Journal of Neurotrauma

Journal of Neurotrauma: http://mc.manuscriptcentral.com/neurotrauma

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

Journal:	*Journal of Neurotrauma*
Manuscript ID	NEU-2017-5135.R2
Manuscript Type:	Regular Manuscript
Date Submitted by the Author:	n/a
Complete List of Authors:	Skrifvars, Markus; Helsinki University Hospital, Department of Anesthesia, Intensive Care and Pain Medicine French, Craig ; Department of Intensive Care, Western Health, Melbourne, Victoria, Australia Bailey, Michael; Monash University, School of Public Health and Preventive Medicine Presneill, Jeffrey; Royal Melbourne Hospital, Department of Intensive Care Nichol, Alistair ; Monash University School of Public Health and Preventive Medicine, ANZIC-RC Little, Lorraine; Monash University School of Public Health and Preventive Medicine, ANZIC-RC Duranteau, Jacques; Hopitaux Universitaires Paris-Sud, Department of Anesthesia and Intensive Care Huet, Olivier; Hopital de la Cavale-Blanche, Departement d'anesthésie-réanimation Haddad, Samir; King Abdullah International Medical Research Center, Intensive Care Department Arabi, Yaseen ; King Saud bin Abdulaziz University for Health Sciences, Intensive Care Department McArthur, Colin; Auckland City Hospital, Department of Critical Care Medicine Cooper, D. James; The Alfred, Intensive Care; Monash University, ANZIC-RC Bellomo, Rinaldo; Monash University, ANZIC-RC
Keywords:	ADULT BRAIN INJURY, CLINICAL MANAGEMENT OF CNS INJURY, HEAD TRAUMA, HUMAN STUDIES, TRAUMATIC BRAIN INJURY
Manuscript Keywords (Search Terms):	ADULT BRAIN INJURY, CLINICAL MANAGEMENT OF CNS INJURY, HEAD TRAUMA, HUMAN STUDIES, TRAUMATIC BRAIN INJURY

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

PhD Markus B Skrifvars[1,2]
Email: markus.skrifvars@monash.edu
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Telephone: +61399030068
Fax: +61399030071

MD Craig French[3,4]
Email: Craig.French@wh.org.au
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Jamie.cooper@monash.edu
Telephone: +61399030343
Fax: +61399030071

PhD Michael Bailey[1]
Email: Michael.Bailey@monash.edu
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Telephone: +61399030343
Fax: +61399030071

PhD Jeffrey Presneill[1,5]
Email: intensive@fastmail.com.au
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Jamie.cooper@monash.edu
Telephone: +61399030343
Fax: +61399030071

PhD Alistair Nichol[1,6,7,8]
Email: alistair.nichol@monash.edu
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Telephone: +61399030343
Fax: +61399030071

MBioethics Lorraine Little[1]
Email: Lorraine.little@monash.edu
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Telephone: +61399030513
Fax: +61399030071

PhD Jacques Durantea[9]
Email: jacques.duranteau@aphp.fr
Department of Anaesthesia and Intensive Care
Hôpitaux universitaires Paris Sud (HUPS)
Université Paris Sud XI
78, rue du Général Leclerc
94275 Le Kremlin Bicêtre, France
Telephone: +33 1 45 21 34 41
Fax: +33 1 45 21 28 75

PhD Olivier Huet[10]
Email: olivier.huet@chu-brest.fr
Address: Departement d'anesthésie-réanimation, Hopital de la Cavale Blanche, Boulevard Tanguy Prigent, CHRU de Brest, Univeristé de Bretagne Occidental, Brest, France
Telephone: +33298347449
Fax: +3329834849

MD Samir Haddad[11]
Email: samir haddads55@yahoo.com
Address: King Saud Bin Abdulaziz University for Health Sciences
King Abdullah International Medical Research Center
Intensive Care Department
ICU 1425 PO Box 22490
Riyadh, 11426, Kingdom of Saudi Arabia
Telephone: +966 (11) 801-1111 Ext 18855/18877
Fax: +966 (11) 801-1111 Ext 18880

MD Yaseen Arabi[11]
Email: yaseenarabi@yahoo.com
Address: King Saud Bin Abdulaziz University for Health Sciences
King Abdullah International Medical Research Center
Intensive Care Department
ICU 1425 PO Box 22490
Riyadh, 11426, Kingdom of Saudi Arabia
Telephone: +966 (11) 801-1111 Ext 18855/18877
Fax: +966 (11) 801-1111 Ext 18880

MBChB Colin McArthur[12]
Email: colinm@adhb.govt.nz
Address: Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand

Telephone: +6493072892
Fax: +6493074927

MD D James Cooper[1,8]
Email: Jamie.cooper@monash.edu
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Jamie.cooper@monash.edu
Telephone: +61399030343
Fax: +61399030071

MD Rinaldo Bellomo[1,13]
Email: Rinaldo.BELLOMO@austin.org.au
Address: Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
Jamie.cooper@monash.edu
Telephone: +61399030343
Fax: +61399030071

For the EPO-TBI investigators and the ANZICS Clinical Trials Group

Affiliations

[1]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[2]Division of Intensive Care, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University and Helsinki University Hospital
[3]Department of Intensive Care, Western Health, Melbourne, Victoria, Australia
[4]University of Melbourne, Melbourne, Victoria, Australia
[5]Department of Intensive Care, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[6]School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland
[7]St Vincent's University Hospital, Dublin, Ireland
[8]Department of Intensive Care and Hyperbaric Medicine, The Alfred, Melbourne, Victoria, Australia
[9]Département d'Anesthésie-Réanimation, Hôpital de Bicêtre, Assistance Publique des Hopitaux de Paris, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Paris, France
[10]Department of Anaesthesiology and Intensive Care Medicine, CHU La Cavale Blanche, Brest, France
[11]King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[12]Auckland City Hospital, Auckland, New Zealand
[13]Department of Intensive Care, Austin Health, Melbourne, Victoria, Australia

