Does Splenectomy Protect Against Immune-Mediated Complications in Blunt Trauma Patients?

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Activation of the innate immune system results from severe trauma and the resultant systemic inflammatory response is thought to mediate remote organ injury. In animal models, vagal-mediated innate immune responses have been shown to modulate proinflammatory cytokine release in response to trauma or sepsis. In those models, vagal nerve transaction and splenectomy decreased cytokine release and protected against lung injury and mortality. We hypothesized that, if similar mechanisms are active in humans, patients who require splenectomy for trauma would have better outcomes than injured patients without splenectomy. We performed a retrospective cohort study on 46,858 patients who sustained blunt liver or spleen injury utilizing the 2002 National Trauma Data Bank (NTDB). Blunt trauma patients who underwent splenectomy were compared with all patients with splenic injuries. Demographic parameters and the following outcome variables were compared: mortality, hospital length of stay (LOS), ICU length of stay (ILOS), mean ventilator days (VENT), and incidence of acute respiratory distress syndrome (ARDS). Groups were compared controlling for age, gender, injury severity score (ISS), emergency department (ED) blood pressure, and ED base deficit (BD) using multiple regression analyses. Patients that underwent splenectomy had significantly shorter LOS than patients who were managed nonoperatively or with splenorrhaphy: LOS,15.1 versus 19.3 d, $P = 0.002$; ILOS, 7.8 versus 10.6 d, $P < 0.001$; and VENT, 7.1 versus 11.4 d, $P < 0.001$. Adjusted mortality rates (OR 1.02; 95% CI 0.98–1.05; $P = 0.29$) and the reported incidence of ARDS were not significantly different between the two groups (2.4% versus 3.6%; $P = 0.213$). Patients who underwent splenectomy demonstrated better secondary outcomes than patients who were managed nonoperatively or with splenorrhaphy, even when controlling for injury severity and physiologic derangements. It is possible that the improved outcomes seen in the group undergoing splenectomy were due to favorable modulation of the human innate immune inflammatory response after trauma.
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INTRODUCTION

The Center for Disease Control and Prevention (CDC) estimates that there are over 8 million nonfatal injuries caused by blunt trauma each year in the United States (1). Blunt abdominal trauma is a major source of morbidity and mortality and solid organs are particularly vulnerable to injury by virtue of their size and vascularity. The spleen is injured in up to 40% of blunt abdominal trauma. Severe splenic injury results in hemorrhagic shock and may lead to exsanguination because the spleen receives 5% of the cardiac output in adults, primarily via the splenic artery (2). However, the hemodynamically stable patient with blunt splenic injury does not absolutely require splenectomy. The experience with nonoperative management initially began in children and arose out of concern for development of overwhelming postsplenectomy sepsis (OPSS) from encapsulated organisms (3). Nonoperative management of splenic injuries in adults has reported success rates ranging from 68% to 83% in the largest series, and is now well-established as the mainstay of treatment in hemodynamically stable patients (4,5,6). The liver is injured in up to 30% of blunt abdominal trauma, but less commonly requires operation for hemostasis, with up to 80% of injuries now successfully managed nonoperatively (7).

Despite the increasing success of nonoperative management of blunt solid organ injuries, exploratory laparotomy with splenectomy or hepatorrhaphy is still the mainstay of care for the hemodynamically unstable patient with evidence of hemoperitoneum (8). This may lead to unanticipated immunologic consequences in addition to the known, delayed risk of OPSS (9), given the spleen's increasingly evident role in immune modulation.

Splenic macrophages are a source of tumor necrosis factor (TNF) in response to an inflammatory stimulus (10). Con-

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centration of TNF in the spleen is much higher than lung or liver concentrations after administration of lipopolysaccharide (LPS) in a rat model (11). Vagal nerve stimulation was found to attenuate this response to levels similar to nonstimulated controls (11). Recent animal models have helped to clarify the central, role of vagal-mediated, cholinergic modulation of the TNF response to sepsis (12). This pathway has been localized in mice to a local, α7-nicotinic acetylcholine receptor subunit on macrophages sequestered in the spleen during the onset of infection and sepsis (8,13). Splenectomy inactivates the cholinergic antiinflammatory pathway during endotoxemia and sepsis, and has been shown to decrease lethality of a septic insult in a murine model (14). If similar mechanisms are active in humans, patients who required emergent splenectomy for trauma may have very different spectra of inflammation-mediated morbidity than similarly injured patients without splenectomy. We hypothesized that splenectomy may lead to unanticipated immunologic effects in addition to the delayed risk of OPSS given the increasingly evident role of the spleen in immune modulation.

