New Developments in Survival Analysis Using SAS® Software

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INTRODUCTION

- **Survival Analysis– methods to analyze time-to-event data that are right, left and/or interval censored**

- **Extensions from single event to repeated (recurrent) events, and multiple events**

- **Methods for different types of analyses:**

  I. Nonparametric†
  II. Parametric†
  III. Semi-parametric
  IV. Bayesian

† Focus of this presentation

I. NONPARAMETRIC ANALYSIS

- **ESTIMATION OF SURVIVAL CURVES**
- **COMPARISON OF SURVIVAL CURVES**

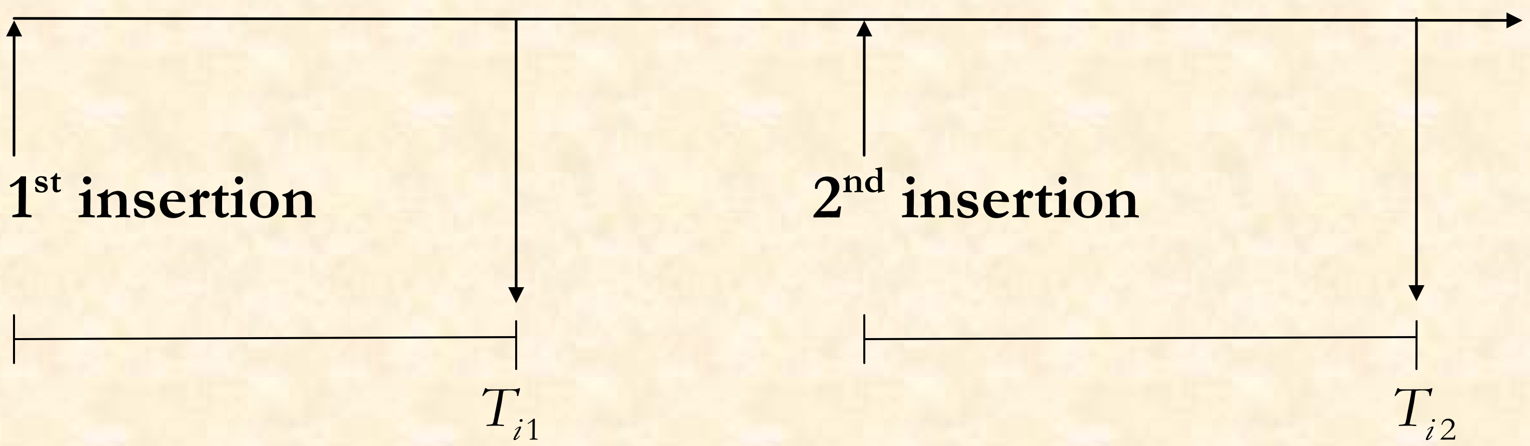
Proc LIFETEST is the main engine for nonparametric analysis

ILLUSTRATIVE EXAMPLE 1

A study by McGilchrist & Aisbett (1991) of 38 kidney dialysis patients:

- **Time in days to infection at the catheter insertion point**

- **Two times in each patient** (T_{i1}, T_{i2}) **with possible right censoring at** (U_{i1}, U_{i2})



Data—3 patients

Obs	patient	insert	time	fail	gender	age
1	1	1	8	1	0	28.0
2	1	2	16	1	0	28.0
3	2	1	23	1	1	48.0
4	2	2	13	0	1	48.0
5	3	1	22	1	0	32.0
6	3	2	28	1	0	32.0

age=average age at catheter insertions

```
proc format;
value gender 0='male'1='female';
value insert 1='first' 2='second';
value fail 0='censored' 1='infected';
run;
```

Analysis Variable : time							
insert	gender	fail	N	Mean	Median	Min	Max
first	female	censored	6	58.2	38.0	5.0	149.0
		infected	22	162.2	124.5	7.0	536.0
	male	infected	10	32.8	16.0	2.0	152.0
second	female	censored	10	47.4	24.5	5.0	159.0
		infected	18	119.3	72.0	8.0	333.0
	male	censored	2	6.0	6.0	4.0	8.0
		infected	8	105.8	26.5	9.0	562.0

