

Supplemental document

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Statistics

1. ICU Admission – Male sex

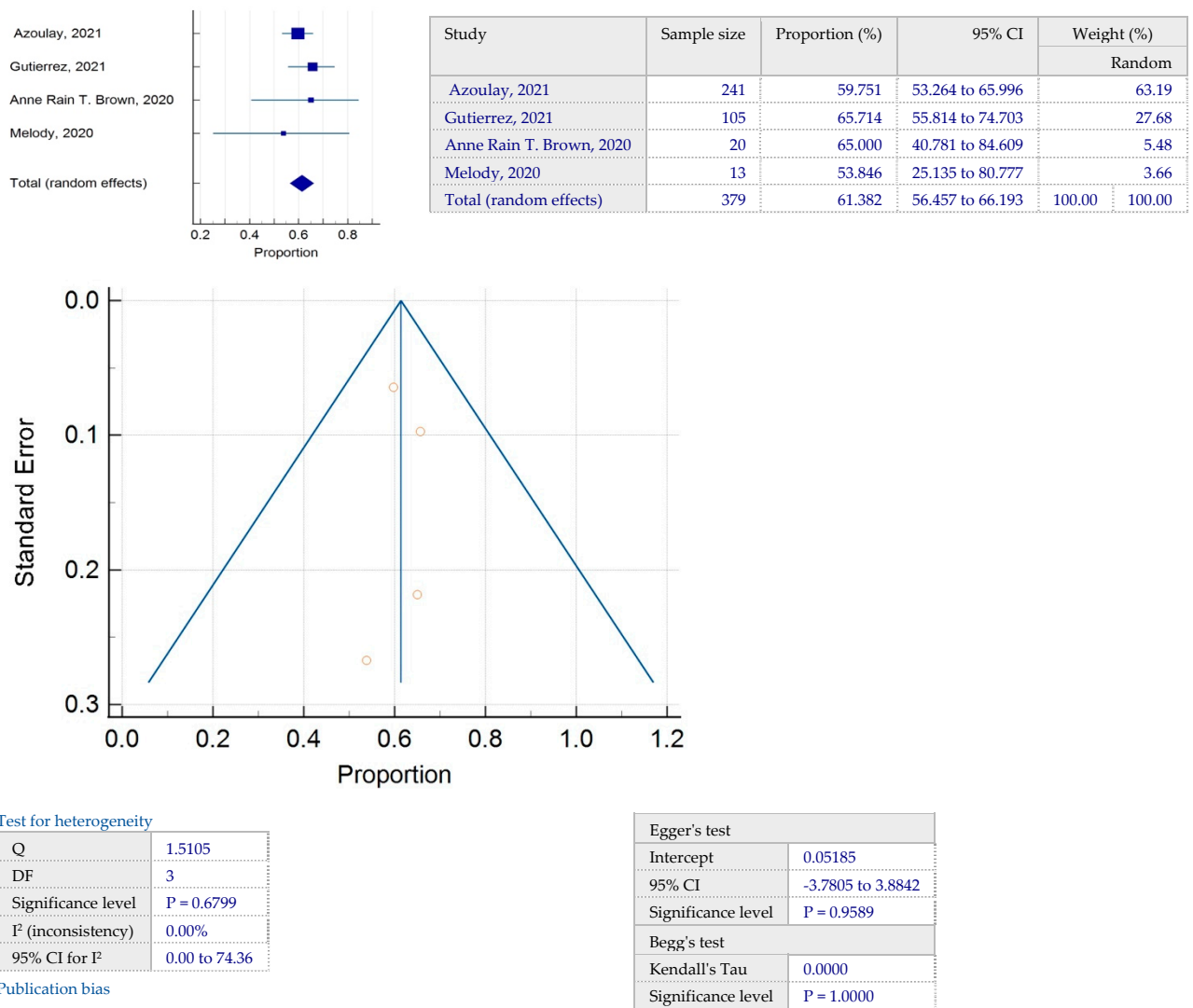


Figure 1. Forest plot of proportions of male patients admitted in the ICU, in published studies.

Figure 1 shows the combined proportion for our outcome of interest – the males admitted to the ICU as a percentage. On average, 61% CI 95%[56-66] of the recipients of CAR-T cells who were admitted to the ICU were males.

2. ICU admitted

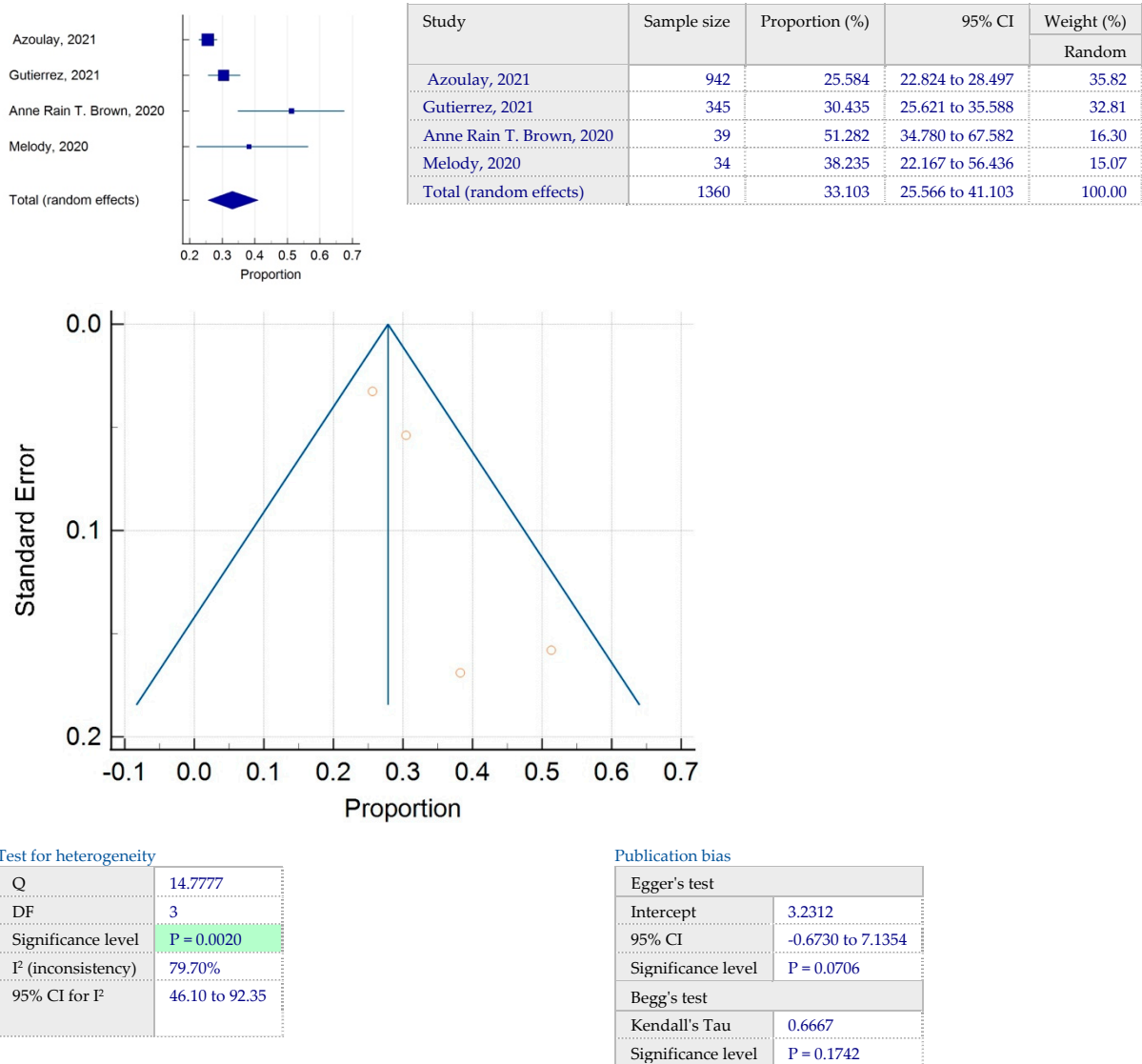


Figure 2. Forest plot of proportions of ICU admitted patients, in published studies.

Figure 2 shows the combined proportion for our outcome of interest – patients admitted to the ICU from total CAR-T recipients, as a percentage. On average, 33% CI-95% [26-41] of the recipients of CAR-T cells were admitted to the ICU. A substantial level of heterogeneity (80%) was reported.

3. ICU mortality

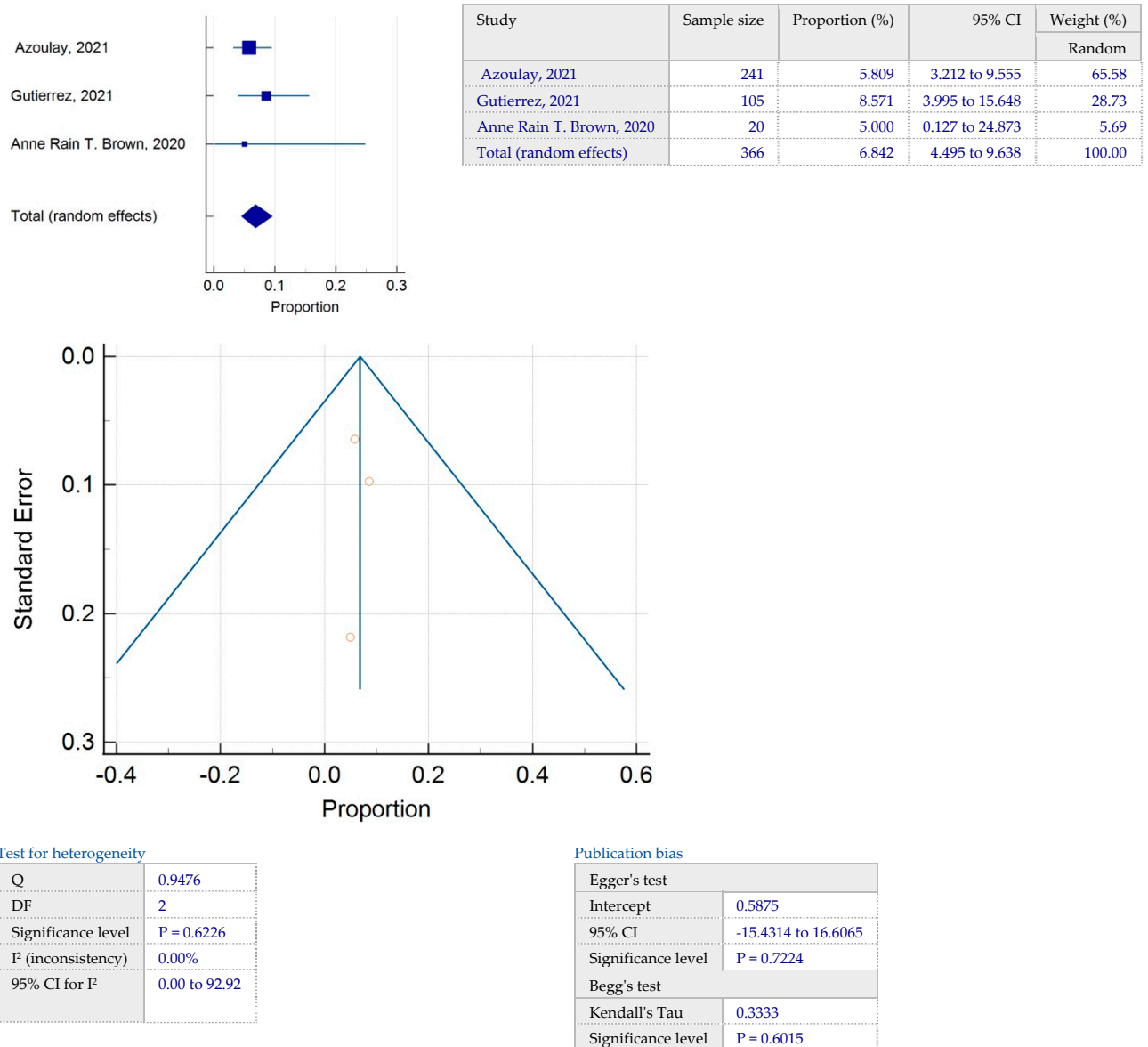


Figure 3. Forest plot of proportions of ICU admitted patients who died, in published studies.

