Supplementary Data

Methods

Search Strategy

We followed the PRISMA [S23] (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement in conducting the current systematic review. EMBASE, Cochrane, and Ovid MEDLINE Databases were systematically searched from database inception through May 2020. We additionally performed an updated literature search in September 2020 to include all relevant studies. The protocol for this meta-analysis is registered with PROSPERO; no. CRD42020184601. Three investigators (S.K., T.P., and S.M) performed an independent literature search. Kappa coefficient of agreement for the investigators was 0.86. Information on the detailed search strategy is provided below. Language restriction was not applied. Potentially related studies were manually reviewed using the references.

Study Selection

Observational studies and clinical trials providing 95% confidence intervals (CI) data on the incidence of AKI, CRS and severe CRS (CRS grade ≥ 3) among adults and pediatric patients receiving CAR-T cells were included in the meta-analysis. Follow up period among these studies ranged from 30 days to one year. We also included cohort studies with smaller sample size to yield more comprehensive outcomes. We further excluded case reports, animal studies, review articles and correspondence. Three investigators (S.K., T.P., and S.M) independently reviewed the titles and abstracts of the studies identified in the search based on inclusion and exclusion criteria. A third reviewer (S.H.) solved inconsistencies that occurred among two investigators by collective agreement. Among included studies, there are modest heterogenicities in AKI definition ranging from criteria of doubling of serum creatinine to 25% increase in serum creatinine from baseline. Additionally, KDIGO definitions [S24] of AKI were used for subgroup analysis. Severe AKI defines as AKI stage 3 or AKI requiring RRT.

Data Collection

The collected data from individual studies included the title, name of authors, publication year, age group/median age, type of cancer, AKI definition, the incidence of AKI and severe AKI requiring RRT, CRS incidence, grades of CRS.

Statistical analysis

Adjusted point estimates of included studies were incorporated by the generic inverse variance method of DerSimonian-Laird, which assigned individual study weight based on its variance [S25]. Due to the probability of between-study variance, we applied a random-effects model to pool outcomes of interest, including AKI incidence. We used Cochran's Q test ($p<0.05$ for a statistical significance) and I^2 statistic (≤25% represents insignificant heterogeneity, 26% to 50% represents low heterogeneity, 51% to 75% represents moderate heterogeneity, and ≥75% represents high heterogeneity) to assess statistical heterogeneity [S26]. Publication bias was analyzed by Funnel plots and Egger test [S27]. Meta-analysis was performed using Comprehensive Meta-Analysis software version 3.3.070 (Biostat Inc, New Jersey, USA). The data for this meta-analysis are publicly available through the Open Science Framework (URL: https://osf.io/872am/).

Search strategies.

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (312 articles)

Search Strategy:

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1 car t-cell therapy.mp.
2 exp car t-cell therapy/
3 chimeric antigen receptor immunotherapy.mp.
4 car-t.mp.
5 car t.mp.
6 chimeric antigen receptor t-cell.mp.
7 car t-cell.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 kidney disease.mp.
10 exp kidney disease/
11 exp acute kidney failure/

12 acute kidney failure.mp.
13 exp acute renal failure/
14 acute renal failure.mp.
15 acute tubular necrosis.mp.
16 acute kidney injury.mp.
17 exp acute kidney injury/
18 AKI.mp.
19 acute kidney disease.mp.
20 dialysis.mp.
21 hemodialysis.mp.
22 peritoneal dialysis.mp.
23 renal replacement therapy.mp
24 ICU.mp.
25 intensive care unit.mp.
26 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 8 and 26

