Index

2 × 2 factorial design 83–8, 141–2
accelerated failure time (AFT) 101, 102–3, 107–12
access to care 245–6
ACT see anti-malarial combination trial
acute leukaemia 178–9
acute rejection of transplants 157
advanced carcinoma of the cervix see cervical cancer
AFT see accelerated failure time
AHSD see arteriosclerotic heart disease
AIC see Akaike’s information criteria
AIDS see HIV/AIDS
Akaike’s information criteria (AIC) 114–15
amenorrhoea 61
angina pectoris 241–2
anti-malarial combination trial (ACT) 247–9
aplastic anaemia 178–9
arteriosclerotic heart disease (ASHD) 167–8
aspirin 87–8, 142
asthma 140
astrocytoma 200
atenolol 241–2
automated searches 172–3
azathioprine 231–2
azoospermic males 6
bivariable screens 172
bleeding irregularities 61
bodyweight 81–2
bone marrow 65, 178–9
Bournemouth score groupings 79
brain cancer
Cox model 126–9, 131–5, 142–3, 145–7, 151, 158–66
non-proportional hazards 224–5
prognostic indices 190–1, 194, 199–205
breast cancer 136–7, 184, 190
Breslow tests 226–7
burns 11–20
busulphan 5
candidate variables 189–90
carcinoma of the cervix see cervical cancer
case-control studies 14
categorical variables 135–8, 166, 169
CD4 count 37–8
censored survival times 2, 3, 24–5, 35, 88
Cox model 151–3
parametric modelling 96–8, 115
cerebrovascular accident (CVA) 167–8
cervical cancer
confidence intervals 10, 66–8
hazard ratio 62, 66–8
Logrank test 52–9, 68–82, 228–9
Mantel-Haenszel test 68–9
non-proportional hazards 228–9
parametric modelling 99–102, 108, 112
CGL see chronic granulocytic leukaemia
change-in-estimates 156, 165–6
chemotherapy 5, 123
chi-squared test 18–19
Cox model 127, 136, 162–4
factorial design 88
homogeneity between groups 76, 79–80
non-proportional hazards 228–9
stratified Logrank test 71
chronic granulocytic leukaemia (CGL) 4–5
chronic heart failure 52
chronic obstructive pulmonary disease (COPD) 167–8
CIM see cumulative incidence method
clinical significance 17–18
clinically important difference 211
clustered data 182, 245–9
colon cancer 215–17
colonisation-free rates 210
colorectal cancer
Cox model 169
parametric modelling 92–8, 105–7
survival curves 26–7, 29–33, 37, 39, 40–4, 46–7
combination treatments 83–8, 123, 241–2, 243–4
competing risks 236–40
complementary log plots 94–8, 121–4, 146–7, 224
computing packages 21

Survival Analysis Second Edition  David Machin, Yin Bun Cheung, Mahesh K.B. Parmar
INDEX

conditional probabilities 29–30
confidence intervals (CI) 10–12, 17, 22
Cox model 127–8, 155
Greenwood’s method 41–2
hazard ratio 65–7
median survival times 44–5
parametric modelling 98, 100, 107–8
Peto’s method 42
survival curves 40–5, 65–7
transformation method 43
confirmatory trials 211
confounders 155–6, 157–8, 165, 172
constant hazard rate 91–8
continuous data 1–2
continuous time-varying covariates 178–9
continuous variables 166–7
contraceptives 45, 60–1, 81–2, 236–40
COPD see chronic obstructive pulmonary disease
coronary artery disease 142
Cox model 121–5, 155–73, 175–86
all possible combinations 164–5
assessing proportionality 146–9
automated searches 172–3
binary variable 176–7
bivariable screens 172
categorical variables 135–8
change-in-estimates 156, 165–6
clustered data 182
comparing groups 125–8
complementary log-plots 121–4, 146–7
continuous time-varying covariates 178–9
delayed entry 176, 183–4, 185–6
discrete time intervals 179–81
efficiency 158
extensions 175–86
factorial design 141–2
fixed and time-varying covariates 177
forced-entry 156–8
interaction model 141–4, 151
interactions 169–70
likelihood ratio 150–1, 162
Logrank test 128, 144–6
missing values 170–1
more than two explanatory variables 134–5
multivariable analysis 155–6
multivariable models 139
nested models 161
non-proportional hazards 179–82
paired observations 242–4
parametric models 139–40
partial likelihood 151–3, 184–6
practicalities 170–3
prognostic indices 155
proportional hazards 124–5, 139–40, 146–9, 159
regression models 128–38
Schoenfeld residuals 148–9
significance levels 171–2
significance testing 156, 158–65
single explanatory variable 128–32
smooth time-varying hazard ratios 181