ESTIMATION OF SURVIVAL CURVES

- **Distribution of infection-free time by insertion and gender**

$S_j(t) = P[T_j > t], \quad T_j$ **- time in days to infection**

- **Nonparametric methods use the data:**

$X_{ij} = \min(T_{ij}, U_{ij}),\ \delta_{ij} = [T_{ij} \le U_{ij}]$ ***j*=1, 2 (stratum),**

$\delta_{ij} = 1$ **if infection time is observed,** $\delta_{ij} = 0,$ **otherwise,**

U_{ij} **- censoring time**

Inputs:

- **accumulating count of events up to time *t*,** $N_j(t) = \sum_{i=1}^{n} [X_{ij} \le t, \delta_{ij} = 1]$
- **number at risk at time *t*,** $Y_j(t) = \sum_{i=1}^{n} [X_{ij} \ge t]$**.**

Estimators:

$S_j(t)$ **and cumulative hazard** $H_j(t)$ **and are estimated by**

$$\hat{H}_j(t) = \int_0^t \{Y_j(u)\}^{-1} dN_j(u),\ \hat{S}_j(t) = \exp(-\hat{H}_j(t))$$

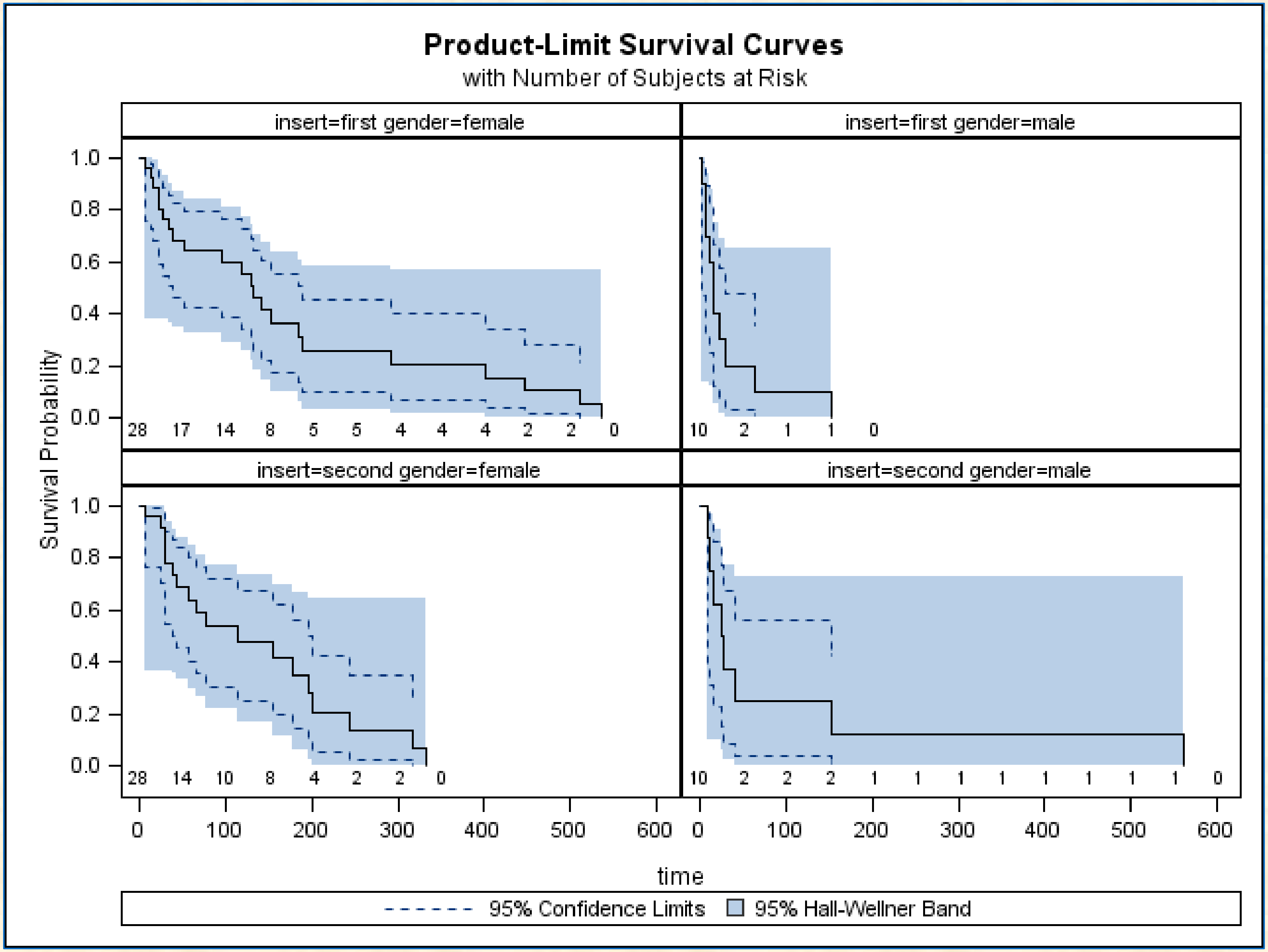
Kaplan-Meier (Product limit) estimator:

