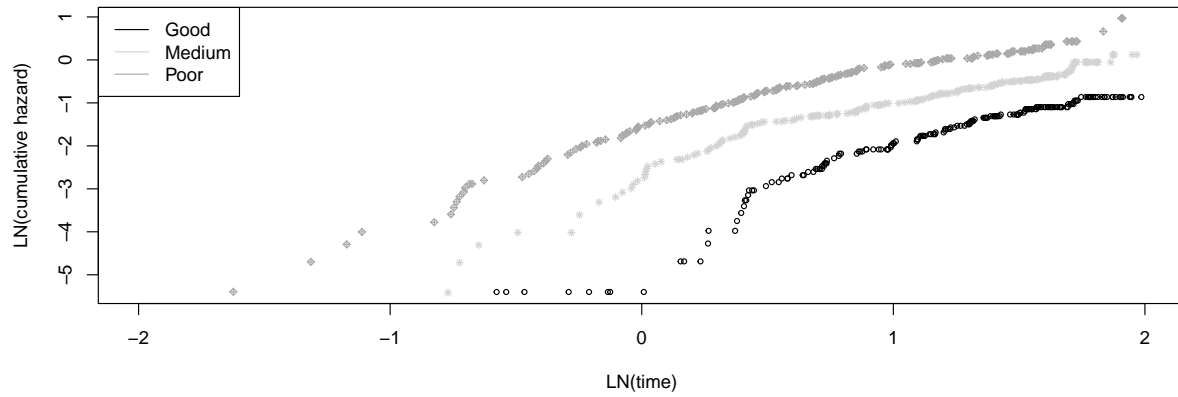
B: Scaled Schoenfeld residuals
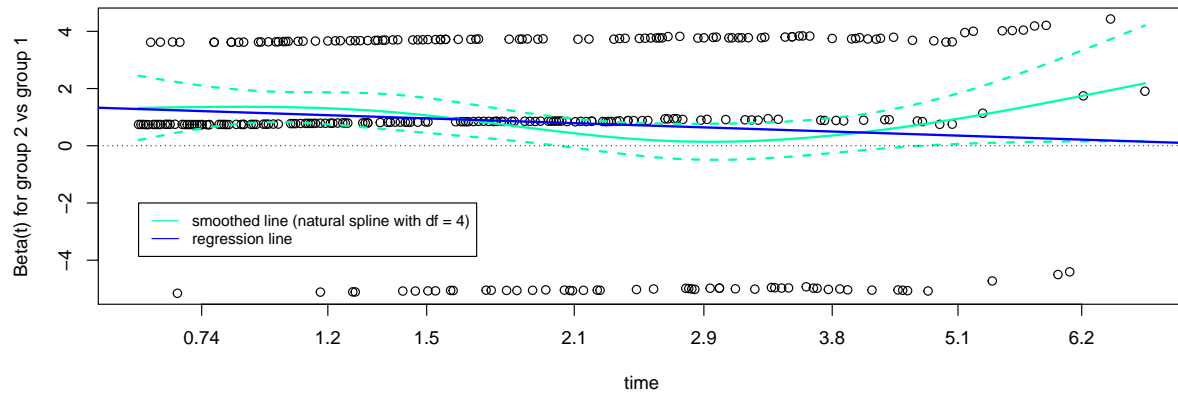
C: Scaled Schoenfeld residuals
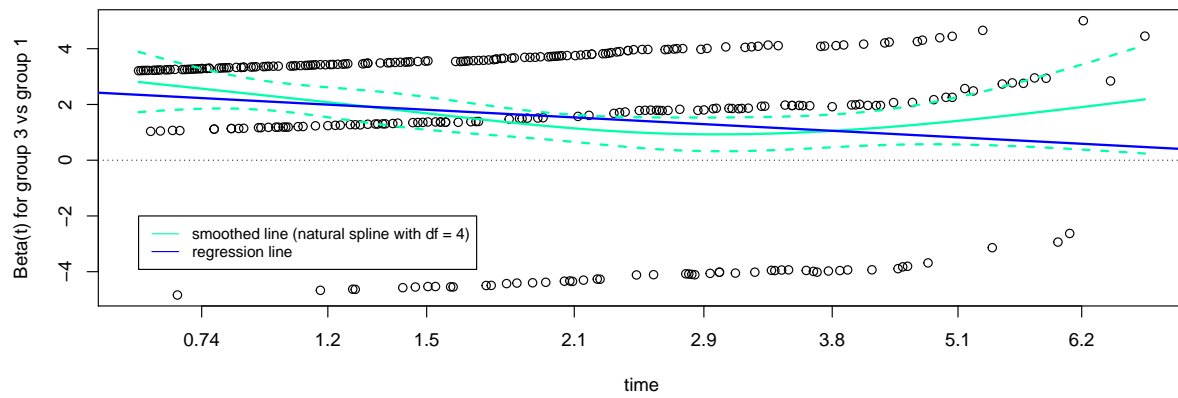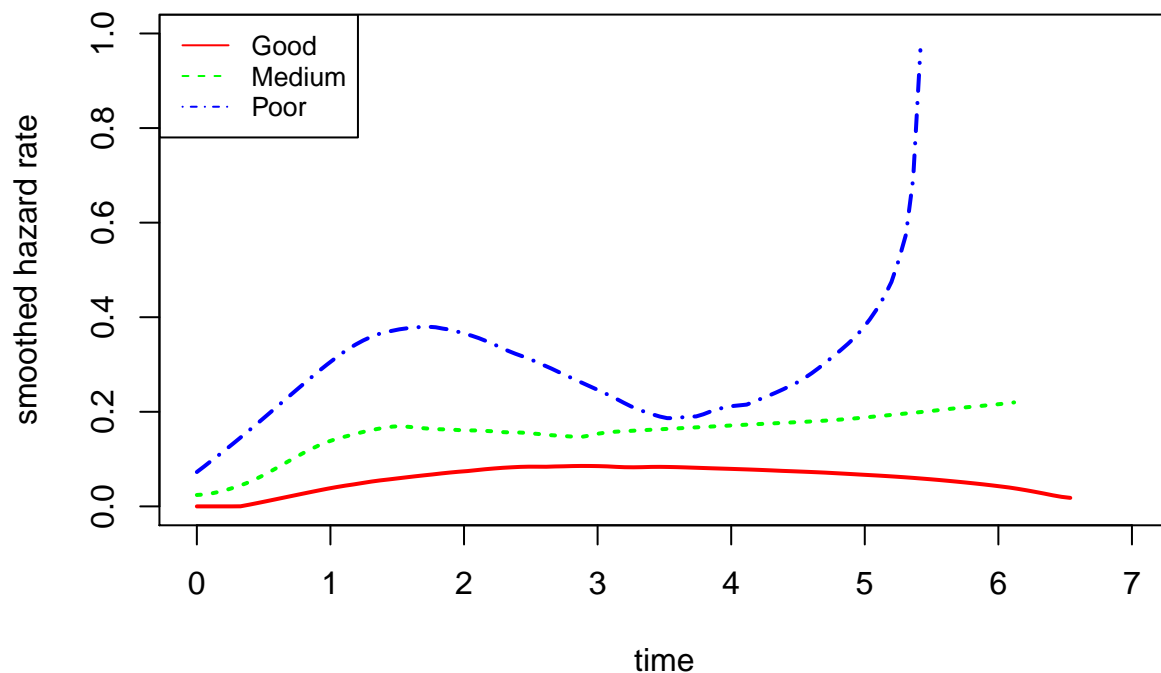
Hazard function

Shape of the observed smoothed hazard function

Should parametric survival models assuming a monotonic hazard rate (i.e. exponential, Weibull, Gompertz) be used?

The Figure below represents the smoothed hazard rate over time for each group. Based on this Figure, an exponential distribution would be considered suitable if the smoothed hazard rate would be constant over time (straight vertical line). The Weibull and Gompertz functions would be considered suitable if the smoothed hazard rate would increase or decrease monotonically (an upward or downward slope with constant gradient). More information on which shape of the hazard function can be estimated by the different parametric survival models can be found here.

Interpretation in this case: Based on this Figure, one can discard all three parametric survival models (exponential, Weibull, and Gompertz), because none of these smoothed hazard rates is constant, or increases/decreases monotonically over time. Based on this information and the fact that the PH assumption does likely not hold in this case, we have decided to fit separate (stratified) parametric survival models to each group.

CAUTION: These smoothed hazard rates apply to the observed period and do not allow to make inferences about the shape of the hazard function after the observation period.

Shape of the predicted hazard function

The following plots dislay how the hazard rates is estimated through the different parametric survival models.

Group Good

Group Good

Group Good

Group Medium

Group Medium

Group Medium

Group Poor

Legend:
1. Exponential
2. Weibull
3. Gompertz
4. Log-normal
5. Log-logistic
6. Gamma
7. Generalised Gamma

Group Poor

Legend:
8. Spline 1 knot hazard
9. Spline 2 knots hazard
10. Spline 3 knots hazard
11. Spline 1 knot odds
12. Spline 2 knots odds
13. Spline 3 knots odds
14. Spline 1 knot normal
15. Spline 2 knots normal
16. Spline 3 knots normal

Group Poor

Legend:
17. Mixture cure Weibull
18. Non-mixture cure Weibull
19. Mixture cure Log-normal
20. Non-mixture cure Log-normal
21. Mixture cure Log-logistic
22. Non-mixture cure Log-logistic

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Standard parametric models

The circle displays the colours that are attributed to each parametric survival model in the graphs on the following pages.

The Table below displays the goodness-of-fit statistics for each parametric survival model, ordered from 'best' fitting to less well fitting, based on the Akaike Information Criterion (AIC). The AIC and Bayesian Information Criterion (BIC) provide a measure of the relative fit of each model to the data, while penalising for the number of parameter included in the fitted models. The lower the AIC or BIC, the better the relative fit of a model compared to other fitted models.

Interpretation in this case: Based on this Table, one can conclude that the generalised gamma and log-normal parametric survival models fit the data best relative to the other fitted models, according to the AIC.

CAUTION: These goodness-of-fit statistics only apply to the observed period of time and do not allow to issue statements about the suitability of the extrapolated survival by these fitted models beyond the observation period.

In the following pages, three plots per fitted parametric survival model are displayed to support the visual inspection of the fit of the models to the observed data. Figure A shows the Kaplan-Meier curves (black and gray) versus the fitted parametric survival models (colour). Figure B displays a comparison of the smoothed hazard rates based on the empirical data (black and gray) versus the estimated transition probabilities (colour, based on the fitted parametric survival models). In all Figures A and B, the Kaplan-Meier curves and the smoothed hazard rates are the same. Figure C shows a specific diagnostic plot for each fitted parametric survival model. For all these plots, the rule is: the closer the coloured lines are to the black and grey lines, the better.

Interpretation in this case: Based on these plots, one can see that the generalised gamma and log-normal parametric survival models seem to estimate the transition probabilities the most closely, but there are still some discrepancies between observed and estimated transition probabilities, especially in the 'Poor' and 'Medium' group. This can be explained by the changing direction of the hazard rates in the 'Poor' group over time. It increases until approximately year 2, then decreases until approximately year 5, and then increases again. Standard parametric survival models are not able to capture multiple changes in the hazard function over time, hence, more flexible models which allow for multiple changes in the hazard functions may be required.

CAUTION: These observations only apply to the observed period of time and do not allow to issue statements about the suitability of the extrapolated survival by these fitted models beyond the observation period. Additionally, the shape of the hazard function (smoothed transition rates) at the end of the observed period may be affected by the low number of observations in the tail of the Kaplan-Meier curves. One should therefore consider these changing hazard at the end of the observed period cautiously.
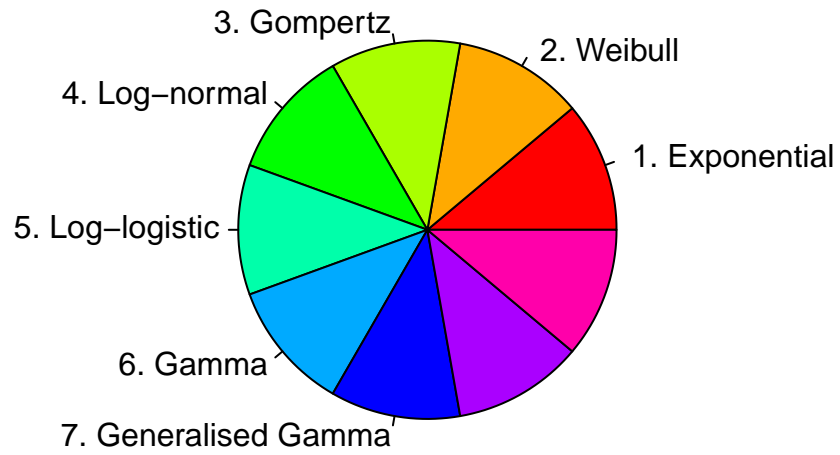
Model	AIC	BIC
7. Generalised Gamma	1589.049	1629.826
4. Log-normal	1592.880	1620.066
5. Log-logistic	1609.294	1636.479
6. Gamma	1621.982	1649.167
2. Weibull	1632.618	1659.803
3. Gompertz	1660.954	1688.140
1. Exponential	1668.212	1681.805

Exponential

A: Kaplan–Meier (Exponential)
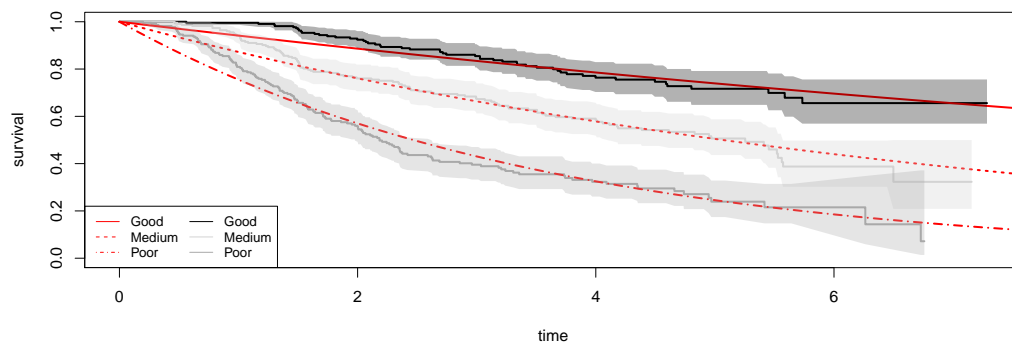
B: Annual transition probability (Exponential)
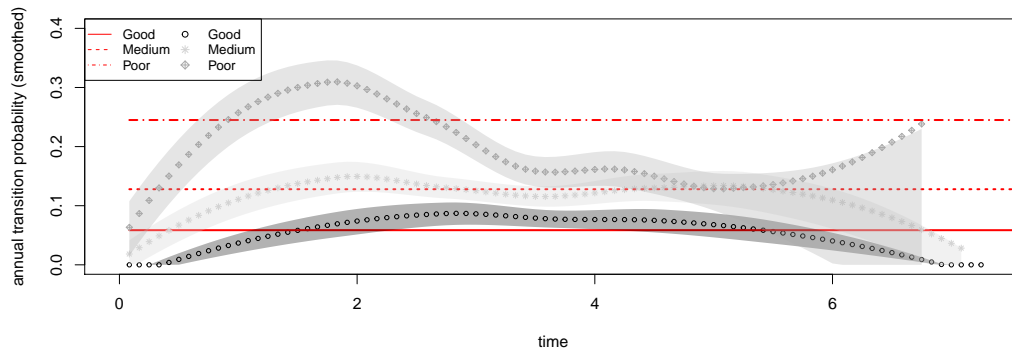
C: Diagnostic plot (Exponential)
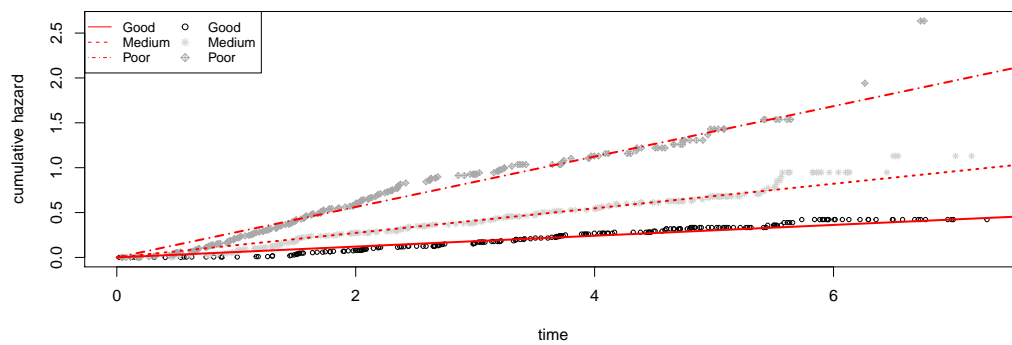
Weibull

