Pages: 15
Words: 2843
Tables: 4
Figures: 1
Appendices: 0
References: 25
Contact: Xandria E. Gutierrez
Email: Xandria.e.gutierrez.ctr@mail.mil

Patients with traumatic brain injury (TBI) transported by Critical Care Air Transport Teams (CCATT): The influence of altitude and oxygenation during transport

Short Title: CCATT Altitude TBI

Lt Col Joseph K Maddry, MC, USAF[1, 2]
Allyson A. Araña, PhD[1]
Lauren K. Reeves, MsPH[1]
Alejandra G. Mora, MS[1]
Xandria E. Gutierrez[1]
Crystal A. Perez, BSN, RN[1]
Capt Patrick C. Ng, MC, USAF[1.2]
Capt Sean A. Griffiths, MC, USAF[2]
Col Vikhyat S. Bebarta, MC, USAF Reserves[3]

[1]United States Air Force En route Care Research Center/59th MDW/ST, San Antonio, TX

[2]Department of Emergency Medicine, San Antonio Military Medical Center, San Antonio, TX

[3]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO

Keywords: Traumatic Brain Injury; Hypoxia; Intensive Care Units; Altitude

Presentation: Presented as a podium presentation at 2019 Military Health System Research Symposium, August 2019, Kissimmee, FL. Presented as an oral presentation at 2019 American College of Emergency Physicians Scientific Assembly, October 2019, Denver, CO.

Funding sources: Air Force Medical Service (AFMS) grant #AC18EC03.

Disclaimers: The opinions of authors do not reflect that of the US Air Force, US Army, Department of Defense, or the US Government. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402. The experiments reported herein were conducted according to the principles set forth in the National Institute of Health Publication No. 80-23, Guide for the Care and use of Laboratory Animals and the Animal Welfare Act of 1966, as amended.

Acknowledgements: None

Introduction

In the course of the Global War on Terror, the high prevalence of traumatic brain injury (TBI) has led to an intense focus on the effects of transport out of the combat zone on the injured.[1-4] Survivability of previously devastating injuries has been increased by bringing highly trained US Air Force Critical Care Air Transport Teams (CCATT) in theater to evacuate the warfighters.[5-7] However, the long-term effects of TBI can significantly impact the injured warfighter's quality of life. Management of TBI patients focuses on minimizing secondary cerebral insults, to include the prevention of hypoxia and hypotension.[2] Aeromedical evacuation brings into question multiple variables, such as altitude and oxygenation levels, and their effects on TBI patient outcomes.[2]

Theoretically, patients may be at increased risk of secondary brain injury when transported at altitude.[1-4] The combat injured are moved within the continuum of military care on various platforms—often via air—and the threat this poses for secondary insult to patients with TBI is poorly understood. In rat models with simulated TBI, hypobaria and hyperoxia were associated with worse neurologic outcome.[8] Swine models with TBI have shown decreased cerebral perfusion pressure, mean arterial pressure, and brain oxygenation levels in subjects exposed to a hypobaric environment versus controls.[9] Civilian studies have evaluated the effects of oxygenation alone on the outcomes of patients with TBI. In one study of 1,547 patients with severe TBI, it was found that hyperoxia and hypoxia were equally harmful to short term outcomes.[10] In a multi-center retrospective study (n=1,212) of ventilated TBI patients, arterial hyperoxia was independently associated with higher in-hospital case fatality.[11] Our study of ventilated CCATT patients found few instances of hypoxia; however, the majority of patients received oxygen in excess of the Joint Trauma System Clinical Practice Guidelines.[12]

During pressurized cabin fixed wing aeromedical evacuation, the standard practice is to transport with a cabin altitude pressure of 8000 feet. Given the concern that this relative

hypobaria and hypoxia may result in secondary brain injury, some patients are transported at a lower cabin altitude, referred to a cabin altitude restriction (CAR), at the discretion of the CCATT, flight surgeon, and pilots.[13] However, whether or not this practice impacts patient outcomes is unknown. We conducted a retrospective study evaluating the impact of CAR during fixed wing aeromedical evacuation on patient oxygenation and outcomes in patients with moderate to severe traumatic brain injury.