Figure 3 shows the combined proportion for our outcome of interest – patients admitted to the ICU who died from total CAR-T recipients admitted in the ICU, as a percentage. On average, 7% CI-95% [5-10] of the recipients of CAR-T therapy who were admitted to the ICU died. A 0% level of heterogeneity was reported with a $p > 0.10$.

4. Hospital mortality

Study	Sample size	Proportion (%)	95% CI	Weight (%)
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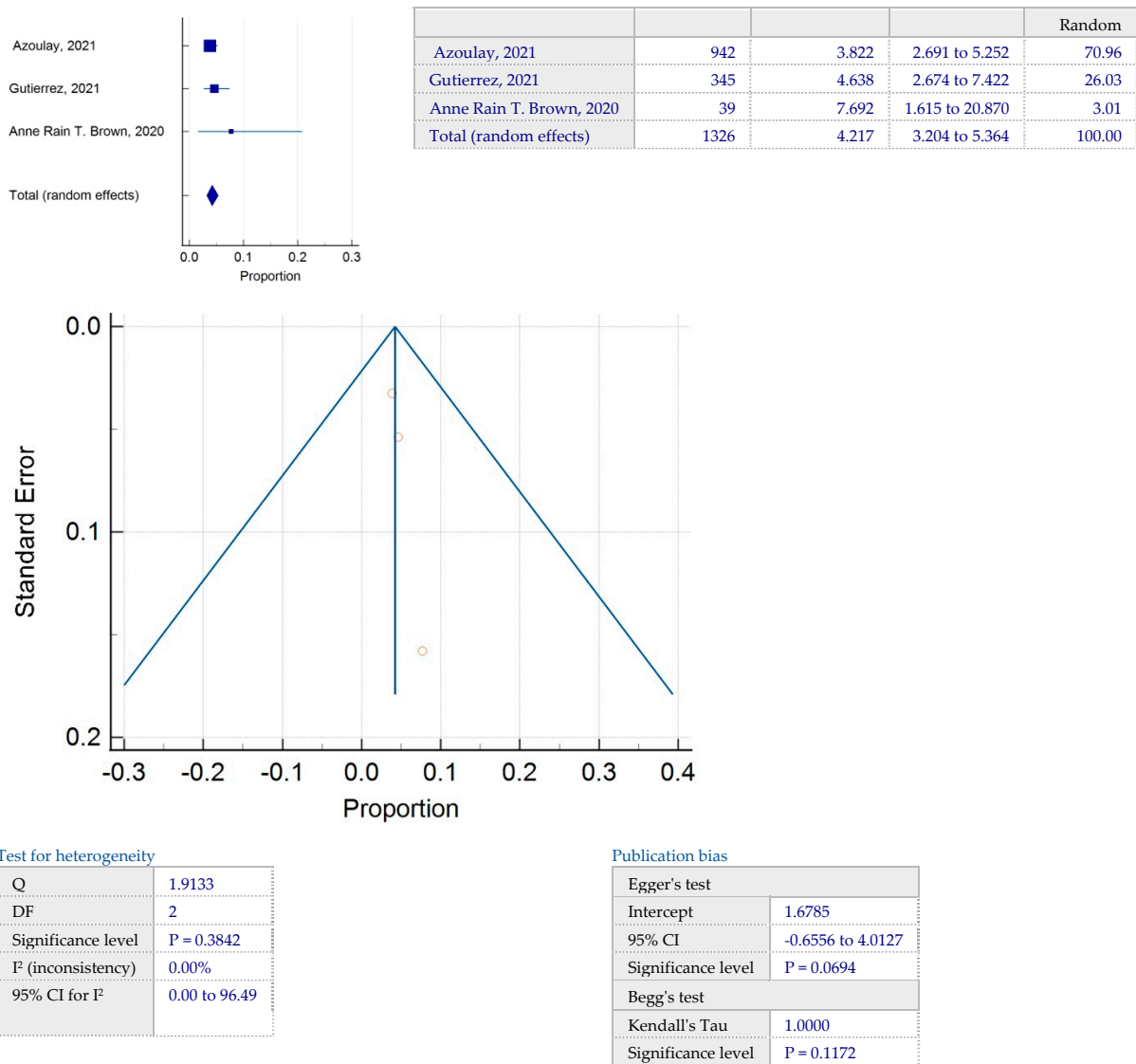


Figure 4. Forest plot of proportions of CAR-T recipients who died in the hospital, in published studies.

Figure 4 shows the combined proportion for our outcome of interest – CAR-T recipients patients who died in the hospital, as a percentage. On average, 4% CI-95% [3-5] of the CAR-T recipients died in the hospital. A 0% level of heterogeneity was reported with a $p > 0.10$.

5. Reasons for ICU admission – hypotension

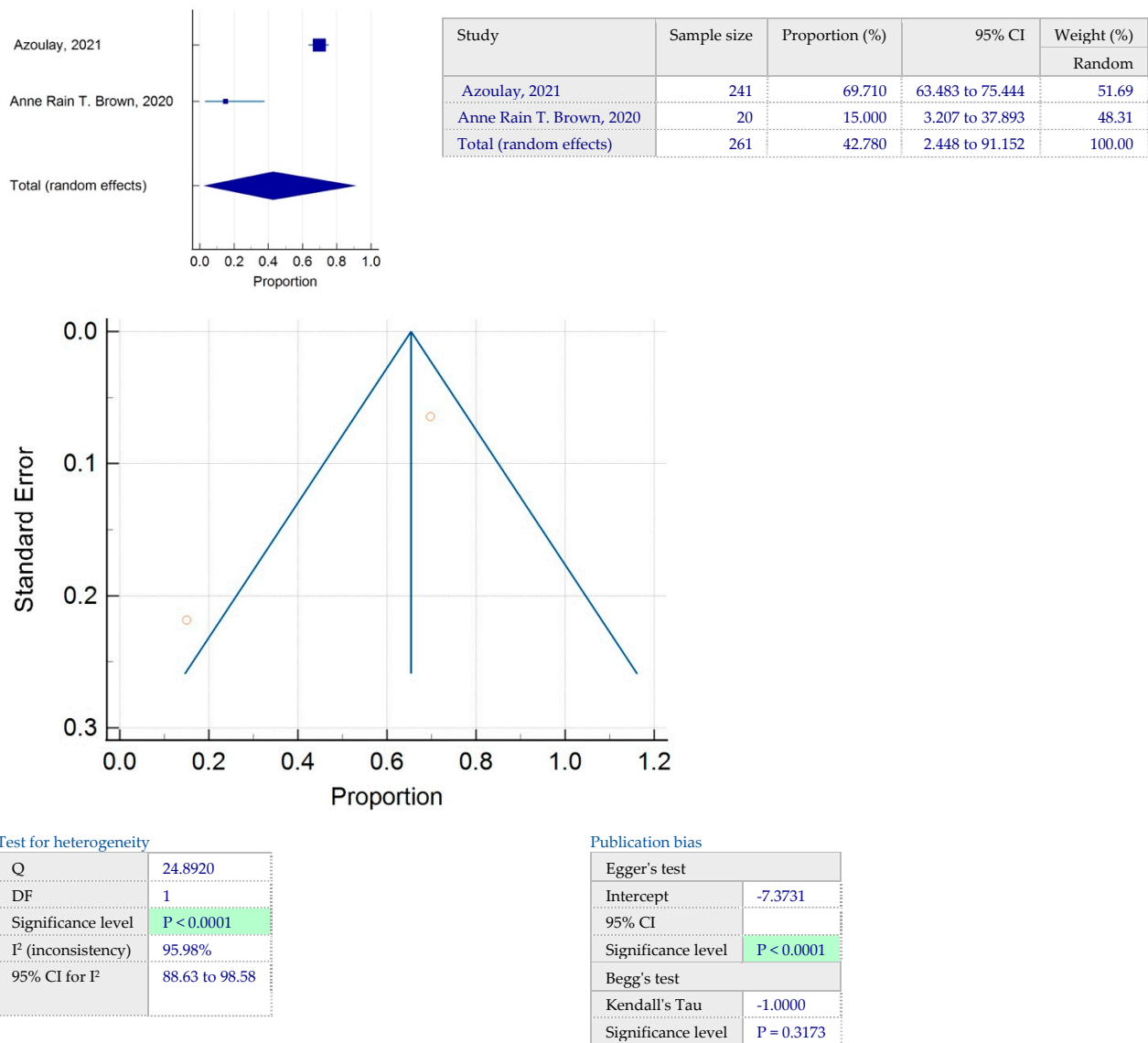


Figure 5. Forest plot of proportions of CAR-T recipients in which the main reason for admission to the ICU was hypotension, in published studies.

Figure 5 shows the combined proportion for our outcome of interest – hypotension as the main reason for admission to the ICU, as a percentage. On average, 42% CI-95% [3-91] of the CAR-T recipients were admitted to the ICU because of hypotension. A considerable level of heterogeneity was reported (96%).

