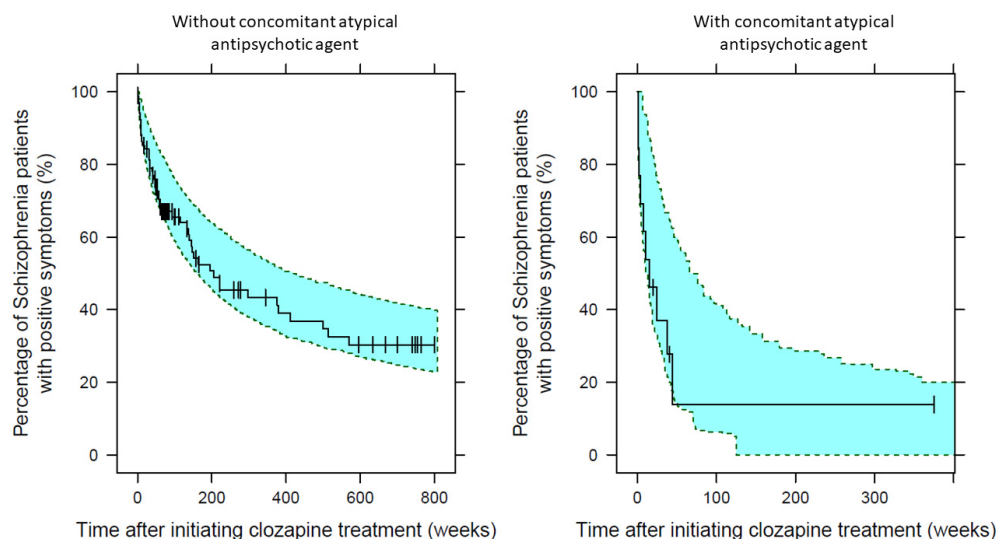


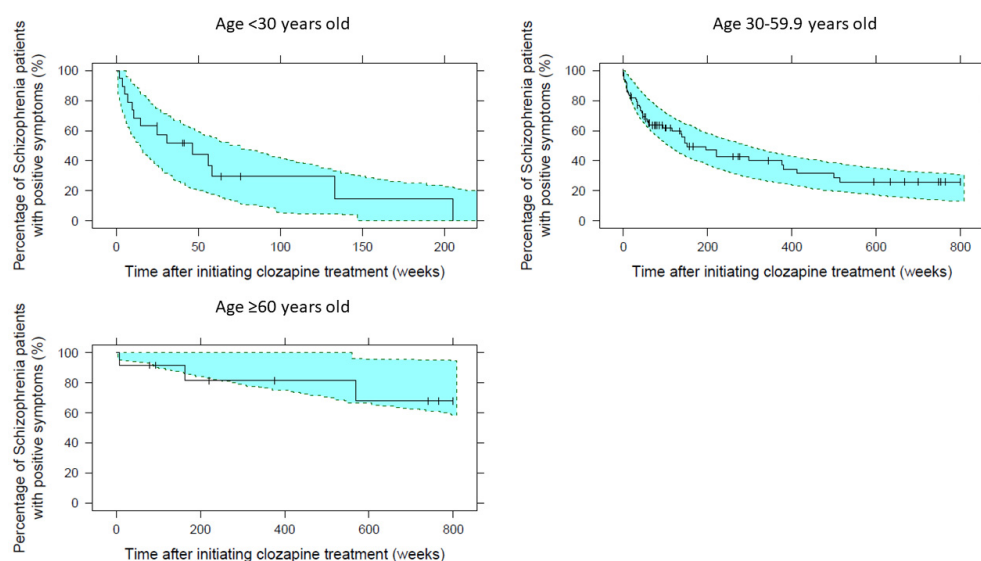


# Supplementary Materials: A Repeated Time-to-Positive Symptoms Improvement among Malaysian Patients with Schizophrenia Spectrum Disorders Treated with Clozapine

Orwa Albitar, Sabariah Noor Harun, Siti Nor Aizah Ahmad and Siti Maisharah Sheikh Ghadzi



**Figure S1.** The final repeated time-to-event model of improving positive symptoms after the onset of clozapine treatment stratified on concomitant atypical antipsychotic. The solid line represents the observed Kaplan–Meier survival plot while vertical lines mark censored observations with a mean time, [range] of 306 weeks [8–800]. Shaded areas represent the 95% prediction interval from 1000 simulated datasets. Patients who received a second atypical antipsychotic agent have shown improvement within 50 weeks of clozapine initiation.



