Addison’s disease associated with advanced HIV may explain the high mortality

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# Table 1

| Variable | N | N = 4311 |
| --- | --- | --- |
| **Age at enrolment** | 430 | 36 (31, 42) |
| **gender** | 429 |  |
| Females |  | 218 (50.8%) |
| Males |  | 211 (49.2%) |
| **Ethnicity** | 428 |  |
| Asian |  | 1 (0.2%) |
| Black African |  | 357 (83.4%) |
| Coloured |  | 68 (15.9%) |
| White |  | 2 (0.5%) |
| **Duration of current illness** | 400 | 14 (14, 21) |
| **Opportunistic infection present** | 428 | 424 (99.1%) |
| **log10 viral load** | 97 | 4.54 (3.16, 5.35) |
| **Total CD4 count** | 428 | 31 (14, 60) |
| **Sodium** | 408 | 134.0 (130.0, 137.0) |
| **Potassium** | 409 | 4.10 (3.60, 4.60) |
| **Haemoglobin** | 426 | 8.70 (7.40, 10.30) |
| **White cell count** | 423 | 5.3 (3.5, 8.0) |
| **Lymphocyte count** | 93 | 0.8 (0.4, 1.8) |
| **Neutrophils** | 93 | 3 (1, 8) |
| **Addisons disease** | 318 | 30 (9.4%) |
| 1Median (IQR); n (%) | | |

# Table 2: comparing Addisons status with other variables

| Variable | N | no, N = 2881 | yes, N = 301 | p-value2 |
| --- | --- | --- | --- | --- |
| **Age at enrolment** | 318 | 36 (31, 42) | 36 (31, 43) | 0.9 |
| **gender** | 318 |  |  | >0.9 |
| Females |  | 151 (52.4%) | 16 (53.3%) |  |
| Males |  | 137 (47.6%) | 14 (46.7%) |  |
| **Ethnicity** | 317 |  |  | 0.5 |
| Black African |  | 235 (81.9%) | 26 (86.7%) |  |
| Other |  | 52 (18.1%) | 4 (13.3%) |  |
| **Duration of current illness** | 300 | 14 (14, 30) | 14 (14, 21) | 0.4 |
| **Opportunistic infection present** | 317 |  |  |  |
| Yes |  | 287 (100.0%) | 30 (100.0%) |  |
| **log10 viral load** | 65 | 4.71 (3.27, 5.37) | 5.04 (4.79, 5.17) | 0.6 |
| **Total CD4 count** | 317 | 31 (14, 56) | 26 (12, 56) | 0.6 |
| **Sodium** | 303 | 133.0 (130.0, 137.0) | 135.0 (131.0, 137.0) | 0.10 |
| **Potassium** | 304 | 4.10 (3.65, 4.60) | 3.90 (3.30, 4.60) | 0.4 |
| **Haemoglobin** | 317 | 8.80 (7.40, 10.40) | 8.30 (7.62, 10.37) | >0.9 |
| **White cell count** | 316 | 5.7 (3.9, 8.2) | 5.1 (2.9, 8.2) | 0.5 |
| **Lymphocyte count** | 62 | 0.7 (0.4, 1.6) | 0.9 (0.6, 1.3) | 0.3 |
| **Neutrophils** | 61 | 3 (1, 7) | 7 (1, 15) | 0.7 |
| 1Median (IQR); n (%) | | | | |
| 2Wilcoxon rank sum test; Pearson's Chi-squared test | | | | |

