

# Trauma and nontrauma damage-control laparotomy: The difference is delirium (data from the Eastern Association for the Surgery of Trauma SLEEP-TIME multicenter trial)

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<b>BACKGROUND:</b>	Damage-control laparotomy (DCL) has been used for traumatic and nontraumatic indications. We studied factors associated with delirium and outcome in this population.
<b>METHODS:</b>	We reviewed DCL patients at 15 centers for 2 years, including demographics, Charlson Comorbidity Index (CCI), diagnosis, operations, and outcomes. We compared 30-day mortality; renal failure requiring dialysis; number of takebacks; hospital, ventilator, and intensive care unit (ICU) days; and delirium-free and coma-free proportion of the first 30 ICU days (DF/CF-ICU-30) between trauma (T) and nontrauma (NT) patients. We performed linear regression for DF/CF-ICU-30, including age, sex, CCI, achievement of primary fascial closure (PFC), small and large bowel resection, bowel discontinuity, abdominal vascular procedures, and trauma as covariates. We performed one-way analysis of variance for DF/CF-ICU-30 against traumatic brain injury severity as measured by Abbreviated Injury Scale for the head.
<b>RESULTS:</b>	Among 554 DCL patients (25.8% NT), NT patients were older ( $58.9 \pm 15.8$ vs. $39.7 \pm 17.0$ years, $p < 0.001$ ), more female (45.5% vs. 22.1%, $p < 0.001$ ), and had higher CCI ( $4.7 \pm 3.3$ vs. $1.1 \pm 2.2$ , $p < 0.001$ ). The number of takebacks ( $1.7 \pm 2.6$ vs. $1.5 \pm 1.2$ ), time to first takeback (32.0 hours), duration of bowel discontinuity (47.0 hours), and time to PFC were similar (63.2 hours, achieved in 73.5%). Nontrauma and T patients had similar ventilator, ICU, and hospital days and mortality (31.0% NT, 29.8% T). Nontrauma patients had higher rates of renal failure requiring dialysis (36.6% vs. 14.1%, $p < 0.001$ ) and postoperative abdominal sepsis (40.1% vs. 17.1%, $p < 0.001$ ). Trauma and NT patients had similar number of hours of sedative ( $89.9$ vs. $65.5$ hours, $p = 0.064$ ) and opioid infusions ( $106.9$ vs. $96.7$ hours, $p = 0.514$ ), but T had lower DF/CF-ICU-30 (51.1% vs. 73.7%, $p = 0.029$ ), indicating more delirium. Linear regression analysis indicated that T was associated with a 32.1% decrease (95% CI, 14.6%–49.5%; $p < 0.001$ ) in DF/CF-ICU-30, while achieving PFC was associated with a 25.1% increase (95% CI, 10.2%–40.1%; $p = 0.001$ ) in DF/CF-ICU-30. Increasing Abbreviated Injury Scale for the head was associated with decreased DF/CF-ICU-30 by analysis of variance ( $p < 0.001$ ).
<b>CONCLUSION:</b>	Nontrauma patients had higher incidence of postoperative abdominal sepsis and need for dialysis, while T was independently associated with increased delirium, perhaps because of traumatic brain injury. ( <i>J Trauma Acute Care Surg.</i> 2021;91: 100–107. Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.)
<b>LEVEL OF EVIDENCE:</b>	Therapeutic study, level IV.
<b>KEY WORDS:</b>	Trauma; damage-control laparotomy; sedation; delirium; nontrauma.

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**D**amage-control laparotomy (DCL) is a well-established practice initially developed to treat critically ill trauma (T) patients with major vascular injuries coupled with major bowel injuries or the *lethal triad* of hypothermia, coagulopathy, and acidosis.<sup>1–3</sup> The DCL technique includes performing an abbreviated laparotomy aimed at controlling acute hemorrhage and limiting peritoneal contamination. A temporary abdominal closure is performed, and the patient is then transferred to an intensive care unit (ICU), allowing time for resuscitation and correction of their acidosis, coagulopathy, and hypothermia, before returning to the operating room for definitive surgical intervention.<sup>4,5</sup> Gradually, surgeons have begun to implement DCL principles to critically ill emergency general surgery patients. Acute mesenteric ischemia, postoperative peritonitis, and bowel perforation are just a few of the diagnoses resulting in the use of DCL in recent literature.