Methods

We performed a retrospective chart review of CCATT patients with TBI transported out of the combat theater between January 2007 and May 2014. This study was approved by the U.S. Air Force 59th Medical Wing Institutional Review Board.

We queried the Department of Defense Trauma Registry (DoDTR), a database of medical charts of combat casualties treated in military medical treatment facilities (MTFs), to obtain a list of patients who suffered a moderate to severe TBI and were transported out of combat theater to LRMC between January 2007 and May 2014. We defined moderate to severe TBI as an Abbreviated Injury Scale (AIS) severity score of the head/neck body region of 3 or greater with an ICD-9-CM diagnosis code for TBI from the CDC's Barell Matrix classification scheme.[14] We excluded those patients who were younger than 18 years of age, did not have a CCATT medical record, or suffered a catastrophic brain injury (i.e., were on the levothyroxine/T4 protocol for organ donors, were being flown for organ donation, or were being flown home for family visitation).

From the remaining patients' CCATT medical records, trained research nurses abstracted demographics, flight information, injury description, oxygenation, medications, procedures, vital signs, and laboratory values. Topography and starting altitudes prior to flight differ between Iraq and Afghanistan; therefore, we collected origination location. We excluded

patients who did not have altitude or CAR data in their record. Data collected were based on provider documentation. We implemented routine quality control measures to ensure accuracy and consistency of data collection.[12,15] We also queried the Theater Medical Data Store (TMDS), a web-based platform containing electronic health records collected at theater-based MTFs, to obtain TBI-specific information for the eligible patients and reconcile data.[16] The initial DoDTR query provided additional injury information as well as outcome measures including mortality, discharge disposition, total days on a ventilator, total days in an intensive care unit (ICU), and total days in a hospital. The outcome measures obtained from DoDTR only capture data for the period from injury to discharge or transfer from the last MTF (Role IV or Role V) reported for each patient in the registry.

Statistical Analysis

We categorized patients as having a CAR if they had a documented CAR or maximum cabin altitude of 5000 feet or lower in their CCATT record. We calculated descriptive statistics as well as univariate comparisons between the CAR and Non-CAR groups on demographics, injuries, pre-flight and in-flight interventions, in-flight events, and outcomes. We reported continuous variables as medians [interquartile range (IQR)], categorical variables as percentages with 95% confidence intervals, and univariate comparisons as median or proportional differences with 95% confidence intervals. Due to imperfect pairing of data (i.e., not all patients had pre-flight and in-flight data for all variables), we used exact conditional logistic regression to determine changes in events from pre-flight to in-flight. Hospital, ICU, and ventilator days were compared between groups using Kaplan-Meier survival curves and log-rank tests while censoring for mortality.

We extended these survival analyses to Cox proportional hazards regression models to determine the independent relationship of CAR with hospital, ICU, and ventilator days while controlling for possible confounds. We adjusted these models for pre-flight factors that were

significantly associated with the outcomes or CAR grouping and clustered the analyses according to theater of operations (Iraq or Afghanistan). We also clustered analyses by the final MTF (Role IV or V) in the DoDTR record to account for the fact that this source of outcome data could differ for each patient. The final list of covariates included time to transport (defined as the days between injury and transport to the Role IV MTF), additional flights in theater, composite injury severity scores (ISS), polytrauma (defined as an AIS severity score greater than 2 in an additional body region), severe TBI (defined as a head AIS severity score greater than 3 and a pre-flight GCS score of 8 or lower), cranial or facial fractures, bone fragments or foreign bodies, pneumocephalus, ICP monitoring, and pre-flight head surgery. We evaluated the functional form of the covariates using Martingale and deviance residual plots with locally weighted scatterplot smoothing (LOWESS) and examined model fit using the likelihood ratio chi square and Akaike Information Criterion (AIC).