MATERIALS AND METHODS

We performed a retrospective cohort study utilizing the National Trauma Data Bank (NTDB 2002, American College of Surgeons, Chicago, IL, USA). The NTDB is a multi-state database of trauma hospitalizations in the United States. This version contains approximately 450,000 records from 131 voluntarily contributing trauma centers. All data submitted to NTDB are de-identified and subjected to quality control using both the quality filters of the National Trauma Registry of the American College of Surgeons and a logical checks system set into place by the NTDB administrators. Permission was granted from the American College of Surgeons to query the data and Institutional Review Board approval was obtained at the home institution.

We identified a total of 46,858 blunt trauma patients reported to the NTDB who sustained either spleen or liver injuries. Of these, 28,002 individuals suffered blunt splenic injuries (59.8%) during the study period and 18,856 patients suffered hepatic injuries (40.2%). To determine the effects of operative intervention after blunt trauma on each specific solid organ, blunt trauma patients with expectantly managed splenic injuries were compared with the subset of patients who underwent splenectomy, and all patients with hepatic injuries were compared with the subset of patients undergoing hepatorrhaphy. In an effort to determine whether there were any immunogenic differences associated with operative intervention between these two solid organs after blunt trauma, we also compared the operative patients who underwent splenectomy to patients requiring hepatorrhaphy. The data set did not include any patients who underwent both splenectomy and hepatorrhaphy.

We limited the study population to patients who underwent their procedure within 12 h of injury to eliminate possible confounding effects from failure of nonoperative management, differences in perceived hemodynamic stability upon presentation, ongoing slow hemorrhage, and different transfusion practices.

Demographic parameters and the following outcome variables were compared: mortality, hospital length of stay (LOS), ICU length of stay (ILOS), ventilator d (VENT), and the incidence of acute respiratory distress syndrome (ARDS). Duration of VENT was tabulated only for patients who were ventilated mechanically at some time during the hospitalization. Mean and standard deviations were calculated and reported for these parameters.

Critical fields used for data analysis were ICD-9 injury codes (spleen 865.00–865.19, liver 864.00–864.19) and ICD-9-CM procedure codes (splenectomy 41.5, splenorrhaphy 41.43, liver laceration repair 50.61, other hepatic repair 50.69). Stata statistical software (College Station, TX, USA) was used to perform bivariate tabulated and subsequent multiple linear and logistic regression analyses with robust standard errors controlling for age, gender, Injury Severity Score (ISS), emergency department (ED) blood pressure, and ED base deficit (BD).

RESULTS

We identified a total of 46,858 blunt trauma patients reported to the NTDB who sustained either spleen or liver injuries. Of these, 28,002 (59.8%) individuals suffered blunt splenic injury during the study period and 1,987 (7.1% of this subgroup) underwent splenectomy. Splenorrhaphy was performed in 48 patients (0.2% of this subgroup). Hepatic injury occurred in 18,856 patients (40.2% of total), with 578 (3.1%) undergoing laceration repair and 109 (0.6%) having some other type of hepatic repair. Operative intervention to control hemorrhage was more frequently needed in patients with splenic injuries than hepatic injuries (7.3% versus 3.6%; $P < 0.05$).

We performed bivariate analysis comparing splenic injury categories and hepatic injury categories individually and then with each other (Tables 1A, 1B). We found that the patients who underwent liver repair had a worse mean BD (–6.3 versus –5.0; $P < 0.05$) and slightly higher mean ISS (31.9 versus 30.2; $P < 0.05$) than patients who underwent splenectomy. Patients with splenic injuries overall also were more likely to be male than patients with hepatic injuries (66% versus 59%; $P < 0.05$). Patients who underwent splenorrhaphy had a lower ISS, and higher first ED systolic blood pressure (SBP), revised trauma score (RTS), and Glasgow Coma Score (GCS) than the rest of the injured spleen group ($P < 0.05$). No other within- or between-group demographic comparisons were statistically significant including age, first ED SBP, ED temperature (ED Temp), GCS, RTS, race, or payment source. Not surprisingly, unadjusted mortality was lower for patients with splenic injury that did not require splenectomy. However, we found that splenectomy survivors had shorter LOS, ILOS, and VENT (Table 2).

