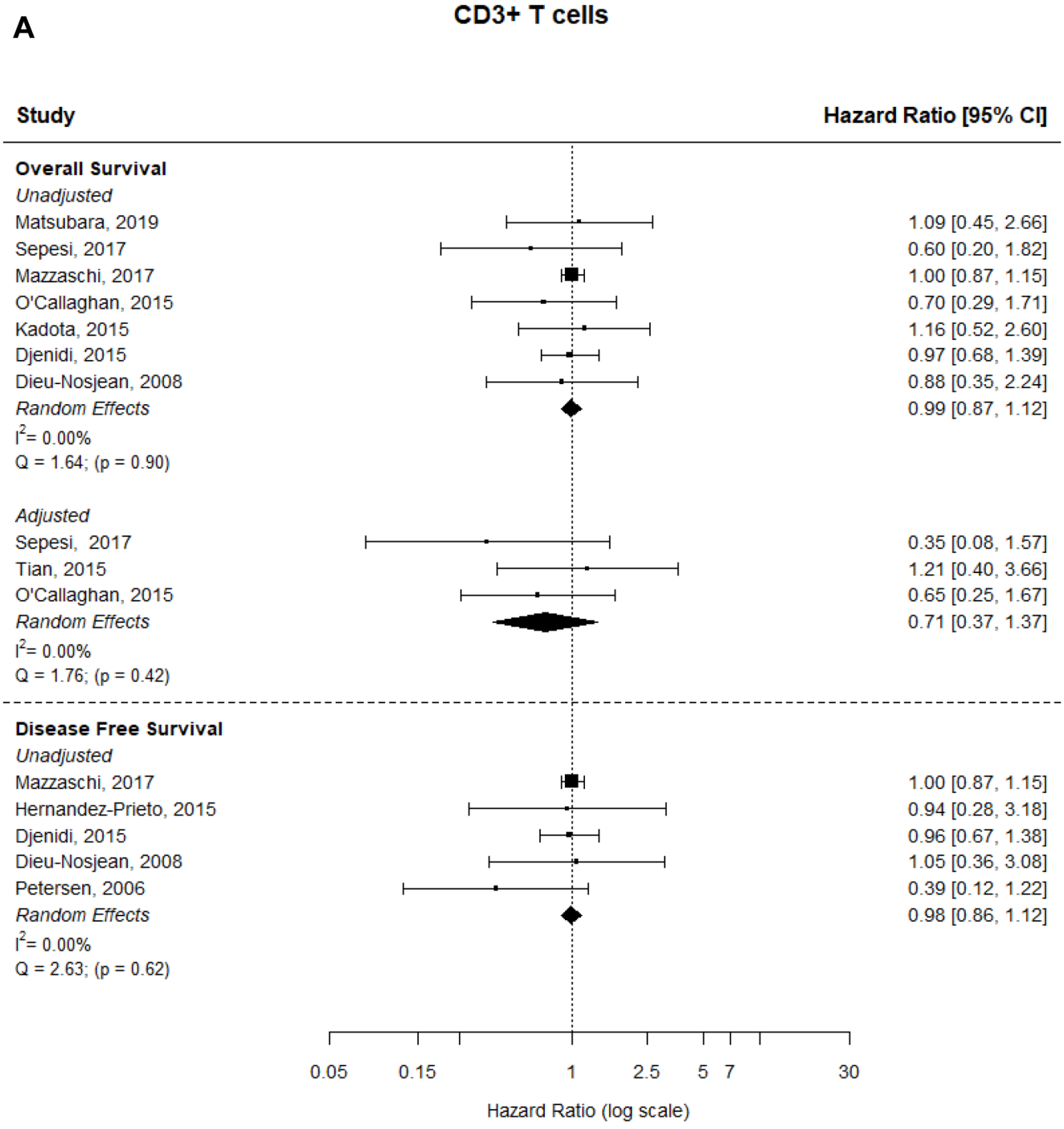
Prognostic value of immune cells in the tumor microenvironment of early-stage lung cancer: a meta-analysis

SUPPLEMENTARY MATERIALS

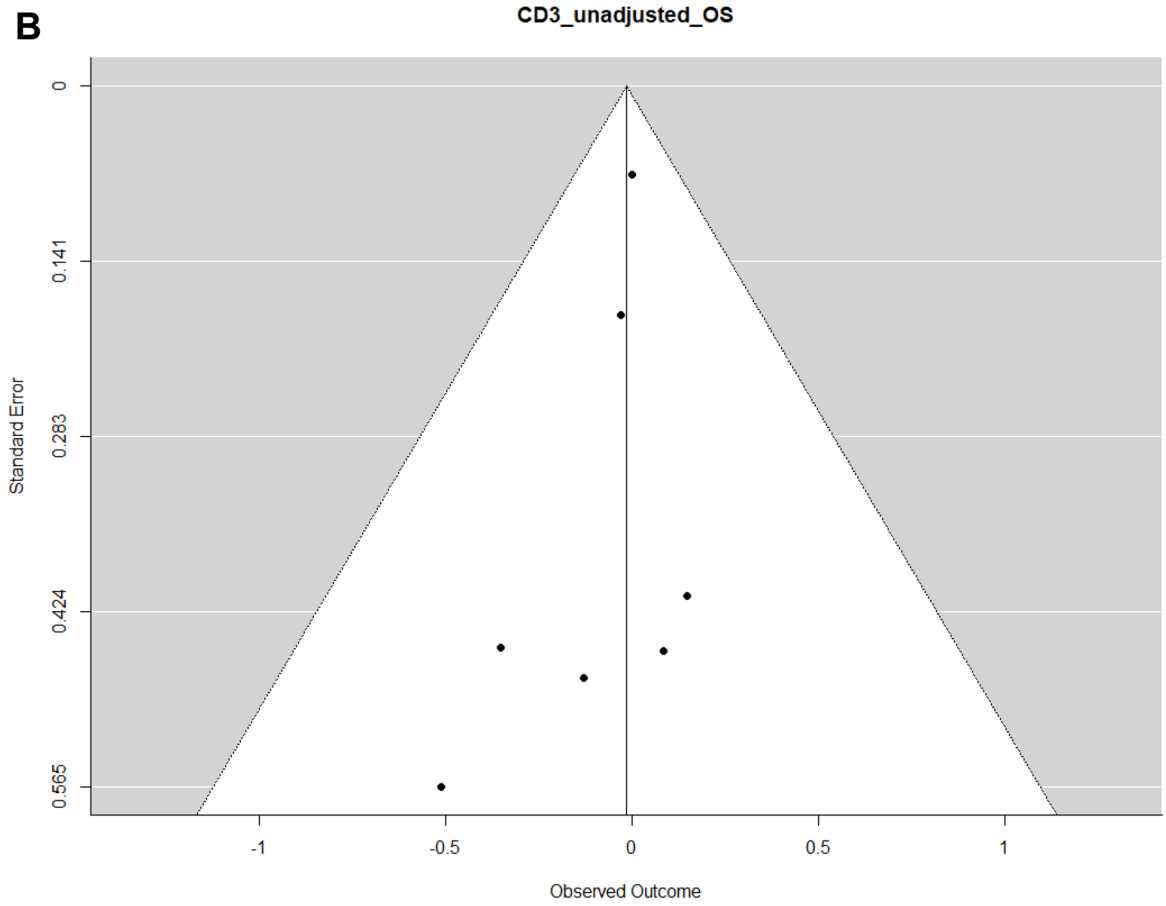
Supplementary Table 1: Reported unadjusted vs. adjusted survival estimates

Name	Year	Biomarker	Survival Type	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
O'Callaghan	2015	CD3	OS	0.70 (0.47–1.05)	0.65 (0.41–1.02)
Sepesi	2017	CD3	OS	0.60 (0.32–1.12)	0.35 (0.11–1.09)
Sepesi	**2017**	**CD4**	**OS**	**0.49 (0.29–0.85)**	**0.35 (0.11–1.09)**
Matsubara	2019	CD4	OS	1.55 (1.03–2.37)	1.65 (1.07–2.55)
O'Callaghan	2015	CD8	OS	0.44 (0.29–0.67)	0.48 (0.30–0.76)
Yazdi	2016	CD8	OS	0.64 (0.40–1.04)	0.62 (0.38–1.01)
Ameratunga	**2016**	**CD8**	**DFS**	**0.82 (0.64–1.04)**	**0.70 (0.50–0.97)**
Teng	**2016**	**CD8**	**OS**	**0.51 (0.29–0.98)**	**0.54 (0.28–1.05)**
Teng	2016	CD8	DFS	0.39 (0.22–0.71)	0.22 (0.05–0.89)
Ye	**2017**	**CD8**	**OS**	**0.71 (0.52–0.99)**	**0.70 (0.44–1.10)**
Kinoshita	2017	CD8	DFS	2.92 (1.69–5.07)	2.01 (1.14–3.56)
Sepesi	2017	CD8	OS	1.88 (0.82–3.34)	1.70 (0.40–7.45)
Kinoshita	2016	CD20	DFS	0.53 (0.34–0.84)	0.51 (0.32–0.80)
Villegas	2002	CD57	OS	0.43 (0.20–0.95)	0.40 (0.17–0.93)
Sepesi	2017	CD57	OS	0.24 (0.03–1.70)	0.60 (0.05–6.51)
Kojima	2002	CD68	OS	1.45 (0.71–2.97)	1.43 (0.66–3.09)
Sepesi	**2017**	**CD68**	**OS**	**0.35 (0.12–0.97)**	**0.79 (0.11–5.63)**
Cao	2019	CD68	OS	4.19 (1.90–9.27)	2.86 (1.13–7.26)
Cao	2019	CD68	DFS	2.09 (1.26–3.46)	1.81 (1.09–3.02)
Hanagiri	**2013**	**FoxP3**	**OS**	**2.56 (1.28–5.10)**	**1.82 (0.90–3.69)**
Hanagiri	2014	FoxP3	OS	2.82 (1.00–7.93)	4.22 (1.11–5.56)
O'Callaghan	2015	FoxP3	OS	4.86 (3.11–7.59)	3.91 (2.33–6.55)
Barua	**2018**	**FoxP3**	**OS**	**1.43 (0.63–3.21)**	**1.52 (1.11–2.07)**
Kojima	**2002**	**Mast Cells**	**OS**	**2.31 (1.09–4.89)**	**1.16 (0.51–2.67)**
Pelosi	**2004**	**Mast Cells**	**OS**	**2.30 (1.20–4.90)**	**1.70 (0.60–4.60)**
Pelosi	**2004**	**Mast Cells**	**DFS**	**2.30 (1.20–4.70)**	**1.50 (0.60–3.60)**
Kojima	**2005**	**Mast Cells**	**OS**	**2.04 (1.05–3.96)**	**1.15 (0.53–2.48)**