**Figure S2.** The final repeated time-to-event model of improving positive symptoms after the onset of clozapine treatment stratified on age groups. Young patients less than 30 years old have improved within 200 weeks of clozapine initiation.

### Control stream

```
$PROB RTTE CLZ
$INPUT ID TIME DV EVID FLAG AGE CTDD ATA
$DATA simdata.csv IGNORE=@
$SUBROUTINES ADVAN=6 TOL=6
$MODEL COMP=(HAZARD)
$PK
IF(NEWIND.NE.2) TP=0; reset the time of the last event.
LAM          = THETA(1)*EXP(ETA(1)); scale parameter of Weibull function
SHP          = THETA(2); shape parameter of Weibull function
COVAGE      = THETA(3); covariate factor of age
COVATA      = THETA(4); covariate factor of concomitant atypical antipsychotics
COVCTDD     = THETA(5); covariate factor of cumulative dose at 6 months
$DES
DEL=1E-6; to keep from taking 0**power
DADT(1)      = LAM*SHP*(LAM*(T-TP)+DEL)**(SHP-1)*EXP(COVAGE*(AGE-
40.8)+COVATA*ATA+COVCTDD*(CTDD-34.15))
$ERROR
;-----RTTE Model-----
IF(NEWIND.NE.2) OLDCHZ = 0; reset the cumulative hazard
CHZ = A(1) - OLDCHZ; cumulative hazard
OLDCHZ = A(1); rename old cumulative hazard
SUR = EXP(-CHZ); survival probability
DELX = 1E-6
HAZNOW=LAM*SHP*(LAM*(TIME-TP)+DELX)**(SHP-1)*EXP(COVAGE*(AGE-
40.8)+COVATA*ATA+COVCTDD*(CTDD-34.15))
IF(DV.EQ.0) Y=SUR; censored event (prob of survival)
IF(DV.NE.0) Y=SUR*HAZNOW; prob density function of event
IF(FLAG.EQ.2) TP = TIME; for RTTE. TP is time of previous event
;----- INITIAL ESTIMATES -----
$THETA (0.0001, 0.002172); LAMBDA
$THETA (0.0001, 0.8526); SHAPE
$THETA -0.043833; COVAGE
$THETA 1.3865; COVATA
$THETA 0.018343; COVCTDD
$OMEGA 1.0236; for RTTE, IIV is needed
$ESTIMATION NOABORT MAXEVAL=0 METHOD=1 LAPLACE LIKE PRINT=1
MSFO=msfb2 SIGL=9 NSIG=3
$COVARIANCE PRINT=E
$TAB ID TIME DV EVID LAM SHP ONEHEADER NOPRINT FILE=sdtab3
```

### Simulated data

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2.00,449.00,1.00,0.00,2.00,33.03,24.97,1.00
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2.00,555.00,1.00,0.00,2.00,35.03,24.97,1.00
```

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49.00,472.00,1.00,0.00,2.00,34.06,31.44,0.00  
49.00,520.00,1.00,0.00,2.00,34.96,31.44,0.00  
49.00,618.00,1.00,0.00,2.00,36.86,31.44,0.00  
49.00,659.00,1.00,0.00,2.00,37.56,31.44,0.00  
49.00,800.00,0.00,0.00,8.00,40.26,31.44,0.00  
50.00,0.00,0.00,3.00,0.00,47.77,30.89,0.00  
50.00,800.00,0.00,0.00,8.00,63.07,30.89,0.00  
51.00,0.00,0.00,3.00,0.00,27.21,41.89,0.00  
51.00,409.00,1.00,0.00,2.00,35.01,41.89,0.00  
51.00,800.00,0.00,0.00,8.00,42.51,41.89,0.00  
52.00,0.00,0.00,3.00,0.00,24.56,46.74,0.00  
52.00,21.00,1.00,0.00,2.00,24.66,46.74,0.00  
52.00,70.00,1.00,0.00,2.00,25.66,46.74,0.00  
