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Cause and timing of death and sub-group differential effects of erythropoietin in the EPO-TBI study

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Cause and timing of death and sub-group differential effects of erythropoietin in the EPO-TBI study

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Abstract

The EPO-TBI study randomised 606 patients with moderate or severe traumatic brain injury (TBI) to be treated with weekly epoetin alfa (EPO) or placebo. Six-month mortality was lower in EPO treated patients in an analysis adjusting for TBI severity. Knowledge of possible differential effects by TBI injury subtype and acute neurosurgical treatment as well as timing and cause of death (COD) will facilitate the design of future interventional TBI trials. We defined COD as cerebral (brain death, cerebral death with withdrawal or death during maximal care) and non-cerebral (death following withdrawal or during maximal care due to a non-cerebral cause). The study included 305 patients treated with EPO and 297 with placebo, with COD recorded in 77 (99%) out of 78 non-survivors. Median time to death in patients dying of cerebral COD was 8 days (IQR 5-16) compared to 29 days (IQR 7-56) ($p=0.01$) with non-cerebral COD. When assessing subgroups by admission computed tomography scan injury findings, we found no significant differential effects of EPO compared to placebo. However, EPO appeared more effective in patients with an injury type not requiring a neurosurgical operation prior to ICU admission (OR 0.29, 95% confidence interval 0.14-0.61, $p=0.001$, p for interaction = 0.003) and in this sub-group, fewer patients died of cerebral causes in the EPO compared to placebo group (5% compared to 14%, $p=0.03$). In conclusion, most TBI deaths were due to cerebral causes that occurred during the first two weeks, and were related to withdrawal of care. EPO appeared to specifically reduce cerebral deaths in the important subgroup of patients with a diffuse type of injury not requiring a neurosurgical intervention prior to randomisation.

Key words: traumatic brain injury, clinical management of CNS injury, head trauma, human studies, adult brain injury

Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality among young people.¹ The mainstay of treatment is rapid transfer to designated and specialised trauma centres with both neurosurgical and neurointensive care expertise.² Mortality after severe TBI remains high in the range of 20-40%,³ and many pharmacological interventions to ameliorate secondary brain injury have been evaluated without success.^{4,5} Timing of death after trauma and TBI is frequently described as early or late.⁶ Early deaths are related to either brain death or treatment withdrawal due to a perceived poor prognosis,⁷ whereas late deaths are believed to be mainly due to infection and multi-organ failure.⁸

In the EPO-TBI trial, 606 critically ill patients with moderate or severe TBI were randomized to the administration of epoetin alfa or placebo.⁹ While, the study failed to show an improvement in neurological function at six months, it did demonstrate a significant decrease in mortality with EPO administration in a pre-specified analysis. Interestingly similar beneficial effects of EPO in trauma and TBI patients were demonstrated in two previous randomized, placebo-controlled trials.^{10,11}

The mechanisms behind this potential decrease in mortality are currently unknown. However, detailed knowledge on timing of death and probable cause of death is logically important for the design of future interventional studies of critically ill TBI patients and might also shed some light on why EPO seems to lower mortality after major trauma. Moreover, given the heterogeneity of both TBI type and neurosurgical treatment, it is possible that there are TBI sub-groups in which EPO is more effective than in others. In the current study, we primarily aimed to explore timing and cause of death in patients treated with EPO or placebo after major or severe TBI. Secondarily we aimed to assess relationships between TBI specific sub-groups and neurosurgical care and intervention effect.

Methods

The EPO-TBI trial was a multi-centre, multi-national, randomised, double-blind, parallel-group, placebo controlled trial that enrolled 606 patients with non-penetrating moderate (best post-resuscitation, pre-intubation Glasgow Coma Score [GCS] 9-12) or severe (GCS 3-8) TBI.⁹ Study centres from Australia, New Zealand, Saudi-Arabia, France, Finland, Germany and Ireland participated. Within 24 hours of ICU admission patients were randomised to receive either weekly doses of 40,000 IU of subcutaneous epoetin alfa (Eprex Janssen-Cilag Pty Ltd, Titusville, NJ, USA) or placebo (0.9% sodium chloride) for a maximum of three doses or until the patients was discharged from the ICU¹²

Data collection

A web based case record form was used including detailed data on patient characteristics, injury mechanism, pre-hospital care and immediate hospital management.¹² Specifically data enabling the calculation of the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT-TBI) risk for poor six month outcome was included.¹³ Trained assessors classified injury severity with Injury Severity Scores (ISS), Abbreviated Injury Scales (AIS) based on radiological findings and hospital notes. Data on performed neurosurgical procedures included daily assessment of whether the patient received any neurosurgical procedure such as mass lesion removal, craniectomy or bifrontal decompressive craniectomy. Data on neuro-intensive care included daily assessment of whether intracerebral pressure was monitored, patient received hyperventilation or whether induced hypothermia was in use.

Trial outcome and cause of death

The primary outcome of the EPO-TBI trial was neurological function at six months categorized with the Glasgow Outcome Scale Extended (GOSE). A good outcome was defined as a GOSE score from 5 to 8. Time of death was recorded prospectively and categorised into the following five different categories: 1. Brain death; 2. Death with therapy withdrawn for severe cerebral damage; 3. Death with therapy withdrawn for non-cerebral reasons (e.g. multiorgan failure [MOF]); 4. Death despite maximal support for

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3 severe cerebral damage, and 5. Death despite maximal support for non-cerebral reasons
4 (e.g. MOF)¹²

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6 For the analysis, brain death and other deaths categorised as cerebral were included as one
7 group i.e. “cerebral deaths”. Similarly, the two non-cerebral death groups were categorised
8 as “non-cerebral”. Admission computed tomography (CT) scans were viewed by an assessor
9 blinded to treatment and categorised according to the Marshall category.¹⁴ **As in previous
10 studies we grouped together Marshall groups V and VI.**^{15, 16}
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16 17 *Statistical analysis*

