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Temporal trends of postinjury multiple-organ failure: Still resource intensive, morbid, and lethal

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Abstract

BACKGROUND—While the incidence of postinjury multiple-organ failure (MOF) has declined during the past decade, temporal trends of its morbidity, mortality, presentation patterns, and health care resources use have been inconsistent. The purpose of this study was to describe the evolving epidemiology of postinjury MOF from 2003 to 2010 in multiple trauma centers sharing standard treatment protocols.

METHODS—“Inflammation and Host Response to Injury Collaborative Program” institutions that enrolled more than 20 eligible patients per biennial during the 2003 to 2010 study period were included. The patients were aged 16 years to 90 years, sustained blunt torso trauma with hemorrhagic shock (systolic blood pressure < 90 mm Hg, base deficit ≥ 6 mEq/L, blood transfusion within the first 12 hours), but without severe head injury (motor Glasgow Coma Scale [GCS] score < 4). MOF temporal trends (Denver MOF score > 3) were adjusted for admission risk factors (age, sex, body mass index, Injury Severity Score [ISS], systolic blood pressure, and base deficit) using survival analysis.

RESULTS—A total of 1,643 patients from four institutions were evaluated. MOF incidence decreased over time (from 17% in 2003–2004 to 9.8% in 2009–2010). MOF-related death rate (33% in 2003–2004 to 36% in 2009–2010), intensive care unit stay, and mechanical ventilation

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AUTHORSHIP

All authors contributed to the study design, data interpretation, manuscript writing, and critical revisions. A.S. conducted the analysis.

DISCLOSURE

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duration did not change over the study period. Adjustment for admission risk factors confirmed the crude trends. MOF patients required much longer ventilation and intensive care unit stay, compared with non-MOF patients. Most of the MOF-related deaths occurred within 2 days of the MOF diagnosis. Lung and cardiac dysfunctions became less frequent (57.6% to 50.8%, 20.9% to 12.5%, respectively), but kidney and liver failure rates did not change (10.1% to 12.5%, 15.2% to 14.1%).

CONCLUSION—Postinjury MOF remains a resource-intensive, morbid, and lethal condition. Lung injury is an enduring challenge and should be a research priority. The lack of outcome improvements suggests that reversing MOF is difficult and prevention is still the best strategy.

LEVEL OF EVIDENCE—Epidemiologic study, level III.

Keywords

Injury; injury death; multiple organ failure; organ failure mortality; adult respiratory distress syndrome

Since the descriptions by Baue¹ and Eiseman et al.² in the 1970s, multiple-organ failure (MOF) has been a major cause of morbidity and late mortality after injury. Studies have shown a steady decline in the incidence of MOF during the past decade, likely owing to new therapeutic approaches.³ Conversely, reports on temporal trends of MOF-related morbidity, mortality, presentation patterns, and health care resources use have been inconsistent.^{4–9} After an initial decrease since MOF was first described, reports of MOF-related death in the last two decades have shown a wide variation from 13% to 33%.^{4–6,9,10} Morbidity and health care use by MOF patients, albeit also variable, have been high in most of these studies.^{4,6–8,11}

Further progress in reducing MOF and, more importantly, improving its prognosis requires a comprehensive assessment of its evolving epidemiology. The purpose of this study was to describe the recent trends in postinjury MOF using a contemporary, longitudinal, prospective study of multiple trauma centers sharing standard operating procedures (SOPs).¹² Our hypotheses were the following: (1) the incidence of postinjury MOF has decreased and (2) rates of MOF-related morbidity and death have not changed significantly.

PATIENTS AND METHODS

We studied injured patients prospectively enrolled in The Inflammation and Host Response to Injury Glue Grant study (IHRI-Glue Grant) study between 2003 and 2010, which was approved by the institutional review board of each institution. SOPs were implemented by participating institutions, minimizing intervention heterogeneity.¹² Specifically, SOPs included trauma resuscitation, mechanical ventilation (including guidelines for ventilator discontinuation), ventilator-associated pneumonia, insulin infusion, nutrition, and venous thromboembolism. Inclusion criteria were the following: age of 16 years to 90 years, emergency department (ED) arrival less than 6 hours after injury, blunt torso trauma and hemorrhagic shock (ED base deficit [BD] $\geq$ 6 mEq/L or ED systolic blood pressure [SBP] $<$ 90 mm Hg and a blood product transfusion within the first 12 hours of ED arrival) with fully/partially intact cervical spinal cord. Severe traumatic brain injury (TBI) was added as

an exclusion criterion in 2005, but the entire data set was reviewed, and all admissions with severe TBI (head Abbreviated Injury Scale [AIS] score ≥ 4 and motor component of the Glasgow Coma Scale [GCS] score < 4) were removed.