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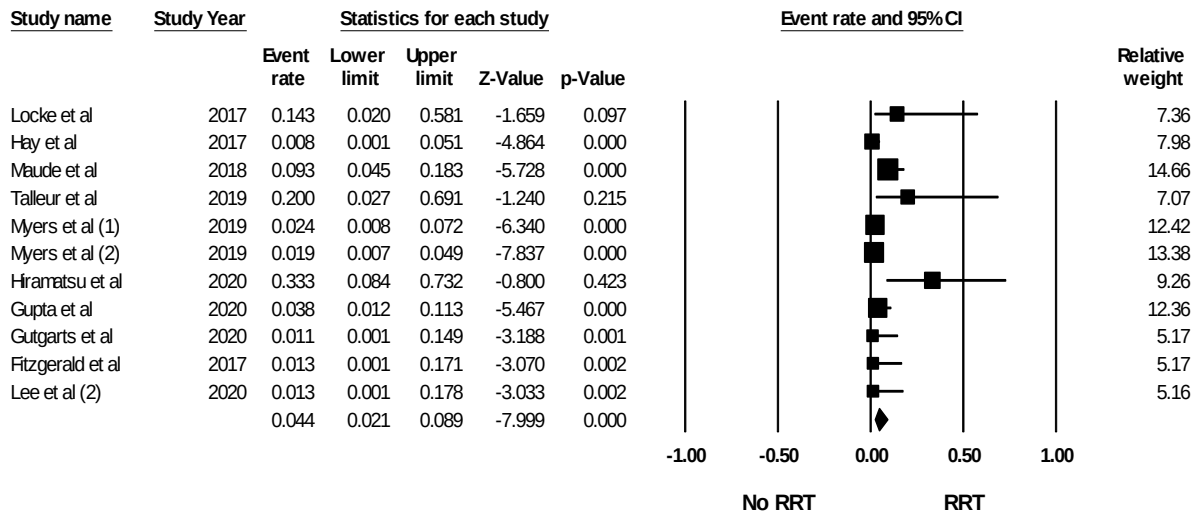
EMBASE and Cochrane Databases

SEARCH QUERY (169 articles)

('chimeric antigen receptor immunotherapy' OR 'car-t' OR 'chimeric antigen receptor t-cell' OR 'car t-cell' OR 'car t-cell therapy') AND ('kidney disease' OR 'acute kidney failure' OR 'acute renal failure' OR 'acute kidney tubule necrosis' OR 'acute tubular necrosis' OR 'acute kidney injury' OR 'aki' OR 'acute kidney injury network criteria' OR 'acute kidney injury network' OR 'acute kidney disease' OR 'acute kidney injury network classification' OR 'renal replacement therapy' OR dialysis OR hemodialysis OR 'peritoneal dialysis' OR 'icu' OR 'intensive care unit').

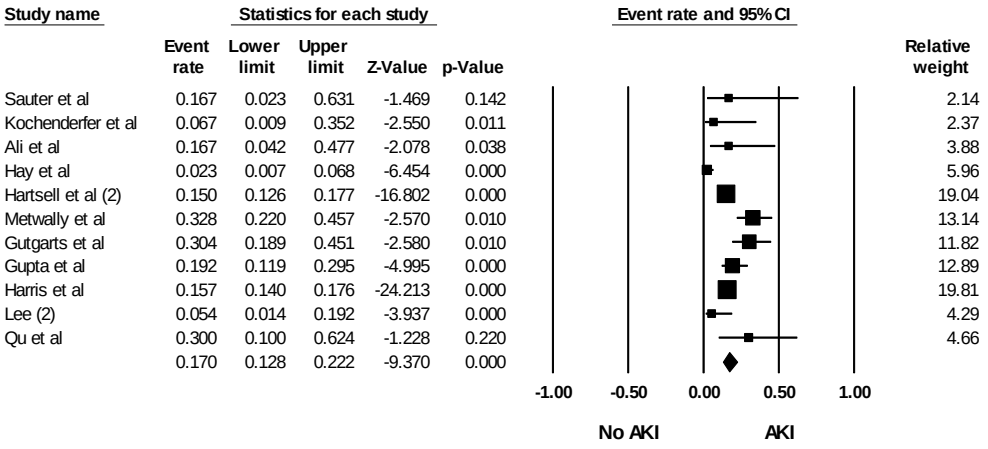
Supplemental figures:

Figure S1. Incidence of severe AKI or AKI – RRT among patients on CAR-T therapies.