6. Reasons for ICU admission – acute kidney injury

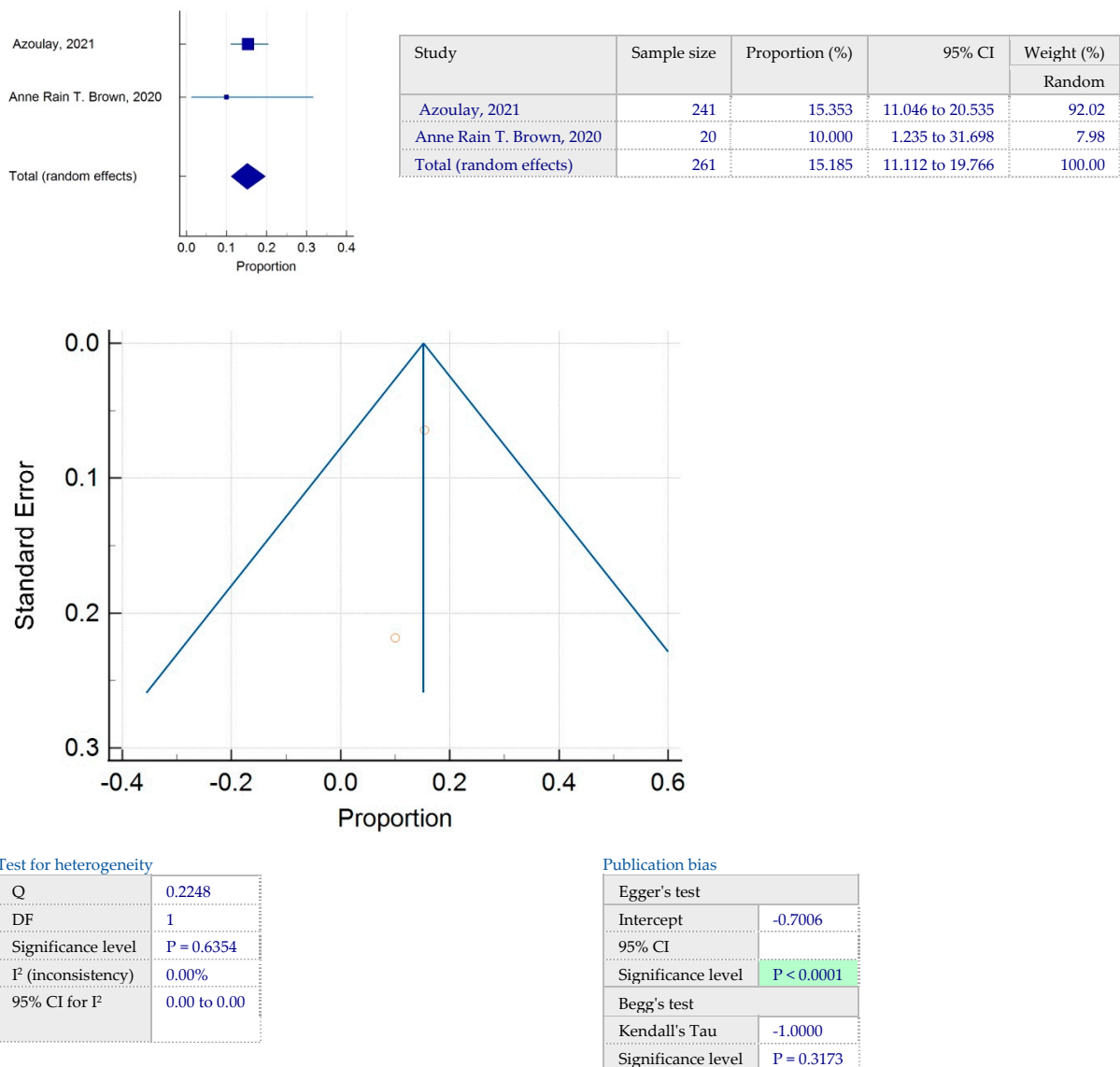


Figure 6. Forest plot of proportions of CAR-T recipients in which the main reason for admission to the ICU was acute kidney injury (AKI), in published studies.

Figure 6 shows the combined proportion for our outcome of interest – AKI as the main reason for admission to the ICU, as a percentage. On average, 15% CI-95% [11-19] of the CAR-T recipients were admitted to the ICU because of AKI. A 0% level of heterogeneity was reported with a $p > 0.10$.

7. Reasons ICU admission – acute respiratory failure

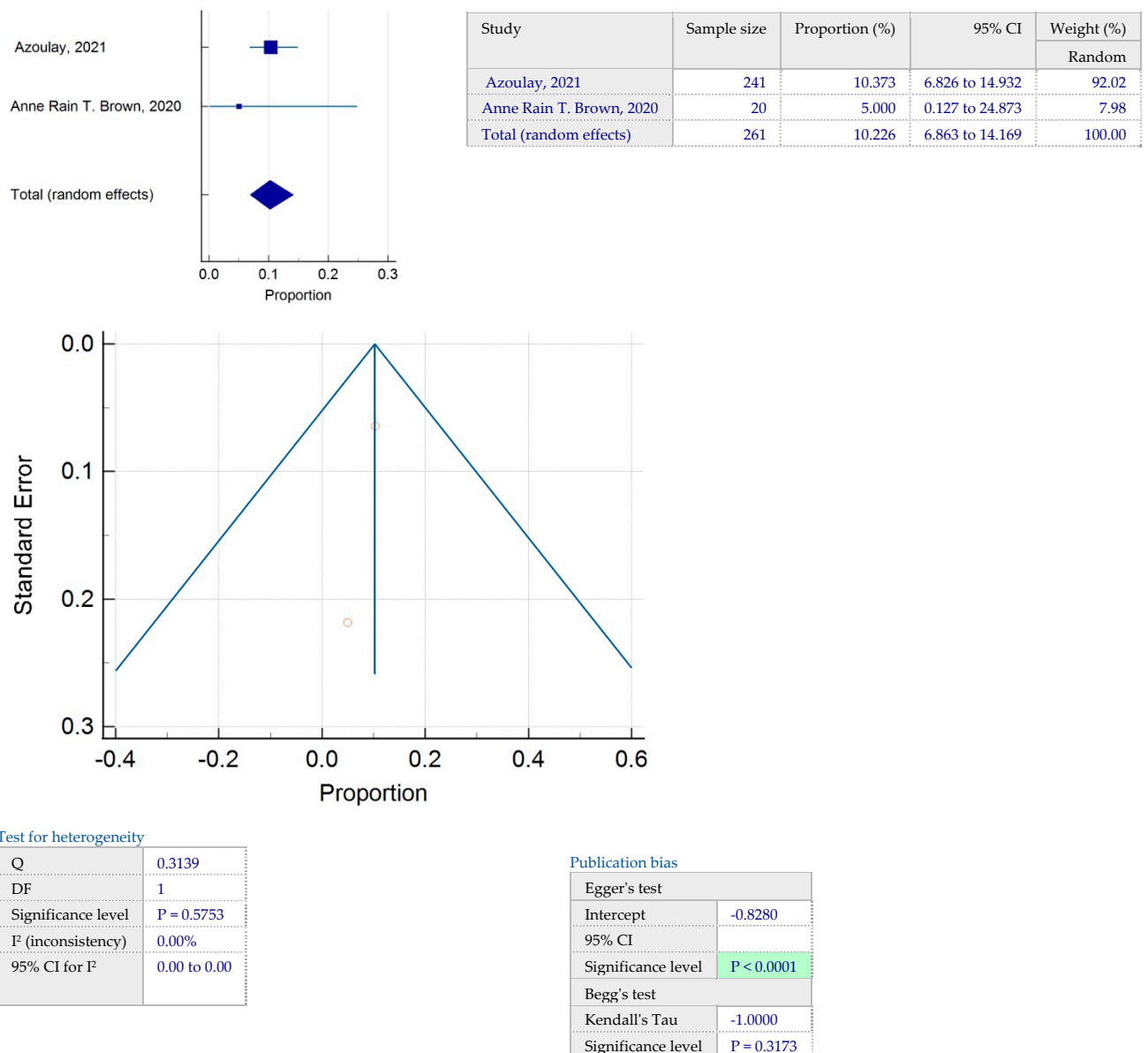


Figure 7. Forest plot of proportions of CAR-T recipients in which the main reason for admission to the ICU was acute respiratory failure, in published studies.

Figure 7 shows the combined proportion for our outcome of interest – acute respiratory failure as the main reason for admission to the ICU, as a percentage. On average, 10% CI-95% [7-14] of the CAR-T recipients were admitted to the ICU because of acute respiratory failure. A 0% level of heterogeneity was reported with a $p > 0.10$.

8. Reasons for ICU admission – altered mental status

Study	Sample size	Proportion (%)	95% CI	Weight (%)
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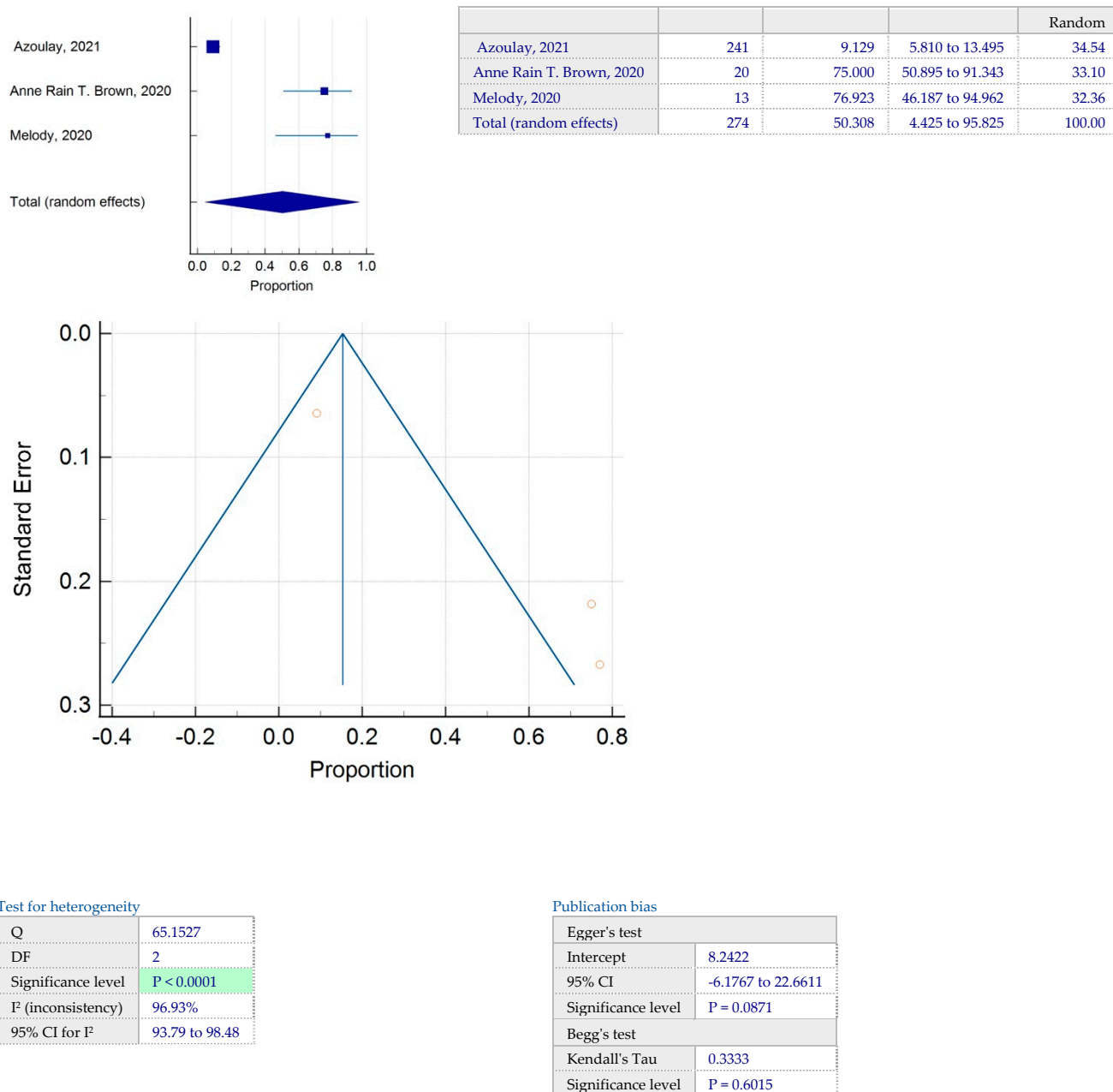


Figure 8. Forest plot of proportions of CAR-T recipients in which the main reason for admission to the ICU was altered mental status, in published studies.

Figure 8 shows the combined proportion for our outcome of interest – altered mental status as the main reason for admission to the ICU, as a percentage. On average, 50% CI-95% [4-95] of the CAR-T recipients were admitted to the ICU because of altered mental status. A considerable level of heterogeneity was reported (96%).