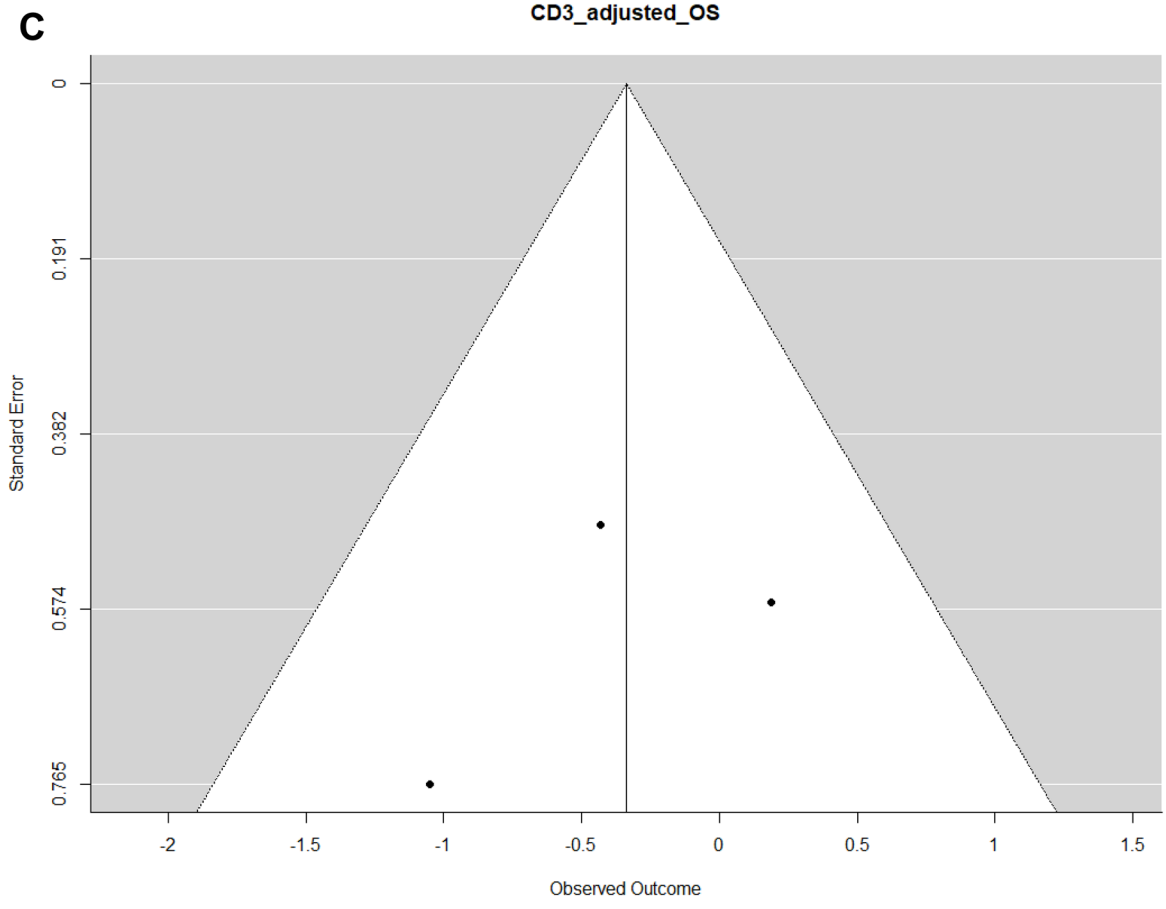
A

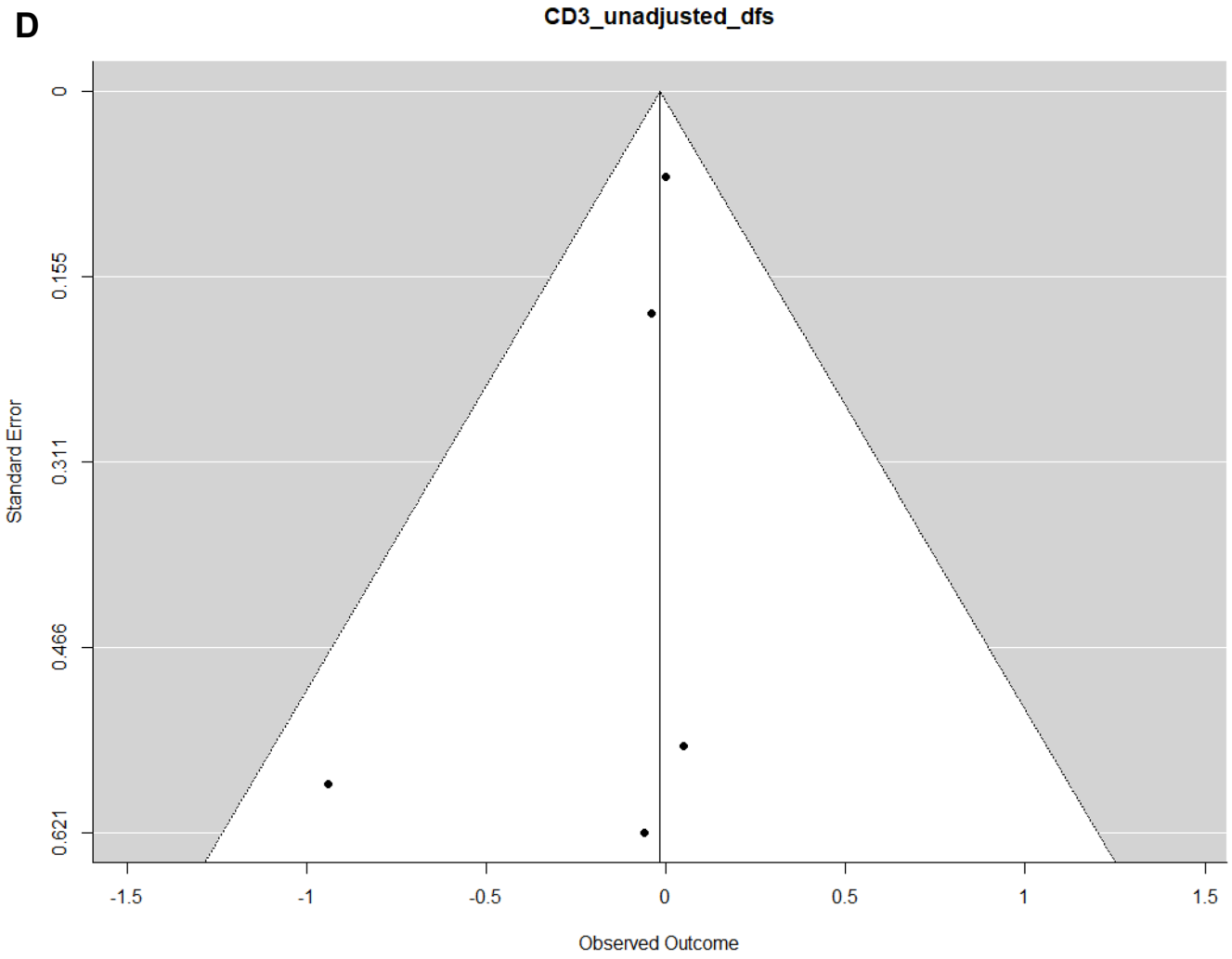

CD3+ T cells
Study
Hazard Ratio [95% CI]
Overall Survival
Unadjusted
Matsubara, 2019
1.09 [0.45, 2.66]
Sepesi, 2017
0.60 [0.20, 1.82]
Mazzaschi, 2017
1.00 [0.87, 1.15]
O'Callaghan, 2015
0.70 [0.29, 1.71]
Kadota, 2015
1.16 [0.52, 2.60]
Djenidi, 2015
0.97 [0.68, 1.39]
Dieu-Nosjean, 2008
0.88 [0.35, 2.24]
Random Effects
0.99 [0.87, 1.12]
I2= 0.00%
Q = 1.64; (p = 0.90)
Adjusted
Sepesi, 2017
0.35 [0.08, 1.57]
Tian, 2015
1.21 [0.40, 3.66]
O'Callaghan, 2015
0.65 [0.25, 1.67]
Random Effects
0.71 [0.37, 1.37]
I2= 0.00%
Q = 1.76; (p = 0.42)
Disease Free Survival
Unadjusted
Mazzaschi, 2017
1.00 [0.87, 1.15]
Hernandez-Prieto, 2015
0.94 [0.28, 3.18]
Djenidi, 2015
0.96 [0.67, 1.38]
Dieu-Nosjean, 2008
1.05 [0.36, 3.08]
Petersen, 2006
0.39 [0.12, 1.22]
Random Effects
0.98 [0.86, 1.12]
I2= 0.00%
Q = 2.63; (p = 0.62)
0.05
0.15
1
2.5
5
7
30
Hazard Ratio (log scale)

B


CD3_unadjusted_OS
Standard Error
0
0.141
0.283
0.424
0.565
-1
-0.5
0
0.5
1
Observed Outcome

C

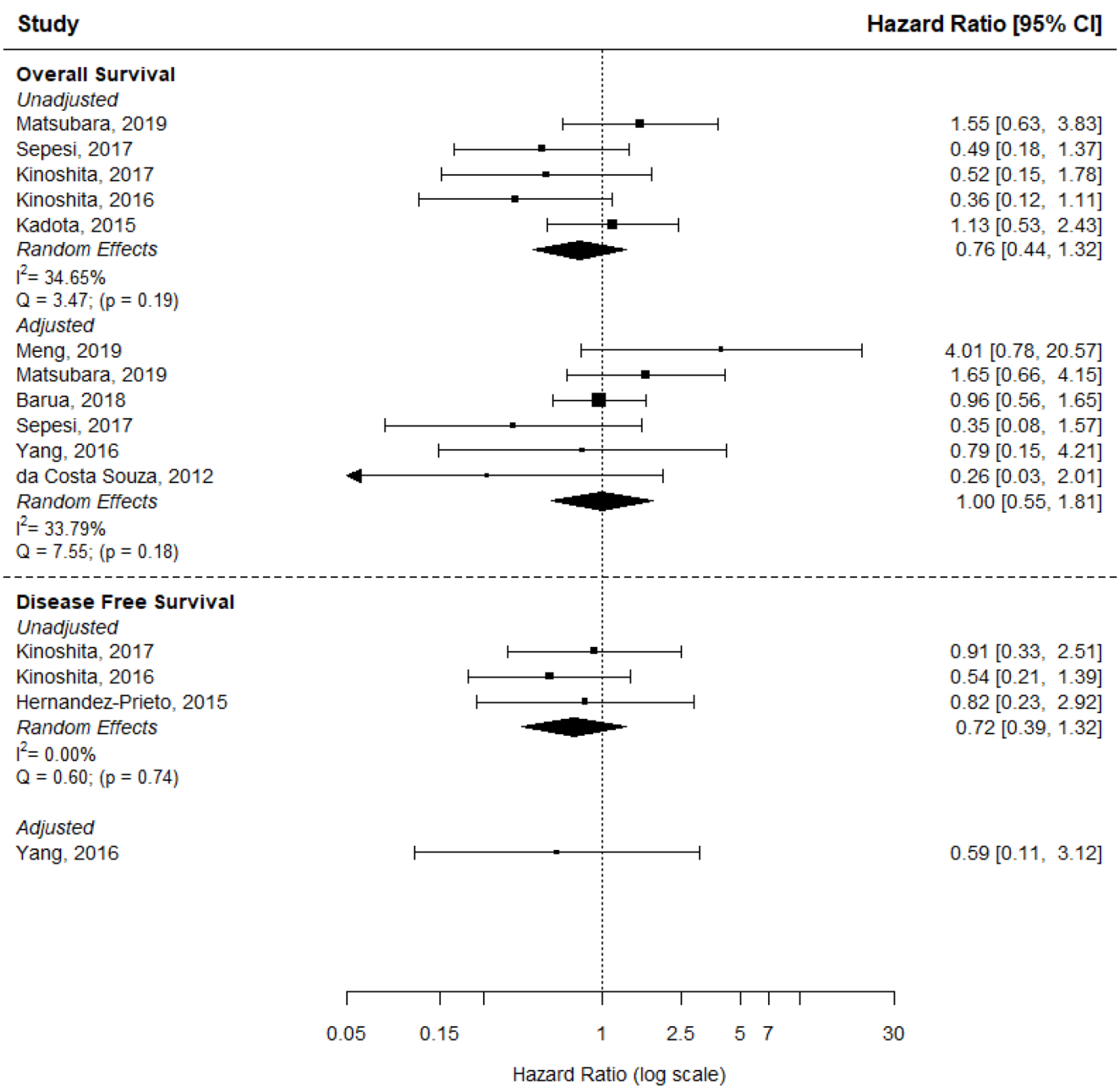

CD3_adjusted_OS
Standard Error
0
0.191
0.382
0.574
0.765
-2
-1.5
-1
-0.5
0
0.5
1
1.5
Observed Outcome



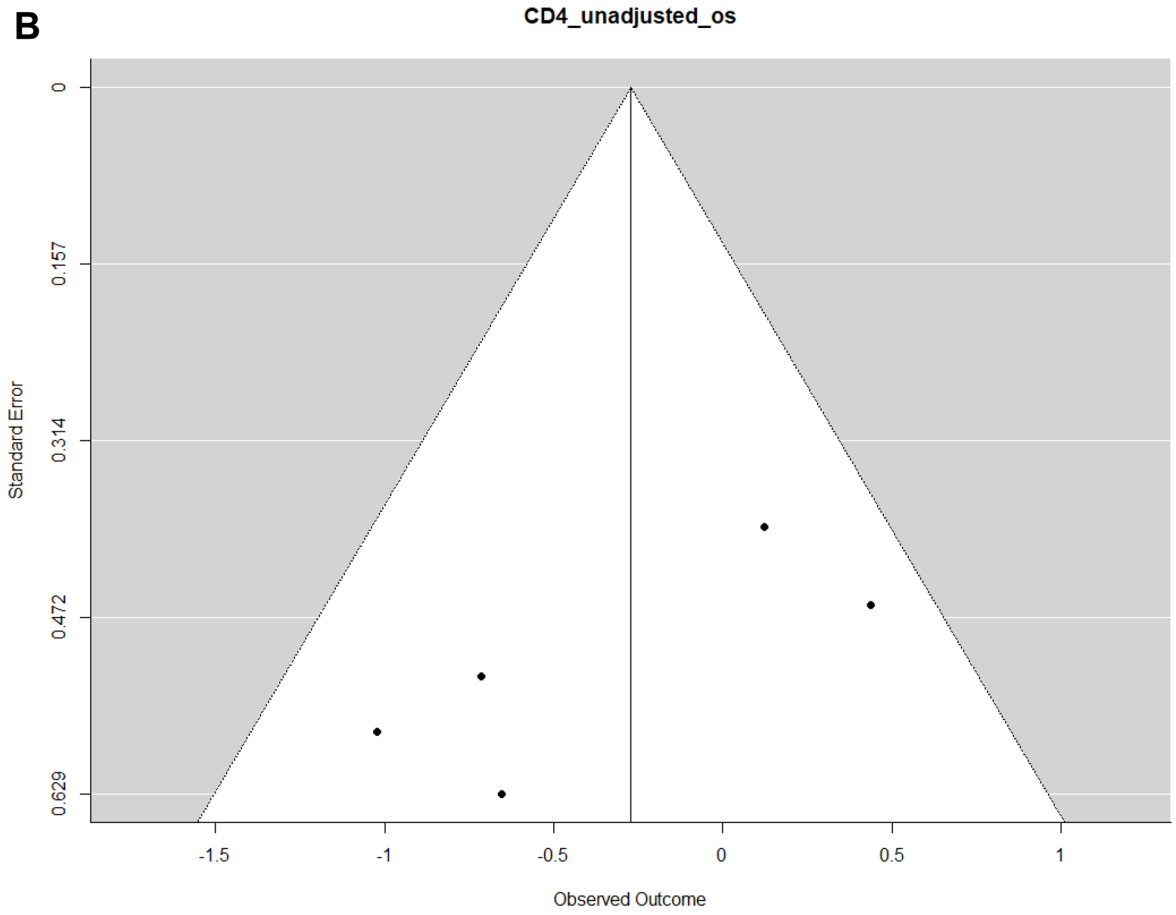
Supplementary Figure 1: (**A**) Forest Plot of CD3+T Cells. (**B**) Funnel Plot of CD3+T Cells Unadjusted OS Studies. (**C**) Funnel Plot of CD3+T Cells Adjusted OS Studies. (**D**) Funnel Plot of CD3+T Cells Unadjusted DFS Studies.