Multivariate linear regression analysis showed that patients undergoing splenec-

Table 1A. Summary demographics of 2002 NTDB patients with blunt splenic or liver injury.[a]

	Nonoperative Splenic Injuries (n = 25,967)	Splenectomy (n = 1,987)	Splenorrhaphy (n = 48)	Nonoperative Liver Injuries (n = 18,169)	Liver Laceration Repair (n = 578)	Other Liver Repair (n = 109)
Mean age ± SD[d]	34 ± 17.7	36.1 ± 18.1[b]	30 ± 19.2[c]	34.5 ± 18.1	35.5 ± 16.1[b]	31.2 ± 15.6[b]
Gender						
Female	8907 (34%)	677 (34%)[b]	20 (42%)[c]	7,505 (41%)	249 (43%)[b]	54 (49%)[c]
Male	17,048 (66%)	1,310 (66%)[b]	28 (58%)[c]	10,650 (59%)	329 (57%)[b]	55 (51%)[c]
Race						
API[e]	157 (0.6%)	7 (0.4%)[b]	0[b]	160 (0.9%)	5 (0.9%)[b]	2 (2%)[b]
Black	3,693 (14.3%)	235 (12%)[b]	6 (13%)[b]	4,329 (24.1%)	121 (21%)[b]	19 (18%)[c]
Latino	1,762 (6.8%)	107 (5.5%)[b]	3 (6%)[b]	1,310 (7.3%)	47 (8%)[b]	9 (8.4%)[b]
Native	98 (0.4%)	8 (0.4%)[b]	1 (2%)[#]	32 (0.2%)	5 (0.9%)[b]	0[b]
Other	332 (1.2%)	24 (1.2%)[b]	0[b]	214 (1.2%)	9 (1.6%)[b]	1 (0.9%)[b]
White	19,472 (75%)	1,570 (80%)[b]	37 (79%)[b]	11,860 (66.2%)	383 (67%)[b]	76 (71%)[b]
Payment source						
Private	12,269 (47.2%)	891 (44.8%)[b]	25 (52%)[b]	7,037 (38.7%)	242 (41.9%)[b]	46 (42.2%)[b]
Medicare	4,710 (18.1%)	373 (18.8%)[b]	6 (12.5%)[c]	3,585 (19.7%)	114 (19.7%)[b]	24 (22%)[b]
Self[f]	3,774 (14.5%)	360 (18.1%)[b]	4 (8.3%)[c]	2,793 (15.4%)	100 (17.3%)[b]	26 (23.8%)
Work[g]	951 (3.7%)	56 (0.5%)[c]	1 (2.1%)[b]	481 (2.6%)	9 (1.6%)[b]	4 (3.7%)[b]

[a]Data expressed as number and % of total for injury type unless otherwise specified. Percentages may not tally 100% owing to missing values in the data set.
[b]*P* = not significant versus nonoperative splenic management.
[c]*P* < 0.05 versus liver injury management.
[d]SD: standard deviation.
[e]API: Asian Pacific Islander.
[f]Self: self-pay.
[g]Work: workers compensation.

Table 1B. Injury severity, physiologic markers, and social history demographics of 2002 NTDB patients with blunt splenic or liver injury.[a]

	Nonoperative Splenic Injuries (n = 25,967)	Splenectomy (n = 1,987)	Splenorrhaphy (n = 48)	Nonoperative Liver Injuries (n = 18,169)	Liver Laceration Repair (n = 578)	Other Liver Repair (n = 109)
ISS[b]	29.2 ± 13.8	30.2 ± 14.6[c]	21.9 ± 12.2[d]	27.3 ± 13.8	31.9 ± 15[d]	31.4 ± 14.2[d]
ED[e] RTS[f]	5.9 ± 2.8	6.1 ± 2.8[c]	7 ± 2.1[d]	5.9 ± 2.9	5.5 ± 3.1[c]	5.2 ± 3.2[d]
ED SBP[g]	117 ± 32	114 ± 31.2[c]	121 ± 22[d]	118 ± 33.2	108 ± 34.8[c]	108 ± 36[d]
ED Temp[h]	35.6 ± 3.7	35.6 ± 3.7[c]	35.8 ± 1.1[c]	35.7 ± 3.6	35.3 ± 3.4[c]	35.9 ± 1.3[c]
ED BD[i]	−5.2 ± 6	−5 ± 7.6[c]	−5.9 ± 5.1[c]	−5.1 ± 6.9	−6.3 ± 8.5[d]	−6.6 ± 8.2[d]
ED GCS[j]	11.2 ± 4.9	11.5 ± 4.9[c]	13.5 ± 3.5[d]	11.3 ± 4.9	10.7 ± 5[c]	10.3 ± 5.1[c]
Alcohol use (number, % of total)						
No	9,938 (64%)	640 (63%)[c]	6 (55%)[c]	6,515 (57%)	164 (56%)[c]	43 (60%)[c]
Yes	5,513 (36%)	373 (37%)[c]	5 (45%)[c]	4,824 (43%)	128 (44%)[c]	29 (40%)[c]
Drug use (number, % of total)						
No	9,644 (68%)	746 (74%)[c]	14 (82%)[c]	7,051 (67%)	231 (76%)[c]	44 (65%)[c]
Yes	4,651 (32%)	265 (26%)[c]	3 (18%)[c]	3,479 (33%)	71 (24%)[c]	24 (35%)[c]