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19 Categorical data are presented as numbers and percentages and compared using chi-square
20 test. Numerical data are presented as means and standard deviation (SD) or as medians and
21 interquartile range (IQR) in parenthesis. Parametric data is compared with a Student’s T test
22 and non-parametric data with the Mann-Whitney U or Kruskal-Wallis test. Kaplan-Meier
23 curves for both cerebral and non-cerebral deaths were constructed and compared between
24 the EPO and placebo treated patients with a log-rank test. The effect of intervention on 6-
25 month mortality was determined using logistic regression and reported as odds ratios with
26 95% confidence intervals, while heterogeneity between subgroups was determined by
27 fitting an interaction between treatment and sub-group. A p-value less than 0.05 was
28 considered significant. Statistical analysis was performed with SPSS version 22.0 (IBM Corp.
29 Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and
30 SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).
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42 *Ethical permits, consent and trial registration*

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44 The main study had ethical approvals at all sites. Consent was obtained from the patient
45 next of kin or legal representative prior to study inclusion. The trial was registered at
46 ClinicalTrials.gov (number NCT00987454), the Australian and New Zealand Clinical Trials
47 Registry (number ACTRN12609000827235), and European Drug Regulatory Authorities
48 Clinical Trials (number011-005235-22).
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Results

A total of 606 patients were included in the study. Consent was withdrawn in three patients and one was lost to follow-up, leaving 602 analysable patients. A total of 78 patients (13%) died prior to 6 months, 59 patients (76%) died while in the ICU, 11 (14%) while in the hospital and 8 patients (10%) after hospital discharge. A total of 32 deaths (41%) occurred during the first week, 20 during the second week (26%) and 26 patients (33%) later than two weeks (Fig.1).

Differences in clinical characteristics between cerebral and non-cerebral deaths

The cause of death (COD) was recorded in 77 (99%) out of 78 patients. Of the 77 deaths, 62 (80%) were due to cerebral reasons and 15 (20%) due to non-cerebral reasons. There were minimal differences in admission characteristics in patients who died from cerebral reasons compared to those dying from non-cerebral reasons (Table 1). Regarding CT findings and COD, only petechial haemorrhages were more common in patients dying from a cerebral COD (Table 2). Median time to death in patients dying of cerebral reasons was 8 days (IQR 5-16) and in those with non-cerebral reasons it was 29 days (IQR 7-56) ($p=0.01$).

Of the 62 cerebral deaths, 16 (26%) were due to brain death, 7 (11%) due to cerebral causes during maximal support and 39 (65%) due to withdrawal of care (Supplemental Table 1 and 2). Of the non-cerebral deaths 7 occurred during (47%) maximal support and in the remaining 8 (53%), due to withdrawal of care (Supplemental Table 1 and 2). A total of 47 (60%) out of 77 deaths were due to treatment withdrawal. Median time to death in those in whom treatment was withdrawn was 11 days (IQR 7-32) and in those who died with full support it was 7 days (IQR 4-10). There were significant differences in clinical characteristics and CT findings in the non-survivors with different COD (Supplemental Tables 1 and 2). Notably patients dying from brain death were younger and had more episodes of raised ICP.

Effect of EPO or placebo on cause and timing of death

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3 During ICU stay, 24 (7.9%) of 305 EPO treated patients died compared to 35 (11.7%) of 297
4 treated with placebo ($p=0.11$). During hospital care 28 (9.2%) of EPO treated patients had
5 died compared to 42 (14.1%) treated with placebo ($p=0.06$). At six months 32 (10.5%) out of
6 305 EPO treated patients had died compared to 46 (15.5%) out of 297 treated with placebo
7 ($p=0.07$). The causes of death in EPO and placebo treated patients are shown in Table 3.
8 There was no difference in the distribution of causes of death for EPO and placebo treated
9 patients ($p=0.44$). Survival curves for cerebral and non-cerebral deaths according to the use
10 of EPO or placebo were similar (Supplemental Fig. 1). Time to death was 11 days (7-28) in
11 the EPO treatment group and 8 days (IQR 5-18) in the placebo group ($p=0.11$). Among the
12 EPO treated patients, death was due to withdrawal of care in 21 (6.9%) out of 305 patients,
13 and the corresponding figure for the placebo treated patients was 27 (9.1%) out of 298
14 patients ($p=0.32$).
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24 *Effect of EPO by admission CT characteristics and neurosurgical operation*

25 The effect of EPO indexed by admission CT findings and neurosurgical treatment are shown
26 in Fig. 2 and Fig. 3. There were no significant differences in treatment effect of EPO
27 according to different subtypes of admission CT brain findings (Fig. 2). There was no
28 differential effect indexed by use of ICP monitoring, hyperventilation or hypothermia during
29 ICU care (Fig. 3).
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35 There was, however, a strong differential effect of EPO in patients that had not undergone
36 a neurosurgical procedure prior to randomisation compared to those who had (Fig. 3). In
37 the group that did not have a neurosurgical operation, EPO decreased mortality (OR 0.29 95%
38 CI 1.14-0.61, $p=0.01$) compared to those who had (OR 1.39 95% CI 0.68-2.85, $p=0.37$) (p for
39 interaction 0.003). Survival curves indexed for the non-neurosurgical group and the
40 neurosurgical groups are shown in Fig. 4. In the non-neurosurgical group, the proportion of
41 patients with good outcome at 6 months appeared higher in the EPO group (64% compared
42 to 58%, $p=0.25$) but this difference was not statistically significant. The distribution of GOSE
43 scores in the non-neurosurgical group treated with EPO or placebo are shown in the
44 Supplementary Appendix (Supplemental Fig. 2). In the neurosurgical group, the proportion
45 of patients with good outcome at 6 months appeared lower with EPO compared to placebo
46 (40% compared to 52%, $p=0.23$) but this difference was not statistically significant
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56 The COD by intervention indexed by neurosurgical group and non-neurosurgical groups are
57 shown in Table 3. There was a significant differences in the distribution of COD between
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3 patients treated with EPO compared to placebo in the non-neurosurgical group, but not in
4 the neurosurgical group (Table 3). Cerebral deaths occurred in 10 (5%) out of 197 patients
5 treated with EPO, and in 28 out of 203 (14%) treated with placebo ($p=0.003$).
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10 Discussion