52.00,110.00,1.00,0.00,2.00,26.36,46.74,0.00  
52.00,111.00,1.00,0.00,2.00,26.36,46.74,0.00  
52.00,248.00,1.00,0.00,2.00,29.06,46.74,0.00  
52.00,390.00,1.00,0.00,2.00,31.76,46.74,0.00  
52.00,467.00,1.00,0.00,2.00,33.26,46.74,0.00  
52.00,800.00,0.00,0.00,8.00,39.56,46.74,0.00  
53.00,0.00,0.00,3.00,0.00,43.73,38.67,0.00  
53.00,124.00,1.00,0.00,2.00,46.03,38.67,0.00  
53.00,418.00,1.00,0.00,2.00,51.73,38.67,0.00  
53.00,800.00,0.00,0.00,8.00,59.03,38.67,0.00  
54.00,0.00,0.00,3.00,0.00,71.97,38.88,0.00

54.00,139.00,1.00,0.00,2.00,74.57,38.88,0.00  
54.00,800.00,0.00,0.00,8.00,87.27,38.88,0.00  
55.00,0.00,0.00,3.00,0.00,20.54,37.16,1.00  
55.00,32.00,1.00,0.00,2.00,21.04,37.16,1.00  
55.00,53.00,1.00,0.00,2.00,21.44,37.16,1.00  
55.00,140.00,1.00,0.00,2.00,23.14,37.16,1.00  
55.00,237.00,1.00,0.00,2.00,24.94,37.16,1.00  
55.00,317.00,1.00,0.00,2.00,26.54,37.16,1.00  
55.00,325.00,1.00,0.00,2.00,26.64,37.16,1.00  
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55.00,367.00,1.00,0.00,2.00,27.44,37.16,1.00  
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55.00,529.00,1.00,0.00,2.00,30.54,37.16,1.00  
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55.00,697.00,1.00,0.00,2.00,33.84,37.16,1.00  
55.00,727.00,1.00,0.00,2.00,34.34,37.16,1.00  
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55.00,800.00,0.00,0.00,8.00,35.74,37.16,1.00  
56.00,0.00,0.00,3.00,0.00,59.35,34.85,0.00  
56.00,222.00,1.00,0.00,2.00,53.05,34.85,0.00  
56.00,800.00,0.00,0.00,8.00,64.05,34.85,0.00  
57.00,0.00,0.00,3.00,0.00,47.68,43.82,0.00  
57.00,800.00,0.00,0.00,8.00,62.38,43.82,0.00  
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59.00,0.00,0.00,3.00,0.00,34.44,53.36,0.00  
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59.00,800.00,0.00,0.00,8.00,49.64,53.36,0.00  
60.00,0.00,0.00,3.00,0.00,60.02,2.38,0.00  
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61.00,0.00,0.00,3.00,0.00,53.46,47.14,0.00  
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62.00,0.00,0.00,3.00,0.00,42.45,63.45,0.00  
62.00,436.00,1.00,0.00,2.00,50.75,63.45,0.00  
62.00,800.00,0.00,0.00,8.00,57.65,63.45,0.00  
63.00,0.00,0.00,3.00,0.00,16.28,20.72,0.00  
63.00,394.00,1.00,0.00,2.00,23.88,20.72,0.00  
63.00,407.00,1.00,0.00,2.00,24.08,20.72,0.00  
63.00,800.00,0.00,0.00,8.00,31.68,20.72,0.00  
64.00,0.00,0.00,3.00,0.00,31.06,46.44,0.00  
64.00,800.00,0.00,0.00,8.00,46.26,46.44,0.00  
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65.00,4.00,1.00,0.00,2.00,30.67,116.43,0.00  
65.00,6.00,1.00,0.00,2.00,30.67,116.43,0.00  
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65.00,383.00,1.00,0.00,2.00,37.87,116.43,0.00  
65.00,449.00,1.00,0.00,2.00,39.17,116.43,0.00  
