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Early markers of acute respiratory distress syndrome development in severe trauma patients☆

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Abstract

Purpose: The aim of the study was to identify early risk factors for development of acute respiratory distress syndrome (ARDS) in severe trauma patients.

Materials and Methods: This was a prospective observational study of 693 severe trauma patients (Injury Severity Score ≥16 and/or Revised Trauma Score ≤11) in 17 hospitals in a Spanish region of 8 million inhabitants from July 2002 to December 2002.

Results: Acute respiratory distress syndrome developed in 6.9% of patients who were more severely ill with higher APACHE II ($P < .001$) and Injury Severity Score ($P = .002$) scores vs patients not developing ARDS. Acute respiratory distress syndrome development was associated ($P < .001$) with fractures of femur (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 820, 821), tibia (*ICD-9* code 823), humerus, and pelvis, with a number (≥2) of long bone fractures, and with chest injuries (rib/sternal fracture [*ICD-9* code 807] and hemo/pneumothorax [*ICD-9* code 860/861]). Patients with ARDS required more colloids ($P = .005$) and red blood cell units ($P = .02$) than patients without ARDS during the first 24 hours. Multivariate analysis showed that ARDS was related to chest trauma diagnosis (*ICD-9* code 807) (odds ratio [OR], 3.85), femoral fracture (OR, 3.16), APACHE II score (OR, 1.05), and blood transfusion during resuscitation (OR, 1.32).

Conclusions: Risk of ARDS development is related to the first 24-hour admission variables, including severe physiologic derangements and specific *ICD-9*–classified injuries. Blood transfusion may play an independent role.

☆ This was a GITAN multicenter project. GITAN is an interdisciplinary group of the Intensive Medical Society of Andalusia devoted to improving the management of severe trauma in Andalusia, Spain.

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1. Introduction

Since the first description of the acute respiratory distress syndrome (ARDS) in 7 trauma patients [1], trauma and ARDS have been recognized as faithful but somewhat mysterious partners. Thirty-six years later, we are still asking why ARDS develops after trauma, what the risk factors are, and whether it can be predicted. Important unresolved questions include whether we can prevent ARDS and even whether we create it. Acute respiratory distress syndrome is the result of an enduring pathological process, of lesser duration in the trauma than sepsis setting, combined with a dynamic and complex inflammatory response [2]. The trauma population probably constitutes a more homogeneous ARDS group compared with others, with a greater physiologic reserve because of their lower age and comorbidity [3], although the accuracy of ARDS criteria in this population has recently been challenged [4]. Two forms of ARDS have been described: early, during the first 48 hours after trauma and related to hemorrhagic shock; and late, after 48 hours and more related to multiple organ failure and sepsis [5]. Acute respiratory distress syndrome is a complication of both blunt and penetrating trauma, and the outcomes and mortality rates are similar in both cases [6].

The relationship between severe trauma and acute lung injury or ARDS, its more severe form, is well documented. Acute lung injury and ARDS have been related to severity of injury, measured by different scoring systems; specific trauma type, notably chest trauma; hypotension or metabolic acidosis [7]; major fractures; and delay in certain treatments [8].

The hypothesis of the present study was that it may be possible to identify patients at risk for ARDS on the basis of observations made in the first 24 hours after admission. The objectives were to identify current risk factors for ARDS that can be observed within this period in a specific regional setting of 8 million inhabitants. The study was conducted by the interdisciplinary trauma research group in Andalusia (GITAN), a multicenter project on continuous quality improvement of trauma management in intensive care units (ICUs) and emergency departments in Southern Spain.

2. Patients and methods

2.1. Participating hospitals

Study participants were the regional emergency health service (EPES-061) and 17 hospitals, 80.6% of hospitals in the Southern Spanish region of Andalusia and including all 5 trauma referral centers (Spanish level III), 4 level II hospitals, and 8 district hospitals (level I). The 4 hospitals that did not participate were all district hospitals. Approval for the research was obtained from ethics committees of all hospitals, and patients or family members were informed of this noninterventional study.