Additionally, we constructed logistic regression models to examine the association between CAR and discharge disposition (mortality, return to duty or home, ventilated at discharge or transfer, and ventilated with a GCS score of 8 or lower at discharge or transfer). These models included the same covariates as the proportional hazards models and were clustered by theater of operations and final MTF. The set of predictors produced variance inflation factors, tolerance, and condition indices that were within the recommended limits to avoid collinearity (i.e., variance inflation factors <2.5, tolerance ≥0.5, and condition indices <15). We examined adjusted R^2, chi-square p-values, and the area under the curve of the receiver operating characteristic (ROC AUC) as measures of model fit.

We did not impute any missing data and excluded cases with missing data for any covariates by listwise deletion. We conducted all statistical analyses in SAS (version 9.4, SAS Institute, Inc., Cary, NC).

Results

We received DoDTR data for 3867 patients with TBI who were transported to LRMC between January 2007 and May 2014, of which 477 patients fit the study inclusion criteria. We further excluded 39 patients with a catastrophic brain injury and 3 patients who were missing all CAR data, leaving a final sample of 435 patients for analysis. Of the 435 patients, 136 (31%) were in the CAR group (had a CAR or maximum cabin altitude of 5000 feet or less) and the remaining 299 (69%) were in the No CAR group.

The sample consisted of over 90% US active duty men and had a median age of 25 (IQR 21-30). More than half of the patients had additional flights in theater and most were transported within 2 days of injury (IQR 1-3 days). About 78% of all patients were transported from Afghanistan, with the remaining 22% coming from Iraq. Blast was the most common mechanism of injury (70%), 65% of patients sustained a penetrating injury, and 60% of patients had polytrauma. The median ISS for the sample was 29 (IQR 21-35), 60% of all patients had a head/neck AIS severity score greater than 3, and 60% had a pre-flight GCS score of 8 or lower. Patients with penetrating injuries, pneumocephalus, cranial or facial fractures, and bone fragments or foreign bodies present were more likely to be flown with a CAR (Table 1).

The most common pre-flight interventions were mechanical ventilation (72% of sample), blood products (50%), ICP monitoring (28%), ventriculostomy (21%), and supplementary oxygen (15%). Patients who had head surgery were more likely to be flown with a CAR (Table 2). Most patients remained mechanically ventilated during flight (69% of all patients). Other common in-flight interventions included sedation (IV infusion; 72% of all patients), anti-seizure medications (36%), 3% saline infusion (26%), vasopressors (21%), and supplementary oxygen (17%). The CAR and No CAR groups did not differ in any of the in-flight interventions (Table 2).

Sodium levels below 145 mmol/L (49% of all patients), body temperatures above 99.5°F (42%), and SBP lower than 110 mm Hg (21%) were among the most common pre-flight events. The most common in-flight events were body temperatures higher than 99.5°F (60% of sample), sodium levels lower than 145 mmol/L (46%), and SBP lower than 110 mm Hg (44%). About 19% of the sample had a PaO_2 lower than 80 mm Hg and 3% of patients experienced a SpO_2 lower than 93% while in flight. The CAR and No CAR groups did not significantly differ in rates of pre-flight or in-flight events (Figure 1).

When comparing pre-flight and in-flight rates of events, we found that the No CAR group experienced a significant increase in the percentage of patients who had a SpO_2 of 93% or lower and SBP higher than 160 mm Hg; the CAR group did not experience a significant change in these variables (Figure 1). Both groups experienced significant increases in the proportion of patients who had an SBP lower than 110 mm Hg and body temperature higher than 99.5°F. Neither group showed a change from pre-flight to in-flight in the percentage of patients with a PaO_2 lower than 80 mm Hg, sodium level lower than 145 mmol/L, or ICP greater than 20 mm Hg.