Using DCL has been associated with improving outcomes and decreasing mortality in critically injured T patients.<sup>2,4</sup> However, there are several complications associated with the DCL technique, including enterocutaneous fistula (ECF) and intra-abdominal sepsis (IAS). The risks of these complications increase if primary fascial closure (PFC) is not promptly achieved within approximately 7 days.<sup>6,7</sup> Failure to achieve PFC is associated with increased complications and longer hospital stays. Prior studies have demonstrated an association between the number of reexplorations and successfully achieving PFC, and that increasing time to initial takeback is negatively associated with achieving PFC. To minimize complications, greater emphasis should be placed on returning to the operating room as early as possible, ideally within 24 hours.<sup>8</sup>

Older studies previously supported the use of diuretic administration, deep sedation, and chemical paralysis to achieve PFC more quickly<sup>9–12</sup>; however, recent literature has failed to support these interventions.<sup>13,14</sup> An increased incidence of delirium in critical patients is associated with the use of deep sedation. Delirium is associated with increased overall mortality and prolonged cognitive dysfunction; therefore, management of sedation is essential to prevent delirium and improve outcomes.<sup>15–23</sup>

Although there are an increasing number of studies related to the use of DCL in nontrauma (NT) patients, studies addressing how patient demographics and outcomes differ between T and NT patients are not well described.<sup>24–31</sup> Evaluation of the demographics, comorbidities, and indications associated with nontrauma DCL is imperative to improve outcomes and complications of patients. To further evaluate the differences between T and NT patients undergoing DCL, the authors reviewed retrospective data from 15 centers for a 2-year period as part of the Eastern Association for the Surgery of Trauma multicenter trial entitled “Sedation Level after Emergency Explap with Packing—TIME to Primary Fascial Closure (SLEEP-TIME).” This was a preplanned analysis of the T and NT cohorts focusing on the endpoints of mortality and delirium. The respective populations were described with respect to demographics, comorbidities, injuries and diagnoses, operative procedures, and ICU and surgical outcomes. We hypothesized that mortality and delirium would both be elevated in the NT cohort because of differences in age and baseline comorbidities.

## PATIENTS AND METHODS

### Inclusion and Exclusion Criteria

We reviewed retrospective data from 15 centers in the Eastern Association for the Surgery of Trauma SLEEP-TIME trial, from January 1, 2017, to December 31, 2018. This study was evaluated by the institutional review board (IRB) at the Loma Linda University Medical Center and judged to be exempt from IRB review. We included all adults undergoing DCL regardless of diagnosis. Patients younger than 18 years, pregnant women, prisoners, and patients who died before the first takeback operation were excluded.

### Data Collection and Analysis

Each center coordinated with the primary site in obtaining appropriate local IRB approvals and in signing standard data use agreements. After the completion of these initial tasks, each center uploaded deidentified patient data to an a priori created database in REDCap (developed at Vanderbilt University, Nashville, TN). These data included age, sex, Injury Severity Score and Abbreviated Injury Scale for the head (AIS-head) for T patients, Acute Physiology and Chronic Health Evaluation II score for NT patients, Charlson Comorbidity Index (CCI), Glasgow Coma Scale, diagnosis, operative interventions performed, and outcomes including mortality and ICU delirium as recorded by analysis of the Richmond Agitation and Sedation Score and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scores.<sup>32–37</sup> Exposure to opioid infusions and sedative infusions, including propofol, dexmedetomidine, and benzodiazepines, was tabulated for each patient.

The primary endpoints were mortality and delirium-free and coma-free proportion of the first 30 ICU days (DF/CF-ICU-30), which is defined as the number of ICU days out of the first 30 ICU days during which the Richmond Agitation Sedation Score was at least  $-3$  and the CAM-ICU score was negative divided by the total number of ICU days for each patient and converted to a percentage. The intent of this measure is to serve as a surrogate marker of freedom from delirium, calculated in a manner that avoids bias from varying lengths of ICU stay. Furthermore, our measure was censored at 30 days to account for the fact that, for the purposes of our study, it was only feasible to collect ICU data for the first 30 days of the patient’s ICU stay. Standard parametric statistics, such as Student’s *t* test and  $\chi^2$  analysis, were used for statistical analysis. In addition, we performed a linear regression analysis with DF/CF-ICU-30 as the endpoint and including age, sex, CCI, achievement of PFC, small and large bowel resection, bowel discontinuity, abdominal vascular procedure, and trauma as covariates. Finally, we performed a specific subset analysis of the relationship between AIS-head and DF/CF-ICU-30 in T patients using one-way analysis of variance. Data were imported from RedCap into SPSS version 25.0 (IBM Inc., Armonk NY).