2.2. Patients and study design

A prospective observational study was conducted of all patients older than 14 years with severe trauma admitted to the 17 participating hospitals from July 1, 2002, to December 31, 2002.

The following variables were recorded: age; sex; trauma type; injury mechanism; accident-admission delay; type of transport; fluids and blood administered in first 24 hours; injury severity by the Revised Trauma Score (RTS) [9]; Injury Severity Score (ISS) [10]; APACHE II [11]; injury diagnosis by *International Classification of Diseases, Ninth Revision* (*ICD-9*) classification [12]; presence and number of bone fractures, and development of ARDS during ICU stay.

2.3. Definitions

Severe trauma was defined by an RTS of 11 points or less at hospital admission and/or ISS of 16 points or higher. Similar resuscitation strategies were followed by all hospitals (see below), including blood pressure targets, colloid and/or crystalloid infusions, and blood transfusions (not leukoreduced in Spain at time of study). Andalusia is divided into 5 regions, each with a trauma referral center and mobile ICU ambulances and helicopter. The trauma centers offer 24-hour availability of all surgical, therapeutic, and diagnostic resources required. Resuscitation in the out-of hospital setting was performed by the regional emergency telephone service (EPES-061), stabilizing in the field (intubation, mechanical ventilation, hemodynamic support), and with presence of specialist physician in mobile ICU ambulance or helicopter. All severe trauma care procedures are set out in a regional protocol available on the Internet (www.csalud.juntadeandalucia.es/gestiondeprocesos/atencionaltraumagrave).

Presence of ARDS was recorded when all American-European Consensus Conference criteria [13] were met, that is, acute onset respiratory failure, PaO_2/FIO_2 of less than 200 mm Hg, presence of bilateral radiologic pulmonary infiltrates, and pulmonary capillary wedge pressure of less than 18 mm Hg or no clinical or radiologic evidence of elevated pressure in left atrium.

2.4. Quality control of data

All participating hospitals designated a physician responsible for data collection who received training for this purpose. Explanatory leaflets and data collection sheets were produced. Any doubts or queries were immediately answered by the data collection central unit (at Virgen de las Nieves University Hospital, Granada, Spain) responsible for checking data from the hospitals and ensuring correct completion of documentation. All data were introduced by a single investigator into a database created using Microsoft Access. Quality control measures included a procedure to prevent entry of data incompatible with possible value ranges and a

Table 1 Severity scores and fluid resuscitation during the first 24 hours in ARDS and non-ARDS trauma population

Independent variables	Without ARDS diagnosis (n = 643)	With ARDS diagnosis (n = 48)	*P*
Age (y)	36.6 ± 19.7	37 ± 17	NS
APACHE II	13 ± 7.3	16.3 ± 7.2	.05
RTS	9.8 ± 2.7	9.6 ± 3	NS
ISS	25.1 ± 10.8	32 ± 13.2	.01
First 24-h fluids			
Colloids (mL)	189 ± 422	539 ± 1.097	.05
Crystalloids (mL)	725 ± 1067	1149 ± 1656	.11
Red blood cells (U)	0.2 ± 0.9	0.8 ± 1.7	.02
Injury-to-admission delay[a] (min)	77.6 ± 110.6	73.7 ± 55.6	NS

NS, non statistically significant.
[a] Excluding transferred patients.

check on the consistency of patient data from hospital and out-of-hospital databases.

2.5. Statistical analysis

Continuous variables were expressed as means ± SD, and categorical variables were expressed as actual numbers and percentages. For quantitative variables, means of 2 categories were compared by using the Student *t* test. Categorical variables were analyzed with the χ^2 test.