Corresponding author:
Dr Markus Skrifvars
Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, 55 Commercial Rd, Melbourne, Victoria, 3004, AUSTRALIA
markus.skrifvars@monash.edu

Funding sources:
EPO-TBI was supported by grants from the National Health and Medical Research Council of Australia (grant 545902) and the Transport Accident Commission of Victoria (grant D162). Markus Skrifvars has received personal research funding from Medicinska Understodsforeningen Liv och Halsa, Finska Lakaresallskapet and Svenska Kulturfonden. Alistair Nichol has received support from the Health Research Board of Ireland.

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 in the EPO compared to placebo group (5% compared to 14%, p=0.03). In conclusion, most TBI deaths were due to cerebral causesthat 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 explored 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 ICU[12]

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

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

For the analysis, brain death and other deaths categorised as cerebral were included as one group i.e. "cerebral deaths". Similarly, the two non-cerebral death groups were categorised as "non-cerebral". Admission computed tomography (CT) scans were viewed by an assessor blinded to treatment and categorised according to the Marshall category.[14] **As in previous studies we grouped together Marshall groups V and VI.[15, 16]**

Statistical analysis

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

Ethical permits, consent and trial registration

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

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

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

Effect of EPO by admission CT characteristics and neurosurgical operation

The effect of EPO indexed by admission CT findings and neurosurgical treatment are shown in Fig. 2 and Fig. 3. There were no significant differences in treatment effect of EPO according to different subtypes of admission CT brain findings (Fig. 2). There was no differential effect indexed by use of ICP monitoring, hyperventilation or hypothermia during ICU care (Fig. 3).

There was, however, a strong differential effect of EPO in patients that had not undergone a neurosurgical procedure prior to randomisation compared to those who had (Fig. 3). In the group that did not have a neurosurgical operation, EPO decreased mortality (OR 0.29 95% 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 interaction 0.003). Survival curves indexed for the non-neurosurgical group and the neurosurgical groups are shown in Fig. 4. In the non-neurosurgical group, the proportion of patients with good outcome at 6 months appeared higher in the EPO group (64% compared to 58%, p00.25) but this difference was not statistically significant. The distribution of GOSE scores in the non-neurosurgical group treated with EPO or placebo are shown in the Supplementary Appendix (Supplemental Fig. 2). In the neurosurgical group, the proportion of patients with good outcome at 6 months appeared lower with EPO compared to placebo (40% compared to 52%, p=0.23) but this difference was not statistically significant

The COD by intervention indexed by neurosurgical group and non-neurosurgical groups are shown in Table 3. There was a significant differences in the distribution of COD between

patients treated with EPO compared to placebo in the non-neurosurgical group, but not in the neurosurgical group (Table 3). Cerebral deaths occurred in 10 (5%) out of 197 patients treated with EPO, and in 28 out of 203 (14%) treated with placebo (p=0.003).

Discussion

In this population of critically ill patients included in a randomised controlled trial (RCT) of TBI therapy, the majority of deaths occurred during the first two weeks following injury and were cerebral in nature. Death was commonly related to withdrawal of treatment, and only a smaller proportion died while receiving maximal medical intervention. Death due to non-cerebral reasons occurred later during the hospital course. We found overall no difference in causes or timing of death between EPO and placebo treated patients. However, with regards to different types of TBI and requirement of neurosurgical interventions, we found that EPO appeared significantly more effective than placebo in patients not receiving a neurosurgical operation prior to randomisation. In this subgroup, EPO appeared to especially decrease the rates of death from a cerebral cause and EPO did not appear to increase the proportion of survivors in a poor neurological state. These findings have implications for future studies on EPO in TBI patients.

The overall mortality of 13% found in the present study was slightly lower than in several previous studies.[17, 18] In a recent large pharmacological study on the use of progesterone in TBI, the six month mortality was 17%, and in trials of ICP monitoring and decompressive craniectomy six month mortality was substantially higher ranging from 30%-48%[18, 19] In a study evaluating prehospital administration of hypertonic saline to TBI patients, mortality was even higher.[20] Patients with this severity of injury are not likely to have been included in the current EPO-TBI trial given the inclusion of patients with moderate TBI and the exclusion of patients, who according to the treating clinician are likely to die within the next 48 hours.[12] In prospective observational studies, six month mortality has been shown to range from 25% to 44%.[21-23] In the current study, non-cerebral deaths occurred significantly later than cerebral deaths. This supports the hypothesis that late deaths are related to multi-organ failure and sepsis.[8]

We have demonstrated that most deaths were due to withdrawal of treatment, irrespective whether the death was attributed to a cerebral or non-cerebral cause. In a prospective

Canadian cross sectional study the number of TBI deaths associated with withdrawal ranged from 45% to 90%. In the current study treatment withdrawal was more common with higher age, lower level of consciousness at presentation and a more severe TBI, in line with findings by Turgeon and colleagues.[23] In the study by Turgeon and colleagues withdrawal most commonly occurred within the first three days of intensive care[23] but in our international multicentre randomized controlled trial, time to death related to withdrawal was longer. The death rate following withdrawal of medical treatment is infrequently reported in RCTs.[15] This mode of death represents a major challenge for the design of future interventional TBI trials and reinforces the need for treatment blinding where feasible. In the current study we observed no difference in the proportion of treatment withdrawal or time to withdrawal between EPO and placebo treated patients.