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12 In this population of critically ill patients included in a randomised controlled trial (RCT) of
13 TBI therapy, the majority of deaths occurred during the first two weeks following injury and
14 were cerebral in nature. Death was commonly related to withdrawal of treatment, and only
15 a smaller proportion died while receiving maximal medical intervention. Death due to non-
16 cerebral reasons occurred later during the hospital course. We found overall no difference
17 in causes or timing of death between EPO and placebo treated patients. However, with
18 regards to different types of TBI and requirement of neurosurgical interventions, we found
19 that EPO appeared significantly more effective than placebo in patients not receiving a
20 neurosurgical operation prior to randomisation. In this subgroup, EPO appeared to
21 especially decrease the rates of death from a cerebral cause and EPO did not appear to
22 increase the proportion of survivors in a poor neurological state. These findings have
23 implications for future studies on EPO in TBI patients.
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34 The overall mortality of 13% found in the present study was slightly lower than in several
35 previous studies.^{17, 18} In a recent large pharmacological study on the use of progesterone in
36 TBI, the six month mortality was 17%, and in trials of ICP monitoring and decompressive
37 craniectomy six month mortality was substantially higher ranging from 30%-48%^{18, 19} In a
38 study evaluating prehospital administration of hypertonic saline to TBI patients, mortality
39 was even higher.²⁰ Patients with this severity of injury are not likely to have been included in
40 the current EPO-TBI trial given the inclusion of patients with moderate TBI and the exclusion
41 of patients, who according to the treating clinician are likely to die within the next 48
42 hours.¹² In prospective observational studies, six month mortality has been shown to range
43 from 25% to 44%.²¹⁻²³ In the current study, non-cerebral deaths occurred significantly later
44 than cerebral deaths. This supports the hypothesis that late deaths are related to multi-
45 organ failure and sepsis.⁸
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55 We have demonstrated that most deaths were due to withdrawal of treatment, irrespective
56 whether the death was attributed to a cerebral or non-cerebral cause. In a prospective
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3 Canadian cross sectional study the number of TBI deaths associated with withdrawal ranged
4 from 45% to 90%. In the current study treatment withdrawal was more common with higher
5 age, lower level of consciousness at presentation and a more severe TBI, in line with findings
6 by Turgeon and colleagues.²³ In the study by Turgeon and colleagues withdrawal most
7 commonly occurred within the first three days of intensive care²³ but in our international
8 multicentre randomized controlled trial, time to death related to withdrawal was longer.
9 The death rate following withdrawal of medical treatment is infrequently reported in
10 RCTs.¹⁵ This mode of death represents a major challenge for the design of future
11 interventional TBI trials and reinforces the need for treatment blinding where feasible. In
12 the current study we observed no difference in the proportion of treatment withdrawal or
13 time to withdrawal between EPO and placebo treated patients.
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23 TBI is without doubt a heterogeneous disease as evidenced by the different possible
24 pathological findings on the admission CT scan.²⁴ Indeed the heterogeneity of TBI has been
25 seen as one reason behind the failures of pharmacological trials performed to date.^{25, 26} In
26 the SYNAPSE trial where TBI patients were administered progesterone after TBI, the main
27 results of the trial was negative, and even extensive sub-group analysis including different
28 admission Marshall Classification, decompressive craniectomy, or the need for surgery did
29 not change the results.²⁷ In the recent trial on the use of therapeutic hypothermia for the
30 treatment of raised ICP, a post hoc analysis revealed that hypothermia was more harmful in
31 patients with less severe TBI, and did not provide beneficial effects with more severe
32 injury²⁸.
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41 In the current study, we observed no difference in frequency of cerebral or non-cerebral
42 deaths between EPO and placebo treated patients in the whole sample. We did however
43 observe a striking differential effect of EPO in the patients admitted to the ICU that had not
44 undergone a neurosurgical operation prior to randomisation. In this sub-cohort EPO
45 appeared to decrease the incidence of cerebral deaths. Non-neurosurgical patients are
46 those with diffuse injury, petechial haemorrhages, and with small haemorrhages not
47 appropriate for neurosurgical evacuations. The proposed mechanism of why EPO could
48 work include a decrease in local tissue hypoxia in the brain, or a decrease in cerebral
49 oedema due to improved function of the blood-brain barrier, and an attenuation of
50 secondary brain injury, which may occur with all types of TBI.^{29, 30} Presence of a mass lesion
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necessitating immediate surgery is a confounder and may have a major independent effect on survival. In contrast, in patients receiving medical therapy only, EPO may provide a degree of independent protective effect. Our study findings indicate that future trials using EPO for neuroprotection in TBI, may need to focus on patients with diffuse injury not likely to require a neurosurgical operation.

Strengths of the current study include a large multicentre randomised double blinded controlled trial with extensive prospective data collection and classification of admission CT scan findings by trained assessors unaware of treatment assignment. Moreover, all decisions on clinical management including withdrawal of care were made by clinicians unaware of treatment allocation. Finally, our findings of a specific effect in patients who did not receive neurosurgery prior to randomization suggest that identification of this specific high yield group could be introduced in a future interventional trial. Nonetheless, our study has certain limitations. Firstly, the performed analysis was not pre-planned, and with multiple testing the risk of finding significant treatment effects by chance increases. Therefore, our findings should be seen as hypothesis generating. Secondly, we do not have detailed data on autopsy results of the deceased patients and therefore the data on COD were ascertained clinically. Determining cause of death based on clinical scenarios is difficult and inter-rater disagreement is not uncommon.³¹

In conclusion, we have demonstrated that, in patients treated for moderate or severe TBI, a large majority of deaths are due to cerebral injury and occur during the first two weeks, whereas deaths due to non-cerebral causes occur after two weeks. Most deaths are related to treatment withdrawal, which represents a challenge for future trials of pharmacologic interventions in TBI. No distinct pattern in cause or time of death in patients treated with EPO or placebo was seen. However, there was a significantly lower mortality with EPO in the 65% of patients who had not undergone a neurosurgical operation prior to randomisation. Our findings are likely to assist the identification of patients most likely to achieve increased survival with EPO treatment and inform the design of more targeted trials of EPO and other interventions in TBI.