The overall survival rate for the sample was 96%. Most patients continued to receive medical care (89% of all patients) and 6% returned to duty or were discharged home. Thirteen percent of the sample were ventilated with a GCS score of 8 or lower at the time of discharge or transfer to another facility. Overall, survivors spent a median time of 15 days (IQR 6-33 days) in the hospital, 9 days (IQR 6-15 days) in the ICU, and 6 days (IQR 2-10 days) on a ventilator. The CAR and Non-CAR groups did not differ on any of these outcomes (Table 3).

We constructed Cox proportional hazards regression models to examine the independent association between CAR (yes vs. no) and total hospital days, total ICU days, or total ventilator days while adjusting for possible confounds and censoring for mortality. Being flown with a CAR was not significantly associated with total hospital days, total ICU days, or

total ventilator days in any of these models (Table 4). Similarly, CAR was not associated with returning to duty or being discharged home, mortality, and poor discharge disposition in multivariable logistic regression models.

Discussion

We found no association between the use of CAR and patient outcomes, to include hospital stay, disposition, and mortality. There was also no significant difference in oxygenation between CAR and Non-CAR patients. Unlike previous animal research, our study evaluated human combat casualties, often with additional injuries. Based upon our findings, we cannot recommend all moderate to severe head injury patients be transported using CAR. Medical personnel will need to use their clinical judgment and surrounding circumstances to determine if CAR is appropriate.

Previous research has demonstrated the adverse impact of hypoxia on TBI.[17,18] Furthermore, evaluation of aeromedically evacuated patients has demonstrated a significant rate of hypoxia during transportation.[2] Our study confirms this finding, as nearly one in five patients experienced a PaO_2 lower than 80 mmHg and the Non-CAR group had a statistically significant higher rate of SpO2 less than 94%. However, we found no difference in clinical outcomes. Our previous research has demonstrated similar findings: When evaluating the impact of the time to transport out of theater we found that those patients transported over 72 hours after their time of injury had higher rates of mild hypoxia during transport, but superior outcomes compared to those evacuated earlier.[15]

There is a growing body of evidence that hyperoxia can exacerbate TBI.[10,11] Our previous research evaluating ventilator management practices in CCATT patients identified that a significant number of patients experienced hyperoxia during transport.[12] One could theorize that those patients transported at a CAR are at higher risk for developing hyperoxia, due to the

combined effect of a less hypoxic aircraft cabin and excogenous oxygen, potentially leading to secondary brain injury. However, we found no statistically significant difference in the percentage of patients with a PaO2 greater than 150 mmHg in the CAR and Non-CAR groups.

Animal research aimed to determine if hypobaria alone exacerbates TBI has yielded conflicting results when evaluating histological evaluation.[9,19] Skovira et al found worsening cognitive deficits and neuronal loss with exposure to hypobaria.[20] Given the potential negative impact of hypobaria on intracranial pressure and cerebral perfusion pressure, it is conceivable that hypobaria may have a different impact on closed versus open skull injuries. We intend to evaluate the association with hypobaria on closed versus open skull injuries in a future study.

In a study by Boyd et al., about 18% of the CCATT missions that involved patients with moderate-to-severe TBI had altitude restrictions.[21] While CAR may be considered for patients with free air in a body cavity (i.e. pneumocephalus, ocular trauma, arterial gas embolism), patients with severe lung disease, and patients at risk for decreased tissue oxygenation, determination of CAR is up to flight surgeon adjudication; yet, we are unable to determine the rationale for CAR based on record abstraction.[22-24]

Hypotension and hyperthermia have also been associated with secondary brain injury.[2] In both the CAR and Non-CAR groups there was a significant number of patients who had an SBP lower than 110 mmHg and body temperature higher than 99.5°F.[25] Further research is warranted to determine the cause of these findings and prevent their occurrence in future CCATT operations.