TBI is without doubt a heterogeneous disease as evidenced by the different possible pathological findings on the admission CT scan.[24] Indeed the heterogeneity of TBI has been seen as one reason behind the failures of pharmacological trials performed to date.[25, 26] In the SYNAPSE trial where TBI patients were administered progesterone after TBI, the main results of the trial was negative, and even extensive sub-group analysis including different admission Marshall Classification, decompressive craniectomy, or the need for surgery did not change the results.[27] In the recent trial on the use of therapeutic hypothermia for the treatment of raised ICP, a post hoc analysis revealed that hypothermia was more harmful in patients with less severe TBI, and did not provide beneficial effects with more severe injury[28].

In the current study, we observed no difference in frequency of cerebral or non-cerebral deaths between EPO and placebo treated patients in the whole sample. We did however observe a striking differential effect of EPO in the patients admitted to the ICU that had not undergone a neurosurgical operation prior to randomisation. In this sub-cohort EPO appeared to decrease the incidence of cerebral deaths. Non-neurosurgical patients are those with diffuse injury, petechial haemorrhages, and with small haemorrhages not appropriate for neurosurgical evacuations. The proposed mechanism of why EPO could work include a decrease in local tissue hypoxia in the brain, or a decrease in cerebral oedema due to improved function of the blood-brain barrier, and an attenuation of secondary brain injury, which may occur with all types of TBI.[29, 30] Presence of a mass lesion

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

Markus Skrifvars reports having received a research grant from GE Healthcare, travel reimbursements and lecture fees from Orion Pharma, COVIDIEN, Astellas Pharma and Axis-Shield. All other authors report no conflicts of interest.

References

1. Roozenbeek, B., Maas, A.I. and Menon, D.K. (2013). Changing patterns in the epidemiology of traumatic brain injury. Nature reviews. Neurology 9, 231-236.
2. Moore, L., Evans, D., Hameed, S.M., Yanchar, N.L., Stelfox, H.T., Simons, R., Kortbeek, J., Bourgeois, G., Clement, J., Lauzier, F., Nathens, A. and Turgeon, A.F. (2016). Mortality in Canadian Trauma Systems: A Multicenter Cohort Study. Annals of surgery.
3. Hukkelhoven, C.W., Steyerberg, E.W., Habbema, J.D., Farace, E., Marmarou, A., Murray, G.D., Marshall, L.F. and Maas, A.I. (2005). Predicting outcome after traumatic brain injury: development and validation of a prognostic score based on admission characteristics. Journal of neurotrauma 22, 1025-1039.
4. Chakraborty, S., Skolnick, B. and Narayan, R.K. (2016). Neuroprotection Trials in Traumatic Brain Injury. Current neurology and neuroscience reports 16, 29.
5. Skolnick, B.E., Maas, A.I., Narayan, R.K. and Committee, S.S. (2015). Progesterone in traumatic brain injury. The New England journal of medicine 372, 1767.
6. Demetriades, D., Kimbrell, B., Salim, A., Velmahos, G., Rhee, P., Preston, C., Gruzinski, G. and Chan, L. (2005). Trauma deaths in a mature urban trauma system: is "trimodal" distribution a valid concept? Journal of the American College of Surgeons 201, 343-348.
7. McCredie, V.A., Alali, A.S., Xiong, W., Rubenfeld, G.D., Cuthbertson, B.H., Scales, D.C. and Nathens, A.B. (2016). Timing of withdrawal of life-sustaining therapies in severe traumatic brain injury: Impact on overall mortality. The journal of trauma and acute care surgery 80, 484-491.
8. Pfeifer, R., Tarkin, I.S., Rocos, B. and Pape, H.C. (2009). Patterns of mortality and causes of death in polytrauma patients--has anything changed? Injury 40, 907-911.
9. Nichol, A., French, C., Little, L., Haddad, S., Presneill, J., Arabi, Y., Bailey, M., Cooper, D.J., Duranteau, J., Huet, O., Mak, A., McArthur, C., Pettila, V., Skrifvars, M., Vallance, S., Varma, D., Wills, J., Bellomo, R., Investigators, E.-T. and Group, A.C.T. (2015). Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet 386, 2499-2506.
10. Corwin, H.L., Gettinger, A., Fabian, T.C., May, A., Pearl, R.G., Heard, S., An, R., Bowers, P.J., Burton, P., Klausner, M.A., Corwin, M.J. and Group, E.P.O.C.C.T. (2007). Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 357, 965-976.
11. Corwin, H.L., Gettinger, A., Pearl, R.G., Fink, M.P., Levy, M.M., Shapiro, M.J., Corwin, M.J., Colton, T. and Group, E.P.O.C.C.T. (2002). Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. JAMA 288, 2827-2835.
12. Nichol, A., French, C., Little, L., Presneill, J., Cooper, D.J., Haddad, S., Duranteau, J., Huet, O., Skrifvars, M., Arabi, Y., Bellomo, R., Investigators, E.-T., the, A. and New Zealand Intensive Care Society Clinical Trials, G. (2015). Erythropoietin in traumatic brain injury: study protocol for a randomised controlled trial. Trials 16, 39.