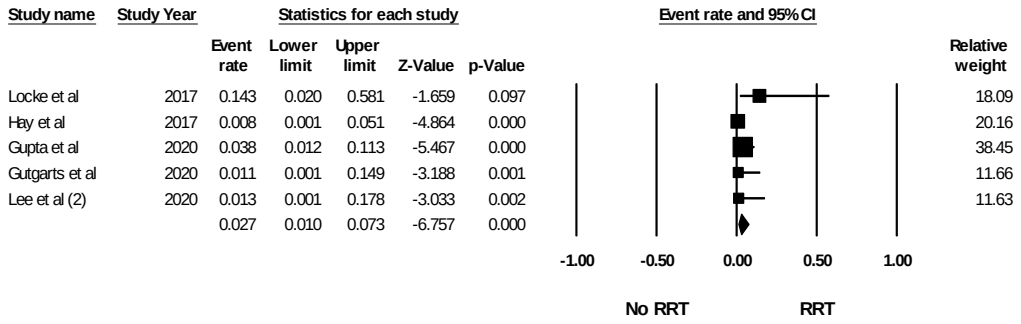
The pooled estimated incidence of severe AKI or AKI requiring RRT was 4.4% (95%CI 2.1-8.9%, I2 = 61%).

Figure S2. Incidence of overall AKI among adults on CAR-T therapies



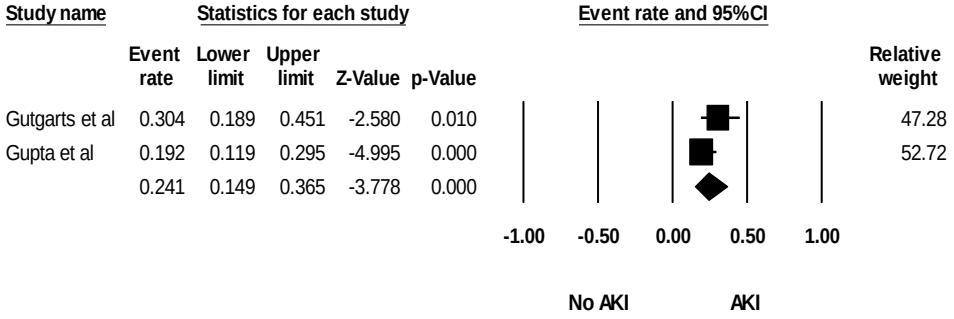
Overall, the pooled estimated incidence of AKI among adults was 17.0% (95%CI 12.8-22.2%, I2 = 73%).

Figure S3. Incidence of AKI- RRT among adults on CAR-T therapies



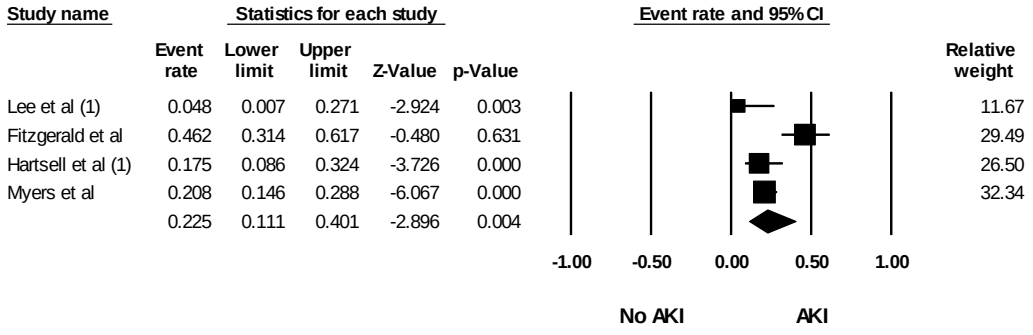
Estimated incidence of AKI- RRT was 2.9% (95%CI 0.9-9.4%, I2 = 41%).