## RESULTS

### Demographics and Diagnoses

A total of 143 NT patients and 411 T patients underwent DCL in the 2-year period. Demographic data are shown in Table 1. The NT cohort was older (mean age,  $58.9 \pm 15.8$  years

**TABLE 1.** Patient Demographics

	T, Mean ± SD or n (%)	NT, Mean ± SD or n (%)	p
Age, y	39.3 ± 17.0	58.9 ± 15.8	<0.001
Male	320/411 (77.9)	78/143 (54.5)	<0.001
CCI	1.2 ± 2.2	4.7 ± 3.3	<0.001
ISS	27.6 ± 14.7		
AIS-head			
0	248/402 (61.7)		
1	19/402 (4.73)		
2	33/402 (8.21)		
3	41/402 (10.2)		
4	30/402 (7.46)		
5	30/402 (7.46)		
6	1/402 (0.249)		
GCS	10.4 ± 5.2	11.0 ± 4.4	0.508
APACHE II		17.9 ± 8.5	

APACHE II, Acute Physiology and Chronic Health Evaluation Score; GCS, Glasgow Coma Scale; ISS, Injury Severity Score.

vs. 39.3 ± 17.01 years;  $p < 0.001$ ) and more likely to be female (45.5% vs. 22.1%,  $p < 0.001$ ) compared with the T cohort. Nontrauma patients also had a higher CCI (mean value, 4.7 ± 3.3 vs. 1.2 ± 2.2,  $p < 0.001$ ). Glasgow Coma Scale was not statistically significant between the two groups.

Figure 1 demonstrates the diverse diagnoses for the NT cohort. Bowel ischemia (28.1%), end-stage liver disease (13.7%),

and bowel perforation (12.2%) were the three most common diagnoses in the NT cohort. The penetrating trauma rate was 48.8%. As expected, procedures performed and indications for these operations were vastly different between NT and T cohorts (Fig. 2).

