Title: Long-range aeromedical transport to a higher-level facility does not influence the development of traumatic extremity compartment syndrome: a multicenter seven-year study.

Short Title: Aeromedical Transport does not influence Compartment Syndrome

Authors:

Lt Col Joseph K. Maddry, MD[1,2] (joseph.k.maddry.mil@mail.mil); Alejandra G. Mora, MS[1] (alejandra.g.mora.ctr@mail.mil); Crystal A. Perez, BSN, RN[1] (crystal.a.perez9.ctr@mail.mil); Lauren K. Reeves, MsPH[1] (lauren.k.reeves.ctr@mail.mil); Joni A. Paciocco[1] (joni.a.paciocco.ctr@mail.mil), Melissa A. Clemons, PhD[1] (melissaann.r.clemons.ctr@mail.mil); Andrew Sheean, MD[3] (Andrew.j.sheean.mil@mail.mil); Nurani M. Kester, MD[4]; Col Vikhyat S. Bebarta, MD[5,6] (vikhyat.bebarta@cuanschutz.edu)

1. Air Force 59th MDW/ST - En route Care Research Center, Lackland Air Force Base, TX
2. Department of Emergency Medicine; Brooke Army Medical Center, Ft Sam Houston, TX
3. Department of Orthopedic Surgery, Brooke Army Medical Center, Ft. Sam Houston, TX
4. Department of Emergency Medicine, University of Texas Health Science Center San Antonio, San Antonio, TX
5. Center for COMBAT Research, University of Colorado School of Medicine, Aurora, CO
6. Department of Emergency Medicine; University of Colorado School of Medicine, Aurora, CO

We have no conflicts of interest to declare.

Disclaimer: The views expressed are those of the author(s) and do not reflect the official views or policy of the Department of Defense or its Components. 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.

Interim results from this study were presented as a poster at the Military Health System Research Symposium, 2018. Kissimmee, FL.

This study was presented locally as a poster at the San Antonio Military Health System and Universities Research Forum, 2019. San Antonio, TX.

This study was presented as a podium presentation at the Military Health System Research Symposium, 2019. Kissimmee, FL

Corresponding Author:
Melissa A. Clemons, PhD
3551 Roger Brooke Dr.
Ft Sam Houston, TX 78234
Preferred email: melissaann.r.clemons.ctr@mail.mil

Abstract

Background: Critically ill and injured patients are aeromedically transported for definitive care, including patients with or at risk for developing compartment syndrome (CS). Compartment pressure changes have not been determined to be associated with factors inherent to aeromedical transport in animal models. Using patient care records, we sought to evaluate time to CS diagnosis relative to aeromedical transport to definitive care. In doing so, we can determine whether there is an ideal time to transport patients that develop compartment syndrome.

Methods: We reviewed patient records with CS who were aeromedically evacuated out of theater from January 2007 to May 2014. Data abstractors collected flight information, laboratory values, vital signs, procedures, in-flight assessments, and outcomes. Time to transport was defined as the time from injury to arrival at Landstuhl Regional Medical Center (LRMC). We compared groups based on time of CS diagnosis relative to injury day and time of transport (Pre-Flight versus Post-Flight). We used descriptive statistics and multivariable regression models to determine associations between time to transport, time to CS diagnosis, and outcomes.

Results: Within our study window, 238 patients had traumatic extremity CS. Patients with CS within 1 day of injury had higher injury severities ($p=0.002$) with blast-related ($p=0.021$) and penetrating injuries ($p=0.04$). We compared 47% of patients with CS Pre-Flight to 53% diagnosed Post-Flight. Over 90% in both groups developed CS within 48 hours of injury; the time to diagnosis was similar for casualties diagnosed Pre- and Post-Flight ($p = 0.65$). There was no associated between time to arrival at LRMC and day of CS diagnosis (Risk ratio: 1.06; 95% CI 0.96-1.16).

Conclusion: The timing of CS diagnosis is not associated with the timing of transport; therefore, aeromedical evacuation likely does not influence development of CS.

Level of Evidence: Level IV; Therapeutic Care/Management

Key Words: Compartment Syndrome; trauma; fasciotomy; aeromedical evacuation

Introduction:

The use of aeromedical evacuation platforms has increased the survival of patients who were traumatically injured in combat.[1-4] Nearly 8,000 critically ill or injured patients were transported via Critical Care Air Transport Team (CCATT) since the beginning of the wars in Iraq and Afghanistan.[1] CCATT is a US Air Force asset tasked with transporting critically ill and injured patients within the theater of operations and to more advanced medical facilities. CCATT teams consist of a critical care physician, a critical care nurse, and a respiratory therapist; thus, the fixed-wing platform has the capacity to transport up to three ventilated and three non-ventilated patients at a time.[5]

An analysis of the 2011 US Transportation Command Regulating and Command and Control Evacuation System (TRAC2ES) data base revealed that musculoskeletal related injuries accounted for 10 of the top 15 diagnoses transported by CCATT.[6] Most injuries are blast-related injuries as a result of improvised explosive devices (IED).[4] Patients with extremity injuries related to blast exposure are at risk for the development of compartment syndrome, a common but emergent complication of trauma in which increased pressure due to injury causes bleeding, edema, and/or decreased blood flow to an extremity.[7] Once compartment syndrome is diagnosed, a fasciotomy should be performed as soon as possible, and a delay in diagnosis and treatment increase morbidity and mortality.[8,9] Though research in support of prophylactic fasciotomy is limited for both civilian and military platforms and treatment is primarily based on expert clinical consensus, [7,10,11] the 2012 Joint Theater Trauma System Clinical Practice Guideline recommends this course of treatment in patients who are at high risk for compartment syndrome (determined in part by limb and overall injury severity) when there is no capability to closely monitor the extremity compartment pressures over time.[12]

Aeromedical evacuation is associated with stressors such as hypobaria, hypoxia, and vibrations that could theoretically increase the likelihood of compartment syndrome, exacerbate compartment pressures, or hasten the presentation of disease process. Research evaluating the impact of the aeromedical environment on compartment pressures is limited. Studies on swine models that investigated the influence of altitude on uninjured limbs[13] or limbs with pressure-induced fractures[14] have shown no increase in the incidence of compartment syndrome due to altitude changes. Similarly, simulated hypobaric, hypoxic conditions in rats with hind-limb ischemia and saw no increase in muscle edema.[15] To date, no studies have investigated the effects of air transported-induced altitude changes on the development or progression of compartment syndrome in humans. Therefore, in this study, our goals were to determine whether the timing of compartment syndrome presentation/development was associated with time of aeromedical transport and intrinsic altitude changes, and to understand whether factors such as injury or transport platform influenced when compartment syndrome developed. Based on existing animal literature,[13,14] we hypothesized that time of traumatic compartment syndrome development of the extremities would not be influenced by time of aeromedical transport in relation to time of injury.

Methods

This study was approved by the Wilford Hall Ambulatory Surgical Center Institutional Review Board. We performed a retrospective record review of combat casualties that had documentation of traumatic compartment syndrome and were transferred via aeromedical transport from Iraq or Afghanistan to Landstuhl Regional Medical Center (LRMC) from January 2007 to May 2014.

