METHODS

Use of the Hillmen Urine Colour Chart

At admission, patients with a history of passing dark urine during the course of their current illness were initially assessed by clinicians based on history, an inquiry about the child passing dark urine, defined as Coca-Cola or tea coloured urine on the day of admission was made. Furthermore, asking the parent/guardian to indicate the grade (by pointing) at the colour against the Hillmen Urine Colour Chart (HUCC) (Figure 1) qualitatively assessed the urine colour. The HUCC has 10 colour codes ranging from mild yellow (colour code 1) to black (colour code 10). A probable and confirmed diagnosis of BWF/dark urine was made (at and during the course of admission). The patient/guardian was first asked to recall and match the colour of urine passed by their child on the day of admission to a colour on the HUCC. If available, urine was collected from the child using paediatric urine collection bags before it was transferred into a the urine collection bottle. Then the attending study clinician then matched the urine colour to the corresponding score on the HUCC scale. Children with clinician- witnessed urine or patient/guardian matched the colour of urine passed by their child (on the day of admission or during the course of admission) corresponding to HUCC >5 on the chart were confirmed to have haemoglobinuric severe malaria. These were the potentially eligible patients for the study. For easy access and efficient use of the HUCC, charts were displayed both in the patient admission area and in the ward with SOPs on how to use them. In addition, regular training of clinicians on how to use the HUCC is done.

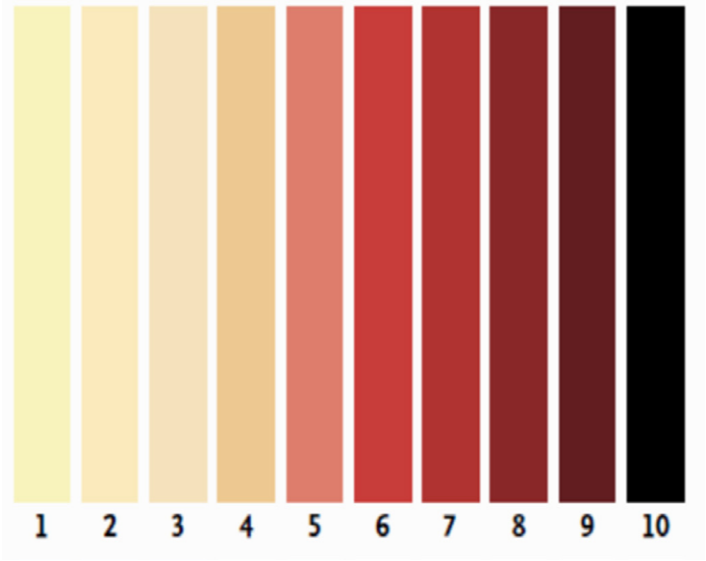
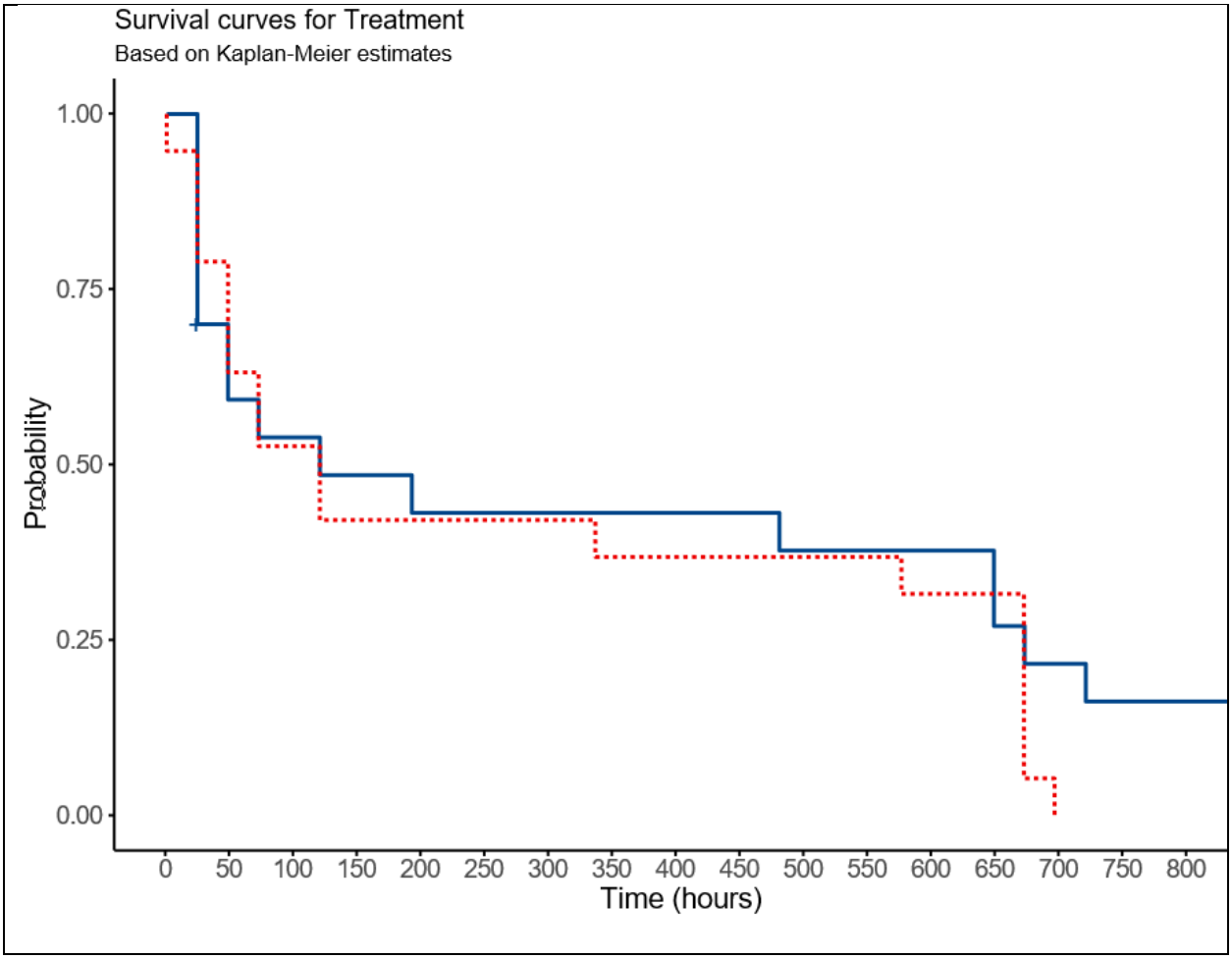