13. Marmarou, A., Lu, J., Butcher, I., McHugh, G.S., Murray, G.D., Steyerberg, E.W., Mushkudiani, N.A., Choi, S. and Maas, A.I. (2007). Prognostic value of the Glasgow Coma Scale and pupil reactivity in traumatic brain injury assessed pre-hospital and on enrollment: an IMPACT analysis. Journal of neurotrauma 24, 270-280.
14. Marshall, L.F., Marshall, S.B., Klauber, M.R., Van Berkum Clark, M., Eisenberg, H., Jane, J.A., Luerssen, T.G., Marmarou, A. and Foulkes, M.A. (1992). The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma 9 Suppl 1, S287-292.
15. Maas, A.I., Hukkelhoven, C.W., Marshall, L.F. and Steyerberg, E.W. (2005). Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery 57, 1173-1182; discussion 1173-1182.
16. Raj, R., Siironen, J., Skrifvars, M.B., Hernesniemi, J. and Kivisaari, R. (2014). Predicting outcome in traumatic brain injury: development of a novel computerized tomography classification system (Helsinki computerized tomography score). Neurosurgery 75, 632-646; discussion 646-637.
17. Wright, D.W., Yeatts, S.D., Silbergleit, R., Palesch, Y.Y., Hertzberg, V.S., Frankel, M., Goldstein, F.C., Caveney, A.F., Howlett-Smith, H., Bengelink, E.M., Manley, G.T., Merck, L.H., Janis, L.S., Barsan, W.G. and Investigators, N. (2014). Very early administration of progesterone for acute traumatic brain injury. The New England journal of medicine 371, 2457-2466.
18. Chesnut, R.M., Temkin, N., Carney, N., Dikmen, S., Rondina, C., Videtta, W., Petroni, G., Lujan, S., Pridgeon, J., Barber, J., Machamer, J., Chaddock, K., Celix, J.M., Cherner, M., Hendrix, T. and Global Neurotrauma Research, G. (2012). A trial of intracranial-pressure monitoring in traumatic brain injury. The New England journal of medicine 367, 2471-2481.
19. Hutchinson, P.J., Kolias, A.G., Timofeev, I.S., Corteen, E.A., Czosnyka, M., Timothy, J., Anderson, I., Bulters, D.O., Belli, A., Eynon, C.A., Wadley, J., Mendelow, A.D., Mitchell, P.M., Wilson, M.H., Critchley, G., Sahuquillo, J., Unterberg, A., Servadei, F., Teasdale, G.M., Pickard, J.D., Menon, D.K., Murray, G.D., Kirkpatrick, P.J. and Collaborators, R.E.T. (2016). Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. The New England journal of medicine 375, 1119-1130.
20. Tisherman, S.A., Schmicker, R.H., Brasel, K.J., Bulger, E.M., Kerby, J.D., Minei, J.P., Powell, J.L., Reiff, D.A., Rizoli, S.B. and Schreiber, M.A. (2015). Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the Resuscitation Outcomes Consortium. Annals of surgery 261, 586-590.
21. Myburgh, J.A., Cooper, D.J., Finfer, S.R., Venkatesh, B., Jones, D., Higgins, A., Bishop, N., Higlett, T., Australasian Traumatic Brain Injury Study Investigators for the, A. and New Zealand Intensive Care Society Clinical Trials, G. (2008). Epidemiology and 12-month outcomes from traumatic brain injury in australia and new zealand. J Trauma 64, 854-862.
22. Raj, R., Skrifvars, M., Bendel, S., Selander, T., Kivisaari, R., Siironen, J. and Reinikainen, M. (2014). Predicting six-month mortality of patients with traumatic brain injury: usefulness of common intensive care severity scores. Critical care 18, R60.
23. Turgeon, A.F., Lauzier, F., Simard, J.F., Scales, D.C., Burns, K.E., Moore, L., Zygun, D.A., Bernard, F., Meade, M.O., Dung, T.C., Ratnapalan, M., Todd, S., Harlock, J., Fergusson, D.A. and Canadian Critical Care Trials, G. (2011). Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 183, 1581-1588.
24. Saatman, K.E., Duhaime, A.C., Bullock, R., Maas, A.I., Valadka, A., Manley, G.T., Workshop Scientific, T. and Advisory Panel, M. (2008). Classification of traumatic brain injury for targeted therapies. J Neurotrauma 25, 719-738.
25. Xydakis, M.S., Ling, G.S. and Ecklund, J.M. (2015). Progesterone in traumatic brain injury. N Engl J Med 372, 1765.
26. Schwamm, L.H. (2014). Progesterone for traumatic brain injury--resisting the sirens' song. N Engl J Med 371, 2522-2523.