All patients were followed for 28 days after injury, with no loss to follow-up. We excluded five (of nine) institutions that enrolled less than 20 eligible patients per biennial during the 2003 to 2010 study period (Supplemental Digital Content 1, SDC1, Figure 1, <http://links.lww.com/TA/A363>). The 2003 to 2010 period was subdivided in biennials to minimize annual fluctuations due to small numbers.

Variables

Outcome variables included MOF, defined using the Denver MOF score greater than 3,¹³ as well as MOF-related death, intensive care unit (ICU), and mechanical ventilation (MV) time. We report “MOF-related death” (death of any cause in MOF patients) and “MOF as a primary cause of death,” two concepts that are subtly different; the former is a relatively unbiased statistic, while the latter may carry some subjectivity. MOF as a primary cause of death was assigned by the attending physician at each institution. ICU-free days and ventilator-free days were calculated as proposed by Schoenfeld and Bernard.¹⁴ Individual organ failures were defined as a Denver score of 1 or greater. In brief, the Denver MOF score grades the dysfunction of lungs, heart, liver, and kidneys daily from 0 to 3. MOF is defined as the sum of simultaneously obtained scores at any day 48 hours after injury being greater than 3. An additional analysis was conducted using MOF defined as a Marshall multiple organ dysfunction score of 6 or greater, excluding the neurologic component, for two or more consecutive days.¹⁵

The temporal trends of MOF incidence and related death were adjusted for admission risk factors as follows: age, sex, body mass index [BMI], Charlson comorbidity index (CCI, SDC3, <http://links.lww.com/TA/A365>), Injury Severity Score (ISS), SBP, and BD.¹⁴ Risk-adjusted expected (E) MOF incidence and related death was compared with observed (O) rates to produce O/E ratios. Confidence intervals (CIs) for the O/E ratios were calculated based on the Byar’s approximation of the exact Poisson distribution.¹⁶ We also evaluated fluids and blood component transfusion during early resuscitation as well as septic and nonseptic complications, as defined elsewhere.¹⁷

Missing data rate for covariates was negligible ($< 3\%$, SDC2, <http://links.lww.com/TA/A364>). MOF score calculation used the last value carried forward method, or if no previous value, the dysfunction was coded as zero.¹⁸ The last value carried forward method was appropriate because most daily score variables were not missing and there was an expected nonrandomness and high predictability of missing values.¹⁹

Cost Evaluation

Dasta et al.²⁰ projected the average daily cost of postinjury critical care as one ICU day for \$5,973 without MV or \$10,299 with MV, two ICU days for \$3,275 without MV or \$4,887 with MV, and three or more ICU days for \$3,059 without MV per day or \$3,876 with MV per day. These national averages were used to estimate the costs associated with providing care for critically injured patients with MOF and without MOF.

Analyses

Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Significance for unadjusted comparisons was set at 0.01 to account for the large number of comparisons and at 0.05 for the adjusted analyses. All tests were two tailed. Data were presented as median (interquartile range [IQR] or frequency (percentages). Associations were tested using the nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and the χ^2 test for categorical variables. Trends were tested with the Cochran-Armitage Trend test (CAT test) for categorical variables and the nonparametric Spearman's correlation test for continuous variables.

Kaplan-Meier curves were produced to examine temporal trends (patients who died without developing MOF before 28 days were censored at the day of death, patients discharged before Day 28 were assigned a survival of 28 days). Inequality over strata was assessed using the log-rank (sensitive to later differences) and the Wilcoxon tests (sensitive to early differences).

Temporal trends were adjusted for the admission risk factors using Cox proportional hazards models. Pertinent interactions between the risk factors were tested, but none were significant. Proportionality assumption violations were assessed by testing interactions between the event-time variable and the covariate. When significant, the interactions were kept in the model.

Although the cluster by institution estimated via a mixed linear model was small (intraclass correlation coefficient, 0.012), we opted for a model with the robust sandwich estimate proposed by Lin²¹ to account for clustering.

This article followed the STROBE reporting standard for cohort studies²² and the *Journal's* Discussion framework.²³

RESULTS

We studied 1,643 patients enrolled by four centers from 2003 to 2010, of whom 252 (15%) died. MOF developed in 223 patients (13.6%), of whom 81 (36%) died. Table 1 details the distribution of admission risk factors, fluids, transfusions, complications, outcomes, as well as MOF incidence and MOF-related outcomes across the biennial periods (statistics of the 2003–2010 population in SDC2, Table 1, <http://links.lww.com/TA/A364>). Median BMI increased across time, while admission BD, admission lactate, Day 1 platelet count, and 12-hour PaO₂/FIO₂ ratio improved. Blood transfusions remained stable, while 12-hour crystalloid volume decreased. We observed no changes in the frequency of nonseptic complications, surgical site infections, and ventilator-associated pneumonia overall and within the subgroup of MOF patients.