Figure S4. Incidence overall AKI (only KDIGO definition) among adults on CAR-T therapies



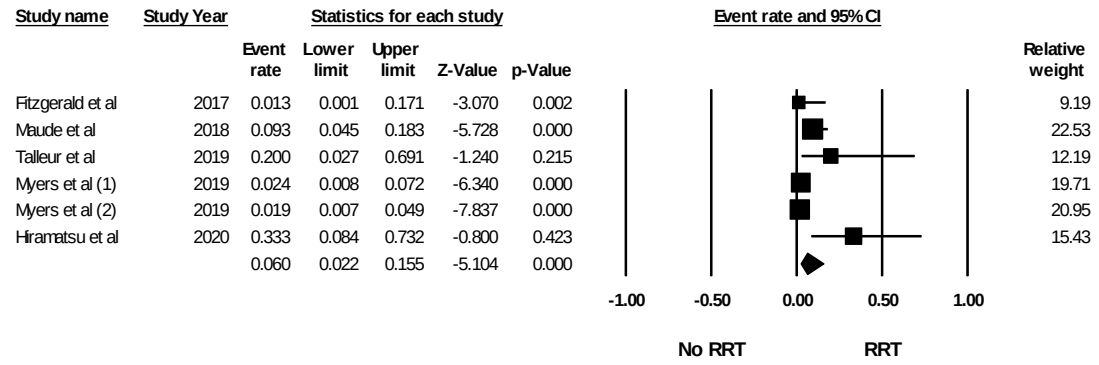
Pooled estimated incidence of AKI was 24.1% (95%CI 14.9-36.5%, I2 = 49%).

Figure S5. Incidence overall AKI among pediatrics and young adults on CAR-T therapies



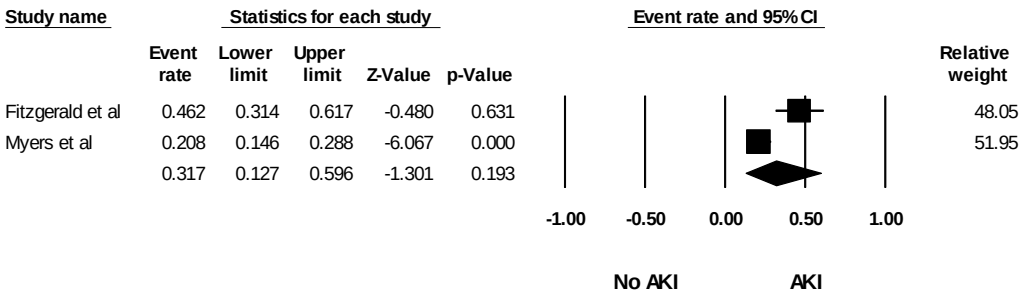
Overall, the pooled estimated incidence of AKI was 22.5% (95%CI 11.1-40.1%, I2 = 79%).