Author Disclosure Statement

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TABLE 1. CHARACTERISTICS OF SURVIVORS AND NON-SURVIVORS BY CAUSE OF DEATH

	Alive at six months (n=524)	Cerebral deaths (n=62)	Non-cerebral deaths (n=15)
Patient characteristics			
Mean age (years)	30 (22-46)	43 (23-55)	52 (41-58)
Female gender	87 (17%)	10 (16%)	4 (27%)
Consciousness			
Initial GCS	7 (5-9)	4 (3-7)	6 (4-10)
Pupillary abnormality			
Both equal and reacting	435 (83%)	42 (68%)	9 (60%)
Both dilated and non-reactive*	0 (0%)	0 (0%)	1 (7%)
Both non-reactive	35 (7%)	9 (15%)	3 (20%)
One non-reactive	46 (9%)	10 (16%)	2 (13%)
Unstable/not documented	8 (2%)	1 (2%)	0 (0%)
Pre-hospital vital signs			
Systolic blood pressure less than 90 mmHg	163 (31%)	23 (37%)	3 (20%)
Oxygen saturation less than 90%	97 (19%)	15 (24%)	3 (20%)
Injury severity			
IMPACT probability of poor outcome	19% (12-34%)	45% (28-59%)	28% (23-65%)
APACHE II score	19 (14-24)	25 (20-30)	21 (16-27)
Injury severity score	26 (18-33)	27 (22-33)	21 (17-35)
Transfusion prior to randomisation			
Red cells (%)	128 (24%)	21 (34%)	5 (33%)
Platelets (%)	43 (8%)	11 (18%)	3 (20%)
Fresh frozen plasma (%)	78 (15%)	11 (18%)	2 (13%)
Other clotting product (%)	40 (8%)	4 (7%)	1 (7%)
None (%)	374 (71%)	37 (60%)	9 (60%)
Neurosurgical interventions			
Mass lesion evacuated	161 (31%)	22 (36%)	5 (33%)
Craniectomy	104 (20%)	16 (26%)	6 (40%)
Bifrontal decompressive craniectomy	17 (3%)	5 (8%)	0 (0%)
ICU interventions			
ICP use	352 (67%)	56 (90%)	13 (87%)
Proportion ICP end hours over 20 mmHg	3% (0-9%)	14% (5-40%)	5% (4-20%)
Hypothermia	76 (15%)	26 (42%)	4 (27%)
Hyperventilation used*	243 (46%)	49 (79%)	6 (40%)

Data on survival missing in one patients and cause of death missing in one patient. Data on survival missing in one patients and cause of death missing in one patient. *p<0.05 for comparison between cerebral and non-cerebral cause of death. **Neurosurgical and ICU interventions refer to any intervention taken place during stay in the intensive care unit.**

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TABLE 2. FINDINGS ON INITIAL COMPUTED TOMOGRAPHY SCANS IN PATIENTS ACCORDING TO SIX MONTHS SURVIVAL AND CEREBRAL AND NON-CEREBRAL CAUSE OF DEATH.

	Alive at six months (n=524)	Dead at six-months (n=78)	
		Cerebral deaths (n=62)	Non-cerebral deaths (n=15)
CT findings			
Subdural hematoma	248 (47%)	41 (66%)	11 (73%)
Extradural haematoma	114 (22%)	10 (16%)	5 (33%)
Contusion	360 (69%)	48 (77%)	10 (67%)
Intracerebral haemorrhage	135 (26%)	34 (55%)	6 (40%)
Subarachnoid haemorrhage	342 (65%)	54 (87%)	12 (80%)
Intraventricular haemorrhage	208 (40%)	28 (45%)	8 (53%)
Petechial haemorrhage*	156 (30%)	36 (58%)	3 (20%)
Midline shift (%)	147 (28%)	28 (45%)	9 (60%)
Midline shift (mm)	0 (0-1)	0 (0-1)	1 (0-1)
Basal cisterns			
Normal	400 (76%)	25 (40%)	7 (47%)
Compressed	113 (22%)	33 (53%)	7 (47%)
Absent	11 (2%)	4 (7%)	1 (7%)
Marshall category			
Diffuse injury I	23 (4%)	0 (0%)	0 (0%)
Diffuse Injury II	337 (64%)	21 (34%)	6 (40%)
Diffuse Injury III	44 (8%)	21 (34%)	2 (13%)
Diffuse Injury IV	16 (3%)	5 (8%)	2 (13%)
Mass lesion	104 (20%)	15 (24%)	5 (33%)

Data on survival missing in one patients and cause of death missing in one patient. *p<0.05 for comparison between cerebral and non-cerebral cause of death. **The Marshall category Mass lesion includes both evacuated and non-evacuated lesions noted on the first computed tomography scan.**

TABLE 3. CAUSE OF DEATH FOLLOWING MODERATE TO SEVERE TRAUMATIC BRAIN INJURY IN THE EPO-TBI STUDY INDEXED BY NEUROSURGICAL OR NON-NEUROSURGICAL GROUPS.

	EPO	Placebo	p-value
Cause of death in all randomized patients			
Brain death	7	9	0.44
Death with therapy withdrawn for severe cerebral damage	16	23	
Death with therapy withdrawn for non-cerebral reasons	4	4	
Death with maximal support for severe cerebral damage	2	5	
Death with maximal support for non-cerebral reasons	2	5	
Cause of death in the neurosurgical group			
Brain death	2	1	0.59
Death with therapy withdrawn for severe cerebral damage	12	8	
Death with therapy withdrawn for non-cerebral reasons	4	1	
Death with maximal support for severe cerebral damage	1	0	
Death with maximal support for non-cerebral reasons	1	2	
Cause of death in the non-neurosurgical group			
Brain death	5	8	0.01
Death with therapy withdrawn for severe cerebral damage	4	15	
Death with therapy withdrawn for non-cerebral reasons	0	3	
Death with maximal support for severe cerebral damage	1	5	
Death with maximal support for non-cerebral reasons	1	3	