MOF Incidence, Morbidity, and Related Death Over Time

MOF crude incidence decreased over time (Table 1, $p = 0.0033$), while MOF-related mortality, ventilator-free days, and ICU-free days remained stable at high levels (Table 1). The Kaplan-Meier analysis confirmed these findings (Fig. 1). Applying the Marshall score–

based definition produced similar results, that is, a significant decline in MOF incidence and no change in MOF mortality over time (SDC1, Figure 2 and 3, <http://links.lww.com/TA/A363>).

The Cox proportional hazards (Cox PH) model demonstrated that the MOF significant downward trend from 2003 to 2010 was independent of included admission risk factors ($p < 0.0001$, SDC2, Table 2, <http://links.lww.com/TA/A364>). The adjusted MOF risk decreased by 16% in each period of 2 years for an estimated 50% decrease during the entire study period. The Cox PH models for MOF-related death did not detect changes over time (SDC2, Table 2, <http://links.lww.com/TA/A364>, $p = 0.6907$). Similar results were observed for ICU stay and ventilation days, adjusted for the same admission risk factors (Cox PH $p = 0.6387$ and $p = 0.1676$, respectively). Inclusion of crystalloids and blood component transfusions in the first 12 hours did not significantly alter the Cox PH models results (SDC2, Table 2, <http://links.lww.com/TA/A364>).

In addition to the temporal trends, advanced age, male sex, BMI, ISS, and admission BD were significantly associated with higher risk for MOF. MOF death was positively associated with female sex and ISS (SDC2, Table 2, <http://links.lww.com/TA/A364>).

Individual Organ Failures

Lung failure was the most common organ failure (OF) across time (Table 1). Kaplan-Meier analysis suggested that dysfunction of the cardiac and pulmonary systems became significantly less frequent while renal and liver failures persisted at similar levels (Fig. 2). Cox PH models adjusting for the admission risk factors confirmed these results (SDC2, Table 4, <http://links.lww.com/TA/A364>). The adjusted risks for lung and cardiac failures fell by 8% and 15% per biennial and by 29% and 49% for the entire study period.

MOF Onset

MOF onset retained a multimodal distribution, with the highest peak within the first 3 days after injury and smaller peaks afterward (Fig. 3A). Approximately half of MOF cases occurred within 3 days (Fig. 3B). The onset of individual OF varied little over the biennials. Median onset day for lung, cardiac, renal, and liver failures were as follows: Day 2 (IQR, 2–3), Day 2 (IQR, 2–4.5), Day 3 (IQR, 2–9), and Day 6 (IQR, 4–9).

MOF-Related Death

The time interval between MOF onset and death also followed a multimodal distribution (Fig. 4A) (median [IQR] by biennial: 2003 to 2004, 2 days [1–6 days]; 2005 to 2006, 2 days [1–8 days]; 2007 to 2008, 1.5 days [0.5–5 days]; 2009 to 2010, 1 day [0–5 days], Spearman's test $p = 0.3153$). More than half of the deaths following MOF (58%) occurred within 2 days of the diagnosis and 80% within a week of MOF onset.

Early MOF (within 3 days after injury) carried a mortality higher than that of later MOF (Figs. 3B and 4B). In the biennial 2009 to 2010, 50% of the early MOF patients died compared with 40% of those with MOF onset between 4 days and 7 days and none of those with late MOF.

Attributed Causes of Death

MOF was assigned as the primary cause of death in 34 fatalities (9%) and as the secondary cause of death in 15 other deaths (6%), which were attributed primarily to sepsis ($n = 5$), cardiac dysfunction ($n = 4$), brain death ($n = 2$), and other causes ($n = 3$).

Among MOF nonsurvivors, OF was listed as the primary cause of death in 44% of the cases (35.8% MOF, 4.9% cardiac dysfunction, 3.7% adult respiratory distress syndrome). The percentage of deaths attributed to sepsis as a primary cause of death in MOF nonsurvivors decreased in the last three biennials, displaced by MOF (SDC1, Figure 5, <http://links.lww.com/TA/A363>).

The O/E ratios for MOF incidence (O/E ratio, 0.97; 95% CI, 0.53–1.64), MOF-related death (O/E ratio, 1.01; 95% CI, 0.71–1.40), and overall mortality regardless of MOF status (O/E ratio, 1.13; 95% CI, 0.64–1.86) for the entire group were not significantly different from 1. Individual institutions' O/E ratios were also not significantly different from 1 (data not shown).

The Burden of MOF

MOF patients endured lengthier ICU stays (median, 18 days; IQR, 9–29 days) compared with all non-MOF patients (median, 8 days; IQR, 4–16). Similarly, MOF patients required much longer MV (median, 14 days; IQR, 7–24 days) compared with all non-MOF patients (median, 5 days; IQR, 2–12 days). Stratification by MOF and survival status showed that MOF survivors were the group who demanded more ICU and MV resources (Fig. 5A). This high did not change over time (Kaplan-Meier: ICU, log-rank test $p = 0.8770$, Wilcoxon test $p = 0.4453$; MV, log-rank test $p = 0.2256$, Wilcoxon test $p = 0.2507$). MOF survivors were responsible for 20% of the total ICU and MV days invested in the critical care of this population (Fig. 5B) although they represented only 9% of the total population (Fig. 5C).

