Preliminary Analysis Report: Mortality Risk in Opioid vs. Poly-Drug Users

A. Crude Mortality Rates

Code block

```
episodes %>%
  group_by(drug) %>%
  summarise(
    deaths = sum(drd_flag),
    person_years = sum(days_at_risk)/365.25,
    mortality_rate = (deaths / person_years) * 1000
  )


# A tibble: 2 × 4
  drug    person_years deaths rate_per_1000
  <chr>          <dbl>  <dbl>         <dbl>
1 opioids      233933.   3413          14.6
2 poly          15774.    220          13.9
```

Results:

- **Opioids-only**:
  - 3,413 deaths
  - 233,933 person-years
  - **14.6 deaths/1,000 PY**

- **Poly-drug**:
  - 220 deaths
  - 15,774 person-years
  - **13.9 deaths/1,000 PY**

Interpretation: The raw mortality rates show marginally lower risk in poly-drug users (-4.8%), but this difference is within expected random variation.

B. Adjusted Survival Analysis (Cox Model)

Code block

```
> # Basic Cox model
> model <- coxph(Surv(days_at_risk, drd_flag) ~ drug + age + sex + nfod_count,
+                data = episodes)
> summary(model)
Call:
coxph(formula = Surv(days_at_risk, drd_flag) ~ drug + age + sex +
    nfod_count, data = episodes)

  n= 723972, number of events= 3633

                coef exp(coef)  se(coef)      z Pr(>|z|)
drugpoly   -0.028492  0.971911  0.069636 -0.409    0.682
age         0.026836  1.027200  0.002031 13.212   <2e-16 ***
sexM        0.047060  1.048185  0.036503  1.289    0.197
nfod_count  0.096347  1.101141  0.005136 18.760   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

           exp(coef) exp(-coef) lower .95 upper .95
drugpoly      0.9719     1.0289    0.8479     1.114
age           1.0272     0.9735    1.0231     1.031
sexM          1.0482     0.9540    0.9758     1.126
nfod_count    1.1011     0.9081    1.0901     1.112

Concordance= 0.597  (se = 0.005 )
Likelihood ratio test= 356.6  on 4 df,   p=<2e-16
Wald test            = 579.2  on 4 df,   p=<2e-16
Score (logrank) test = 589.7  on 4 df,   p=<2e-16
```

Parameter	exp(coef)	z-value	p-value	95% CI
drugpoly	0.972	-0.409	0.682	(0.848, 1.114)
age	1.027	13.212	<0.001	(1.023, 1.031)
sexM	1.048	1.289	0.197	(0.976, 1.126)
nfod_count	1.101	18.76	<0.001	(1.090, 1.112)

Key conclusion

1. drug type

   There was no significant difference in the risk of death between the -poly group and the opioids group (HR=0.97, p=0.68).

   - Possible causes:

   The number of people in the poly group in the sample is relatively small.

   The true effect of the drug may be masked by other variables, such as nfod_count.

2. age

   The older the age, the higher the risk of death (for every additional year, the risk increases by 2.7%).

   - Possible explanation:

   Elderly patients may have other concurrent diseases, increasing the risk of drug-related deaths.

3. Non-fatal drug overdose

   For each additional non-fatal drug overdose, the risk of death increases by 10.1%.

   - Non-fatal drug overdoses are strong predictors and can be used to identify high-risk patients.

4. Gender

   The risk of death for men was slightly higher (+4.8%), but the statistics were not significant (p=0.197).

   - Possible causes:

   Gender differences have a relatively small impact on drug-related deaths.

Interaction Effects in Opioid-Related Mortality Risk

1. Executive Summary

This analysis examines how the interaction between drug type (opioids vs. poly-drug use) and key risk factors (non-fatal overdose [NFO] history and age) influences drug-related death (DRD) risk. Using Cox proportional hazards models with interaction terms, we identified significant effect modifications that have important clinical implications.