[a]Data expressed as number ± SD of total for injury type unless otherwise specified. Percentages may not tally 100% owing to missing values in the data set.
[b]ISS: injury severity score.
[c]*P* = not significant versus nonoperative splenic management.
[d]*P* < 0.05 versus liver injury management.
[e]ED: emergency department.
[f]RTS: revised trauma score.
[g]SBP: systolic blood pressure.
[h]Temp: temperature.
[i]BD: base deficit.
[j]GCS: Glasgow Coma Score.

Table 2. Unadjusted Outcomes of 2002 NTDB patients with blunt splenic or liver injury.[a]

	Nonoperative Splenic Injuries (n = 25,967)	Splenectomy (n = 1,987)	Splenorrhaphy (n = 48)	Nonoperative Liver Injuries (n = 18,169)	Liver Laceration Repair (n = 578)	Other Liver Repair (n = 109)
Mortality (N, % total)	3,922 (15%)	385 (19%)[b]	2 (4%)[c]	2,870 (16%)	179 (31%)[c]	29 (27%)[c]
LOS[d]	19.3 ± 20	15.1 ± 17.4[c]	13.7 ± 13.6[c]	17.9 ± 20.3	18 ± 19.2[b]	17.5 ± 16.6[b]
ICU[e] Days	10.6 ± 14.9	7.8 ± 12.6[c]	6.5 ± 10[c]	9.4 ± 15.4	10.1 ± 13.5[b]	9.9 ± 12.7[b]
VENT[f]	11.4 ± 39.6	7.1 ± 12.6[c]	11.3 ± 19.3[b]	11.7 ± 44)	14.3 ± 54.6[c]	5.7 ± 7.2[c]
ARDS[g] (N, % total)	545 (2%)	43 (2.1%)[b]	0	378 (2.1%)	18 (3.1%)[b]	7 (6.4%)[b]

[a]Data expressed as number ± SD (standard deviation) of total for injury type unless otherwise specified. Percentages may not tally 100% owing to missing values in the data set.
[b]P = not significant versus nonoperative splenic management.
[c]$P < 0.05$ versus liver injury management.
[d]LOS: length of stay.
[e]ICU: intensive care unit.
[f]VENT: mechanical ventilation days.
[g]ARDS: acute respiratory distress syndrome.

tomy had significantly better secondary outcomes than the overall population of all patients with splenic injuries ($P < 0.05$ for LOS, ILOS, and VENT). Mortality, however, was not impacted when controlling for injury severity (OR 1.02; 95% CI 0.98–1.05; $P = 0.29$). Patients who underwent hepatorrhaphy did not demonstrate any significant differences for either mortality or the secondary outcomes from the overall group of patients with liver injuries. The reported incidence of ARDS was very low overall and was not significantly different between any of the groups when controlling for severity of illness.

In multivariate models, patients who underwent splenectomy had a lower overall mortality (OR 0.73; 95% CI 0.54–0.89; $P < 0.001$) than patients who underwent hepatorrhaphy. Furthermore, despite similar overall injury severity, patients that had splenectomy were found to have better secondary outcomes than patients undergoing hepatorrhaphy. Multiple linear regression showed that splenectomized patients had significantly shorter LOS (15.1 versus 18.0 d; $P = 0.002$), ILOS (7.8 versus 10.1 d; $P < 0.001$), and VENT (7.1 versus 14.3 d; $P < 0.001$).