step-down selection 163–4
step-up selection 161–3
stepwise selection 165–6
stratified analysis 144–6, 181–2
technical details 151–3, 184–6
tied data 153
time-dependent 176–81
time-scales 182–3
truncation 176, 185–6
two explanatory variables 132–4
updated covariates 184–5
variable selection 155–73
variable types 155–6, 157–8, 165, 166–70
Wald test 127, 150
Weibull model 140
see also prognostic indices
Cox-Snell residuals 115–17
crossover trials 240–3
cumulative hazard 87–8, 95
cumulative incidence method (CIM) 239–40
cumulative rates 6, 34–5, 60–1, 237–9
cure models 38, 232–6
cut-point 138
CVA see cerebrovascular accident
cystic fibrosis 210, 211, 214
daily hazard 47–8
database packages 21
delayed entry 7–8, 176, 183–4, 185–6
design variables 156, 157
diabetes mellitus 167–8, 170
diagnostics 115–17
discontinuation 60–1, 237–9
discrete time intervals 179–81
distribution
exponential 91–103, 105–7, 112, 113–19
generalised Gamma 110–12, 113–14
log-Logistic 112, 113–14
log-Normal 108–10, 113–14
Normal 9–10
survival curves 48–9
Weibull 93, 95, 103–8, 112, 113–19, 140
Dukes’ A/B/C see colorectal cancer
dummy variables 135, 167–8
ECMV see etoposide, cyclophosphamide, methotrexate and vincristine
effect size 208–10
efficiency 158
INDEX

end-stage renal disease 167–8
endpoint 189
epidemiology 12–13
etoposide, cyclophosphamide, methotrexate and vincristine (ECMV) 123
Ewing’s sarcoma 187, 235–6
exploratory variables 156
exponential distribution 91–103, 105–7, 112, 113–19
exponential survival curves 208–9
factorial design 83–8, 141–2
fertility 60–1, 81–2, 139
fits 133–5, 142–3, 145–7, 159–66, 175, 224–5
fixed covariates 175, 177
fixed-time points 28, 40, 41–2
fluorouracil 141–2
follow-up
discontinuation 237–9
maturity 38–40, 88–90
sample sizes 215–16
forced-entry 156–8
gag (p24) antibodies 59–60
gaps in exposure time 7–8
Gehan tests 226–7
generalised Gamma distribution 110–12, 113–14
generalised Wilcoxon tests 226–7
glyceril trinitrate 37
gold therapy 33–4
gossypol 6, 139
graft versus host disease (GVHD) 178–9
greenwood’s method 41–2
GVHD see graft versus host disease
hazard rate constant 91–8
cumulative hazard 95
estimation 93–4
parametric modelling 91–102
proportional 124–5
survival curves 45–9
variable 103–4, 115, 124
verification 94–8
see also Cox model
hazard ratio (HR) 12–15
median survival times 67–8
paired observations 243
parametric modelling 99–102
sample sizes 207–8
smooth time-varying 181
survival curves 62–9
HCC see hepatocellular carcinoma
heart transplantation 2–3, 24–6, 176–7, 184–5
heparin 87–8, 142
hepatocellular carcinoma (HCC) 23–4, 26, 197–8, 201, 218–20
history of fits 133–5, 142–3, 145–7, 159–66, 175, 224–5
HIV/AIDS 36–8, 44, 59–60
Hodgkin’s lymphoma 233–4
homogeneity between groups 76, 79
HR see hazard ratio
incontinence 225–7
influential variables 156
infusion times 37
initial events 7
injectable contraceptives 60–1
inoperable hepatocellular carcinoma 197–8, 201, 218–20
intention-to-treat (ITT) 7
interactions
Cox model 141–4, 151, 169–70
factorial design 86–8
intrauterine devices (IUDs) 45, 237–40
ITT see intention-to-treat
IUDs see intrauterine devices
Kaplan-Meier estimates 2, 4, 21
Censor estimate 237, 238–40
Cox model 133
cure models 234
follow-up maturity 39
non-proportional hazards 226
parametric modelling 96, 106
prognostic indices 194, 196, 198
survival curves 28–32, 36–41, 51–4, 60, 74–5, 84, 89
knowingly influential variables 156
levamisole 215–17
life-table estimates 4–5
likelihood ratio (LR) 19–20, 112, 113–14, 150–1, 162
linearity 79–82, 169, 217–18
log-Logistic distribution 112, 113–14
log-Normal distribution 108–10, 113–14
Logrank test 12, 21
Cox model 128, 144–6
stratified 70–4, 85–6, 144–6
survival curves 51–61, 63–4, 69, 74–9
weighted 228–9
LR see likelihood ratio
lumpectomies 136
lung cancer 90, 122–4
malaria 247–9
Mantel-Cox test see Logrank test
Mantel-Haenszel test 68–9, 226–7, 228
marital status 148–9, 158, 177
mature data 38–40, 88–90
maximum likelihood estimate (MLE) 101, 105, 110, 118–19
median survival 8–9, 35–7, 39, 44–5, 67–8
mesothelioma 13–14
meta-analysis 229–32