A

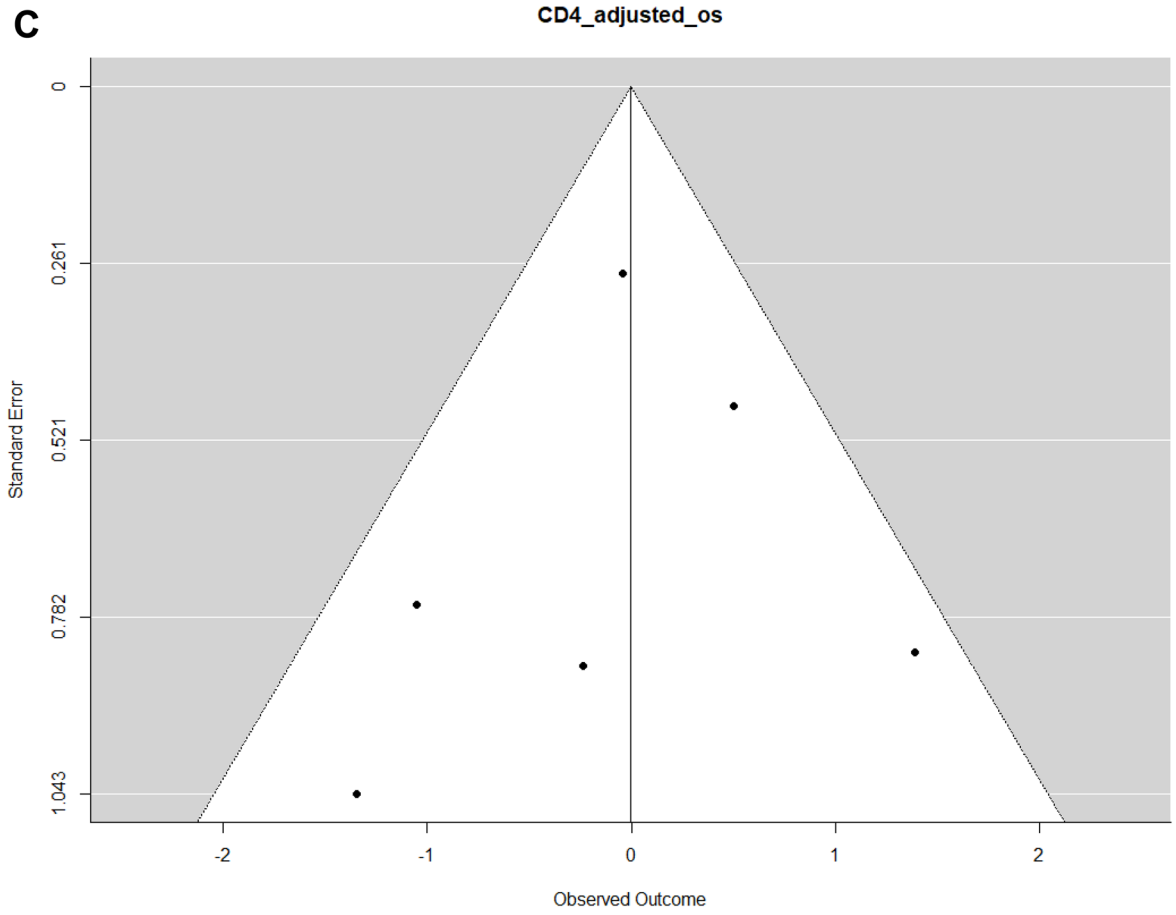
CD4+ T Helper cells

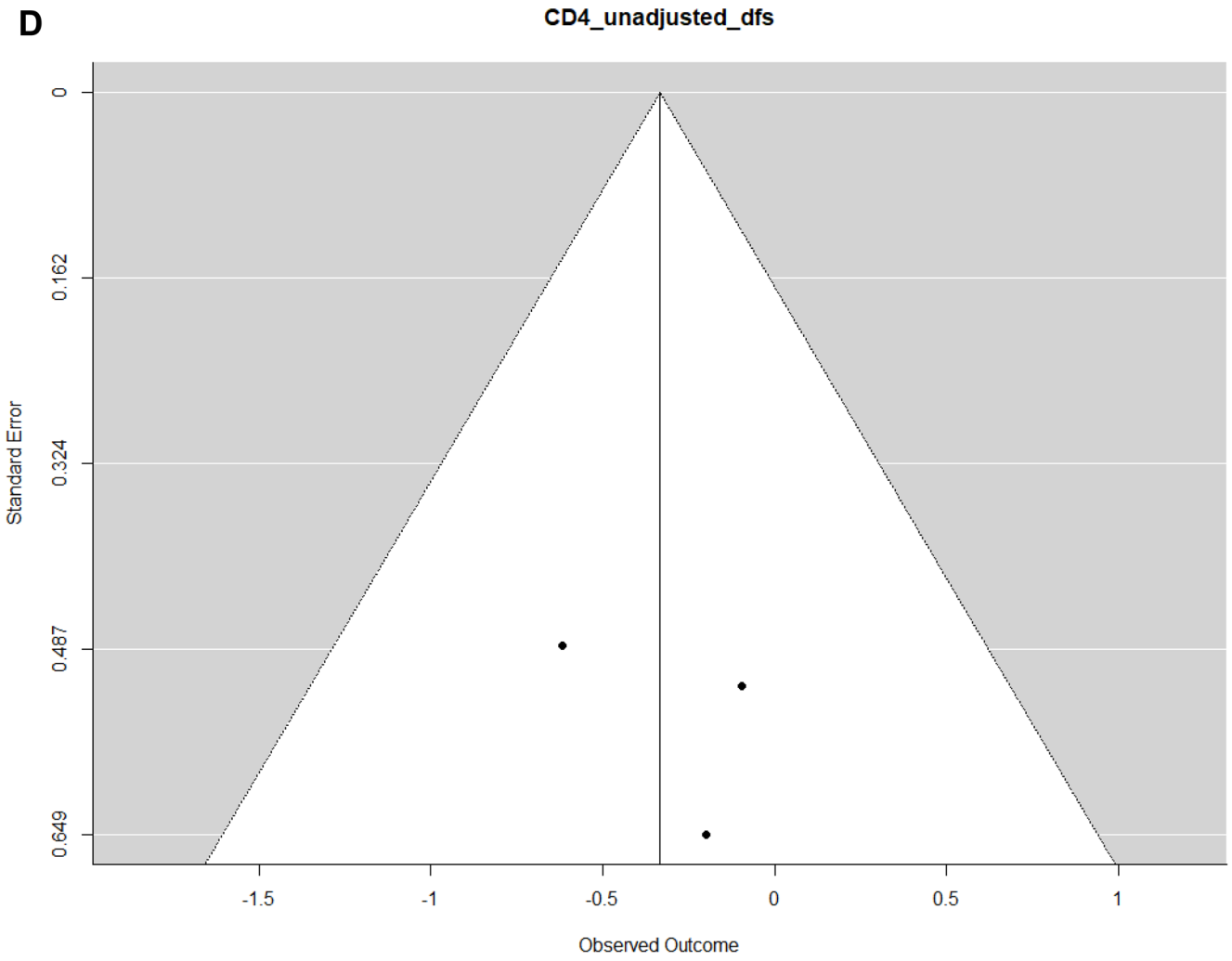


B


CD4_unadjusted_os
Standard Error
0
0.157
0.314
0.472
0.629
-1.5
-1
-0.5
0
0.5
1
Observed Outcome

C

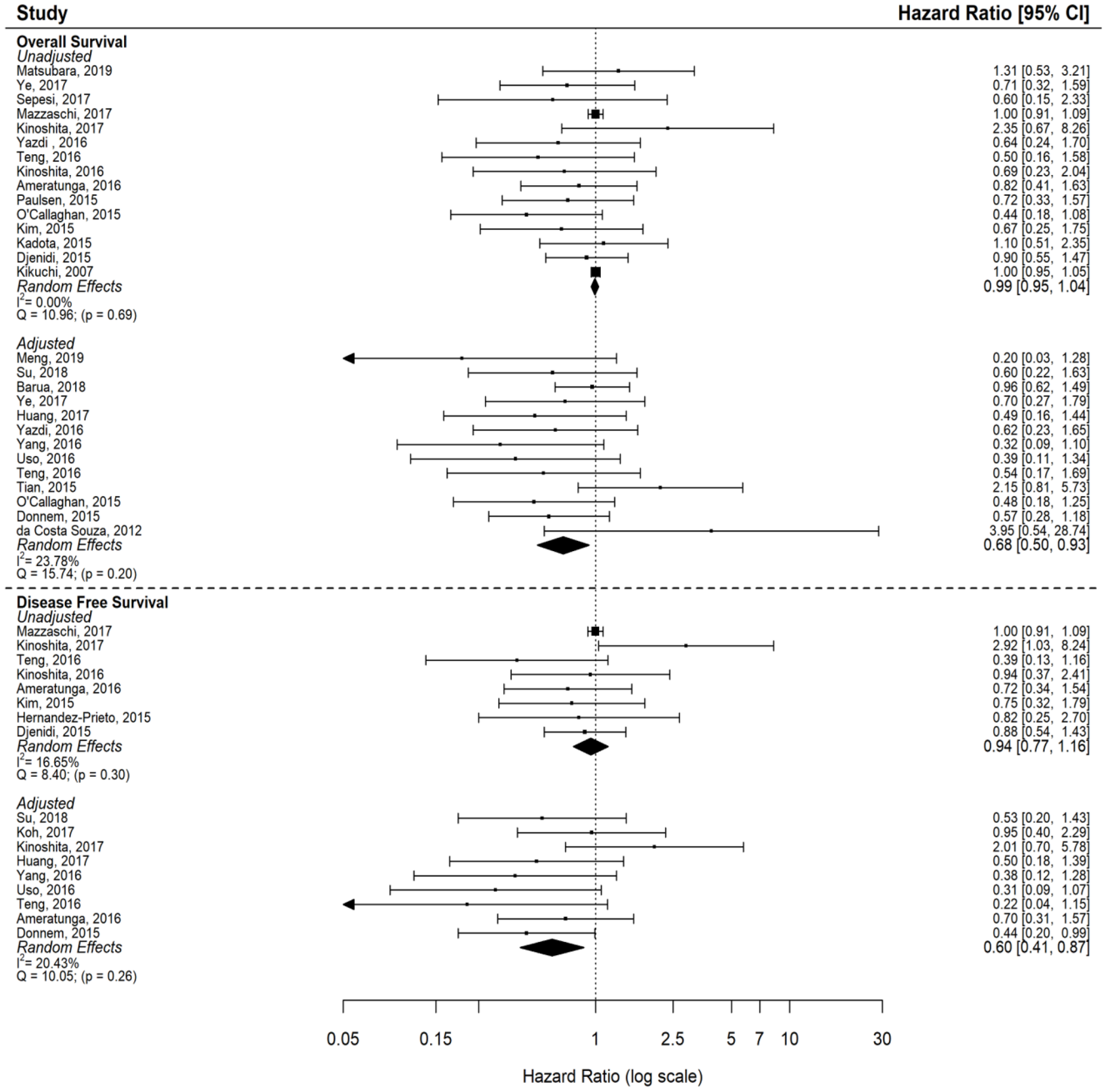

CD4_adjusted_os
Standard Error
0
0.261
0.521
0.782
1.043
-2
-1
0
1
2
Observed Outcome



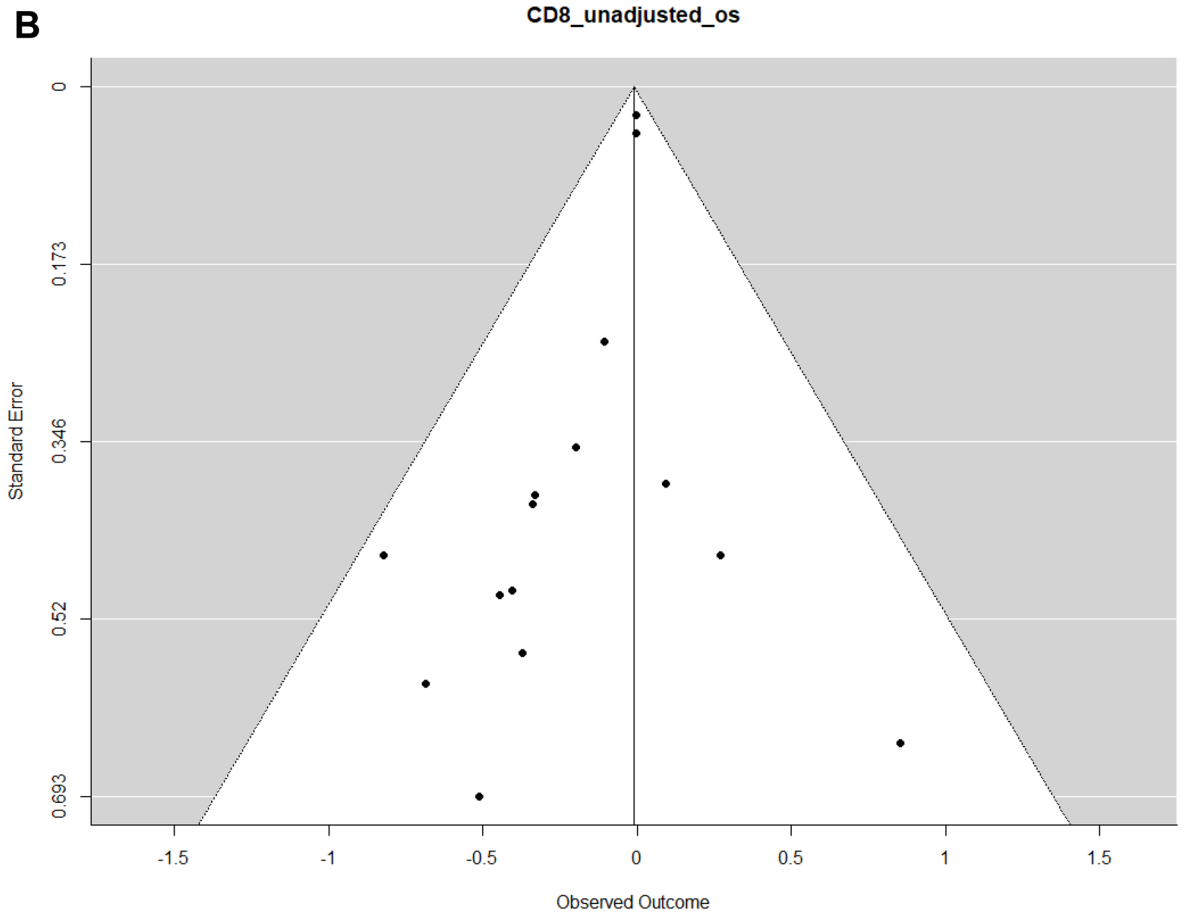
Supplementary Figure 2: (**A**) Forest Plot of CD4+ T Helper cells. (**B**) Funnel Plot of CD4+ T Helper cells Unadjusted OS Studies. (**C**) Funnel Plot of CD4+ T Helper cells Adjusted OS Studies. (**D**) Funnel Plot of CD4+ T Helper cells Unadjusted DFS Studies.