65.00,478.00,1.00,0.00,2.00,39.77,116.43,0.00  
65.00,518.00,1.00,0.00,2.00,40.47,116.43,0.00  
65.00,546.00,1.00,0.00,2.00,41.07,116.43,0.00  
65.00,620.00,1.00,0.00,2.00,42.47,116.43,0.00  
65.00,700.00,1.00,0.00,2.00,43.97,116.43,0.00  
65.00,707.00,1.00,0.00,2.00,44.17,116.43,0.00  
65.00,800.00,0.00,0.00,8.00,45.87,116.43,0.00  
66.00,0.00,0.00,3.00,0.00,20.63,11.67,0.00  
66.00,714.00,1.00,0.00,2.00,33.73,11.67,0.00  
66.00,800.00,0.00,0.00,8.00,35.43,11.67,0.00  
67.00,0.00,0.00,3.00,0.00,26.35,59.85,0.00  
67.00,1.00,1.00,0.00,2.00,26.35,59.85,0.00  
67.00,95.00,1.00,0.00,2.00,28.15,59.85,0.00  
67.00,161.00,1.00,0.00,2.00,29.45,59.85,0.00  
67.00,204.00,1.00,0.00,2.00,30.25,59.85,0.00  
67.00,302.00,1.00,0.00,2.00,32.15,59.85,0.00  
67.00,379.00,1.00,0.00,2.00,33.55,59.85,0.00  
67.00,468.00,1.00,0.00,2.00,35.25,59.85,0.00  
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67.00,523.00,1.00,0.00,2.00,36.35,59.85,0.00  
67.00,532.00,1.00,0.00,2.00,36.55,59.85,0.00  
67.00,618.00,1.00,0.00,2.00,38.15,59.85,0.00  
67.00,722.00,1.00,0.00,2.00,40.15,59.85,0.00  
67.00,800.00,0.00,0.00,8.00,41.65,59.85,0.00  
68.00,0.00,0.00,3.00,0.00,19.28,33.82,0.00  
68.00,199.00,1.00,0.00,2.00,23.08,33.82,0.00  
68.00,603.00,1.00,0.00,2.00,30.78,33.82,0.00  
68.00,800.00,0.00,0.00,8.00,34.58,33.82,0.00  
69.00,0.00,0.00,3.00,0.00,34.12,34.58,0.00  
69.00,27.00,1.00,0.00,2.00,34.52,34.58,0.00  
69.00,71.00,1.00,0.00,2.00,35.42,34.58,0.00  
69.00,513.00,1.00,0.00,2.00,43.92,34.58,0.00  
69.00,699.00,1.00,0.00,2.00,47.52,34.58,0.00  
69.00,800.00,0.00,0.00,8.00,49.42,34.58,0.00  
70.00,0.00,0.00,3.00,0.00,54.98,51.52,0.00  
70.00,42.00,1.00,0.00,2.00,48.48,51.52,0.00  
70.00,86.00,1.00,0.00,2.00,49.28,51.52,0.00  
70.00,261.00,1.00,0.00,2.00,52.68,51.52,0.00  
70.00,800.00,0.00,0.00,8.00,62.98,51.52,0.00  
71.00,0.00,0.00,3.00,0.00,31.44,31.86,0.00  
71.00,23.00,1.00,0.00,2.00,31.94,31.86,0.00  
71.00,110.00,1.00,0.00,2.00,33.64,31.86,0.00  
71.00,578.00,1.00,0.00,2.00,42.54,31.86,0.00  
71.00,800.00,0.00,0.00,8.00,46.84,31.86,0.00  
72.00,0.00,0.00,3.00,0.00,24.14,98.06,1.00  
72.00,17.00,1.00,0.00,2.00,20.24,98.06,1.00  
72.00,44.00,1.00,0.00,2.00,20.74,98.06,1.00  
72.00,62.00,1.00,0.00,2.00,21.14,98.06,1.00  
72.00,87.00,1.00,0.00,2.00,21.54,98.06,1.00  
72.00,160.00,1.00,0.00,2.00,22.94,98.06,1.00



72.00,177.00,1.00,0.00,2.00,23.34,98.06,1.00  
72.00,196.00,1.00,0.00,2.00,23.64,98.06,1.00  
72.00,199.00,1.00,0.00,2.00,23.74,98.06,1.00  
72.00,220.00,1.00,0.00,2.00,24.14,98.06,1.00  
72.00,259.00,1.00,0.00,2.00,24.84,98.06,1.00  
72.00,279.00,1.00,0.00,2.00,25.24,98.06,1.00  
72.00,340.00,1.00,0.00,2.00,26.44,98.06,1.00  
72.00,353.00,1.00,0.00,2.00,26.64,98.06,1.00  