metastatic disease 122–4, 137, 187, 235–6
MI see myocardial infarction
milrinone 52
misonidazole 126–9, 133–5, 147, 190–1
missing values 170–1
mixture models 233–4, 236
MLE see maximum likelihood estimate
mock-ultrasound 63
model based comparison 100–2, 106–7
motor development 110
multiple endpoints 221
multiple groups 74–82
multiple recurrences 111–17
multiple sclerosis 231–2
myelodysplastic syndromes 65, 79
myocardial infarction (MI) 87–8, 142
nasopharyngeal carcinoma 110–17
negative failure times 8
neonates 47, 110, 179–81, 207
nested models 113, 161
NHL see non-Hodgkin’s lymphoma
nifedipine 241–2
node-positive breast cancer 190
non-Hodgkin’s lymphoma (NHL) 196–7
non-linear trend 82
non-mixture models 234–6
non-nested models 114–15
non-observed events see censored survival times
non-proportional hazards 223–9
Cox model 179–82
Gehan tests 226–7
Peto-Prentice tests 227–9
Tarone-Ware tests 227
weighted Mantel-Haenszel tests 226–7, 228
non-scaled residuals 148
non-small cell lung cancer (NSCLC) 90, 122–4, 219
Normal distributions 9–10
NSCLC see non-small cell lung cancer
observed separation (OSEP) 198–201, 205
odds ratio (OR) 13–15
one-sided tests 212
optimal cut-point 138
OR see odds ratio
OSEP see observed separation
ovarian cancer 230
p-values 16–17, 155, 163–4
pain relief 67, 83
paired observations 240–9
analysis of correlated data 244–9
clustered data 245–7
Cox model 242–4, 246
crossover trials 240–2, 243–4
recurrent events 247–9
parametric modelling 91–119
accelerated failure time 101, 102–3, 107–12
comparing models 112–15
complementary log plots 94–8
confidence intervals 98, 100, 107–8
constant hazard rate 91–8
Cox model 139–40
Cox-Snell residuals 115–17
cumulative hazard 95
diagnostics 115–17
exponential distribution 91–103, 105–7,
112–19
generalised Gamma distribution 110–12,
113–14
Kaplan-Meier estimates 96, 106
likelihood ratio test 112, 113–14
log-Logistic distribution 112, 113–14
log-Normal distribution 108–10, 113–14
maximum likelihood estimate 101, 105,
110, 118–19
modelling strategies 117–18
nested models 113
non-nested models 114–15
proportional hazards 99, 101–3, 107–9
sample sizes 220
survival curve comparisons 99–102, 106–7
technical details 118–19
variable hazard rate 103–4
Weibull distribution 93, 95, 103–8, 112,
113–19
parsimonious models 155
partial likelihood (PL) 151–3, 184–6
pelvic inflammatory disease (PID) 45
Peto-Prentice tests 227–9
Peto’s method 42
PH see proportional hazards
PI see prognostic indices
PID see pelvic inflammatory disease
PL see partial likelihood
Ponderal Index 179–81
power, sample sizes 212–13
predicted separation (PSEP) 198–201, 205
pregnancy rates 81–2
Prentice, Williams and Peterson (PWP) model
247–9
pressure sores 63
product-limit estimator see Kaplan-Meier
estimates
prognosis 129, 131–2, 136–8, 175
prognostic indices (PI) 187–206
candidate subjects 188–9
candidate variables 189–90
Cox model 155
devising a new index 192–9
endpoint 189
established indices 205–6
fitting the model 192
modification 205
multivariable models 191–2
predicted prognostic information 198–9
scoring the patients 192–4
selecting the model 190–2
simplifying the model 194–8
testing 199–202
training data 188, 198–9
univariate models 190
updating the index 202–5
validation data 188–9, 198–9
validation sets 199–200
verification 205
progression 37–8, 59–60
proportional hazards (PH) 99, 101–3, 107–9
see also Cox model
PSEP see predicted separation
Pseudomonas aeruginosa 210
PWP see Prentice, Williams and Peterson
quadratic trend 82
query variables 156
RA see rheumatoid arthritis
radiosensitisers 52–3, 126–9, 133–5
radiotherapy 5, 52–3, 89, 122, 126–9, 133–5, 141–2, 158–66, 190–1, 199–202
randomised trials
Cox model 157
crossover trials 241
cumulative incidence 240
factorial designs 83–7
follow-up 88–9
hazard ratio 63–4
initial events 7
Logrank test 52–9, 71, 74
recurrent events 247–9
significance tests 17
survival curves 23
recovery rates 6
recurrent events 110–17, 175, 247–9
regression comparison 100–2, 106–7
regression models see Cox model
rejection of transplants 157