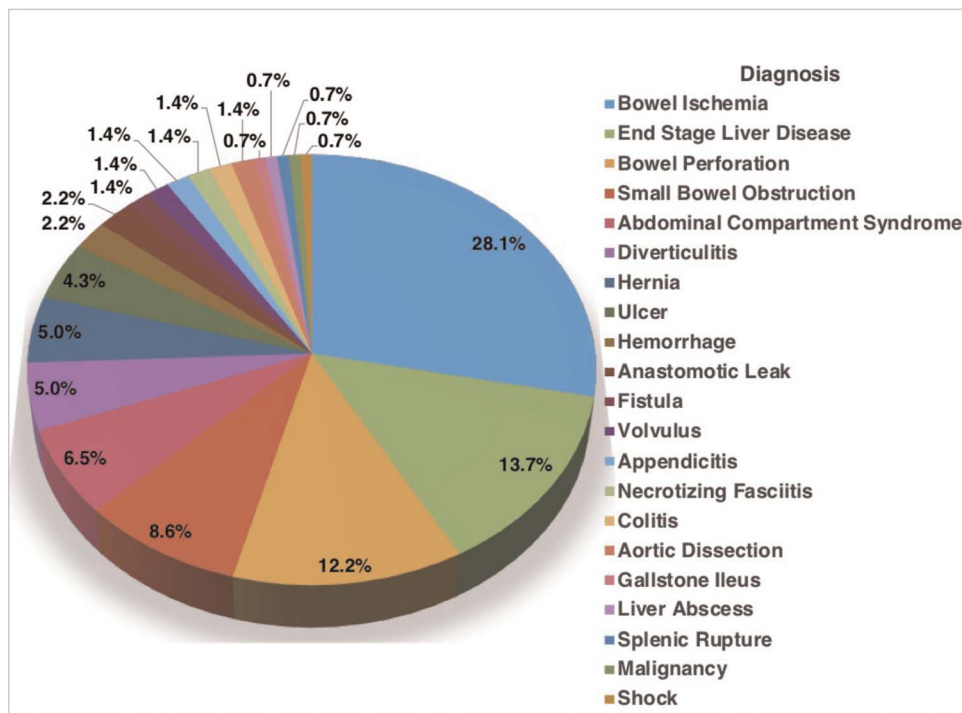
### Outcomes and Complications

Complications and surgical outcomes are shown in Table 2. The number of takebacks, time to first takeback, duration of bowel discontinuity, unplanned return to the operating room, and time to PFC were not statistically different between the two groups. Rate of evisceration (2.1% vs. 2.0%,  $p = 0.908$ ), dehiscence (4.9% vs. 5.1%  $p = 0.924$ ), ECF (1.4% vs. 0%,  $p = 0.016$ ), and pneumonia (27.1% vs. 24%,  $p = 0.460$ ) was similar between NT and T cohorts. The NT cohort had a higher incidence of postoperative abdominal sepsis (40.1% vs. 17.1%,  $p < 0.001$ ) and need for dialysis (36.6% vs. 14.1%,  $p < 0.001$ ).

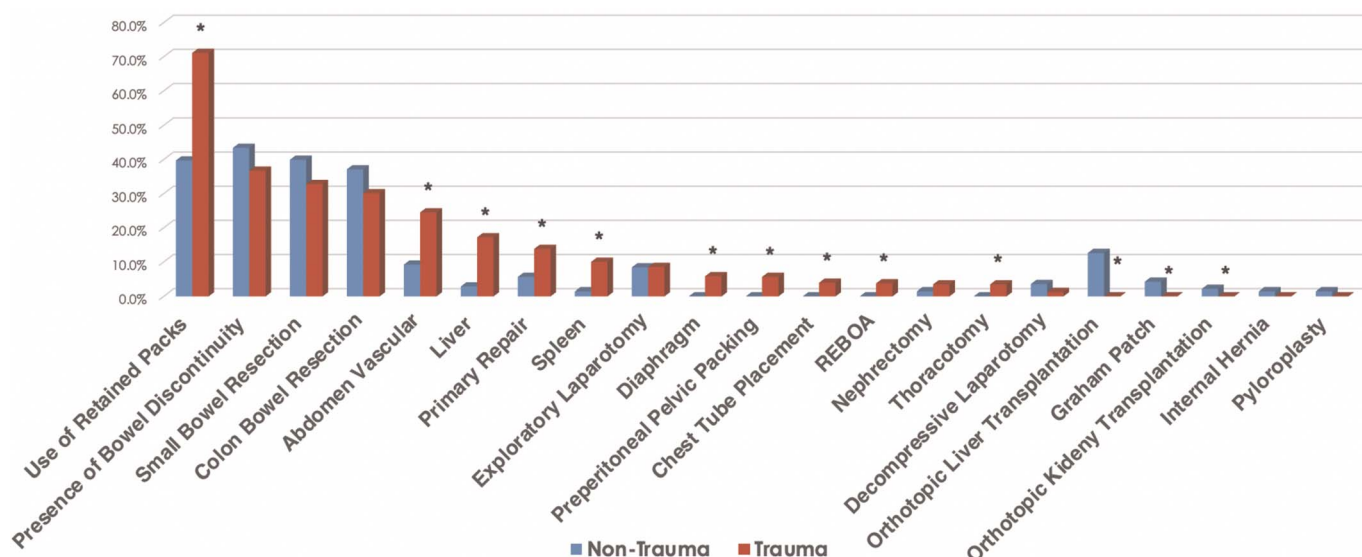
Table 3 presents ICU and hospital outcomes. Ventilator (9.4 ± 11.6 vs. 7.9 ± 9.6), ICU (13.2 ± 13.9 vs. 10.8 ± 12), and hospital days (28.0 ± 27.0 vs. 23.0 ± 34.7) were similar for both groups. Discharge disposition was also similar between both groups. Mortality was similar between both cohorts (31.0% vs. 29.8%).