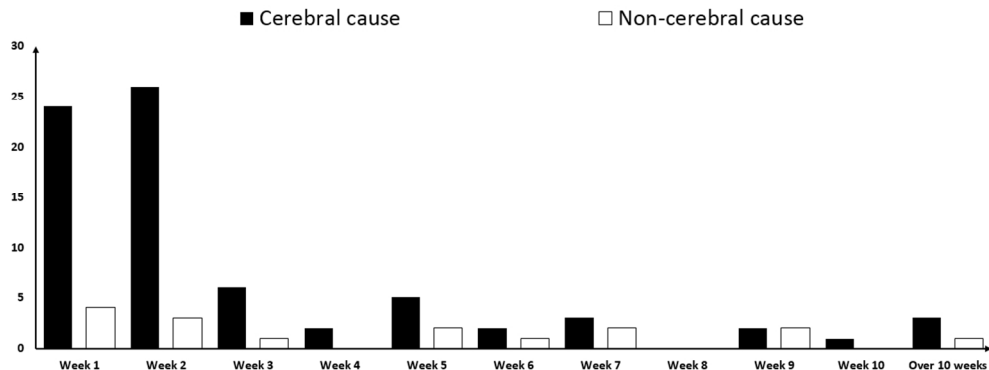
Figure legends

FIG. 1. Timing of cerebral and non-cerebral deaths in patients with moderate to severe traumatic brain injury.

FIG.2. Survival curves for EPO and placebo groups according to whether patients had received a neurosurgical operation prior to randomisation or not.

FIG.3. Post-hoc analysis of differential treatment effects of erythropoietin indexed by admission computed tomography scan findings.

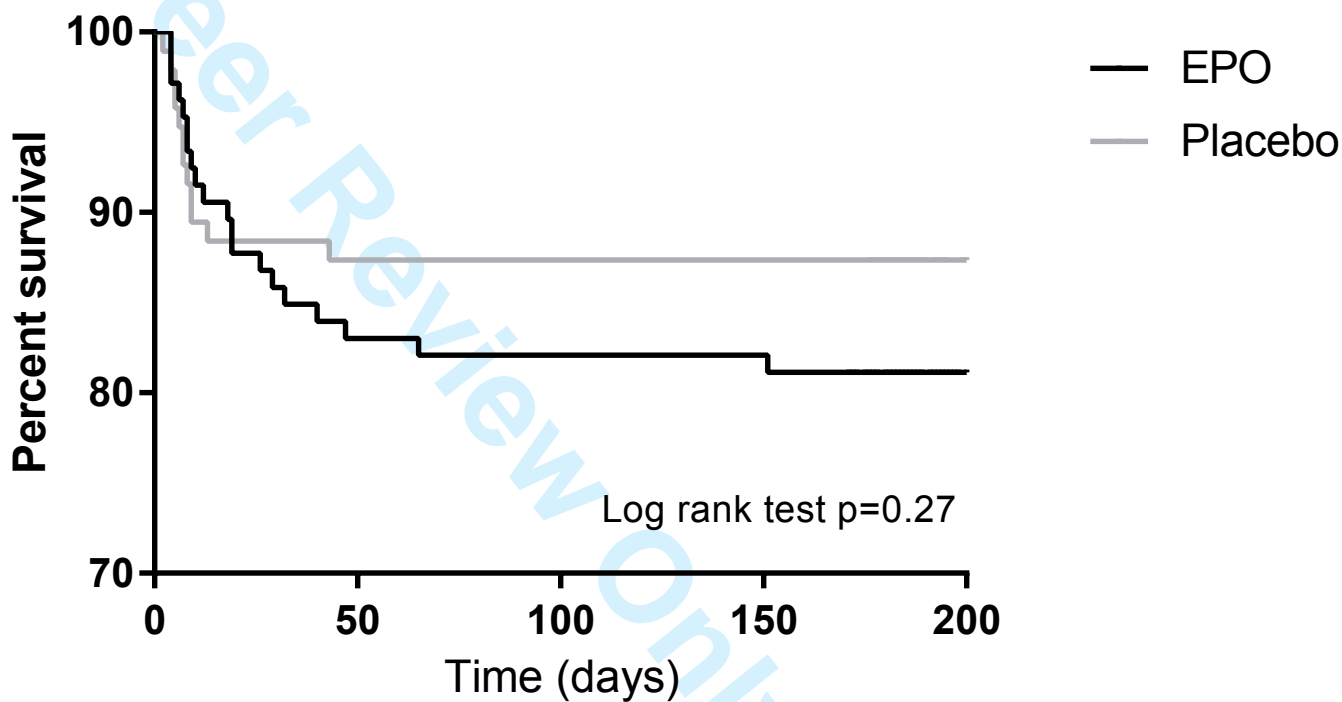
FIG.4. Post-hoc analysis of differential treatment effects of erythropoietin indexed by neurointensive care and neurosurgical interventions prior to randomisation and during ICU care.