A

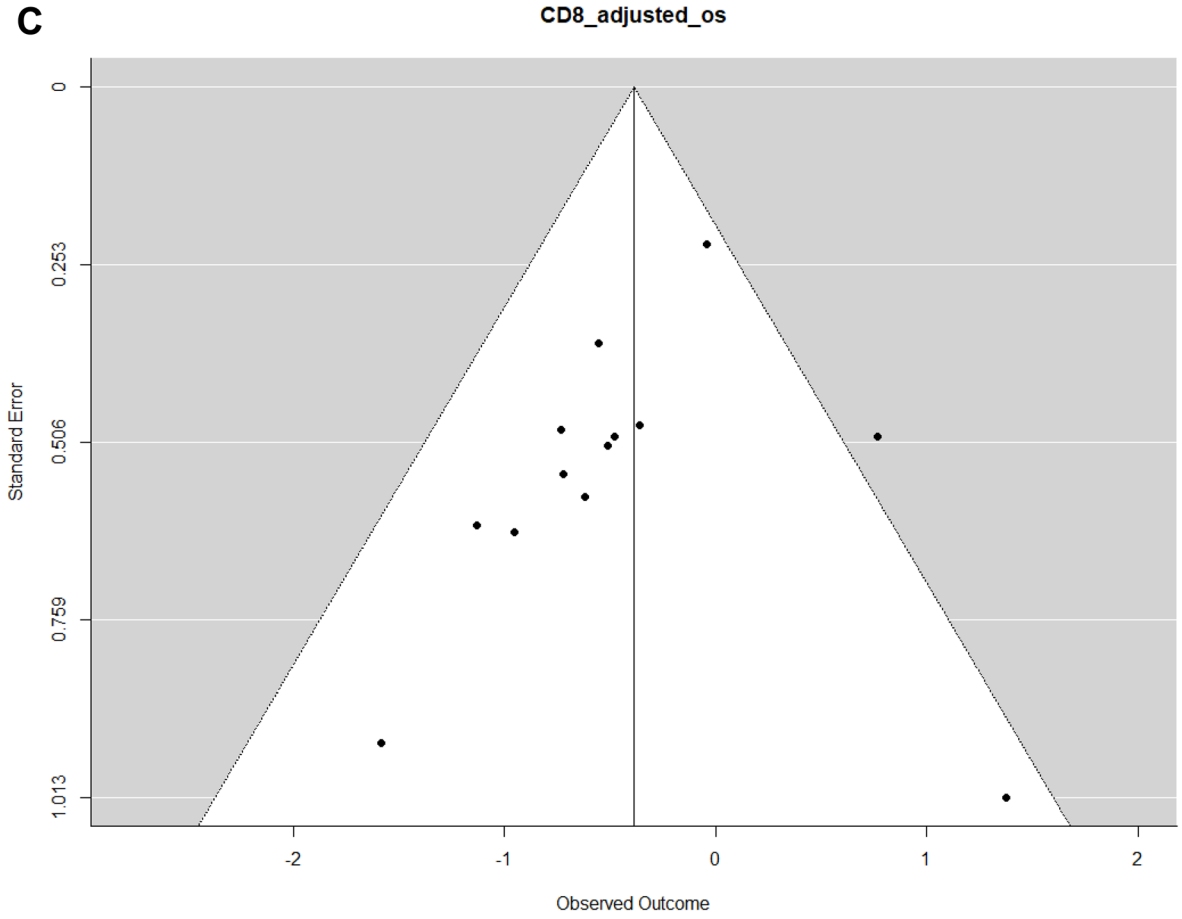
CD8+ T cytotoxic cells

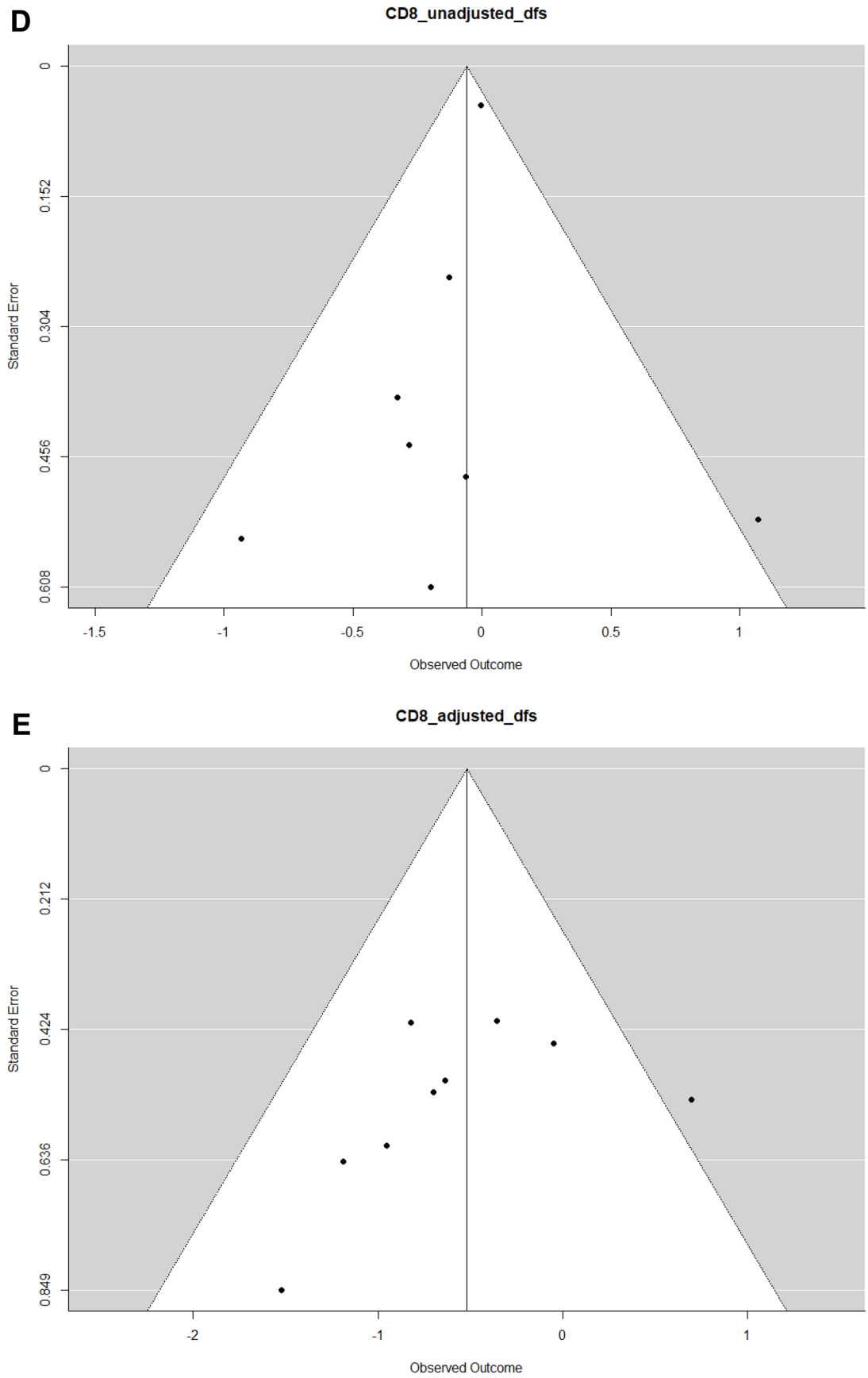


B


CD8_unadjusted_os
Standard Error
0
0.173
0.346
0.52
0.693
-1.5
-1
-0.5
0
0.5
1
1.5
Observed Outcome

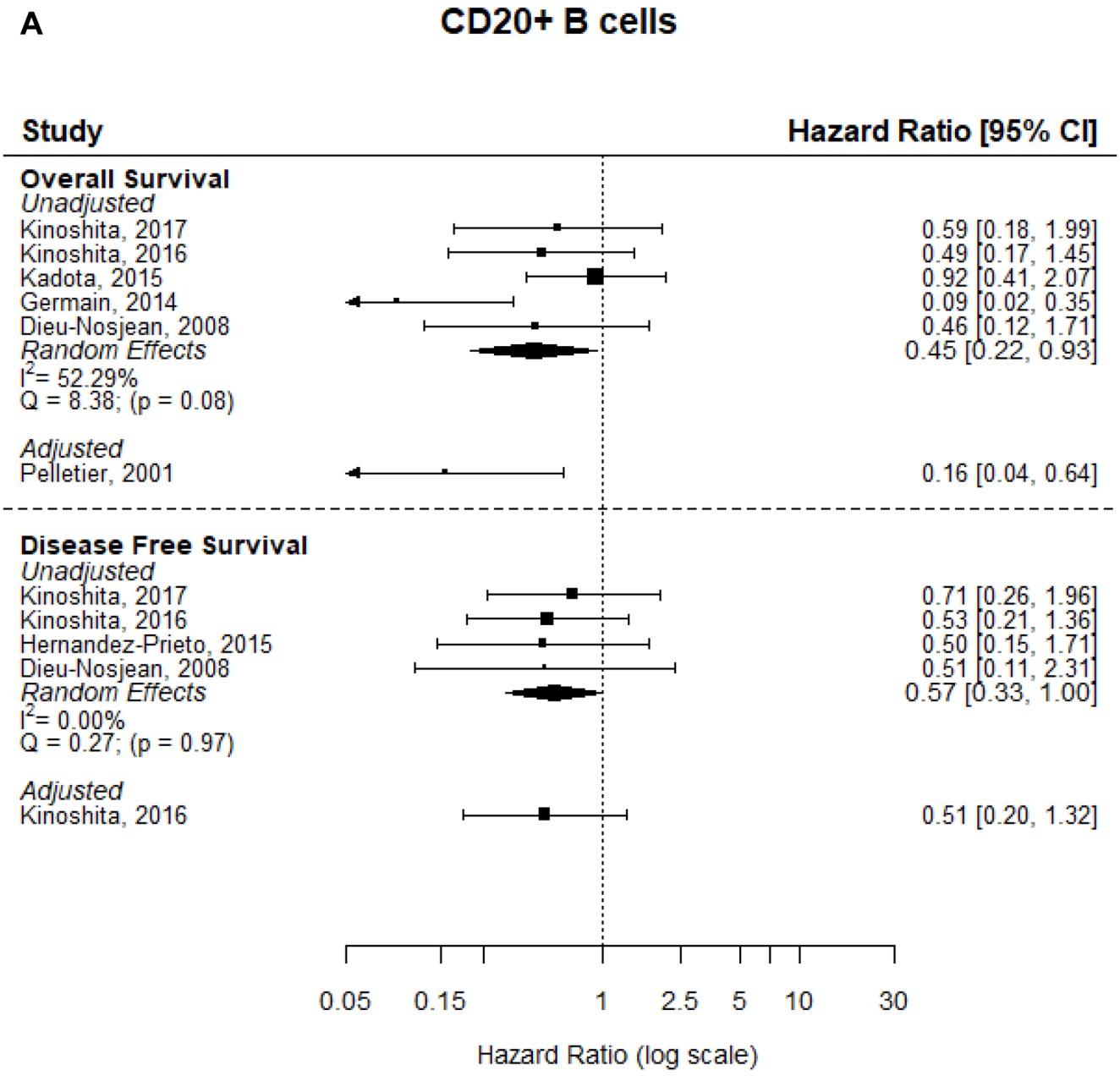
C

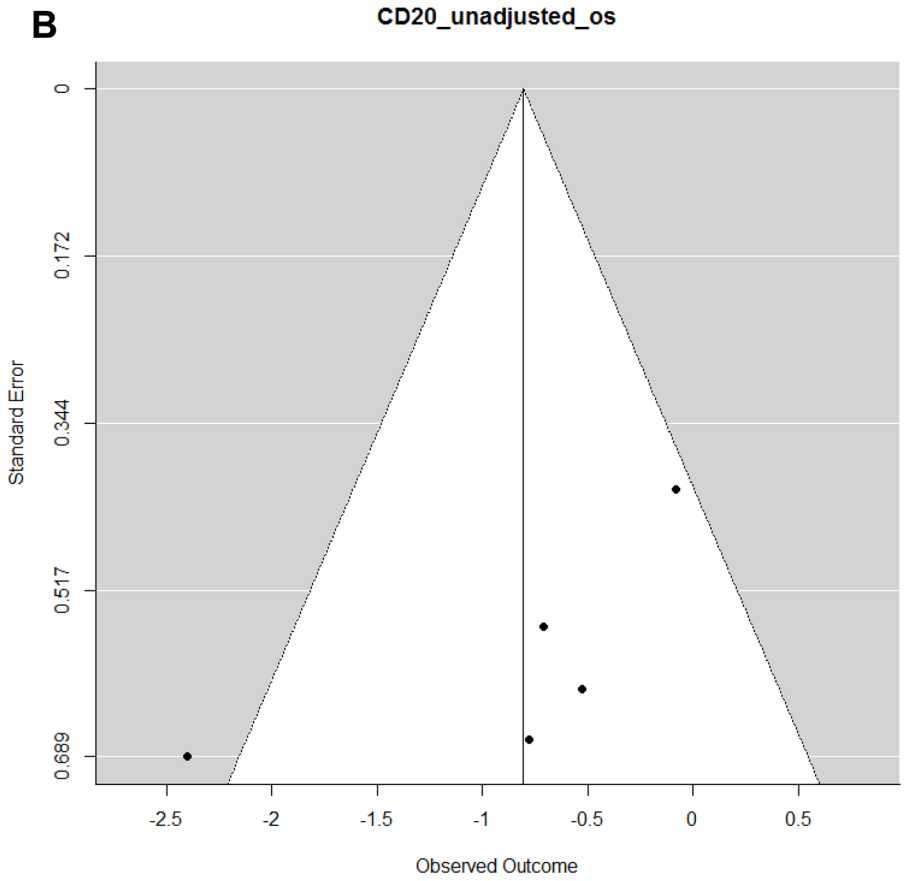

CD8_adjusted_os
Standard Error
0
0.253
0.506
0.759
1.013
-2
-1
0
1
2
Observed Outcome