We found no association between the use of CAR and patient outcomes; however, the retrospective methodology of our study does not permit us to determine causation. Therefore, while we cannot recommend the use of CAR restriction, neither are we able to certainly state that CAR does not provide benefit to TBI patients. In addition, there may be other types of injury

for which CAR may confer a benefit. A prospective study during future conflicts or in civilian aeromedical evacuation may provide a clear answer. For now, we recommend that the clinician consider the findings of our study, use clinical judgement, and account for the circumstances of the mission to determine if CAR is indicated.

Limitations

Our study has limitations. The study is retrospective and therefore we are unable to determine causation however the data did not suggest an association between the use of CAR and patient outcomes With the outcomes studied, multiple factors could be contributory; however, we attempted to correct for any confounding by using multivariable linear regression. Second, the abstracted data was dependent on documentation within the medical records, leaving the potential for missing and inaccurate data due to imprecise documentation. As with any retrospective study, there is the potential for subjectivity in data abstraction; however, we incorporated abstractor training and periodic quality reviews in our protocol to minimize this risk. With regards to the external validity of our findings, our patient population consisted predominately of young male adults who were not on anticoagulation therapy at their time of injury. Extrapolation of our findings to pediatric, female, and elderly patients is limited. However, given the difficulty of obtaining a similarly large database, extrapolation of our findings to these populations may be prudent. Finally, detailed neurocognitive outcome data of our patient population is not available. Therefore, we are unable to determine the impact of CAR on neurocognitive function and quality of life.

Conclusion

Patients with moderate or severe TBI who were evacuated with a recorded cabin altitude restriction had a lower rate of hypoxia during transport; however, they did not significantly differ

from those who flew without a CAR with regards to mortality rates, hospital days, ICU days, or ventilator days.

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Table 1. Patient characteristics and injuries

Variable	No CAR (n=299)	CAR (n=136)	Difference (95% CI)
Age	25 [21-30]	24 [21-29]	-1 (-2 to 0)
Male gender	97 (95-99)	99 (97-101)	-2 (-4 to 1)
US active duty	91 (88-95)	97 (94-100)	-6 (-10 to -1)*
Theater of operations			
Afghanistan	78 (74-83)	77 (69-84)	1 (-7 to 10)
Iraq	22 (17-26)	24 (16-31)	-2 (-10 to 7)
Additional flight(s) in theater	56 (51-62)	54 (45-62)	2 (-8 to 13)
Time to transport, days	2 [1-3]	2 [1-2]	0 (0 to 0)
Mechanism of injury			
Blast	69 (63-74)	74 (67-82)	-5 (-15 to 3)
GSW	14 (10-18)	13 (7-18)	1 (-5 to 8)
MVC	8 (5-12)	5 (1-9)	3 (-2 to 8)
Other	9 (6-12)	8 (3-13)	1 (-5 to 7)
Type of injury			
Penetrating	62 (56-67)	72 (64-80)	-10 (-20 to -1)*
Blunt	38 (32-43)	27 (20-35)	11 (1 to 20)*
Burn	1 (0-2)	1 (-1-2)	0 (-2 to 2)
Polytrauma	59 (54-65)	60 (52-69)	-1 (-11 to 9)
Composite ISS	27 [21-35]	29 [21-38]	0 (-2 to 3)
Head/neck AIS severity score >3	59 (54-65)	62 (54-70)	-3 (-12 to 7)
Pre-flight GCS score ≤8	52 (46-58)	49 (41-58)	3 (-8 to 13)
Severe TBI†	33 (28-39)	35 (27-43)	-2 (-12 to 7)
Intracranial hemorrhage	47 (41-53)	47 (39-56)	0 (-10 to 10)
Cranial or facial fractures	61 (56-67)	79 (73-86)	-18 (-27 to -9)*
Pneumocephalus	15 (11-19)	31 (23-39)	-16 (-25 to -7)*
Bone fragments or foreign bodies present	17 (13-21)	32 (24-40)	-15 (-24 to -6)*
Contusion	19 (14-23)	15 (9-22)	4 (-4 to 11)
Midline shift	10 (7-13)	15 (9-22)	-5 (-12 to 2)
Mass effect	8 (5-11)	9 (4-14)	-1 (-7 to 5)