Figure 1. Hillmen urine color chart

RESULTS

Although Kaplan-Meier survival analysis and Cox proportional hazards regression were pre-specified in the study protocol to evaluate treatment effects on survival, these methods were not appropriate for the analysis due to a violation of the proportional hazards assumption (PH). Specifically, the Schoenfeld residuals test indicated that the hazard ratio for treatment was not constant over time. This was evident from the residual plot (Figure 2), where the trend of the residuals deviated significantly from zero, particularly at later time points, suggesting that the assumption of proportional hazards was violated. As a result, we chose to use Restricted Mean Survival Time (RMST), an alternative approach that does not rely on the proportional hazards assumption. RMST estimates the mean survival time within a pre-specified time window and compares these estimates between treatment groups. Unlike the Cox model, RMST does not require the proportionality assumption and is robust to violations of this assumption.


Survival curves for Treatment
Based on Kaplan-Meier estimates
Probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
Time (hours)

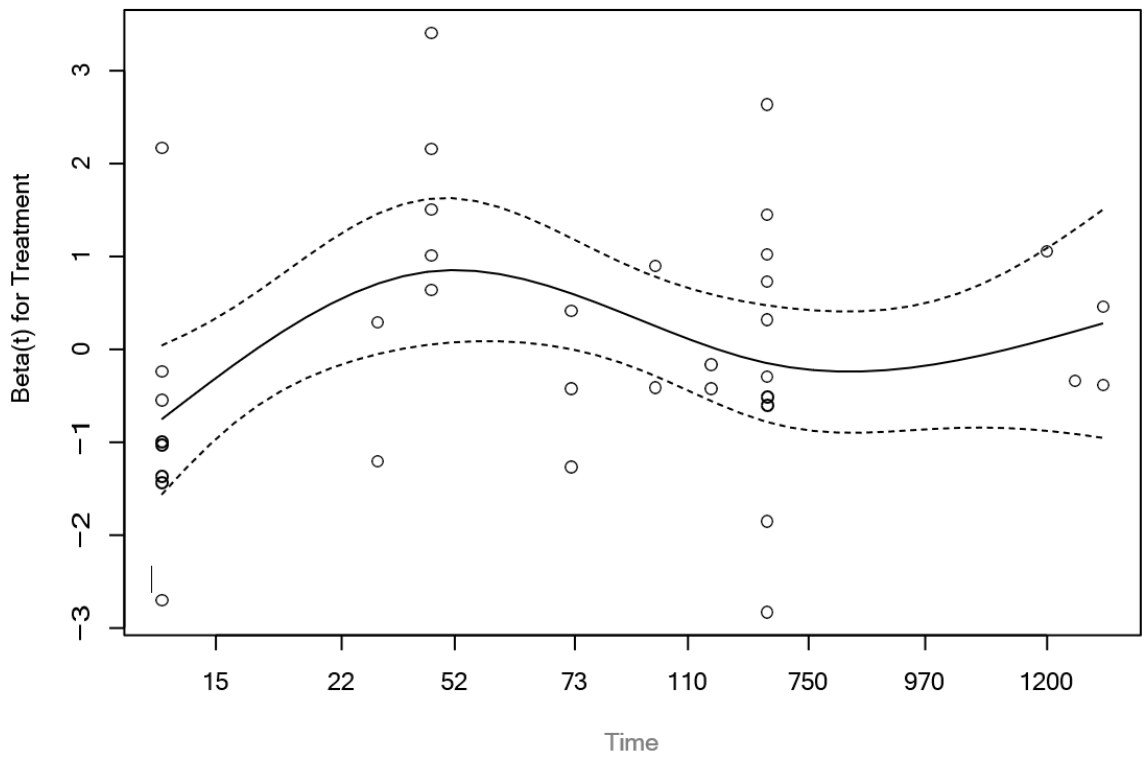


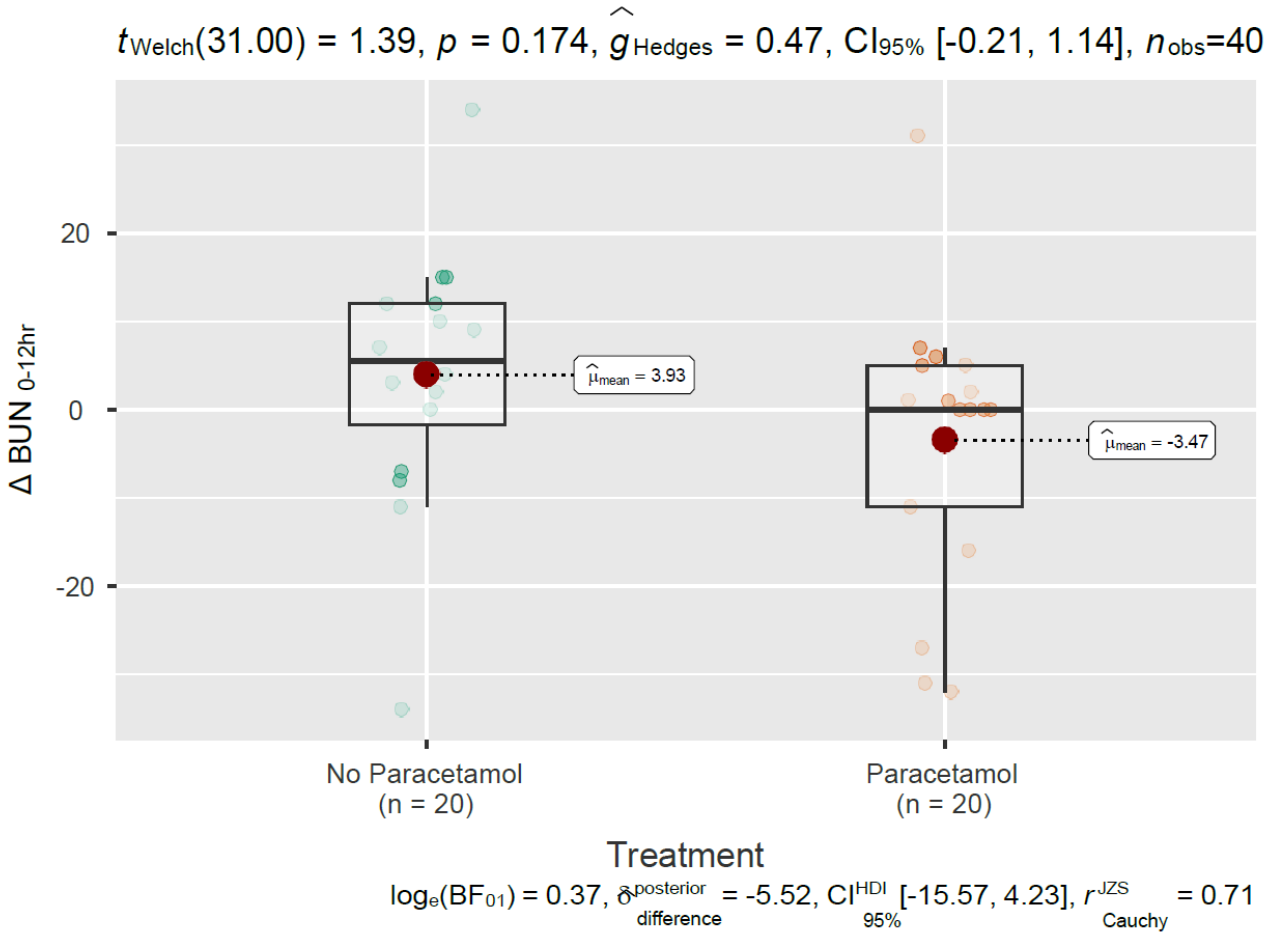
Figure 2. The plot shows the Schoenfeld residuals for the treatment. The solid line is not flat and appears to have a curved trend over time. The residuals deviate from zero, particularly in the middle and toward the end of the time axis. The PH assumption is violated for the Treatment because the hazard ratio for treatment changes over time.