### Critical Care Management

The T cohort had more hours of sedative infusion (89.9 vs. 65.5 hours,  $p < 0.064$ ) and slightly higher opioid infusion use (106.9 vs. 96.7 hours,  $p < 0.514$ ); however, these differences were not statically significant. Trauma patients had a statically significant lower proportion of DF/CF-ICU-30 days with a



**Figure 1.** Most common diagnoses requiring DCL for NT patients include bowel ischemia (28.1%), end-stage liver disease (13.7%), bowel perforation (12.2%), small bowel obstruction (8.6%), abdominal compartment syndrome (6.5%), diverticulitis (5.0%), and hernia (5.0%).



**Figure 2.** Operative procedures performed for NT (blue, left bar) and T (red, right bar) patients. Procedures that were performed at statistically significant rates between groups are marked with an asterisk.

mean of 51.1% versus NT patients with a mean of 73.7% ( $p = 0.029$ ).

### Linear Regression Analysis

Linear regression analysis indicated that achievement of PFC was associated with an increase of 25.1% (95% CI, 10.2–40.1%;  $p = 0.001$ ) in the DF/CF-ICU-30, correlating with a reduced incidence of delirium. Trauma was associated with a decrease of 32.1% (95% CI, 14.6–49.5%;  $p < 0.001$ ) in the DF/CF-ICU-30, correlating with an increased incidence of delirium. Age, sex, CCI, the presence of small or large bowel resection, the presence of bowel discontinuity, or the performance of a vascular procedure did not have a significant effect on DF/CF-ICU-30 (Table 4).

### One-Way Analysis of Variance for AIS-Head and DF/CF-ICU-30

We performed a one-way analysis of variance to determine the relationship between AIS-head and DF/CF-ICU-30.

The results of the analysis are graphically displayed in Figure 3. The analysis of variance yielded a highly statistically significant result with  $p < 0.001$ . Of note, there is a sharp decrease in DF/CF-ICU-30 between the patients with AIS-head score of 3 to 5 as compared with those with AIS-head score of 0 to 2, and the patients with AIS-head score of 3 to 5 have a mean DF/CF-ICU-30 of less than 20%.

## DISCUSSION

Since the introduction of DCL in trauma management, the concept has been accepted as a standard for treating patients with intra-abdominal emergencies. There is a growing number of NT patients undergoing DCL; however, the level of evidence supporting the use of DCL in a nontrauma setting is still evolving. The most important findings of this retrospective multicenter study are that mortality and discharge disposition were similar between the NT and T cohorts and that the NT cohort had a significantly higher incidence of postoperative abdominal sepsis and need for dialysis.

**TABLE 2.** Postoperative Outcomes

	T, Mean ± SD or n (%)	NT, Mean ± SD or n (%)	<i>p</i>
No. takebacks	1.7 ± 2.6	1.5 ± 1.2	0.088
Time to first takeback, h	31.5 ± 29.2	33.6 ± 18.6	0.354
Duration of bowel discontinuity	46.7 ± 39.6	43.8 ± 22.2	0.537
Time to PFC, h	58.3 ± 69.8	66.5 ± 80.8	0.326
PFC achieved	284/402 (70.6)	108/137 (78.8)	0.451
Unplanned return to OR	104/408 (25.5)	35/142 (24.6)	0.842
Evisceration	8/409 (2.0)	3/142 (2.1)	0.908
Dehiscence	21/409 (5.1)	7/142 (4.9)	0.924
Abdominal sepsis	69/403 (17.1)	57/142 (40.1)	<0.001
ECF	0/412 (0)	2/143 (1.4)	0.016
Pneumonia	98/408 (24.0)	38/140 (27.1)	0.460
Dialysis	58/412 (14.1)	52/142 (36.6)	<0.001

OR, operating room.