9. Number of chemotherapy lines before CAR-T infusion

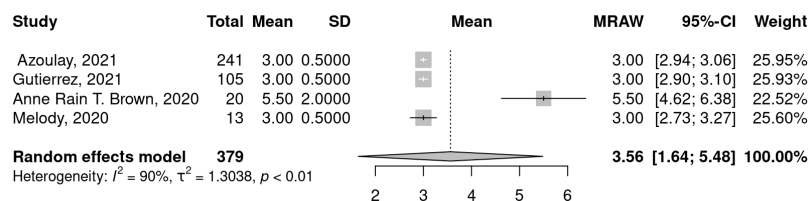
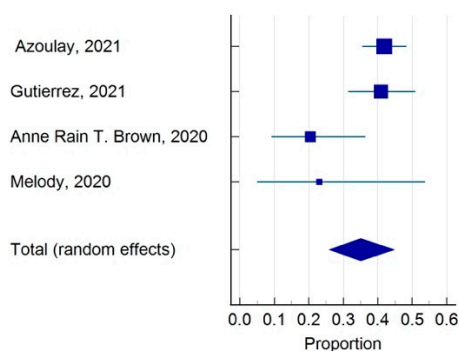


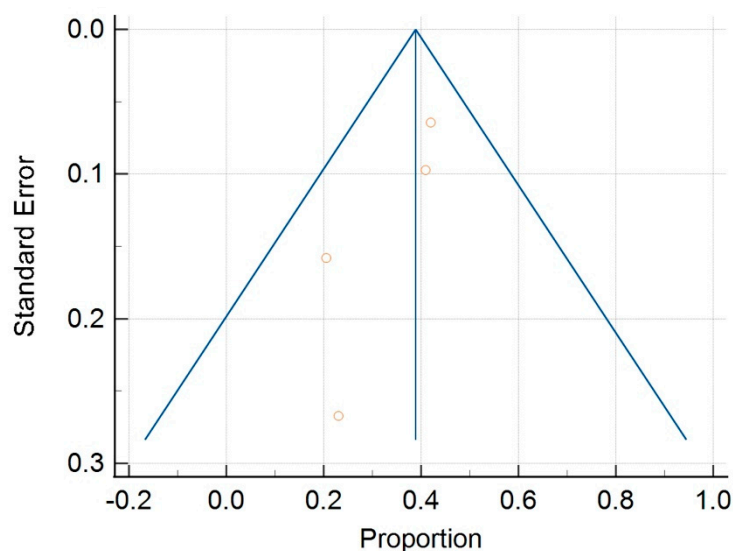
Figure 9. Forest plot of proportions of the number of chemotherapy lines patients received before CAR-T infusion, in published studies.

Figure 9 shows the combined proportion for our outcome of interest – the number of chemotherapy lines patients received before CAR-T infusion, as a crude mean. On average, the number of chemotherapy lines patients received before CAR-T infusion was 3,56, CI-95% [1,64; 5,48]. A considerable level of heterogeneity was reported (90%).

10. Isolated CRS



Study	Sample size	Proportion (%)	95% CI	Weight (%)
Azoulay, 2021	241	41.909	35.606 to 48.413	36.79
Gutierrez, 2021	105	40.952	31.451 to 50.978	31.02
Anne Rain T. Brown, 2020	39	20.513	9.296 to 36.464	21.24
Melody, 2020	13	23.077	5.038 to 53.813	10.95
Total (random effects)	398	35.071	25.854 to 44.887	100.00



Test for heterogeneity

Q	8.4614
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DF	3
Significance level	P = 0.0374

I ² (inconsistency)	64.55%
95% CI for I ²	0.00 to 87.99

Publication bias

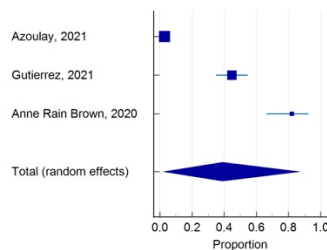
Egger's test	
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Intercept	-2.7338
95% CI	-8.1989 to 2.7313
Significance level	P = 0.1643
Begg's test	
Kendall's Tau	-0.6667
Significance level	P = 0.1742

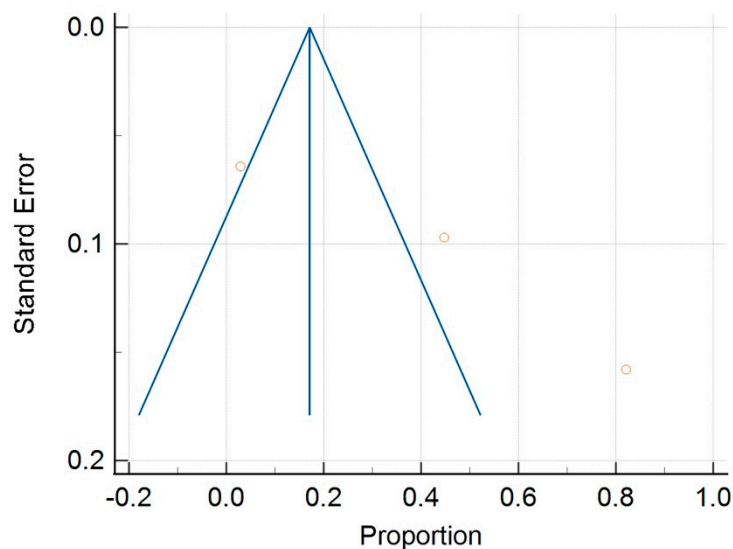
Figure 10. Forest plot of proportions of CAR-T recipients who were admitted to the ICU with isolated CRS, in published studies.

Figure 10 shows the combined proportion for our outcome of interest – isolated CRS at admission to the ICU, as a percentage. On average, 35% CI-95% [26-45] of the CAR-T recipients were admitted to the ICU with isolated CRS. A substantial level of heterogeneity was reported (65%).

11. Isolated ICANS



Study	Sample size	Proportion (%)	95% CI	Weight (%)
				Random
Azoulay, 2021	241	2.905	1.176 to 5.893	33.67
Gutierrez, 2021	105	44.762	35.047 to 54.780	33.46
Anne Rain Brown, 2020	39	82.051	66.465 to 92.465	32.87
Total (random effects)	385	38.970	2.084 to 87.105	100.00



Test for heterogeneity

Q	177.9161
DF	2
Significance level	P < 0.0001
I ² (inconsistency)	98.88%
95% CI for I ²	98.12 to 99.33

Publication bias

Egger's test	
Intercept	22.2152
95% CI	-61.0877 to 105.5181
Significance level	P = 0.1827
Begg's test	
Kendall's Tau	1.0000
Significance level	P = 0.1172

Figure 11. Forest plot of proportions of CAR-T recipients who were admitted to the ICU with isolated ICANS, in published studies.

Figure 11 shows the combined proportion for our outcome of interest – isolated ICANS at admission to the ICU, as a percentage. On average, 39% CI-95% [2-87] of the CAR-T recipients were admitted to the ICU with isolated ICANS. A considerable level of heterogeneity was reported (99%).

12.CRS and ICANS

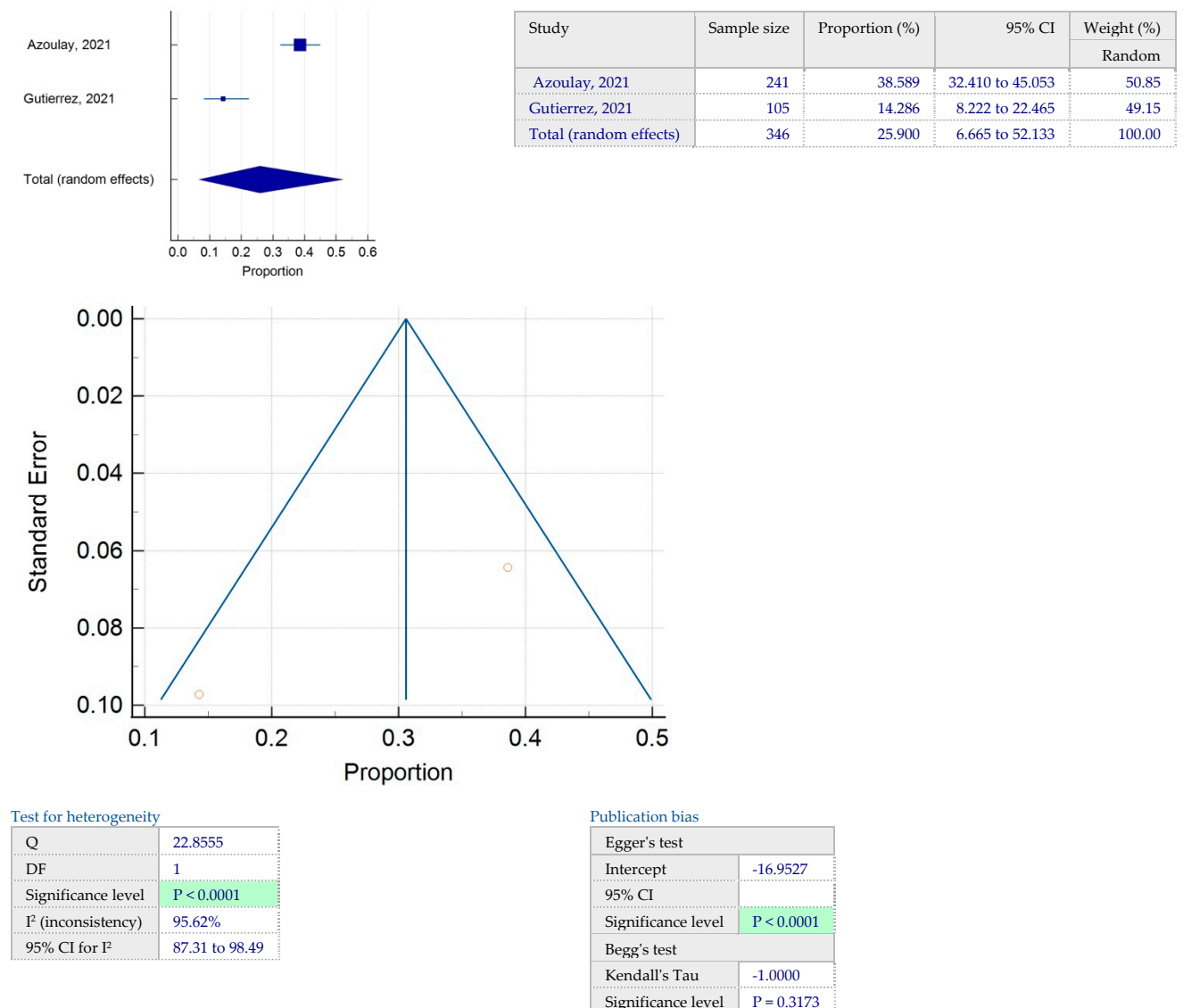


Figure 12. Forest plot of proportions of CAR-T recipients who were admitted to the ICU with CRS and ICANS, in published studies.

Figure 12 shows the combined proportion for our outcome of interest – CRS and ICANS at admission to the ICU, as a percentage. On average, 26% CI-95% [7-52] of the CAR-T recipients were admitted to the ICU with CRS and ICANS. A considerable level of heterogeneity was reported (95%).