Based on national estimates, the total cost of the critical care delivered to MOF patients in this data set amounted to \$19,990,420 (ICU with MV, \$16,479,606 + ICU without MV, \$3,510,814). This corresponded to approximately 22.2% of the total ICU cost for this population (ICU with MV, \$69,238,641 + ICU without MV, \$20,580,321 = total ICU cost, \$89,818,962). The estimated median cost per MOF patient was \$77,202, compared with \$38,442, the presumed cost of caring for non-MOF patients.

DISCUSSION

We confirmed our preestablished hypotheses that (1) the adjusted MOF incidence has halved from 2003 to 2010, independently of admission risk factors and (2) the high rates of MOF-related death and morbidity have not changed over time. Lung failure decreased over time but remained highly prevalent in this population.

Admission risk factors remained essentially the same or worsened (e.g., increased BMI, older age), thus suggesting that evidence-based improved resuscitation and critical care have mitigated the MOF-inducing effect of initial and subsequent insults.

MOF's unchanged somber prognosis may be related to infections and noninfectious complications, which remained frequent and essentially unabated in this series. While they may no longer induce MOF, they may negatively affect MOF's outcomes.¹⁷ The inability to pinpoint the precise moment when these events actually start hinders the assessment of their association with MOF.

A differential adherence to SOPs within the IHRI-Glue Grant cohort has been recently reported: resuscitation-related SOPs had an adherence higher than adult respiratory distress syndrome and nutrition protocols.²⁴ It is conceivable that the high compliance to resuscitation SOPs successfully alleviated the MOF-inducing effect of initial insults, while low adherence to later SOPs diminished their effectiveness in reversing established MOF.

Recent studies implicate blood components and crystalloids ratios on postinjury outcomes.^{25–28} Ratios averaged over 6 hours, the shortest time interval in this data set, did not change over time, and were not associated with MOF. However, these ratios should be calculated within shorter time intervals to avoid masking “catch-up” practices and to account for time-varying ratios.

MOF has retained a multimodal distribution, a hallmark of the two-hit model, although the later peaks have decreased considerably compared with previous studies.^{17,29} Rather than a true change in MOF mechanisms, the “fading” of later peaks may be a function of the reduced overall incidence.

MOF patients continue to require prolonged ventilation and ICU stay, consuming a large amount of health care resources. Based on national estimates,²⁰ 22% of the total ICU cost for this population was spent caring for MOF although MOF patients represented a mere 13.5% of the studied population. The cost per MOF patient was more than twice the cost of caring for non-MOF patients. Albeit these are rough estimates and cannot be construed as a cost-analysis, they provide some insight on the financial implications of this morbid condition.

Findings in the Context of Current Evidence

To our knowledge, this is the first study to examine MOF temporal trends in a data set prospectively generated by multiple centers sharing SOPs. We confirmed the findings of Ciesla et al.⁴ in a single trauma center population regarding risk-adjusted MOF incidence and related death rate. Our observed MOF incidence of 13.6% was lower compared with other studies using the same IHRI-Glue Grant data set.^{12,17} These studies applied the less stringent Marshall score, while we favored the more specific Denver MOF score. Regardless of score, however, temporal trends remained the same, that is, significant decline in MOF incidence and no change in MOF-related death, further supporting our findings. Both scores have been validated and shown to have an excellent association with objective adverse outcomes.¹³ A discussion about which score adequately reflects MOF is beyond the scope of this article and possibly futile given the absence of a gold-standard.³⁰

A notable result, albeit not new, was the sex dimorphism in MOF incidence and related death. This effect, also observed by others, seems to be hormone and injury severity independent.³¹

Level of Evidence

This epidemiologic prospective study with decreased intervention heterogeneity through shared SOPs provides Level 3 evidence.³² An important study strength is the minimization of selection bias by analyzing all eligible patients (including those who died in the first 48 hours) through analytic techniques that account for censoring. It has been common practice to exclude those surviving less than 48 hours (by our group as well), based on the premise that physiologic derangements in the immediate postinjury period were caused by resuscitation efforts and not to organ failure.³³ More recently, however, it became evident that critical events leading to MOF take place immediately after injury.³⁴ Excluding early deaths, that is, considering them “not at risk” for MOF could result in survivor bias. In fact, early nonsurvivors and MOF patients had similar injury severity (early nonsurvivors ISS, 34 [IQR, 22–42] vs. MOF ISS, 36 [IQR, 29–45]), age (46 years [IQR, 32–63 years] vs. 47 years [IQR, 30–63 years]), admission SBP (100 mm Hg [IQR, 80–116 mm Hg] vs. 102 mm Hg [IQR, 87–128 mm Hg]), and admission BD (–12 mEq/L [IQR, –18 mEq/L to –8 mEq/L] vs. –9.8 mEq/L [IQR, –13.5 mEq/L to –6.3 mEq/L]). Additional strengths included the control of cluster effects by center and meticulous inspection and remediation of hazards proportionality assumption violations, often overlooked in survival analyses.³⁵