To identify combat casualties that developed compartment syndrome, we submitted a query to the Department of Defense Trauma Registry (DoDTR).[16] The DoDTR is a performance improvement, military medical charts database of combat casualties treated in Afghanistan/Iraq, Germany, and/or continental US military medical facilities that contains International Classification of Diseases-9 (ICD-9) along with demographic, injury codes and descriptions, outcome measures.[16] Our query captured the following ICD-9 codes related to compartment syndrome: 958.9 (traumatic compartment syndrome), 958.91 (traumatic compartment syndrome of upper extremity), 958.92 (traumatic compartment syndrome of lower extremity), 958.93 (traumatic compartment syndrome of abdomen), and 958.99 (traumatic compartment syndrome of other sites). Demographics, injury location, injury severity, and outcome measures were included in the data query provided by DoDTR.[16] However, we only included patient records with confirmed documentation of traumatic compartment syndrome of at least one extremity during the study window.

Medical care encounters occurring in the theater of operations are housed within the Theater Medical Data Store (TMDS). Study abstractors confirmed traumatic compartment syndrome from documentation within TMDS. Using a pre-determined data collection tool, research personnel abstracted medical care and patient disposition. The data collection tool enabled abstractors to collect data based on the facility rendering care (i.e. care rendered at a Role 2 versus care rendered at a Role 3). In addition, we collected treatment and complications related to fasciotomies performed and compartment syndrome diagnosis along with data detailing anatomical location of the fasciotomies, fasciotomy revisions, and compartment syndrome.

Through collaboration with the CCATT Pilot Unit, we obtained transport medical records (Form 3899) from TMDS for the casualties that were transported via CCATT.[17] CCATT medical records were abstracted using methodologies established in prior studies.[17] Casualties transported via Aeromedical Evacuation (AE) platform did not have available transport records and so were documented as being AE transports without data regarding care and disposition en route.

We linked all abstracted data of patients with a confirmed compartment syndrome diagnosis with that of the DoDTR query that included outcome measures. Outcomes measures were inclusive of adverse events such as (but not limited to) coagulopathy, infection, the number of days on mechanical ventilation, length of stay in the Intensive Care Unit, total number of hospitalization days, discharge disposition, and final survival. In our study dataset, we included all available dates and times of injury, treatments, complications, transport, and outcomes. All data underwent standardized quality assurance methods.

We calculated the duration of time from injury to documented diagnosis of compartment syndrome. As data on the precise timing was limited, we binned records based on number of days between the documentation of injury and compartment syndrome in an attempt to be more accurate in our interpretation. When a timestamp nor date of compartment syndrome diagnosis was available, we used the timestamp or date of first fasciotomy to approximate the post-injury day of compartment syndrome diagnosis. We used Pearson product-moment correlation coefficient with the restricted maximum likelihood estimation method to ensure adequate correlation between duration of time measures using the compartment syndrome diagnosis versus the fasciotomy procedure. In addition, we considered whether the compartment syndrome diagnosis was made prior to (Pre-Flight) or after transport to LRMC (Post-Flight).

A secure electronic study database was created (Microsoft Excel 2010, Redmond, WA) to consolidate DoDTR, TMDS, and CCATT data. We performed statistical analyses with JMP Pro version 14 (SAS Institute Inc., Cary, NC). We analyzed the data using two different grouping schemes. First, we established time interval groupings based on the duration of time from the injury until the diagnosis of compartment syndrome: within 24 hours (1-Day), 25-48 hours (2-Day), 49-72 hours (3-Day), 73-96 hours (4-Day). Second, we grouped our study sample based on when the compartment syndrome diagnosis was made in relation to their aeromedical transport out of theater and to LRMC (Pre-Flight versus Post-Flight). Continuous data were tested for normality using the Shapiro-Wilks test. Continuous data were reported as mean ± standard deviation (SD) and median [Interquartile Range, IQR]. For data that were not normally distributed we used the Wilcoxon rank-sum test. Chi-square or Fisher's exact tests, when needed, were used to compare categorical data and reported percentages with 95% confidence intervals. To evaluate trends based on times, we used Cochran-Armitage tests. For analysis of time to compartment syndrome diagnosis, we evaluated Kaplan-Meier plots with log-rank statistics and reported corresponding cumulative incidence plots. We used Cox proportional hazard regression models to evaluate time-to-compartment syndrome diagnosis and time-to-LRMC arrival analyses. To identify factors associated with traumatic compartment syndrome of the lower extremities within 24 hours we evaluated logistic regression models.

Results

Demographics

We identified 238 unique records that reported a confirmed diagnosis of traumatic extremity compartment syndrome during our study window. Of those, 91% (n=216) had data

available for the date and time of injury and, at least, an approximated date for compartment syndrome diagnosis. A total of 43 records had provider documentation of compartment syndrome diagnosis but did not have a date or timestamp associated with the documentation of compartment syndrome diagnosis; for those patients, we used the time of fasciotomy as a substitute data point. Using records that had timestamps (injury, fasciotomy procedure, and compartment syndrome diagnosis), we calculated the time of compartment syndrome diagnosis, using either compartment syndrome diagnosis or fasciotomy timestamps. We found that the time of diagnosis and the time of fasciotomy were correlated ($r=0.77$) and therefore either could be used to approximate the time of compartment syndrome development for the purposes of our analysis.

The majority of casualties included in this study were males (98%) and the average age of patients was 23 years. (Table 1). The greatest proportion of injuries were penetrating injury types (72%) and the average injury severity score was 16. The majority had traumatic compartment syndrome in the lower extremities (88%). In this study sample we were able to confirm using available provider documentation that 24.7% had fasciotomies performed prior to compartment syndrome diagnosis. Of these, 9.4% had fasciotomy revisions or extensions. The rate of documented fasciotomy revision was 4.9% in those without documentation of fasciotomy procedure prior to compartment syndrome diagnosis ($p=0.3157$).

For 80% of the study sample, compartment syndrome diagnosis was made within 1 day of injury (Table 1). Documentation for the platform of transport to LRMC was available for 222 records (n=129; 58%, AE and n=93; 42%, CCATT). While the majority of casualties arrived at LRMC two days following injury (45%, n=107), 23% (n=55) arrived one day, 24% (n=58) three days, and 8% (n=18) more than 3 days following injury.

We had cabin altitude documentation for 15 records (all CCATT) and only 5 had altitude restrictions (two were diagnosed with compartment syndrome in-theater and three following arrival at LRMC). Of the 5 with a cabin altitude restriction, four had severe head injuries and one had a moderate head injury, severe extremity injury, coagulopathy, hemorrhage shock, or rhabdomyolysis and received cardiopulmonary resuscitation. Due to the overwhelming lack of documentation of cabin altitude restrictions, we were not able to use cabin altitude restrictions as a variable in determining whether time of transport following time of injury influenced diagnosis of compartment syndrome.