relative risk (RR) 12–13, 14–15
renal disease 167–8
renal transplants 157
replication errors 219
resectable colon cancer 215–17
retinal infarctions 40
retrospective studies 14
rheumatoid arthritis (RA) 33–4
robust standard error 245, 246–7
RR see relative risk
sample sizes 207–21
clinically important difference 211
duration of study 216–17
effect size 208–10
follow-up losses 215–16
limited resources 221
linear relationships 217–18
multiple endpoints 221
number of events 213–14
number of subjects 214
number of variables 218–19
one- or two-sided tests 212
parametric modelling 220
power 212–13
practicalities 220–1
regression problems 217–20
sample size tables 214–15
test size 211–12
training data 219–20
two-group comparative studies 213–17
validation data 219–20
scaled residuals 148–9
Schoenfeld residuals 148–9
SCLC see small cell lung cancer
SE see standard error
segment depression 241–2, 243
severe burns 11–20
severe pain 67, 83
significance tests 15–20
chi-squared test 18–19
clinical/statistical significance 17–18
confidence intervals 17
Cox model 156, 158–65, 171–2
likelihood ratio test 19–20
z-test 15–17
small cell lung cancer (SCLC) 47, 123–4
smooth time-varying hazard ratios 181
software packages 21
sperm function 6
sperm recovery 139
stage of disease 70–4
standard error (SE) 245, 246–7
statistical computing 21
statistical significance 17–18
step-down selection 163–4
step-up selection 161–3
sterility 6
stratified analysis 181–2
stratified Logrank test 70–4, 85–6, 144–6
stroke 129–30
study endpoint 189
survival curves 23–49, 51–90
  comparison 51–90, 99–102
  confidence intervals 40–5, 65–7
  crossover trials 243–4
  cumulative healing rates 34–5
cure models 234
daily hazard 47–8
distribution 48–9
estimating survival 28–32
exponential 208–9
factorial designs 83–8
fixed-time points 28, 40, 41–2
follow-up maturity 38–40, 88–90
graphical display 32–5, 99
Greenwood’s method 41–2
hazard rate 45–9
hazard ratio 62–9
interpretation 37–8
linear trend 79–82
Logrank test 51–61, 63–4, 69, 74–9
Mantel-Haenszel test 68–9
median survival times 35–7, 39, 44–5, 67–8
non-linear trend 82
non-proportional hazards 226
notation 27–8
parametric modelling 99–102
Peto’s method 42
prognostic indices 194, 196, 198
regression comparison 100–2, 106–7
sample sizes 208–9
stratified Logrank test 70–4, 85–6
survival time data 23–8
technical details 48–9
tests for trend 79–82
three or more groups 74–82
transformation method 43
survival outcomes 156
survival times
  censored 2, 3, 24–5, 35, 88, 96–8, 115, 151–3
  confidence intervals 10–12
definitions 1, 6–8
delayed entry 7–8
distribution 48–9
gaps in exposure time 7–8
initial events 7
median 67–8
median survival 8–9
Normal distributions 9–10
survival curves 23–8
zero failure times 8
tamoxifen 218
Tarone-Ware tests 227
TENS see transcutaneous electrical nerve stimulus
test size 211–12
tests for trend 79–82
three-dose comparisons 218
tied data 96–7, 153
time ratios (TR) 102–3, 110
time to progression 37–8, 59–60
time-dependent Cox model 176–81
TR see time ratios
training data 188, 198–9, 219–20
transcutaneous electrical nerve stimulus (TENS) 63–4, 83–7
transformation method 42
transplants 2–3, 24–6, 157, 176–7, 184–5
treatment combinations 83–8
treatment effect homogeneity 232
trend, test for 79–82
truncation 176, 185–6
tumour grade 136, 159–66, 175
two-group comparative studies 213–17
two-sided tests 212
ultrasound 63
univariate models 190
unknown variables 156
unstable coronary artery disease 142
updated covariates 184–5
vaginal rings 81–2
validation data 188–9, 198–200, 202, 219–20
variable hazard rate 103–4, 115, 124
VAS see visual analogue scale
VCT see voluntary counselling and HIV testing
venous ulceration 34–5
visual analogue scale (VAS) 63–4, 83
voluntary counselling and HIV testing (VCT) 245–6
Wald test 127, 150
Weibull distribution 93, 95, 103–8, 112, 113–19, 140
weighted Logrank tests 228–9
weighted Mantel-Haenszel tests 226–7, 228
Wilcoxon tests, generalised 226–7
z-test 15–17
zero failure times 8
Zimbabwe Project on Access to Care and Treatment (ZIMPACT) 245–6

Index prepared by Neil Manley