$$\tilde{S}_j(t) = \prod_{u \le t} \left(1 - \frac{\Delta N_j(u)}{Y_j(u)}\right)$$

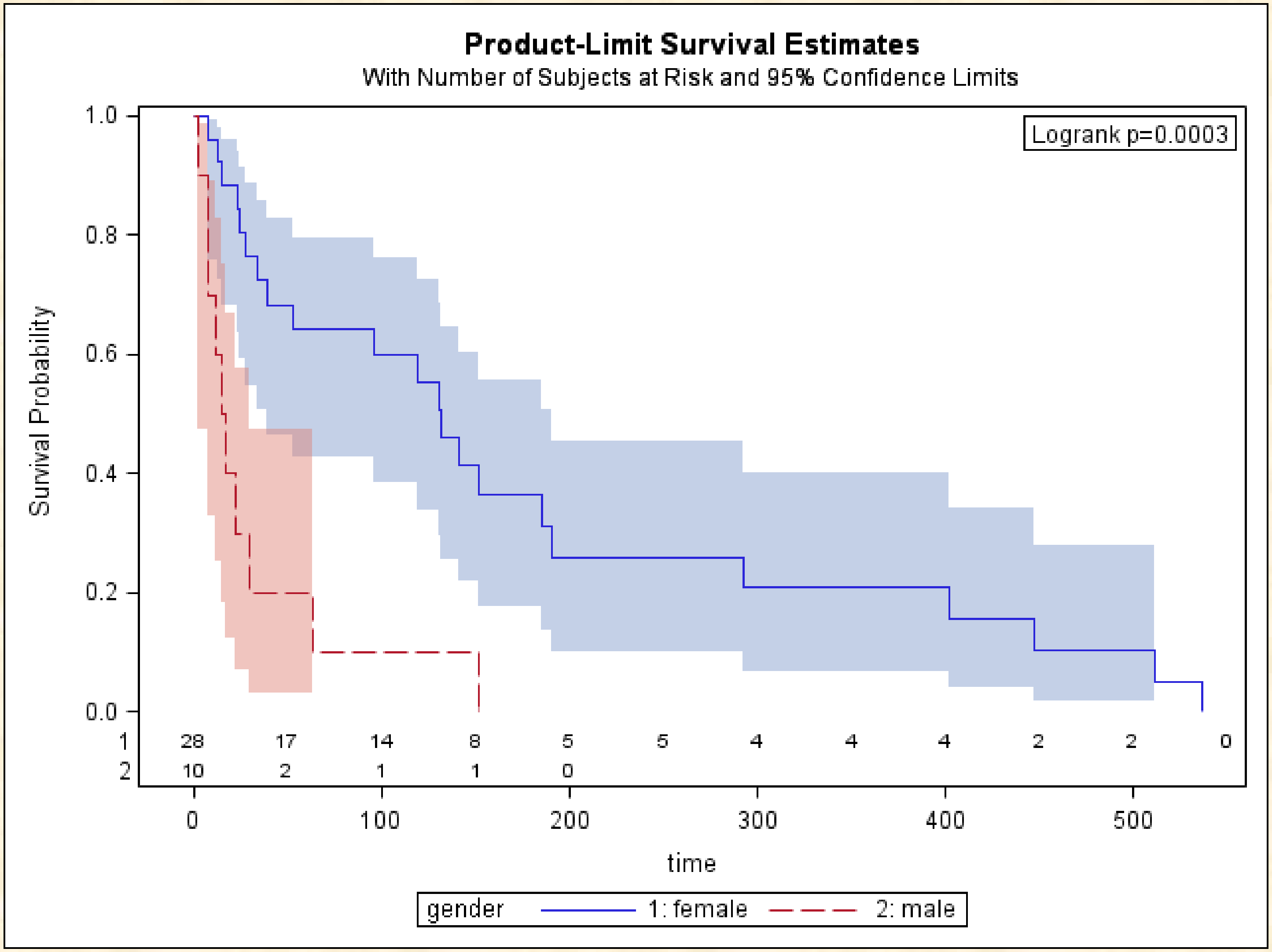
SAS SYNTAX

```
ods graphics on;
proc lifetest data=kidney Method=km
plots=survival(nocensor cb=hw cl strata=panel
                atrisk=0 to 600 by 50);
strata insert gender;
time time*fail(0);
format gender gender. insert insert.;
run;
ods graphics off;
```