Limitations

The analysis of four Level I trauma centers sharing SOPs may not generalize to other institutions. A second limitation was the lack of standardization in assigning the cause of death and unavailability of autopsy data. The absence of early point-of-care coagulation and inflammation measures in the data set prevented further insight into the mechanisms of postinjury MOF. Finally, the decreased frequency of mild/moderate TBI in recent years was likely caused by imperfect enrollment rather than a true change in incidence. The addition in 2005 of the severe TBI exclusion may have influenced enrollment of patients with any TBIs because it is often difficult to determine TBI severity immediately after injury.

In conclusion, these findings suggest that postinjury MOF, once dubbed the syndrome of 1970s,¹ is in decline but remains a resource-intensive, morbid, and lethal condition. Reversing it once it is established is still challenging. Approximately one third of MOF patients do not survive, and the majority dies rapidly after the diagnosis, suggesting that the therapeutic window is narrow and that prevention remains the best strategy.

In response to the insightful question posed by Baue et al.:³⁶ “Multiple organ failure: are we winning the battle?”: it seems that we have won the battle but not the war.

In memoriam: This study is a humble tribute to the memory of two legends in the study of postinjury MOF, Drs. Arthur Baue and Ben Eiseman.

References

1. Baue AE. Multiple, progressive, or sequential systems failure. A syndrome of the 1970s. *Arch Surg.* 1975; 110(7):779–781. [PubMed: 1079720]
2. Eiseman B, Beart R, Norton L. Multiple organ failure. *Surg Gynecol Obstet.* 1977; 144(3):323–326. [PubMed: 841449]
3. Sauaia, A.; Moore, FA.; Moore, EE. Postinjury Multiple Organ Failure. In: Mattox, KLFD.; Moore, EE.; Feliciano, DV., editors. *Trauma.* 7. New York: McGraw Hill; 2012.
4. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? *Arch Surg.* 2005; 140(5):432–438. [PubMed: 15897438]
5. Laudi S, Donaubaue B, Busch T, Kerner T, Bercker S, Bail H, Feldheiser A, Haas N, Kaisers U. Low incidence of multiple organ failure after major trauma. *Injury.* 2007; 38(9):1052–1058. [PubMed: 17572416]
6. Nast-Kolb D, Aufmkolk M, Rucholtz S, Obertacke U, Waydhas C. Multiple organ failure still a major cause of morbidity but not mortality in blunt multiple trauma. *J Trauma.* 2001; 51(5):835–841. [PubMed: 11706328]
7. Durham RM, Moran JJ, Mazuski JE, Shapiro MJ, Baue AE, Flint LM. Multiple organ failure in trauma patients. *J Trauma.* 2003; 55(4):608–616. [PubMed: 14566110]
8. Wafaisade A, Lefering R, Bouillon B, Sakka SG, Thamm OC, Paffrath T, Neugebauer E, Maegele M. Trauma Registry of the German Society for Trauma S. Epidemiology and risk factors of sepsis after multiple trauma: an analysis of 29,829 patients from the Trauma Registry of the German Society for Trauma Surgery. *Crit Care Med.* 2011; 39(4):621–628. [PubMed: 21242798]
9. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. *J Trauma Acute Care Surg.* 2013; 74(3):774–779. [PubMed: 23425734]
10. Fröhlich, M.; Schneider, M.; Lefering, R.; Probst, C.; Paffrath, T.; Bouillon, B.; Wafaisade, A. Epidemiology and Risk Factors of Multiple Organ Failure (MOF) After Multiple Trauma: An Analysis of 31154 Patients From the Trauma Registry of the German Trauma Society. San Francisco, CA: American Association for the Surgery of Trauma; 2013.
11. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. *Injury.* 2009; 40(9): 912–918. [PubMed: 19541301]
12. Cuschieri J, Johnson JL, Sperry J, West MA, Moore EE, Minei JP, Bankey PE, Nathens AB, Cuenca AG, Efron PA, et al. Benchmarking outcomes in the critically injured trauma patient and the effect of implementing standard operating procedures. *Ann Surg.* 2012; 255(5):993–999. [PubMed: 22470077]
13. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffi WL, Banerjee A. Validation of postinjury multiple organ failure scores. *Shock.* 2009; 31(5):438–47. [PubMed: 18838942]
14. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med.* 2002; 30(8): 1772–1777. [PubMed: 12163791]
15. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med.* 1995; 23(10):1638–1652. [PubMed: 7587228]
16. Breslow, N.; Day, N. *Statistical Methods in Cancer Research. Vol. II, The Design and Analysis of Cohort Studies* (IARC Scientific Publication No. 82). Lyon, France: International Agency for Research on Cancer; 1987.
17. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, O’Keefe GE, Cohen MJ, Moldawer LL, Tompkins RG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. *Crit Care Med.* 2012; 40(4):1129–1135. [PubMed: 22020243]
18. Sauaia A, Moore FA, Moore EE, Norris JM, Lezotte DC, Hamman RF. Multiple organ failure can be predicted as early as 12 hours after injury. *J Trauma.* 1998; 45(2):291–301. [PubMed: 9715186]

