**SUPPLEMENTAL FILE**

**Mortality after acute kidney injury and acute interstitial nephritis in patients prescribed immune checkpoint inhibitor therapy**

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# Contents

*Table S1. ICD10 codes used to define immune-related adverse events*

| Irae | Icd10_code |
|---|---|
| **Pnuemonitis** | J69.0, J69.8 |
| **Hepatitis** | K75.0, K75.3, K75.4, K75.81, K75.89, K75.9 |
| **Adrenalitis** | E27.0, E27.1, E27.2, E27.3, E27.40, E27.49, E27.8, E27.9 |
| **Dermatitis** | L20.84, L20.9, L21.8, L21.9, L23.1, L23.2, L23.5, L23.9, L24.4, L24.5, L24.89, L24.9, L25.1, L25.5, L25.8, L25.9, L27.0, L27.1, L27.2, L30.0, L30.1, L30.4, L30.8, L30.9 |
| **Hypophysitis** | E23.0, E23.1, E23.3, E23.6, E23.7 |
| **Thyroiditis** | E06.0, E06.1, E06.2, E06.3, E06.4, E06.5, E06.9 |
| **Colitis** | K52.0, K52.1, K52.81, K52.82, K52.831, K52.839, K52.89, K52.9 |
| **Nephritis** | N10, N11.8, N11.9, N12 |

*Table S2. Participant characteristics at the time of AKI*

| **Variables** | **Result** |
|---|---|
| Total with AKI (in the first year after starting ICI) | 549/2207 |
| AKI characteristics | |
| Time to First AKI, days | 79.7 (33.5,158.9) |
| Duration of AKI, days | 6.5 (1.5,15.1) |
| Duration of AKI > 7 Days | 280 (51%) |
| Stage 1 | 317 (57.7%) |
| Stage 2 or Higher | 232 (42.3%) |
| Dialysis | 15 (2.7%) |
| Diagnostic evaluation of AKI | |
| Urinalysis | 356 (64.8%) |
| Clostridium Difficile Testing | 81 (14.8%) |
| Ultrasound | 75 (13.7%) |
| Medication use before AKI (30 days) | |
| PPI | 62 (11.3%) |
| NSAID | 32 (5.8%) |
| Cisplatin | 14 (2.6%) |
| Medication use after AKI (30 days) | |
| Steroid after AKI - Overall | 126 (23%) |
| Steroid after AKI - Stage 1 | 52 (16%) |
| Steroid after AKI - Stage 2 or Higher | 74 (32%) |
| Time to Steroid | 2.5 (0.5,9.9) |
| Steroid after AKI - Overall (Excluded Prior use) | 93 (16.9%) |
| Steroid after AKI - Stage 1 (Excluded Prior use) | 38 (12%) |
| Steroid after AKI - Stage 2 or Higher (Excluded Prior use) | 55 (24%) |
| Time to Steroid (Excluded Prior use) | 4 (1,12.6) |
| Received ICI after AKI | 255 (46.4%) |
| Time to Next ICI Dose, weeks | 7 (0.1,16.5) |
| Other immune related adverse events | |
| Pneumonitis | 1 (0.2%) |
| Autoimmune hepatitis | 11 (2%) |
| Adrenalitis | 10 (1.8%) |
| Dermatitis | 22 (4%) |
| Hypophysitis | 41 (7.5%) |
| Thyroiditis | 25 (4.6%) |
| Colitis | 91 (16.6%) |

*Table S3. Baseline characteristics by AKI status*

| Variables | AKI (N=549) | No AKI (N=1658) | P value |
|---|---|---|---|
| **Demographics** | | | |
| Age | 65.4 (57.3,73.3) | 67 (58.5,75.1) | 0.02 |
| Female sex | 250 (45.5%) | 709 (42.8%) | 0.26 |
| Black race | 35 (6.4%) | 111 (6.7%) | 0.79 |
| **Comorbidities** | | | |
| Diabetes | 129 (23.5%) | 326 (19.7%) | 0.05 |
| Hypertension | 364 (66.3%) | 961 (58%) | <0.001 |
| Cirrhosis | 11 (2%) | 31 (1.9%) | 0.84 |
| CKD | 71 (12.9%) | 163 (9.8%) | 0.04 |
| **Cancer type and stage** | | | |
| Lung | 196 (35.7%) | 690 (41.6%) | 0.01 |
| Melanoma | 88 (16%) | 294 (17.7%) | 0.36 |
| Kidney | 87 (15.8%) | 202 (12.2%) | 0.03 |
| Digestive | 35 (6.4%) | 75 (4.5%) | 0.08 |
| Head and neck | 8 (1.5%) | 59 (3.6%) | 0.01 |
| Breast | 41 (7.5%) | 77 (4.6%) | 0.01 |
| Other | 94 (17.1%) | 261 (15.7%) | 0.45 |
| Stage 4 cancer | 465 (84.7%) | 1357 (81.8%) | 0.13 |
| **Laboratory findings** | | | |
| Creatinine | 0.8 (0.7,1) | 0.9 (0.7,1.1) | <0.001 |
| eGFR | 86.3 (65.5,99.3) | 81.8 (62.2,95.2) | 0.0005 |
| BUN | 16 (12,21) | 16 (12,20) | 0.66 |
| BUN:Creatinine ratio | 18.8 (14.5,23.5) | 17.6 (14,22.2) | 0.002 |
| Hemoglobin | 12 (10.4,13.5) | 12.4 (10.9,13.8) | <0.001 |
| Platelet count | 257 (198,334) | 245 (194,310) | 0.01 |
| Bicarbonate | 26 (24,27) | 26 (24,27) | 0.47 |
| Anion gap | 13 (11,14) | 12 (11,14) | 0.03 |
| **Medication use** | | | |
| PPI | 140 (25.5%) | 382 (23%) | 0.24 |
| NSAID | 129 (23.5%) | 355 (21.4%) | 0.31 |
| Antibiotic | 314 (57.2%) | 896 (54%) | 0.20 |
| **Immune checkpoint inhibitor (ICI)** | | | |
| Ipilimumab | 118 (21.5%) | 281 (16.9%) | 0.02 |
| Nivolumab | 268 (48.8%) | 729 (44%) | 0.05 |
| Pembrolizumab | 164 (29.9%) | 582 (35.1%) | 0.02 |
| Other ICI | 86 (15.7%) | 271 (16.3%) | 0.71 |
| Combination of ICI use | 96 (17.5%) | 244 (14.7%) | 0.12 |