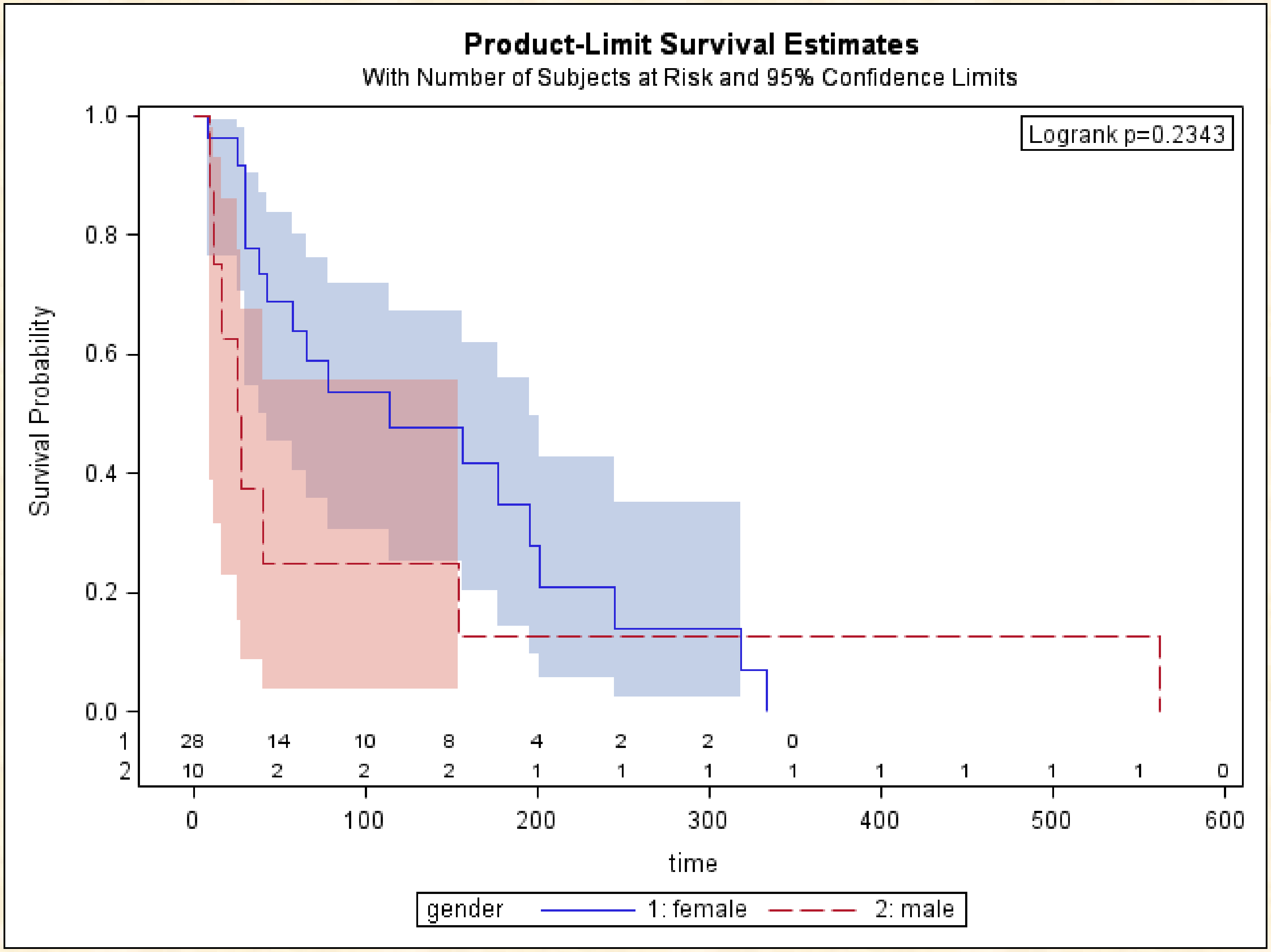
```
nocensor to suppress plotting of censored times
cl for confidence (pointwise) limits
cb=  for confidence bands
atrisk=  to display patients at risk at specified times
strata=panel to display of plots in a panel
```