Time to Compartment Syndrome Diagnosis

To identify trends related to the timing of compartment syndrome presentation, we evaluated casualties based on when compartment syndrome was documented relative to their time of injury (1-Day, 80%; 2-Day, 16%; 3-Day, 3%; 4-Day, 1%; Table 2). We were not able to determine the time between injury and compartment syndrome diagnosis for 22 patients (9%).

Age and gender proportions were similar across groups (Table 2). There was an injury severity gradient effect based on timing of compartment syndrome diagnosis such that the more severely injured patients presented with traumatic compartment syndrome of the extremities at times more proximal to their respective injury times. The 1-Day group trended towards having higher overall and extremity related injury severity based on the Cochran-Armitage trend test (Table 2). Likewise, casualties that had compartment syndrome diagnosis sooner had a greater proportion of explosive device-related and penetrating injuries, but had the lowest proportion of blunt injury types (Table 2). There was a similar proportion of casualties with polytrauma in each

group. Proportions of diagnosed upper and lower extremity compartment syndrome did not differ across groups. However, 1-Day and 2-Day groups were more likely to have had a fasciotomy performed in-theater. The 1- and 2-Day casualty groups arrived at LRMC one median day sooner than the 3- and 4-Day groups (Table 2).

Casualties transported by CCATT were more likely to have developed compartment syndrome within 1 day following injury (Table 2). In our study sample, none of the casualties that developed traumatic compartment syndrome longer than 2 days from the injury date were transported by CCATT. Of note, CCATT transported casualties with higher injury severity (median ISS=10 for AE versus 20 for CCATT; $p<0.0001$) and a higher proportion of polytrauma compared to AE (88% AE versus 97% CCATT; $p=0.0158$). In contrast, AE transported a higher proportion of casualties with blunt related injuries (72% for AE versus 28% for CCATT; $p=0.0115$). However, times to transport casualties to LRMC were similar for the two modes of transport (median of 2 days, $p=0.9676$). AE and CCATT were equally likely to transport casualties to LRMC one (23% AE vs 25% CCATT, $p=0.7994$) and two days (67% AE vs 69% CCATT, $p=0.9778$) following injury. Comparison of cumulative incidence profiles of compartment syndrome diagnoses relative to injury time between AE and CCATT platforms did not differ (Log-rank statistic, $\chi^2=1.7403$; $p=0.1871$; Figure 1).

Analysis based on pre- and post-flight diagnosis of Compartment Syndrome

For the 22 patients that did not have available timestamps for time of compartment syndrome diagnosis, we were able to determine whether the diagnosis was made prior to (Pre-Flight, n=6) or after transport to LRMC (Post-Flight, n=16) based on the facility in which the compartment syndrome was diagnosed. Casualties that developed compartment syndrome Pre-

Flight versus Post-Flight were of similar age and sustained similar injuries compared to the Post-Flight group. The Post-Flight group however were more severely injured (Table 3). Both groups had similar proportion of casualties who had tourniquets placed in-theater and received direct pressure to their injuries. Compartment syndrome developed and fasciotomies were performed at similar times following injury; however, the groups of casualties for whom compartment syndrome was diagnosed at LRMC (Post-Flight) arrived at LRMC more quickly than those who had compartment syndrome diagnosed in-theater (Pre-Flight). Albeit small numbers, casualties in the Pre-Flight group were more likely to have a secondary compartment syndrome diagnosis of another extremity and so, were more likely to have additional fasciotomies performed.

We re-assessed all records based on whether the compartment syndrome diagnosis was made in theater (Pre-Flight) or at LRMC (Post-Flight). A total of 113 (47%) casualties had a compartment syndrome diagnosis Pre-Flight and 123 casualties had the diagnosis made Post-Flight. To determine whether the time of compartment syndrome diagnosis (Pre- or Post-Flight) was influenced by the time of transport following injury, we compared the proportion of patients that had Pre- and Post-Flight diagnosis of compartment syndrome based on the number of hours after injury that they arrived at LRMC (Figure 2). We found that the time of compartment syndrome diagnosis (pre- or post-flight) was not associated with the number of hours following injury that the patients arrived at LRMC. When evaluating the influence of flight on patients that did not have CS prior to flight, we limited our analysis to casualties in the Post-Flight group. We determined that the incidence of compartment syndrome was similar regardless of the length of the delay in transport following injury (Supplemental Figure 1). Therefore, for those that did not have compartment syndrome at the time of transport, time of compartment syndrome diagnosis did not differ based on LRMC arrival day.

Time-to-event analysis

In an attempt to understand factors associated with time-to-LRMC arrival in casualties with confirmed compartment syndrome, we used Cox proportional hazard regression techniques. When considering age, sex, injury, country of military operation, procedures performed in-theater, disposition in-theater, and transport platform, we found that casualties with head injuries arrived at LRMC faster than those without a head injury (Table 4). We also evaluated whether specific factors in the presence of aeromedical transport contributed to the timing of the development of compartment syndrome accounting for factors similar to the time-to-LRMC analysis. We did not identify any factors to be associated with faster time-to-compartment syndrome development.

When considering causalities that developed lower extremity compartment syndrome, there were higher odds of compartment syndrome within 24 hours with a concomitant head injury (Odds Ratio 3.72, 1.08-12.8) regardless of tourniquet application, amount of fluids, or blood product administration in-theater. In this study, tourniquet application, crystalloids, colloids, and blood products were not associated with developing compartment syndrome within 24 hours.

Outcomes

Comparing outcomes among the groups, the 1-Day group was more likely to have documented coagulopathy and lung dysfunction (Supplemental Table 1). Likewise, the 1-Day group had more ventilator days, ICU, and hospital days. Conversely, when comparing casualties that developed compartment syndrome Pre-Flight versus Post-Flight there were no differences in

the outcome measures (Supplemental Table 2). We had a high survival rate in this study sample—only n=3 did not survive their injuries.

Discussion

From January 2007 to May 2014, we documented 238 casualties that developed compartment syndrome. The time when compartment syndrome diagnosis was made did not differ according to the timing of aeromedical transport. If aeromedical evacuation accelerated the time to development of compartment syndrome such that we could infer an increased risk of compartment syndrome with aeromedical transport, we would have expected to discover an increased incidence of compartment syndrome diagnoses following aeromedical transport. However, the incidence rate of compartment syndrome diagnosis following flight was comparable to the incidence rate prior to flight. Based on the results of this study, we are not able to conclude that aeromedical transport influences the timing of the development compartment syndrome, nor can we conclude that aeromedical transport poses additional risks to casualties with compartment syndrome. To our knowledge, this is the first human study evaluating the impact of the hypobaric aeromedical transport environment on compartment syndrome and subsequent patient outcomes.