27. Skolnick, B.E., Maas, A.I., Narayan, R.K., van der Hoop, R.G., MacAllister, T., Ward, J.D., Nelson, N.R., Stocchetti, N. and Investigators, S.T. (2014). A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med 371, 2467-2476.
28. Andrews, P.J.D., Rodriguez, A., Suter, P., Battison, C.G., Rhodes, J.K.J., Puddu, I. and Harris, B.A. (2017). Mortality Risk Stratification After Traumatic Brain Injury and Hazard of Death With Titrated Hypothermia in the Eurotherm3235Trial. Crit Care Med 45, 883-890.
29. Chu, H., Ding, H., Tang, Y. and Dong, Q. (2014). Erythropoietin protects against hemorrhagic blood-brain barrier disruption through the effects of aquaporin-4. Laboratory investigation; a journal of technical methods and pathology 94, 1042-1053.
30. He, H.J., Wang, Y., Le, Y., Duan, K.M., Yan, X.B., Liao, Q., Liao, Y., Tong, J.B., Terrando, N. and Ouyang, W. (2012). Surgery upregulates high mobility group box-1 and disrupts the blood-brain barrier causing cognitive dysfunction in aged rats. CNS neuroscience & therapeutics 18, 994-1002.
31. Ridgeon, E., Bellomo, R., Myburgh, J., Saxena, M., Weatherall, M., Jahan, R., Arawwawala, D., Bell, S., Butt, W., Camsooksai, J., Carle, C., Cheng, A., Cirstea, E., Cohen, J., Cranshaw, J., Delaney, A., Eastwood, G., Eliott, S., Franke, U., Gantner, D., Green, C., Howard-Griffin, R., Inskip, D., Litton, E., MacIsaac, C., McCairn, A., Mahambrey, T., Moondi, P., Newby, L., O'Connor, S., Pegg, C., Pope, A., Reschreiter, H., Richards, B., Robertson, M., Rodgers, H., Shehabi, Y., Smith, I., Smith, J., Smith, N., Tilsley, A., Whitehead, C., Willett, E., Wong, K., Woodford, C., Wright, S. and Young, P. (2016). Validation of a classification system for causes of death in critical care: an assessment of inter-rater reliability. Crit Care Resusc 18, 50-54.

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%)
Untestable/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.**

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			0.01
Brain death	5	8	
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	

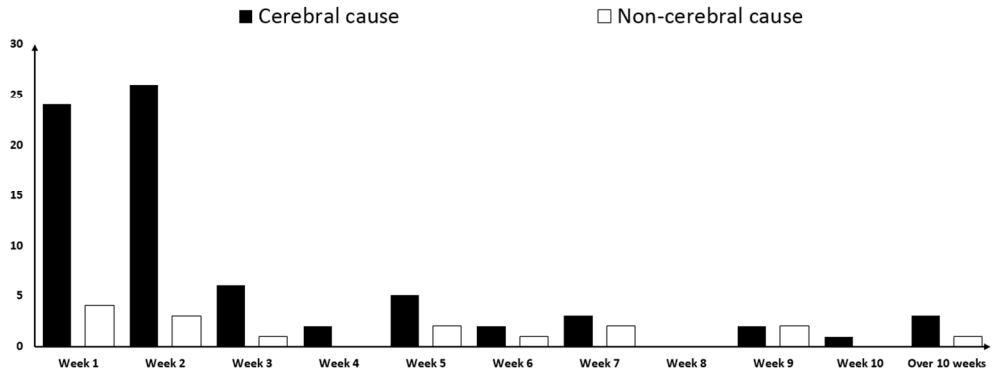
Figure legends

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

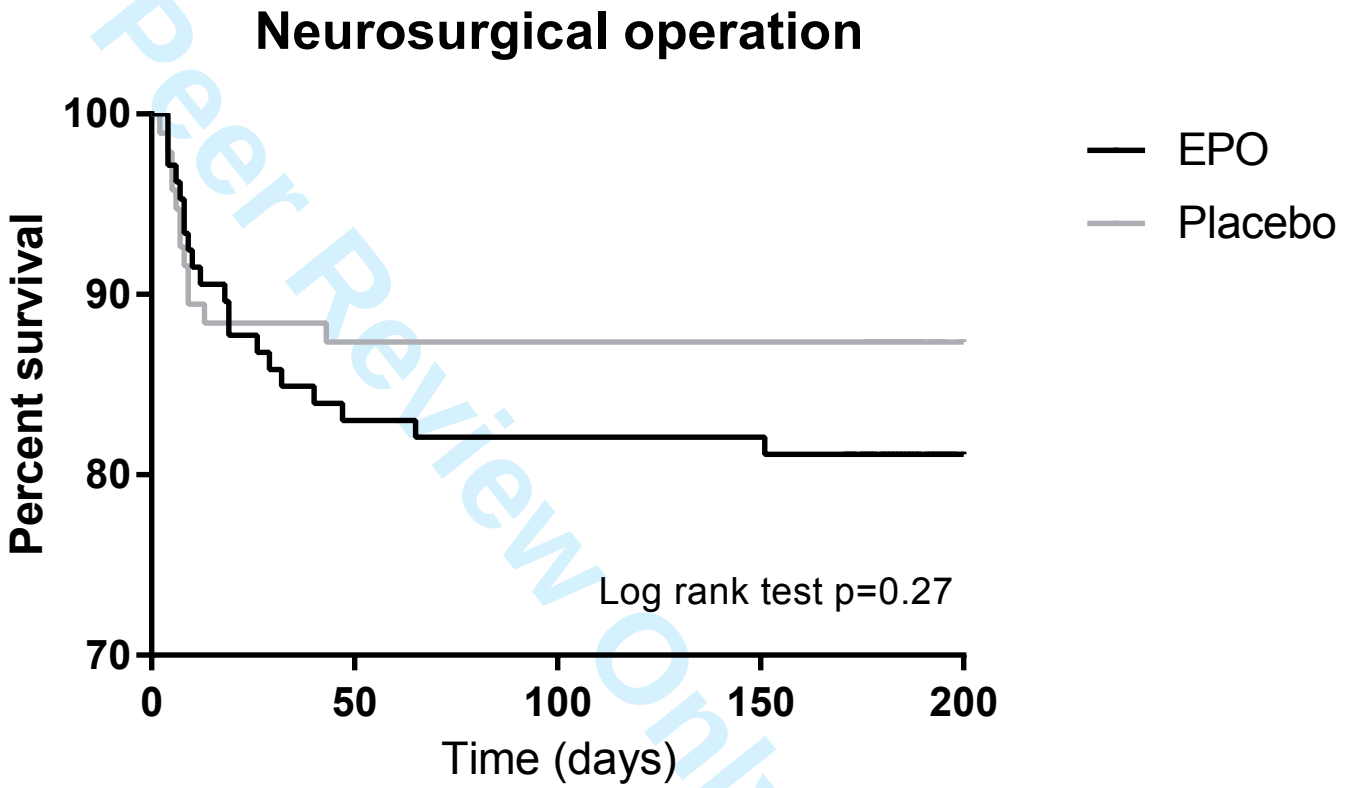
FIG.2. Survival curves for EPO and placebo groups according to whether patients had received a neurosurgical operation prior to randomisation or not.