Values given are median [interquartile range] or column percent (95% confidence interval).
*The difference is significant if its confidence interval does not include or cross zero.
†Severe TBI is defined as head/neck AIS >3 and pre-flight GCS ≤8.

Table 2. Pre-flight and in-flight interventions

Variable	No CAR (n=299)	CAR (n=136)	Difference (95% CI)
Pre-flight			
Mechanical ventilation	72 (66-77)	73 (65-80)	-1 (-10 to 8)
Any blood products	51 (45-57)	49 (40-57)	2 (-7 to 13)
ICP monitoring	25 (20-30)	33 (25-41)	-8 (-17 to 1)
Ventriculostomy	20 (16-25)	24 (17-32)	-4 (-13 to 4)
Supplementary oxygen	14 (10-18)	16 (10-22)	-2 (-9 to 6)
Craniotomy	11 (7-15)	17 (11-23)	-6 (-13 to 1)
Craniectomy	9 (6-13)	13 (7-18)	-4 (-10 to 3)
Massive transfusion	9 (5-12)	8 (3-13)	1 (-5 to 6)
Globe Repair	7 (4-10)	10 (5-15)	-3 (-9 to 3)
Hematoma Evacuation	6 (4-9)	10 (5-15)	-4 (-10 to 2)
Fragment Removal	5 (3-8)	8 (3-13)	-3 (-8 to 3)
Any surgery - head	51 (45-57)	68 (60-76)	-17 (-26 to -7)*
Any surgery - extremities	49 (43-55)	51 (42-59)	-2 (-12 to 9)
Any surgery - abdomen	21 (17-26)	26 (18-33)	-5 (-13 to 4)
Any surgery - neck	12 (8-15)	16 (10-22)	-4 (-12 to 3)
In-flight			
Sedation (IV drip)	72 (66-77)	74 (66-81)	-2 (-11 to 7)
Mechanical ventilation	69 (64-74)	71 (63-78)	-2 (-11 to 8)
Anti-seizure medications	34 (28-39)	42 (34-50)	-8 (-2 to 18)
Acetaminophen	30 (25-36)	23 (16-30)	7 (-1 to 16)
3% saline infusion	25 (20-30)	30 (22-38)	-5 (-15 to 4)
Vasopressors	21 (16-26)	21 (14-27)	0 (-8 to 9)
Any blood products	16 (12-20)	17 (11-23)	-1 (-9 to 6)
Supplementary oxygen	17 (13-21)	15 (9-22)	2 (-6 to 9)
Sedation (IV push)	16 (12-20)	11 (6-16)	5 (-2 to 11)
Paralytics	9 (5-12)	10 (5-15)	-1 (-7 to 5)
Mannitol	4 (2-6)	4 (1-8)	0 (-5 to 4)
Steroids	4 (2-6)	3 (0-6)	1 (-3 to 5)

Values given are column percent (95% confidence interval).

*The difference is significant if its confidence interval does not include or cross zero.