A: Kaplan–Meier (Weibull)
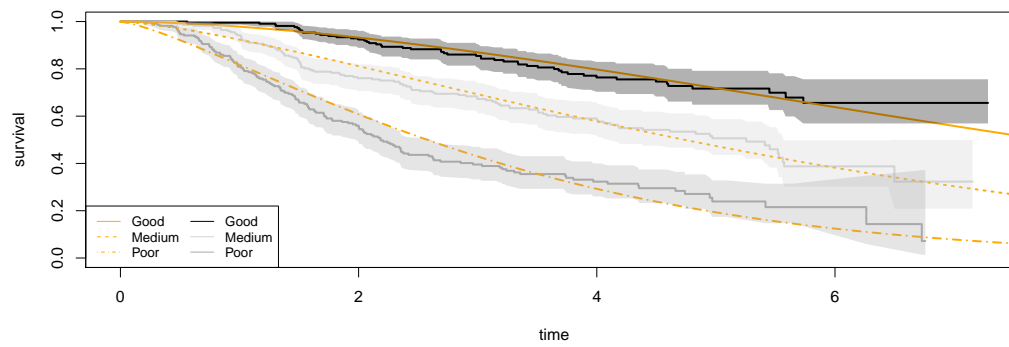
B: Annual transition probability (Weibull)
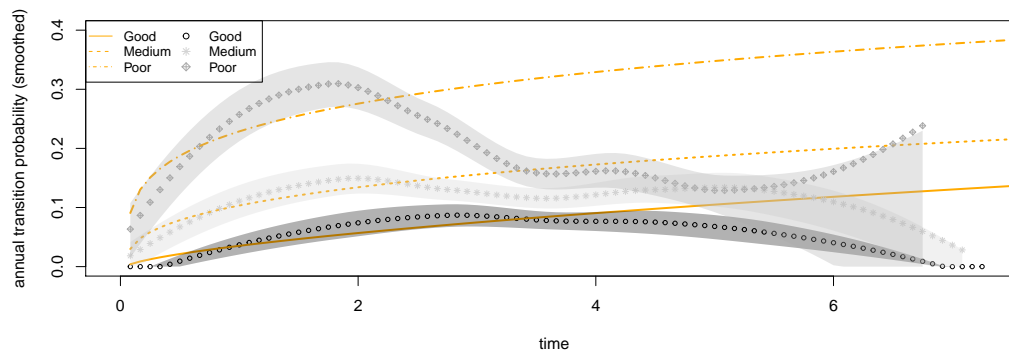
C: Diagnostic plot (Weibull)
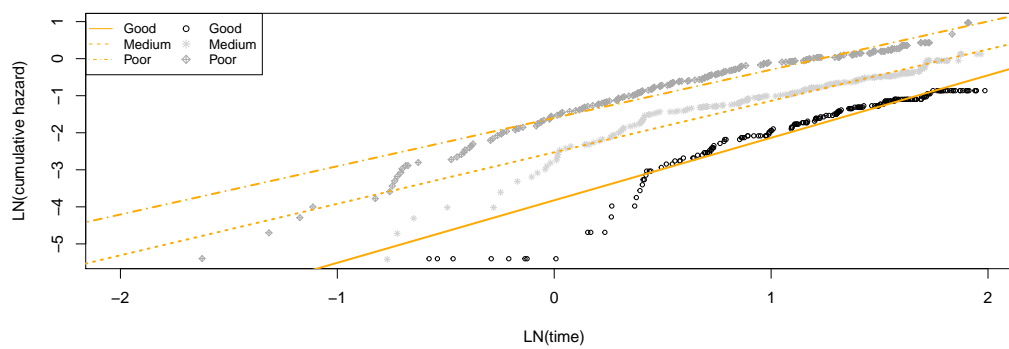
Gompertz

A: Kaplan–Meier (Gompertz)
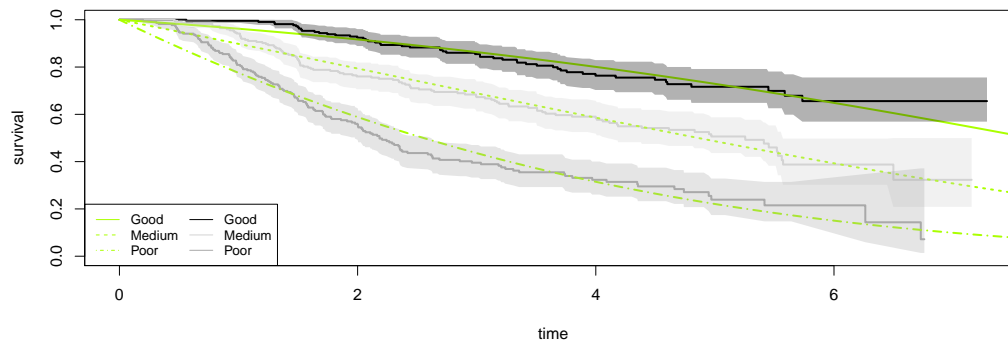
B: Annual transition probability (Gompertz)
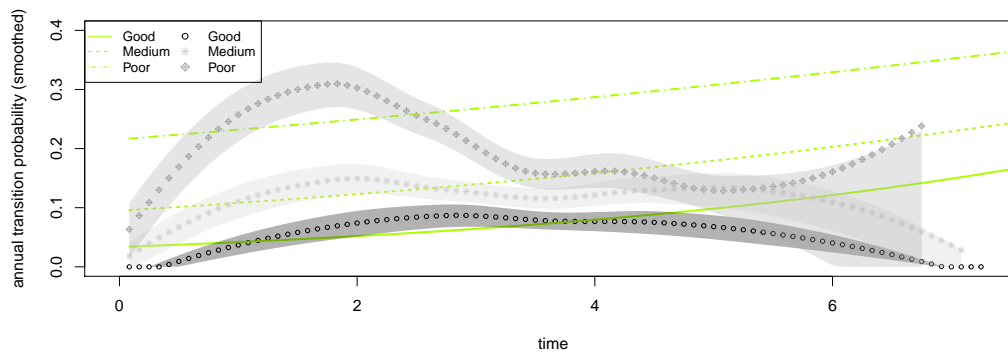
C: Diagnostic plot (Gompertz)
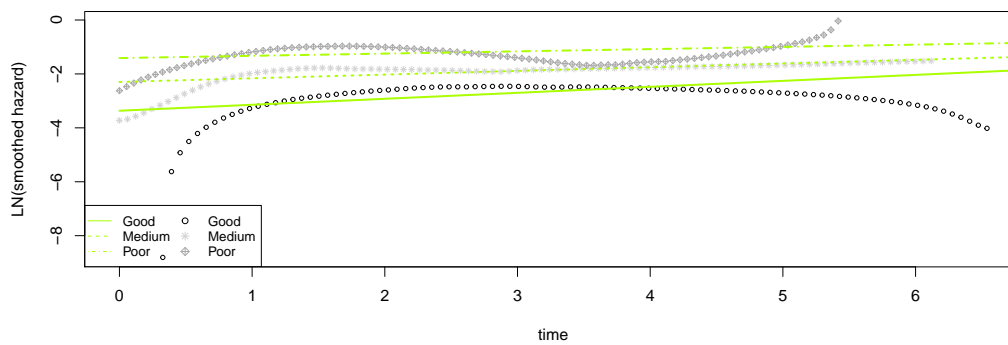
Log-normal

A: Kaplan–Meier (Log–normal)
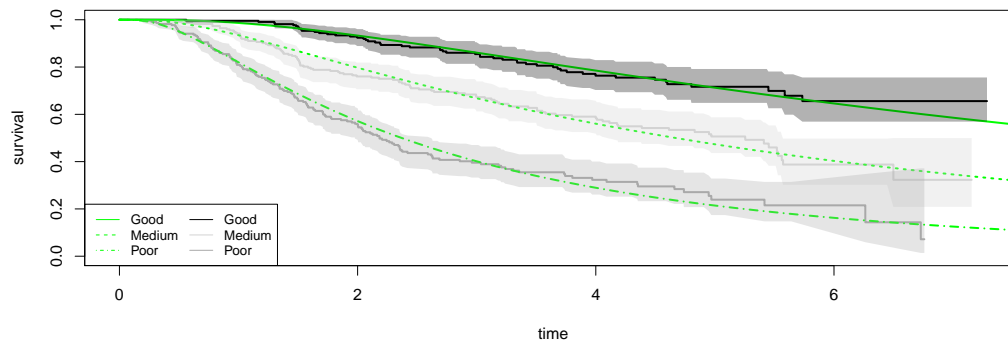
B: Annual transition probability (Log–normal)
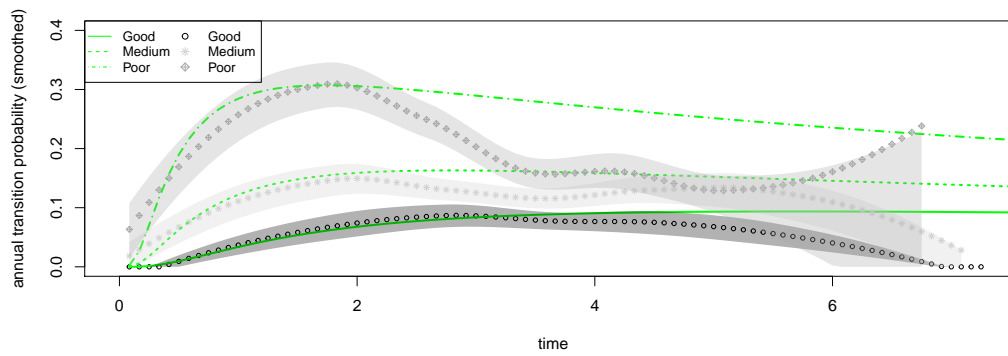
C: Diagnostic plot (Log–normal)
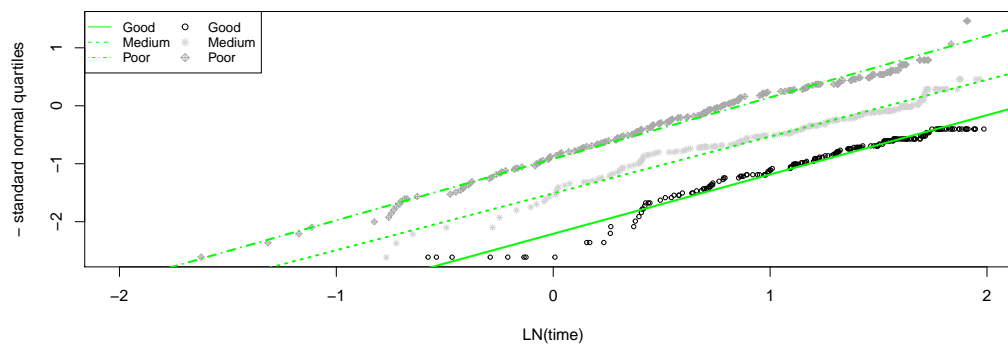
Log-logistic

A: Kaplan–Meier (Log–logistic)
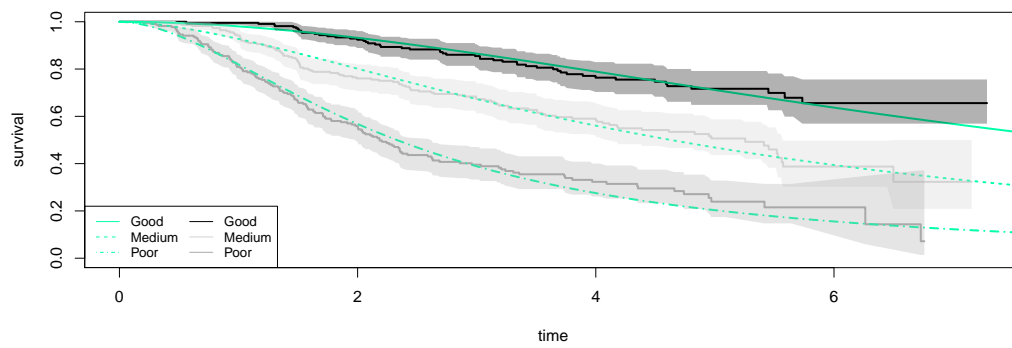
B: Annual transition probability (Log–logistic)
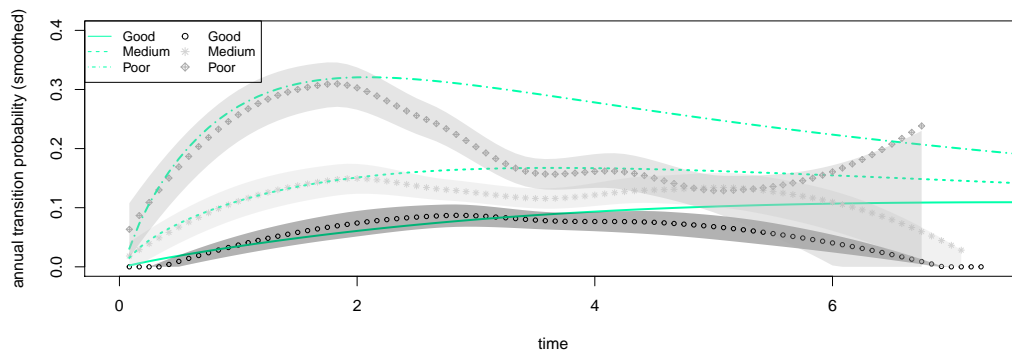
C: Diagnostic plot (Log–logistic)
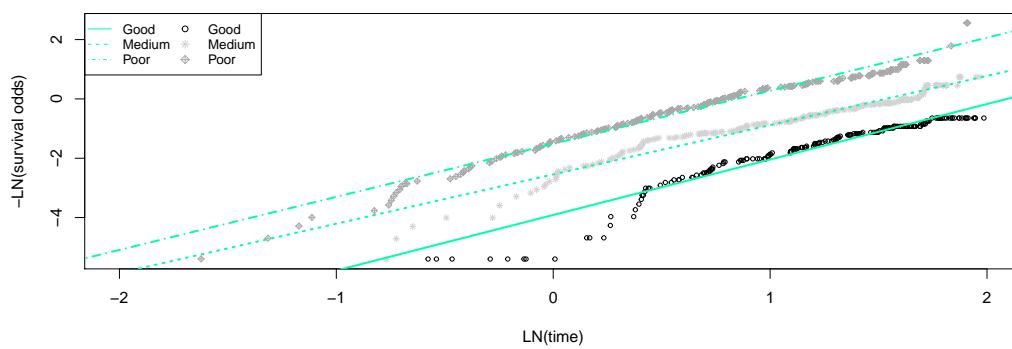
Gamma

A: Kaplan–Meier (Gamma)
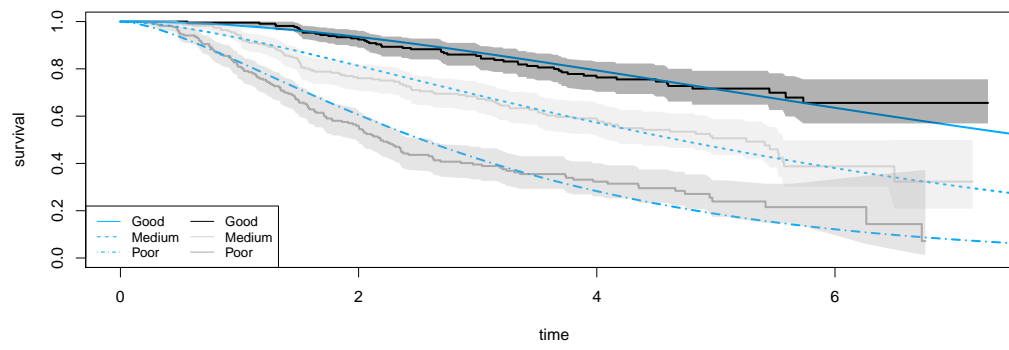
B: Annual transition probability (Gamma)
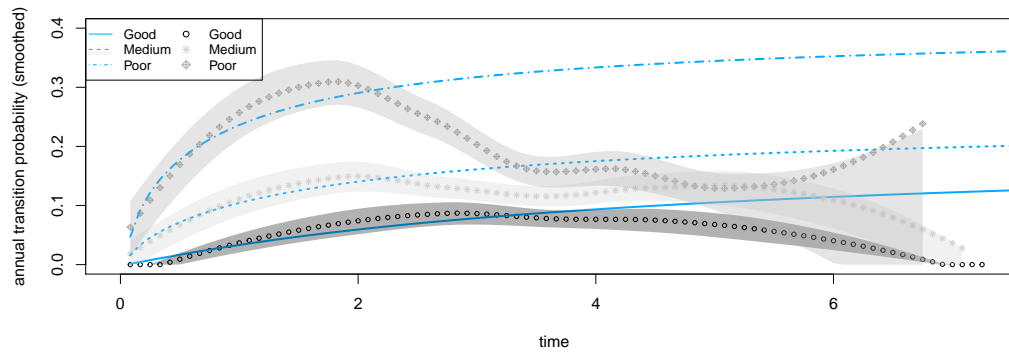
C: Diagnostic plot (Gamma)
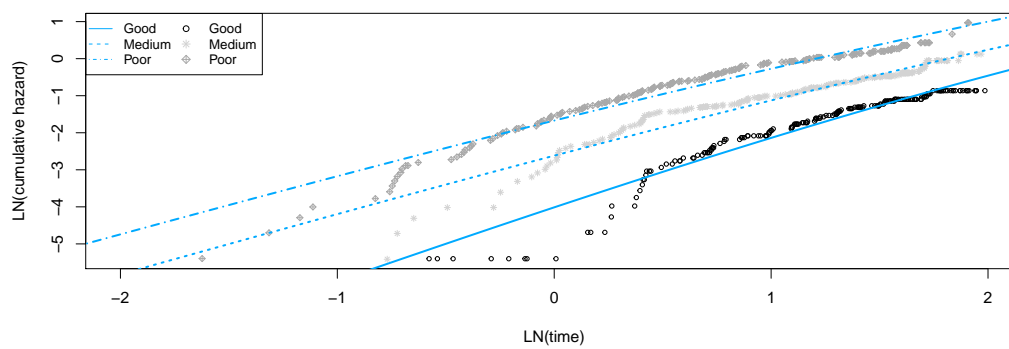
Generalised Gamma

A: Kaplan–Meier (Generalised gamma)
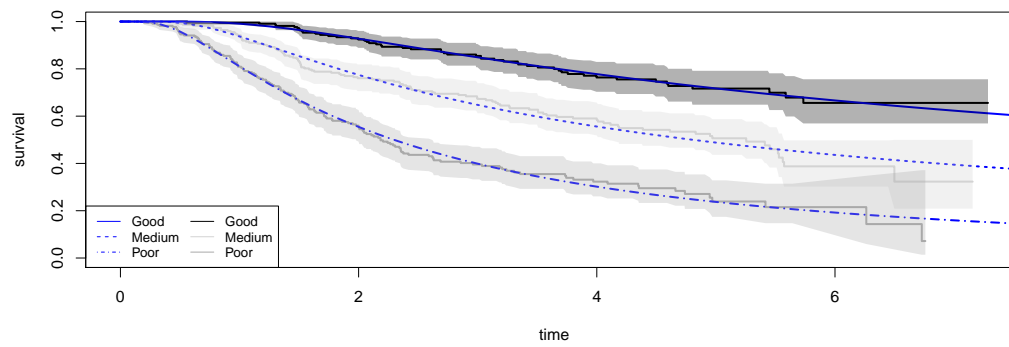
B: Annual transition probability (Generalised Gamma)
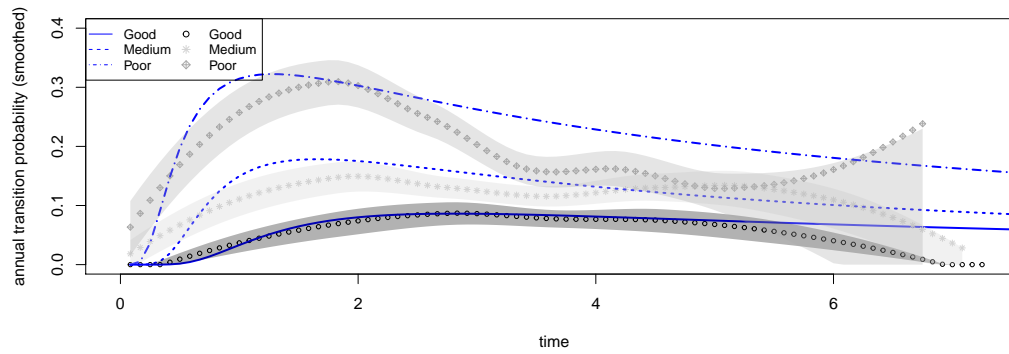
C: Diagnostic plot (Generalised gamma)
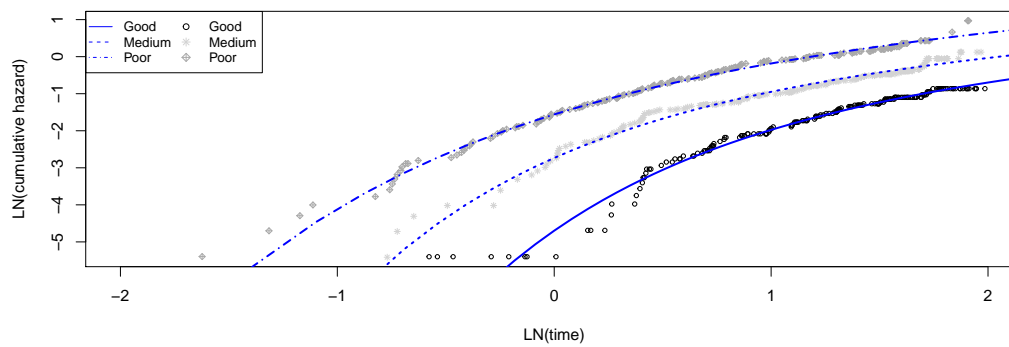
Parametric natural cubic spline models

If standard parametric models do not provide a satisfactory fit to the data based on previous observations, do spline models provide a more satisfactory fit to the data?