Multivariate analysis with multiple logistic regression was performed to study the relationship of ARDS development as dependent variable with the independent study variables that could be gathered in the first 24 hours of admission and showed significant or close-to-significant association with ARDS development (in univariate analyses) or were considered potential confounding factors. A stepwise method was used to select variables, studying interactions among variables in the model and testing for presence of colinearity [14]. The discriminative capacity of the model was assessed by calculating the area under the receiver operating characteristic curve [15].

All statistical tests were 2-tailed, and statistical significance was accepted at $P < .05$. Statistical analysis was performed using the SPSS 11 statistical software package (SPSS, Chicago, Ill).

3. Results

3.1. General characteristics of trauma population

3.1.1. Epidemiologic characteristics

During the study period, 693 patients were admitted to ICUs enrolled in the Trauma Registry of the GITAN project; 78.6% were males, and mean age was 36.3 ± 19.5 years.

Cause of injury was blunt trauma in 99.4% of cases. The most frequent injury mechanisms were road traffic accidents (65.3% [motorcycles, 30.4%; automobiles, 24.3%]) and falls from heights (14.1%). The remainder (13.7%) included work- and sports-related injuries, among others (Table 1). Regarding transport, 69.6% of patients were transferred directly from the accident site to their definitive and appropriate hospital (trauma referral center), and 59.2% of all patients were transported to the hospital by fully equipped and physician-staffed mobile ICU ambulance. The mean severity scores were as follows: ISS, 25.7 ± 11.0; RTS, 9.7 ± 2.4; and APACHE II, 13.2 ± 7.4 points. The overall hospital mortality rate was 22.3% (154 patients), with a higher mortality (44.5%) among those older than 60 years.

3.1.2. Type of injury

The most frequent diagnoses were head trauma (*ICD-9* codes 800, 859, 852) (37.9%); chest trauma, that is, rib and sternal fractures (*ICD-9* code 807) (24%) and hemothorax and/or pneumothorax (20.6%); long bone femoral, tibial, and humeral fractures (*ICD-9* codes 813, 821, 823) (24.5%); abdominal trauma, including 57 cases of spleen injury (*ICD-9* code 865) and 42 of liver injury (*ICD-9* code 864) (17.9%); pelvic fracture (*ICD-9* code 808) (8.1%); and maxillofacial trauma (*ICD-9* code 802) (7.7%).

3.1.3. Resource consumption

The mean ICU stay of patients was 10.6 ± 11.7 days.

3.2. General characteristics of trauma ARDS population

Two trauma patients were excluded from the study for presence of severe burns. Of the 691 remaining trauma patients admitted to the ICUs, 48 (6.9%) developed ARDS, 23 of them during the first 48 hours and the remaining 25 at

Table 2 Relationship between ARDS development and APACHE II– or ISS-measured severity

	Without ARDS diagnosis (n = 643)	With ARDS diagnosis (n = 48)
APACHE II range (%)		
<5	100	0
5-9	95.5	4.5
10-14	90.4	9.4
15-19	89.9	10.1
20-24	92.6	7.4
≥25	81.8	18.2*
ISS range (%)		
≤15	93.5	6.5
15-24	95.8	4.2
25-29	96.3	3.7
30-44	83.5	16.5
≥45	83.3	16.7**

* $P = .019$; $\chi^2 = 13.51$.
** $P < .001$; $\chi^2 = 24.2$.

more than 48 hours after the trauma. The overall ICU mortality rate was 45.8% (22/48), with a similar rate between early (43.5%, 10/23) and late (48%, 12/25) patients with ARDS, but with a much higher rate for trauma patients with ARDS diagnosis than for those without (45.8%, 22/48 vs 20.5%, 132/645; $P < .001$). The mean ICU stay of patients with ARDS was 22.2 ± 13.2 days.