# Table 3: Bivariate table (without imputed data)

| Characteristic | N | HR1 | 95% CI1 | p-value |
| --- | --- | --- | --- | --- |
| Age\_at\_enrolment | 430 | 1.02 | 0.99, 1.05 | 0.2 |
| gender | 429 | 0.78 | 0.45, 1.34 | 0.4 |
| Ethnicity | 428 | 0.89 | 0.42, 1.88 | 0.8 |
| Duration\_of\_current\_illness | 400 | 1.00 | 0.99, 1.01 | 0.6 |
| Log10\_viralload | 97 | 1.57 | 1.00, 2.47 | 0.049 |
| Total\_CD4\_count | 428 | 0.99 | 0.98, 1.00 | 0.2 |
| Sodium | 408 | 0.99 | 0.95, 1.04 | 0.7 |
| Potassium | 409 | 0.85 | 0.63, 1.15 | 0.3 |
| Haemoglobin | 426 | 1.00 | 0.97, 1.02 | 0.8 |
| White\_cell\_count | 423 | 1.00 | 1.00, 1.00 | 0.8 |
| Lymphocyte\_count | 93 | 0.86 | 0.68, 1.09 | 0.2 |
| Neutrophils | 93 | 0.99 | 0.96, 1.02 | 0.5 |
| Addisons\_disease | 318 | 1.18 | 0.47, 2.97 | 0.7 |
| 1HR = Hazard Ratio, CI = Confidence Interval | | | | |

# Table 3: Bivariate table with inmputed data

iter imp variable 1 1 Age\_at\_enrolment gender Ethnicity Duration\_of\_current\_illness Log10\_viralload Total\_CD4\_count Sodium Potassium Haemoglobin White\_cell\_count Lymphocyte\_count Neutrophils Addisons\_disease 1 2 Age\_at\_enrolment gender Ethnicity Duration\_of\_current\_illness Log10\_viralload Total\_CD4\_count Sodium Potassium Haemoglobin White\_cell\_count Lymphocyte\_count Neutrophils Addisons\_disease 1 3 Age\_at\_enrolment gender Ethnicity Duration\_of\_current\_illness Log10\_viralload Total\_CD4\_count Sodium Potassium Haemoglobin White\_cell\_count Lymphocyte\_count Neutrophils Addisons\_disease 1 4 Age\_at\_enrolment gender Ethnicity Duration\_of\_current\_illness Log10\_viralload Total\_CD4\_count Sodium Potassium Haemoglobin White\_cell\_count Lymphocyte\_count Neutrophils Addisons\_disease 1 5 Age\_at\_enrolment gender Ethnicity Duration\_of\_current\_illness Log10\_viralload Total\_CD4\_count Sodium Potassium Haemoglobin White\_cell\_count Lymphocyte\_count 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| Characteristic | N | HR1 | 95% CI1 | p-value |
| --- | --- | --- | --- | --- |
| Age\_at\_enrolment | 431 | 1.02 | 0.99, 1.05 | 0.2 |
| gender | 431 | 0.77 | 0.45, 1.33 | 0.3 |
| Ethnicity | 431 | 0.88 | 0.41, 1.86 | 0.7 |
| Duration\_of\_current\_illness | 431 | 1.00 | 0.99, 1.01 | 0.7 |
| Log10\_viralload | 431 | 1.51 | 1.22, 1.87 | <0.001 |
| Total\_CD4\_count | 431 | 0.99 | 0.98, 1.00 | 0.2 |
| Sodium | 431 | 0.99 | 0.95, 1.03 | 0.6 |
| Potassium | 431 | 0.86 | 0.65, 1.14 | 0.3 |
| Haemoglobin | 431 | 1.00 | 0.97, 1.02 | 0.8 |
| White\_cell\_count | 431 | 1.00 | 1.00, 1.00 | 0.8 |
| Lymphocyte\_count | 431 | 0.95 | 0.90, 1.00 | 0.068 |
| Neutrophils | 431 | 0.98 | 0.96, 0.99 | 0.010 |
| Addisons\_disease | 431 | 0.95 | 0.38, 2.38 | >0.9 |
| 1HR = Hazard Ratio, CI = Confidence Interval | | | | |

# multivariate table (generated with imputed data)

The rule of thumb for MV models such as this on you need at least 10 people per outcome. We have 53 people with the outcome, yet we have 6 variables adjusted for in the model (using stepwise regression). I suggest we remove one variable from the list that you think may not be biologically contributing in the relationship. (see accompanying file)

# ————————————————————————————————–

# Initial Model:

Call: coxph(formula = as.formula(paste(“Surv(”, Time, “,”, Status, “) ~”, paste(in.variable, collapse = “+”), sep = ““)), data = data, method =”efron”)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.05267 0.94869 0.46993 -0.112 0.911