An explanation concerning these natural cubic spline models, henceforth spline models, is provided in Royston and Pamar - 2002.

As in the previous section, the circle provides the colours attributed to each parametric survival model, spline models in this case. The Table below provides the AIC and BIC for all fitted models. This allows for a comparison of the fit of the spline models to the 'standard' parametric survival models.

Interpretation in this case: Based on this Table, one can conclude that four spline models fit the data relatively better than the generalised gamma survival model, due to their lower AIC. The difference in AIC is however marginal (4 AIC points).

CAUTION: These goodness-of-fit statistics only apply to the observed period of time and do not allow to issue statements about the suitability of the extrapolated survival by these fitted models beyond the observation period.

In the following pages, the same three plots per fitted parametric spline model are displayed to support the visual inspection of the fit of the models to the observed data, as in previous section. The interpretation of these plots remains the same.

Interpretation in this case: Based on these plots, one can see that the four spline models fit the data marginally better than the generalised gamma model.

CAUTION: These observations only apply to the observed period of time and do not allow to issue statements about the suitability of the extrapolated survival by these fitted models beyond the observation period. Additionally, the shape of the hazard function (smoothed transition rates) at the end of the observed period may be affected by the low number of observations in the tail of the Kaplan-Meier curves. One should therefore consider these changing hazard at the end of the observed period cautiously.
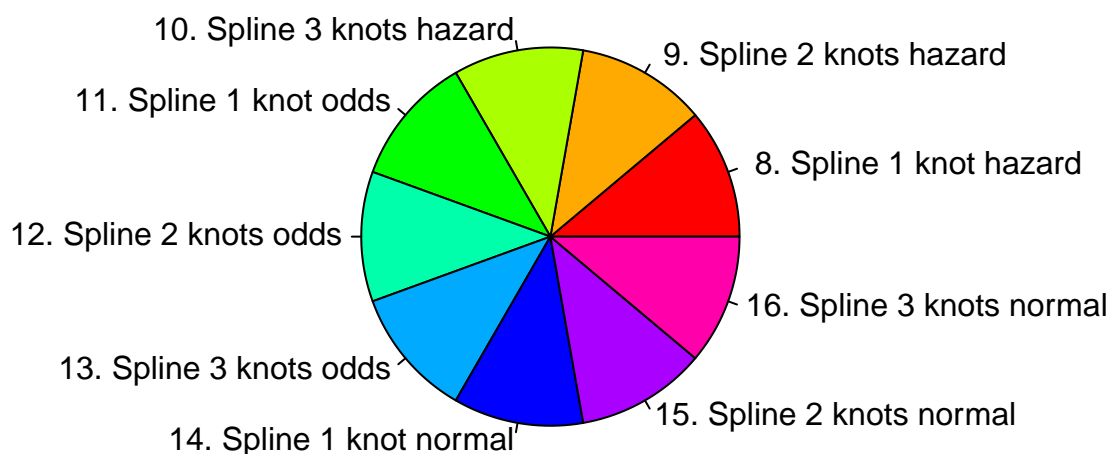
Model	AIC	BIC
9. Spline 2 knots hazard	1585.894	1640.264
12. Spline 2 knots odds	1587.289	1641.659
14. Spline 1 knot normal	1587.682	1628.460
15. Spline 2 knots normal	1588.343	1642.714
7. Generalised Gamma	1589.049	1629.826
8. Spline 1 knot hazard	1589.327	1630.105
16. Spline 3 knots normal	1589.832	1657.795
10. Spline 3 knots hazard	1589.875	1657.838
11. Spline 1 knot odds	1590.221	1630.999
13. Spline 3 knots odds	1590.720	1658.683
4. Log-normal	1592.880	1620.066
5. Log-logistic	1609.294	1636.479
6. Gamma	1621.982	1649.167
2. Weibull	1632.618	1659.803
3. Gompertz	1660.954	1688.140
1. Exponential	1668.212	1681.805

Spline 1 knot hazard

A: Kaplan–Meier (Spline, 1 knot, hazard scale)

B: Annual transition probability (Spline, 1 knot, hazard scale)

C: Diagnostic plot (Spline, 1 knot, hazard scale)
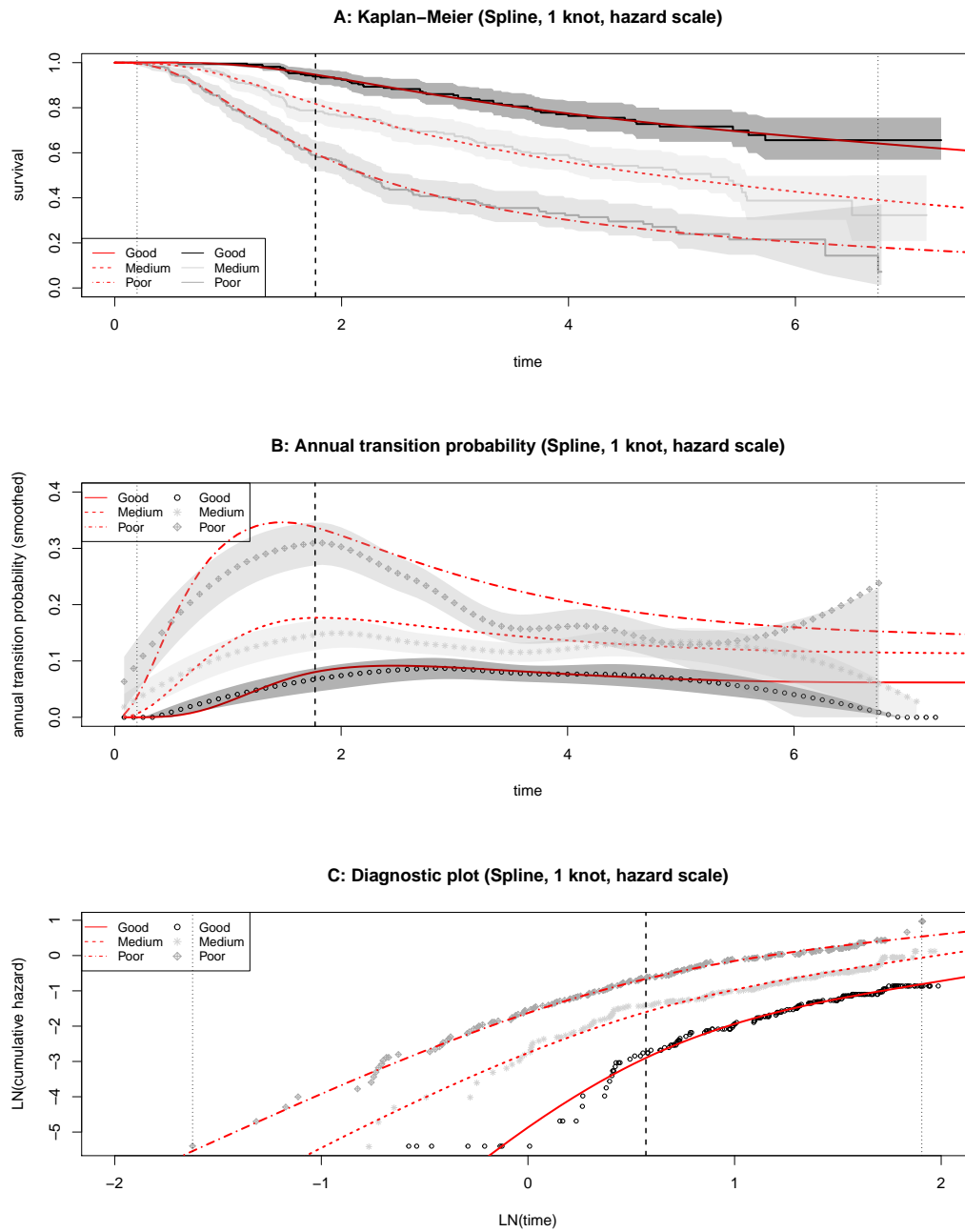
Spline 2 knots hazard

A: Kaplan–Meier (Spline, 2 knots, hazard scale)
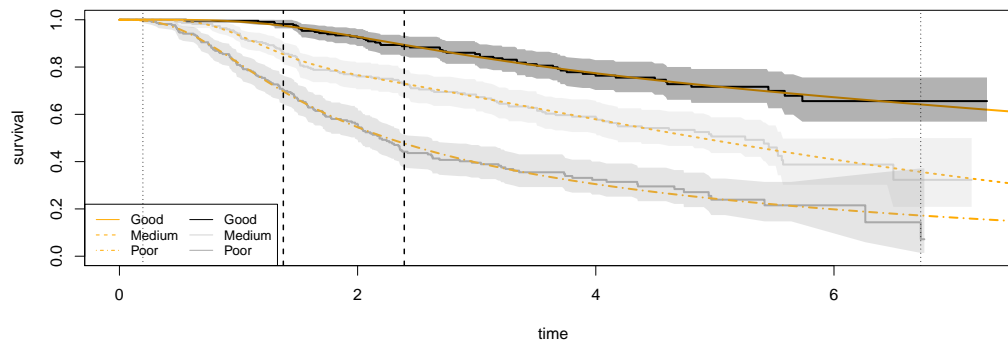
B: Annual transition probability (Spline, 2 knots, hazard scale)
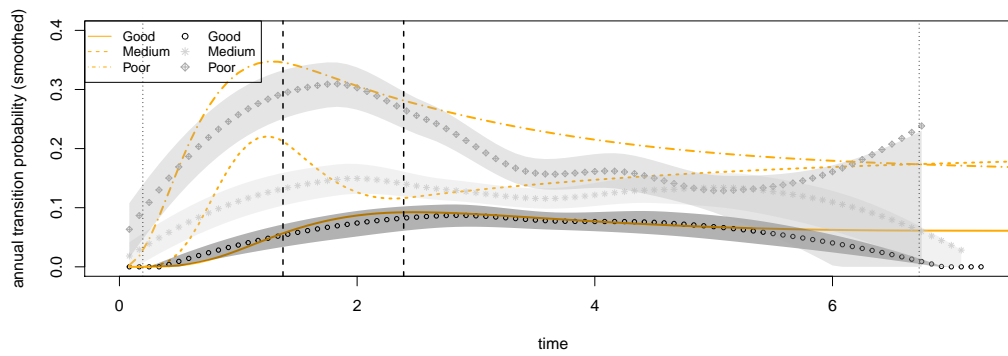
C: Diagnostic plot (Spline, 2 knots, hazard scale)
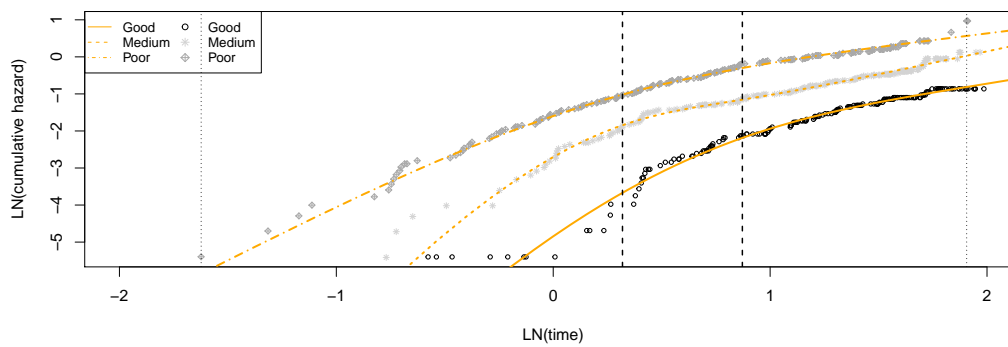
Spline 3 knots hazard

A: Kaplan–Meier (Spline, 3 knots, hazard scale)
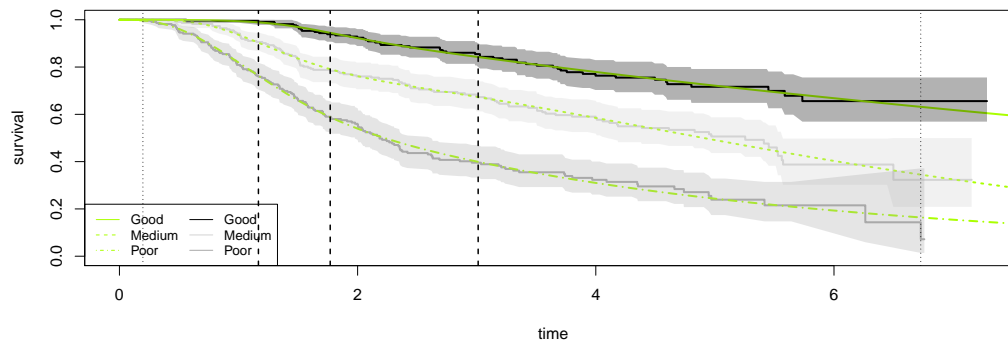
B: Annual transition probability (Spline, 3 knots, hazard scale)
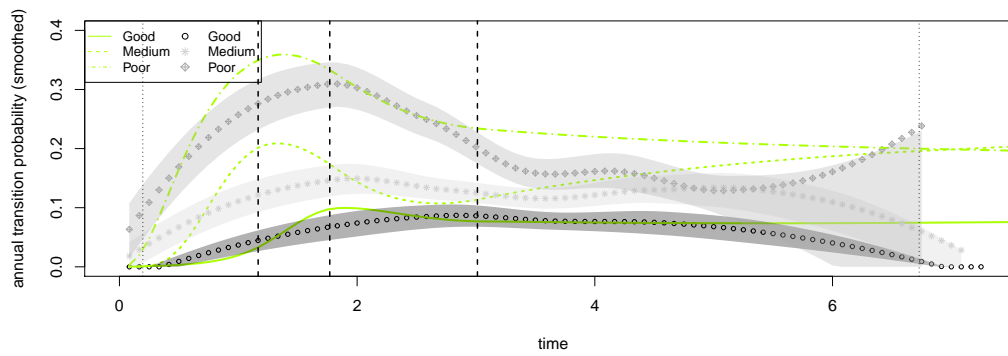
C: Diagnostic plot (Spline, 3 knots, hazard scale)
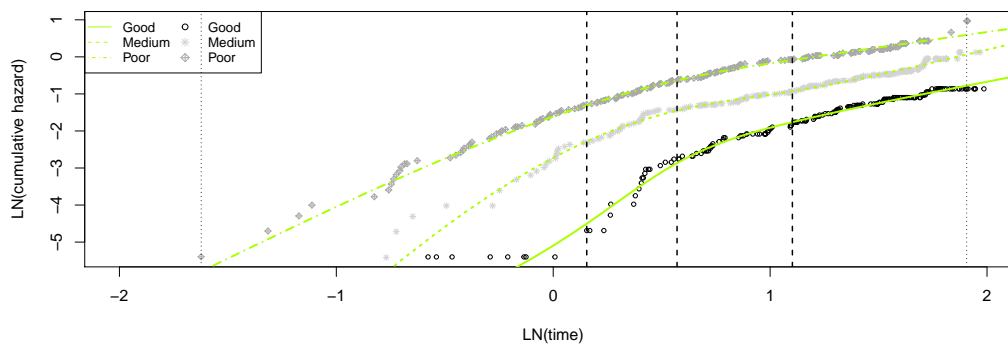
Spline 1 knot odds