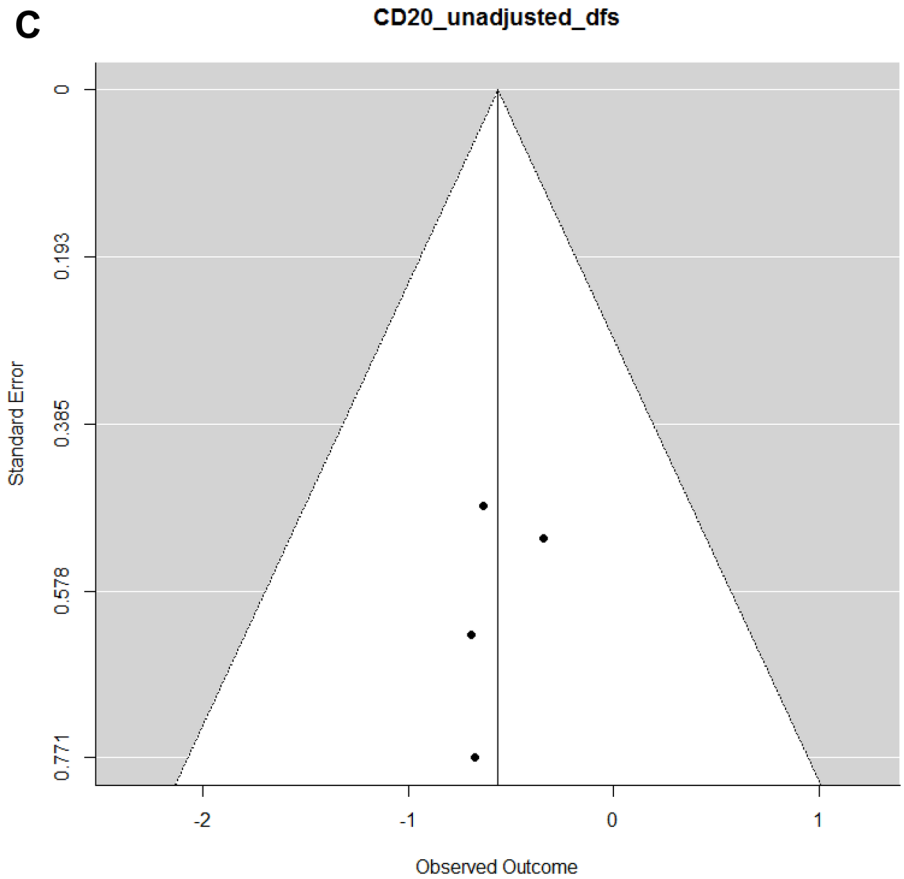


Supplementary Figure 3: (**A**) Forest Plot of CD8+ T cytotoxic cells. (**B**) Funnel Plot of CD8+ T cytotoxic cells Unadjusted OS Studies. (**C**) Funnel Plot of CD8+ T cytotoxic cells Adjusted OS Studies. (**D**) Funnel Plot of CD8+ T cytotoxic cells Unadjusted DFS Studies. (**E**) Funnel Plot of CD8+ T cytotoxic cells Adjusted DFS Studies.

A

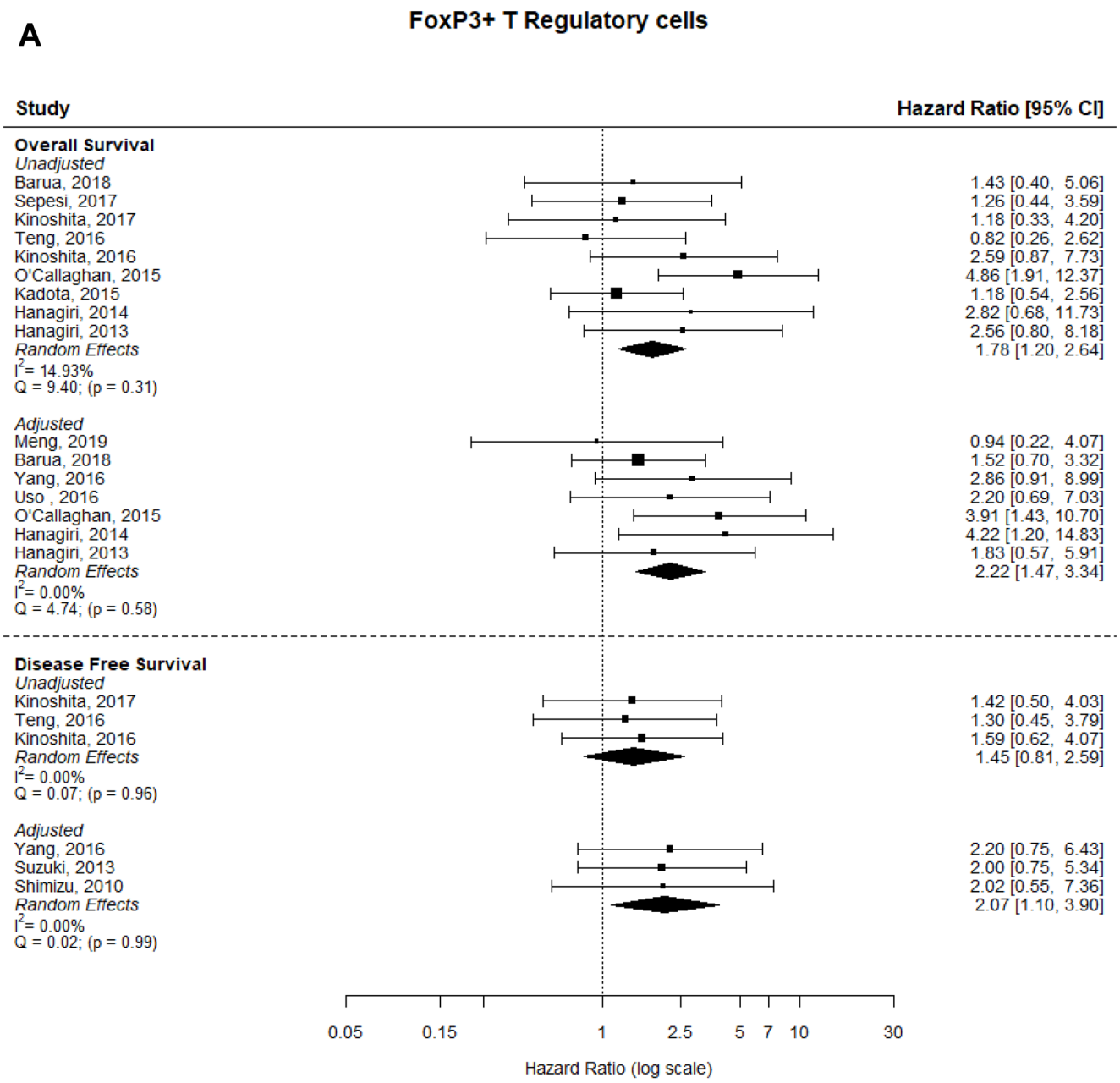

CD20+ B cells
Study
Hazard Ratio [95% CI]
Overall Survival
Unadjusted
Kinoshita, 2017
0.59 [0.18, 1.99]
Kinoshita, 2016
0.49 [0.17, 1.45]
Kadota, 2015
0.92 [0.41, 2.07]
Germain, 2014
0.09 [0.02, 0.35]
Dieu-Nosjean, 2008
0.46 [0.12, 1.71]
Random Effects
0.45 [0.22, 0.93]
I²= 52.29%
Q = 8.38; (p = 0.08)
Adjusted
Pelletier, 2001
0.16 [0.04, 0.64]
Disease Free Survival
Unadjusted
Kinoshita, 2017
0.71 [0.26, 1.96]
Kinoshita, 2016
0.53 [0.21, 1.36]
Hernandez-Prieto, 2015
0.50 [0.15, 1.71]
Dieu-Nosjean, 2008
0.51 [0.11, 2.31]
Random Effects
0.57 [0.33, 1.00]
I²= 0.00%
Q = 0.27; (p = 0.97)
Adjusted
Kinoshita, 2016
0.51 [0.20, 1.32]
0.05
0.15
1
2.5
5
10
30
Hazard Ratio (log scale)



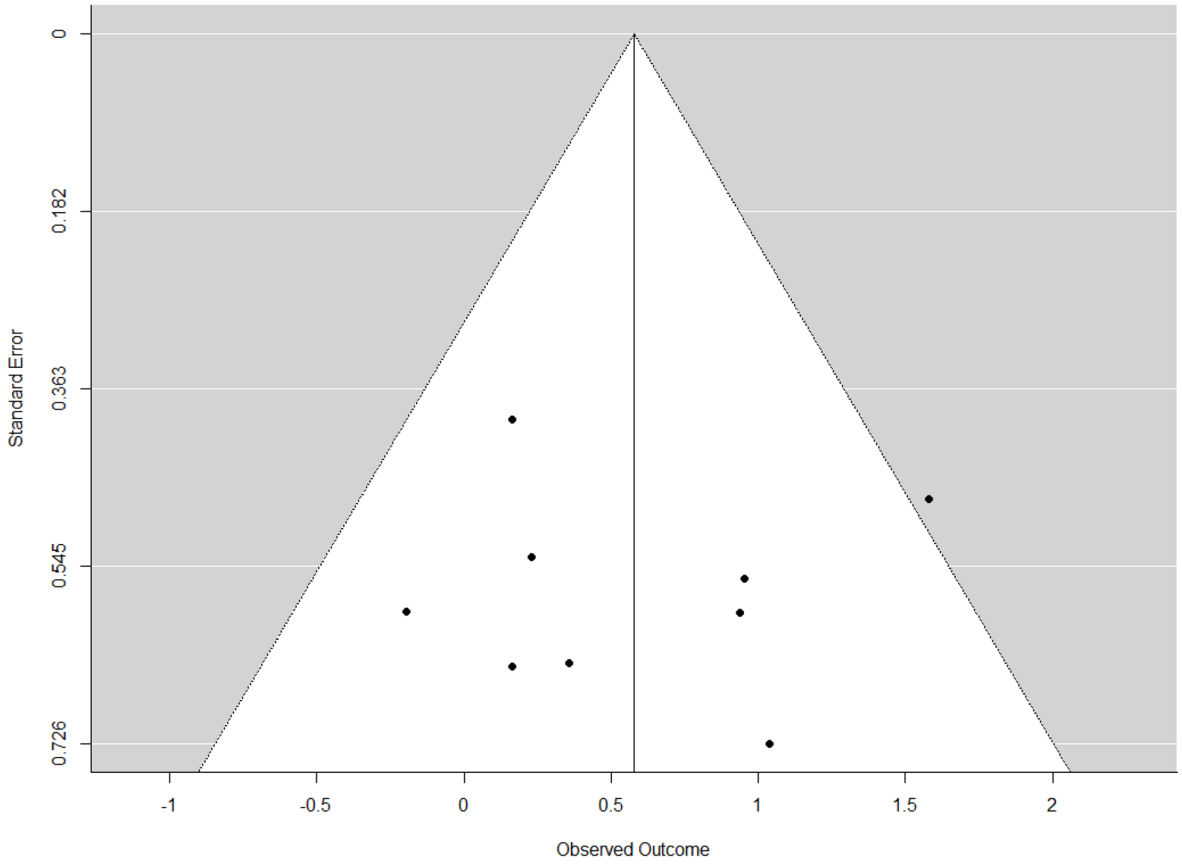


Supplementary Figure 4: (**A**) Forest Plot of CD20+ B cells. (**B**) Funnel Plot of CD20+ B cells Unadjusted OS Studies. (**C**) Funnel Plot of CD20+ B cells Unadjusted DFS Studies.