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.9487 1.054 0.3777 2.383

Concordance= 0.502 (se = 0.021 ) Likelihood ratio test= 0.01 on 1 df, p=0.9 Wald test = 0.01 on 1 df, p=0.9 Score (logrank) test = 0.01 on 1 df, p=0.9

# ————————————————————————————————–

### iter num = 1, Forward Selection by LR Test: + Log10\_viralload

Call: coxph(formula = Surv(ttdeath, mortality) ~ Addisons\_disease + Log10\_viralload, data = data, method = “efron”)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.5212 0.5938 0.4800 -1.086 0.278  
Log10\_viralload 0.4420 1.5557 0.1124 3.930 8.49e-05 \*\*\* — Signif. codes: 0 ‘***’ 0.001 ’****’ 0.01 ’*’ 0.05 ‘.’ 0.1 ’ ’ 1

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.5938 1.6840 0.2318 1.521 Log10\_viralload 1.5557 0.6428 1.2480 1.939

Concordance= 0.662 (se = 0.038 ) Likelihood ratio test= 17.55 on 2 df, p=2e-04 Wald test = 15.53 on 2 df, p=4e-04 Score (logrank) test = 16.37 on 2 df, p=3e-04

————— Variance Inflating Factor (VIF) ————— Multicollinearity Problem: Variance Inflating Factor (VIF) is bigger than 10 (Continuous Variable) or is bigger than 2.5 (Categorical Variable) Addisons\_disease Log10\_viralload 1.040355 1.040355 # ————————————————————————————————– ### iter num = 2, Forward Selection by LR Test: + Neutrophils Call: coxph(formula = Surv(ttdeath, mortality) ~ Addisons\_disease + Log10\_viralload + Neutrophils, data = data, method = “efron”)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.502222 0.605184 0.482248 -1.041 0.29768  
Log10\_viralload 0.481114 1.617876 0.111753 4.305 1.67e-05 \* **Neutrophils -0.028440 0.971960 0.009859 -2.885 0.00392**  — Signif. codes: 0 ‘***’ 0.001 ’****’ 0.01 ’*’ 0.05 ‘.’ 0.1 ’ ’ 1

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.6052 1.6524 0.2352 1.5573 Log10\_viralload 1.6179 0.6181 1.2996 2.0140 Neutrophils 0.9720 1.0288 0.9534 0.9909

Concordance= 0.719 (se = 0.031 ) Likelihood ratio test= 33.08 on 3 df, p=3e-07 Wald test = 25.53 on 3 df, p=1e-05 Score (logrank) test = 19.86 on 3 df, p=2e-04

————— Variance Inflating Factor (VIF) ————— Multicollinearity Problem: Variance Inflating Factor (VIF) is bigger than 10 (Continuous Variable) or is bigger than 2.5 (Categorical Variable) Addisons\_disease Log10\_viralload Neutrophils 1.048458 1.056044 1.008101 # ————————————————————————————————– ### iter num = 3, Forward Selection by LR Test: + Lymphocyte\_count Call: coxph(formula = Surv(ttdeath, mortality) ~ Addisons\_disease + Log10\_viralload + Neutrophils + Lymphocyte\_count, data = data, method = “efron”)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.482495 0.617241 0.479344 -1.007 0.31414  
Log10\_viralload 0.549491 1.732371 0.113891 4.825 1.4e-06  ***Neutrophils -0.027433 0.972939 0.009859 -2.782 0.00539***  *Lymphocyte\_count -0.076341 0.926500 0.030302 -2.519 0.01176*   
— Signif. codes: 0 ‘***’ 0.001 ’****’ 0.01 ’*’ 0.05 ‘.’ 0.1 ’ ’ 1

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.6172 1.6201 0.2412 1.5793 Log10\_viralload 1.7324 0.5772 1.3858 2.1656 Neutrophils 0.9729 1.0278 0.9543 0.9919 Lymphocyte\_count 0.9265 1.0793 0.8731 0.9832

Concordance= 0.751 (se = 0.032 ) Likelihood ratio test= 41.85 on 4 df, p=2e-08 Wald test = 33.17 on 4 df, p=1e-06 Score (logrank) test = 29.39 on 4 df, p=7e-06