Changes in renal markers over time

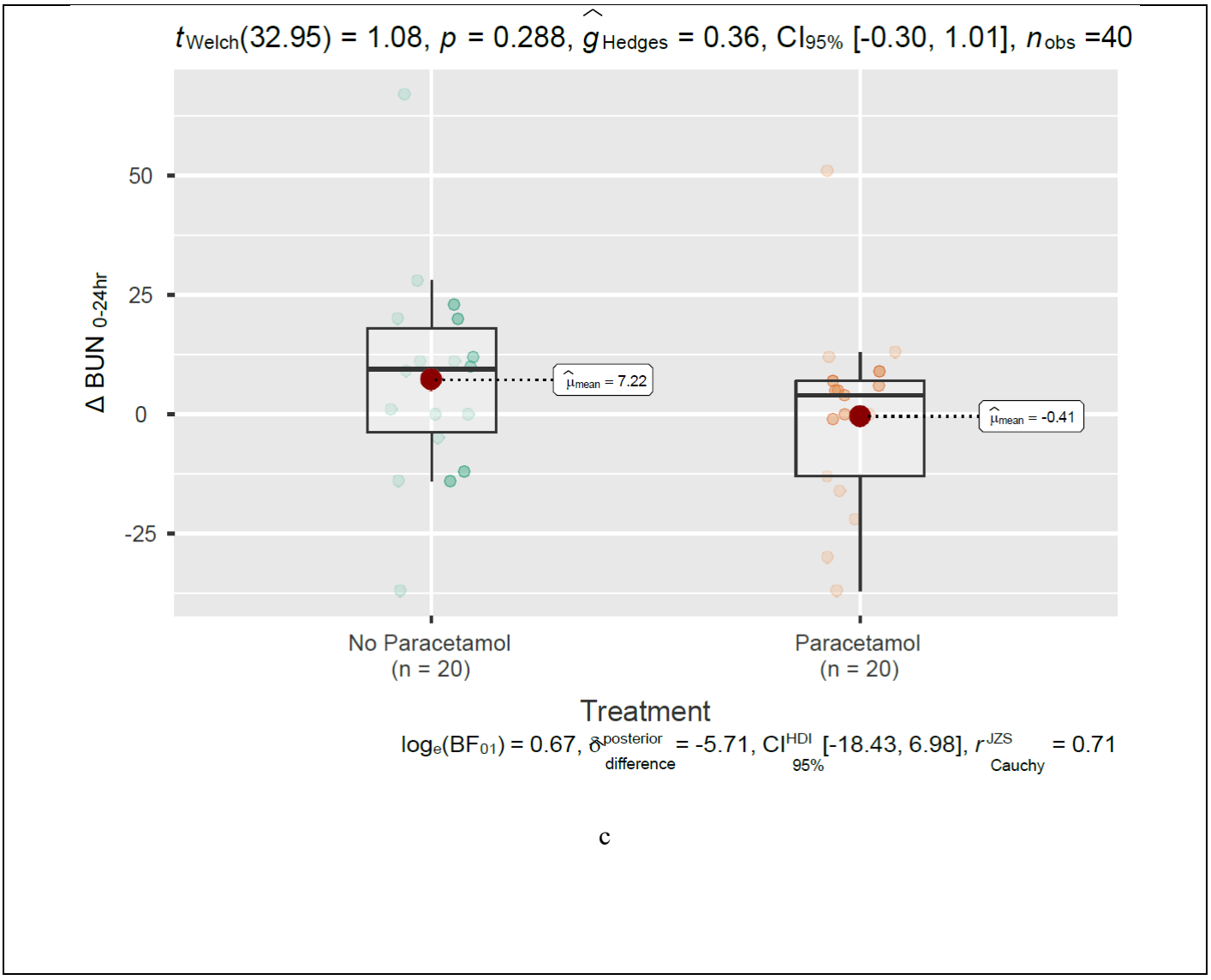
The mean difference in BUN levels at 12 hours was higher in the no paracetamol group (mean = 3.93) compared to the paracetamol group (mean = -3.47); however, this difference was not statistically significant (t(31.00) = 1.39, p = 0.174, 95% CI: -5.52 to 15.57). Similarly, changes in creatinine levels at 12 hours were minimal between groups (mean = 0.03 for no paracetamol and -0.33 for paracetamol; t(25.64) = 1.44, p = 0.163, 95% CI: -0.77 to 0.15). At 24 hours, the mean