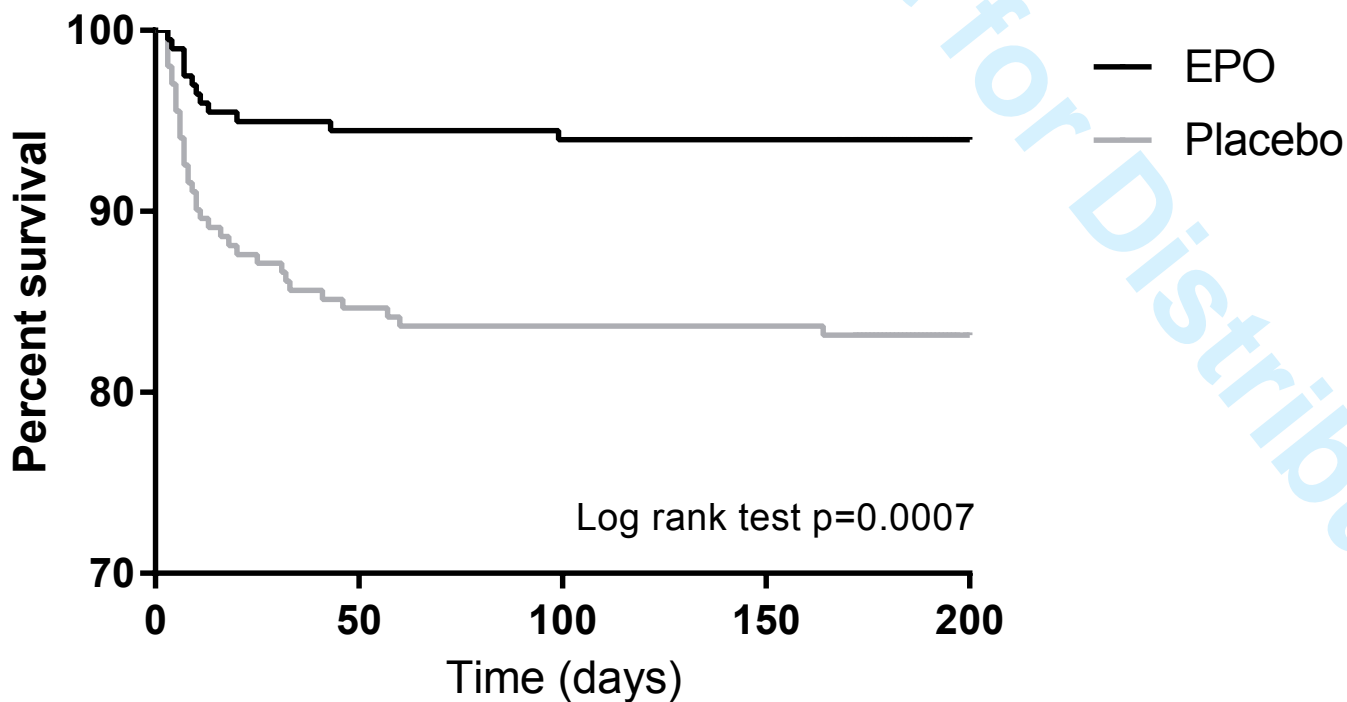
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Neurosurgical operation