19. Clermont G, Kaplan V, Moreno R, Vincent JL, Linde-Zwirble WT, Hout BV, Angus DC. Dynamic microsimulation to model multiple outcomes in cohorts of critically ill patients. *Intensive Care Med.* 2004; 30(12):2237–2244. [PubMed: 15502934]
20. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med.* 2005; 33(6):1266–1271. [PubMed: 15942342]
21. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med.* 1994; 13(21):2233–2247. [PubMed: 7846422]
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, Initiative S. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007; 370(9596):1453–1457. [PubMed: 18064739]
23. Sauaia A, Moore EE, Crebs J, Maier R, Hoyt DB, Shackford SR. The anatomy of an article: the discussion section: “how does the article I read today change what I will recommend to my patients tomorrow?”. *J Trauma Acute Care Surg.* 2013; 74(6):1599–1602. [PubMed: 23694892]
24. Rice TW, Morris S, Tortella BJ, Wheeler AP, Christensen MC. Deviations from evidence-based clinical management guidelines increase mortality in critically injured trauma patients*. *Crit Care Med.* 2012; 40(3):778–786. [PubMed: 22036858]
25. Spoerke N, Michalek J, Schreiber M, Brasel KJ, Vercruysse G, MacLeod J, Dutton RP, Duchesne JC, McSwain NE, et al. Trauma Outcomes G. Crystalloid resuscitation improves survival in trauma patients receiving low ratios of fresh frozen plasma to packed red blood cells. *J Trauma.* 2011; 71(2 Suppl 3):S380–S383. [PubMed: 21814108]
26. Brown LM, Aro SO, Cohen MJ, Holcomb JB, Wade CE, Brasel KJ, Vercruysse G, MacLeod J, Dutton RP, et al. Trauma Outcomes G. A high fresh frozen plasma: packed red blood cell transfusion ratio decreases mortality in all massively transfused trauma patients regardless of admission international normalized ratio. *J Trauma.* 2011; 71(2 Suppl 3):S358–S363. [PubMed: 21814104]
27. Holcomb JB, Wade CE, Brasel KJ, Vercruysse G, MacLeod J, Dutton RP, Hess JR, Duchesne JC, McSwain NE, et al. Trauma Outcomes G. Defining present blood component transfusion practices in trauma patients: papers from the Trauma Outcomes Group. *J Trauma.* 2011; 71(2 Suppl 3):S315–S317. [PubMed: 21814098]
28. Halmin M, Bostrom F, Brattstrom O, Lundahl J, Wikman A, Ostlund A, Edgren G. Effect of plasma-to-RBC ratios in trauma patients: a cohort study with time-dependent data*. *Crit Care Med.* 2013; 41(8):1905–1914. [PubMed: 23782963]
29. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. *J Trauma.* 1996; 40(4):501–510. [PubMed: 8614027]
30. Baue AE. MOF, MODS, and SIRS: what is in a name or an acronym? *Shock.* 2006; 26(5):438–449. [PubMed: 17047513]
31. Sperry JL, Nathens AB, Frankel HL, Vanek SL, Moore EE, Maier RV, Minei JP. Inflammation the Host Response to Injury I. Characterization of the gender dimorphism after injury and hemorrhagic shock: are hormonal differences responsible? *Crit Care Med.* 2008; 36(6):1838–1845. [PubMed: 18496363]
32. Sauaia A, Moore EE, Crebs JL, Maier RV, Hoyt DB, Shackford SR. Evidence level of individual studies: a proposed framework for surgical research. *J Trauma Acute Care Surg.* 2012; 72(6):1484–1490. [PubMed: 22695411]
33. Ciesla DJ, Moore EE, Johnson JL, Sauaia A, Cothren CC, Moore JB, Burch JM. Multiple organ dysfunction during resuscitation is not postinjury multiple organ failure. *Arch Surg.* 2004; 139(6):590–594. [PubMed: 15197083]
34. Cryer HG, Leong K, McArthur DL, Demetriades D, Bongard FS, Fleming AW, Hiatt JR, Kraus JF. Multiple organ failure: by the time you predict it, it's already there. *J Trauma.* 1999; 46(4):597–604. [PubMed: 10217221]
35. Altman DG, De Stavola BL, Love SB, Stepniowska KA. Review of survival analyses published in cancer journals. *Br J Cancer.* 1995; 72(2):511–518. [PubMed: 7640241]

36. Baue AE, Durham R, Faist E. Systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF): are we winning the battle? *Shock*. 1998; 10(2):79–89. [PubMed: 9721973]

*Figure legend: stratum 2004=2003-2004; stratum 2006=2005-2006; stratum 2008=2007-2008; stratum=2009-2010

Figure 1.