A: Kaplan–Meier (Spline, 1 knot, odds scale)
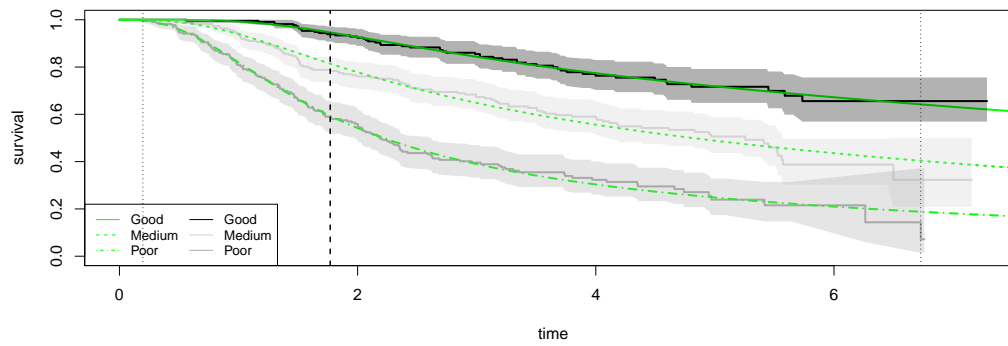
B: Annual transition probability (Spline, 1 knot, odds scale)
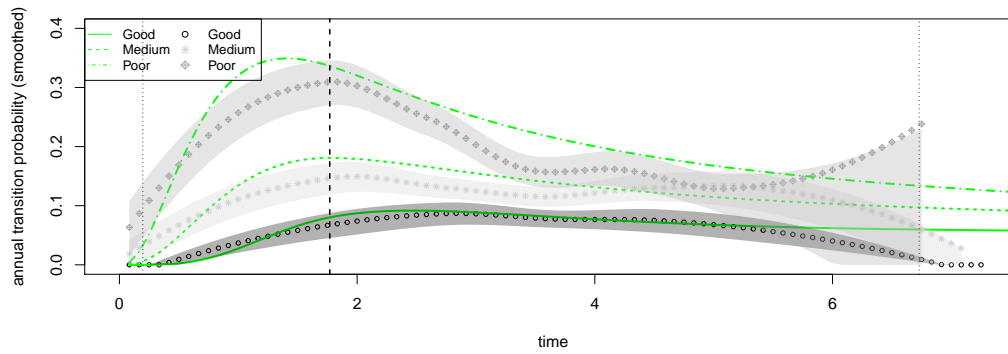
C: Diagnostic plot (Spline, 1 knot, odds scale)
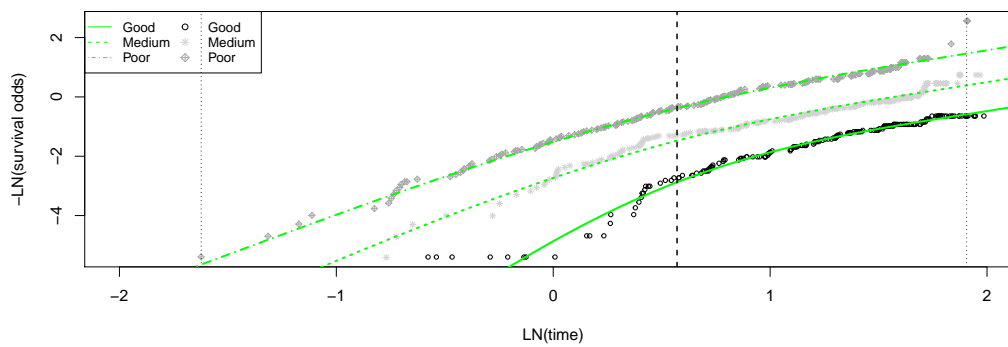
Spline 2 knots odds

A: Kaplan–Meier (Spline, 2 knots, odds scale)
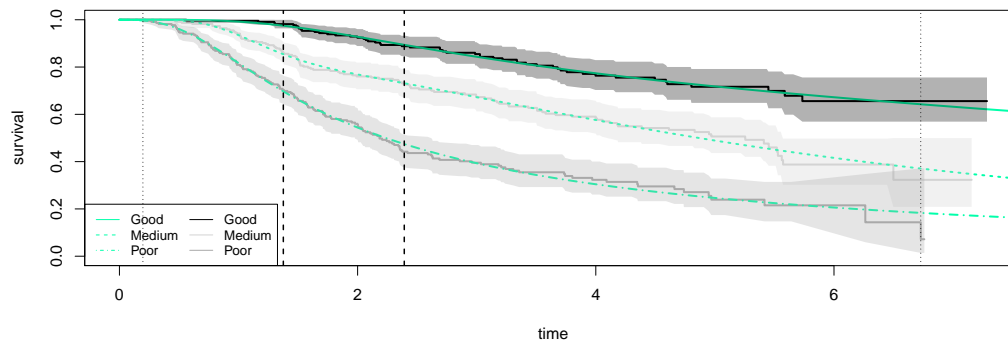
B: Annual transition probability (Spline, 2 knots, odds scale)
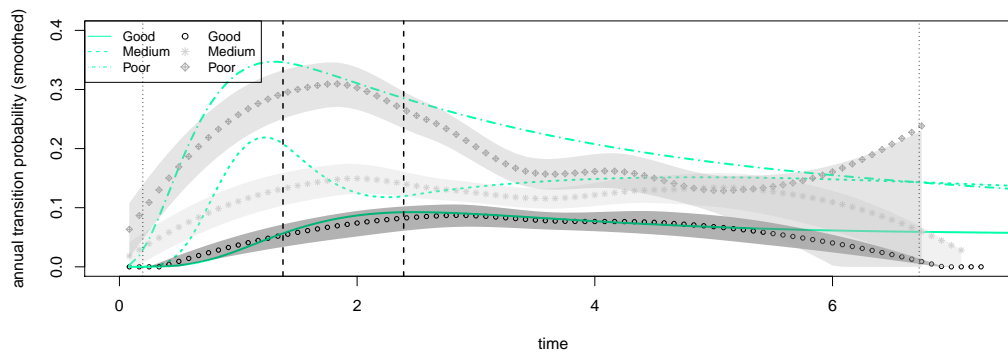
C: Diagnostic plot (Spline, 2 knots, odds scale)
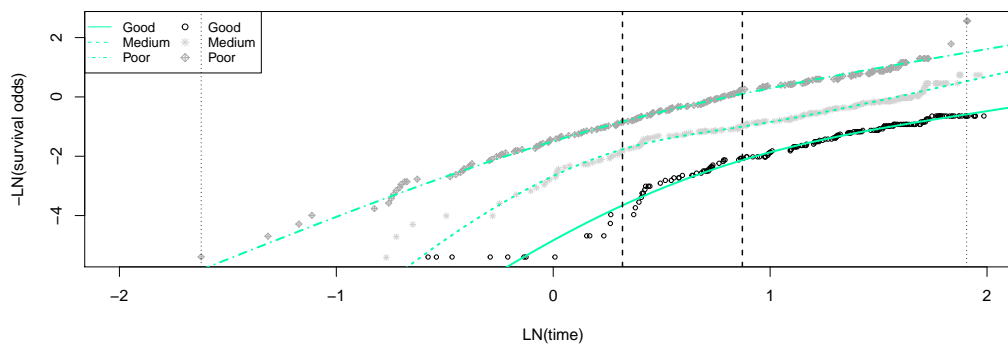
Spline 3 knots odds

A: Kaplan–Meier (Spline, 3 knots, odds scale)
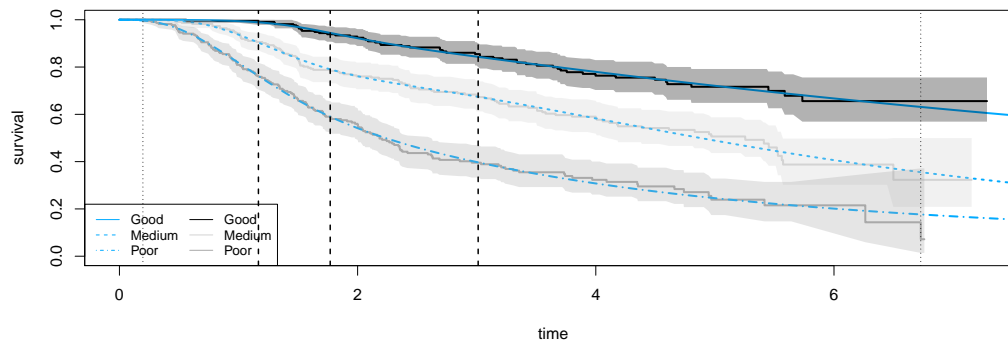
B: Annual transition probability (Spline, 3 knots, odds scale)
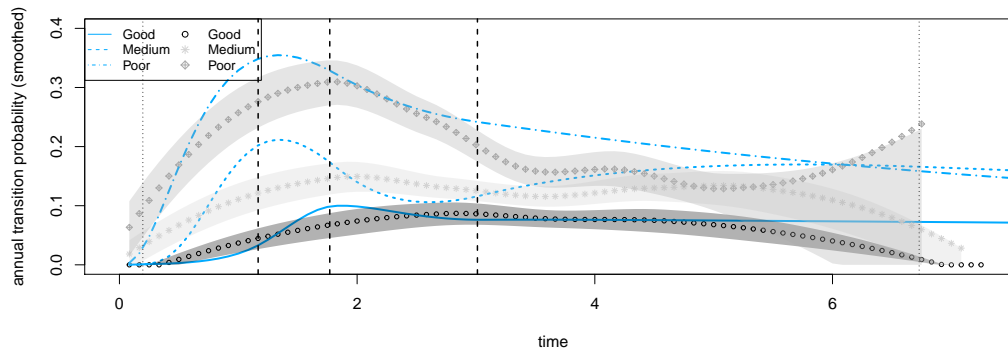
C: Diagnostic plot (Spline, 3 knots, odds scale)
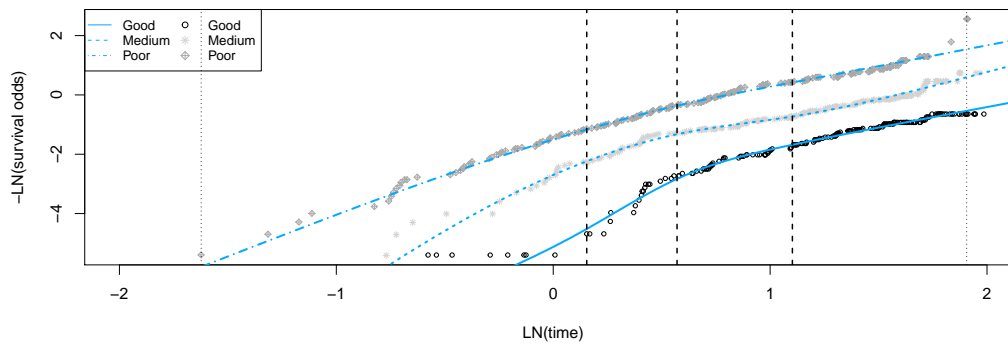
Spline 1 knot normal

A: Kaplan–Meier (Spline, 1 knot, normal scale)
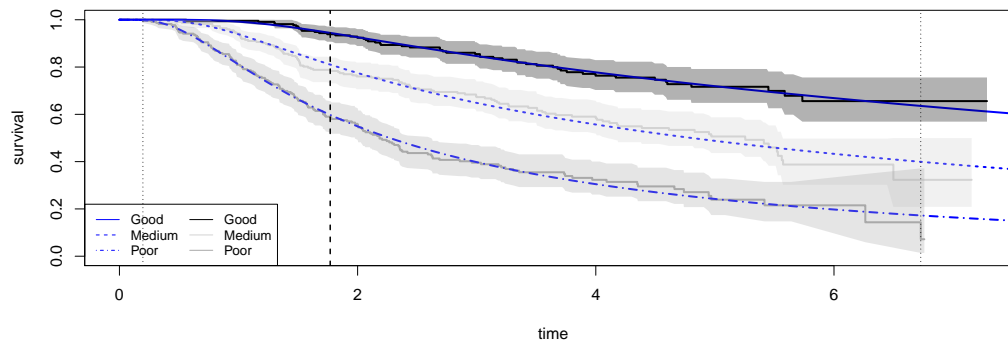
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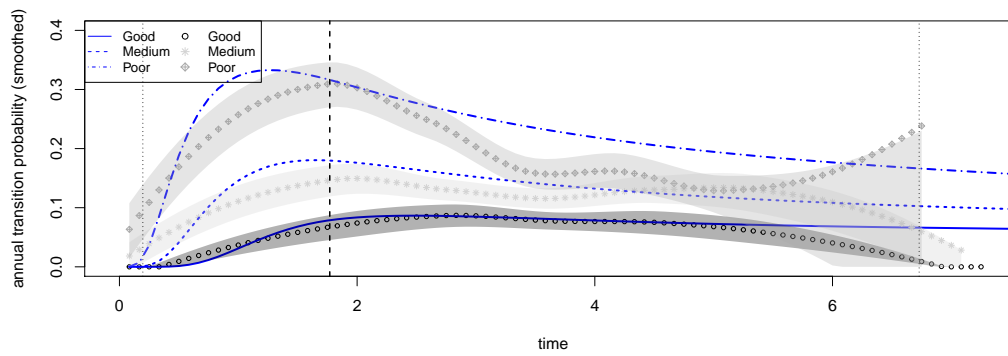
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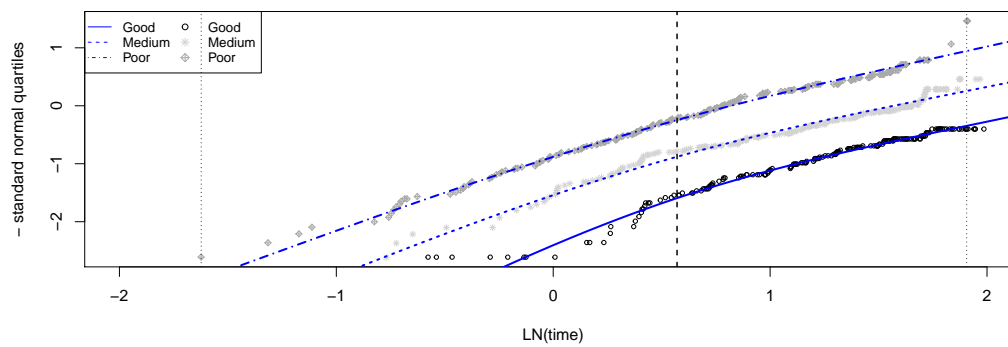
Spline 2 knots normal

A: Kaplan–Meier (Spline, 2 knots, normal scale)
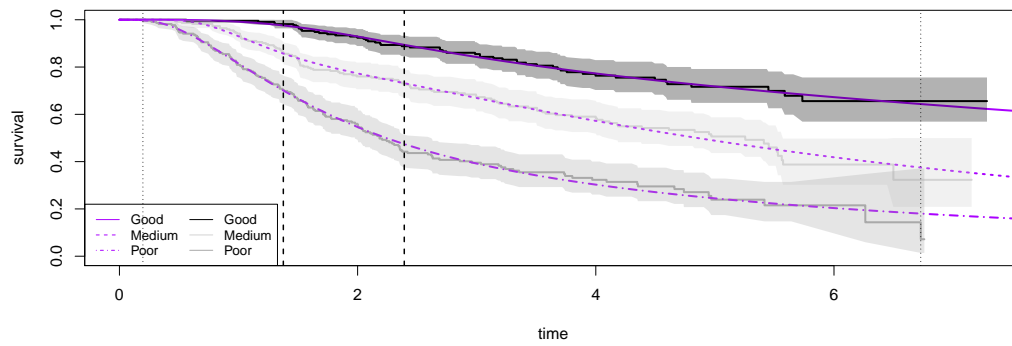
B: Annual transition probability (Spline, 2 knots, normal scale)
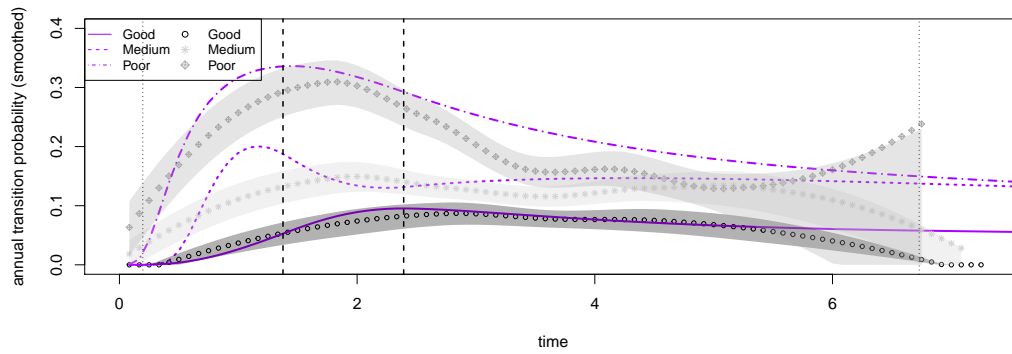
C: Diagnostic plot (Spline, 2 knots, normal scale)
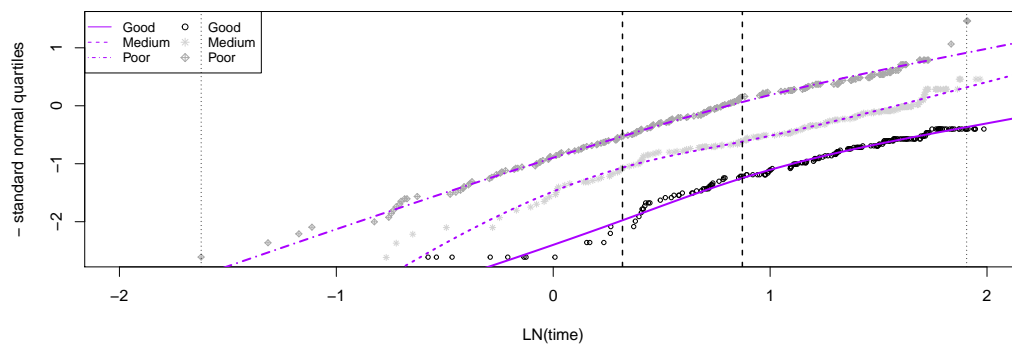
Spline 3 knots normal