Figure S6. Incidence severe AKI- RRT among pediatric and young adults



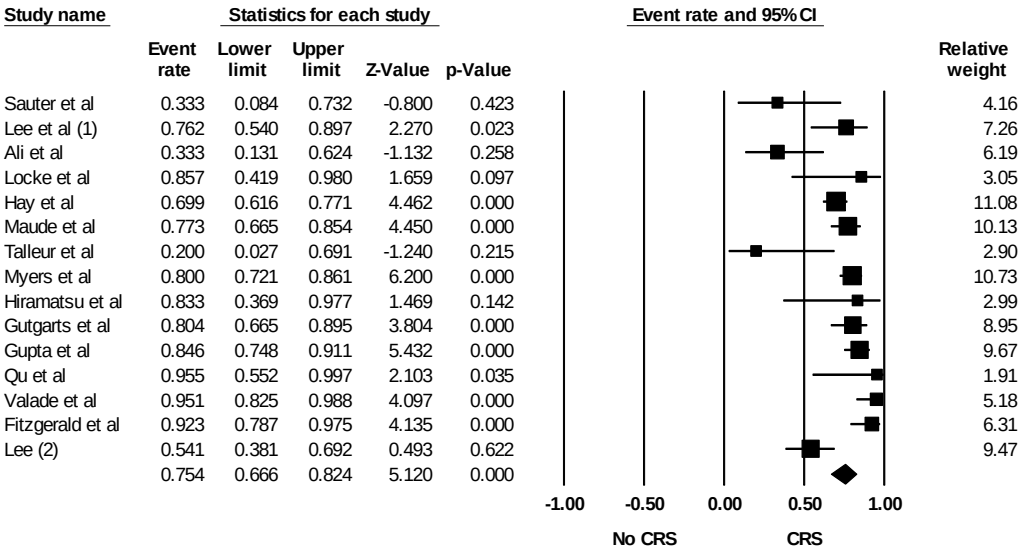
Estimated incidence of severe AKI -RRT was 6.0% (95%CI 2.2-15.5%, I2 = 72%).

Figure S7. Incidence overall AKI (only KDIGO definition) among pediatric and young adults



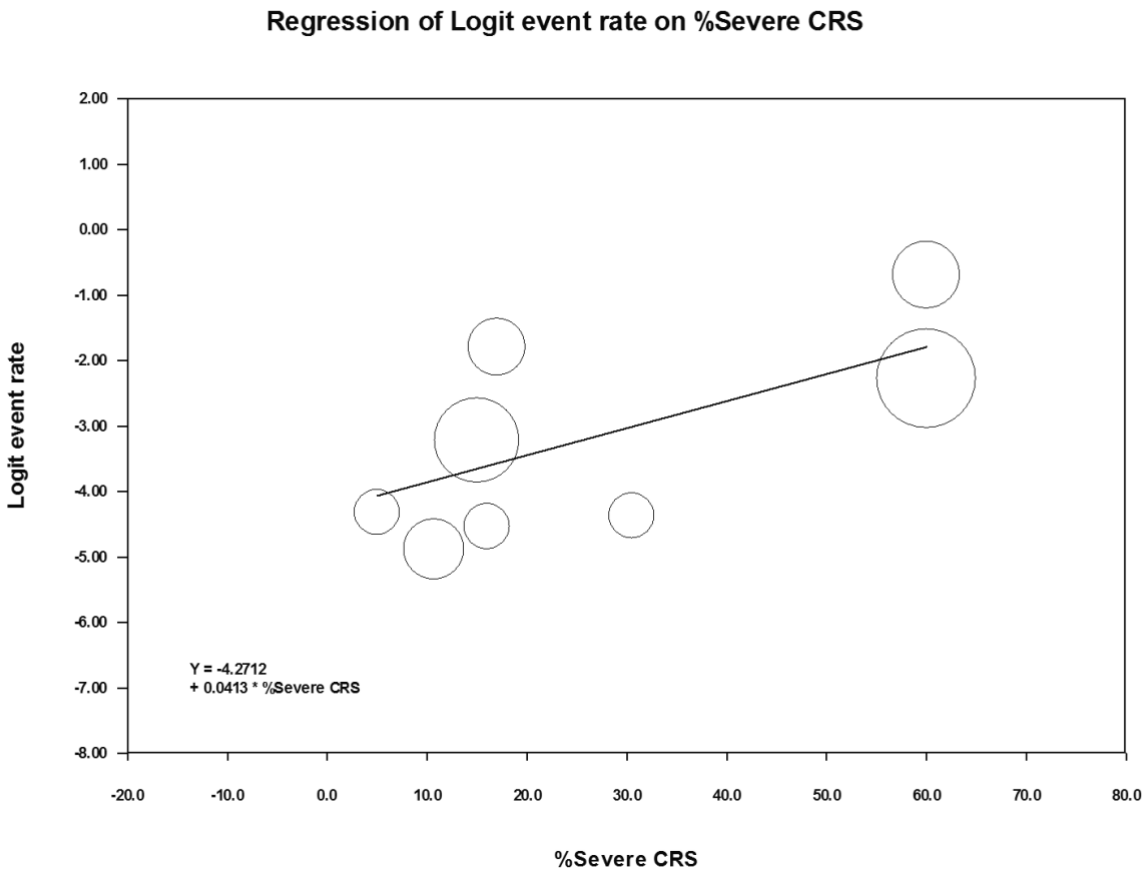
The estimated incidence of AKI was 31.7% (95%CI 12.7-59.6%, I2 = 89%).