————— Variance Inflating Factor (VIF) ————— Multicollinearity Problem: Variance Inflating Factor (VIF) is bigger than 10 (Continuous Variable) or is bigger than 2.5 (Categorical Variable) Addisons\_disease Log10\_viralload Neutrophils Lymphocyte\_count 1.038052 1.087942 1.009247 1.041191 # ————————————————————————————————– ### iter num = 4, Forward Selection by LR Test: + Potassium Call: coxph(formula = Surv(ttdeath, mortality) ~ Addisons\_disease + Log10\_viralload + Neutrophils + Lymphocyte\_count + Potassium, data = data, method = “efron”)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.570177 0.565425 0.485979 -1.173 0.24069  
Log10\_viralload 0.573367 1.774231 0.116422 4.925 8.44e-07 \* **Neutrophils -0.026815 0.973541 0.009989 -2.685 0.00726**  Lymphocyte\_count -0.079017 0.924024 0.030314 -2.607 0.00915 \*\* Potassium -0.148740 0.861793 0.140028 -1.062 0.28814  
— Signif. codes: 0 ‘***’ 0.001 ’****’ 0.01 ’*’ 0.05 ‘.’ 0.1 ’ ’ 1

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.5654 1.7686 0.2181 1.4657 Log10\_viralload 1.7742 0.5636 1.4122 2.2290 Neutrophils 0.9735 1.0272 0.9547 0.9928 Lymphocyte\_count 0.9240 1.0822 0.8707 0.9806 Potassium 0.8618 1.1604 0.6550 1.1340

Concordance= 0.755 (se = 0.032 ) Likelihood ratio test= 45.25 on 5 df, p=1e-08 Wald test = 34.27 on 5 df, p=2e-06 Score (logrank) test = 31.28 on 5 df, p=8e-06

————— Variance Inflating Factor (VIF) ————— Multicollinearity Problem: Variance Inflating Factor (VIF) is bigger than 10 (Continuous Variable) or is bigger than 2.5 (Categorical Variable) Addisons\_disease Log10\_viralload Neutrophils Lymphocyte\_count 1.059779 1.100280 1.012553 1.046427 Potassium 1.018546 # ————————————————————————————————– ### iter num = 5, Forward Selection by LR Test: + gender Call: coxph(formula = Surv(ttdeath, mortality) ~ Addisons\_disease + Log10\_viralload + Neutrophils + Lymphocyte\_count + Potassium + gender, data = data, method = “efron”)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.62034 0.53776 0.48611 -1.276 0.20191  
Log10\_viralload 0.57125 1.77047 0.11518 4.960 7.07e-07 \* **Neutrophils -0.02841 0.97199 0.01014 -2.801 0.00509**  Lymphocyte\_count -0.08293 0.92041 0.03048 -2.721 0.00651 \*\* Potassium -0.11776 0.88891 0.12420 -0.948 0.34307  
gender -0.42063 0.65664 0.28399 -1.481 0.13857  
— Signif. codes: 0 ‘***’ 0.001 ’****’ 0.01 ’*’ 0.05 ‘.’ 0.1 ’ ’ 1

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.5378 1.8596 0.2074 1.3943 Log10\_viralload 1.7705 0.5648 1.4127 2.2189 Neutrophils 0.9720 1.0288 0.9529 0.9915 Lymphocyte\_count 0.9204 1.0865 0.8670 0.9771 Potassium 0.8889 1.1250 0.6968 1.1339 gender 0.6566 1.5229 0.3764 1.1457

Concordance= 0.763 (se = 0.032 ) Likelihood ratio test= 47.46 on 6 df, p=2e-08 Wald test = 37.02 on 6 df, p=2e-06 Score (logrank) test = 32.74 on 6 df, p=1e-05