difference in BUN levels remained higher in the no paracetamol group (mean = 7.22) compared to the paracetamol group (mean = -0.41), however, the difference was not significant (t(32.95) = 1.08, p = 0.288, 95% CI: -5.71 to 18.43). Similarly, changes in creatinine at 24 hours were minimal (mean = 0.05 for no paracetamol and -0.54 for paracetamol; t(29.98) = 1.32, p = 0.196, 95% CI: -0.43 to 1.25). At 48 hours, the reduction in BUN levels was more pronounced in the no paracetamol group (mean = -14.12) compared to the paracetamol group (mean = -5.29), but this difference was not statistically significant (t(31.64) = -0.96, p = 0.345, 95% CI: -8.61 to 24.17). Similarly, creatinine levels at 48 hours showed no significant difference between groups (mean = -0.28 for no paracetamol and 0.46 for paracetamol; t(27.90) = -1.02, p = 0.314, 95% CI: -1.03 to 0.33). By Day 28, both groups demonstrated substantial reductions in BUN and creatinine levels compared to baseline. The mean reduction in BUN was slightly greater in the paracetamol group (mean = -66.01) compared to the no paracetamol group (mean = -59.07), though this difference was not significant (t(24.48) = 0.38, p = 0.704, 95% CI: -35.83 to 26.57). Similarly, creatinine reductions were comparable between groups (mean = -1.85 for paracetamol and -2.42 for no paracetamol; t(21.37) = -0.42, p = 0.678, 95% CI: -1.91 to 2.61). These findings indicate no significant differences in renal biomarker changes between the treatment and control groups across all time points, as shown in **Error! Reference source not found.** below.

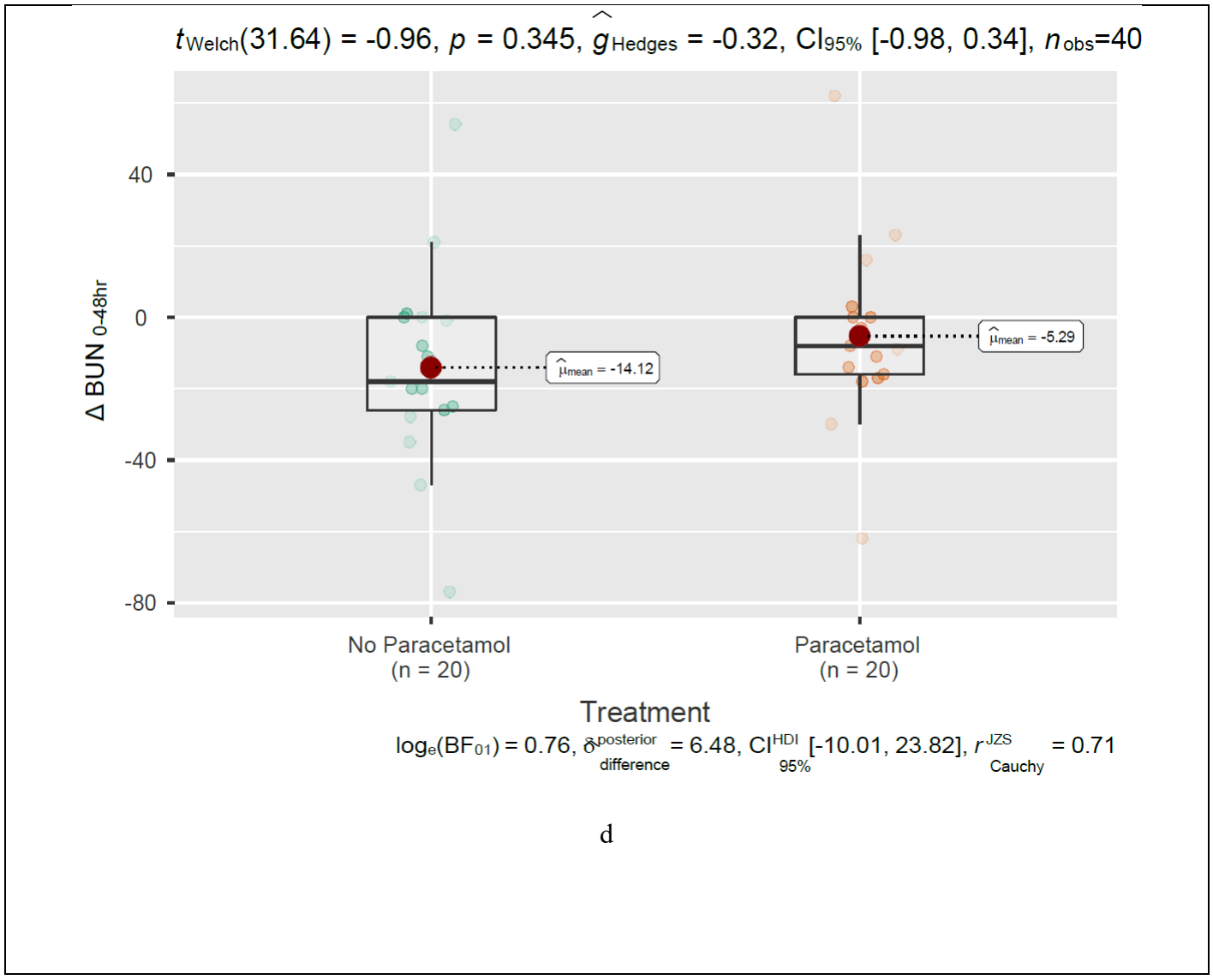
a


$t_{Welch}(31.00) = 1.39$, $p = 0.174$, $\hat{g}_{Hedges} = 0.47$, $CI_{95\%}$ [-0.21, 1.14], n_{obs}=40
20
0
-20
Δ BUN 0-12hr
$\hat{\mu}_{mean}$ = 3.93
$\hat{\mu}_{mean}$ = -3.47
No Paracetamol
(n = 20)
Paracetamol
(n = 20)
Treatment
$\log_e(BF_{01}) = 0.37$, $\hat{\delta}^{posterior}_{difference} = -5.52$, $CI^{HDI}_{95\%}$ [-15.57, 4.23], $r^{JZS}_{Cauchy} = 0.71$