Figure S8. Overall Incidence of CRS among patients on CAR-T therapies



Estimated incidence of CRS in all included studies was 75.4% (95%CI 66.6-82.4%, I2 = 71%).

Figure S9. Relation between CRS severity and Incidence of AKI-RRT among patients on CAR-T therapies.



Severity of CRS was significantly correlated with the incidence of severe AKI requiring RRT (slope = +0.0413, p = 0.01).

Figure S10. Funnel plot adults with AKI- CAR-T therapy

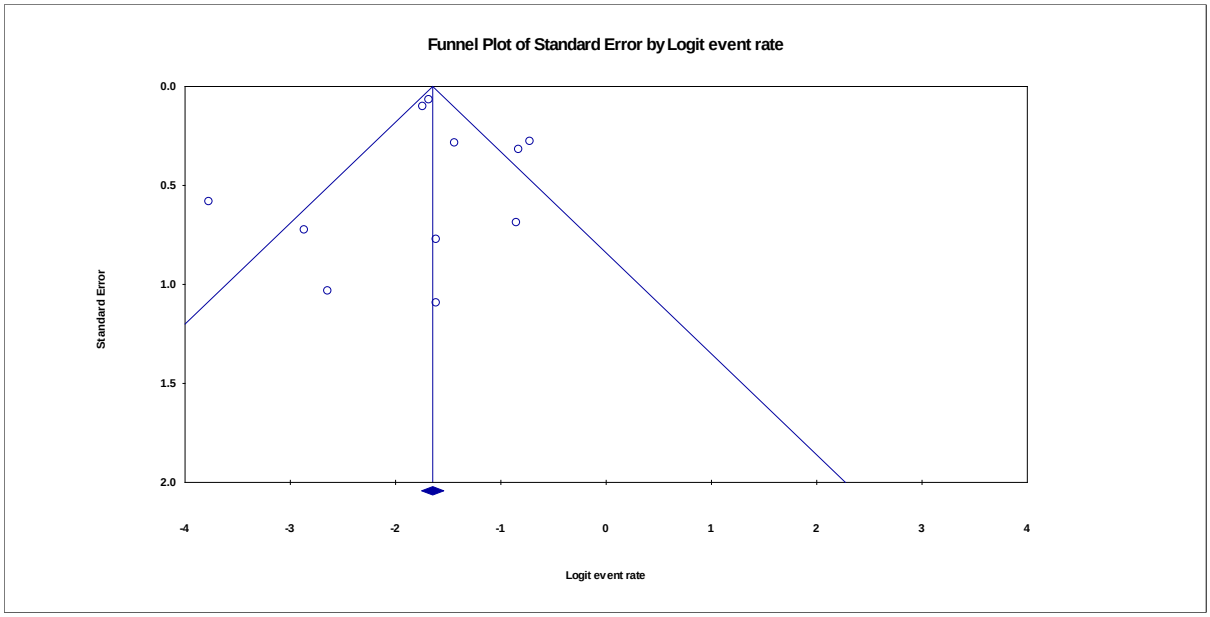


Figure S11. Funnel plot adults with severe AKI- RRT on CAR-T therapy

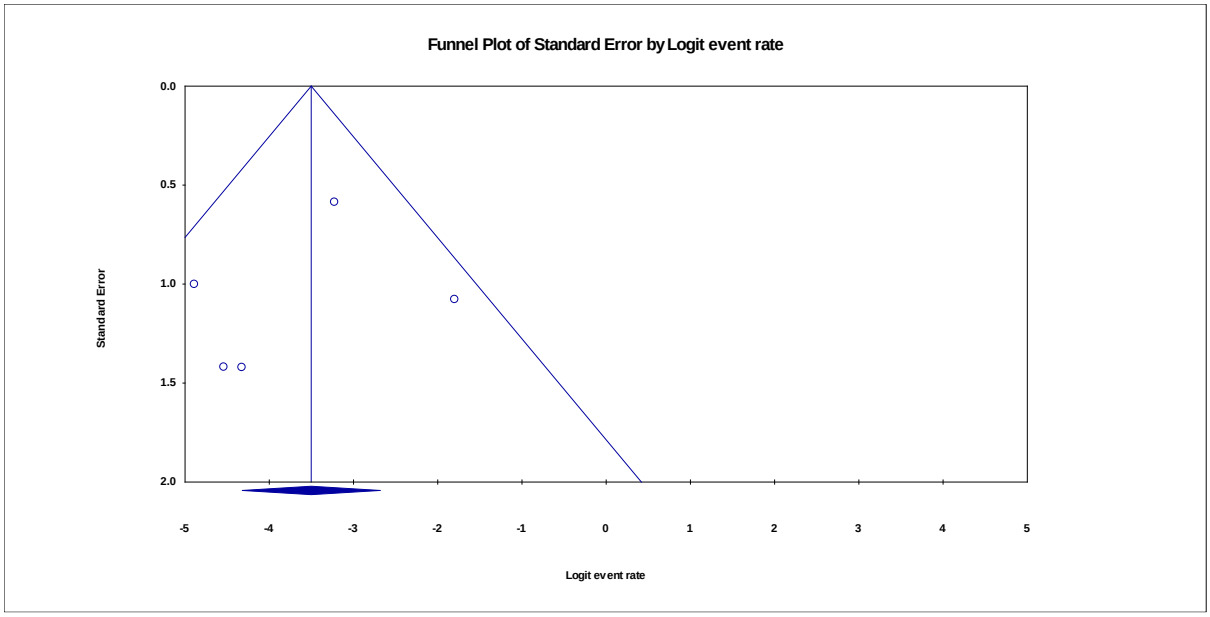