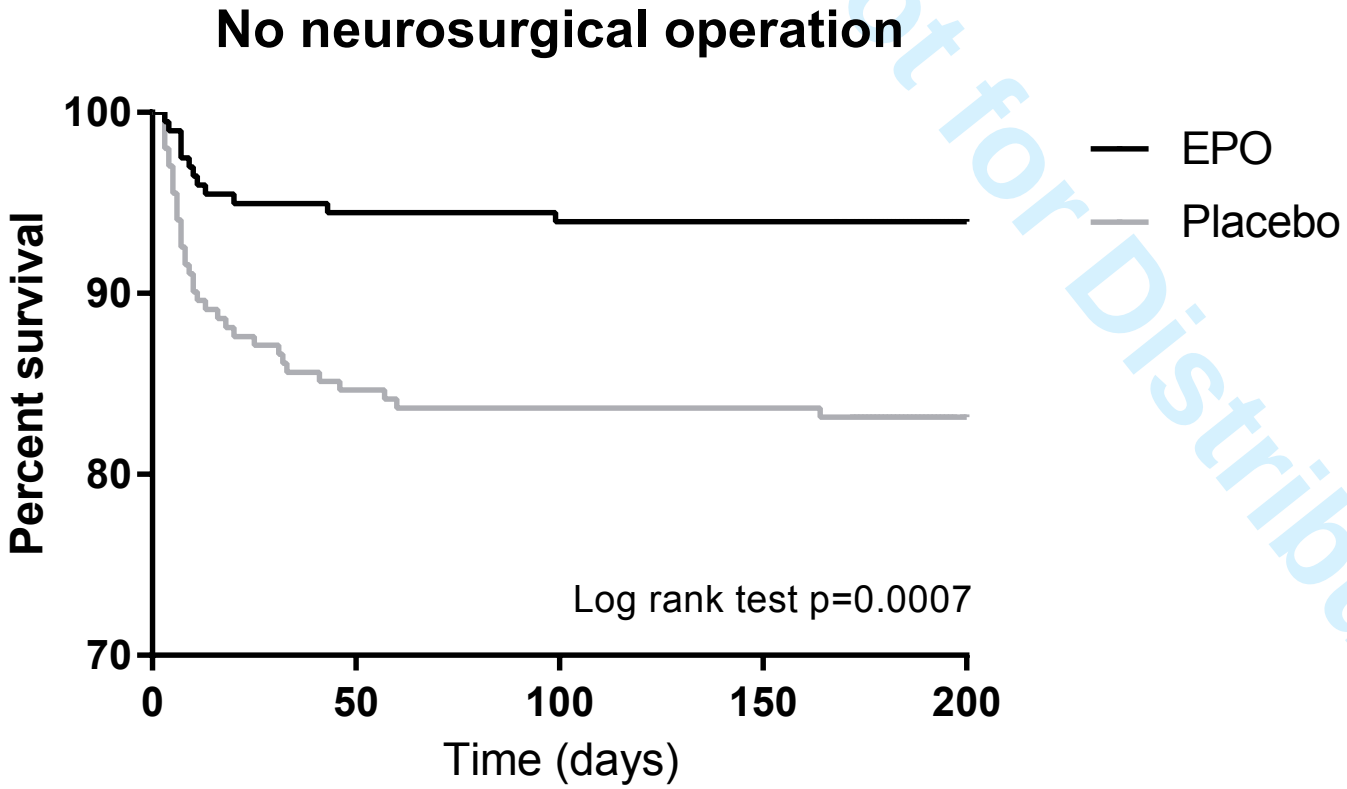
FIG.3. Post-hoc analysis of differential treatment effects of erythropoietin indexed by admission computed tomography scan findings.