It has been postulated that the hypobaric environment of aeromedical evacuation could increase the risk of compartment syndrome.[13,18-20] McGill et al. found that a cabin altitude pressure of 10,000 feet resulted in a 2.7 mmHg increase in compartment pressures of healthy swine.[13] However, the clinical significance of this small increase is unknown. This is in part due to conflicting literature on what compartment pressure is necessary to induce compartment syndrome. Ouellette and Kelly report the occurrence of compartment syndrome with pressures as

low as 15 mmHg.[18] Conversely, Allen et al. claimed that the development of compartment syndrome occurred at pressures greater than 40 mmHg.[19] Other authors have contended that compartment syndrome occurs when the diastolic pressure minus the compartment pressure is less than 30 mmHg,[20] while still others have argued the mean arterial pressure minus compartment pressure is more accurate.[20,21]

The results of our study are similar to animal models of compartment syndrome that have found no clinically significant impact of hypobaria. Rietnour et al. induced elevated compartment pressures in a rat model using limb ischemia and found no difference in compartment pressures when comparing animals at sea level versus 10,000 feet.[15] Similarly, Kalns et al. found no difference in compartment pressures in swine with elevated compartment pressure were exposed to hypobaria, but did find that hypobaria resulted in reduced muscle degeneration and microvascular thrombi.[14]

In our study, prophylactic fasciotomies performed before compartment syndrome diagnosis were not associated with subsequent revisions of an existing fasciotomy. Given the retrospective nature of our study, it is unclear if our findings support the need to perform prophylactic fasciotomies, or if prophylactic fasciotomies were performed on individuals who would not have developed compartment syndrome. Of note, in order to avoid the morbidity and mortality associated with delayed compartment syndrome diagnosis, aggressive employment of fasciotomy was used during OIF/OEF in accordance with the clinical practice guideline.

When comparing the Pre-Flight and Post-Flight groups, we noted that casualties who developed compartment syndrome at LRMC (Post-Flight) arrived at LRMC more quickly than the Pre-Flight group. Albeit small numbers, casualties in the Pre-Flight group were more likely to have secondary compartment syndrome diagnosis of another extremity and so, were more

likely to have additional fasciotomies performed. These findings support our hypothesis that for patients vulnerable to compartment syndrome development, the greatest risk period is one to three days following injury, independent of aeromedical evacuation. This contrasts with our study evaluating the impact of time to transport patients with traumatic brain injury, which found an association between delayed evacuation and improved outcomes regardless of injury severity.[22]

Deployed clinicians must remain aware that the incidence of extremity compartment syndrome remains to be one to three days following the time of injury.[9] A significant proportion of casualties are flown out of theater during this critical time; however, aeromedical evacuation of stabilized patients with diagnosed compartment syndrome does not confer greater risks and is not contraindicated. Furthermore, given our study demonstrating a clinically significant rate of subsequent fasciotomy revision, efforts should be made to ensure combat surgeons are well versed in this surgery.

Limitations

Our study has several limitations. We found no association between time of aeromedical evacuation and the development of compartment syndrome relative to injury, but, as with any retrospective study, we are unable to determine causation or a lack thereof. Second, the data was abstracted from the medical records and was subject to the availability of records and documentation practices of clinicians. Granularity of care provided to include timestamps and temporal order is limited; thus, we used surrogate data measures to best interpret care and outcomes. Third, there is the potential for subjectivity in data abstraction. However, to mitigate these risks, we incorporated abstractor training, adhered to periodic quality reviews per our center's protocol, and reconciled discrepancies with supplemental data. Finally, the ability to

extrapolate our findings to civilian trauma may be limited given that our patient population consisted predominately of young male adults who suffered from mechanisms of injury uncommon outside of military conflict. However, information derived from this study provides insight regarding the influence of altitude and related factors on the pathophysiology of the critically injured patients.

Conclusion

We found no association between the timing of compartment syndrome development and time of aeromedical transport. Further, combat casualties diagnosed with compartment syndrome who underwent aeromedical evacuation out of the combat theater to a higher level of care were not associated with worse outcomes. We can infer that aeromedical transport may not pose additional risk for the development of compartment syndrome.

References

1. Ingals N, Zonies D, Bailey JA, et al. A review of the first 10 years of critical care aeromedical transport during operation iraqi freedom and operation enduring freedom: the importance of evacuation timing. *JAMA Surg*. 2014;149(8):807–813.

2. Lairet J, King J, Vojta L, Beninati W. Short-term outcomes of US Air Force Critical Care Air Transport Team (CCATT) patients evacuated from a combat setting. *Prehosp Emerg Care*. 2013;17(4):486–490.

3. Carlton PK, Jenkins DH. The mobile patient. *Crit Care Med*. 2008;36(7 Suppl):S255–7.

4. Galvagno SM, Dubose JJ, Grissom TE, Fang R, Smith R, Bebarta VS, Shackelford S, Scalea TM. The epidemiology of Critical Care Air Transport Team operations in contemporary warfare. *Mil Med*. 2014 Jun;179(6):612-8.

5. Maddry, J. K., Mora, A. G., Savell, S. C., Perez, C. A., Mason, P. E., Aden, J. K., & Bebarta, V. S. (2018). Impact of Critical Care Air Transport Team (CCATT) ventilator management on combat mortality. Journal of Trauma and Acute Care Surgery, 84(1), 157-164.

6. US Transportation Command Regulating and Command and Control Evacuation System (TRAC2ES) Data Base. Retrieved from: https://trac2es.transport.mil/

7. Via, A. G., Oliva, F., Spoliti, M., & Maffulli, N. (2015). Acute compartment syndrome. Muscles, ligaments and tendons journal, 5(1), 18.

8. Sheridan, G. W. (1976). Fasciotomy in the treatment of the acute compartment syndrome. The Journal of bone and joint surgery. American volume, 58(1), 112-115.

9. Ritenour AE, Dorlac WC, Fang R, Woods T, Jenkins DH, Flaherty SF, Wade CE, Holcomb JB. Complications after fasciotomy revision and delayed compartment release in combat patients. *J Trauma*. 2008 Feb;64(2 Suppl):S153-61; discussion S161-2.

10. Kragh JF Jr, San Antonio J, Simmons JW, Mace JE, Stinner DJ, White CE, Fang R, Aden JK, Hsu JR, Eastridge BJ, Jenkins DH, Ritchie JD, Hardin MO, Ritenour AE, Wade CE, Blackbourne LH. Compartment syndrome performance improvement project is associated with increased combat casualty survival. *J Trauma Acute Care Surg*. 2013 Jan;74(1):259-63.

11. Wall, CJ, Lynch, J, Harris, IA, Richardson, MD, Brand, C, Lowe, AJ, Sugrue, M. Clinical practice guidelines for the management of acute limb compartment syndrome following trauma. Australian Journal of Surgery. 2010: 80,151–156.

12. Joint Theater Trauma System Clinical Practice Guideline March 2012 Compartment Syndrome (CS) and the Role of Fasciotomy in Extremity War Wounds. Retrieved from: https://www.east.org/.../a/Compartment_Syndrome_and_Fasciotomy_9_Mar_12.pdf

13. McGill R1, Jones E, Robinson B, et al Correlation of altitude and compartment pressures in porcine hind limbs. J Surg Orthop Adv. 2011 Spring;20(1):30-3.