*Table S4. Association of acute kidney injury duration and stage with mortality after immune checkpoint inhibitor therapy*

| Predictor | Hazard ratio (HR) | Adjusted HR |
|---|---|---|
| AKI duration | | |
| ≤7days | Ref | Ref |
| >7days | 2.12 (1.51, 2.98) | 1.84 (1.30, 2.62) |
| AKI stage | | |
| Stage 1 | Ref | Ref |
| Stage 2 or 3 | 1.28 (0.96, 1.71) | 1.32 (0.98, 1.79) |

*Model 1 tests univariable association of AKI with mortality*
*Model 2 controls for age, sex, race, ethnicity, presence of comorbidities (CKD, CHF, COPD, cirrhosis, diabetes, Elixhauser comorbidity score), cancer type (lung, melanoma, other), metastasis, baseline creatinine, and time-updated administration of ICI.*
*Follow-up starts at AKI.*

*Table S5. Concordance between model predicted diagnosis and that obtained by various other methods*

| Diagnosis method | Agreement | Kappa |
|---|---|---|
| **Nephrologist adjudication** | 90% | 0.80 (P<0.001) |
| **Treating clinician impression** | 78% | 0.59 (P=0.008) |
| **Gupta/Leaf classification** | 85% | 0.70 (P<0.001) |

*Data from 20 participants from the highest and lowest deciles of AIN probability. Chart reviewed by a board-certified nephrologist to determine their probability of AIN and collect information on treating oncologist's presumed etiology of AKI. We also determined etiology of AKI based on a schema proposed by Gupta and Leaf (Kidney 360 2020 DOI: https://doi.org/10.34067/KID.0000852019 ).*

*Table S6. AIN probability by histological diagnosis*

| Characteristic | AIN on histology (n=8) | Other diagnosis (n=3) | P-value |
|---|---|---|---|
| **AIN probability of model** | 0.30 (0.26, 0.37) | 0.13 (0.10, 0.20) | 0.03 |

**excludes kidney biopsy performed to evaluate renal mass*

*Table S7. Association of estimated acute interstitial nephritis with mortality controlling for AKI stage and duration*

| **Predictor** | **Adjusted hazard ratio (95% CI)** | |
|---|---|---|
| | **Model1** | **Model2** |
| eAIN vs. no eAIN | 0.40 (0.18, 0.91) | 0.39 (0.18, 0.83) |

*Both analyses control for age, sex, race, ethnicity, presence of comorbidities (CKD, CHF, COPD, cirrhosis, diabetes, Elixhauser comorbidity score), cancer type (lung, melanoma, other), metastasis, and time-updated administration of ICI. Model 1 additionally controls for AKI stage and model 2 additionally controls for AKI duration.*

*Table S8. Association of individual components of AIN score with mortality after AKI*

| Component | Hazard ratio | Adjusted Hazard ratio |
|---|---|---|
| Creatinine* | 1.14 (0.82, 1.56) | 1.40 (0.97, 2.01) |
| BUN to creatinine ratio* | **4.60 (2.88, 7.35)** | **4.98 (3.05, 8.12)** |
| Urine specific gravity | **1.02 (1.01, 1.03)** | 1.00 (0.99, 1.02) |
| Urine protein, >=2+ | **1.63 (1.09, 2.42)** | **1.70 (1.12, 2.59)** |

**per log increase; multivariable model adjusts for each component of the score; follow-up starts at AKI*

*Table S9. Mortality rate by deciles of predicted probability of AIN*

| AIN probability Decile | AIN probability | Mortality rate (95% CI) |
|---|---|---|
| **1** | 0.00-0.06 | 4061 (2620,6295) |
| **2** | 0.06-0.09 | 2020 (1255,3249) |
| **3** | 0.09-0.11 | 1893 (1193,3004) |
| **4** | 0.11-0.14 | 1485 (843,2614) |
| **5** | 0.14-0.17 | 1549 (934,2570) |
| **6** | 0.17-0.22 | 1036 (589,1825) |
| **7** | 0.22-0.25 | 751 (391,1443) |
| **8** | 0.25-0.31 | 1149 (652,2023) |
| **9** | 0.31-0.39 | 1279 (726,2252) |
| **10** | 0.40-0.75 | 690 (345,1381) |

*Mortality rate after AKI per 1000 person-years*

*Figure S1. Components of AIN probability model*

```
EHR model= (Log serum creatinine at AKI* 0.8367518) + (Log blood urea
nitrogen to creatinine ratio* -0.9181938)) + ((Urine dipstick specific
gravity-1)*1000*(-0.0501203)) + (Urine dipstick protein*0. 9360127) +
0.770398
```