72.00,540.00,1.00,0.00,2.00,30.24,98.06,1.00  
72.00,546.00,1.00,0.00,2.00,30.34,98.06,1.00  
72.00,572.00,1.00,0.00,2.00,30.84,98.06,1.00  
72.00,646.00,1.00,0.00,2.00,32.24,98.06,1.00  
72.00,747.00,1.00,0.00,2.00,34.24,98.06,1.00  
72.00,800.00,0.00,0.00,8.00,35.24,98.06,1.00  
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73.00,21.00,1.00,0.00,2.00,22.44,47.76,0.00  
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76.00,0.00,0.00,3.00,0.00,41.27,88.63,0.00  
76.00,40.00,1.00,0.00,2.00,42.07,88.63,0.00  
76.00,73.00,1.00,0.00,2.00,42.67,88.63,0.00  
76.00,94.00,1.00,0.00,2.00,43.07,88.63,0.00  
76.00,135.00,1.00,0.00,2.00,43.87,88.63,0.00  
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76.00,578.00,1.00,0.00,2.00,52.37,88.63,0.00  
76.00,755.00,1.00,0.00,2.00,55.77,88.63,0.00  
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77.00,0.00,0.00,3.00,0.00,37.50,39.35,0.00  
77.00,190.00,1.00,0.00,2.00,41.10,39.35,0.00  
77.00,432.00,1.00,0.00,2.00,45.70,39.35,0.00  
77.00,800.00,0.00,0.00,8.00,52.80,39.35,0.00  
78.00,0.00,0.00,3.00,0.00,52.57,52.13,0.00  
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78.00,800.00,0.00,0.00,8.00,67.87,52.13,0.00  
79.00,0.00,0.00,3.00,0.00,45.65,27.30,0.00  
79.00,44.00,1.00,0.00,2.00,46.35,27.30,0.00  
79.00,137.00,1.00,0.00,2.00,48.15,27.30,0.00  
79.00,208.00,1.00,0.00,2.00,49.45,27.30,0.00  
79.00,781.00,1.00,0.00,2.00,60.45,27.30,0.00  
79.00,800.00,0.00,0.00,8.00,60.85,27.30,0.00  
80.00,0.00,0.00,3.00,0.00,35.58,43.02,0.00  
80.00,23.00,1.00,0.00,2.00,29.38,43.02,0.00  
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80.00,800.00,0.00,0.00,8.00,44.28,43.02,0.00  
81.00,0.00,0.00,3.00,0.00,44.72,83.78,0.00  
81.00,800.00,0.00,0.00,8.00,59.82,83.78,0.00  
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82.00,480.00,1.00,0.00,2.00,48.18,33.57,0.00  
82.00,603.00,1.00,0.00,2.00,50.48,33.57,0.00  
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83.00,0.00,0.00,3.00,0.00,65.61,8.79,0.00  
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84.00,0.00,0.00,3.00,0.00,60.16,114.94,0.00

84.00,57.00,1.00,0.00,2.00,61.16,114.94,0.00  
84.00,210.00,1.00,0.00,2.00,64.16,114.94,0.00  
84.00,218.00,1.00,0.00,2.00,64.26,114.94,0.00  
84.00,548.00,1.00,0.00,2.00,70.66,114.94,0.00  
84.00,674.00,1.00,0.00,2.00,73.06,114.94,0.00  
84.00,800.00,0.00,0.00,8.00,75.46,114.94,0.00  
85.00,0.00,0.00,3.00,0.00,39.18,57.43,1.00  
85.00,47.00,1.00,0.00,2.00,37.58,57.43,1.00  
85.00,53.00,1.00,0.00,2.00,37.68,57.43,1.00  
85.00,99.00,1.00,0.00,2.00,38.58,57.43,1.00  
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85.00,178.00,1.00,0.00,2.00,40.08,57.43,1.00  
85.00,598.00,1.00,0.00,2.00,48.08,57.43,1.00  