Product-Limit Survival Curves
with Number of Subjects at Risk
insert=first gender=female
insert=first gender=male
insert=second gender=female
insert=second gender=male
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
28 17 14 8 5 5 4 4 4 2 2 0
10 2 1 1 0
28 14 10 8 4 2 2 0
10 2 2 2 1 1 1 1 1 1 1 1 0
0 100 200 300 400 500 600
time
95% Confidence Limits
95% Hall-Wellner Band

Comparisons: by gender at each insertion–First insertion



Second insertion



Some Conclusions

- Logrank test-comparison by gender- obtained from

```
strata insert/group=gender test=logrank;
```

  This is a stratified test (p=.0009). Separately by first, second insertion,

- First insertion– gender effect is significant. Females have longer infection-free duration

- Second insertion– gender effect is not significant

- 95% pointwise confidence intervals are displayed–little overlap for first insertion

II. PARAMETRIC MODELS-ACCELERATED FAILURE TIME MODEL

- **FITTING PARAMETRIC MODELS**
- **ESTIMATION OF PERCENTILES**
- **JOINT MODELING OF INFECTION TIMES**

Procedures LIFEREG and RELIABILITY can be used. Also a new PROC SEVERITY

ACCELERATED FAILURE TIME MODEL

- $\log T = \mu + \sigma\varepsilon$, **where** μ **=location and** σ **=scale are parameters**
- **Covariate effects are modeled by** $\mu = \mathbf{z}'\beta_1$
- **heteroscedasticity by** $\log\sigma = \mathbf{z}'\beta_2$
- **distribution on** ε **independent of z, induces a distribution on** T

Use MLE to estimate (β_1, β_2)

AFT class includes exponential, Weibull, lognormal and loglogistic.

General form: $S(t) = S_0((t/\alpha)^\gamma)$ **where** $\sigma = \gamma^{-1}, \mu = \log\alpha,\ \alpha > 0, \gamma > 0$**,**
and S_0 **is a known survival distribution**

Generalized Gamma (GG) Distribution

- **Additional shape parameter**
- **AFT form:** $\log T = \mathbf{z}'\beta_1 + \sigma_0 Z$ **where** $k = \delta^{-2}, \sigma_0 = \sigma\delta$,

  $Z = \sqrt{k}(\varepsilon - \log k)$
- **SAS calls** δ **the** ***shape*** **and** σ_0 **the** ***scale*** **of the GG**

GG returns three special cases:

(1) with δ**=0 the log normal. As** $\delta \to 0$, Z **converges to the standard normal;**

(2) with δ**=1 the Weibull;**

(3) with δ**=1 and** σ_0 **=1 the exponential;**

FITTING PARAMETRIC MODELS

Assume the within-patient times (T_{i1}, T_{i2}) are independent, making our sample comprise of 76 individual catheter insertions.

```
proc lifereg data=kidney;
class gender;
model time*fail(0)=age gender/dist=gamma;
format gender gender.;
run;
```

For lognormal: $H_0 : \delta = 0$. **Use dist=gamma noshape1 shape1=0;**

For Weibull: $H_0 : \delta = 1$. **Use dist=gamma noshape1 shape1=1;**

For exponential: $H_0 : \delta = 1, \sigma_0 = 1$.