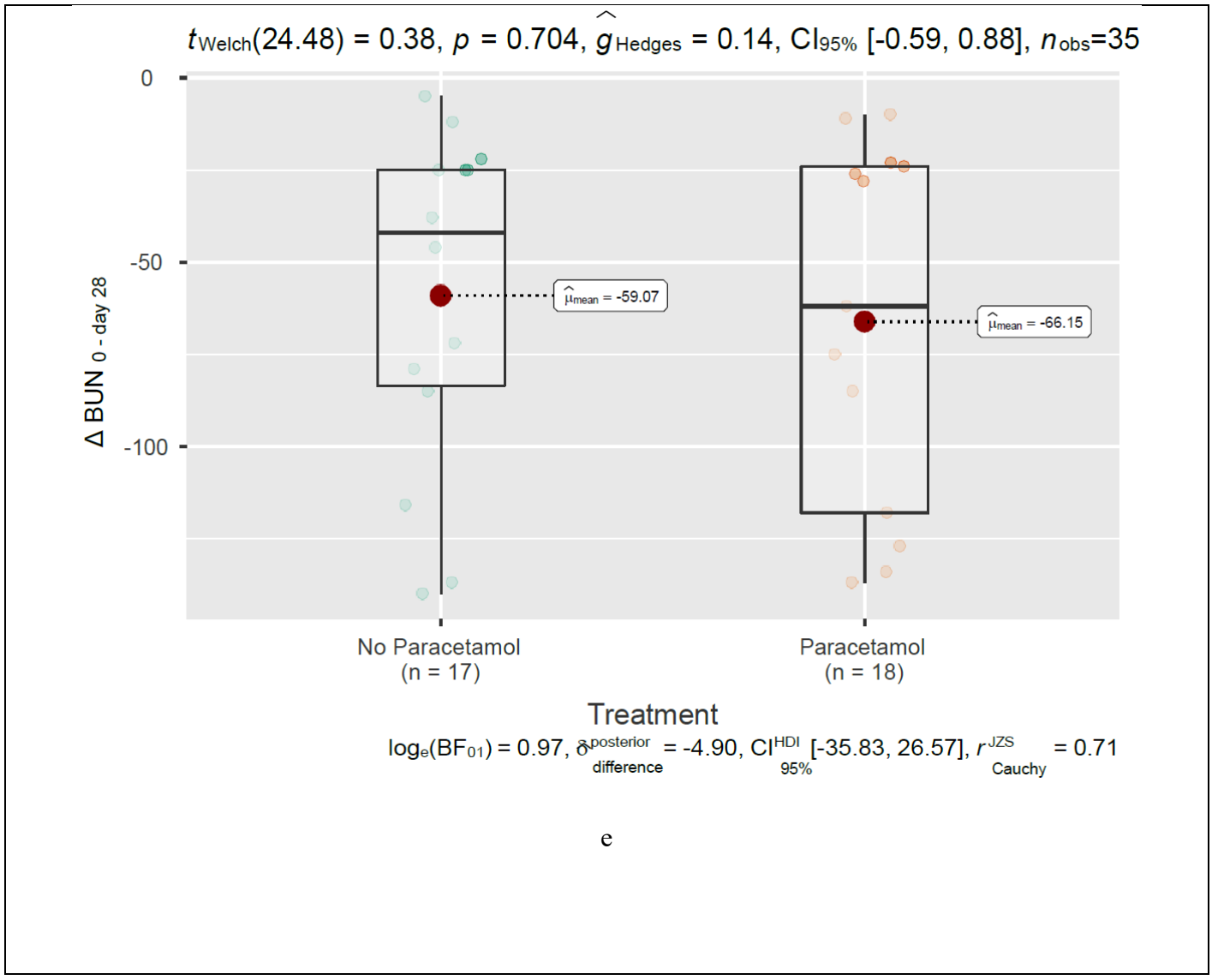
b


$t_{Welch}(32.95) = 1.08$, $p = 0.288$, $\hat{g}_{Hedges} = 0.36$, $CI_{95\%}$ [-0.30, 1.01], $n_{obs} = 40$
Δ BUN 0-24hr
50
25
0
-25
$\hat{\mu}_{mean} = 7.22$
$\hat{\mu}_{mean} = -0.41$
No Paracetamol
(n = 20)
Paracetamol
(n = 20)
Treatment
$\log_e(BF_{01}) = 0.67$, $\delta^{posterior}_{difference} = -5.71$, $CI^{HDI}_{95\%}$ [-18.43, 6.98], $r^{JZS}_{Cauchy} = 0.71$