13.CRS presentation - fever

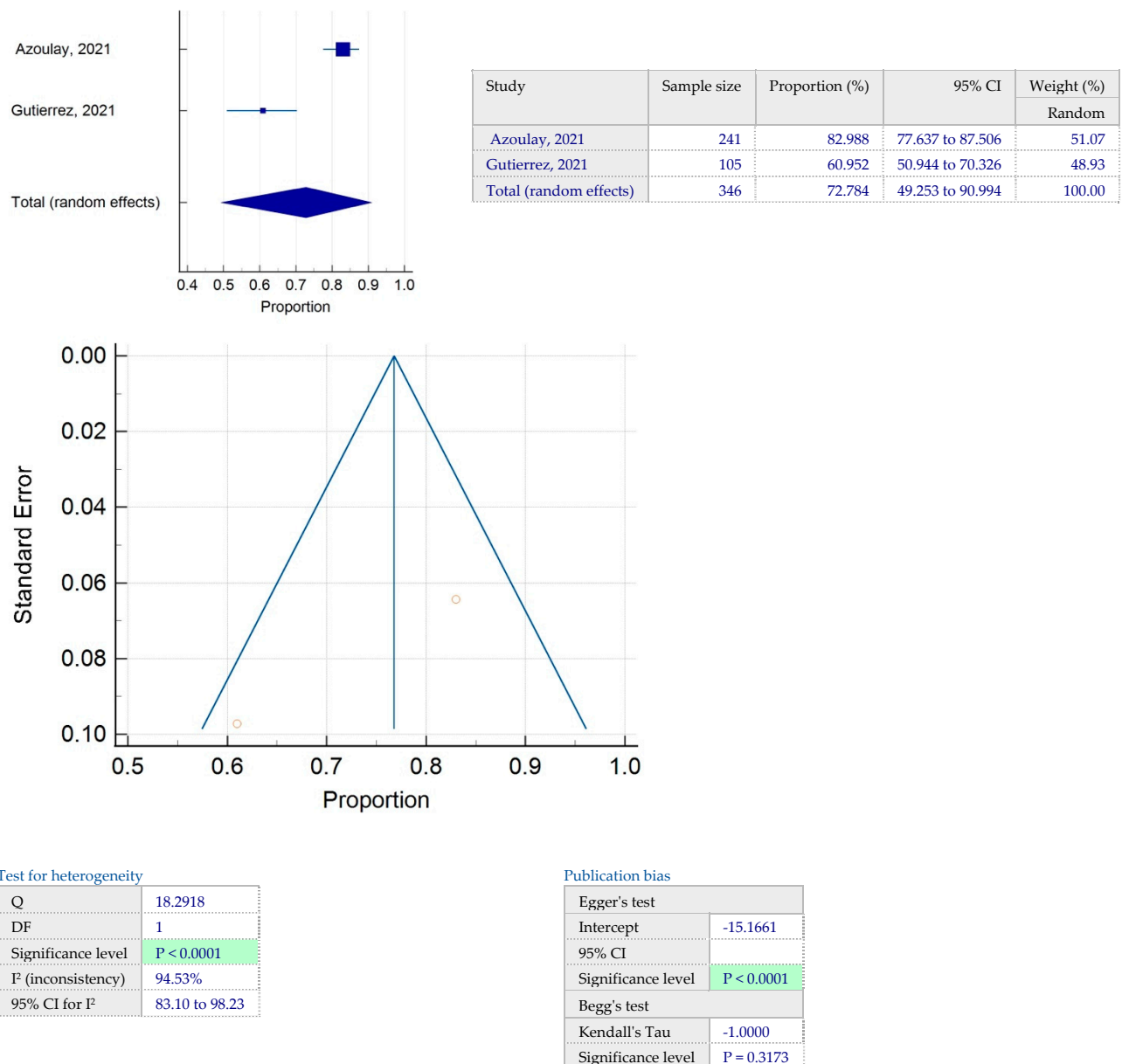


Figure 13. Forest plot of proportions of CAR-T recipients who were admitted to the ICU with fever as the main symptom of CRS, in published studies.

Figure 13 shows the combined proportion for our outcome of interest – fever as the main symptom of CRS at admission to the ICU, as a percentage. On average, 72% CI-95% [49-91] of the CAR-T recipients were admitted to the ICU with fever as the main symptom of CRS. A considerable level of heterogeneity was reported (95%).

14. CRS presentation - hypotension

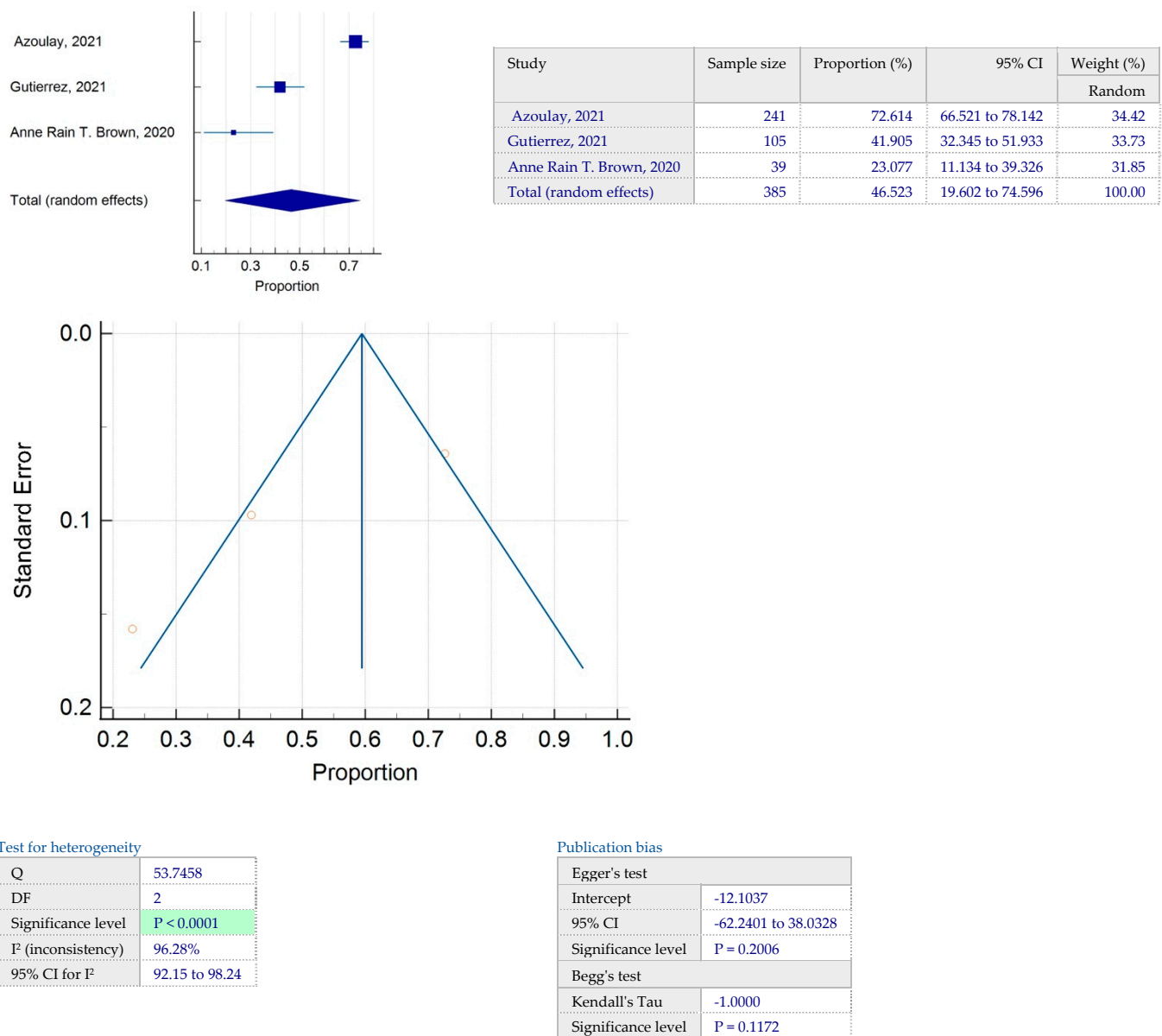


Figure 14. Forest plot of proportions of CAR-T recipients who were admitted to the ICU with hypotension as the main symptom of CRS, in published studies.

Figure 14 shows the combined proportion for our outcome of interest – hypotension as the main symptom of CRS at admission to the ICU, as a percentage. On average, 46% CI-95% [20-75] of the CAR-T recipients were admitted to the ICU with hypotension as the main symptom of CRS. A considerable level of heterogeneity was reported (96%).

15.CRS presentation – arrhythmias

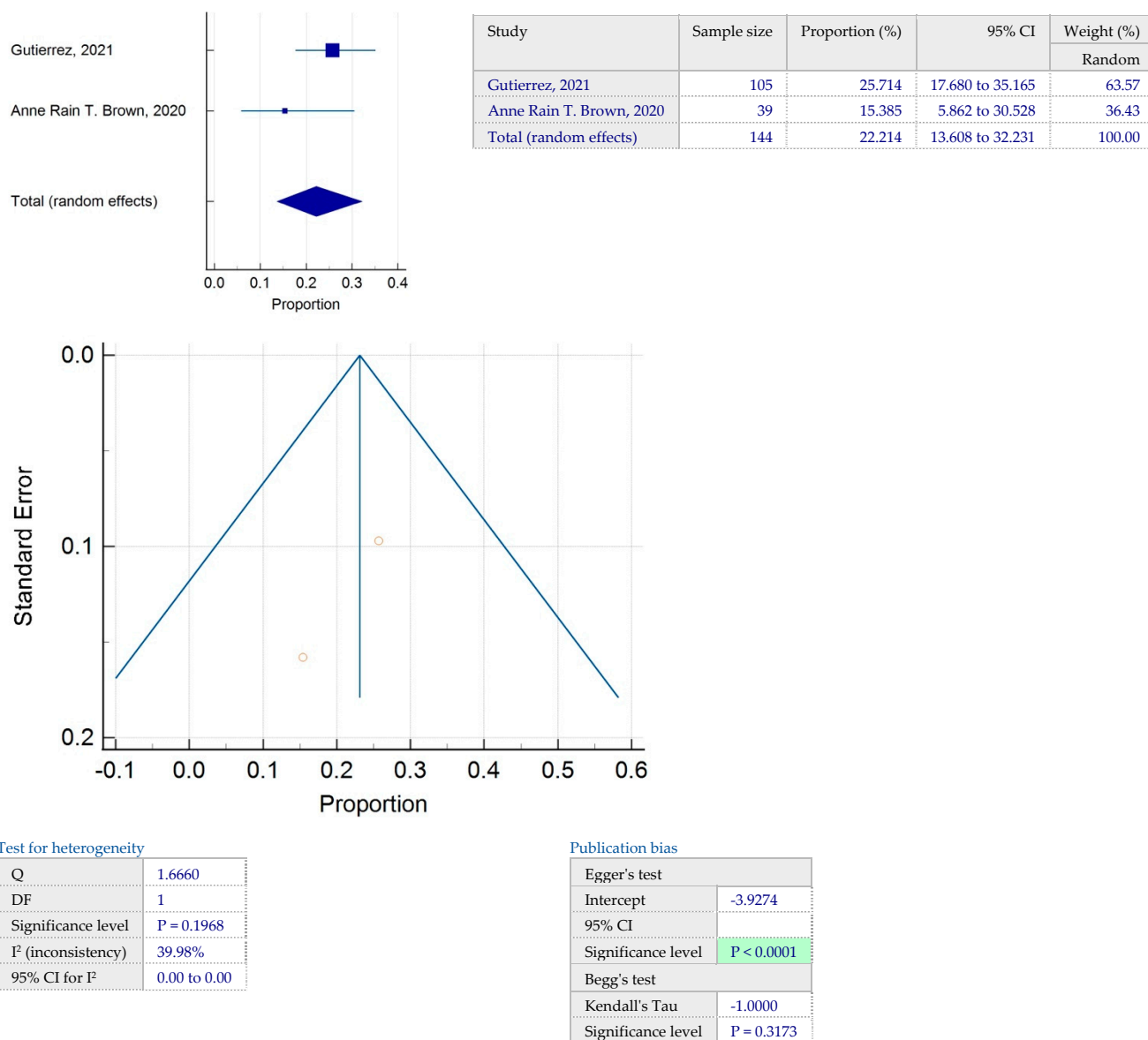
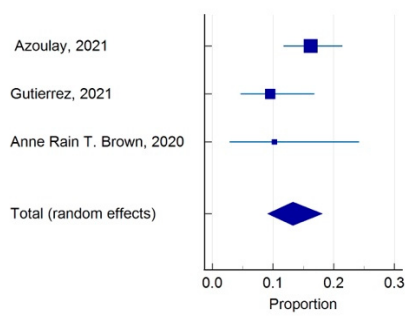


Figure 15. Forest plot of proportions of CAR-T recipients who were admitted to the ICU with arrhythmias as the main symptom of CRS, in published studies.