14. Kalns J, Cox J, Baskin J, Santos A, et al Extremity compartment syndrome in pigs during hypobaric simulation of aeromedical evacuation. Aviat Space Environ Med. 2011 Feb; 82(2):87-91.

15. Ritenour AE, Christy RJ, Roe JL, Baer DG, Dubick MA, Wade CE, Holcomb JB, Walters TJ. The effect of a hypobaric, hypoxic environment on acute skeletal muscle edema after ischemia-reperfusion injury in rats. J Surg Res. 2010;160(2):253-9.

16. Spott, M. A., & Jenkins, D. H. (2015). Joint Trauma Registry. Encyclopedia of Trauma Care, 859-860.

17. Krueger, C. A., Ching, W., & Wenke, J. C. (2013). Completing records-based research within the military: a user's guide. ARMY INST OF SURGICAL RESEARCH FORT SAM HOUSTON TX.

18. Ouellette, E. A., & Kelly, R. (1996). Compartment syndromes of the hand. JBJS, 78(10), 1515-22.

19. Allen, M. J., & Barnes, M. R. (1986). Exercise pain in the lower leg. Chronic compartment syndrome and medial tibial syndrome. The Journal of bone and joint surgery. British volume, 68(5), 818-823.

20. Mars, M., & Hadley, G. P. (1998). Raised compartmental pressure in children: a basis for management. Injury, 29(3), 183-185.

21. McQueen, M. M., & Court-Brown, C. M. (1996). Compartment monitoring in tibial fractures: the pressure threshold for decompression. The Journal of Bone and Joint Surgery. British Volume, 78(1), 99-104.

22. Maddry, J. K., Arana, A. A., Perez, C. A., Medellin, K. L., Paciocco, J. A., Mora, A. G., ... & Bebarta, V. S. (2020). Influence of Time to Transport to a Higher Level Facility on the Clinical Outcomes of US Combat Casualties with TBI: A Multicenter 7-Year Study. Military Medicine, 185(1-2), e138-e145.

Acknowledgements: We thank the En route Care Research Center and the USAF 59th Medical Wing Office of Science and Technology for support during the execution of this study and preparation of this manuscript.

Conflicts of Interest Statement: We declare no conflicts of interest.

Funding Statement: This study was funded by a Congressionally Directed Medical Research Programs JPC-6 award mechanism.

Table 1. Descriptive summary of the total study population

	Total Population Mean±SD; Median [IQR] **OR** % (95% CI) n=238
Age	25±6.2; 23 [21-28]
Gender, % male	98 (96-99)
Injury Description	
ISS	16±11.5; 13 [9-18]
Max AIS of Extremity Injuries	3±0.8; 3 [2-3]
Polytrauma	91 (87-94)
Explosive Device	69 (63-74)
Gunshot Wound	18 (14-24)
Penetrating	72 (66-77)
Blunt	26 (21-32)
Burn	3 (1-5)
Compartment Syndrome	
Upper Extremity	14 (10-20)
Lower Extremity	88 (82-92)
Dx Within 24 hours	80 (74-84)
Transport	
Iraq	46 (40-53)
Afghanistan	54 (47-60)
CCATT Platform	42 (36-48)
AE Platform	58 (52-64)

Arrived to LRMC Within 2 Days	45 (39-52)

Penetrating, blunt, and burn are mutually exclusive. Unable to determine body region (upper/lower extremity) of compartment syndrome diagnosis for n=59 records. Transport platform was unknown for n=16.

ISS, injury severity score; AIS, abbreviated injury scale; Dx, diagnosis; AE, Aeromedical Evacuation platform; CCATT, Critical Care Air Transport Team; LRMC, Landstuhl Regional Medical Center; SD, standard deviation; IQR, interquartile range; CI, confidence interval

Table 2. Comparison of groups based on time of compartment syndrome diagnosis (in hours)

	1-Day mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=172	**2-Day** mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=35	**3-Day** mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=7	**4-Day** mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=2	**p-value***
Age	24.9±5.5; 23.0 [21.0-28.0]	26.1±7.8; 23.0 [20.0-30.0]	27.6±8.1; 24.0 [22.0-37.0]	22.0±1.4; 22.0 [21.0-23.0]	0.7451
Gender (% male)	99.4 (97-100); (170/172)	91.4 (77.6-97.0) (32/35)	100.0; (7/7)	100.0; (2/2)	0.0738
Injury Description					
ISS	16.8±12.1; 14.0 [9.0-20.0]	11.2±7.0; 9.0 [6.0-17.0]	8.1±4.2; 6.0 [4.0.0-13]	9.0±0.0; 9.0 [9.0-9.0]	0.0022
AIS of Extremity Injuries	2.9±0.8; 3.0 [2.0-3.0]	2.5±0.6; 2.0 [2.0-3.0]	2.5±0.5; 2.5 [2.0-3.0]	2.0±0.0; 2.0 [2.0-2.0]	0.0119
Polytrauma	92.4 (87.5-95.5)	85.7 (70.6-93.7)	71.4 (35.9-91.8)	100.0 (34.2-100.0)	0.0996
Explosive Device	73.7 (66.6-79.9); (126/171)	60.0 (43.6-74.4); (21/35)	42.9 (15.8-75.0) (3/7)	50.0 (9.5-90.5) (1/2)	0.0211
Gunshot Wounds	16.4 (11.6-22.6); (28/171)	17.1 (8.1-32.7); (6/35)	14.3 (2.6-51.3) (1/7)	0.0; (0/2)	0.7522
Penetrating	75.4 (68.5-81.3); (129/171)	60.0 (43.6-74.4); (3/7)	42.9 (25.0-84.2) (3/7)	50.0 (9.5-90.5); (1/1)	0.0371
Blunt	22.0 (16.6-29.0); (38/171)	40.0 (25.6-56.4); (14/35)	42.9 (15.8-75.0) (3/7)	50.0 (9.5-90.5); (1/2)	0.0157
Burn	2.3 (0.9-5.9) (4/171)	0.0; (0/35)	0.0; (0/7)	0.0; (0/2)	0.3546