Code block

```
model_drug_nfod <- coxph(
  Surv(days_at_risk, drd_flag) ~ drug * nfod_count + age + sex,
  data = episodes
)


model_drug_age <- coxph(
  Surv(days_at_risk, drd_flag) ~ drug * age + nfod_count + sex,
  data = episodes
)


> summary(model_drug_nfod)
Call:
coxph(formula = Surv(days_at_risk, drd_flag) ~ drug * nfod_count +
    age + sex, data = episodes)

  n= 723972, number of events= 3633

                       coef exp(coef)  se(coef)      z Pr(>|z|)
drugpoly           -0.083315  0.920061  0.073964 -1.126  0.25999
nfod_count          0.094918  1.099569  0.005281 17.974  < 2e-16 ***
age                 0.026857  1.027221  0.002032 13.216  < 2e-16 ***
```

```
sexM                0.046669  1.047776  0.036500  1.279  0.20103
drugpoly:nfod_count 0.097658  1.102586  0.035956  2.716  0.00661 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

                    exp(coef) exp(-coef) lower .95 upper .95
drugpoly               0.9201     1.0869    0.7959     1.064
nfod_count             1.0996     0.9094    1.0882     1.111
age                    1.0272     0.9735    1.0231     1.031
sexM                   1.0478     0.9544    0.9754     1.125
drugpoly:nfod_count    1.1026     0.9070    1.0276     1.183

Concordance= 0.597  (se = 0.005 )
Likelihood ratio test= 362.4  on 5 df,   p=<2e-16
Wald test            = 575.8  on 5 df,   p=<2e-16
Score (logrank) test = 590.3  on 5 df,   p=<2e-16

> summary(model_drug_age)
Call:
coxph(formula = Surv(days_at_risk, drd_flag) ~ drug * age + nfod_count +
    sex, data = episodes)

  n= 723972, number of events= 3633

                  coef exp(coef)  se(coef)      z Pr(>|z|)
drugpoly     -0.972495  0.378139  0.365367 -2.662  0.00777 **
age           0.025495  1.025823  0.002093 12.181  < 2e-16 ***
nfod_count    0.096591  1.101410  0.005145 18.773  < 2e-16 ***
sexM          0.045737  1.046799  0.036508  1.253  0.21028
drugpoly:age  0.022782  1.023044  0.008520  2.674  0.00749 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
drugpoly        0.3781     2.6445    0.1848    0.7738
age             1.0258     0.9748    1.0216    1.0300
nfod_count      1.1014     0.9079    1.0904    1.1126
sexM            1.0468     0.9553    0.9745    1.1244
drugpoly:age    1.0230     0.9775    1.0061    1.0403

Concordance= 0.598  (se = 0.005 )
Likelihood ratio test= 363.7  on 5 df,   p=<2e-16
Wald test            = 583.3  on 5 df,   p=<2e-16
Score (logrank) test = 594.5  on 5 df,   p=<2e-16
```

2. Key Findings

A. Interaction: Drug Type × NFO Count

Variable	HR	P-value	Interpretation
Baseline (opioids)	Ref	-	Reference group
Poly-drug use	0.92	0.260	8% lower baseline risk (NS)
NFO count (opioids)	1.10	<0.001	Each NFO → +9.96% risk
Interaction (poly:NFO)	1.10	0.007	Additional +10.26% risk in poly group

Combined Effect:

- Opioids-only: Each NFO → **+9.96%** DRD risk
- Poly-drug: Each NFO → **+20.22%** (9.96% + 10.26%) DRD risk

B. Interaction: Drug Type × Age

Variable	HR	P-value	Interpretation
Poly-drug use	0.38	0.008	62.2% lower baseline risk
Age (opioids)	1.03	<0.001	Each year → +2.58% risk
Interaction (poly:age)	1.02	0.007	Additional +2.30% risk/year in poly group

Combined Effect:

- Opioids-only: Each year → **+2.58%** DRD risk
- Poly-drug: Each year → **+4.88%** (2.58% + 2.30%) DRD risk

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3. Clinical Implications

Risk Amplification in Poly-Drug Users

1. **NFO History**
   - The mortality risk per NFO episode **doubles** in poly-drug users (+20.22% vs +9.96% in opioids-only).
   - *Mechanism*: Potential synergistic cardiotoxicity from opioid-cocaine combinations.

2. **Aging Effect**
   - Age-related risk increases **1.9× faster** in poly-drug users (+4.88%/year vs +2.58%/year).
   - *Mechanism*: Reduced drug metabolism exacerbates poly-drug toxicity in older patients.

3. **Baseline Paradox**
   - Despite lower baseline HR (0.38, p=0.008), poly-drug users experience:
     - Faster "risk acceleration" with NFOs/aging

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4. Limitations

- **Sample Size**: Poly-drug subgroup may be underpowered

6. Conclusion

Poly-drug use significantly amplifies the mortality risk associated with NFO history and aging. While these patients show lower baseline risk, their vulnerability to clinical deterioration escalates more rapidly than opioids-only users.