Table 3. Outcomes

Variable	No CAR (n=299)	CAR (n=136)	Log-rank p-value or difference (95% CI)
Total ventilator days*	6 [2-10]	5 [2-10]	0.8847
Total ICU days*	9 [6-15]	8 [5-14]	0.6247
Total hospital days*	16 [6-35]	11 [5-30]	0.2293
Mortality	3 (1-5)	5 (1-9)	-2 (-6 to 2)
Returned to duty or discharged home	7 (4-10)	4 (1-8)	3 (-2 to 7)
Continued medical care	89 (85-92)	89 (84-94)	0 (-7 to 6)
Ventilated at discharge or transfer	23 (19-28)	24 (16-31)	-1 (-9 to 8)
GCS score ≤8 at discharge or transfer	15 (11-19)	12 (6-17)	3 (-3 to 10)
Ventilated and GCS ≤8 at discharge or transfer	14 (10-18)	12 (6-17)	2 (-4 to 9)

Values given are median [interquartile range] or column percentage (95% confidence interval).
*Values are for survivors only. Log-rank p-values are from survival analysis censored by mortality.

Table 4. Results of multivariable models

Variable	Cox proportional hazards models Adjusted hazard ratio (95% confidence intervals)			Logistic regression models Adjusted odds ratio (95% confidence interval)			
	Hospital days	ICU days	Ventilator days	Mortality	Return to duty or discharged home†	Ventilated at discharge or transfer†	Ventilated with GCS <8 at discharge or transfer†
CAR (vs. No CAR)	**1.2 (0.9-1.5)**	**1.1 (0.9-1.4)**	**1.1 (0.9-1.4)**	**1.3 (1.0-1.7)**	**0.8 (0.4-1.5)**	**0.9 (0.4-1.9)**	**0.7 (0.4-1.4)**
Time to transport, days	0.8 (0.8-0.9)*	0.9 (0.8-1.0)	1.0 (0.9-1.0)	0.9 (0.8-1.0)	1.1 (1.0-1.2)	0.9 (0.9-1.0)	0.9 (0.7-1.2)
Additional flights in theater (vs. no)	1.0 (0.8-1.3)	1.1 (0.9-1.3)	1.1 (0.9-1.4)	0.7 (0.1-3.9)	2.1 (1.5-2.8)*	0.9 (0.4-2.2)	0.6 (0.3-1.3)
Composite ISS	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.1 (1.0-1.1)	1.0 (0.9-1.0)	1.0 (1.0-1.0)	1.0 (0.9-1.0)
Polytrauma (vs. isolated TBI)	0.7 (0.5-0.9)*	0.8 (0.6-1.1)	0.7 (0.6-1.0)	0.5 (0.1-1.9)	1.0 (0.5-2.1)	0.8 (0.4-1.6)	1.5 (1.2-1.7)*
Severe TBI (vs. no)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.7 (0.6-0.9)*	3.0 (0.6-14.2)	0.4 (0.0-3.9)	3.3 (2.7-4.2)*	4.5 (3.0-6.5)*
Penetrating injury (vs. no)	0.8 (0.6-1.0)	0.9 (0.7-1.1)	0.8 (0.6-1.0)	1.8 (0.5-6.1)	1.1 (0.7-1.6)	1.1 (0.8-1.5)	1.1 (0.7-1.8)
Cranial/facial fractures (vs. no)	1.2 (0.9-1.5)	1.2 (0.9-1.5)	1.0 (0.8-1.3)	1.4 (0.3-6.4)	1.6 (1.3-1.9)*	0.9 (0.8-1.1)	0.8 (0.6-0.9)*
Bone fragments/foreign bodies (vs. no)	1.2 (0.9-1.7)	1.2 (0.9-1.6)	1.4 (1.0-1.9)	1.4 (0.3-5.9)	0.3 (0.2-0.4)*	1.1 (0.4-3.0)	0.7 (0.6-0.9)*
Pneumocephalus (vs. no)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.8 (0.6-1.1)	1.8 (0.6-5.1)	0.3 (0.1-0.7)*	1.3 (0.9-1.9)	1.4 (1.2-1.7)*
ICP monitoring (vs. no)	0.9 (0.7-1.2)	0.7 (0.5-0.9)*	0.6 (0.5-0.8)*	0.4 (0.1-1.4)	2.5 (0.5-13.9)	2.1 (0.8-5.5)	4.9 (2.5-9.4)*
Pre-flight head surgery (vs. no)	0.9 (0.7-1.1)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.6 (0.3-1.0)	0.7 (0.3-1.7)	1.1 (0.8-1.6)	1.5 (1.0-2.2)

Hazard and odds ratios are adjusted for all other covariates listed, and all models are clustered by theater operations and final MTF (source of outcome data).