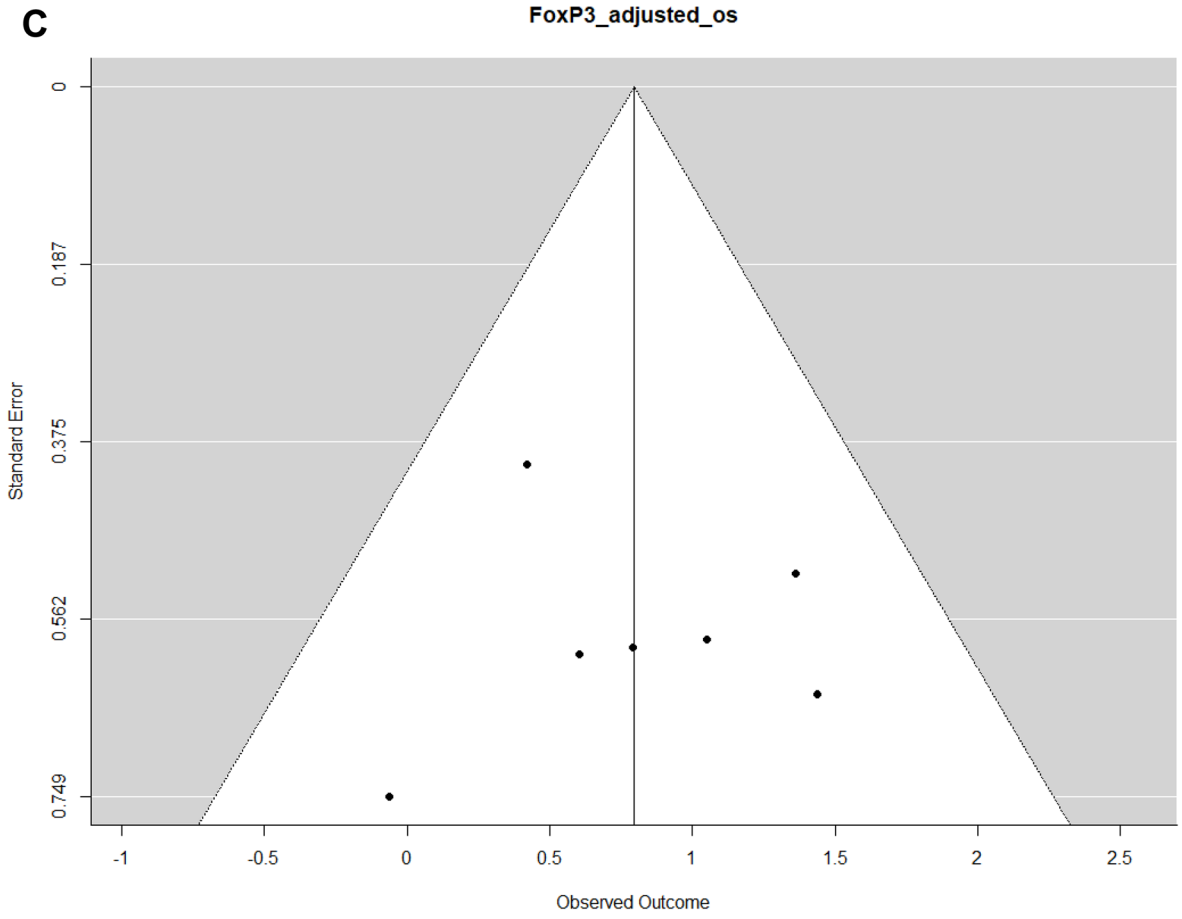
A

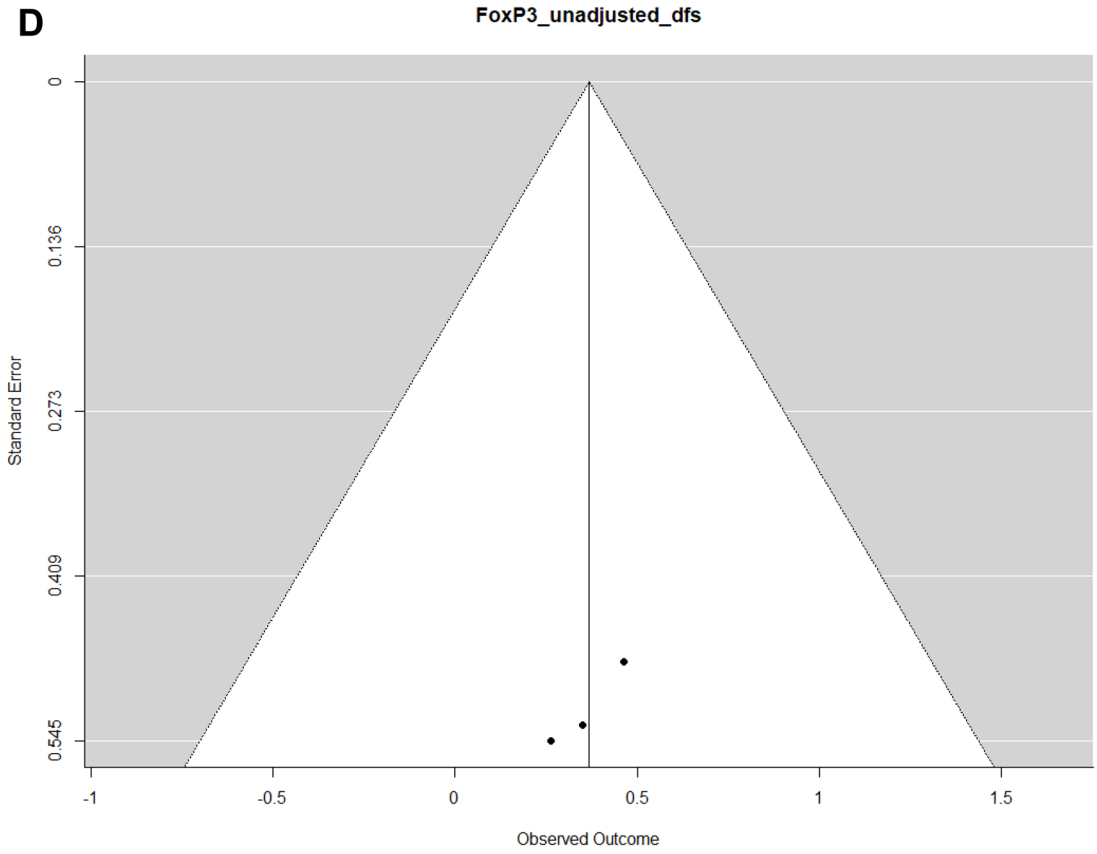

FoxP3+ T Regulatory cells
Study
Hazard Ratio [95% CI]
Overall Survival
Unadjusted
Barua, 2018 1.43 [0.40, 5.06]
Sepesi, 2017 1.26 [0.44, 3.59]
Kinoshita, 2017 1.18 [0.33, 4.20]
Teng, 2016 0.82 [0.26, 2.62]
Kinoshita, 2016 2.59 [0.87, 7.73]
O'Callaghan, 2015 4.86 [1.91, 12.37]
Kadota, 2015 1.18 [0.54, 2.56]
Hanagiri, 2014 2.82 [0.68, 11.73]
Hanagiri, 2013 2.56 [0.80, 8.18]
Random Effects 1.78 [1.20, 2.64]
I2= 14.93%
Q = 9.40; (p = 0.31)
Adjusted
Meng, 2019 0.94 [0.22, 4.07]
Barua, 2018 1.52 [0.70, 3.32]
Yang, 2016 2.86 [0.91, 8.99]
Uso , 2016 2.20 [0.69, 7.03]
O'Callaghan, 2015 3.91 [1.43, 10.70]
Hanagiri, 2014 4.22 [1.20, 14.83]
Hanagiri, 2013 1.83 [0.57, 5.91]
Random Effects 2.22 [1.47, 3.34]
I2= 0.00%
Q = 4.74; (p = 0.58)
Disease Free Survival
Unadjusted
Kinoshita, 2017 1.42 [0.50, 4.03]
Teng, 2016 1.30 [0.45, 3.79]
Kinoshita, 2016 1.59 [0.62, 4.07]
Random Effects 1.45 [0.81, 2.59]
I2= 0.00%
Q = 0.07; (p = 0.96)
Adjusted
Yang, 2016 2.20 [0.75, 6.43]
Suzuki, 2013 2.00 [0.75, 5.34]
Shimizu, 2010 2.02 [0.55, 7.36]
Random Effects 2.07 [1.10, 3.90]
I2= 0.00%
Q = 0.02; (p = 0.99)
0.05
0.15
1
2.5
5
7
10
30
Hazard Ratio (log scale)

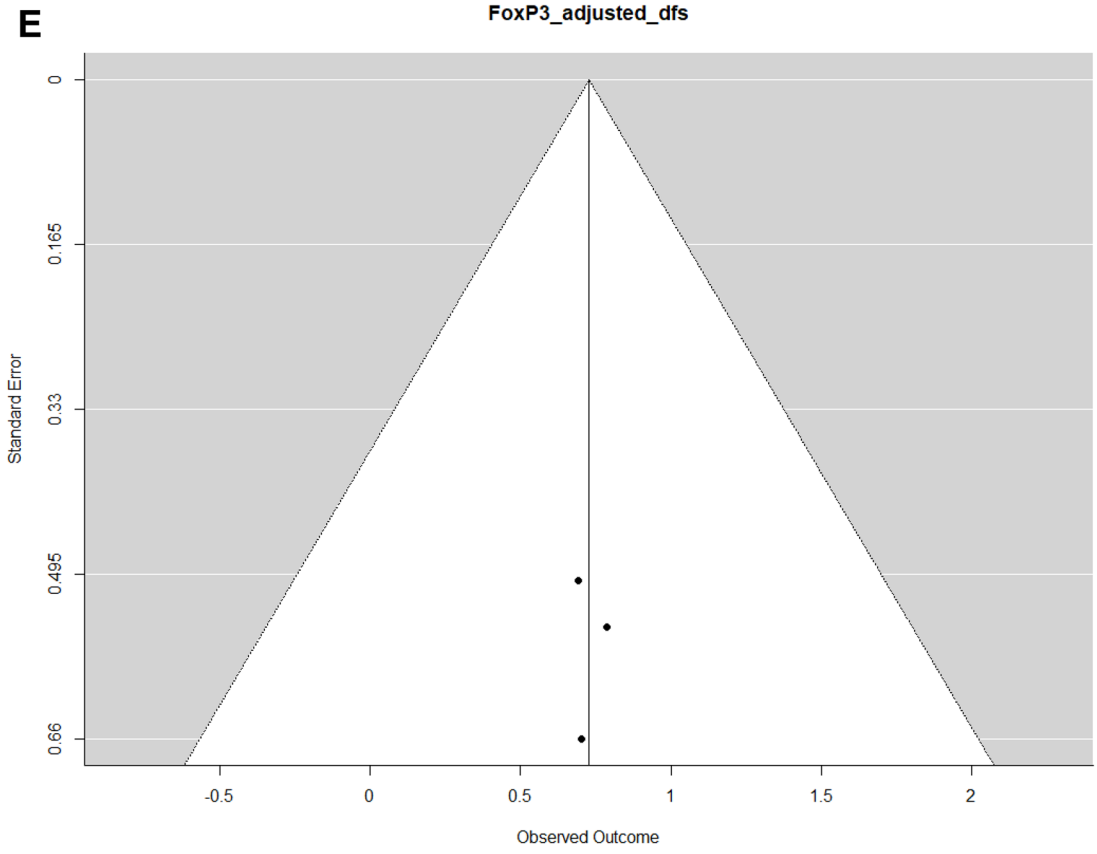
B


FoxP3_unadjusted_os
Standard Error
0
0.182
0.363
0.545
0.726
-1
-0.5
0
0.5
1
1.5
2
Observed Outcome

C


FoxP3_adjusted_os
Standard Error
0
0.187
0.375
0.562
0.749
-1
-0.5
0
0.5
1
1.5
2
2.5
Observed Outcome