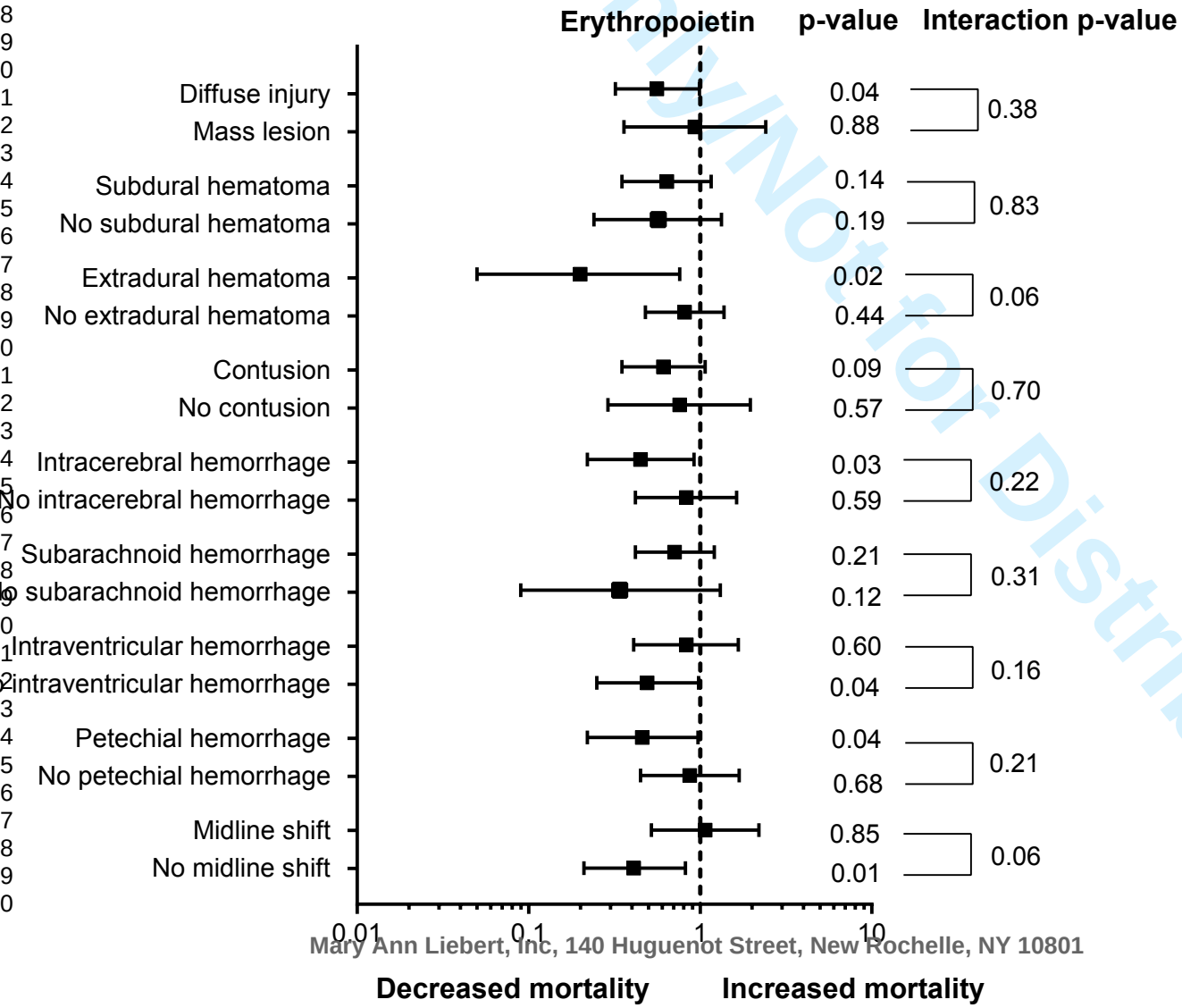
FIG.4. Post-hoc analysis of differential treatment effects of erythropoietin indexed by neurointensive care and neurosurgical interventions prior to randomisation and during ICU care.