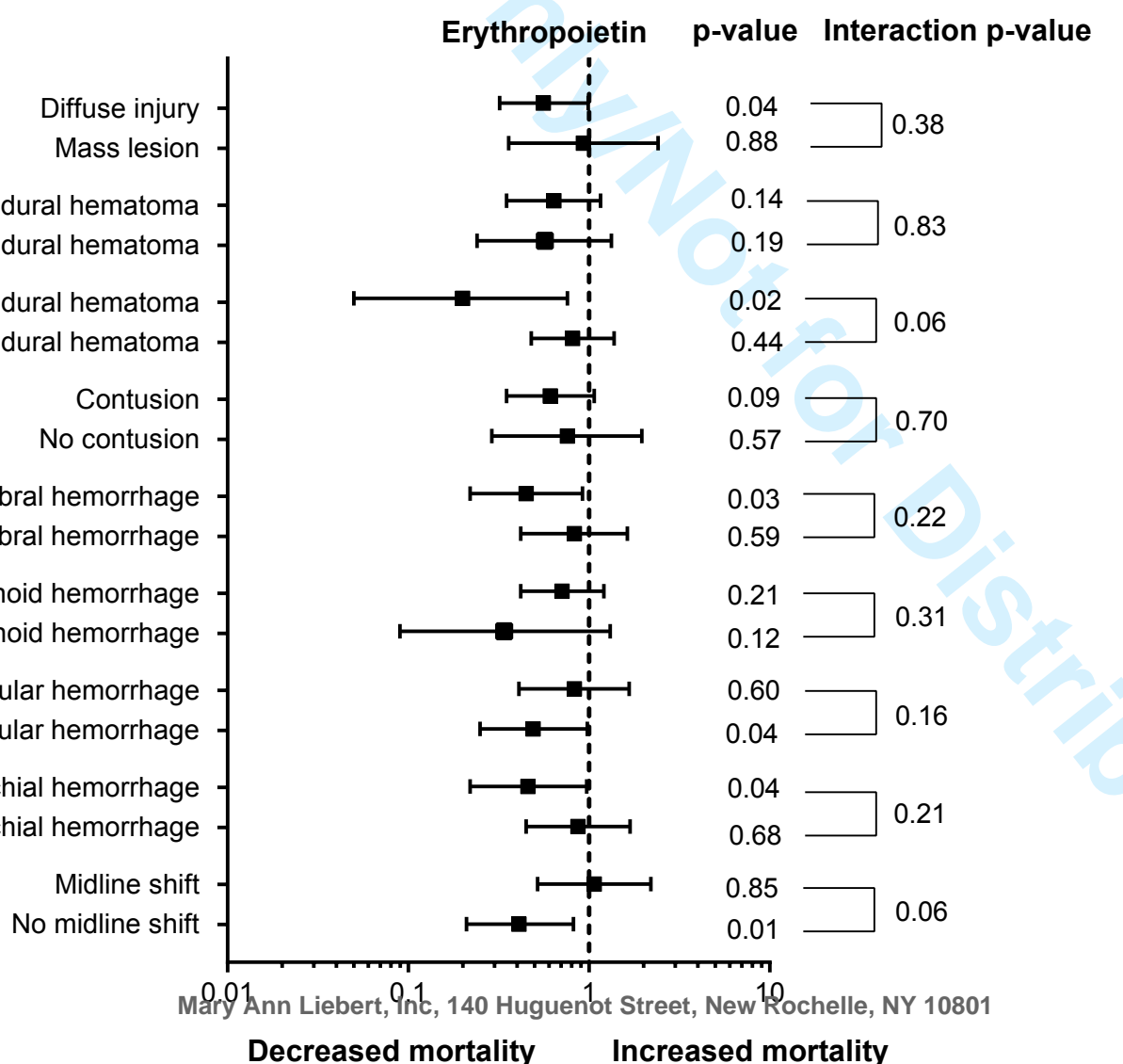


No neurosurgical operation



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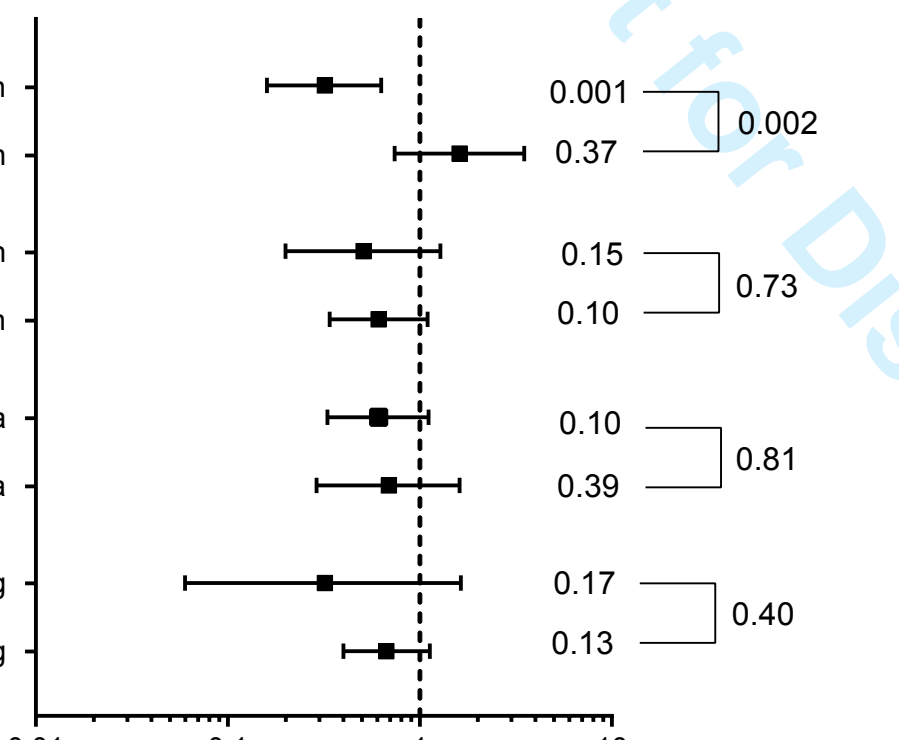
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Decreased mortality Increased mortality

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Erythropoietin p-value Interaction p-value

No neurosurgical operation
Neurosurgical operation
No hyperventilation
Hyperventilation
No hypothermia
Hypothermia
No ICP-monitoring
ICP-monitoring



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Decreased mortality Increased mortality

Appendix

SUPPLEMENTAL TABLE 1. A DETAILED EXPLORATION OF DIFFERENCES IN CLINICAL CHARACTERISTICS INDEXED BY CAUSE OF DEATH.

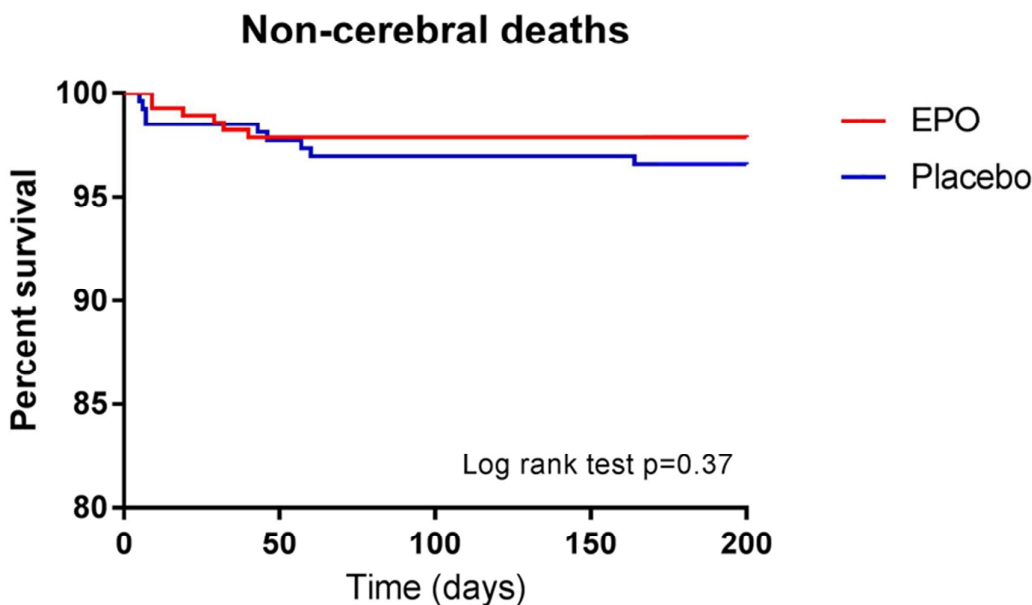
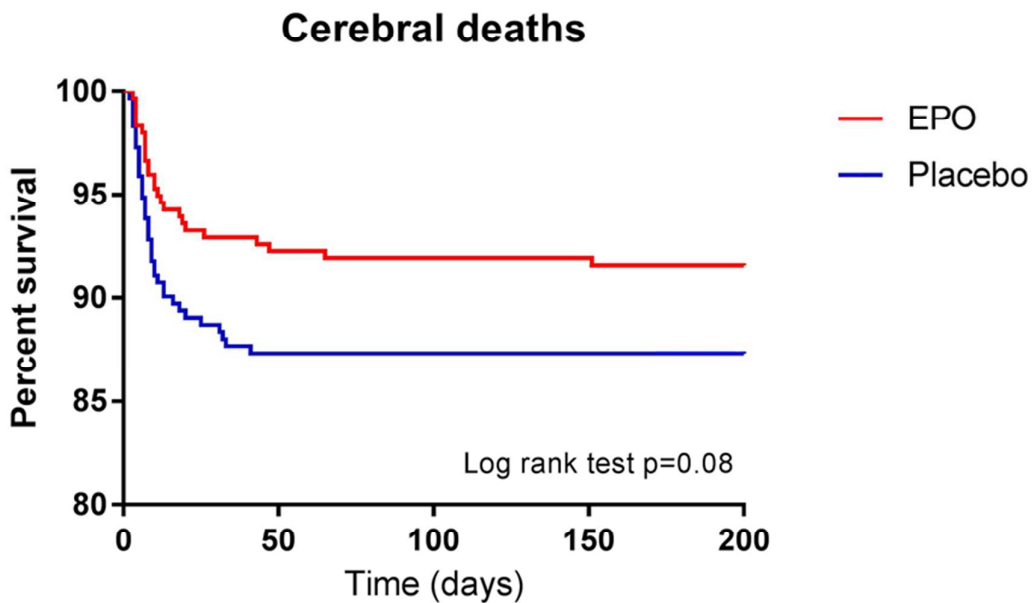
	Brain death (n=16)	Therapy withdrawn cerebral reason (n=39)	Therapy withdrawn non-cerebral reason (n=8)	Cerebral death during maximal support (n=7)	Non-cerebral death during maximal support (n=7)
Patient characteristics					
Mean age (years)*	26 (22-45)	51 (24-59)	49 (44-59)	43 (24-48)	52 (25-58)
Female gender	3 (19%)	7 (18%)	1 (13%)	0 (0%)	3 (43%)
Consciousness					
Initial GCS	6 (4-7)	4 (3-7)	4 (4-9)	3 (3-8)	7 (4-10)
Pupillary abnormality					
Both equal and reacting	12 (75%)	25 (64%)	4 (50%)	5 (72%)	5 (71%)
Both dilated and non-reactive*	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)
Both non-reactive	3 (19%)	5 (13%)	2 (25%)	1 (14%)	1 (14%)
One non-reactive	1 (6%)	8 (21%)	2 (25%)	1 (14%)	0 (0%)
Untestable/not documented	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Pre-hospital vital signs					
Systolic blood pressure less than 90 mmHg	3 (19%)	17 (44%)	1 (13%)	3 (43%)	2 (29%)
Oxygen saturation less than 90%	5 (31%)	9 (23%)	1 (13%)	1 (14%)	2 (29%)
Injury severity					
IMPACT probability of poor outcome	37% (25-59%)	46% (28-59%)	37% (25-60%)	28% (24-65%)	23% (19-65%)
APACHE II score	24 (20-28)	26 (20-33)	19 (15-26)	22 (21-22)	25 (16-28)
Injury severity score	27 (22-35)	26 (21-34)	18 (11-30)	29 (21-33)	22 (20-45)
Transfusion prior to randomisation					
Red cells (%)	5 (31%)	15 (39%)	2 (25%)	1 (14%)	3 (43%)
Platelets (%)	1 (6%)	9 (23%)	2 (25%)	1 (14%)	1 (14%)
Fresh frozen plasma (%)	2 (13%)	8 (21%)	1 (13%)	1 (14%)	1 (14%)
Other clotting product (%)	0 (0%)	4 (10%)	0 (0%)	0 (0%)	1 (14%)
None (%)	11 (69%)	20 (51%)	5 (63%)	6 (86%)	4 (57%)
Neurosurgical interventions					
Mass lesion evacuated	4 (25%)	17 (44%)	3 (38%)	1 (14%)	2 (29%)
Craniectomy	2 (13%)	12 (31%)	3 (38%)	2 (29%)	3 (43%)
Bifrontal decompressive craniectomy	1 (6%)	4 (10%)	0 (0%)	0 (0%)	0 (0%)
ICU interventions					
ICP use	13 (81%)	37 (95%)	8 (100%)	6 (86%)	5 (71%)
Proportion ICP end hours over 20 mmHg**	41% (22-62%)	10 % (5-24%)	3% (0-16%)	28% (11-46%)	10% (5-67%)
Hypothermia	8 (50%)	13 (33%)	2 (25%)	5 (71%)	2 (29%)
Hyperventilation used*	11 (69%)	33 (85%)	4 (50%)	5 (71%)	2 (29%)