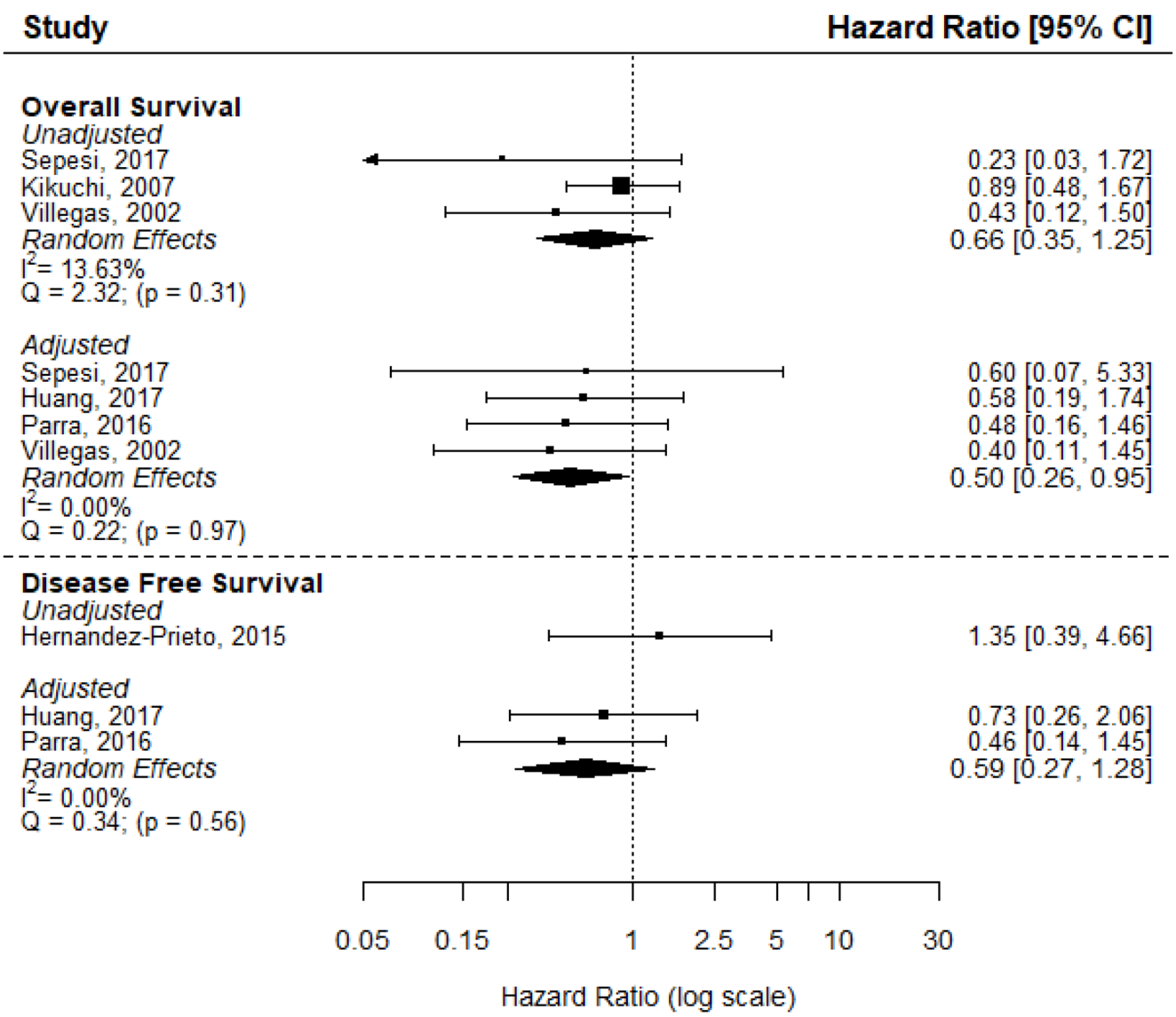


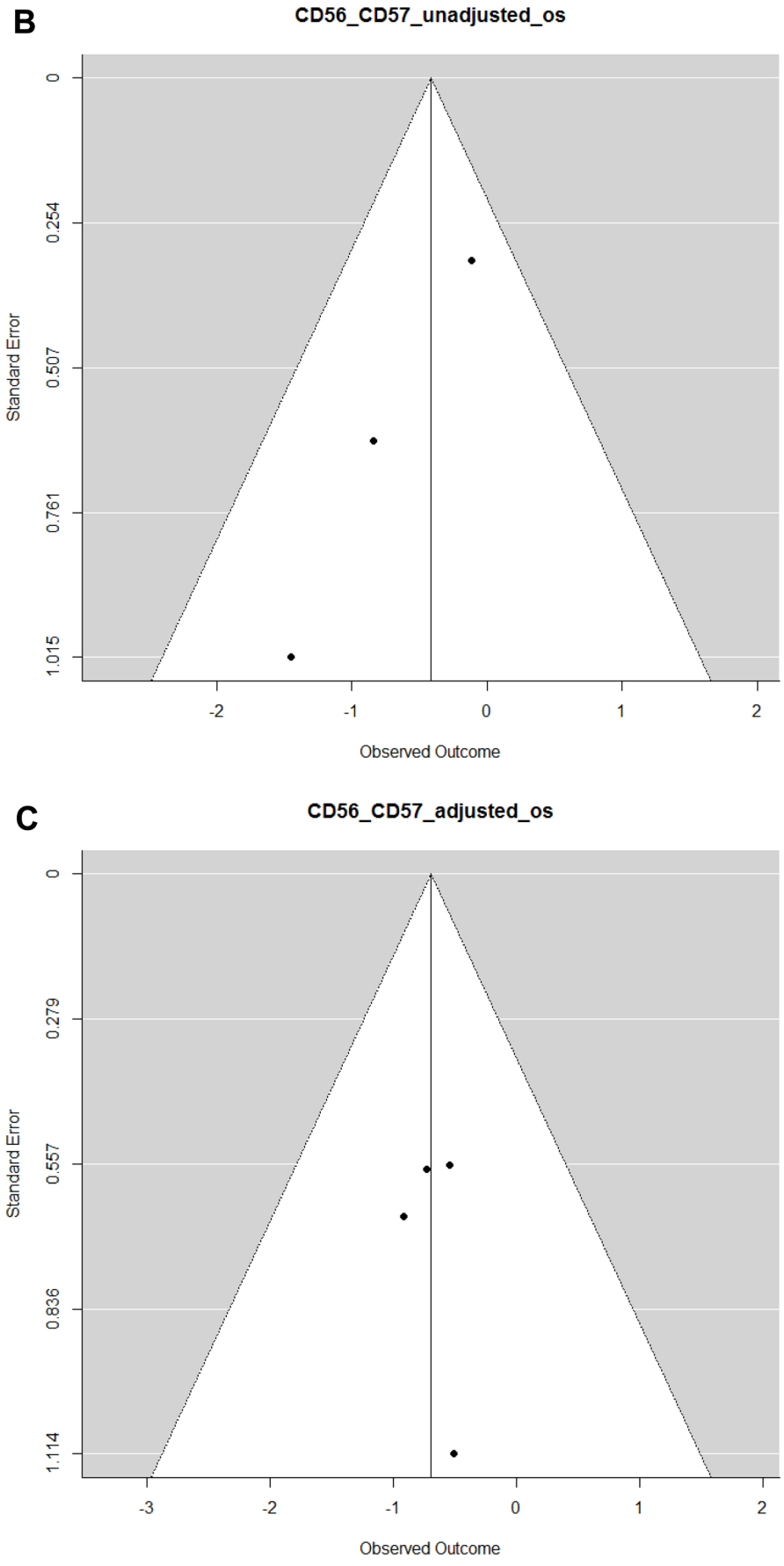


Supplementary Figure 5: (**A**) Forest Plot of FoxP3+T Regulatory cells. (**B**) Funnel Plot of FoxP3+T Regulatory cells Unadjusted OS Studies. (**C**) Funnel Plot of FoxP3+T Regulatory cells Adjusted OS Studies. (**D**) Funnel Plot of FoxP3+T Regulatory cells Unadjusted DFS Studies. (**E**) Funnel Plot of FoxP3+T Regulatory cells Adjusted DFS Studies.

A

Natural Killer cells (CD56/CD57+)

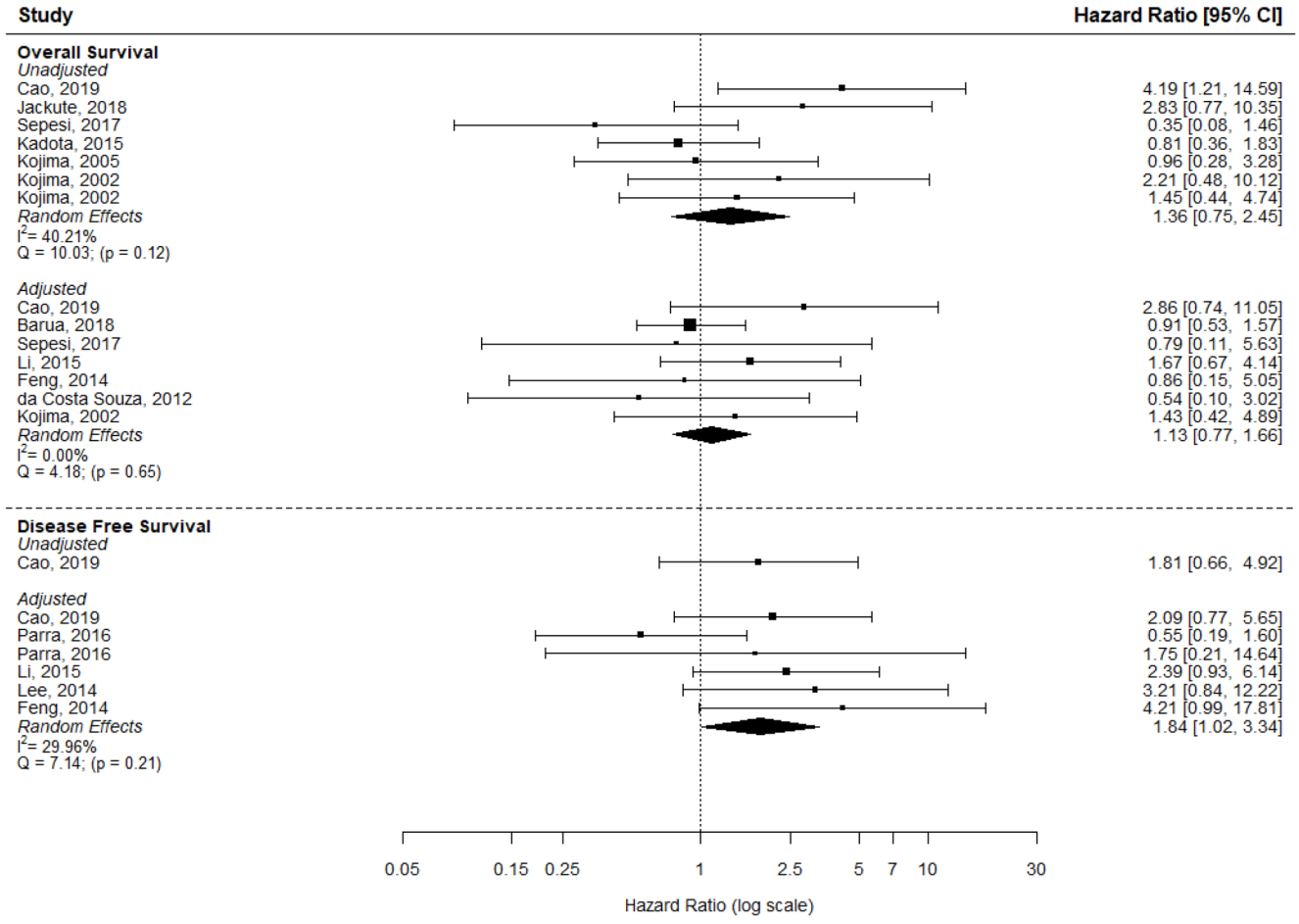




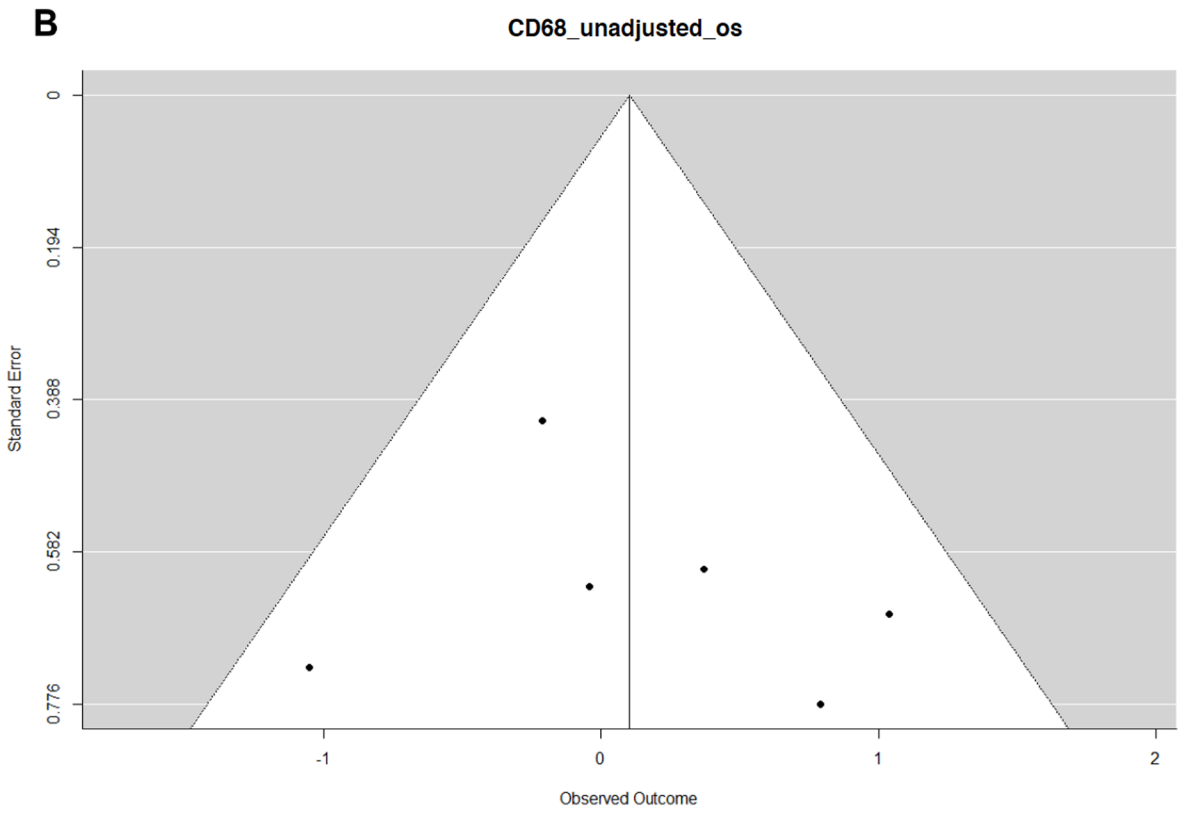
Supplementary Figure 6: (**A**) Forest Plot of NK cells (CD56/CD57+). (**B**) Funnel Plot of NK cells (CD56/CD57+) Unadjusted OS Studies. (**C**) Funnel Plot of NK cells (CD56/CD57+) Adjusted OS Studies.

A

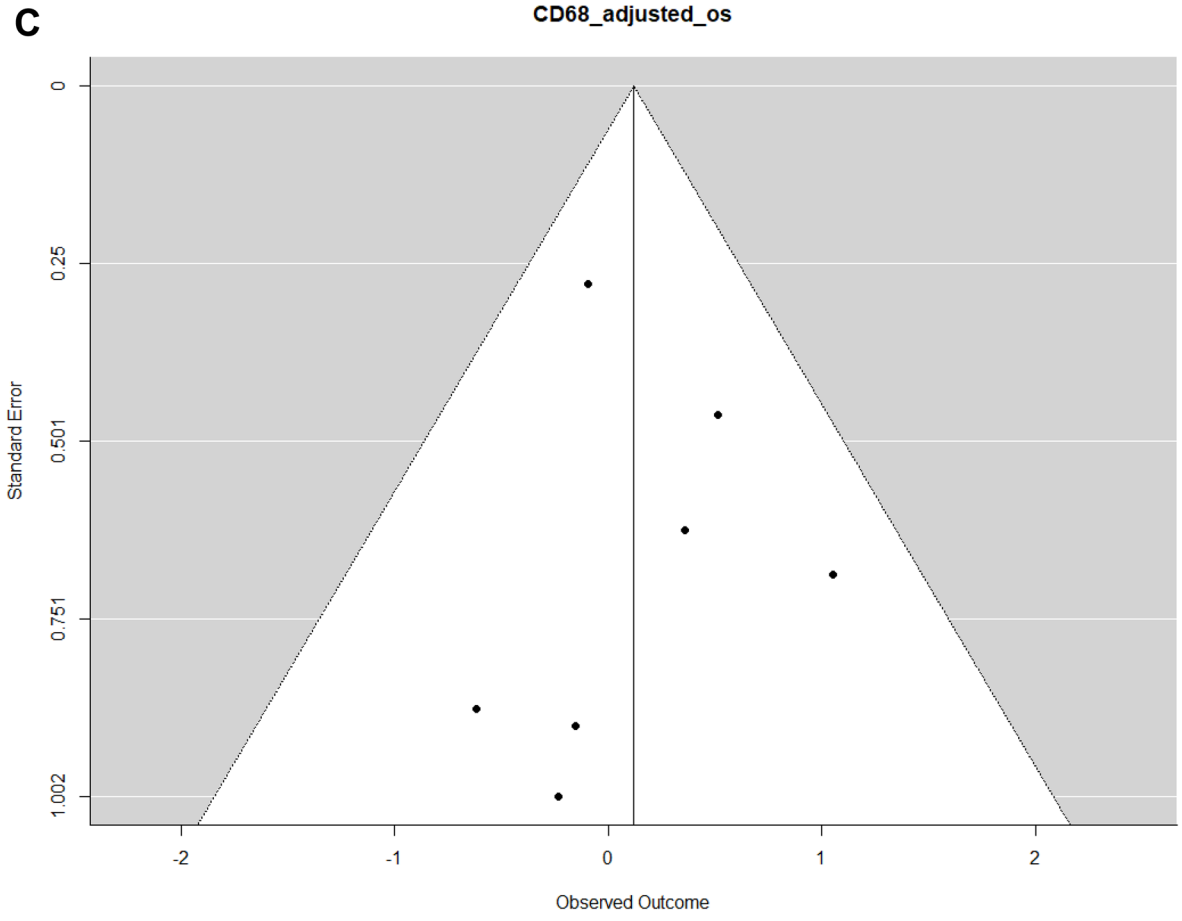
Macrophages (CD68+)