*Serum creatinine (in mg/dl), blood urea nitrogen to creatinine ratio (dimensionless), dipstick urine specific gravity (dimensionless) and dipstick urine protein coded as 1+ or lower=1 and 2+ or higher=0. Probability calculated as (probability of AIN)=e^(EHR model)/(1+e^(EHR model))*

*Figure S2. Incidence of AKI over time*

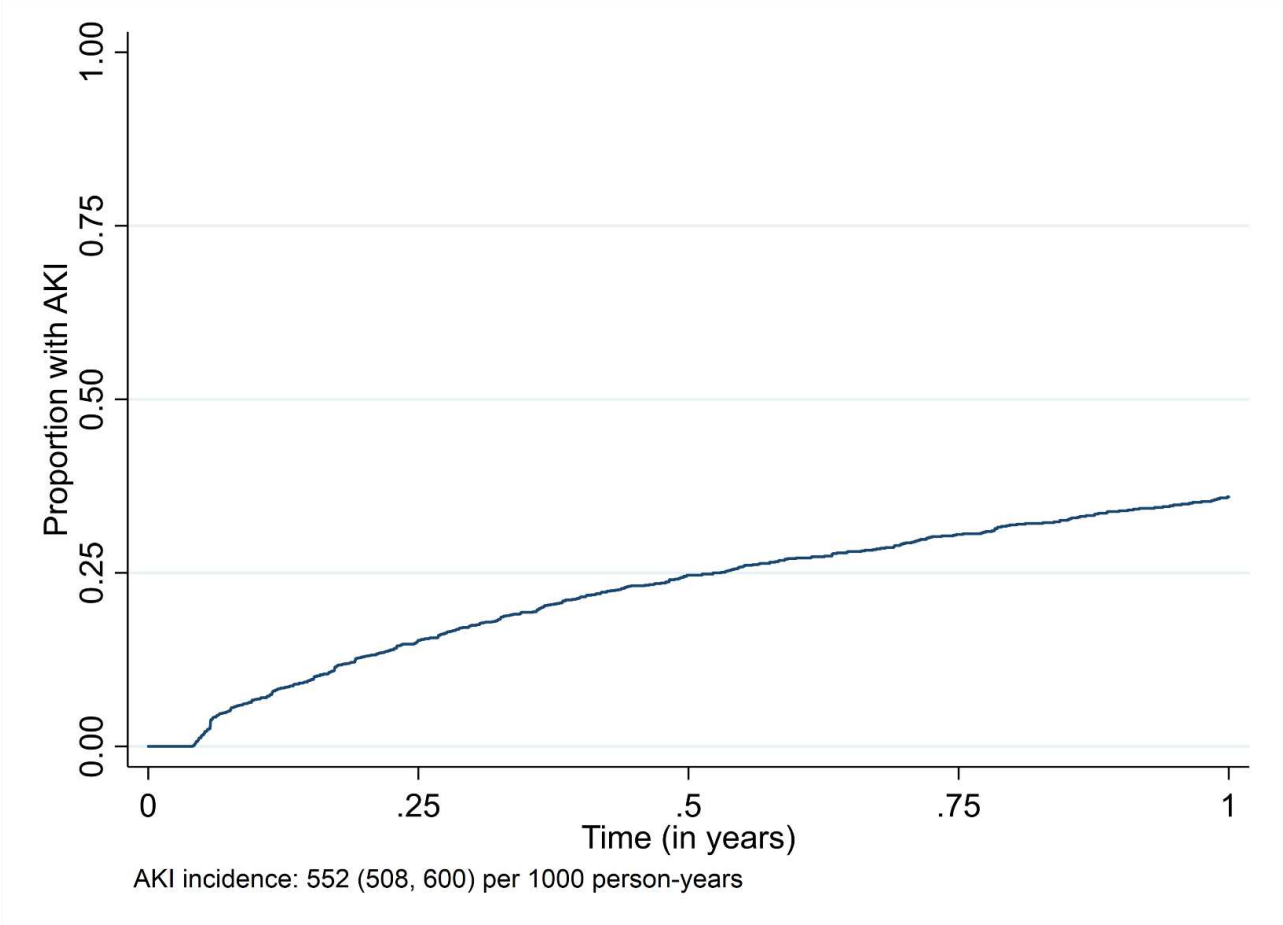
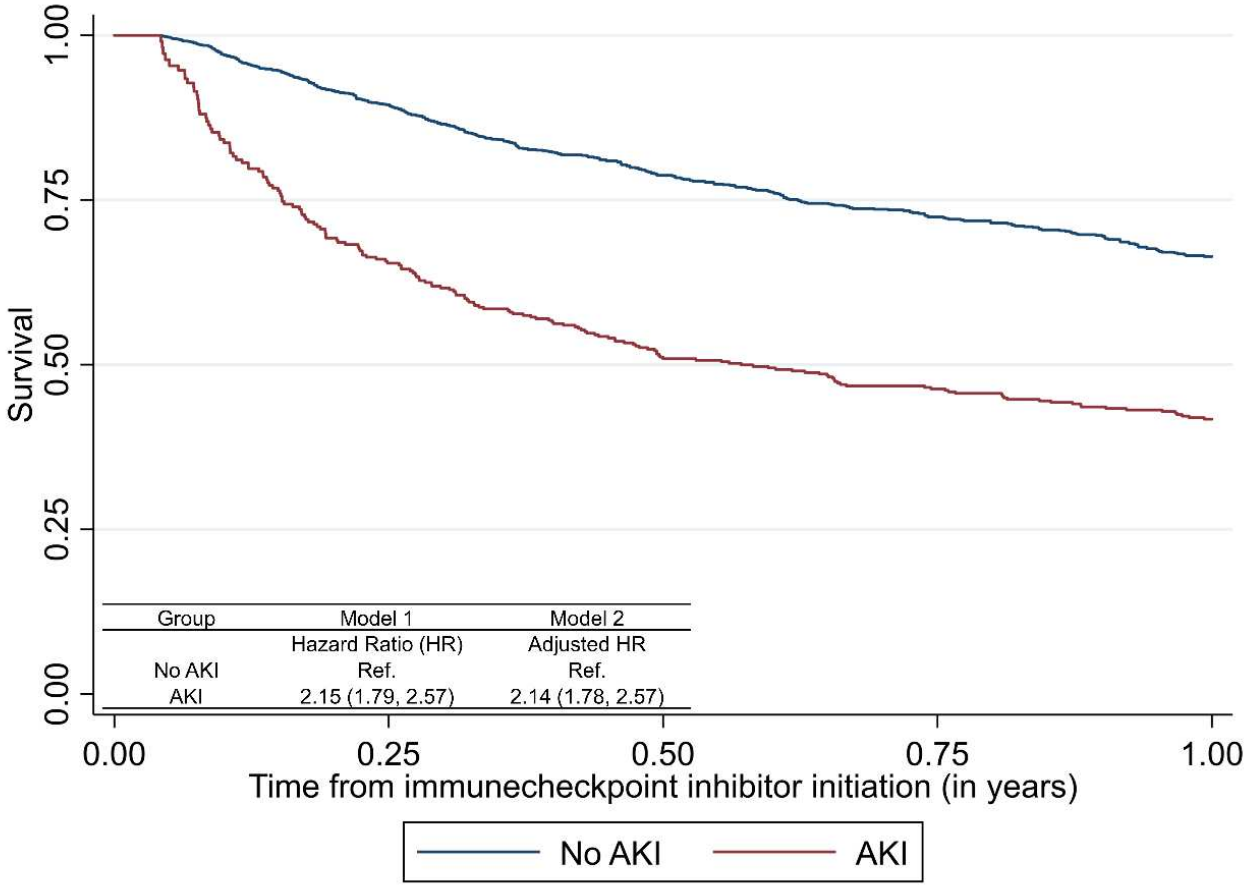