A: Kaplan–Meier (Spline, 3 knots, normal scale)
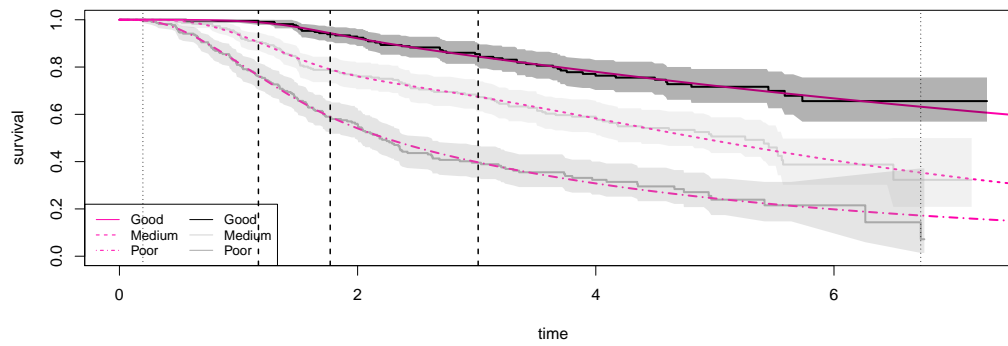
B: Annual transition probability (Spline, 3 knots, normal scale)
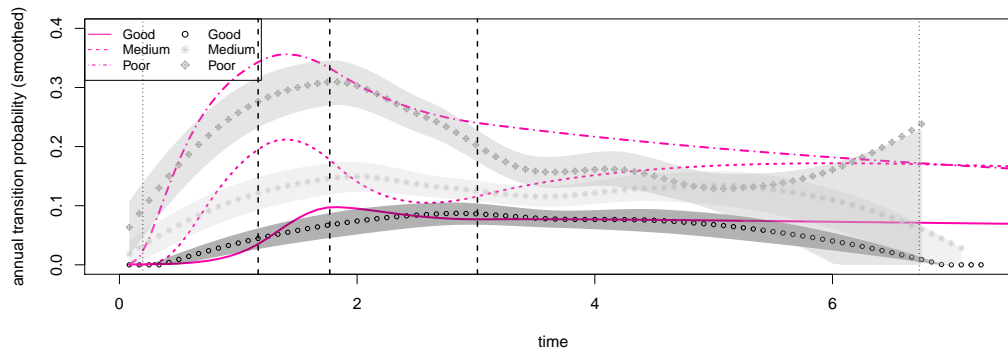
C: Diagnostic plot (Spline, 3 knots, normal scale)
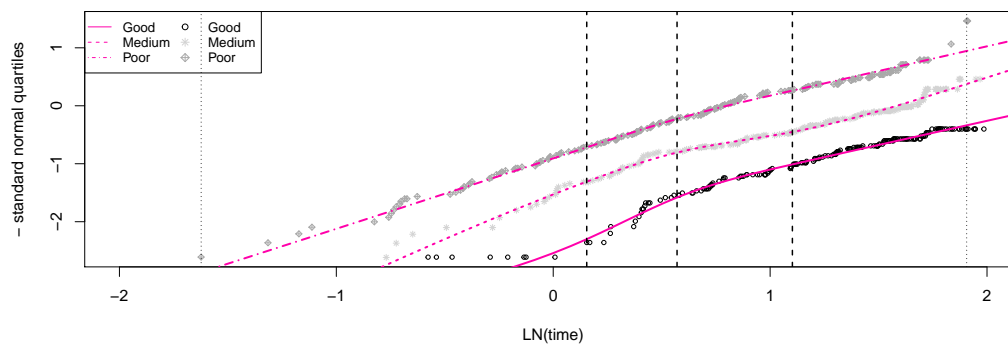
Parametric (non-)mixture cure models

If standard parametric models do not provide a satisfactory fit to the data based on previous observations, do cure models provide a more satisfactory fit to the data?

mixture cure models: S * (1 - theta) + theta * 1 (theta * 1 assumes that the cure fraction has 100% survival)
non-mixture cure models: exp((1-S) * log(theta))
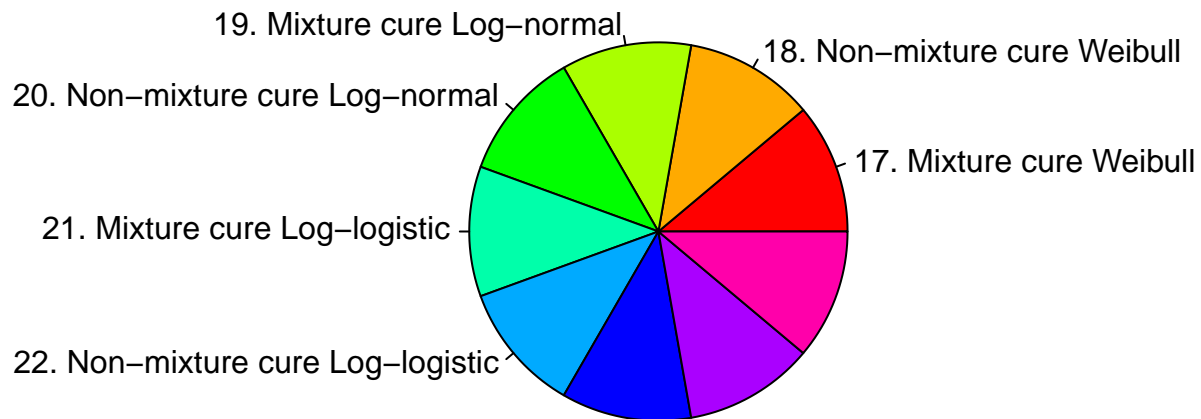
Model	AIC
7. Generalised Gamma	1589.049
4. Log-normal	1592.880
19. Mixture cure Log-normal	1593.762
20. Non-mixture cure Log-normal	1593.793
21. Mixture cure Log-logistic	1604.290
22. Non-mixture cure Log-logistic	1605.960
5. Log-logistic	1609.294
18. Non-mixture cure Weibull	1615.016
6. Gamma	1621.982
17. Mixture cure Weibull	1622.730
2. Weibull	1632.618
3. Gompertz	1660.954
1. Exponential	1668.212

Model	Cure fraction Good	Cure fraction Medium	Cure fraction Poor
17. Mixture cure Weibull	65.2% (30.9% - 17.9%)	57.1% (19.3% - 10.7%)	60.3% (23.4% - 13.6%)
18. Non-mixture cure Weibull	53.9% (15% - 10.2%)	35.1% (2.9% - 2.6%)	44.6% (7.3% - 5.6%)
19. Mixture cure Log-normal	75% (53.1% - 29.5%)	76.7% (65.8% - 35.3%)	74.2% (54.4% - 29.6%)
20. Non-mixture cure Log-normal	64.9% (29.6% - 16.8%)	56% (20.3% - 9.9%)	60.4% (25% - 15.5%)
21. Mixture cure Log-logistic	53.2% (12.9% - 9.1%)	32.6% (4.7% - 2.7%)	44.8% (9.7% - 8%)
22. Non-mixture cure Log-logistic	75.1% (54.5% - 28.8%)	77% (56.9% - 30.2%)	74.2% (51% - 27.9%)

Mixture cure Weibull

A: Kaplan–Meier (Weibull mixture cure)
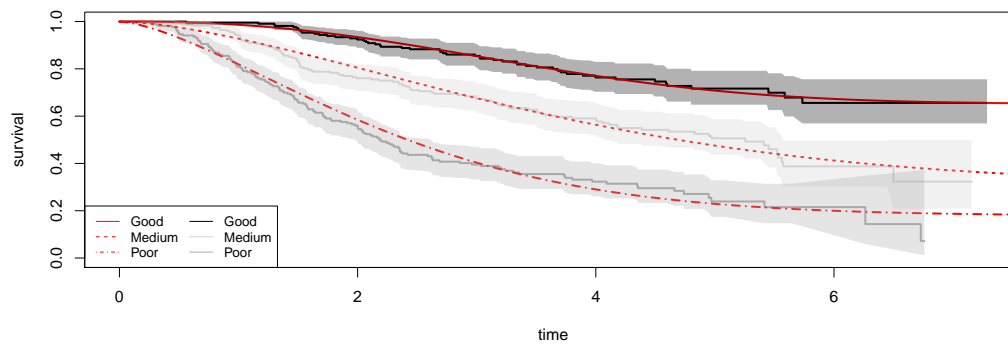
B: Annual transition probability (Weibull mixture cure)
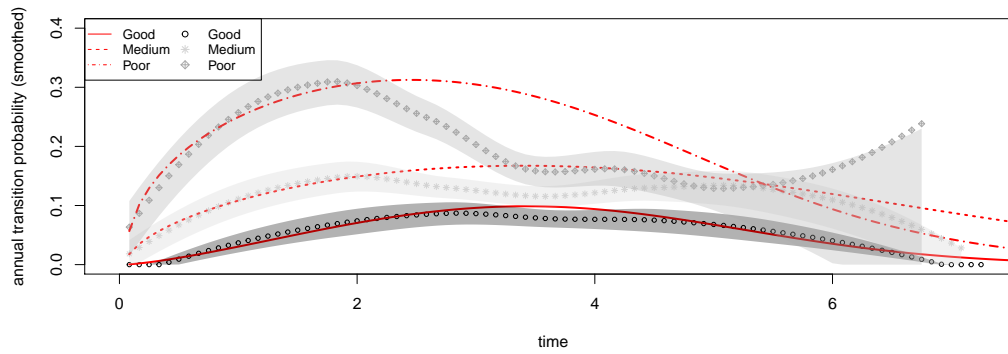
C: Diagnostic plot (Weibull mixture cure)
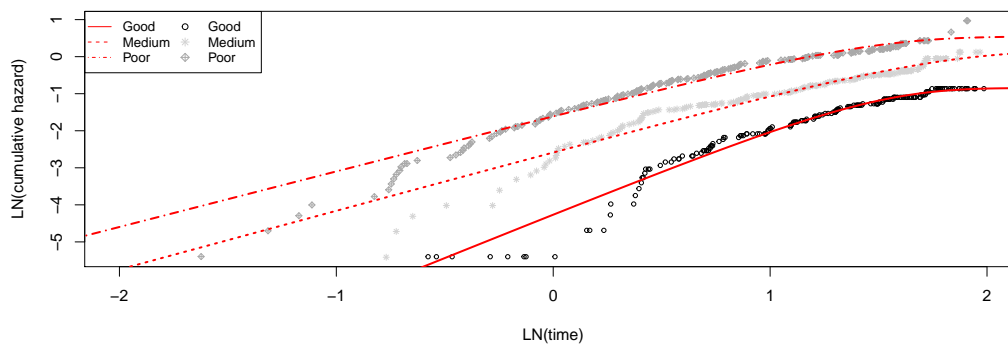
Non-mixture cure Weibull

A: Kaplan–Meier (Weibull non–mixture cure)
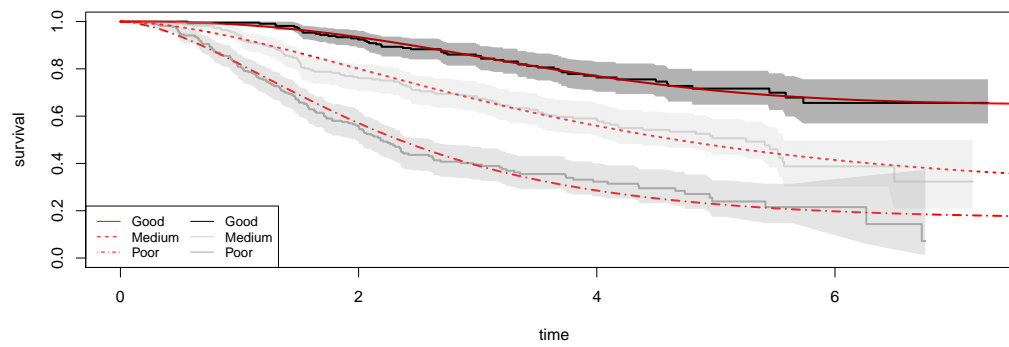
B: Annual transition probability (Weibull non–mixture cure)
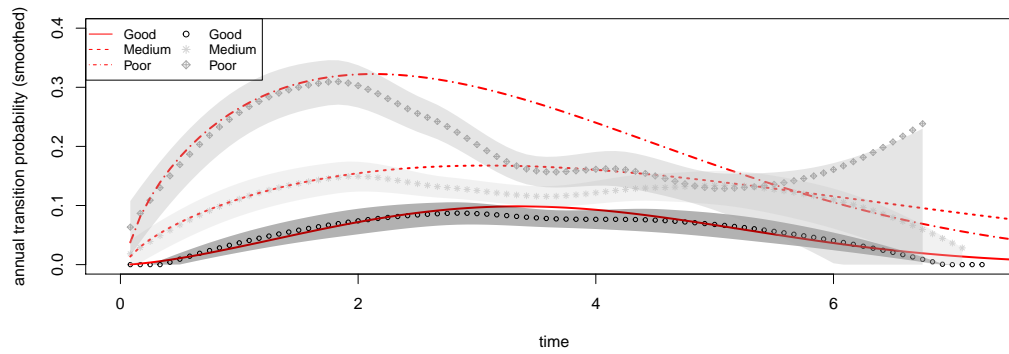
C: Diagnostic plot (Weibull non–mixture cure)
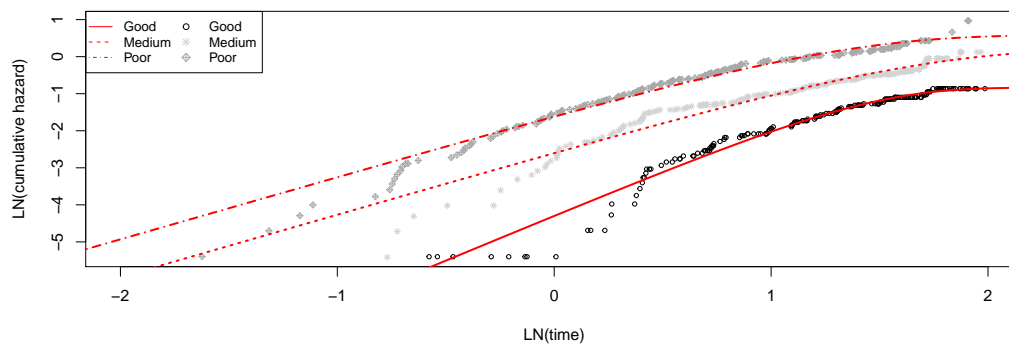
ADD OTHER 4 CURE models

Long-term extrapolation

Which model(s) is/are more appropriate/plausible for long-term extrapolation?

Are/is the selected model(s) plausible in comparison with general population mortality?

In this section, we present the estimated survival probabilities by through fitted parametric survival models for the period of time within and beyond data collection, i.e. the extrapolation. This is done by 1) plotting the survival curves (Figures A and B), 2) displaying the survival probabilities at multiple time points (first Table), 3) ploting conditional annual transition probabilities (Figures C and D), and providing the summary statistics of the estimated conditional transition probabilities (second Table). This information is provided for each group separately.

One way to assess the plausibility of the extrapolated survival probabilities is to compare the estimated survival probabilities at different time points with external data (e.g. observational data), and/ or to ask clinical experts about the plausibility of these extrapolations. Another way to check for plausibility is to compare the conditional transition probability with general population mortality rates (these can be obtained through national statistics). Parametric survival models providing conditional transition probabilities which are lower than the general population mortality rates may not be suitable because this would mean patients may have a lower probability of death than the general population values. Such finding require either to select an alternative model or to adjust the selected model for general population mortality rates.

Interpretation in this case: The conditional annual probabilities estimated by the two-knots spline-based model on the hazard scale was most consistent with general population mortality data of the Netherlands (although it might still require adjustment). Ideally, one would validate the plausibility of the long-term extrapolations of the two-knots spline-based model against external data.

Group Good

A: Kaplan−Meier (parametric curves)

Legend:
- 1. Exponential
- 2. Weibull
- 3. Gompertz
- 4. Log−normal
- 5. Log−logistic
- 6. Gamma
- 7. Generalised Gamma

B: Kaplan−Meier (spline curves)

Legend:
- 8. Spline 1 knot hazard
- 9. Spline 2 knots hazard
- 10. Spline 3 knots hazard
- 11. Spline 1 knot odds
- 12. Spline 2 knots odds
- 13. Spline 3 knots odds
- 14. Spline 1 knot normal
- 15. Spline 2 knots normal
- 16. Spline 3 knots normal

C: Kaplan−Meier (cure curves)

Legend:
- 17. Mixture cure Weibull
- 18. Non−mixture cure Weibull
- 19. Mixture cure Log−normal
- 20. Non−mixture cure Log−normal
- 21. Mixture cure Log−logistic
- 22. Non−mixture cure Log−logistic

Table 1: Survival probability at different time points

	T= 0	T= 1	T= 2	T= 3	T= 4	T= 5	T= 10	T= 15	T= 20	T= 25	T= 30	T= 35
1. Exponential	1	0.941	0.886	0.834	0.785	0.739	0.547	0.404	0.299	0.221	0.163	0.121
2. Weibull	1	0.978	0.932	0.870	0.797	0.719	0.345	0.122	0.033	0.007	0.001	0.000
3. Gompertz	1	0.962	0.917	0.863	0.801	0.729	0.280	0.015	0.000	0.000	0.000	0.000
4. Log-normal	1	0.986	0.933	0.861	0.785	0.713	0.441	0.287	0.196	0.139	0.102	0.076
5. Log-logistic	1	0.980	0.932	0.865	0.789	0.712	0.403	0.240	0.156	0.108	0.080	0.061
6. Gamma	1	0.982	0.935	0.869	0.793	0.714	0.367	0.165	0.069	0.027	0.011	0.004
7. Generalised Gamma	1	0.991	0.928	0.849	0.778	0.717	0.526	0.425	0.362	0.319	0.286	0.261
8. Spline 1 knot hazard	1	0.992	0.927	0.843	0.774	0.719	0.521	0.381	0.279	0.205	0.151	0.111
9. Spline 2 knots hazard	1	0.992	0.928	0.843	0.774	0.719	0.523	0.384	0.283	0.210	0.156	0.116
10. Spline 3 knots hazard	1	0.994	0.922	0.843	0.779	0.721	0.486	0.319	0.205	0.130	0.081	0.050
11. Spline 1 knot odds	1	0.992	0.927	0.843	0.774	0.718	0.532	0.415	0.338	0.283	0.242	0.211
12. Spline 2 knots odds	1	0.992	0.928	0.843	0.774	0.718	0.533	0.418	0.340	0.285	0.245	0.213
13. Spline 3 knots odds	1	0.994	0.922	0.844	0.780	0.721	0.498	0.363	0.277	0.220	0.180	0.151
14. Spline 1 knot normal	1	0.992	0.926	0.847	0.778	0.719	0.515	0.391	0.308	0.250	0.207	0.174
15. Spline 2 knots normal	1	0.992	0.929	0.842	0.773	0.718	0.538	0.426	0.350	0.295	0.253	0.220
16. Spline 3 knots normal	1	0.994	0.921	0.845	0.780	0.721	0.503	0.371	0.285	0.225	0.182	0.150
17. Mixture cure Weibull	1	0.986	0.934	0.853	0.770	0.708	0.652	0.652	0.652	0.652	0.652	0.652
18. Non-mixture cure Weibull	1	0.987	0.934	0.852	0.770	0.708	0.649	0.649	0.649	0.649	0.649	0.649
19. Mixture cure Log-normal	1	0.991	0.930	0.845	0.771	0.715	0.600	0.578	0.573	0.572	0.571	0.571
20. Non-mixture cure Log-normal	1	0.991	0.930	0.845	0.771	0.715	0.597	0.571	0.564	0.561	0.561	0.560
21. Mixture cure Log-logistic	1	0.989	0.933	0.846	0.767	0.712	0.624	0.610	0.607	0.605	0.604	0.604
22. Non-mixture cure Log-logistic	1	0.989	0.933	0.846	0.767	0.712	0.624	0.611	0.607	0.606	0.605	0.605