Use dist=gamma noshape1 shape1=1 noscale scale=1;

Table 1: Results of fitting parametric AFT models to infection times					
	Maximum likelihood estimate (standard error)				
Parameter	**GG**	**Lognormal**	**Weibull**	**Exponential**	**Loglogistic**
Intercept	3.4188 (0.5322)	3.4490 (0.4939)	4.2916 (0.5505)	4.4025 (0.4971)	3.4052 (0.4636)
AGE	–0.0054 (0.0097)	–0.0054 (0.0097)	–0.0042 (0.0103)	–0.0046 (0.0094)	–0.0073 (0.0093)
GENDER-female	1.3830 (0.3283)	1.3269 (0.3261)	0.9655 (0.3248)	0.8853 (0.2871)	1.5526 (0.3265)
Scale	1.1863 (0.1085)	1.1847 (0.1077)	1.1031 (0.1035)	1(fixed)	0.6793 (0.0720)
Shape	–0.0473 (0.3164)	0(fixed)	1(fixed)	1(fixed)	na
–2 log L	197.032	197.053	206.197	207.348	198.532
BIC	218.686	214.375	223.520	220.340	215.855
LM test p-value	na	.887	<.0001	Shape <.001 Scale .316	na

ESTIMATION OF PERCENTILES

- **Given a covariate profile z: the 100(1−p)-th percentile t_p of the event time T is $t_p = \exp(\mathbf{z}'\beta + \sigma w_p)$ where w_p is the corresponding percentile of ε.**
- **Work with $\log \hat{t}_p = \mathbf{z}'\hat{\beta} + \hat{\sigma} w_p$ to obtain 95% CI for t_p**
- **Use PROC RELIABILITY**

See SGF 2010: Paper 252-2010 for an example and syntax

JOINT MODELING OF INFECTION TIMES

- **Allow correlation between** (T_{i1}, T_{i2}) **via a shared frailty model**

  $\log T_{ij} = \mathbf{z}'_{ij}\beta + \nu_i + \sigma\varepsilon_{ij}$ **where** ν_i **is a random effect**