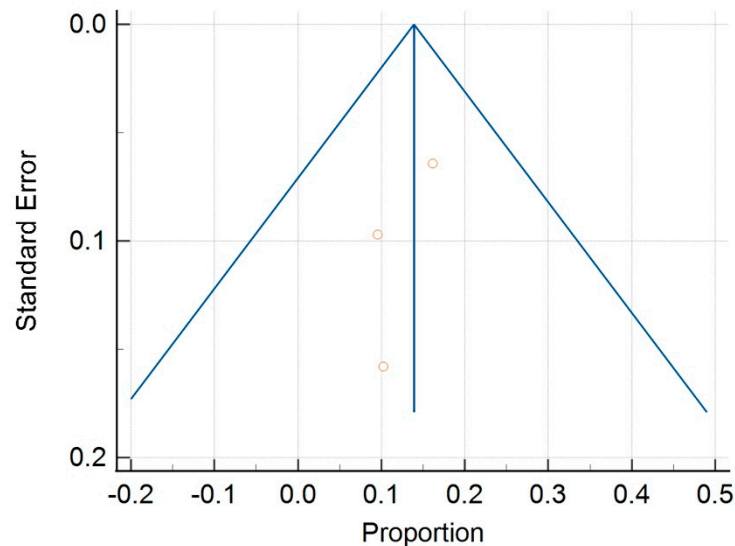
Figure 15 shows the combined proportion for our outcome of interest – arrhythmias as the main symptom of CRS at admission to the ICU, as a percentage. On average, 22% CI-95% [14-32] of the CAR-T recipients were admitted to the ICU with arrhythmias as the main symptom of CRS. A moderate level of heterogeneity was reported (40%) with a $p > 0.10$.

16.CRS presentation – acute kidney injury

Study	Sample size	Proportion (%)	95% CI	Weight (%)
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				Random
Azoulay, 2021	241	16.183	11.768 to 21.451	51.76
Gutierrez, 2021	105	9.524	4.662 to 16.818	32.61
Anne Rain T. Brown, 2020	39	10.256	2.866 to 24.221	15.63
Total (random effects)	385	13.282	9.078 to 18.144	100.00



Test for heterogeneity

Q	2.9984
DF	2
Significance level	P = 0.2233
I ² (inconsistency)	33.30%
95% CI for I ²	0.00 to 97.76

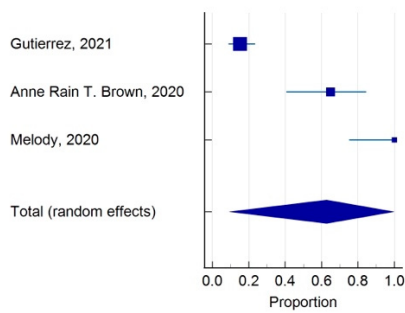
Publication bias

Egger's test	
Intercept	-2.2177
95% CI	-28.0187 to 23.5833
Significance level	P = 0.4720
Begg's test	
Kendall's Tau	-0.3333
Significance level	P = 0.6015

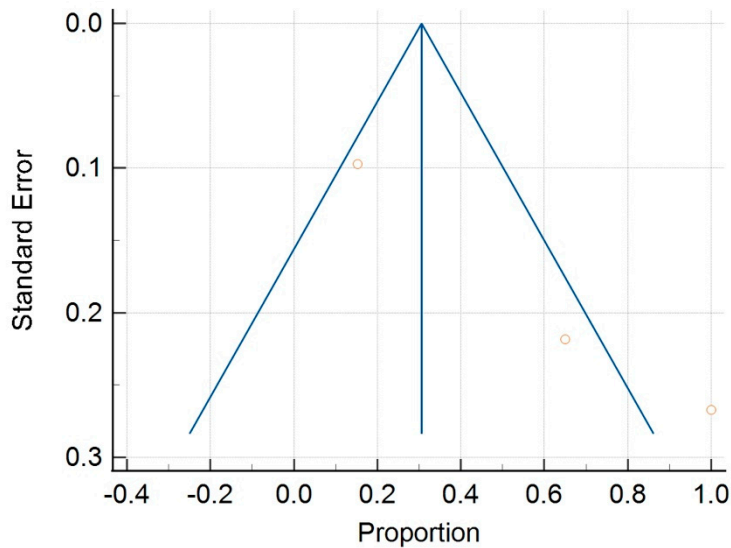
Figure 16. Forest plot of proportions of CAR-T recipients who were admitted to the ICU with AKI as the main symptom of CRS, in published studies.

Figure 16 shows the combined proportion for our outcome of interest – AKI as the main symptom of CRS at admission to the ICU, as a percentage. On average, 13% CI-95% [9-18] of the CAR-T recipients were admitted to the ICU with AKI as the main symptom of CRS. A low level of heterogeneity was reported (33%) with a $p > 0.10$.

17. CRS developed during ICU stay



Study	Sample size	Proportion (%)	95% CI	Weight (%)
Gutierrez, 2021	105	15.238	8.968 to 23.563	34.32
Anne Rain T. Brown, 2020	20	65.000	40.781 to 84.609	33.18
Melody, 2020	13	100.000	75.295 to 100.000	32.50
Total (random effects)	138	62.760	9.366 to 99.720	100.00



Test for heterogeneity

Q	64.1914
DF	2
Significance level	P < 0.0001
I ² (inconsistency)	96.88%
95% CI for I ²	93.67 to 98.47

Publication bias

Egger's test	
Intercept	10.7162
95% CI	-14.0078 to 35.4402
Significance level	P = 0.1144
Begg's test	
Kendall's Tau	1.0000
Significance level	P = 0.1172

Figure 17. Forest plot of proportions of CAR-T recipients who developed CRS during ICU stay, in published studies.

Figure 17 shows the combined proportion for our outcome of interest – patients who developed CRS during ICU stay, as a percentage. On average, 62% CI-95% [9,3-99] of the CAR-T recipients developed CRS during ICU stay. A considerable level of heterogeneity was reported (97%).

18.ICANS developed during ICU stay

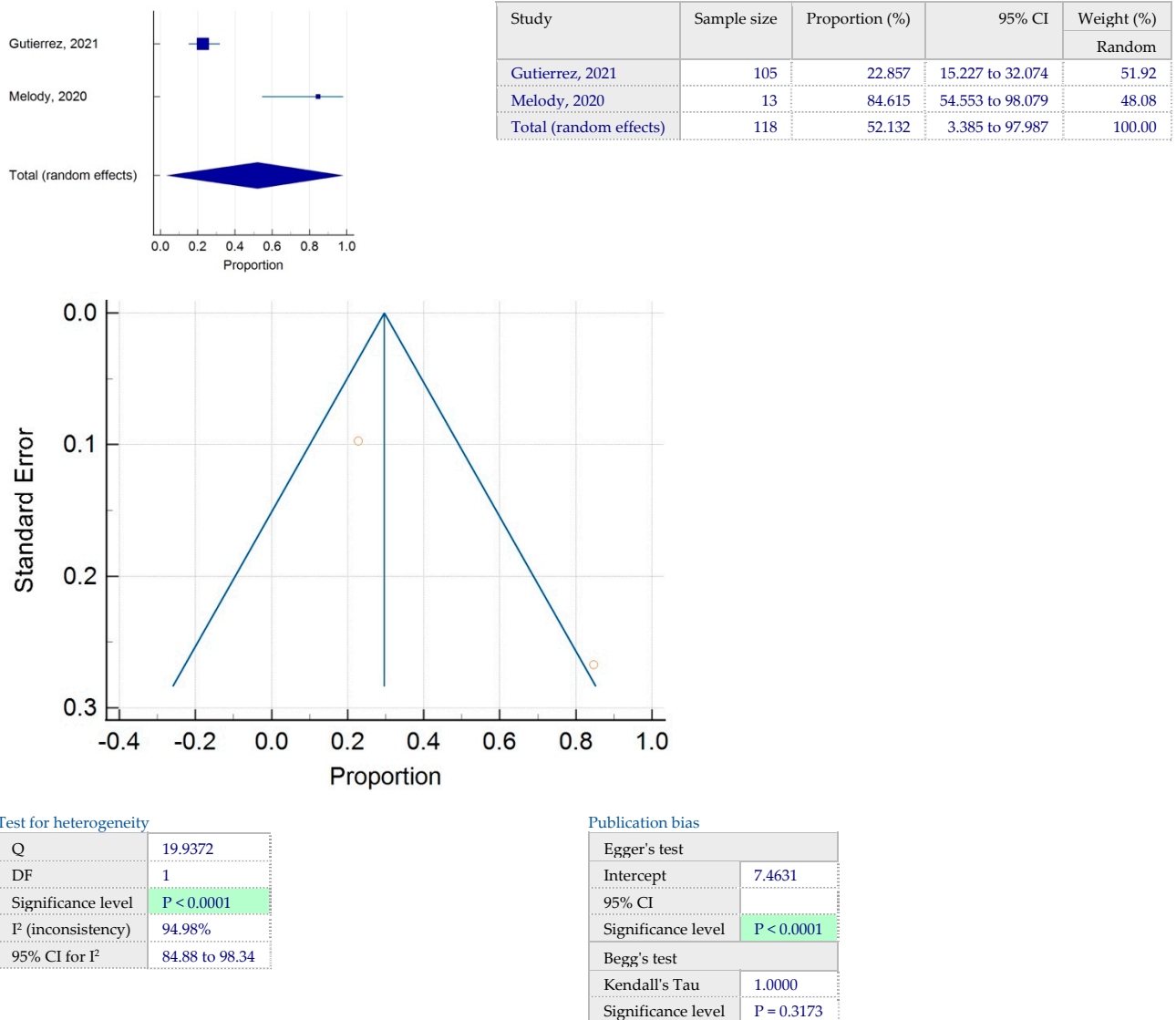


Figure 18. Forest plot of proportions of CAR-T recipients who developed ICANS during ICU stay, in published studies.

Figure 18 shows the combined proportion for our outcome of interest – patients who developed ICANS during ICU stay, as a percentage. On average, 52% CI-95% [3,3-98] of the CAR-T recipients developed ICANS during their ICU stay. A considerable level of heterogeneity was reported (95%).