Patients who developed ARDS had a higher APACHE II score than those who did not (16.4 ± 7.3 vs 12.9 ± 7.2 points, $P < .001$), and they required more fluids in the first 24 hours of ICU admission, specifically more colloids (539.02 ± 1097.64 vs 189.36 ± 422.23 mL; $P = .05$) and red blood cells (0.83 ± 1.69 vs 0.23 ± 0.91 U; $P = .02$), with no difference between them in first 24-hour crystalloid volumes (1.149 ± 1656 vs 725 ± 1067 mL; $P = .11$). The injury-admission delay was similar in both groups (Table 1).

Table 2 shows the relationship between ARDS development and APACHE II– and ISS-measured severity, evidencing increased frequency of the syndrome with worse physiologic and anatomical severity scores. Table 3 provides detailed information on the association between ARDS development and presence of specific anatomic *ICD-9* classified injuries (eg, long bone and pelvic fractures and chest and abdominal injuries).

Only variables gathered in the first 24 hours were considered for inclusion in the logistic regression analysis. Hence hemo- and pneumothorax diagnoses were not included because they could often not be assessed on day 1, so that chest trauma was represented by rib/sternal fracture (*ICD-9* code 807). Variables considered for inclusion in the model were APACHE II, ISS, total fluid volumes, red blood cells, colloids and crystalloids during resuscitation, diagnoses of fracture of femur, tibia, humerus, pelvis, and rib/sternum (*ICD-9* code 807), and diagnosis of traumatic brain injury. Variables were selected by a stepwise method. According to this analysis, ARDS development was significantly associated with the *ICD-9* code 807 chest trauma diagnosis (odds ratio [OR], 3.85), presence of femoral fracture (OR, O.16), APACHE II score (OR, 1.056), and number of red blood cells administered during resuscitation (OR, 1.32) (Table 4). The Hosmer-Lemeshow test goodness-of-fit statistic was 8.044 ($df = 8$, $P = .429$). No interaction was found among the variables, and no colinearity was detected. The discrimination of the model assessed by the area under the receiver operating characteristic curve was 0.764.

Table 3 Incidence of ARDS by abdominal injury, number of long bone fractures, and *ICD-9*–coded diagnoses, expressing the percentage of their presence in trauma patients with and without ARDS diagnosis

	Without ARDS diagnosis (n = 643)	With ARDS diagnosis (n = 48)	*P*
Type of injury (%)			
Abdominal trauma	16.8	33.3	.007
Long bone fractures (%)			.001
n ≥ 2	77.1	54.7	
n = 1	12.2	14.3	
n = 0	10.7	31	
ICD-9 diagnosis codes (%)			
C-860/861	16.5	50	.001
C-807	18.5	47.6	.001
C-820/821	9.1	28.6	.001
C-823	7.3	21.4	.001
C-812	6.2	16.7	.001
C-808	7.5	16.7	.03

ICD-9 codes C-860/861 indicate hemo/pneumothorax; C-807, sternal and rib fractures; C-820/821, femoral fractures; C-823, tibial fracture; C-812, humeral fracture; C-808, pelvic fracture.

Table 4 Multivariate analysis by logistic regression: variables related to ARDS development

Variables	B	SE	OR	CI
APACHE II[a]	0.05	0.02	1.056	1.01-1.10
Blood transfusion[b]	0.28	0.12	1.325	1.05-1.67
Chest trauma[c] (*ICD-9* code 807)	1.35	0.35	3.85	1.94-7.62
Femoral fracture[d] (*ICD-9* code 820-821)	1.15	0.41	3.16	1.42-7.03
Constant	−4.03	0.43		

B indicates regression coefficient; CI, 95% confidence interval.
[a] APACHE II score on first day of ICU admission.
[b] Number of red blood cell units administered during resuscitation.
[c] Rib/sternal fractures codified by *ICD-9*; 0 = absence, 1 = presence.
[d] Femoral fracture codified by *ICD-9*; 0 = absence, 1 = presence.