*Figure S3. Association of alternate AKI definition with mortality after immune checkpoint inhibitor therapy*




- *Association of AKI with mortality in all participant using time-varying Cox proportional hazards models where exposure (presence or absence of AKI) was treated as a time-varying covariate updated once if it occurred and patient considered as exposed for the remainder of the analysis period*
- *Follow-up starts at 15 days after initiation of immune-checkpoint inhibitor therapy*
- *AKI defined as 50% increase in creatinine over mean of all serum creatinine values obtained within 6 months prior to ICI initiation.*
- *Model 1 tests univariable association of AKI with mortality; Model 2 controls for age, sex, race, ethnicity, presence of comorbidities (CKD, CHF, COPD, cirrhosis, diabetes, Elixhauser comorbidity score), cancer type (lung, melanoma, other), metastasis, and time-updated administration of ICI.*

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*Figure S4. Risk of mortality after AKI over time*

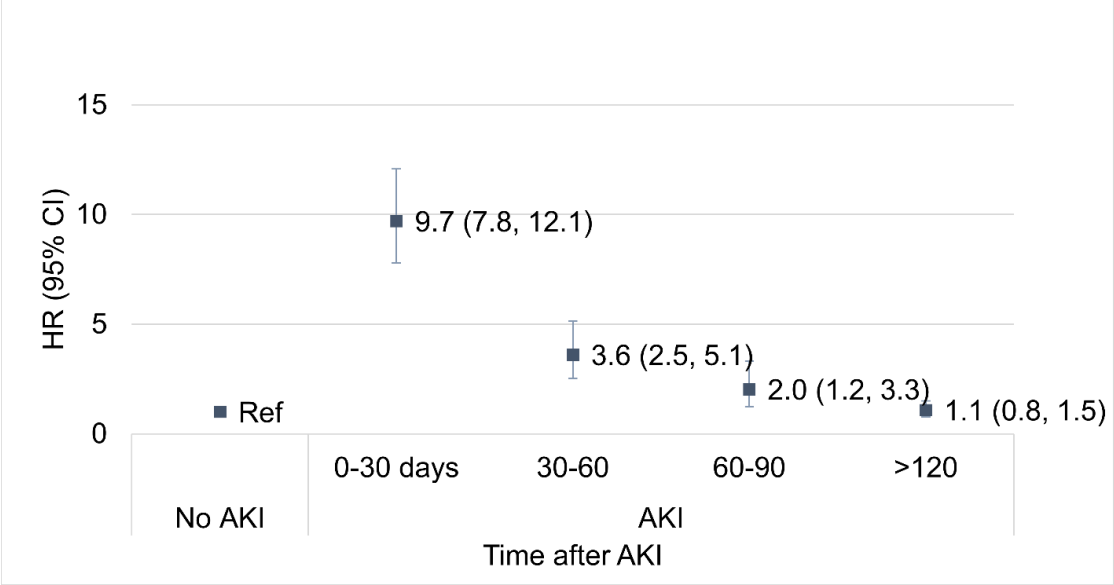
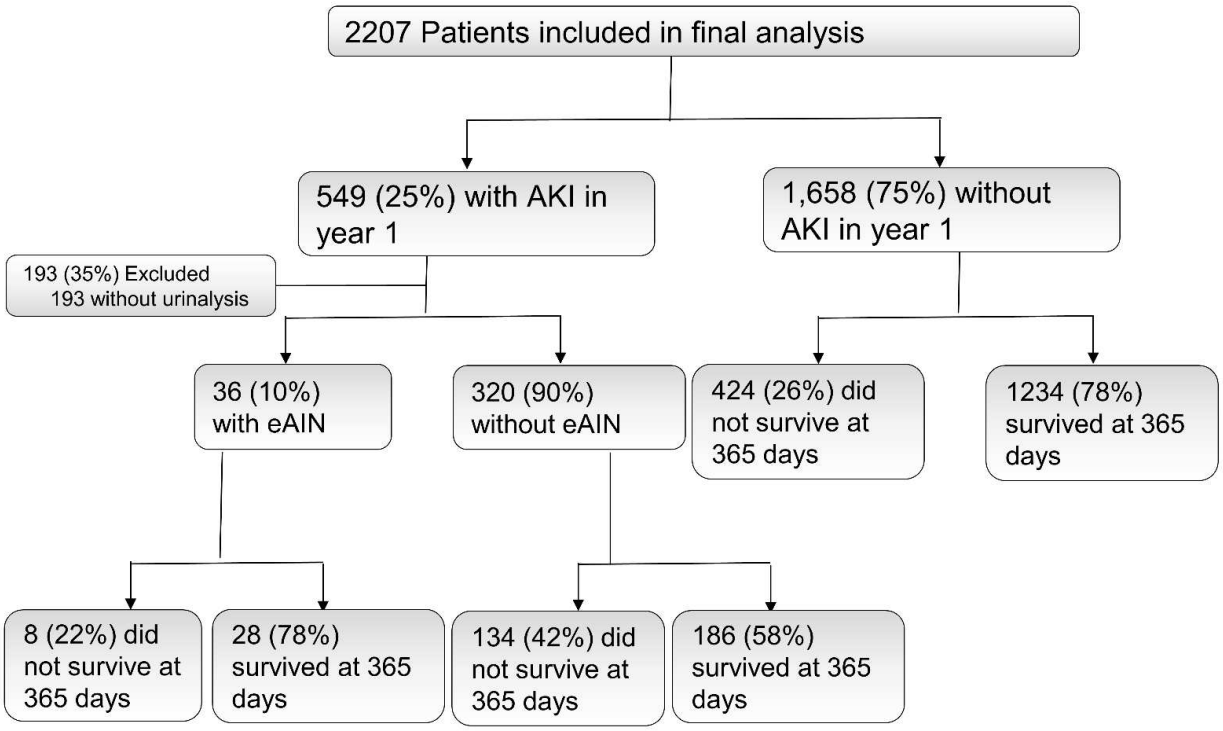
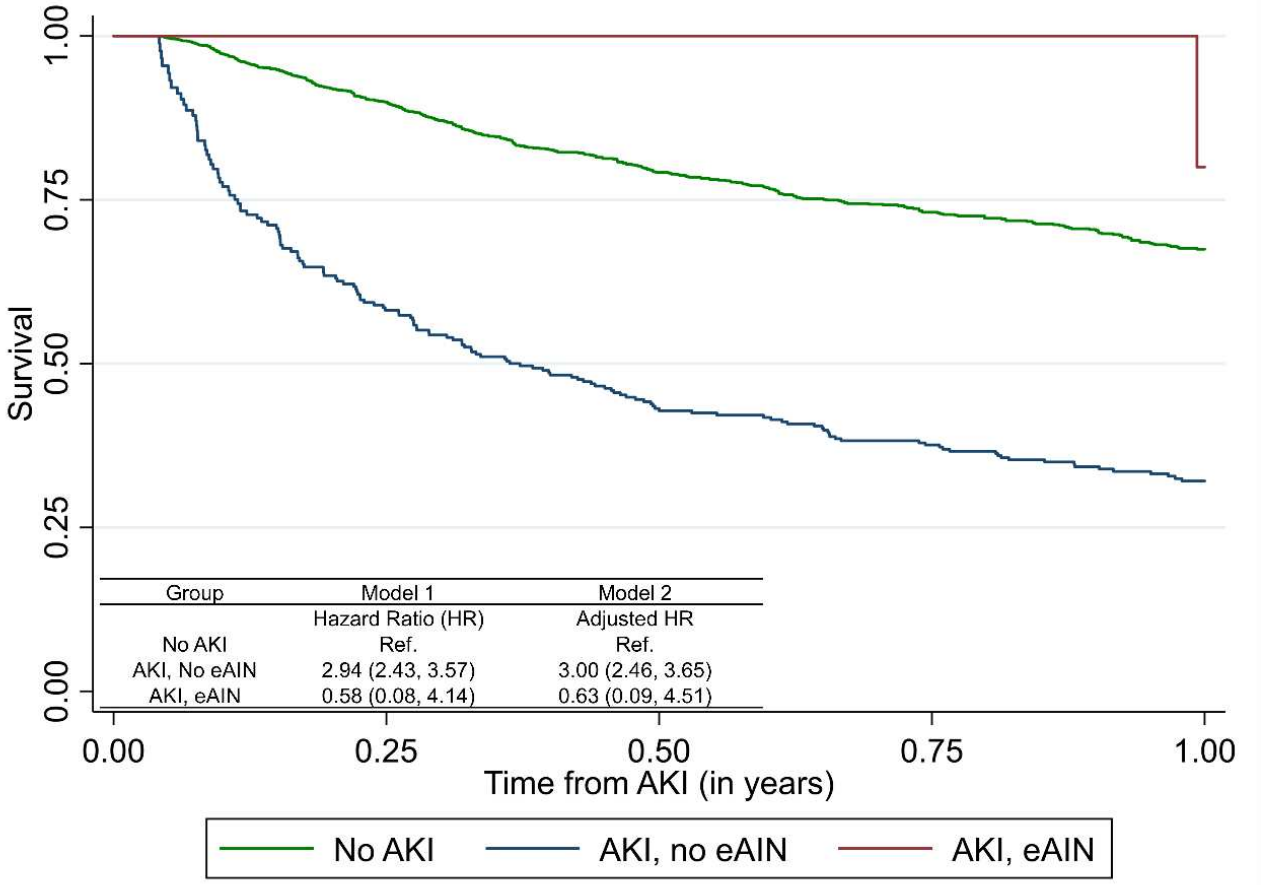