D: Annual transition probability (parametric curves)
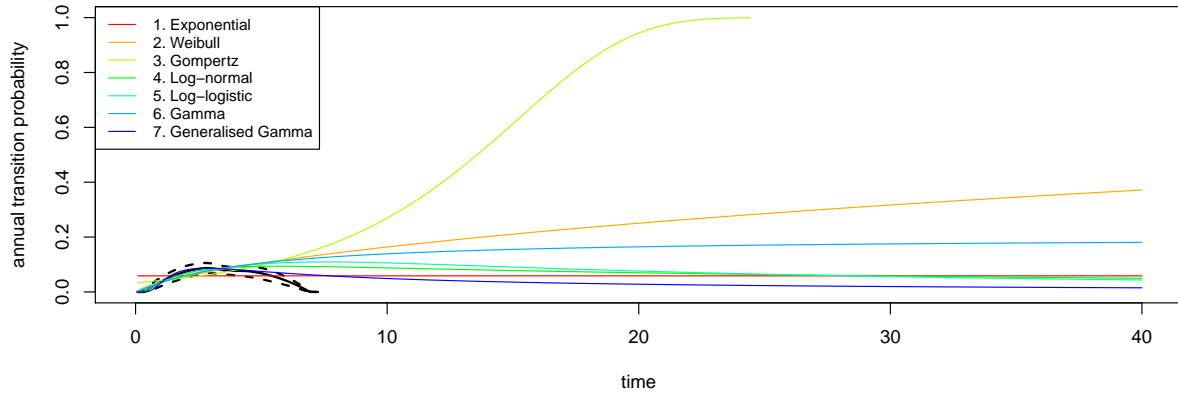
E: Annual transition probability (spline curves)
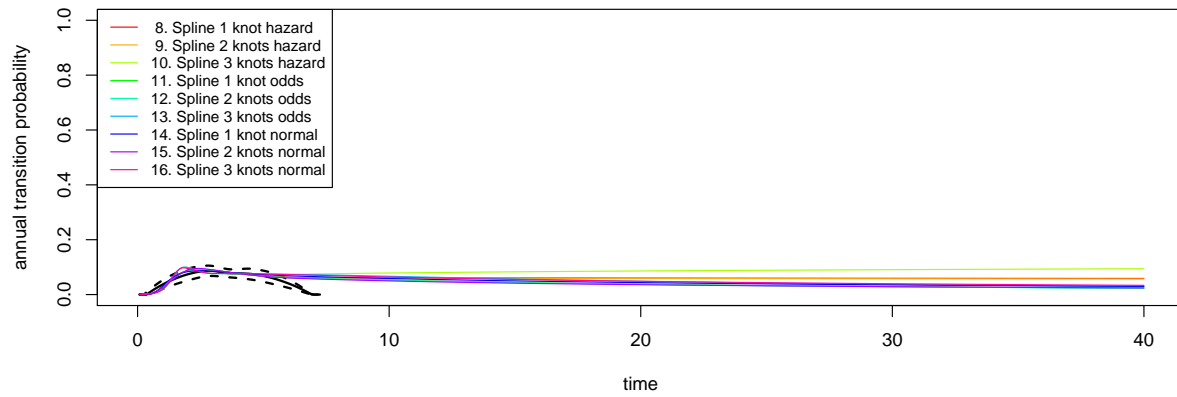
F: Annual transition probability (cure curves)
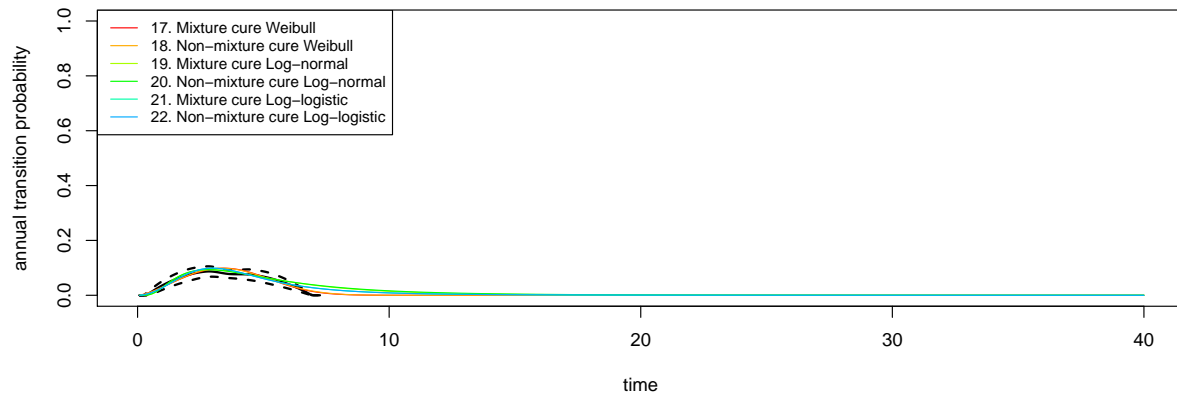
G: Hazard function (parametric curves)
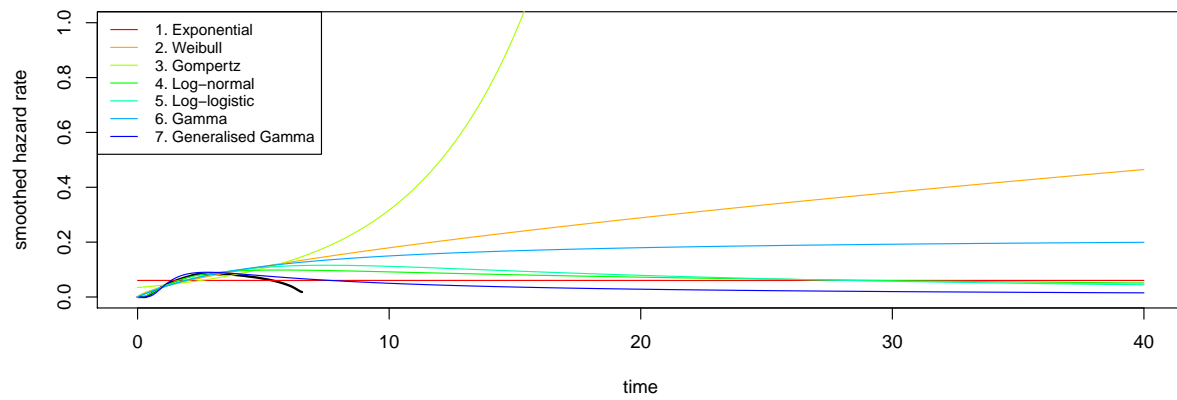
Table 2: Summary statistics of annual transition probabilities

	Min	Q1	Median	Q3	Max
1. Exponential	0.0585969	0.0585969	0.0585969	0.0585969	0.0585969
2. Weibull	0.0039603	0.1641779	0.2507544	0.3170901	0.3714738
3. Gompertz	0.0342601	0.1256322	0.4037134	0.8634656	1.0000000
4. Log-normal	0.0000121	0.0563972	0.0670524	0.0819079	0.0936091
5. Log-logistic	0.0022936	0.0533146	0.0700441	0.0935993	0.1092616
6. Gamma	0.0014181	0.1390361	0.1644882	0.1750195	0.1807519
7. Generalised Gamma	0.0000000	0.0191123	0.0269247	0.0452063	0.0862100
8. Spline 1 knot hazard	0.0000002	0.0592140	0.0598953	0.0610195	0.0916043
9. Spline 2 knots hazard	0.0000002	0.0576502	0.0585313	0.0599923	0.0923962
10. Spline 3 knots hazard	0.0003310	0.0798260	0.0865334	0.0909988	0.0996328
11. Spline 1 knot odds	0.0000002	0.0281269	0.0363823	0.0502992	0.0917044
12. Spline 2 knots odds	0.0000002	0.0278516	0.0359503	0.0497462	0.0924439
13. Spline 3 knots odds	0.0003253	0.0358147	0.0466608	0.0638606	0.0999099
14. Spline 1 knot normal	0.0000000	0.0345970	0.0424046	0.0560095	0.0865141
15. Spline 2 knots normal	0.0000006	0.0281480	0.0348987	0.0473455	0.0953359
16. Spline 3 knots normal	0.0007793	0.0386308	0.0470013	0.0611992	0.0975846
17. Mixture cure Weibull	0.0000000	0.0000000	0.0000000	0.0001031	0.0987558
18. Non-mixture cure Weibull	0.0000000	0.0000000	0.0000000	0.0001575	0.0985854
19. Mixture cure Log-normal	0.0000000	0.0000929	0.0008027	0.0116086	0.0931907
20. Non-mixture cure Log-normal	0.0000000	0.0001962	0.0012968	0.0132969	0.0934968
21. Mixture cure Log-logistic	0.0000516	0.0001512	0.0006917	0.0075147	0.0986522
22. Non-mixture cure Log-logistic	0.0000517	0.0001509	0.0006881	0.0074554	0.0987027

H: Hazard function (spline curves)

I: Hazard function (cure curves)

Group Medium

A: Kaplan−Meier (parametric curves)

Legend:
- 1. Exponential
- 2. Weibull
- 3. Gompertz
- 4. Log−normal
- 5. Log−logistic
- 6. Gamma
- 7. Generalised Gamma

B: Kaplan−Meier (spline curves)

Legend:
- 8. Spline 1 knot hazard
- 9. Spline 2 knots hazard
- 10. Spline 3 knots hazard
- 11. Spline 1 knot odds
- 12. Spline 2 knots odds
- 13. Spline 3 knots odds
- 14. Spline 1 knot normal
- 15. Spline 2 knots normal
- 16. Spline 3 knots normal

C: Kaplan−Meier (cure curves)

Legend:
- 17. Mixture cure Weibull
- 18. Non−mixture cure Weibull
- 19. Mixture cure Log−normal
- 20. Non−mixture cure Log−normal
- 21. Mixture cure Log−logistic
- 22. Non−mixture cure Log−logistic

Table 3: Survival probability at different time points

|	T= 0	T= 1	T= 2	T= 3	T= 4	T= 5	T= 10	T= 15	T= 20	T= 25	T= 30	T= 35
1. Exponential	1	0.872	0.761	0.663	0.578	0.505	0.255	0.128	0.065	0.033	0.016	0.008
2. Weibull	1	0.923	0.811	0.693	0.578	0.474	0.141	0.032	0.006	0.001	0.000	0.000
3. Gompertz	1	0.898	0.794	0.689	0.586	0.486	0.117	0.007	0.000	0.000	0.000	0.000
4. Log-normal	1	0.935	0.797	0.668	0.560	0.473	0.228	0.126	0.077	0.050	0.034	0.024
5. Log-logistic	1	0.927	0.801	0.673	0.561	0.468	0.218	0.124	0.081	0.057	0.043	0.034
6. Gamma	1	0.930	0.813	0.689	0.572	0.469	0.154	0.045	0.013	0.003	0.001	0.000
7. Generalised Gamma	1	0.937	0.774	0.648	0.556	0.488	0.310	0.232	0.187	0.158	0.138	0.122
8. Spline 1 knot hazard	1	0.939	0.782	0.652	0.558	0.486	0.265	0.150	0.087	0.052	0.031	0.019
9. Spline 2 knots hazard	1	0.935	0.766	0.673	0.579	0.490	0.184	0.061	0.018	0.005	0.001	0.000
10. Spline 3 knots hazard	1	0.936	0.761	0.674	0.585	0.491	0.159	0.040	0.008	0.001	0.000	0.000
11. Spline 1 knot odds	1	0.939	0.778	0.648	0.556	0.489	0.301	0.213	0.162	0.131	0.109	0.093
12. Spline 2 knots odds	1	0.935	0.769	0.673	0.576	0.489	0.235	0.136	0.089	0.063	0.048	0.037
13. Spline 3 knots odds	1	0.937	0.761	0.675	0.583	0.489	0.207	0.108	0.066	0.044	0.032	0.024
14. Spline 1 knot normal	1	0.938	0.775	0.648	0.557	0.488	0.290	0.195	0.141	0.107	0.084	0.067
15. Spline 2 knots normal	1	0.930	0.773	0.669	0.572	0.489	0.240	0.135	0.083	0.054	0.037	0.026
16. Spline 3 knots normal	1	0.937	0.761	0.675	0.583	0.489	0.198	0.091	0.047	0.026	0.015	0.010
17. Mixture cure Weibull	1	0.928	0.804	0.676	0.563	0.475	0.319	0.310	0.309	0.309	0.309	0.309
18. Non-mixture cure Weibull	1	0.929	0.801	0.670	0.559	0.475	0.314	0.297	0.296	0.296	0.296	0.296
19. Mixture cure Log-normal	1	0.936	0.790	0.658	0.556	0.479	0.295	0.238	0.215	0.205	0.200	0.197
20. Non-mixture cure Log-normal	1	0.937	0.787	0.654	0.555	0.482	0.315	0.261	0.237	0.225	0.218	0.214
21. Mixture cure Log-logistic	1	0.931	0.793	0.658	0.553	0.477	0.318	0.275	0.259	0.250	0.246	0.243
22. Non-mixture cure Log-logistic	1	0.931	0.793	0.659	0.554	0.479	0.327	0.287	0.272	0.265	0.261	0.258