19. High-flow nasal oxygen, non-invasive ventilation required

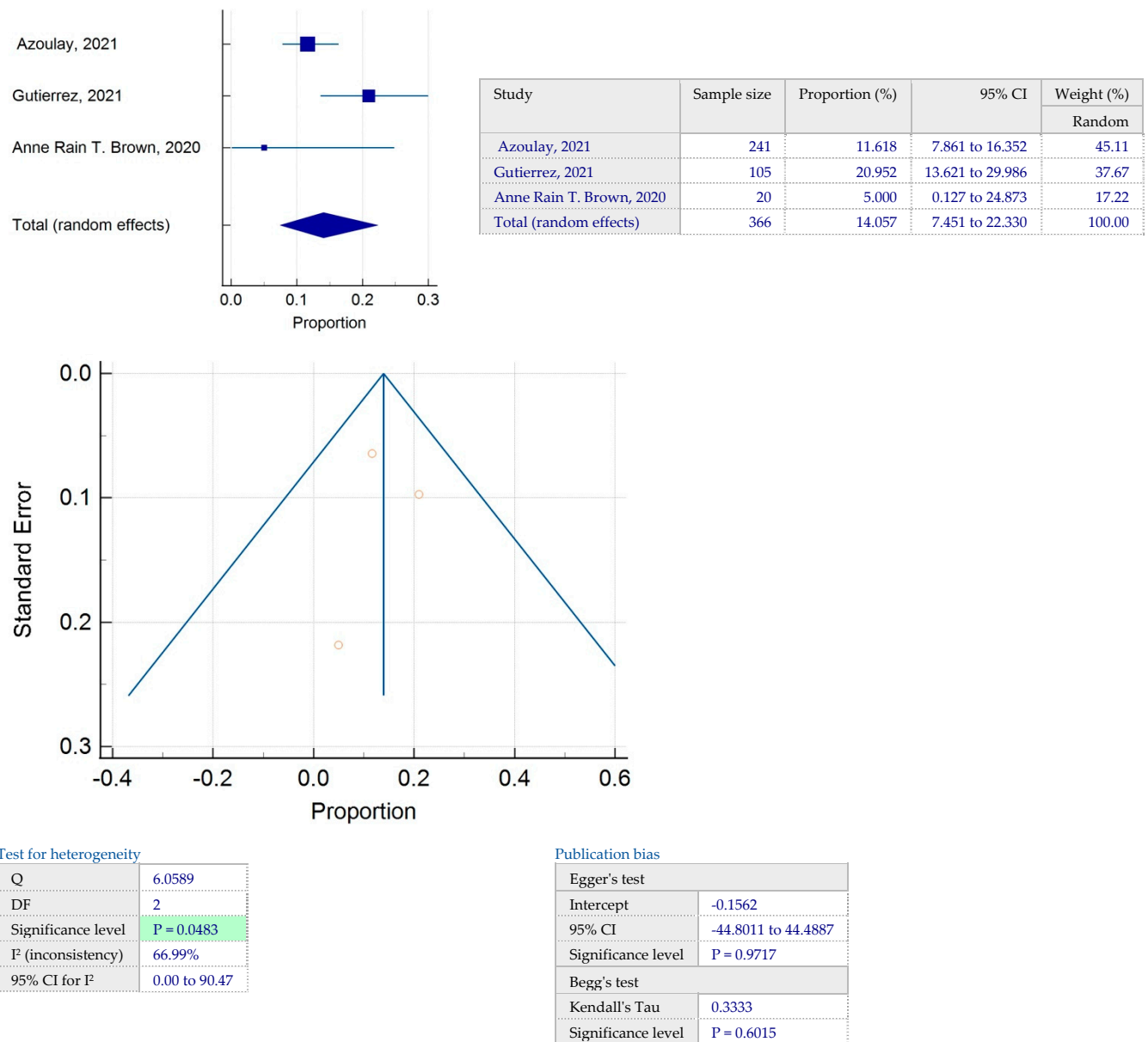


Figure 19. Forest plot of proportions of CAR-T recipients who required high-flow nasal oxygen or noninvasive ventilation during their ICU stay, in published studies.

Figure 19 shows the combined proportion for our outcome of interest – patients who required high-flow nasal oxygen or noninvasive ventilation during their ICU stay, as a percentage. On average, 14% CI-95% [7,5-22] of the CAR-T recipients required high-flow nasal oxygen or noninvasive ventilation during their ICU stay. A substantial level of heterogeneity was reported (67%).

20. Vasoactive drugs

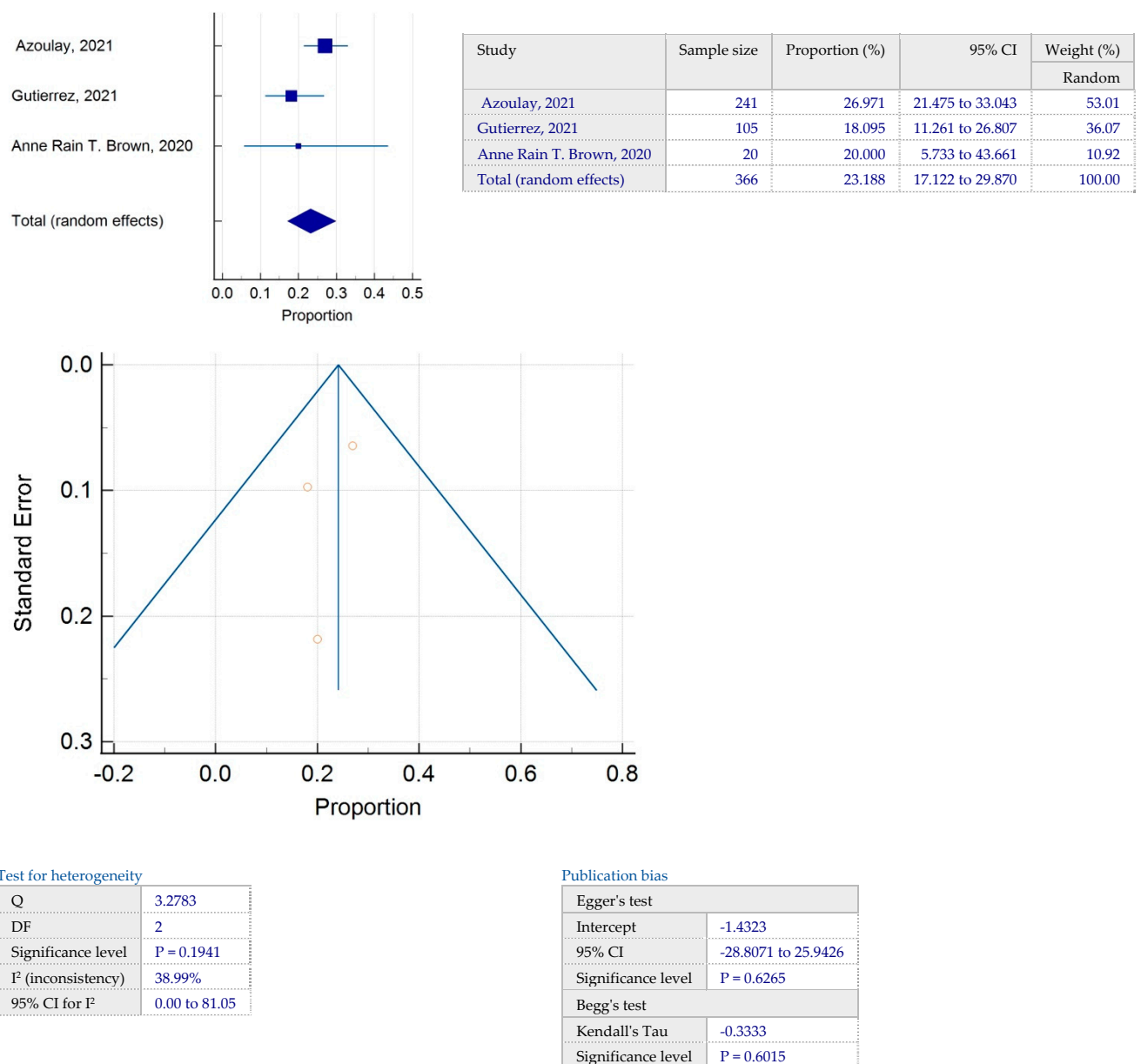


Figure 20. Forest plot of proportions of CAR-T recipients who required vasoactive drugs during ICU stay, in published studies.

Figure 20 shows the combined proportion for our outcome of interest – patients who required vasoactive drugs during ICU stay, as a percentage. On average, 23% CI-95% [17-29] of the CAR-T recipients required vasoactive drugs during their ICU stay. A moderate level of heterogeneity was reported (39%) with a $p > 0.10$.

21. Renal replacement therapy

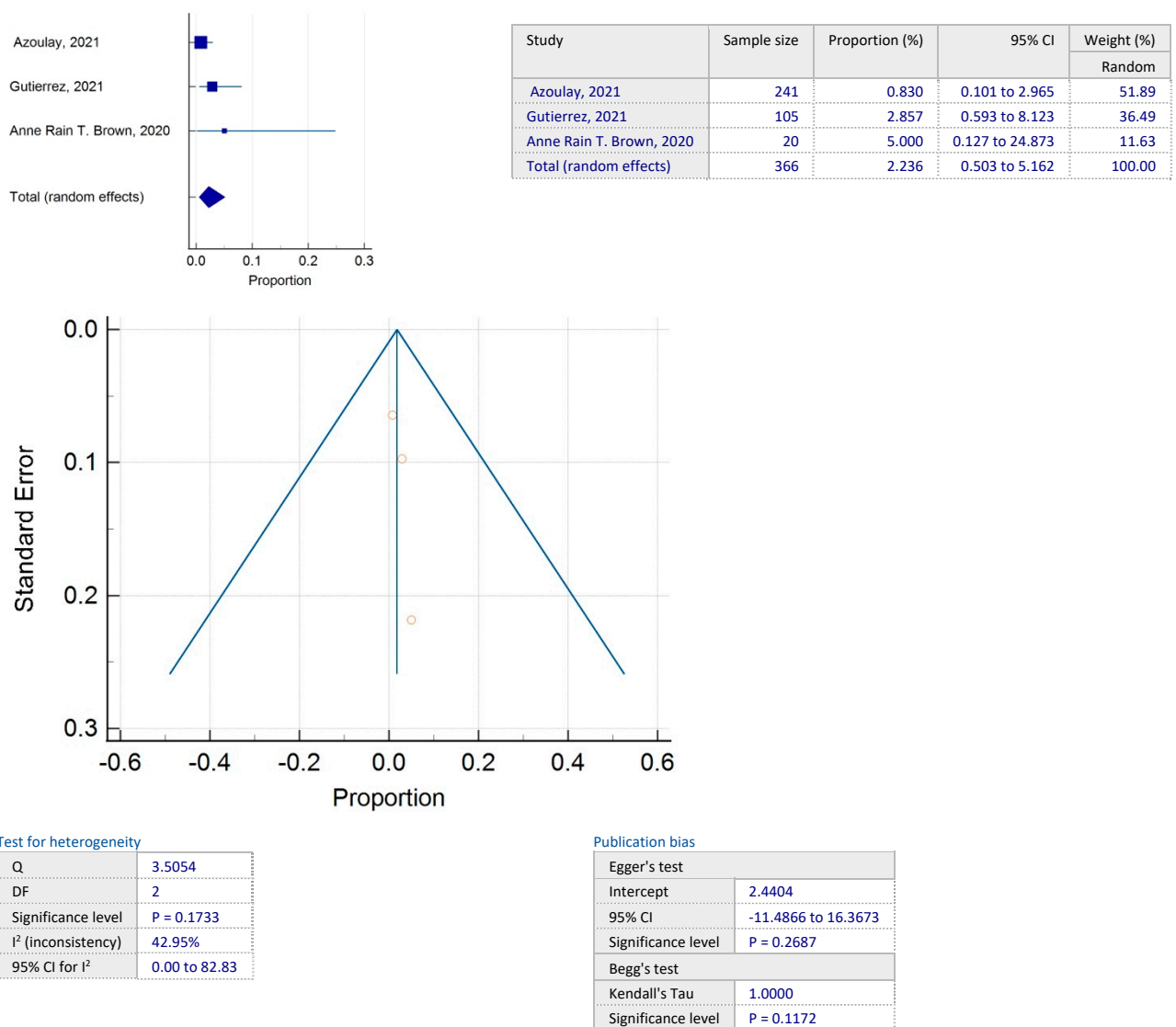
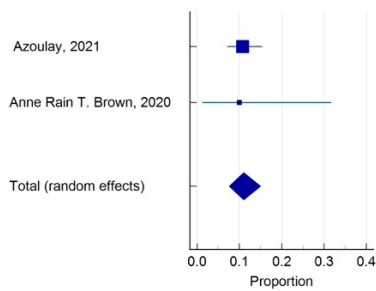