Kaplan-Meier curves for MOF incidence and outcomes across biennial periods from 2003 to 2010. A, MOF incidence. B, Mortality in MOF patients. C, ICU stay in MOF patients. D, Ventilation days in MOF patients.

Figure 2.

Kaplan-Meier curves for the incidence of individual organ failures across biennial periods from 2003 to 2010. *A*, Lung failure incidence. *B*, Cardiac failure incidence. (log-rank $p = 0.0042$, Wilcoxon $p = 0.0012$) (log-rank $p = 0.0117$, Wilcoxon $p = 0.0111$). *C*, Renal failure incidence. *D*, Liver failure incidence (log-rank $p = 0.9158$, Wilcoxon $p = 0.8927$) (log-rank $p = 0.3978$, Wilcoxon $p = 0.4082$). Stratum 2004, 2003 to 2004; Stratum 2006, 2005 to 2006; Stratum 2008, 2007 to 2008; Stratum 2010, 2009 to 2010.

Figure 3. MOF onset by biennial period. *A*, Onset of MOF by postinjury day. *B*, Percentage of all MOF cases (and respective mortality) that started ≤3, 4-7 days, > 7 days.

A Timing of death among MOF patients relative to MOF onset

B Mortality of MOF by onset of MOF (e.g., in the biennial 2009-2010, 50% of the patients diagnosed with MOF within 3 days postinjury died during this hospitalization)

Figure 4.

MOF-related mortality. *A*, Timing of death among MOF patients relative to MOF onset. *B*, Mortality of MOF by onset of MOF (e.g., in the biennial 2009 to 2010, 50% of the patients diagnosed with MOF within 3 days after injury died during this hospitalization).

A Median days and Interquartile range in intensive care unit (ICU) and on mechanical ventilation (MV)

B Proportion of total ICU days (Left chart) and MV days (Right chart) by MOF and survivor status

C Proportion of patients by MOF and survival status

Figure 5.

Resource use by MOF and survival status. A, Median days and IQR in the ICU and on MV.

B, Proportion of total ICU days (*left chart*) and MV days (*right chart*) by MOF and survivor status.

C, Proportion of patients by MOF and survival status.

TABLE 1
Population Characteristics, Admission Risk Factors, Resuscitation Fluids and Blood Transfusions, Outcome, and Complications (Total and by Biennial Period)

Variable	2003–2004				2005–2006				2007–2008				2009–2010				Spearman's correlation coefficient	p*
	n = 335				n = 506				n = 546				n = 256					
	Median or Percentage	LQ	UQ		Median or Percentage	LQ	UQ		Median or Percentage	LQ	UQ		Median or Percentage	LQ	UQ			
Demographic																		
Age, y	40	26	54	41	26	54	43	28	57	45.5	25.5	58	0.05	0.0246				
BMI, kg/m ²	25.7	23.1	29.9	26.7	23.7	31.4	27.1	23.8	31.3	27.3	24.1	32.0	0.08	0.0017				
Male sex, %	64.5			66.6			67.2			67.6				0.3940				
Comorbidity index	8.4			12.9			8.4			10.2				0.8276				
Antiplatelet therapy, %**	6.6			7.1			10.1			8.2				0.1414				
Injury																		
Moderate TBI, %†	30.2			18.0			21.6			18.0				0.0037				
ISS	29	22	41	32	22	41	34	24	41	34	22	43	0.05	0.0622				
Prehospital GCS score	13	4	15	14	10	15	14	9	15	14	9	15	0.11	<0.0001				
Prehospital SBP (lowest)	89.0	72.5	104.5	86.0	71.0	102.0	88.0	73.0	108.0	85.0	74.0	100.0	−0.01	0.8425				
Prehospital HR (highest)	116	95	131	118	100	130	115	97	130	118	102	132	0.02	0.4810				
Admission GCS score	6	3	15	10	3	15	11	3	15	3	3	15	0.04	0.1534				
Admission SBP, mm Hg	110	93	135	111	90	132	110	90	131	109.5	89	128	−0.05	0.0429				
Admission SBP 90 mm Hg	22.1			25.9			26.7			29.9				0.0350				
Admission HR, beats/min	108	86	127	110	90	126	109	91	127	110	92	127.5	0.03	0.2080				
Fluids/blood																		
PRBC units/12 h	5	3	11	6	3	12	5	2	9	5	2	9	−0.04	0.0739				
FFP units/12 h	3	0	8	3	0	8	2	0	6	3	0	7	0.04	0.0798				
0–6 h PRBC/FFP ratio	0.6	0	1.5	0.5	0	1.6	0	0	1.5	0.6	0	1.4	−0.04	0.1224				
Platelet units/12 h	0	0	1	0	0	1	0	0	1	0	0	1	0.02	0.4160				
Prehospital crystalloids, mL	1.6	0.6	3.0	1.8	0.7	3.3	1.4	0.5	2.9	1.8	0.7	3.1	−0.02	0.3504				
Crystalloids/12 h, mL	10.3	7.2	15.7	10.0	7.6	13.6	8.7	5.9	12.3	9.0	6.3	12.0	−0.16	<0.0001				
Laboratory tests																		
ED BD, mEq/L	−8.9	−11.4	−6	−8.4	−11.2	−6	−7.6	−0.8	−5	−8	−11.1	−5.35	0.08	0.0012				