*Figure S5. Flow diagram of mortality by estimated acute interstitial nephritis*



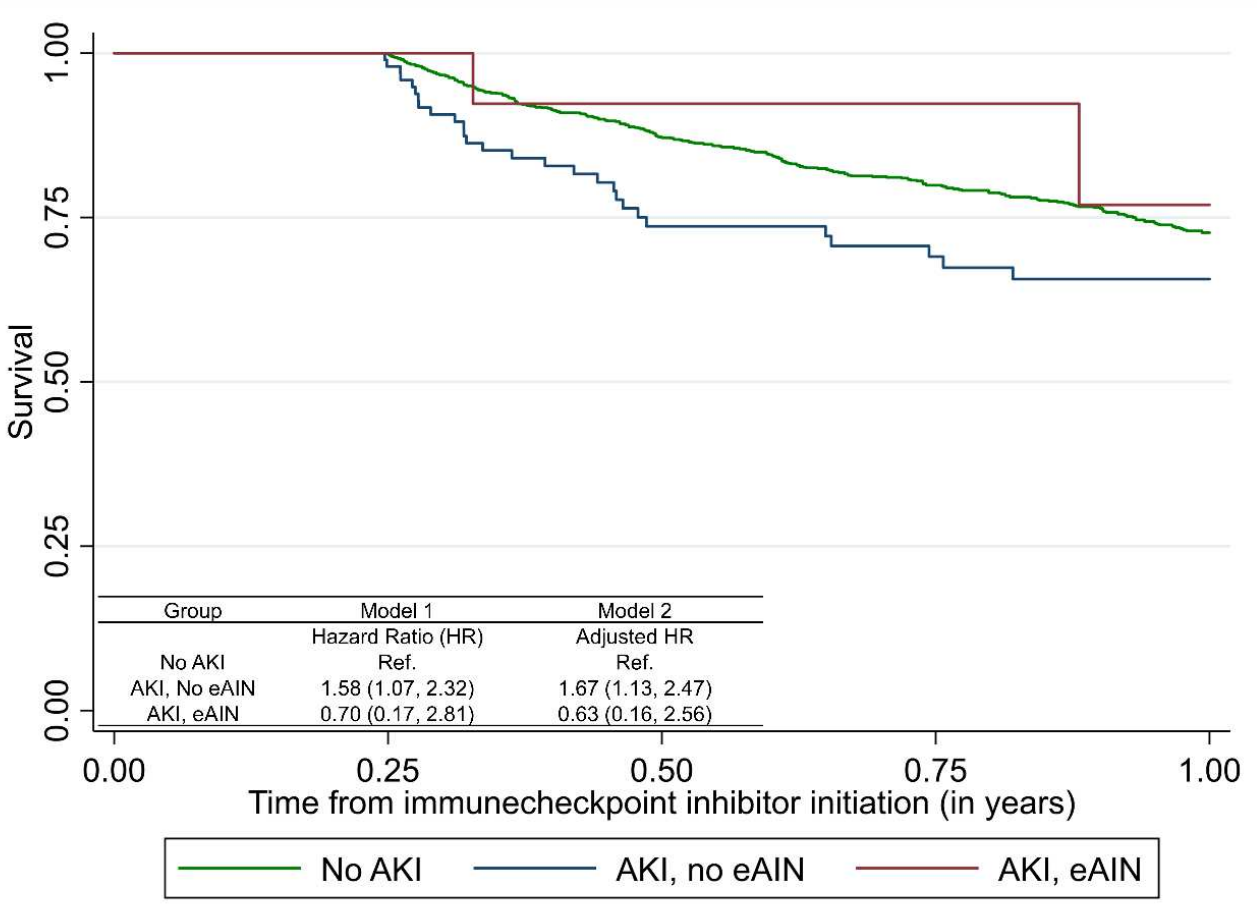

**26% mortality among those with missing UA*

*Figure S6. Association of eAIN with mortality where eAIN was defined as those with the top 3% AIN probability*