DISCUSSION

In an attempt to determine whether the spleen had a major role in an acute 'inflammatory reflex' after traumatic injury, we tried to take advantage of the 'natural experiment' arising out of routine care of intra-abdominal injuries reported to the NTDB. Using a large retrospective cohort, we found no statistically significant difference in mortality for patients with splenic injury who underwent splenectomy compared with patients with splenic injuries managed nonoperatively or with splenorrhaphy. Our findings are consistent with the widespread acceptance of the safety and efficacy of nonoperative management of splenic injuries (4,15). However, our surprising finding was that patients who underwent splenectomy had significantly shorter hospital LOS, VENT, and ICU days than the splenorrhaphy or nonoperatively-managed groups, even when controlling for injury severity and patient demographics. It is possible that splenectomy after trauma may decrease TNF production and may ameliorate acute inflammation via modulation of the innate immune response after trauma. Although this interpretation of the data supports our hypothesis, the scope of this study and the nature of the data available from the NTDB did not permit us to assess for alteration in immune modulation.

There are several limitations to this study. First, these data are derived from a clinical database not generated specifically for this type of analysis. This study relies on medical records coding to assign diagnoses, demographics, and outcomes. Hence, systematic errors in diagnostic coding might result in misleading data interpretation and conclusions. However, this particular database has been used reliably for other trauma research (16,17,18,19), and is the largest database of its kind available for analysis. There are several methodologic concerns that are specific to this data set including heterogeneity of the contributing institutions and geographic variations in trauma practice patterns. Contributors to the data set include rural and urban centers, as well as teaching and nonteaching centers. This concern has been addressed in a recent study by Nathens *et al*. that examined variation among trauma centers using the NTDB. They found that the parameters we included, such as ISS, age, and SBP, accounted for most of the variation between trauma center mortality rates, irrespective of trauma center level designation or hospital teaching status (20).

A second limitation is that the management of blunt splenic and hepatic injuries continues to evolve and our data query involved information from 2002. Detailed information on transfusions, transfusion protocols, and angioembolization are not available from this data set. No information is available from the database regarding ICU or ventilator management, nor is it possible to obtain any direct information about intra-operative findings. The low incidence of ARDS reported to the NTDB in our sample is somewhat surprising, given the very high ISS in the study population.

This version of the NTDB also did not record complete information about other manifestations of posttraumatic MODS, such as acute renal failure, nosocomial infections, or need for vasopressors, so the impact of splenectomy on any of these potentially immune-mediated outcomes could not be assessed. The overall severity of injury is reflected in the fact that LOS and ILOS were quite prolonged in all patient cohorts (operative versus nonoperative and spleen injury versus liver injury). This finding also supports the hypothesis that the traumatic insult elicited a significant and prolonged proinflammatory innate immune response.

A small subset of patients reported to the NTDB underwent splenorrhaphy and information for these patients is included. It is noteworthy that the subset of patients undergoing operative splenic intervention had short LOS and ILOS, although they had an intact spleen. Although this might seem to contradict our hypothesis, this subgroup was also younger (30 versus 36.1), had a lower ISS (21.9 versus 31.2), and a higher ED systolic blood pressure (121 versus 114).

The innate immune system is essential for protection against lethal infections. Endotoxin and other pathogens stimulate the production of proinflammatory cytokines, including TNF (21). Through mechanisms which help localize and contain invasive organisms, TNF is essential for host defenses (22,23). However, the magnitude of the inflammatory response appears to be a critical factor determining outcome. Unmodulated inflammation can lead not only to autoimmune disorders like Crohn's Disease (24) or rheumatoid arthritis (25), but also can cause the extensive tissue damage and hemodynamic compromise associated with traumatic injury (26). Examples of clinically significant morbidities that may be meditated by excessive proinflammatory cytokines include septic shock and ARDS (27,28,29).

In summary, we found that patients who underwent splenectomy had a lower mortality, a shorter duration of pulmonary failure (decreased VENT), and shorter ILOS and LOS than similarly injured patients. Further studies need to be done, particularly with tissue and biologic samples posttrauma and post-splenectomy, measuring cytokine levels, and correlating results with outcomes to better ascertain the immunomodulatory role of the spleen in posttraumatic pro- and antiinflammatory pathways.

DISCLOSURES

We declare that the authors have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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