Figure S12. Funnel plot pediatric and young adults with AKI on CAR-T therapy

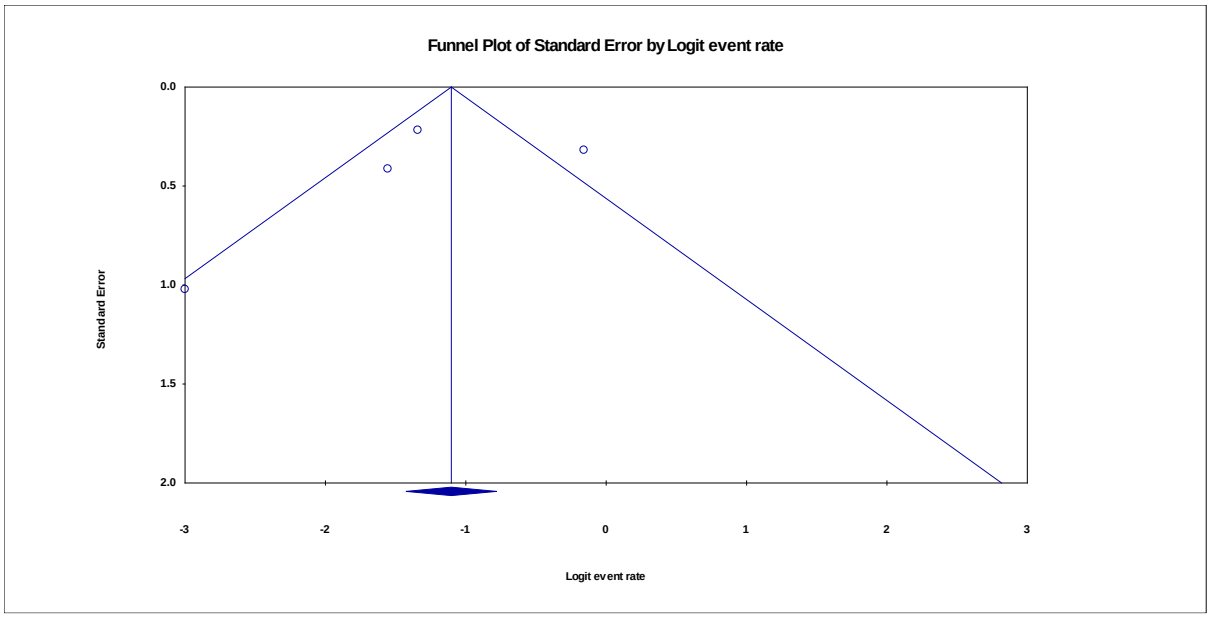
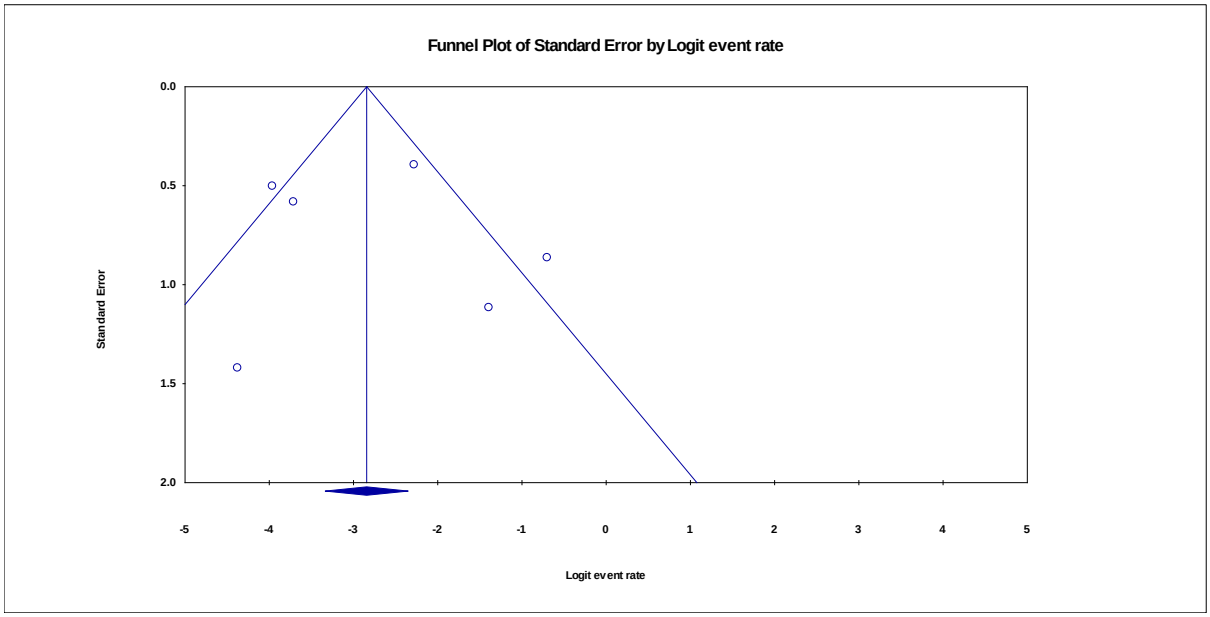


Figure S13. Funnel plot pediatric and young adults with severe AKI – RRT on CAR-T therapy.



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