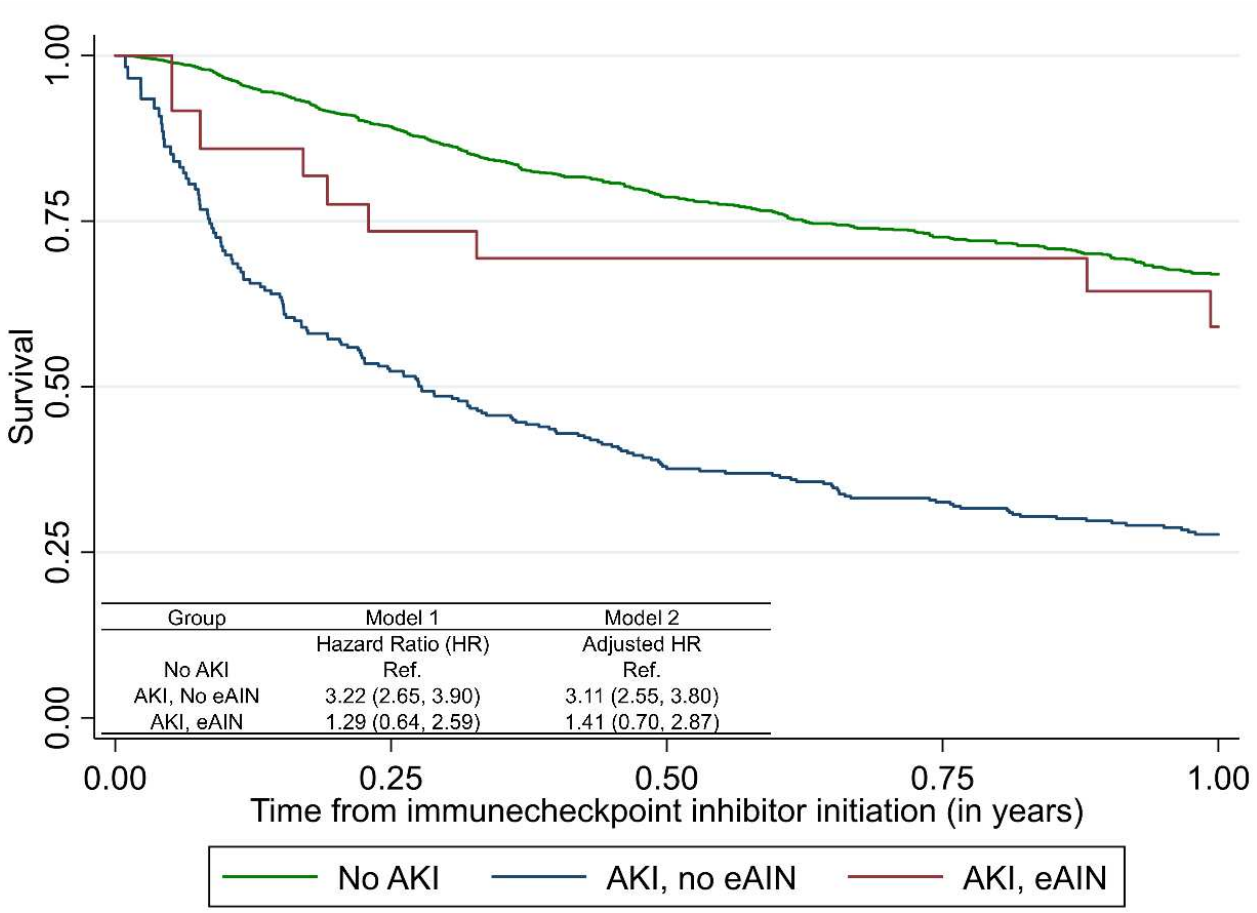

- *Association of estimated AIN with mortality in all participants initiated on immune-checkpoint inhibitor therapy using time-varying Cox proportional hazards models where exposure (presence or absence of AKI or eAIN) was treated as a time-varying covariate updated once if it occurred and patient considered as exposed for the remainder of the analysis period.*
- *Follow-up starts at 15 days after initiation of immune-checkpoint inhibitor therapy*
- *eAIN defined as those in the top 3% of AIN probability as determined by the diagnostic model.*
- *Model 1 tests univariable association of AKI with mortality; Model 2 controls for age, sex, race, ethnicity, presence of comorbidities (CKD, CHF, COPD, cirrhosis, diabetes, Elixhauser comorbidity score), cancer type (lung, melanoma, other), metastasis, and time-updated administration of ICI.*
- *Extended Kaplan Meier curve accounting for time-varying covariate.*

*Figure S7. Association of eAIN with mortality using landmark analysis set at 90 days after initiation of immune checkpoint inhibitors*