85.00,637.00,1.00,0.00,2.00,48.88,57.43,1.00  
85.00,681.00,1.00,0.00,2.00,49.68,57.43,1.00  
85.00,800.00,0.00,0.00,8.00,51.98,57.43,1.00  
86.00,0.00,0.00,3.00,0.00,23.42,43.68,0.00  
86.00,258.00,1.00,0.00,2.00,29.02,43.68,0.00  
86.00,403.00,1.00,0.00,2.00,31.82,43.68,0.00  
86.00,507.00,1.00,0.00,2.00,33.82,43.68,0.00  
86.00,679.00,1.00,0.00,2.00,37.12,43.68,0.00  
86.00,800.00,0.00,0.00,8.00,39.42,43.68,0.00  
87.00,0.00,0.00,3.00,0.00,20.05,51.75,1.00  
87.00,6.00,1.00,0.00,2.00,26.65,51.75,1.00  
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87.00,86.00,1.00,0.00,2.00,28.25,51.75,1.00  
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87.00,248.00,1.00,0.00,2.00,31.35,51.75,1.00  
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87.00,558.00,1.00,0.00,2.00,37.25,51.75,1.00  
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87.00,657.00,1.00,0.00,2.00,39.15,51.75,1.00

87.00,659.00,1.00,0.00,2.00,39.15,51.75,1.00  
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87.00,697.00,1.00,0.00,2.00,39.95,51.75,1.00  
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88.00,0.00,0.00,3.00,0.00,40.91,32.19,0.00  
88.00,800.00,0.00,0.00,8.00,56.31,32.19,0.00  
89.00,0.00,0.00,3.00,0.00,42.86,33.24,0.00  
89.00,800.00,0.00,0.00,8.00,58.96,33.24,0.00  
90.00,0.00,0.00,3.00,0.00,34.38,20.42,0.00  
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91.00,0.00,0.00,3.00,0.00,24.84,23.36,0.00  
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91.00,800.00,0.00,0.00,8.00,40.14,23.36,0.00  
92.00,0.00,0.00,3.00,0.00,38.61,51.00,0.00  
92.00,10.00,1.00,0.00,2.00,38.71,51.00,0.00  
92.00,104.00,1.00,0.00,2.00,40.51,51.00,0.00  
92.00,800.00,0.00,0.00,8.00,53.81,51.00,0.00  
93.00,0.00,0.00,3.00,0.00,30.79,61.71,0.00  
93.00,436.00,1.00,0.00,2.00,39.09,61.71,0.00  
93.00,505.00,1.00,0.00,2.00,40.49,61.71,0.00  
93.00,643.00,1.00,0.00,2.00,43.09,61.71,0.00  
93.00,800.00,0.00,0.00,8.00,46.09,61.71,0.00  
94.00,0.00,0.00,3.00,0.00,54.02,20.08,0.00  
94.00,800.00,0.00,0.00,8.00,69.22,20.08,0.00  
95.00,0.00,0.00,3.00,0.00,33.43,47.46,0.00  
95.00,800.00,0.00,0.00,8.00,48.83,47.46,0.00  
96.00,0.00,0.00,3.00,0.00,30.55,39.05,0.00  
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96.00,755.00,1.00,0.00,2.00,45.05,39.05,0.00  
96.00,800.00,0.00,0.00,8.00,45.85,39.05,0.00  
97.00,0.00,0.00,3.00,0.00,51.89,15.11,0.00  
97.00,207.00,1.00,0.00,2.00,52.19,15.11,0.00  
97.00,642.00,1.00,0.00,2.00,60.59,15.11,0.00  
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117.00,0.00,0.00,3.00,0.00,61.00,20.20,0.00  
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118.00,0.00,0.00,3.00,0.00,48.66,45.44,0.00  
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