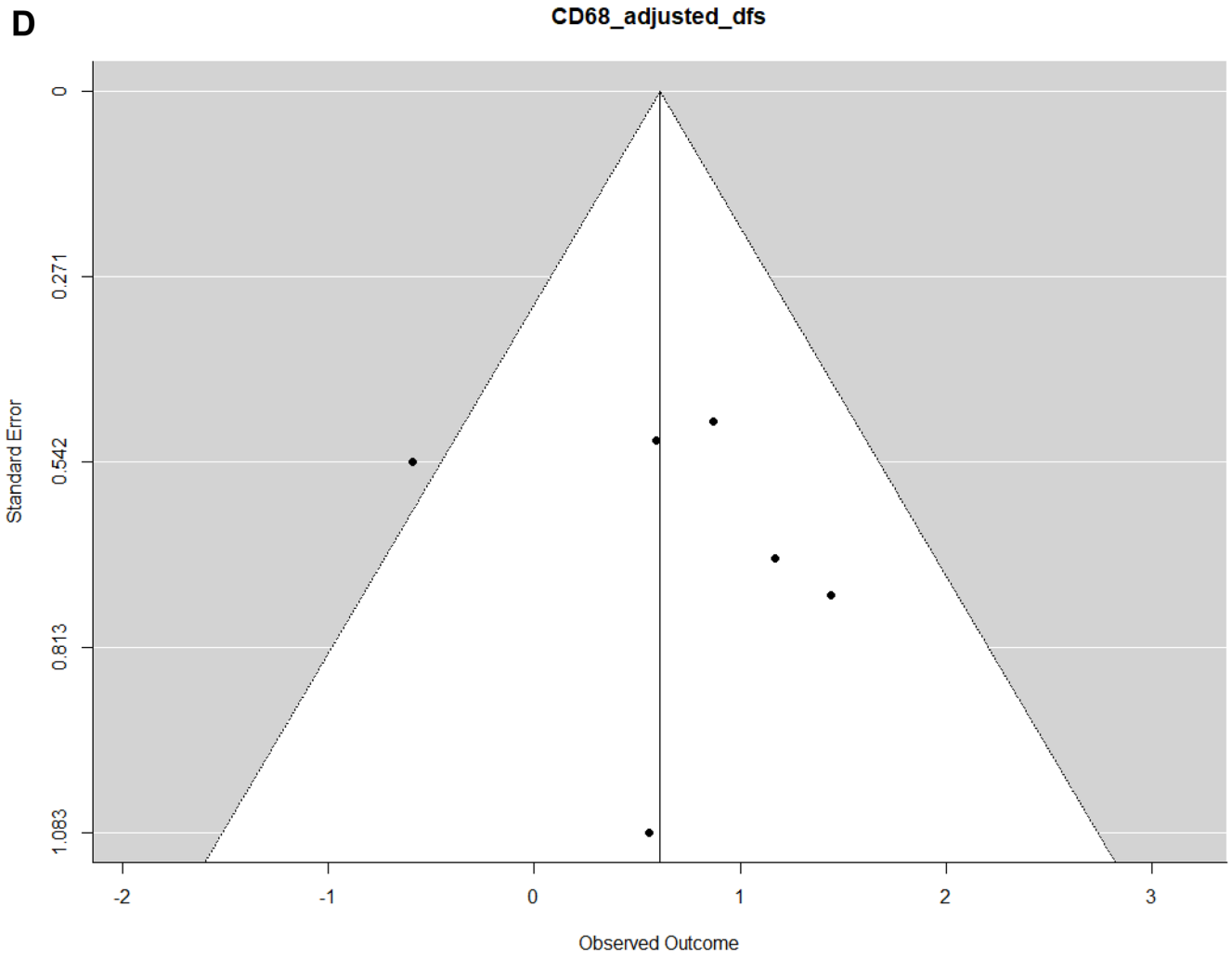


B


CD68_unadjusted_os
Standard Error
0
0.194
0.388
0.582
0.776
-1
0
1
2
Observed Outcome

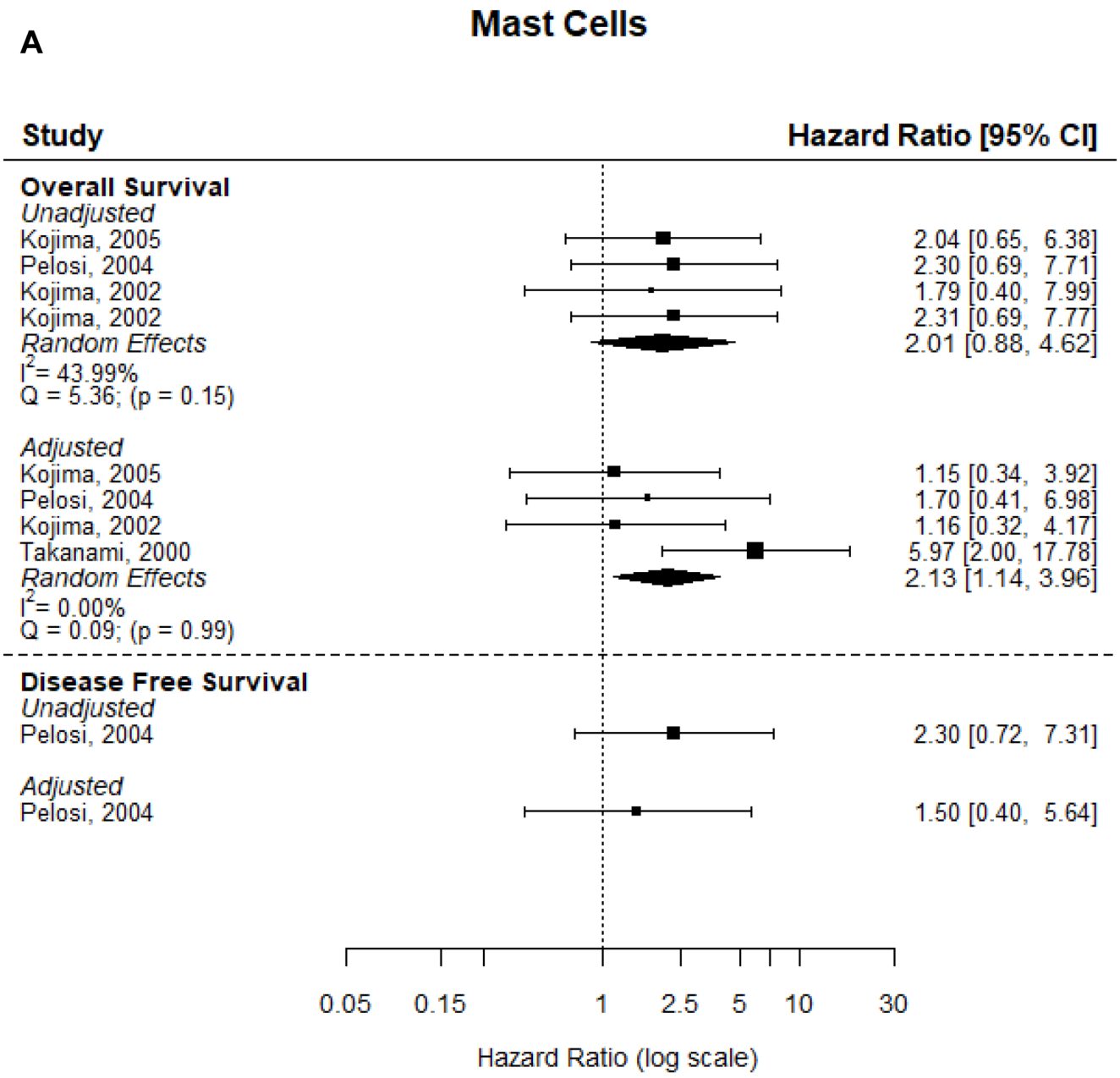
C

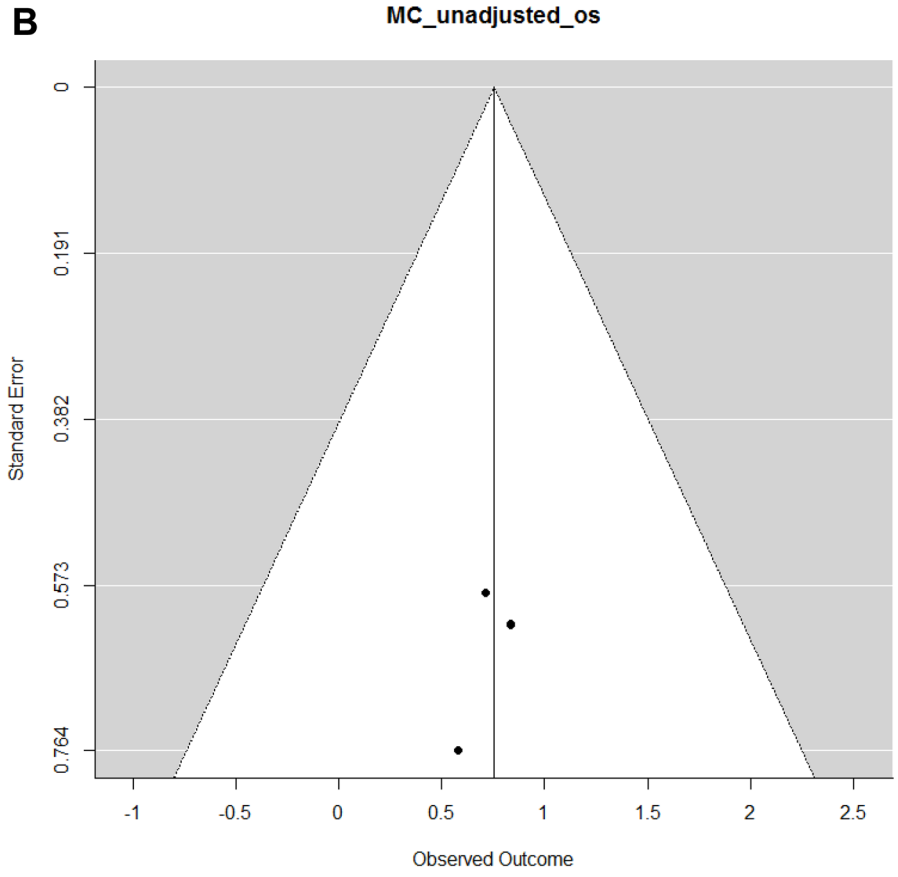

CD68_adjusted_os
Standard Error
0
0.25
0.501
0.751
1.002
-2
-1
0
1
2
Observed Outcome

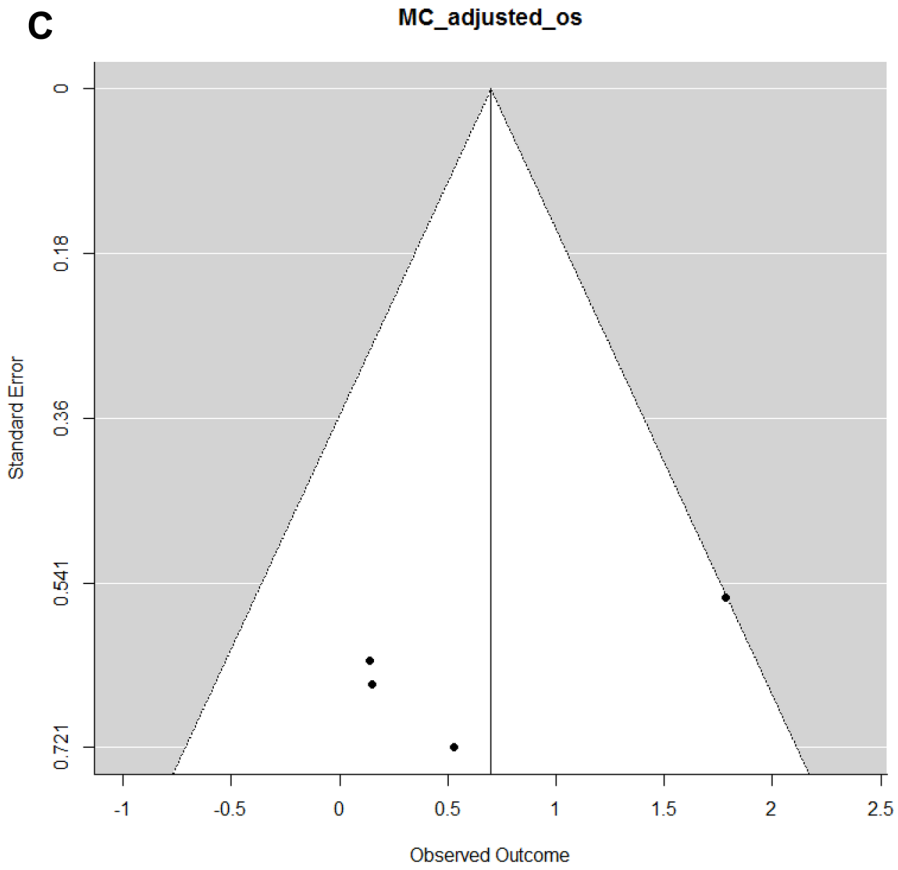


Supplementary Figure 7: (**A**) Forest Plot of macrophages (CD68+). (**B**) Funnel Plot of macrophages (CD68+) Unadjusted OS Studies. (**C**) Funnel Plot of macrophages (CD68+) Adjusted OS Studies. (**D**) Funnel Plot of macrophages (CD68+) Adjusted DFS Studies.

A


Mast Cells
Study
Hazard Ratio [95% CI]
Overall Survival
Unadjusted
Kojima, 2005
2.04 [0.65, 6.38]
Pelosi, 2004
2.30 [0.69, 7.71]
Kojima, 2002
1.79 [0.40, 7.99]
Kojima, 2002
2.31 [0.69, 7.77]
Random Effects
2.01 [0.88, 4.62]
I2= 43.99%
Q = 5.36; (p = 0.15)
Adjusted
Kojima, 2005
1.15 [0.34, 3.92]
Pelosi, 2004
1.70 [0.41, 6.98]
Kojima, 2002
1.16 [0.32, 4.17]
Takanami, 2000
5.97 [2.00, 17.78]
Random Effects
2.13 [1.14, 3.96]
I2= 0.00%
Q = 0.09; (p = 0.99)
Disease Free Survival
Unadjusted
Pelosi, 2004
2.30 [0.72, 7.31]
Adjusted
Pelosi, 2004
1.50 [0.40, 5.64]
0.05
0.15
1
2.5
5
10
30
Hazard Ratio (log scale)





Supplementary Figure 8: (**A**) Forest Plot of MCs. (**B**) Funnel Plot of MCs Unadjusted OS Studies. (**C**) Funnel Plot of MCs Adjusted OS Studies.