Compartment Syndrome					
Upper Extremities	13.3 (8.4-20.2); (17/128)	10.0 (3.5-25.6); (3/30)	20.0 (3.6-62.4); (1/5)	ND	0.9424
Lower Extremities	89.1 (82.5-93.4); (114/128)	90.0 (74.4-96.5); (27/30)	80.0 (37.6-96.4); (4/5)	ND	0.7693
Time to 1st CS Dx (hours)	7.3±7.0; 4.45 [1.9-12.2]	ND	ND	ND	-
In Theater Fasciotomy (% yes)	96.0 (90.1-98.3); (120/125)	100.0 (87.1-100); (26/26)	50.0 (15.0-85.0); (2/4)	0.0; (0/2)	<0.0001
Fasciotomy (hours)	7.3±6.4; 4.3 [3.0-9.1]	ND	ND	ND	-
Transport					
Iraq	39.2 (32.2-46.7)	62.9 (46.3-76.8)	85.7 (48.7-97.4)	100.0 (34.2-100.0)	0.0002
Afghanistan	60.8 (53.3-67.8)	37.1 (23.2-53.7)	14.3 (2.6-51.3)	0	0.0002
Pre-Flight (%) or In-Theater	52.0 (44.6-59.4); (89/172)	40.0 (25.6-56.4); (14/35)	28.6 (35.9-91.8); (2/7)	50.0 (9.5-90.5); (1/2)	0.1348
Post-Flight (%) or At LRMC	47.9 (40.6-55.4); (82/172)	60.0 (43.6-74.4); (21/35)	71.4 (35.9-91.8); (5/7)	50.0 (9.5-90.5); (1/2)	0.1348
LRMC Arrival (days)	2.1±0.9; 2.0 [1.0-3.0]	2.6±0.9; 2.0 [2.0-3.0]	2.6±0.5; 3.0 [2.0-3.0]	3.0±0.0; 3.0 [3.0-3.0]	0.0054
% CCATT	48.2 (40.7-55.7); (80/172)	18.5 (8.2-36.7); (5/27)	0.0; (0/7)	0.0; (0/2)	0.0001
% AE	51.4 (44.3-59.3); (86/172)	81.5 (63.3-91.8); (22/27)	100.0 (64.6-100.0); (7/7)	100 (34.2-100.0); (2/2)	0.0001

Other					
Revision (% yes)	6.4 (3.6-11.1); (11/172)	2.9 (0.5-14.5); (1/35)	14.3 (2.6-51.3); (1/7)	0.0; (0/2)	0.8734
Additional CS Diagnoses (% yes)	3.5 (1.6-7.4); (6/172)	0.0; (0/35)	0.0; (0/7)	0.0; (0/2)	0.2560
Additional Fasciotomies (% yes)	7.8 (4.6-12.9); (13/167)	0.0; (0/33)	0.0; (0/6)	0.0; (0/2)	0.0958

*Categorical data analyzed using Cochran-Armitage trend test methodology.

CS, compartment syndrome; ISS, injury severity score; AIS, Abbreviated Injury Scale; CS Dx, compartment syndrome diagnosis; LRMC, Landstuhl Regional Medical Center; CCATT, Critical Care Air Transport Team; AE, Aeromedical Evacuation platform; SD, standard deviation; IQR, interquartile range; CI, confidence interval; tot; total; ND, no documentation available

Table 3. Comparison of groups based on whether compartment syndrome diagnosis was documented before or after aeromedical evacuation out of the theater of operations

	Pre-Flight CS mean±SD; median [IQR] or % (95% CI) n=113	**Post-Flight CS** mean±SD; median [IQR] or % (95% CI) n=123	**p-value**
Age	25±6.1; 23 [21-28]	26±6.3; 24 [21-28]	0.6260
Gender (% male)	98 (94-100)	98 (94-100)	1.0000
Injury Description			
ISS	14±10.7; 11 [6-17]	17±12.0; 14 [10-20]	0.0144
Max AIS of Extremity Injuries	2.7±0.7; 3.0 [2.0-3.0]	2.9±0.8; 3.0 [2.0-3.0]	0.0173
Polytrauma	90.3 (83.4-94.5)	92.0 (85.9-95.6)	0.6378
Explosive Device	68 (59-76)	70 (61-77)	0.7726
Gunshot Wounds	18 (12-26)	18 (12-26)	0.9138
Penetrating	72 (63-80)	71 (63-79)	0.8482
Blunt	27 (19-36)	25 (19-34)	0.7271
Burn	1 (0.2-5)	3 (1-8)	0.2170
In-Theater Interventions			
Tourniquet	38 (30-48); (43/113)	37 (29-46); (46/125)	0.8004
Direct Pressure	14 (9-22); (16/113)	12 (7-19); (15/112)	0.6027
Wound Vac	3 (1-8); (3/113)	1 (0.1-4); (1/125)	0.2543
Compartment Syndrome			

Upper Extremity	14 (7-25)	14 (10-22)	0.9121
Lower Extremity	88 (77-94)	88 (80-92)	0.9028
Dx Within 24 hours	84 (76-90)	72 (66-82)	0.9031
Dx Within 48 hours	12 (8-21)	19 (13-28)	0.9031
Time to 1st CS Dx (hours)	7.6±7.1; 4.6 [1.5-10.0]	8.0±7.4; 3.8 [2.1-15.3]	0.6496
In Theater Fasciotomy (% yes)	96 (90-99)	92 (84-96)	0.2502
Fasciotomy (hours)	7.3±6.5; 4.8 [2.6-9.1]	7.1±6.4; 4.0 [3.0-8.8]	0.8455
Transport			
Iraq	37.5 (29.1-46.7)	54.4 (45.7-62.9)	0.0090
Afghanistan	62.5 (53.3-70.9)	45.6 (37.1-54.3)	0.0090
LRMC Arrival (days)	2.4±1.1; 2 [2-3]	2.1±1.0; 2 [1-3]	0.0156
% CCATT	36 (27-45)	48 (39-57)	0.0710
% AE	64 (55-73)	52 (43-61)	0.0710
Other			
Revision	6 (3-12)	5 (2-10)	0.7769
Additional CS Diagnoses (% yes)	5 (2-11)	0	0.0104
Additional Fasciotomies (% yes)	9 (5-17)	2 (1-7)	0.0411

*Lung dysfunction; atelectasis, pulmonary edema, acute respiratory distress syndrome, pneumonia

CS, compartment syndrome; ISS, injury severity score; AIS, Abbreviated Injury Scale; CS Dx, compartment syndrome diagnosis; LRMC, Landstuhl Regional Medical Center; AE, Aeromedical Evacuation platform; SD, standard deviation; IQR, interquartile range; CI, confidence interval

Table 4. Cox proportional hazard regression model results

	Time-to-LRMC Arrival Risk Ratio (95% CI)	Time-to-CS Dx Risk Ratio (95% CI)
CS Dx Time Groups (days)	1.06 (0.96-1.16)	-
Age (years)	0.98 (0.94-1.03)	1.00 (0.96-1.04)
Male (vs. no)	0.84 (0.20-5.79)	1.55 (0.38-10.62)
Explosives-related (vs. no)	0.80 (0.43-1.5)	1.19 (0.66-2.23)
Penetrating (vs. no)	0.07 (0.0-2.35)	0.81 (0.05-25.8)
Blunt (vs. no)	0.05 (0.0-1.96)	0.73 (0.04-24.77)
ISS (score)	0.98 (0.94-1.02)	0.99 (0.96-1.03)
Max AIS of Extremity (score)	0.82 (0.55-1.23)	1.11 (0.76-1.62)
Head injury (vs. no)	**2.27 (1.26-4.11)***	0.94 (0.53-1.68)
CS of Lower Extremity (vs. no)	1.21 (0.63-2.56)	1.01 (0.52-2.14)
In-theater fasciotomy (vs. no)	1.64 (0.47-7.11)	1.91 (0.65-7.70)
In-theater tourniquet (vs. no)	1.04 (0.60-1.8)	0.96 (0.58-1.58)
In-theater crystalloids (ml)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
In-theater colloids (ml)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
In-theater blood products (num. units)	1.00 (0.98-1.01)	1.00 (0.99-1.01)
In-theater opioids (vs. no)	1.10 (0.63-1.93)	1.02 (0.63-1.66)
In-theater ketamine (vs. no)	0.86 (0.33-1.99)	0.79 (0.32-1.77)
In-theater rhabdomyolysis (vs. no)	1.11 (0.20-4.76)	1.68 (0.31-7.12)
In-theater shock (vs. no)	1.49 (0.29-5.81)	1.25 (0.25-4.61)
In-theater coagulopathy (vs. no)	1.16 (0.41-2.86)	1.28 (0.45-3.21)
Iraq (vs. Afghanistan)	1.57 (0.90-2.76)	0.88 (0.53-1.45)
CCATT transport (vs. AE)	1.66 (0.83-3.34)	1.10 (0.58-2.07)
LRMC Arrival (days)	-	0.88 (0.66-1.14)