Variable	2003–2004				2005–2006				2007–2008				2009–2010			
	n = 335				n = 506				n = 546				n = 256			
	Median or Percentage	LQ	UQ		Median or Percentage	LQ	UQ		Median or Percentage	LQ	UQ		Median or Percentage	LQ	UQ	
ED lactate, mg/dL	4.3	3	5.9		3.9	2.7	5.6		3.6	2.4	5.2		4	2.4	6	–0.08
Day 1 platelet 1,000/ μ L	100	79	129		95	76	123		107	87	133		101	84	128.5	0.0016
PaO ₂ /FIO ₂ ratio/12 h	119	66	213		161	86.5	256		158	89	269		163	79	285	0.0028
ED hemoglobin, g/dL	10.9	9.33	13		11.3	9.5	13.1		11.9	10	13.3		11.5	9.6	12.9	0.09
ED INR	1.2	1.1	1.5		1.3	1.1	1.5		1.21	1.1	1.5		1.3	1.1	1.5	0.0003
Complications																0.0217
Nonseptic complication, %	44.5				47.2				44.1				40.4			0.06
Surgical site infection, %	13.1				16.4				14.8				8.2			0.3152
VAP, %	26.6				26.5				24.4				23.1			0.03
Outcomes																
MOF, %	17.0				15.0				11.9				9.8			0.2365
Lung failure, %	57.6				56.5				55.3				50.8			0.1180
Cardiac failure, %	20.9				17.6				16.1				12.5			0.2335
Liver failure, %	15.2				16.2				13.4				14.1			
Renal failure, %	10.1				10.7				11.9				12.5			0.3762
ICU days	8	4	19		9	4	17		10	5	18		9	5	17	0.2804
ICU-free days	11	0	21		15	4	23		15	3	22		17	8	22	0.1070
Ventilator days	6	2	14		5	2	13		7	2	13		6	2	12	0.0002
Ventilator-free days	16	0	24		19	7	25		20	8	25		21	12	25	–0.005
Mortality, %	23.9				15.4				12.3				10.5			0.12
MOF-related outcomes																<0.0001
Case-fatality, %	33.3				38.2				36.9				36.0			<0.0001
ICU days	22	9	34		17	8.5	8.0		15	9	27		19	10	24	0.7800
ICU-free days	0	0	4		0	0	8		0	0	10		4	0	7	0.1889
Ventilator days	20	9	26		15	6.5	27		12	7	21		13	6	19	0.2289
Ventilator-free days	0	0	8		0	0	11.5		0	0	14		4	0	14	0.0642
MOF-related complications																0.1969
Nonseptic complication, %	77.2				75.0				83.1				80.0			0.4481
Surgical site infection, %	22.8				27.6				16.9				20.0			0.4042

Variable	2003–2004		2005–2006		2007–2008		2009–2010		Spearman's correlation coefficient	p*
	Median or Percentage	LQ	UQ	Median or Percentage	LQ	UQ	Median or Percentage	LQ		
VAP, %	47.3			43.4			50.8		44.0	0.8946

* CAT test for trend was used for categorical variables and the nonparametric Spearman's correlation coefficient and test for continuous variables; negative correlation coefficients indicate values decreased over time, while positive coefficients indicate values increased over time; significance set at $p < 0.01$ to account for large number of comparisons.

** Antiplatelet medication before injury.

† Moderate TBI, head AIS score greater than 3 with motor GCS score greater than 3.

Data are expressed in median and LQ and UQ or percentages.

FFP, fresh frozen plasma; HR, heart rate; INR, international normalized ratio; LQ, lower quartile; PRBC, packed red blood cells; UQ, upper quartile; VAP, ventilator-associated pneumonia.