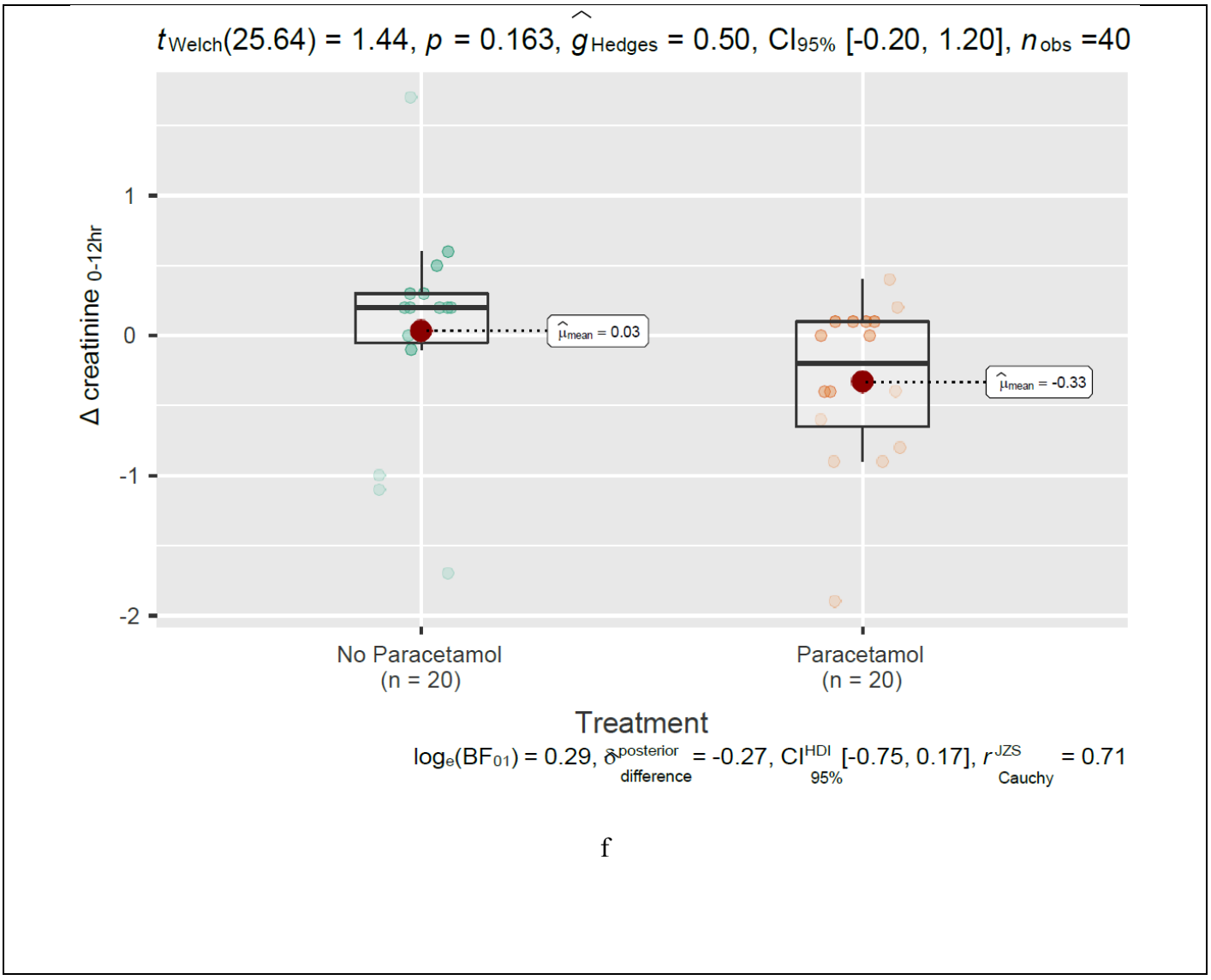
c


$t_{Welch}(31.64) = -0.96$, $p = 0.345$, $\hat{g}_{Hedges} = -0.32$, $CI_{95\%}$ [-0.98, 0.34], n_{obs}=40
40
0
-40
-80
Δ BUN 0-48hr
$\hat{\mu}_{mean}$ = -14.12
$\hat{\mu}_{mean}$ = -5.29
No Paracetamol
(n = 20)
Paracetamol
(n = 20)
Treatment
$\log_e(BF_{01}) = 0.76$, $\delta^{posterior}_{difference} = 6.48$, $CI^{HDI}_{95\%}$ [-10.01, 23.82], $r^{JZS}_{Cauchy} = 0.71$