————— Variance Inflating Factor (VIF) ————— Multicollinearity Problem: Variance Inflating Factor (VIF) is bigger than 10 (Continuous Variable) or is bigger than 2.5 (Categorical Variable) Addisons\_disease Log10\_viralload Neutrophils Lymphocyte\_count 1.064418 1.105895 1.028173 1.062836 Potassium gender 1.031642 1.056035 # ================================================================================================== \*\*\* Stepwise Final Model (in.lr.test: sle = 0.2; out.lr.test: sls = 0.2; variable selection restrict in vif = 999): Call: coxph(formula = Surv(ttdeath, mortality) ~ Addisons\_disease + Log10\_viralload + Neutrophils + Lymphocyte\_count + Potassium + gender, data = data, method = “efron”)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.62034 0.53776 0.48611 -1.276 0.20191  
Log10\_viralload 0.57125 1.77047 0.11518 4.960 7.07e-07 \* **Neutrophils -0.02841 0.97199 0.01014 -2.801 0.00509**  Lymphocyte\_count -0.08293 0.92041 0.03048 -2.721 0.00651 \*\* Potassium -0.11776 0.88891 0.12420 -0.948 0.34307  
gender -0.42063 0.65664 0.28399 -1.481 0.13857  
— Signif. codes: 0 ‘***’ 0.001 ’****’ 0.01 ’*’ 0.05 ‘.’ 0.1 ’ ’ 1

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.5378 1.8596 0.2074 1.3943 Log10\_viralload 1.7705 0.5648 1.4127 2.2189 Neutrophils 0.9720 1.0288 0.9529 0.9915 Lymphocyte\_count 0.9204 1.0865 0.8670 0.9771 Potassium 0.8889 1.1250 0.6968 1.1339 gender 0.6566 1.5229 0.3764 1.1457

Concordance= 0.763 (se = 0.032 ) Likelihood ratio test= 47.46 on 6 df, p=2e-08 Wald test = 37.02 on 6 df, p=2e-06 Score (logrank) test = 32.74 on 6 df, p=1e-05

————— Variance Inflating Factor (VIF) ————— Multicollinearity Problem: Variance Inflating Factor (VIF) is bigger than 10 (Continuous Variable) or is bigger than 2.5 (Categorical Variable) Addisons\_disease Log10\_viralload Neutrophils Lymphocyte\_count 1.064418 1.105895 1.028173 1.062836 Potassium gender 1.031642 1.056035 Call: survival::coxph(formula = Surv(ttdeath, mortality) ~ Addisons\_disease + Log10\_viralload + Neutrophils + Lymphocyte\_count + Potassium + gender, data = model\_dataset)

n= 431, number of events= 53

coef exp(coef) se(coef) z Pr(>|z|)

Addisons\_disease -0.62034 0.53776 0.48611 -1.276 0.20191  
Log10\_viralload 0.57125 1.77047 0.11518 4.960 7.07e-07 \* **Neutrophils -0.02841 0.97199 0.01014 -2.801 0.00509**  Lymphocyte\_count -0.08293 0.92041 0.03048 -2.721 0.00651 \*\* Potassium -0.11776 0.88891 0.12420 -0.948 0.34307  
gender -0.42063 0.65664 0.28399 -1.481 0.13857  
— Signif. codes: 0 ‘***’ 0.001 ’****’ 0.01 ’*’ 0.05 ‘.’ 0.1 ’ ’ 1

exp(coef) exp(-coef) lower .95 upper .95

Addisons\_disease 0.5378 1.8596 0.2074 1.3943 Log10\_viralload 1.7705 0.5648 1.4127 2.2189 Neutrophils 0.9720 1.0288 0.9529 0.9915 Lymphocyte\_count 0.9204 1.0865 0.8670 0.9771 Potassium 0.8889 1.1250 0.6968 1.1339 gender 0.6566 1.5229 0.3764 1.1457

Concordance= 0.763 (se = 0.032 ) Likelihood ratio test= 47.46 on 6 df, p=2e-08 Wald test = 37.02 on 6 df, p=2e-06 Score (logrank) test = 32.74 on 6 df, p=1e-05

Addisons\_disease Log10\_viralload Neutrophils Lymphocyte\_count -0.62033692 0.57124642 -0.02841188 -0.08293436 Potassium gender -0.11775709 -0.42062579 2.5 % 97.5 % Addisons\_disease -1.57309989 0.332426058 Log10\_viralload 0.34549554 0.796997300 Neutrophils -0.04829079 -0.008532977 Lymphocyte\_count -0.14267113 -0.023197598 Potassium -0.36118742 0.125673241 gender -0.97723351 0.135981936