**TABLE 3.** Outcomes

	T, Mean ± SD or n (%)	NT, Mean ± SD or n (%)	Significance
Mortality	122/409 (29.8)	44/142 (31.0)	0.796
Total ventilator days	7.9 ± 9.6	9.4 ± 11.6	0.157
Total ICU days	10.8 ± 12.3	13.2 ± 13.9	0.069
Total hospital days	23.0 ± 34.7	28.0 ± 27.0	0.076
DF/CF-ICU-30, %	51.0 ± 38.8	73.7 ± 96.4	0.0292
Sedative infusions, h	89.9 ± 154.9	65.5 ± 81.1	0.064
Opioid infusions, h	106.9 ± 166.8	96.7 ± 112.4	0.514
Discharge disposition			0.203
Home	152/412 (36.9)	51/142 (35.9)	
Skilled nursing facility	29/412 (7.0)	15/142 (10.6)	
Inpatient rehab hospital	60/412 (14.6)	15/142 (10.6)	
Long-term acute care facility	26/412 (6.3)	14/142 (9.9)	

Another important finding was that, although the T cohort had similar exposure to sedation, they had a statistically significant lower proportion of DF/CF-ICU-30 days. Finally, multivariate linear regression verified that traumatic injury was associated with a lower proportion of DF/CF-ICU-30 days, while achieving PFC was associated with an increased proportion of DF/CF-ICU-30 days, after adjusting for age, sex, comorbidities, surgical interventions performed, and presence of bowel discontinuity.

Shock in the T patient population is often hemorrhagic, compared with the NT population where it is often due to sepsis. This could explain why the NT cohort in our study had a significantly higher rate of postoperative abdominal sepsis. The lethal triad (hypothermia, acidosis, and coagulopathy) is used to guide management decisions in the T patient population, yet this is not always applicable in NT patients. Becher et al.<sup>38</sup> conducted a study examining 53 NT patients who underwent DCL. The study concluded that different acute physiologic indicators should be used to guide operative decisions in NT patients. Advanced age, acidosis, severe coagulopathy, elevated lactate (>3), and multiple comorbidities (>3) have been associated with increased mortality and may be better criteria for application of DCL in the NT population.<sup>38,39</sup> More data need to be conducted to examine the use of DCL in NT patient populations, but our data indicate that they are at elevated risk of postoperative renal failure requiring dialysis and postoperative abdominal sepsis, but not delirium or mortality. In addition, the importance of achieving PFC was emphasized by

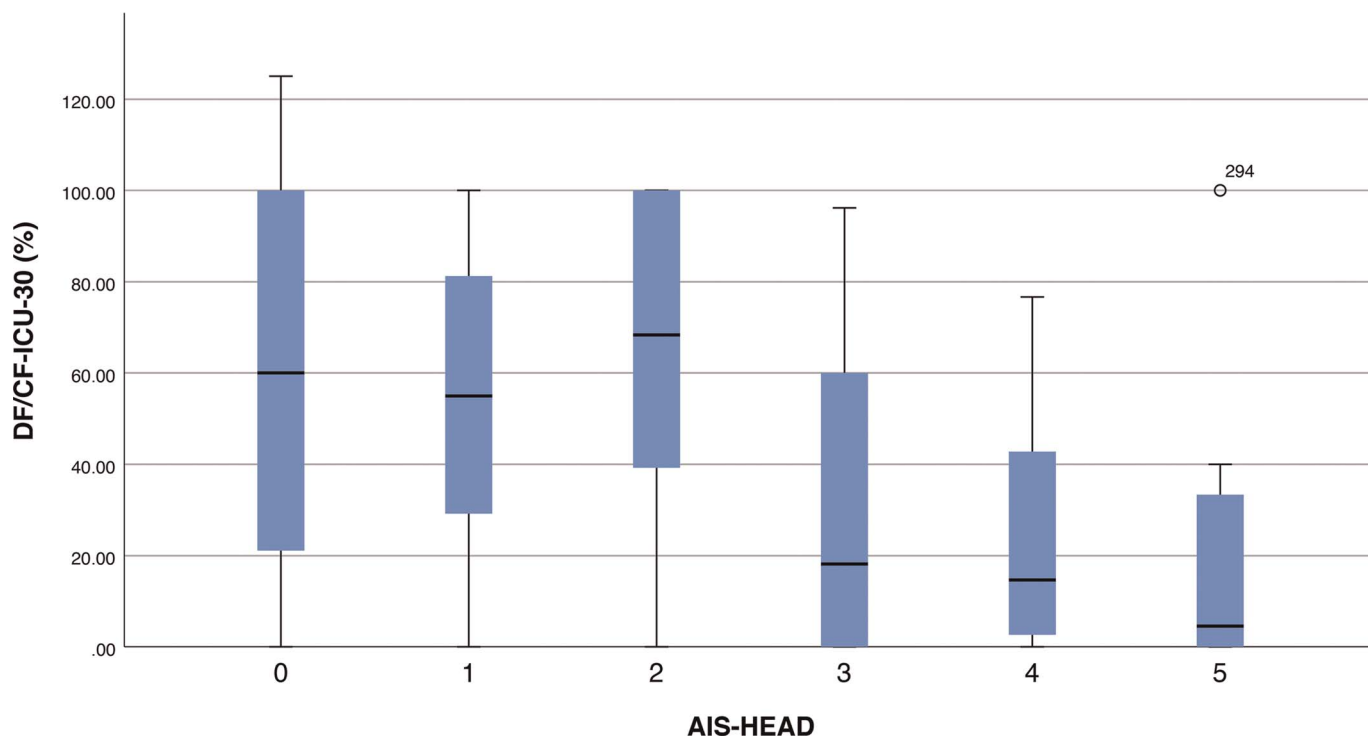
indicating that it is associated with reduced delirium, in addition to the other benefits as indicated in the existing literature.<sup>6,7</sup>