*The hazard ratio or odds ratio is significant if its confidence interval does not include or cross 1.

†Models for these outcomes only include surviving patients (n=418).

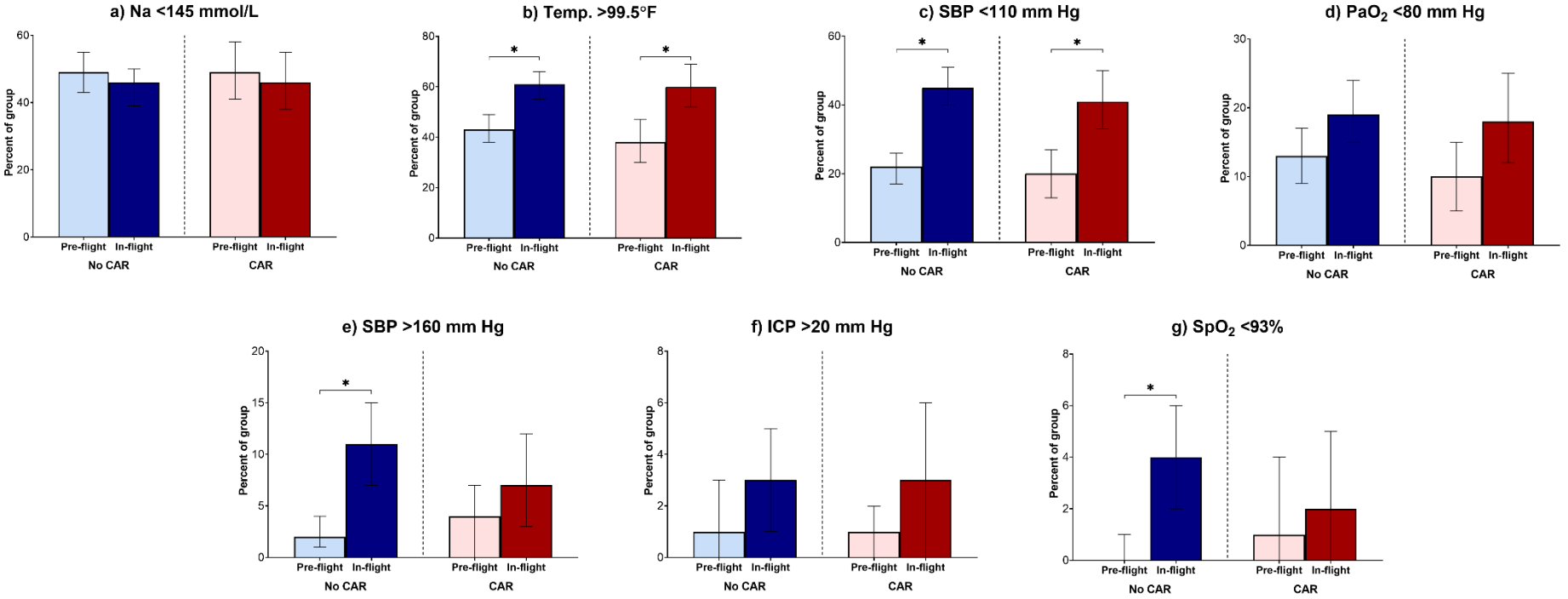

Figure 1a-g. Comparison of events for CAR and No CAR groups from pre-flight to in-flight. Error bars represent 95% confidence intervals. Brackets and asterisks (*) represent significant differences in an exact conditional logistic regression at p<0.025 after correction for multiple comparisons.