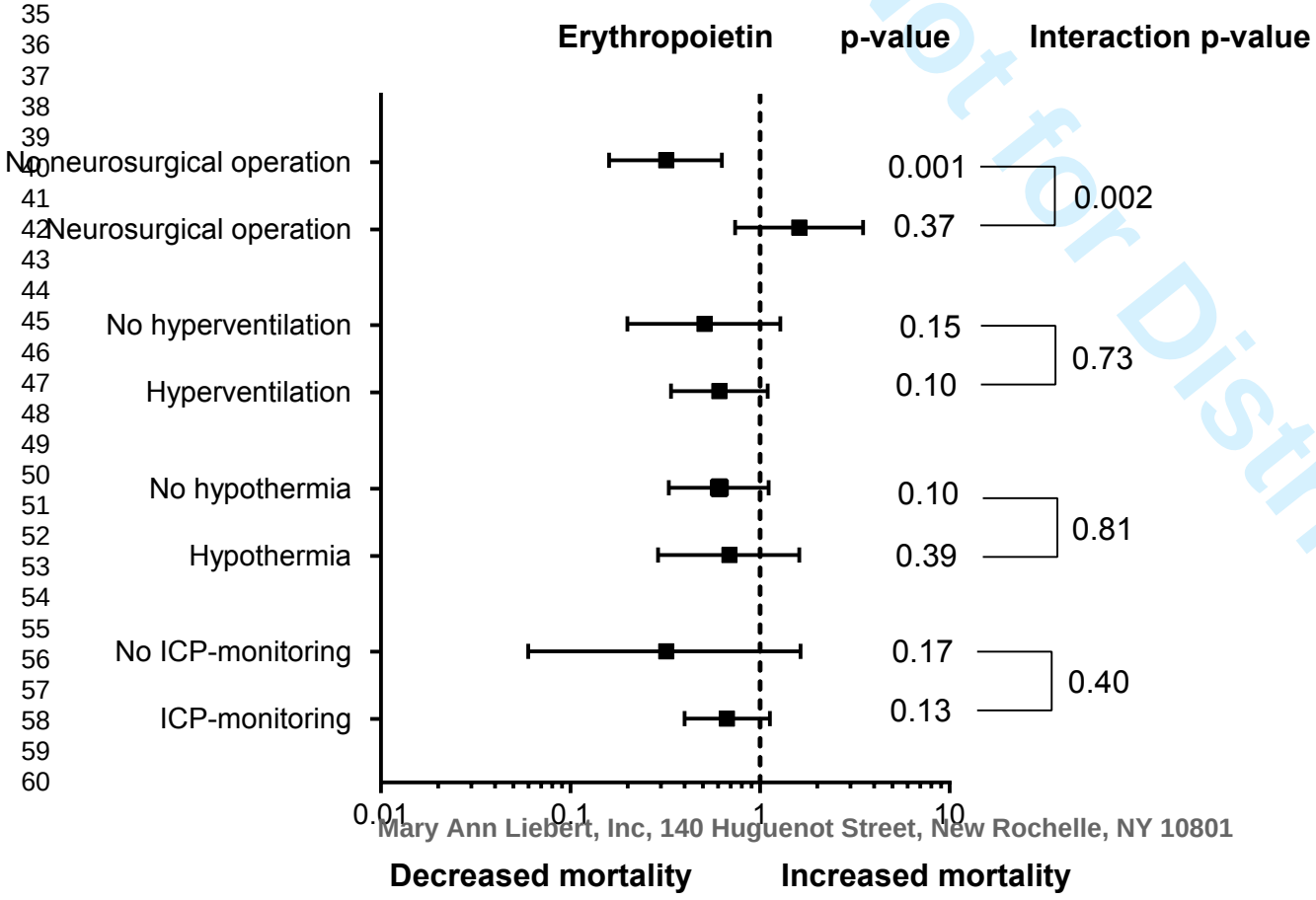


329x123mm (96 x 96 DPI)









Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801

Appendix

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

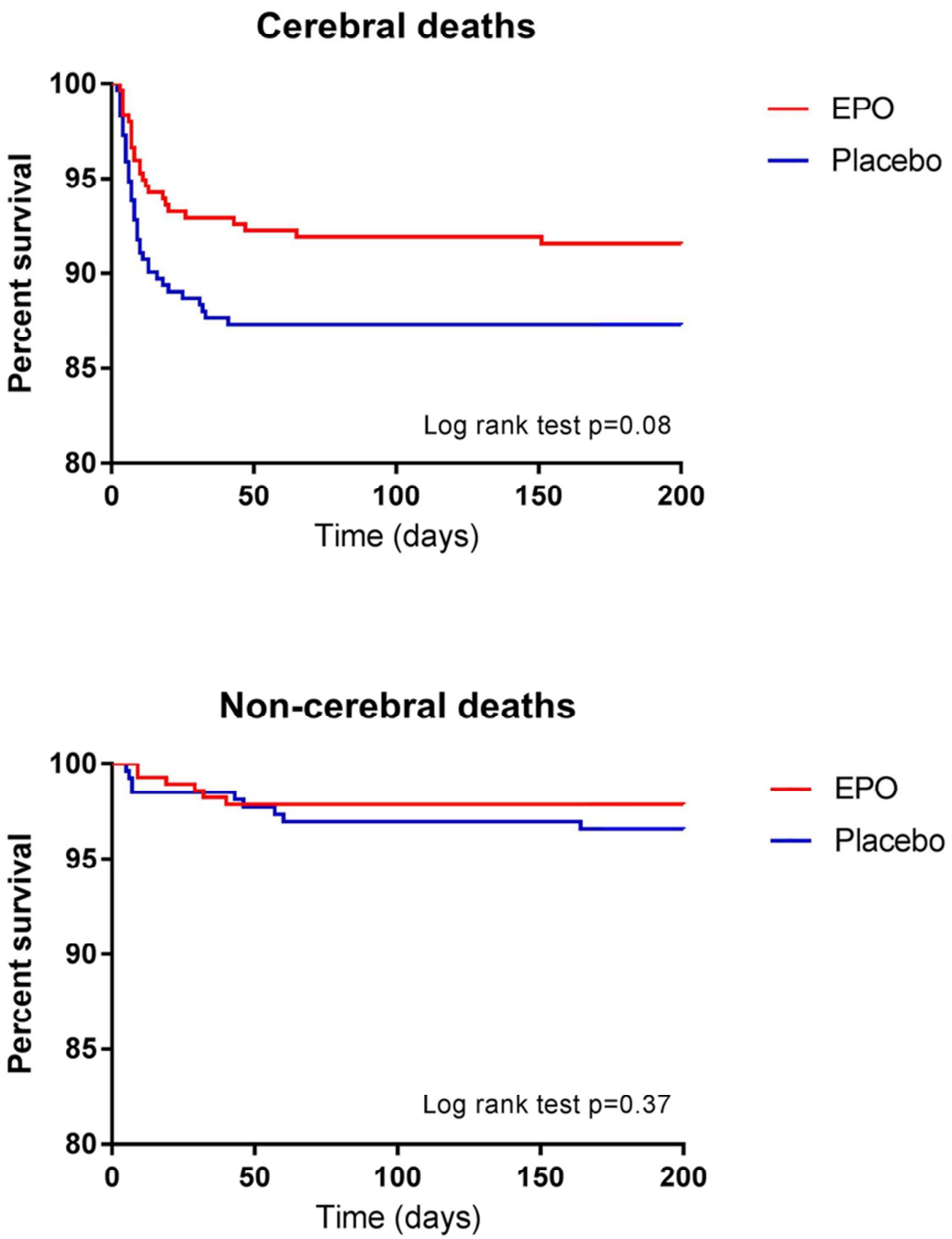
	Brain death (n=16)	Therapy withdrawn cerebral reason (n=39)	Therapy withdrawn non-cerebral reason (n=8)	Cerebral death during maximal support (n=7)	Non-cerebral death during maximal support (n=7)
Patient characteristics					
Mean age (years)*	26 (22-45)	51 (24-59)	49 (44-59)	43 (24-48)	52 (25-58)
Female 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.