CS, compartment syndrome; Dx, diagnosis; ISS, injury severity score; AIS, abbreviated injury scale; CCATT, Critical Care Air Transport Team; AE, Aeromedical Evacuation platform; LRMC, Landstuhl Regional Medical Center; Hr, hour; CI, confidence interval

Supplemental Table 1. Comparison of outcomes by day of compartment syndrome diagnosis groups.

	1-Day mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=172	**2-Day** mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=35	**3-Day** mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=7	**4-Day** mean±SD; median [IQR] **OR** % (95% CI); (count/tot) n=2	**p-value**
Abdominal CS	15.1 (10.5-21.2); (26/172)	14.3 (6.3-29.4); (5/35)	14.3 (2.6-51.3); (1/7)	0; (0/2)	0.6929
Infection/Sepsis	22.7 (17.0-29.5); (39/172)	17.1 (8.1-32.7); (6/35)	0; (0/7)	50.0 (9.5-90.5); (1/2)	0.4182
Coagulopathy	43.0 (35.9-50.5); (74/172)	22.9 (12.1-39.0); (8/35)	14.3 (2.6-51.3); (1/7)	50.0 (9.5-90.5); (1/2)	0.0355
Lung Dysfunction	23.8 (18.1-30.7); (41/172)	5.7 (1.6-18.6); (2/35)	0; (0/7)	0; (0/2)	0.0062
Ventilator Days	3.1±8.0; 0 [0-3]	0.8±2.0; 0 [0-1]	0±0; 0 [0-0]	0±0; 0 [0-0]	0.0233
ICU Days	6.1±9.9; 3 [0-7]	2.3±3.0; 1 [0-4]	0.6±1.0; 0 [0-2]	0±0; 0 [0-0]	0.0050
Hospital Days	25.1±29.0; 15 [5-34]	15.6±14.0; 10 [6-20]	18.4±13.9; 10 [7-29]	33.5±34.7; 34 [9-58]	0.5679
Mortality	1.2 (0.3-4.1) n=2	0; (0/35)	0; (0/7)	0; (0/2)	0.5148

*Lung dysfunction; atelectasis, pulmonary edema, acute respiratory distress syndrome, pneumonia

CS, compartment syndrome; ICU, intensive care unit; , standard deviation; IQR, interquartile range; CI, confidence interval; tot, total

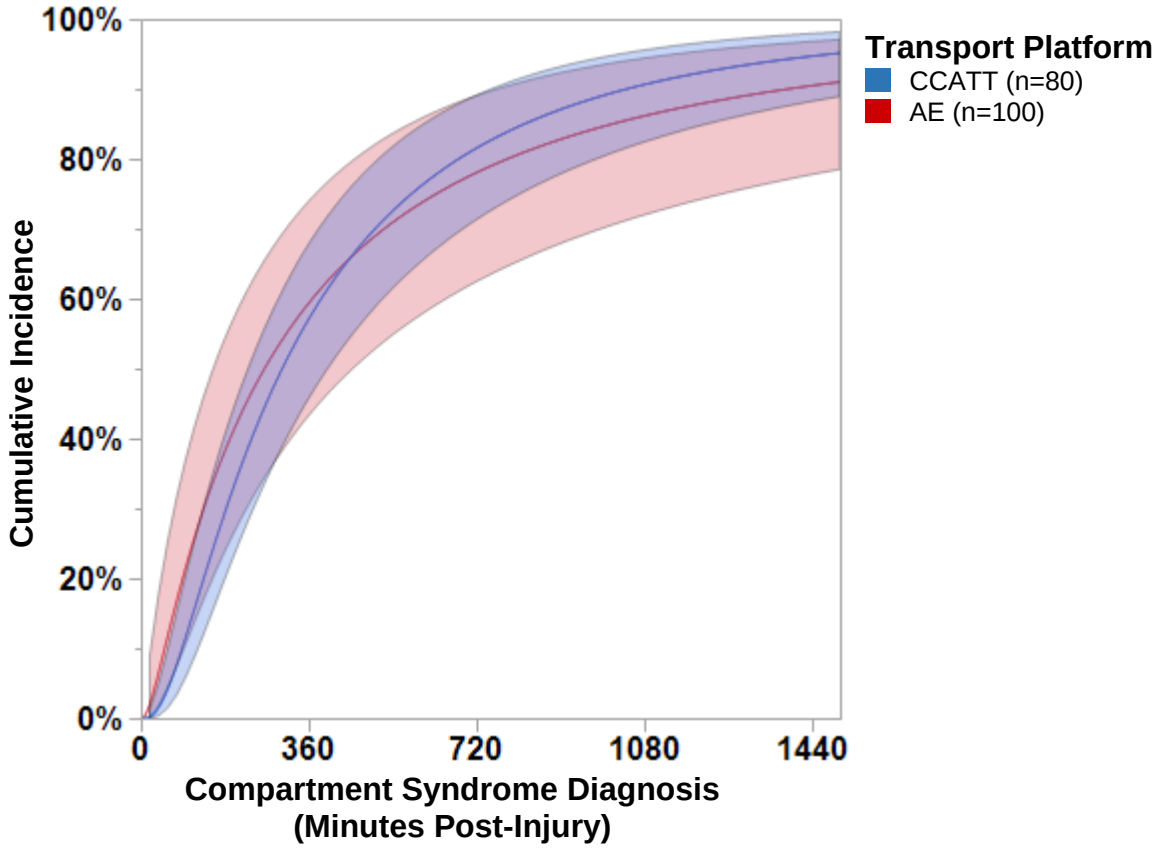
Supplemental Table 2. Comparison of outcomes (Pre-Flight versus Post-Flight groups)