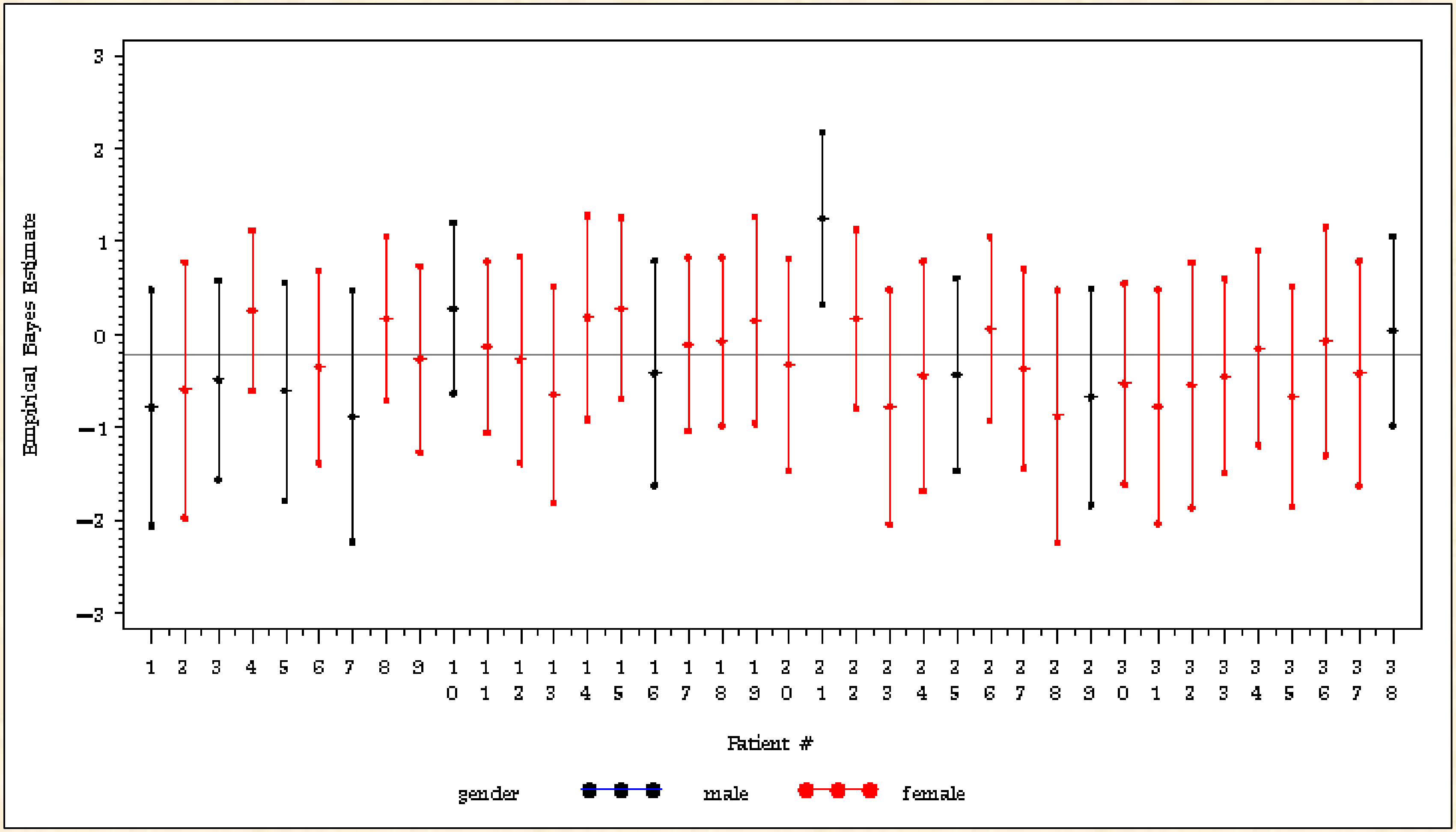
- **Assume** (T_{i1}, T_{i2}) **conditionally independent given** $(\nu_i, \mathbf{z}_{i1}, \mathbf{z}_{i2})$,

  parametric distribution for $(\nu_i, \varepsilon_{ij})$ **given** $(\mathbf{z}_{i1}, \mathbf{z}_{i2})$

- **Perform ML estimation of the marginal model using PROC NLMIXED**

Example: Weibull model, ε_{ij} **~extreme-value,** $\nu_i \sim N(-\frac{1}{2}\sigma_\nu^2, \sigma_\nu^2)$.

Get MLE of (β, σ_ν^2) **and empirical Bayes estimates of** ν_i**, that is** $E(\nu_i \mid data)$



LRT for frailty effect p<.01; but the effect appears to be from patient #21

Remarks

- **Other frailty models**

  $\varepsilon_{ij} \sim \textit{extreme-value},\ \xi_i = \exp(\nu_i) \sim \textit{Gamma}$

  $\varepsilon_{ij} \sim \textit{normal},\ \nu_i \sim \textit{normal}$

  can be fitted by NLMIXED

- **Use MLE from (non-frailty model) LIFEREG to suggest starting values**

- **PROC QLIM in SAS/ETS can fit a joint log-normal model**

  $y_{ij}^* = \log T_{ij} = \mathbf{z}'_{ij}\beta + u_{ij}$ **with** (u_{i1}, u_{i2})**~Normal** $(\mathbf{0}, \rho, \sigma_1, \sigma_2)$ **and observed range of** y_{ij}^* **is restricted**

  See SGF 2010: Paper 252-2010 for details

SUMMARY

- **Procedures LIFETEST, LIFEREG, PHREG provide tools for comprehensive analyses**
- **PHREG for analyses the Cox model and its extensions**
- **ODS GRAPHICS and PLOT options in above procedures provide exquisite enhancements**
- **BAYES option in LIFEREG, PHREG give additional capabilities**
- **PROC MCMC can be used for more complex survival analyses**
- **Future enhancements could include frailty models, finite mixture models, hyper-prior specification for Bayes models**

ACKNOWLEDGEMENTS

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Paper 252-2010: Gardiner JC. "Survival Analysis: Overview of Parametric, Nonparametric and Semiparametric approaches and New Developments"

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Thank you for your attendance