Previous research has validated the use of the American College of Surgeons National Surgical Quality Improvement Program surgical risk calculator to estimate the probability of an unfavorable outcome after surgery. Increased age and number of comorbidities are both factors that should increase the likelihood of unfavorable outcomes.<sup>40,41</sup> Our study demonstrates that there is a significant difference in the demographics between NT and T patients who undergo DCL. However, except for the increased incidence of sepsis and need for dialysis, we did not find a significant difference in outcomes between the two cohorts, despite the NT being comprised of significantly older patients with more comorbidities. The mortality rate for the NT cohort was high (31.0%); however, this was similar to the T cohort (29.8%) and to be expected in a population of critically ill patients. Both cohorts also had similar discharge dispositions. Traditionally, surgeons have counseled older patients to expect to be discharged to facilities such as inpatient acute rehabilitation hospitals or nursing homes; however, this study questions this practice. Additional research on discharge disposition of the elderly DCL patients could improve quality of patient care.

Enterocutaneous fistula and IAS are a few potential complications surgeons face as they care for patients with an open abdomen. Enterocutaneous fistulas are associated with increased morbidity and mortality, as they can lead to many complications including fluid loss, electrolyte abnormalities, complex wound care issues, malnutrition, and increased ICU and hospital length of stay. Large bowel resection, large-volume fluid resuscitation, and increased number of reexplorations have previously been demonstrated as significant predictors of ECF, enteroatmospheric fistula, or IAS in patients who underwent a DCL.<sup>7</sup> Achieving PFC is important to prevent major complications, such as intra-abdominal abscess, ECF, respiratory failure, sepsis, and renal failure.<sup>42</sup> Literature has shown the impact of timing of abdominal closure after DCL on outcomes in T patients. A study of 247 T patients who underwent DCL, conducted by Hatch et al.,<sup>43</sup> demonstrated that fascial closure at first take back is associated with significantly fewer pulmonary complications, postoperative complications, infectious complications, and non-infectious complications. In our study, there was not a significant difference in the time to achieve PFC or in the percent of

**TABLE 4.** Linear Regression Analysis for Proportion of DF/CF-ICU-30

Factor	Coefficient (95% CI)	p
Age	-0.388 (-0.824 to 0.048)	0.081
Male	4.38 (-10.3 to 19.1)	0.558
CCI	-0.176 (-2.78 to 2.43)	0.894
PFC	25.1 (10.2-40.1)	0.001
Small bowel resection	5.49 (-11.7 to 22.7)	0.530
Large bowel resection	-4.42 (-22.8 to 14.0)	0.637
Bowel discontinuity	-3.33 (-24.7 to 18.0)	0.759
Abdominal vascular procedure	10.1 (-6.86 to 27.1)	0.241
Traumatic injury	-32.1 (-49.5 to -14.6)	<0.001



**Figure 3.** The proportion of DF/CF-ICU-30 is stratified by AIS-head. There is a marked decrease in DF/CF-ICU-30 for patients with AIS-head score of 3 to 5 as compared with AIS-head score of 0 to 2. One-way ANOVA for these variables yielded a highly significant result ( $p < 0.001$ ). ANOVA, analysis of variance.

patients PFC was achieved between the two cohorts. However, the NT cohort had a higher incidence of postoperative abdominal sepsis and need for dialysis compared with the T cohort. A multicenter study done by Bradley et al.<sup>7</sup> found that large bowel resection, large-volume fluid resuscitation, and increasing number of abdominal reexplorations were statistically significant predictors of IAS in patients who underwent DCL.