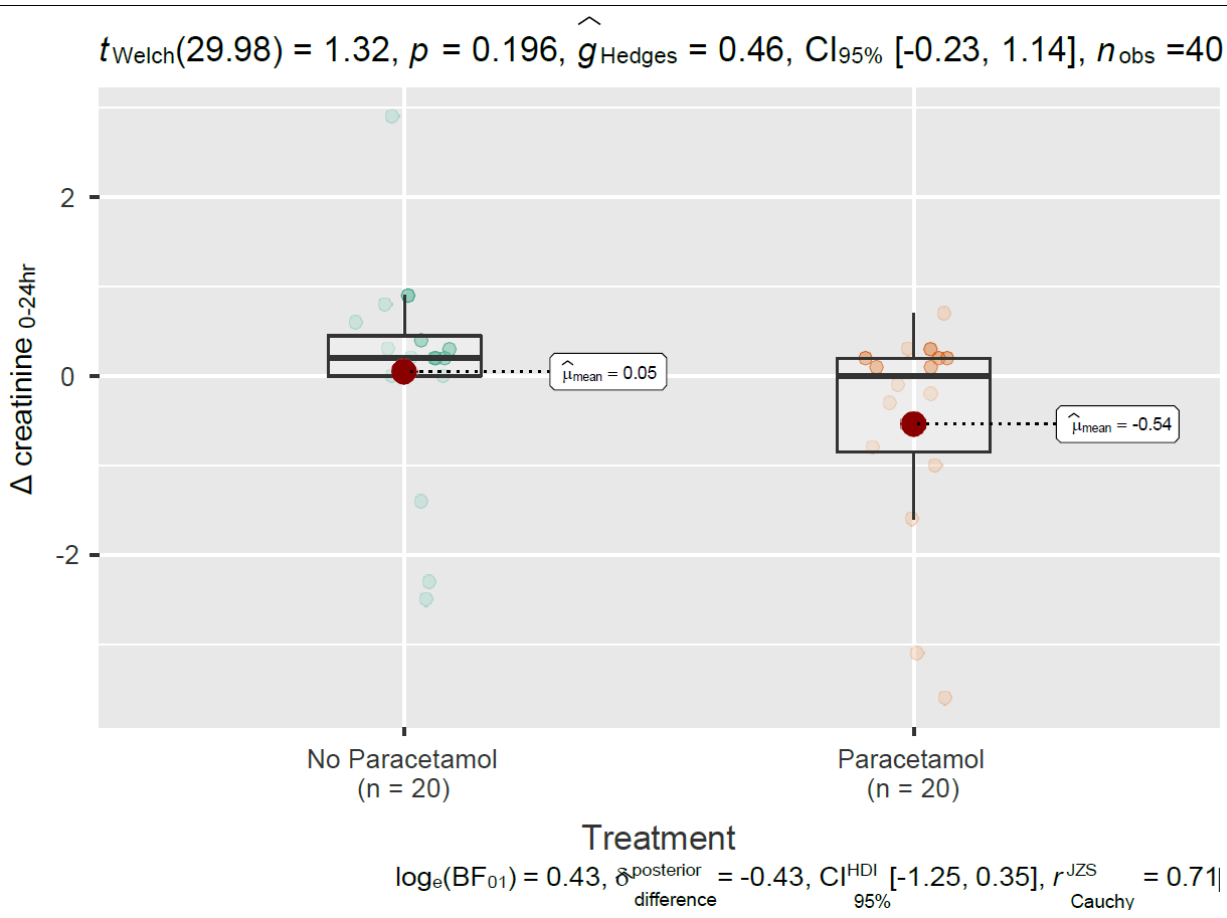
d


$t_{Welch}(24.48) = 0.38$, $p = 0.704$, $\hat{g}_{Hedges} = 0.14$, $CI_{95\%}$ [-0.59, 0.88], n_{obs}=35
0
-50
-100
Δ BUN 0 - day 28
$\hat{\mu}_{mean}$ = -59.07
$\hat{\mu}_{mean}$ = -66.15
No Paracetamol
(n = 17)
Paracetamol
(n = 18)
Treatment
$\log_e(BF_{01}) = 0.97$, $\delta^{posterior}_{difference} = -4.90$, $CI^{HDI}_{95\%}$ [-35.83, 26.57], $r^{JZS}_{Cauchy} = 0.71$

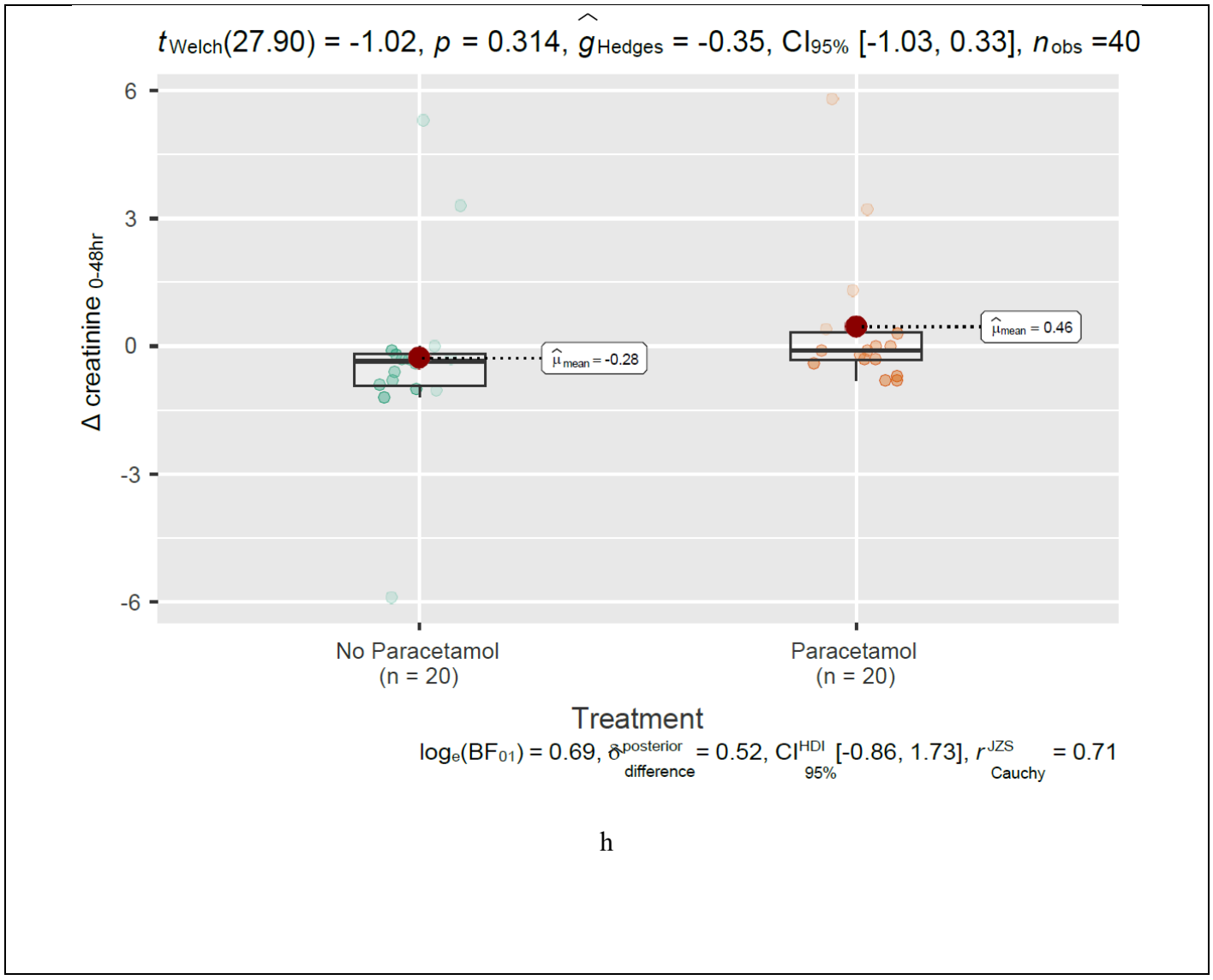
e


$t_{Welch}(25.64) = 1.44$, $p = 0.163$, $\hat{g}_{Hedges} = 0.50$, $CI_{95\%}$ [-0.20, 1.20], n_{obs} =40
Δ creatinine 0-12hr
1
0
-1
-2
$\hat{\mu}_{mean} = 0.03$
$\hat{\mu}_{mean} = -0.33$
No Paracetamol
(n = 20)
Paracetamol
(n = 20)
Treatment
$\log_e(BF_{01}) = 0.29$, $\delta^{posterior}_{difference} = -0.27$, $CI^{HDI}_{95\%}$ [-0.75, 0.17], $r^{JZS}_{Cauchy} = 0.71$

f


$t_{Welch}(29.98) = 1.32$, $p = 0.196$, $\hat{g}_{Hedges} = 0.46$, $CI_{95\%}$ [-0.23, 1.14], n_{obs} =40
Δ creatinine 0-24hr
2
0
-2
$\hat{\mu}_{mean} = 0.05$
$\hat{\mu}_{mean} = -0.54$
No Paracetamol
(n = 20)
Paracetamol
(n = 20)
Treatment
$\log_e(BF_{01}) = 0.43$, $\delta^{posterior}_{difference} = -0.43$, $CI^{HDI}_{95\%}$ [-1.25, 0.35], $r^{JZS}_{Cauchy} = 0.71$