D: Annual transition probability (parametric curves)
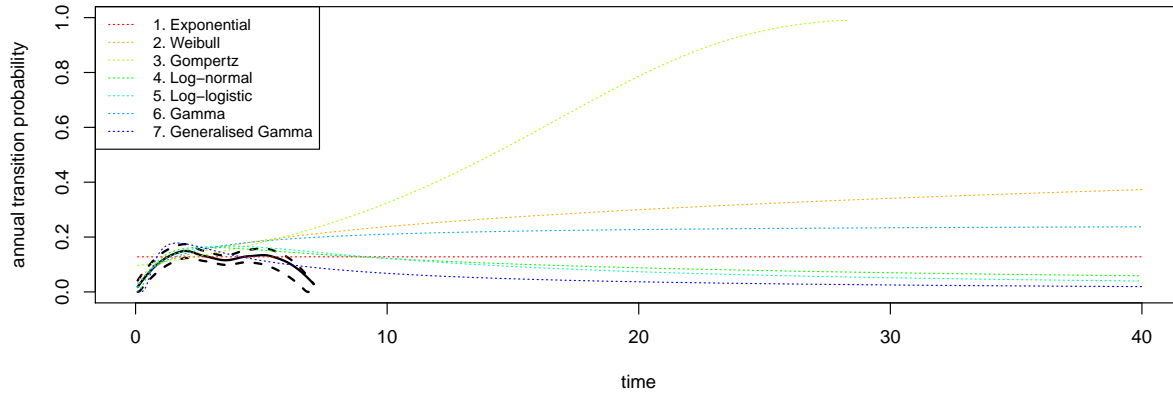
E: Annual transition probability (spline curves)
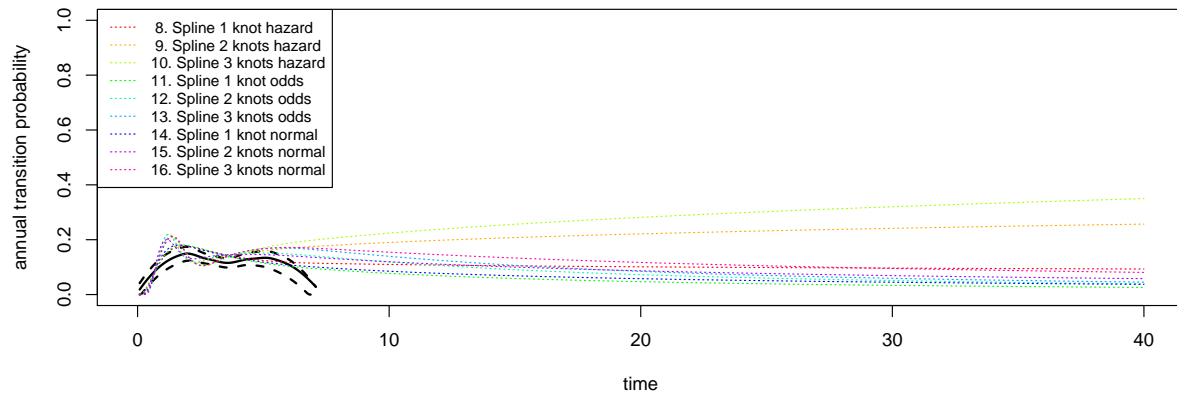
F: Annual transition probability (cure curves)
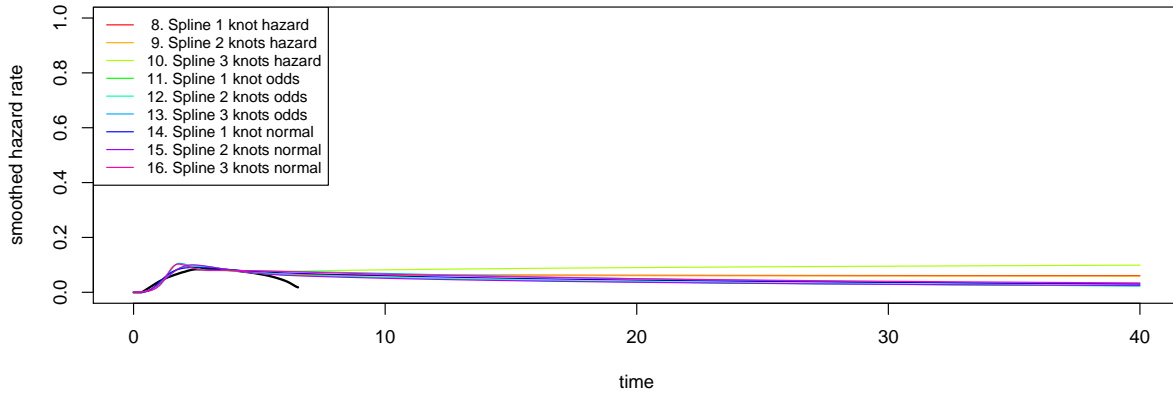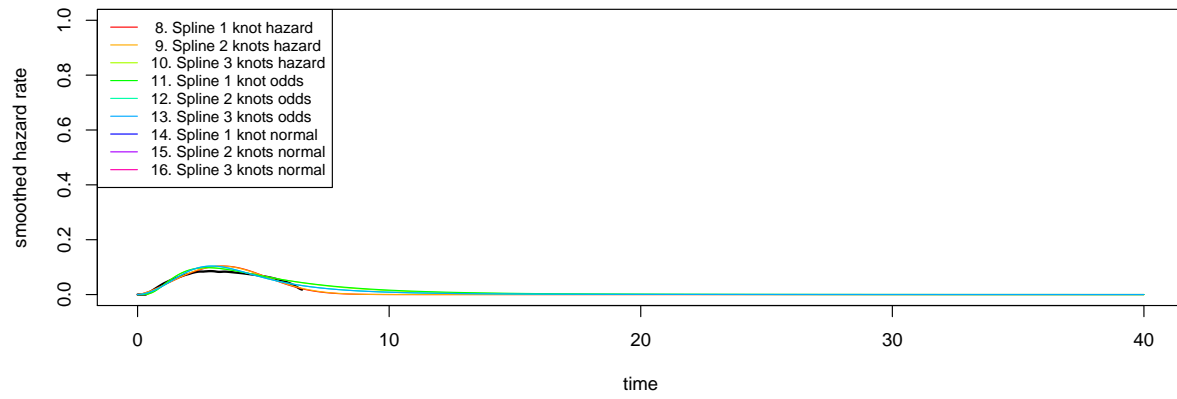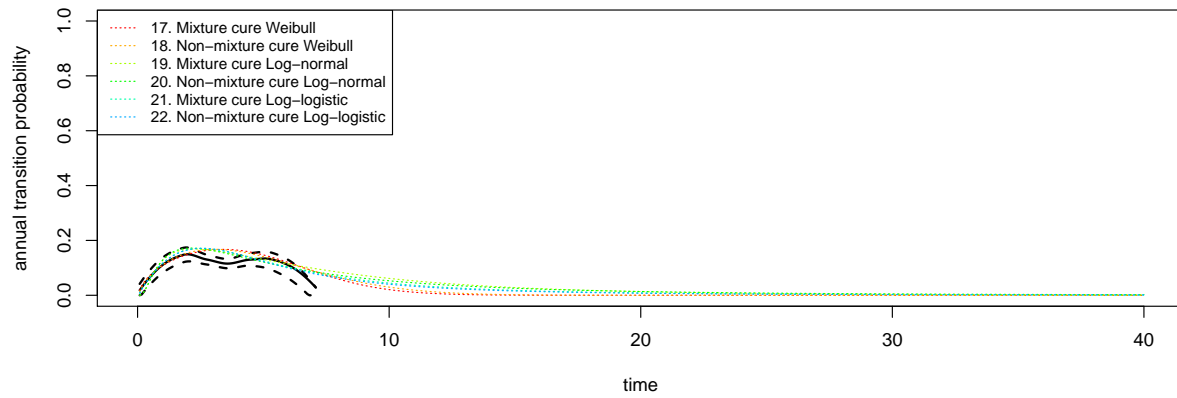

G: Hazard function (parametric curves)
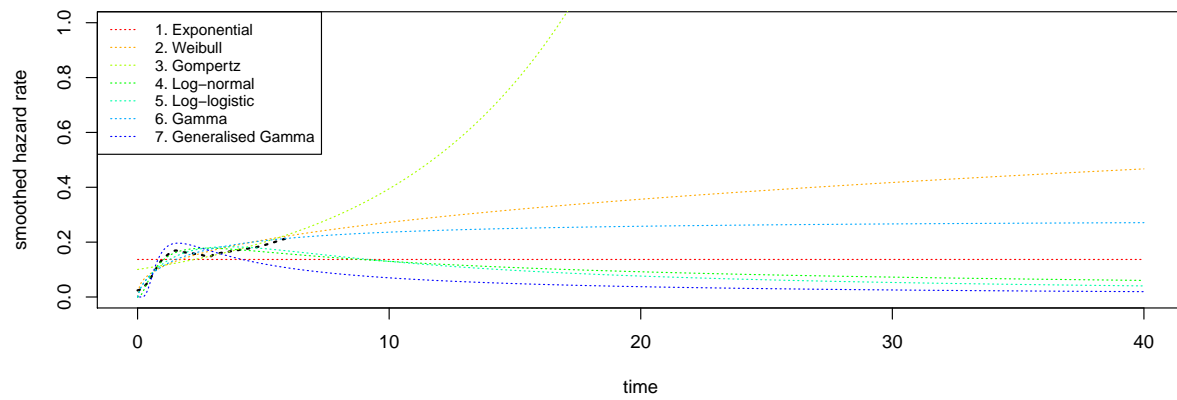
Table 4: Summary statistics of annual transition probabilities

	Min	Q1	Median	Q3	Max
1. Exponential	0.1278820	0.1278820	0.1278820	0.1278820	0.1278820
2. Weibull	0.0298491	0.2382194	0.2998675	0.3413164	0.3730304
3. Gompertz	0.0960264	0.2326209	0.5026105	0.8415103	1.0000000
4. Log-normal	0.0004751	0.0692201	0.0864990	0.1175437	0.1630482
5. Log-logistic	0.0150627	0.0512119	0.0722192	0.1148301	0.1673124
6. Gamma	0.0159374	0.2105278	0.2273428	0.2338793	0.2373538
7. Generalised Gamma	0.0000000	0.0249765	0.0361491	0.0643696	0.1783037
8. Spline 1 knot hazard	0.0005533	0.0961200	0.1007177	0.1087714	0.1767370
9. Spline 2 knots hazard	0.0000006	0.1921569	0.2213494	0.2415978	0.2568265
10. Spline 3 knots hazard	0.0000040	0.2243467	0.2816554	0.3202621	0.3498686
11. Spline 1 knot odds	0.0004610	0.0331955	0.0461415	0.0743721	0.1809477
12. Spline 2 knots odds	0.0000004	0.0500917	0.0706148	0.1135216	0.2192447
13. Spline 3 knots odds	0.0000052	0.0581364	0.0821832	0.1255993	0.2117141
14. Spline 1 knot normal	0.0000012	0.0444894	0.0569700	0.0823605	0.1804334
15. Spline 2 knots normal	0.0000000	0.0682231	0.0852159	0.1164045	0.2005479
16. Spline 3 knots normal	0.0000001	0.0939627	0.1132858	0.1426801	0.2122248
17. Mixture cure Weibull	0.0000000	0.0000000	0.0000059	0.0191609	0.1672892
18. Non-mixture cure Weibull	0.0000000	0.0000000	0.0000548	0.0281639	0.1675628
19. Mixture cure Log-normal	0.0001478	0.0035974	0.0128314	0.0569406	0.1684663
20. Non-mixture cure Log-normal	0.0001962	0.0048679	0.0133317	0.0491721	0.1721086
21. Mixture cure Log-logistic	0.0012991	0.0028998	0.0085638	0.0419015	0.1712400
22. Non-mixture cure Log-logistic	0.0010967	0.0024492	0.0073855	0.0377612	0.1712106

H: Hazard function (spline curves)

I: Hazard function (spline curves)

Legend:
- 17. Mixture cure Weibull
- 18. Non−mixture cure Weibull
- 19. Mixture cure Log−normal
- 20. Non−mixture cure Log−normal
- 21. Mixture cure Log−logistic
- 22. Non−mixture cure Log−logistic

smoothed hazard rate
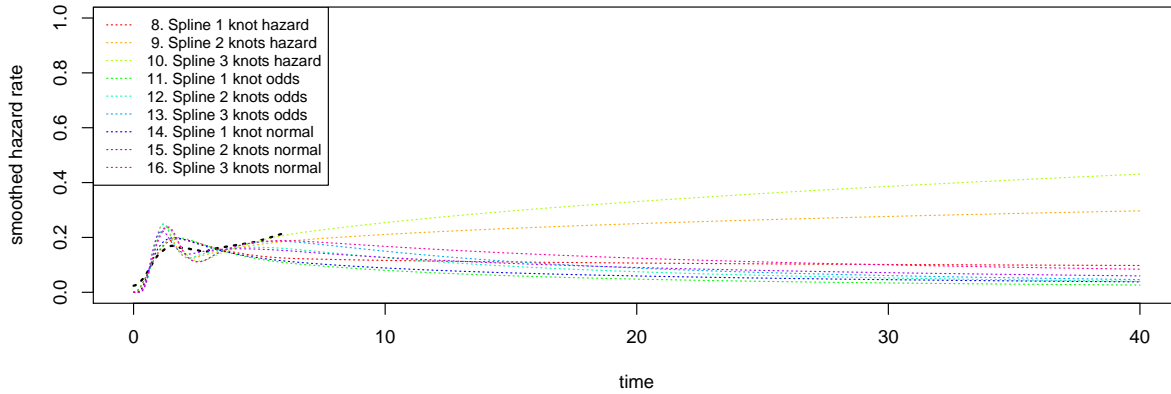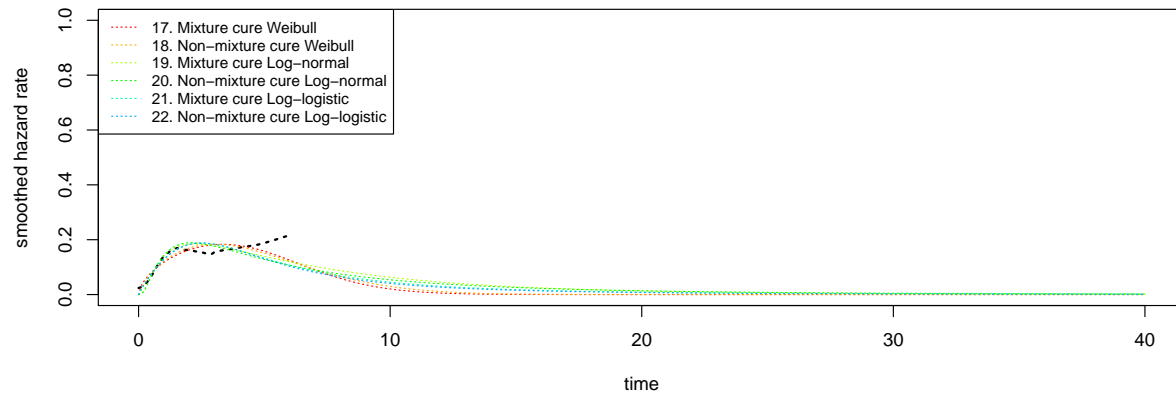
time

Group Poor

A: Kaplan−Meier (parametric curves)

Legend:
- 1. Exponential
- 2. Weibull
- 3. Gompertz
- 4. Log−normal
- 5. Log−logistic
- 6. Gamma
- 7. Generalised Gamma

B: Kaplan−Meier (spline curves)

Legend:
- 8. Spline 1 knot hazard
- 9. Spline 2 knots hazard
- 10. Spline 3 knots hazard
- 11. Spline 1 knot odds
- 12. Spline 2 knots odds
- 13. Spline 3 knots odds
- 14. Spline 1 knot normal
- 15. Spline 2 knots normal
- 16. Spline 3 knots normal

c: Kaplan−Meier (cure curves)

Legend:
- 17. Mixture cure Weibull
- 18. Non−mixture cure Weibull
- 19. Mixture cure Log−normal
- 20. Non−mixture cure Log−normal
- 21. Mixture cure Log−logistic
- 22. Non−mixture cure Log−logistic

Table 5: Survival probability at different time points

	T= 0	T= 1	T= 2	T= 3	T= 4	T= 5	T= 10	T= 15	T= 20	T= 25	T= 30	T= 35
1. Exponential	1	0.755	0.570	0.430	0.325	0.245	0.060	0.015	0.004	0.001	0.000	0.000
2. Weibull	1	0.817	0.608	0.430	0.292	0.193	0.017	0.001	0.000	0.000	0.000	0.000
3. Gompertz	1	0.776	0.588	0.436	0.315	0.221	0.022	0.001	0.000	0.000	0.000	0.000
4. Log-normal	1	0.820	0.572	0.401	0.289	0.214	0.063	0.025	0.012	0.006	0.004	0.002
5. Log-logistic	1	0.819	0.568	0.389	0.275	0.203	0.069	0.034	0.021	0.014	0.010	0.008
6. Gamma	1	0.829	0.605	0.420	0.283	0.187	0.020	0.002	0.000	0.000	0.000	0.000
7. Generalised Gamma	1	0.810	0.555	0.399	0.302	0.237	0.100	0.057	0.037	0.026	0.019	0.015
8. Spline 1 knot hazard	1	0.822	0.545	0.390	0.301	0.244	0.109	0.056	0.031	0.018	0.011	0.007
9. Spline 2 knots hazard	1	0.817	0.546	0.396	0.305	0.243	0.096	0.043	0.021	0.010	0.005	0.003
10. Spline 3 knots hazard	1	0.819	0.540	0.400	0.310	0.243	0.081	0.030	0.012	0.005	0.002	0.001
11. Spline 1 knot odds	1	0.820	0.542	0.390	0.303	0.248	0.127	0.082	0.060	0.047	0.038	0.032
12. Spline 2 knots odds	1	0.817	0.544	0.393	0.304	0.246	0.120	0.075	0.054	0.041	0.033	0.027
13. Spline 3 knots odds	1	0.818	0.542	0.398	0.308	0.246	0.110	0.065	0.044	0.033	0.026	0.021
14. Spline 1 knot normal	1	0.811	0.549	0.398	0.305	0.242	0.102	0.054	0.033	0.021	0.015	0.011
15. Spline 2 knots normal	1	0.815	0.546	0.392	0.303	0.245	0.113	0.065	0.042	0.029	0.021	0.016
16. Spline 3 knots normal	1	0.818	0.541	0.398	0.308	0.244	0.100	0.051	0.030	0.019	0.013	0.009
17. Mixture cure Weibull	1	0.819	0.585	0.403	0.290	0.229	0.179	0.179	0.179	0.179	0.179	0.179
18. Non-mixture cure Weibull	1	0.820	0.570	0.391	0.285	0.228	0.169	0.168	0.168	0.168	0.168	0.168
19. Mixture cure Log-normal	1	0.818	0.558	0.394	0.295	0.235	0.134	0.116	0.111	0.109	0.108	0.108
20. Non-mixture cure Log-normal	1	0.818	0.551	0.390	0.297	0.241	0.143	0.118	0.109	0.105	0.103	0.101
21. Mixture cure Log-logistic	1	0.822	0.549	0.381	0.290	0.240	0.163	0.148	0.143	0.140	0.139	0.138
22. Non-mixture cure Log-logistic	1	0.823	0.549	0.380	0.293	0.246	0.178	0.165	0.161	0.158	0.157	0.157

D: Annual transition probability (parametric curves)
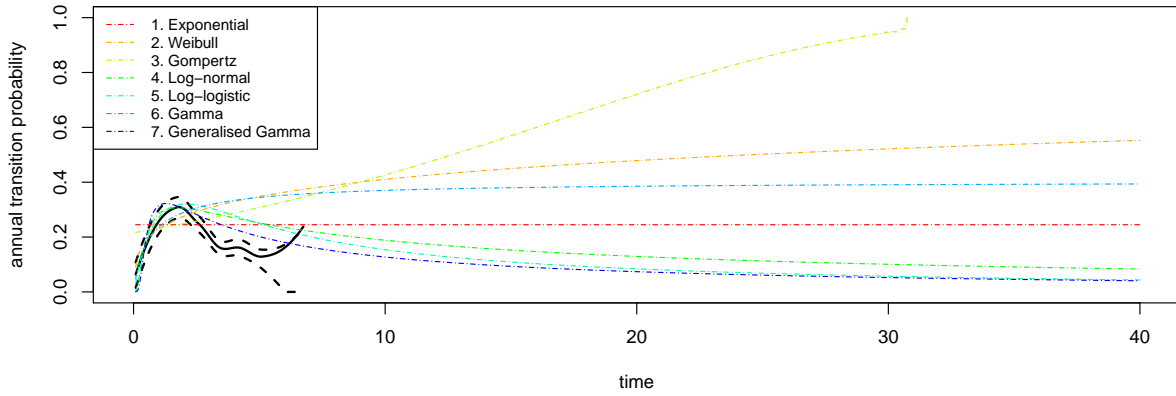
E: Annual transition probability (spline curves)

Legend:
- 8. Spline 1 knot hazard
- 9. Spline 2 knots hazard
- 10. Spline 3 knots hazard
- 11. Spline 1 knot odds
- 12. Spline 2 knots odds
- 13. Spline 3 knots odds
- 14. Spline 1 knot normal
- 15. Spline 2 knots normal
- 16. Spline 3 knots normal

F: Annual transition probability (cure curves)

Legend:
- 17. Mixture cure Weibull
- 18. Non–mixture cure Weibull
- 19. Mixture cure Log–normal
- 20. Non–mixture cure Log–normal
- 21. Mixture cure Log–logistic
- 22. Non–mixture cure Log–logistic

G: Hazard function (parametric curves)