	Pre-Flight CS mean±SD; median [IQR] **OR** % (95% CI) n=113	**Post-Flight CS** mean±SD; median [IQR] **OR** % (95% CI) n=125	**p-value**
Abdominal CS	14.0 (8.9-21.8)	13.6 (8.7-20.7)	0.9008
Infection/Sepsis	15.9 (10.3-23.8)	24.8 (18.0-33.0)	0.0891
Coagulopathy	39.8 (31.3-49.0)	36.8 (28.9-45.5)	0.6318
Lung Dysfunction*	20 (14.0-28.7)	20.8 (14.6-28.7)	0.9323
Ventilator Days	2.6±8.1; 0.0 [0.0-2.0]	4.5±17.6; 0.0 [0.0-3.0]	0.3174
ICU Days	4.9±9.5; 2.0 [0.0-6.0]	7.2±19.2; 3.0 [0.0-7.0]	0.6342
Hospital Days	21.7±24.1; 13.0 [6.0-29.0]	27.4±43.2; 15.0 [5.0-31.0]	0.7141
Mortality	0.9 (0.2-4.9) n=1	1.6 (0.4-5.6) n=2	1.0000

*Lung dysfunction; atelectasis, pulmonary edema, acute respiratory distress syndrome, pneumonia

CS, compartment syndrome; ICU, intensive care unit

Supplemental Figure 1. Cumulative incidence of compartment syndrome diagnosis within 24 hours post-injury by transport platform (CCATT versus AE)*



*Data limited to records with available injury and approximated compartment syndrome diagnosis timestamps along with documented transport platform
*Shaded region represents confidence interval

Figure 1: Percent of groups with compartment syndrome (CS) diagnosis based on LRMC Arrival in number of hours post-injury

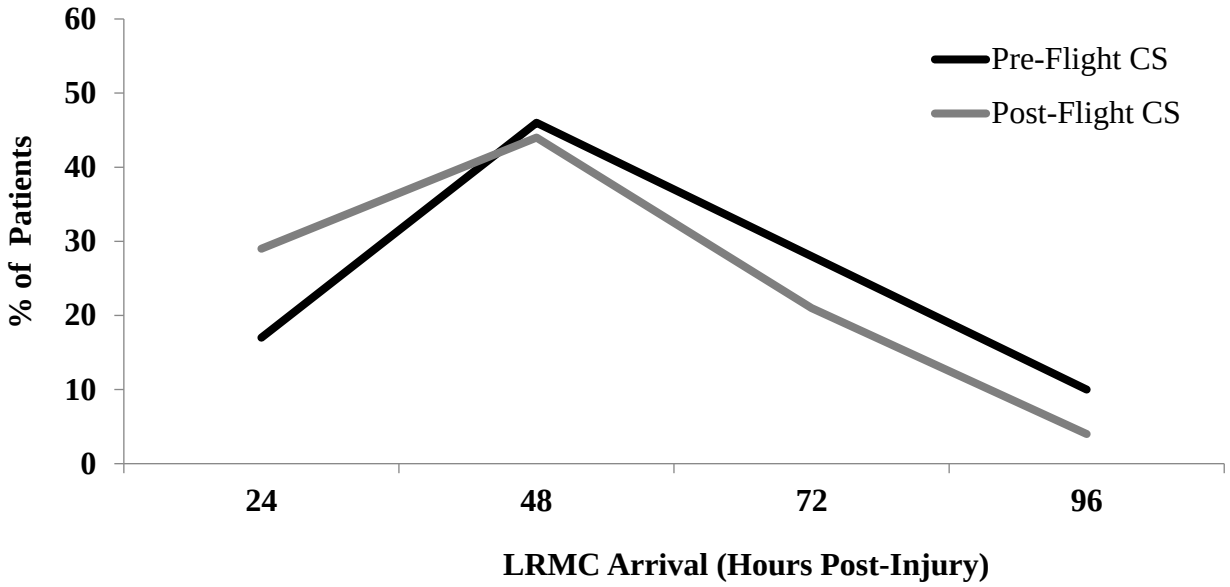
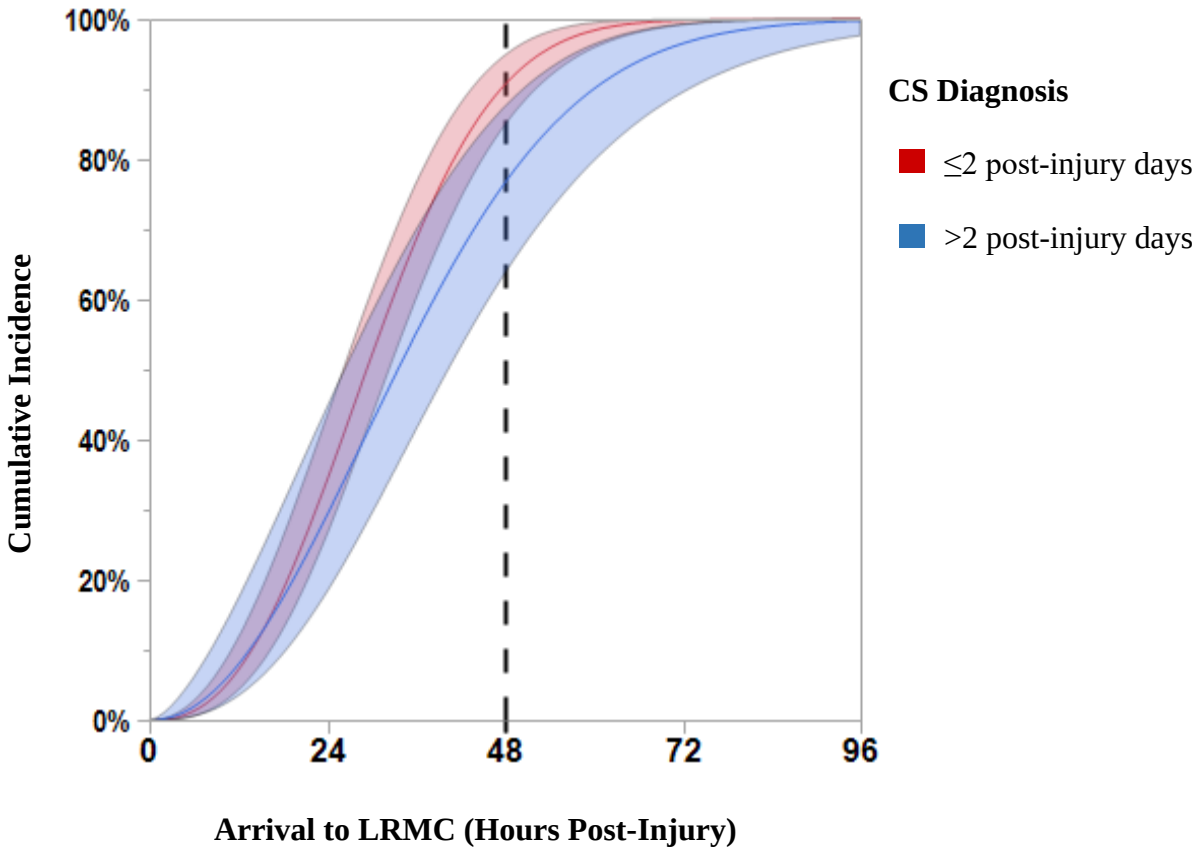


Figure 2 Cumulative incidence of compartment diagnosis following arrival to LRMC (Post-Flight only)



CS, compartment syndrome
*Shaded region represents confidence interval