g


$t_{Welch}(27.90) = -1.02$, $p = 0.314$, $\hat{g}_{Hedges} = -0.35$, $CI_{95\%}$ [-1.03, 0.33], $n_{obs} = 40$
Δ creatinine 0-48hr
6
3
0
-3
-6
$\hat{\mu}_{mean} = -0.28$
$\hat{\mu}_{mean} = 0.46$
No Paracetamol
(n = 20)
Paracetamol
(n = 20)
Treatment
$\log_e(BF_{01}) = 0.69$, $\delta^{posterior}_{difference} = 0.52$, $CI^{HDI}_{95\%}$ [-0.86, 1.73], $r^{JZS}_{Cauchy} = 0.71$

h

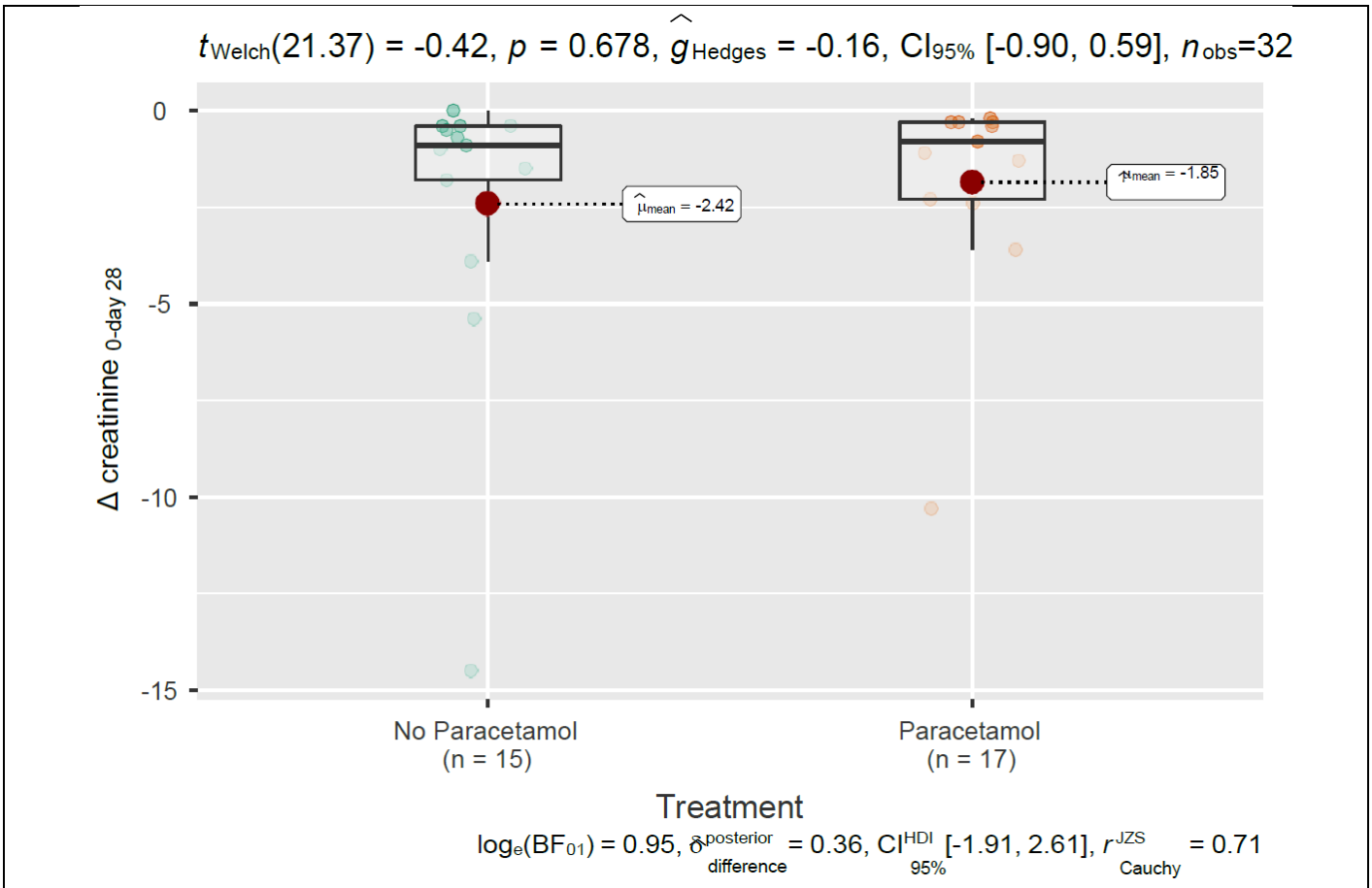


Figure 3. Changes in renal biomarker between the treatment and control groups: a-d represents changes in BUN from baseline at 12 hours, 24 hours, 48 hours and day 28 while e-h represents changes in serum creatinine from baseline at 12 hours, 24 hours, 48 hours and day 28.

Supplementary table 1. Between group comparison for renal recovery at day 28

Paracetamol vs No paracetamol	**Estimate**	**95% Confidence Interval**	**p-value**
Difference in RMST	-29.62 hours	(-229.97, 170.73)	0.772
Ratio of RMST (1 / 0)	0.904	(0.457, 1.787)	0.772

Supplementary table 2. Adjusted RMST analysis model summary for renal recovery within 28 days

Difference of RMST					
Variable	**Coefficient**	**Standard Error**	**z-value**	**p-value**	**95% Confidence Interval**
Intercept	-355.592	357.521	-0.995	0.320	(-1056.32, 345.14)
Arm (1 - 0)	-9.103	93.433	-0.097	0.922	(-192.23, 174.02)
Age	-9.144	43.029	-0.213	0.832	(-93.48, 75.19)
Weight	38.818	31.886	1.217	0.223	(-23.68, 101.32)

Ratio of RMST						
Variable	**Coefficient**	**Standard Error**	**z-value**	**p-value**	**Exp (Coefficient)**	**95% CI**
Intercept	3.463	1.209	2.865	0.004	31.905	(2.99, 341.01)
Arm (1 / 0)	0.003	0.319	0.009	0.992	1.003	(0.536, 1.875)

Age	-0.008	0.130	-0.064	0.949	0.992	(0.768, 1.280)
Weight	0.119	0.090	1.327	0.185	1.126	(0.945, 1.342)