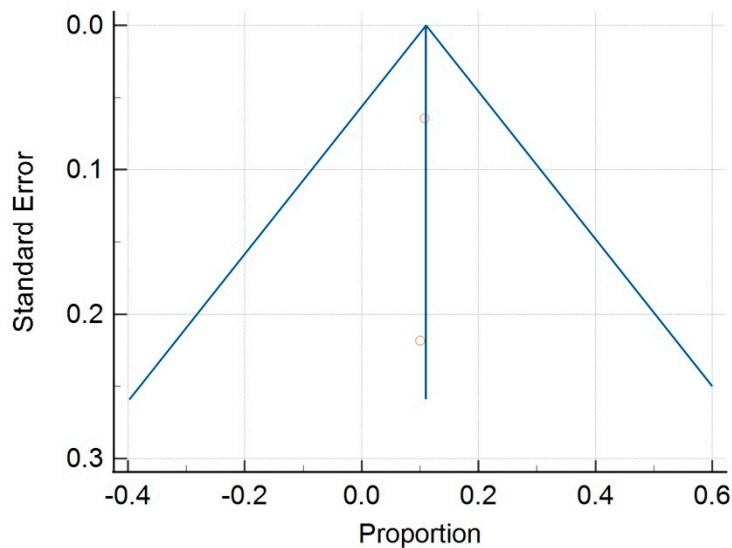
Figure 21. Forest plot of proportions of CAR-T recipients who required renal replacement therapy (RRT) during ICU stay, in published studies.

Figure 21 shows the combined proportion for our outcome of interest – patients who required RRT during ICU stay, as a percentage. On average, 2% CI-95% [0.5-5] of the CAR-T recipients required RRT during ICU stay. A moderate level of heterogeneity was reported (43%) with a $p > 0.10$.

22. Mechanical ventilation during ICU stay



Study	Sample size	Proportion (%)	95% CI	Weight (%)
Azoulay, 2021	241	10.788	7.169 to 15.407	92.02
Anne Rain T. Brown, 2020	20	10.000	1.235 to 31.698	7.98
Total (random effects)	261	11.016	7.526 to 15.076	100.00



Test for heterogeneity

Q	0.01389
DF	1
Significance level	P = 0.9062
I ² (inconsistency)	0.00%
95% CI for I ²	0.00 to 0.00

Publication bias

Egger's test	
Intercept	0.1741
95% CI	
Significance level	P < 0.0001
Begg's test	
Kendall's Tau	1.0000
Significance level	P = 0.3173

Figure 22. Forest plot of proportions of CAR-T recipients who required invasive mechanical ventilation during ICU stay, in published studies.

Figure 22 shows the combined proportion for our outcome of interest – patients who required invasive mechanical ventilation during ICU stay, as a percentage. On average, 11% CI-95%[7,5-15] of the CAR-T recipients required invasive mechanical ventilation during ICU stay. A 0% level of heterogeneity was reported with a $p > 0.10$.

23. Readmission to the ICU within 30 days

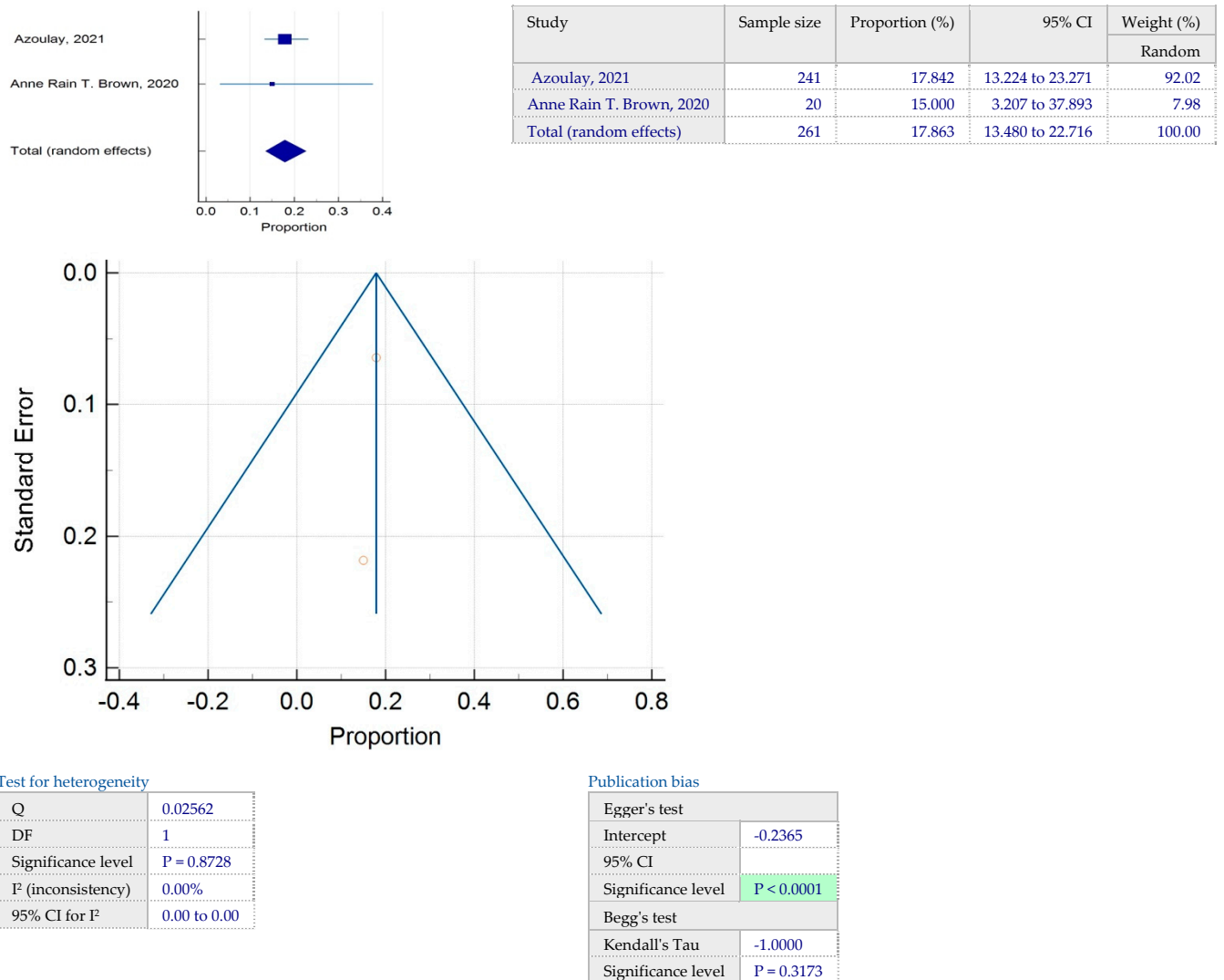
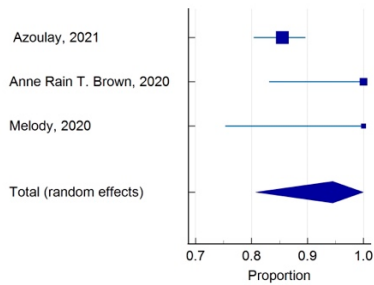


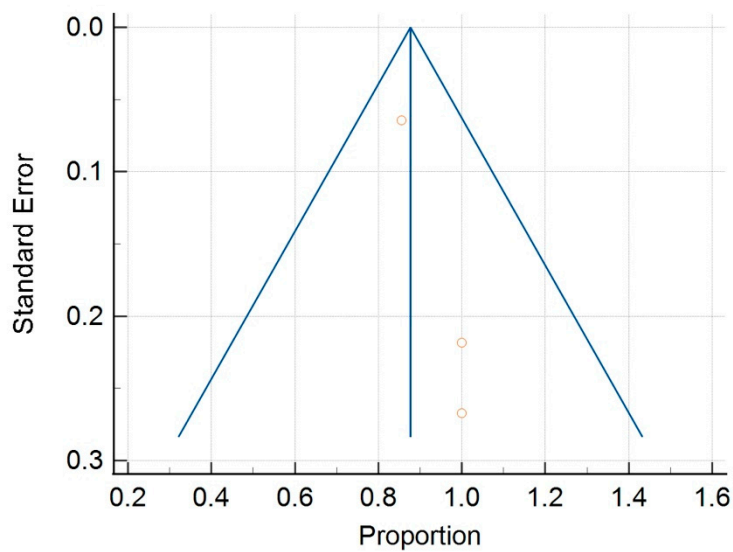
Figure 23. Forest plot of proportions of CAR-T recipients who were readmitted to the ICU within 30 days, in published studies.

Figure 23 shows the combined proportion for our outcome of interest – patients who were readmitted to the ICU within 30 days, as a percentage. On average, 18% CI-95% [13,5-23] of the CAR-T recipients were readmitted to the ICU within 30 days. A 0% level of heterogeneity was reported with a $p > 0.10$.

24.Malignancy



Study	Sample size	Proportion (%)	95% CI	Weight (%)
Azoulay, 2021	241	85.477	80.385 to 89.671	42.31
Anne Rain T. Brown, 2020	20	100.000	83.157 to 100.000	30.84
Melody, 2020	13	100.000	75.295 to 100.000	26.85
Total (random effects)	274	94.508	80.730 to 99.965	100.00



Test for heterogeneity

Q	9.1328
DF	2
Significance level	P = 0.0104
I ² (inconsistency)	78.10%
95% CI for I ²	29.36 to 93.21

Publication bias

Egger's test	
Intercept	3.0556
95% CI	-4.6350 to 10.7462
Significance level	P = 0.1245
Begg's test	
Kendall's Tau	0.3333
Significance level	P = 0.6015

Figure 24. Forest plot of proportions of patients who had the diagnosis of lymphoma or follicular lymphoma for which they received CAR-T therapy, in published studies.

Figure 24 shows the combined proportion for our outcome of interest – patients who had a diagnosis of lymphoma or follicular lymphoma for which they received CAR-T therapy, as a percentage. On average, 95% CI-95%[80-99] of the CAR-T recipients had a diagnosis of lymphoma or follicular lymphoma. A considerable level of heterogeneity was reported (78%).