4. Discussion

The frequency of ARDS development in our large series of severe trauma patients in Southern Spain was 6.9%. Multivariate analysis showed association between ARDS development and variables observable during the first 24 hours after admission, including APACHE II–measured severity of illness at ICU admission, specific *ICD-9*–classified diagnoses related to chest injury and long bone (femoral) fracture, and amount of blood transfusion during the first 24 hours. Our results indicate that groups at greater risk of ARDS can be identified, allowing preventive and therapeutic measures to be implemented.

Hypotension and metabolic acidosis [16], among other physiologic markers of the severity of systemic traumatic shock, have been related to the development of ARDS in trauma. As the present results indicate, ARDS development is more closely related to a physiologic severity score that includes these metabolic and hemodynamic variables (APACHE II) than to an anatomic score (ISS). These findings suggest that severity assessment at admission should consider

secondary physiologic alterations as well as anatomical injuries [17].

Onset of ARDS in trauma has long been associated with injury severity and presence of injuries in more than 1 anatomical region, whereas delayed stabilization of femoral fracture has been described as an independent predictor factor [18,19]. A recent study associated ARDS development with lung contusion severity at admission and proposed assessment of lung contusion by 3-dimensional CT reconstruction to identify high-risk patients [20]. Our multivariate model confirmed the association of ARDS with femoral fracture (*ICD-9* codes 820-821) and chest trauma (*ICD-9* code 807), with an OR of 3.16 and 3.85, respectively. Other long bone and pelvic fractures did not enter the final logistic regression model.

The *ICD-9* classification system was used to assess the types of injury in this study population because of reports in the literature of the prognostic implications of this system in severe trauma patients [21,22]. These data can complement the information yielded by other types of index, such as APACHE II, as demonstrated by the present study.

Administration of fluids during resuscitation, especially crystalloids, has also been implicated as a risk factor in ARDS. The absence of a significant association with ARDS onset in our multivariate analysis is consistent with previous findings by our group that questioned the role of fluid administration in the genesis of ARDS [23]. Our patients with ARDS were more severely ill and received more colloids than the patients without ARDS. Colloids are more efficient than crystalloids to expand intravascular volumes, so that less fluid is required. However, this theoretical advantage has long been controversial because increased permeability of the capillary membrane in severe hemorrhagic shock can allow colloids to enter the interstitial space, which can worsen edema and tissue oxygenation [24].

In contrast, a significant relationship was observed between ARDS development and blood transfusions during resuscitation. This can be interpreted in 2 ways, with blood transfusion as an etiologic factor in the development of ARDS or as a severity marker that complements the APACHE II score. Although it is difficult to separate these 2 aspects, the possibility is raised that blood transfusion might be an independent etiologic factor [25]. Transfusion-related acute lung injury is a relatively new concept and is related more to the triggering of enzymatic cascades by donor antileukocyte antibodies than to transfusion volume [26]. In fact, at the time of this study, transfused blood was not yet leukoreduced in our setting, and the above effect may have played a role. Recent studies identified a risk of acute lung injury after blood transfusion in mechanically ventilated patients [27]. It is possible that the systemic inflammatory response in severe trauma may be exacerbated by blood transfusion.

New approaches to mechanical ventilation, renal failure, and vasoactive drug therapy appear to have achieved a reduction in the overall mortality of traumatic ARDS over the past decade [28]. According to the present results, it may be possible to identify, within 24 hours of admission, trauma patients who could receive early measures to reduce the severity of a possible ARDS development, such as the application of prophylactic PEEP and limitation of tidal volume. Although this approach was initially ruled out 20 years ago, its evaluation was not based on a major study [29], and there is experimental evidence supporting its protective effect, with earlier application yielding greater benefit [30].

5. Conclusions

Our findings support the importance of early assessment based on first-24-hour physiologic and anatomic scores and presence of high-risk injuries such as chest trauma and bone fractures to identify patients who may be at greater risk of ARDS. Blood transfusion may play an independent role by exacerbating the inflammatory response.

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