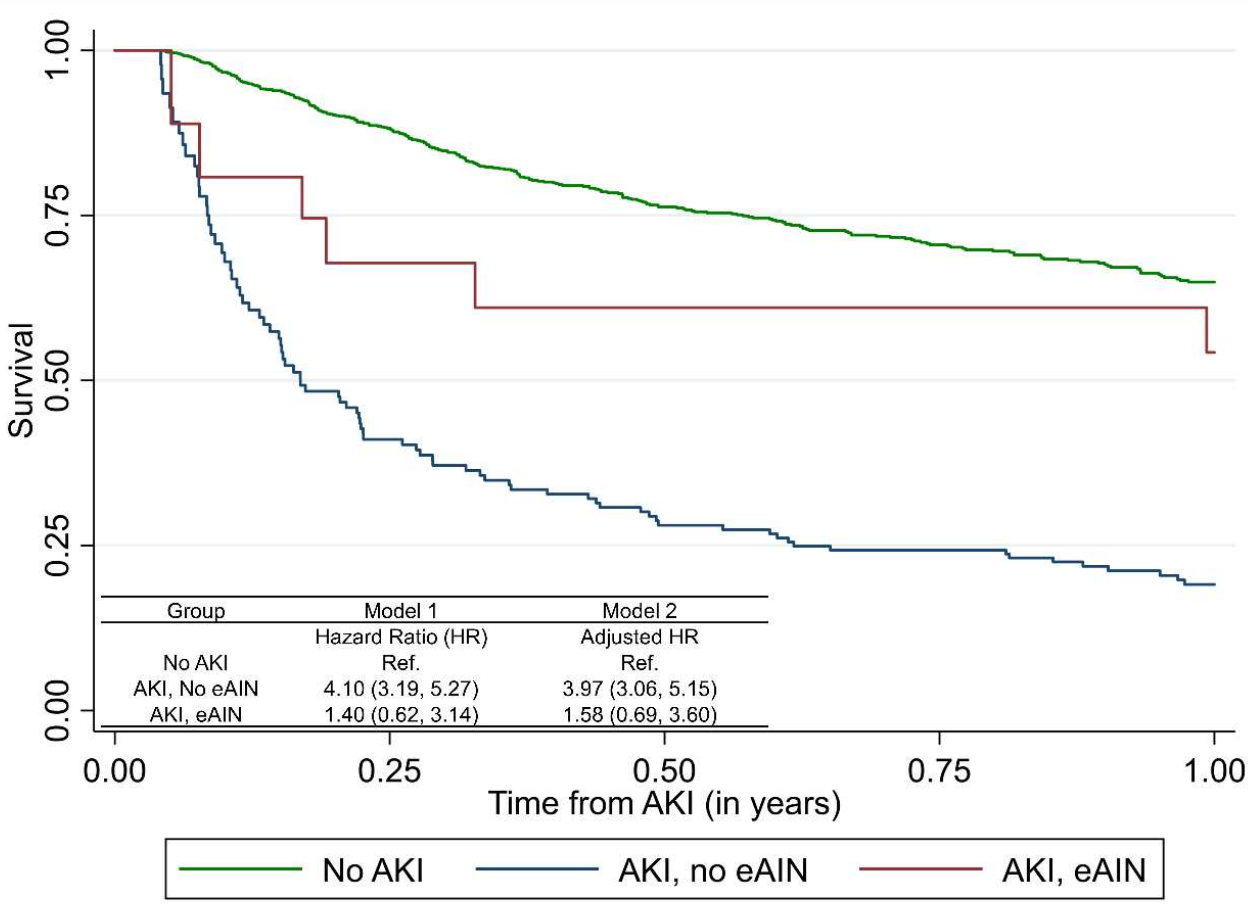

- *Association of estimated AIN with mortality in all participants initiated on immune-checkpoint inhibitor therapy using landmark analysis using Cox proportional hazards models where exposure (presence or absence of AKI or eAIN) was determined at 90 days and held constant for the remainder of the analysis period.*
- *Follow-up starts at 90 days after initiation of immune-checkpoint inhibitor therapy. Only includes those who survived till 90 days after initiation of ICI therapy.*
- *eAIN defined as those in the top 10% of AIN probability as determined by the diagnostic model.*
- *Model 1 tests univariable association of AKI with mortality; Model 2 controls for age, sex, race, ethnicity, presence of comorbidities (CKD, CHF, COPD, cirrhosis, diabetes, Elixhauser comorbidity score), cancer type (lung, melanoma, other), metastasis, and time-updated administration of ICI.*
- *Extended Kaplan Meier curve accounting for time-varying covariate.*

*Figure S8. Association of eAIN with mortality without excluding first 15 days after initiation of immune checkpoint inhibitors*




- *Association of estimated AIN with mortality in all participants initiated on immune-checkpoint inhibitor therapy using time-varying Cox proportional hazards models where exposure (presence or absence of AKI or eAIN) was treated as a time-varying covariate updated once if it occurred and patient considered as exposed for the remainder of the analysis period.*
- *Follow-up starts at initiation of immune-checkpoint inhibitor therapy*
- *eAIN defined as those in the top 10% of AIN probability as determined by the diagnostic model.*
- *Model 1 tests univariable association of AKI with mortality; Model 2 controls for age, sex, race, ethnicity, presence of comorbidities (CKD, CHF, COPD, cirrhosis, diabetes, Elixhauser comorbidity score), cancer type (lung, melanoma, other), metastasis, and time-updated administration of ICI.*
- *Extended Kaplan Meier curve accounting for time-varying covariate.*

*Figure S9. Association of eAIN with mortality after excluding those who received immune checkpoint inhibitor therapy as part of a clinical trial*




- *Association of estimated AIN with mortality in all participants initiated on immune-checkpoint inhibitor therapy using time-varying Cox proportional hazards models where exposure (presence or absence of AKI or eAIN) was treated as a time-varying covariate updated once if it occurred and patient considered as exposed for the remainder of the analysis period.*
- *Excludes those who received ICI therapy as part of a clinical trial (n=781, 34%)*
- *Follow-up starts 15 days after initiation of immune-checkpoint inhibitor therapy*
- *eAIN defined as those in the top 10% of AIN probability as determined by the diagnostic model.*
- *Model 1 tests univariable association of AKI with mortality; Model 2 controls for age, sex, race, ethnicity, presence of comorbidities (CKD, CHF, COPD, cirrhosis, diabetes, Elixhauser comorbidity score), cancer type (lung, melanoma, other), metastasis, and time-updated administration of ICI.*
- *Extended Kaplan Meier curve accounting for time-varying covariate.*