Legend:
- 1. Exponential
- 2. Weibull
- 3. Gompertz
- 4. Log–normal
- 5. Log–logistic
- 6. Gamma
- 7. Generalised Gamma
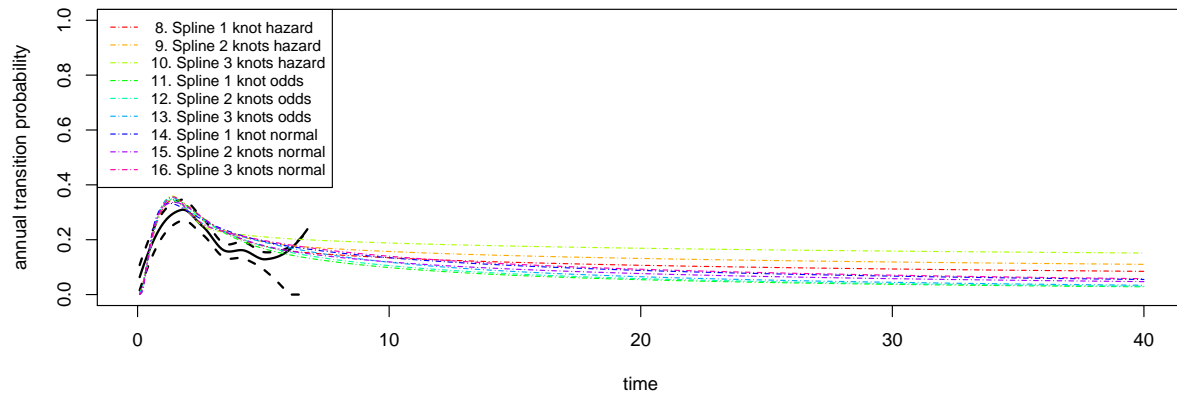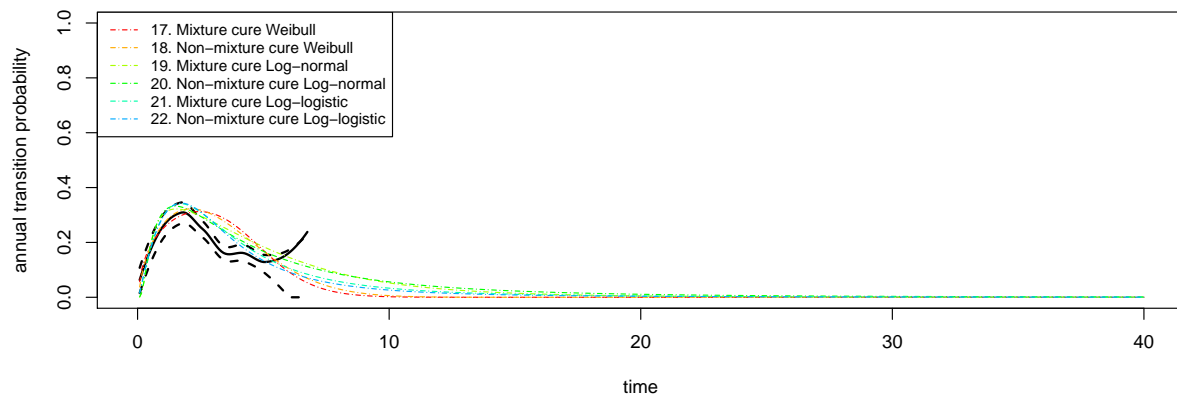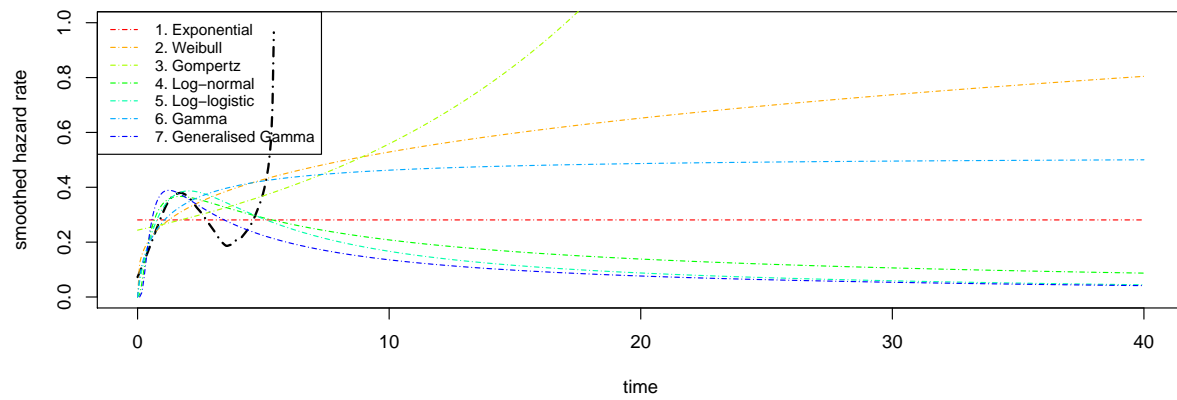
Table 6: Summary statistics of annual transition probabilities

	Min	Q1	Median	Q3	Max
1. Exponential	0.2449482	0.2449482	0.2449482	0.2449482	0.2449482
2. Weibull	0.0907442	0.4105709	0.4790585	0.5216195	0.5525972
3. Gompertz	0.2169796	0.3698466	0.5818235	0.8071868	1.0000000
4. Log-normal	0.0022958	0.1000774	0.1279068	0.1841659	0.3070152
5. Log-logistic	0.0305143	0.0571627	0.0832145	0.1494462	0.3207417
6. Gamma	0.0471845	0.3701940	0.3852535	0.3907371	0.3935697
7. Generalised Gamma	0.0000317	0.0518395	0.0728961	0.1237607	0.3222943
8. Spline 1 knot hazard	0.0048605	0.0929348	0.1060806	0.1322263	0.3462113
9. Spline 2 knots hazard	0.0027621	0.1183362	0.1309295	0.1552006	0.3471134
10. Spline 3 knots hazard	0.0031604	0.1581132	0.1681704	0.1865373	0.3590229
11. Spline 1 knot odds	0.0040186	0.0370407	0.0534928	0.0956147	0.3493116
12. Spline 2 knots odds	0.0029239	0.0397013	0.0573770	0.1025038	0.3469030
13. Spline 3 knots odds	0.0031346	0.0443526	0.0641665	0.1145082	0.3547245
14. Spline 1 knot normal	0.0001727	0.0667705	0.0870224	0.1315769	0.3327152
15. Spline 2 knots normal	0.0003302	0.0575542	0.0758377	0.1164719	0.3361441
16. Spline 3 knots normal	0.0005575	0.0702242	0.0912163	0.1362709	0.3562720
17. Mixture cure Weibull	0.0000000	0.0000000	0.0000000	0.0019526	0.3124571
18. Non-mixture cure Weibull	0.0000000	0.0000000	0.0000000	0.0058137	0.3224039
19. Mixture cure Log-normal	0.0002039	0.0008353	0.0048810	0.0495432	0.3220204
20. Non-mixture cure Log-normal	0.0012590	0.0032428	0.0107457	0.0537620	0.3323853
21. Mixture cure Log-logistic	0.0005930	0.0014141	0.0047437	0.0321531	0.3414361
22. Non-mixture cure Log-logistic	0.0004619	0.0010900	0.0036280	0.0253772	0.3434417

H: Hazard function (spline curves)

I: Hazard function (spline curves)

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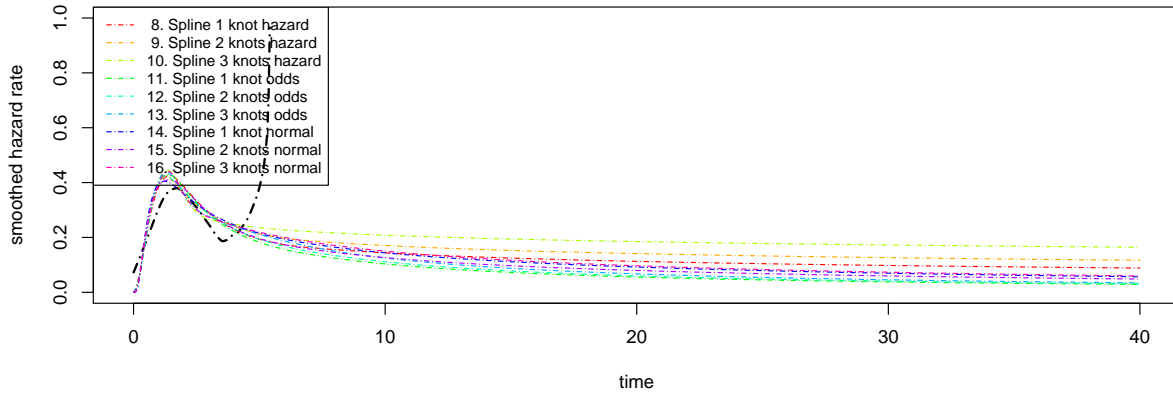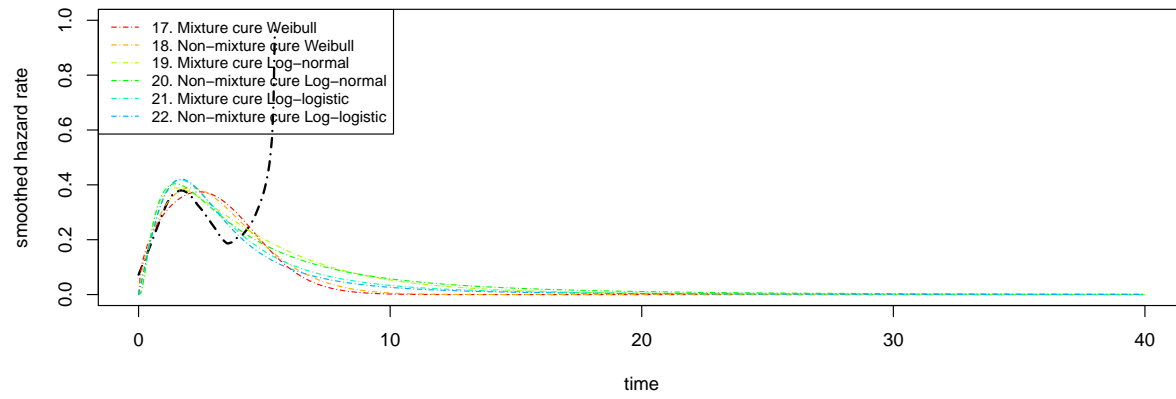
PERSUADE object information

```
## List of 6
##  $ name      : chr "BC_OS"
##  $ input     :List of 11
##   ..$ years               : num [1:686] 3.68 4.32 4.82 3.16 2.65 ...
##   ..$ status              : num [1:686] 0 0 0 0 0 0 0 1 0 0 ...
##   ..$ group               : Factor w/ 3 levels "Good","Medium",..: 1 1 1 1 1 1 1 1 1 1 ...
##   ..$ strata              : logi TRUE
##   ..$ spline_mod          : logi TRUE
##   ..$ cure_mod            : logi TRUE
##   ..$ cure_link           : chr "logistic"
##   ..$ time_unit           : num 0.0833
##   ..$ time_horizon        : num 40
##   ..$ time_pred_surv_table: num [1:12] 0 12 24 36 48 60 120 180 240 300 ...
##   ..$ time_pred           : num [1:481] 0 0.0833 0.1667 0.25 0.3333 ...
##  $ surv_obs  :List of 6
##   ..$ km       :List of 23
##   .. ..- attr(*, "class")= chr [1:2] "npsurv" "survfit"
##   ..$ km_names: num [1:646] 1 1 1 1 1 1 1 1 1 1 ...
##   ..$ cum_haz :'data.frame': 256 obs. of  15 variables:
##   ..$ haz      :List of 5
##   ..$ tp       :List of 4
##   ..$ cox_reg  :List of 21
##   .. ..- attr(*, "class")= chr "coxph"
##  $ surv_model:List of 26
##   ..$ expo           :List of 28
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ weib           :List of 28
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ gom            :List of 28
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ lnorm          :List of 28
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ llog           :List of 28
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ gam            :List of 28
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ ggam           :List of 28
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ IC             :'data.frame':  7 obs. of  3 variables:
##   ..$ spl_hazard1    :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_hazard2    :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_hazard3    :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_odds1      :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_odds2      :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_odds3      :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_normal1    :List of 31
```

```
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_normal2    :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ spl_normal3    :List of 31
##   .. ..- attr(*, "class")= chr "flexsurvreg"
##   ..$ IC_spl         :'data.frame':  9 obs. of  3 variables:
##   ..$ cure_weib_mix  :List of 3
##   ..$ cure_weib_nmix :List of 3
##   ..$ cure_lnorm_mix :List of 3
##   ..$ cure_lnorm_nmix:List of 3
##   ..$ cure_llog_mix  :List of 3
##   ..$ cure_llog_nmix :List of 3
##   ..$ IC_cure        :'data.frame':  6 obs. of  5 variables:
##   ..$ survmod        : chr [1:21, 1:105] "1. Exponential" "rate" "-2.80703426596042" "-3.08148409638
##   .. ..- attr(*, "dimnames")=List of 2
## $ surv_pred :List of 3
##   ..$ model:List of 44
##   ..$ gr   :List of 3
##   ..$ tp_gr:List of 3
## $ misc       :List of 8
##   ..$ form       :Class 'formula'  language Surv(years, status) ~ group
##   .. .. ..- attr(*, ".Environment")=<environment: 0x00000000250d1568>
##   ..$ group_names: chr [1:3] "Good" "Medium" "Poor"
##   ..$ ngroups    : int 3
##   ..$ lbls_all   : chr [1:23] "time" " 1. Exponential" " 2. Weibull" " 3. Gompertz" ...
##   ..$ lbls       : chr [1:7] " 1. Exponential" " 2. Weibull" " 3. Gompertz" " 4. Log-normal" ...
##   ..$ lbls_spline: chr [1:9] " 8. Spline 1 knot hazard" " 9. Spline 2 knots hazard" "10. Spline 3 kn
##   ..$ lbls_cure  : chr [1:6] "17. Mixture cure Weibull" "18. Non-mixture cure Weibull" "19. Mixture
##   ..$ cols_tp    : num 23
## NULL
```

Session information

```
## R version 4.0.1 (2020-06-06)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 19041)
##
## Matrix products: default
##
## Random number generation:
##  RNG:     Mersenne-Twister
##  Normal:  Inversion
##  Sample:  Rejection
##
## attached base packages:
## [1] splines   stats     graphics  grDevices utils     datasets  methods
## [8] base
##
## other attached packages:
##  [1] sft_2.2-1           SuppDists_1.1-9.5  fda_5.1.7          fds_1.8
##  [5] RCurl_1.98-1.2      rainbow_3.6        pcaPP_1.9-73       MASS_7.3-51.6
##  [9] Matrix_1.2-18       kableExtra_1.3.1   knitr_1.30         summarytools_0.9.6
## [13] data.table_1.13.4   survminer_0.4.8    ggpubr_0.4.0       muhaz_1.2.6.1
## [17] flexsurv_1.1.1      rms_6.1-0          SparseM_1.78       Hmisc_4.4-2
## [21] ggplot2_3.3.2       Formula_1.2-4      survival_3.2-7     lattice_0.20-41
##
## loaded via a namespace (and not attached):
##   [1] TH.data_1.0-10     colorspace_2.0-0   ggsignif_0.6.0
##   [4] pryr_0.1.4         ellipsis_0.3.1     rio_0.5.16
##   [7] mclust_5.4.7       htmlTable_2.1.0    base64enc_0.1-3
##  [10] rstudioapi_0.13    farver_2.0.3       MatrixModels_0.4-1
##  [13] mvtnorm_1.1-1      lubridate_1.7.9.2  xml2_1.3.2
##  [16] codetools_0.2-16   broom_0.7.2        km.ci_0.5-2
##  [19] cluster_2.1.0      png_0.1-7          compiler_4.0.1
##  [22] httr_1.4.2         backports_1.2.0    htmltools_0.5.0
##  [25] quantreg_5.75      tools_4.0.1        gtable_0.3.0
##  [28] glue_1.4.2         dplyr_1.0.2        Rcpp_1.0.5
##  [31] carData_3.0-4      cellranger_1.1.0   vctrs_0.3.5
##  [34] nlme_3.1-148       conquer_1.0.2      xfun_0.19
##  [37] stringr_1.4.0      openxlsx_4.2.3     rvest_0.3.6
##  [40] lifecycle_0.2.0    gtools_3.8.2       rstatix_0.6.0
##  [43] polspline_1.1.19   zoo_1.8-8          scales_1.1.1
##  [46] hms_0.5.3          sandwich_3.0-0     RColorBrewer_1.1-2
##  [49] yaml_2.2.1         curl_4.3           gridExtra_2.3
##  [52] KMsurv_0.1-5       pander_0.6.3       rpart_4.1-15
##  [55] latticeExtra_0.6-29 stringi_1.5.3     checkmate_2.0.0
##  [58] zip_2.1.1          hdrcde_3.3         bitops_1.0-6
##  [61] rlang_0.4.9        pkgconfig_2.0.3    matrixStats_0.57.0
##  [64] evaluate_0.14      purrr_0.3.4        labeling_0.4.2
##  [67] ks_1.11.7          rapportools_1.0    htmlwidgets_1.5.2
##  [70] tidyselect_1.1.0   deSolve_1.28       plyr_1.8.6
##  [73] magrittr_2.0.1     R6_2.5.0           magick_2.5.2
##  [76] generics_0.1.0     multcomp_1.4-15    pillar_1.4.7
##  [79] haven_2.3.1        foreign_0.8-80     withr_2.3.0
##  [82] abind_1.4-5        nnet_7.3-14        flexsurvcure_1.2.0
```

```
##  [85] tibble_3.0.4       mstate_0.2.12      crayon_1.3.4
##  [88] car_3.0-10         survMisc_0.5.5     KernSmooth_2.23-17
##  [91] rmarkdown_2.5      jpeg_0.1-8.1       grid_4.0.1
##  [94] readxl_1.3.1       forcats_0.5.0     digest_0.6.27
##  [97] webshot_0.5.2      xtable_1.8-4       tidyr_1.1.2
## [100] munsell_0.5.0      viridisLite_0.3.0  tcltk_4.0.1
## [103] quadprog_1.5-8
```