Bowel ischemia is one of the most common indications for a DCL in our NT cohort. Freeman and Graham<sup>27</sup> conducted a retrospective study of 20 patients who present with acute mesenteric ischemia. They found that patients with bowel ischemia could benefit from undergoing a DCL procedure; however, because of their small sample size, more research needed to be conducted. Brilliantino et al.<sup>44</sup> reviewed 30 patients who underwent a DCL procedure for peritonitis as a result of a bowel perforation and concluded that DCL could be a feasible strategy for managing patients with a bowel perforation. Studies examining the use of DCL for bowel obstruction and abdominal compartment syndrome are insufficient. Our study indicates that NT patients with bowel ischemia or bowel perforations could be treated with a DCL procedure without major complications.

The most important outcome difference revealed between the T and NT cohorts was the higher incidence of delirium in the T cohort. Delirium associated with critical illness is a common complication in this patient population and has been implicated in increased mortality.<sup>16</sup> Furthermore, we demonstrated validity to the observation that delirium was more frequent in the T cohort by conducting a multivariate linear regression that validated the results from the standard statistics. A single-center review of delirium in T patients after DCL indicated a very high incidence of

delirium in this population, as well as revealing a negative association between the duration of sedation infusion exposure and the proportion of delirium-free/coma-free ICU days.<sup>45</sup> It is interesting to see, therefore, that the incidence of delirium in the T cohort is even higher than in the NT cohort, despite the T cohort being younger and the mortality and ICU utilization being similar. One key factor unique to the T cohort is traumatic brain injury. Although this factor could not be studied across cohorts, we were able to reveal a significant association between increasing AIS-head and decreasing DF/CF-ICU-30 in our analysis of variance analysis. This indicates that traumatic brain injury, particularly in severe cases, may play a role in the higher incidence of delirium and coma in the T cohort.

This study has potential limitations. First, our study is a retrospective study and there were data points missing in some patients. We did not use imputation, although this could be a potential solution. Several centers did not record CAM-ICU scores, reducing our sample size when examining delirium and thus introducing the possibility of selection bias. We did not collect data on the critical care management practices at each institution, including the level of implementation of the ABCDEF Bundle as advocated by the Society of Critical Care Medicine. We also did not collect toxicology data, and use of intoxicants could be a confounder associated with delirium. One center conducted a higher than average number of liver transplants using DCL techniques. Another potential limitation is that the primary diagnoses for the NT and T group were different at baseline, potentially contributing to bias.

In conclusion, despite the NT cohort being older with more comorbidities, they had similar mortality rate and discharge

disposition to the T cohort. The NT cohort had a higher incidence of postoperative abdominal sepsis and need for dialysis. The T cohort had a higher incidence of delirium, including in multivariate analysis. In both cohorts, achieving PFC is shown to reduce the frequency of delirium.

#### AUTHORSHIP

K. McArthur contributed in the data collection, analysis of data, generation of figures, and writing of the article and is the presenting author. C.K., E.K., and X.L.-O. contributed in the data collection, analysis of data, and critical review of the article. M.C.-Y., L.S., S.B., D.T., C.K., A.G., J. Nahmias, A.B., A.G., A.L., M.K., M.N.F., N.G., S.T., E.L., S.R.L., O.D.G., J.M.B., C.D., S.M.W., K.L., N.T.D., J. Nunez, S.M., J.P., L.N., H. Kaafarani, H. Kemmer, M.J.L., A.D., G.C., and Z.N. contributed in the critical editing of article and approval of final article. K. Mukherjee is the principal investigator and contributed in the statistical analysis, editing, and detailed revision of the article.

#### DISCLOSURE

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