*p<0.05 for comparison between causes of death

SUPPLEMENTAL TABLE 2. A DETAILED EXPLORATION OF CAUSE OF DEATH INDEXED BY ADMISSION CT FINDINGS.

	Brain death (n=16)	Therapy withdrawn cerebral reason (n=40)	Therapy withdrawn non-cerebral reason (n=8)	Cerebral death during maximal support (n=7)	Non-cerebral death during maximal support (n=7)
CT findings					
Subdural hematoma	11 (69%)	27 (69%)	5 (63%)	3 (43%)	6 (86%)
Extradural haematoma	2 (13%)	7 (18%)	3 (38%)	1 (14%)	2 (29%)
Contusion	12 (75%)	29 (74%)	6 (75%)	7 (100%)	4 (57%)
Intracerebral haemorrhage	9 (56%)	21 (54%)	5 (63%)	4 (57%)	1 (14%)
Subarachnoid haemorrhage	16 (100%)	33 (85%)	6 (75%)	5 (72%)	6 (86%)
Intraventricular haemorrhage	7 (44%)	20 (51%)	1 (14%)	5 (63%)	3 (43%)
Petechial haemorrhage	7 (44%)	25 (64%)	4 (57%)	2 (25%)	1 (14%)
Midline shift (%)	9 (56%)	18 (46%)	4 (50%)	1 (14%)	5 (71%)
Midline shift (mm)	3 (0-6)	3 (0-7)	6 (0-9)	0 (0-2)	6 (2-7)
Basal cisterns**					
Normal	5 (31%)	16 (41%)	4 (50%)	4 (57%)	3 (43%)
Compressed	10 (63%)	20 (51%)	3 (38%)	3 (43%)	4 (57%)
Absent	1 (6%)	3 (8%)	1 (12%)	0 (0%)	0 (0%)
Marshall category					
Diffuse injury I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diffuse Injury II	4 (25%)	13 (33%)	3 (38%)	4 (57%)	3 (43%)
Diffuse Injury III	6 (38%)	12 (31%)	1 (12%)	3 (43%)	1 (14%)
Diffuse Injury IV	3 (19%)	2 (5%)	1 (12%)	0 (0%)	1 (14%)
Evacuated mass lesion	0 (0%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)
Non-evacuated mass lesion	3 (19%)	10 (26%)	3 (38%)	0 (0%)	2 (29%)

SUPPLEMENTAL FIG.1. Survival curves for cerebral and non-cerebral deaths indexed by whether patients were treated with EPO or placebo.



SUPPLEMENTAL FIG.2. Distribution of neurological outcomes defined by the Glasgow Outcome Scale Extended in patients with a non-neurosurgically treated traumatic brain injury administered erythropoietin or placebo.

Distribution of GOSE at 180 days

