## ORIGINAL INVESTIGATIONS

### Pathogenesis and Treatment of Kidney Disease and Hypertension

# Acute Renal Failure Due to Crush Syndrome During Marmara Earthquake

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• **During the earthquake in Marmara, Turkey (August 17, 1999), 87 of 476 victims (18.3%) admitted to Marmara University Hospital (Istanbul, Turkey) experienced renal failure caused by crush injuries. Fifty-nine patients (68%; 40 men, 19 women) required renal replacement therapy (RRT), whereas 28 patients (32%; 20 men, 16 women) recovered renal function under conservative treatment. The aim of the present study is to compare clinical and laboratory data from patients with crush syndrome who needed RRT with those who could be maintained on conservative medical treatment. Data for demographic, clinical, and laboratory findings of patients who had renal problems were collected retrospectively and analyzed. The proportion of men was significantly greater (68% versus 42%; $P < 0.05$), and time spent under the rubble was significantly shorter (9.4 ±6.9 versus 19.1 ± 22.5 hours; $P < 0.05$) among patients who required RRT compared with those who recovered under conservative treatment. Patients who required RRT had significantly less urine output in the first 24 hours, underwent more fasciotomies, and needed more blood and fresh frozen plasma transfusions ($P < 0.05$). Blood urea nitrogen, creatinine, potassium, creatine kinase, and aspartate aminotransferase levels were significantly greater compared with patients managed conservatively both on admission and for the mean of values obtained during the first 2 weeks ($P < 0.05$). Furthermore, fasciotomies were the most powerful predictors of a later need for RRT. In a similar disaster in the future, these factors should be taken into consideration for priority in referral to medical centers with dialysis facilities.**



**INDEX WORDS: Crush injury; crush syndrome; acute renal failure (ARF); hemodialysis (HD).**

A CATASTROPHIC earthquake with an intensity of 7.4 on the Richter scale struck the entire region surrounding the Marmara Sea on August 17, 1999. This region is the most densely populated area in Turkey, and the disaster affected approximately 15 million people in diverse ways. The registered number of deceased victims was 17,000, but local authorities suspect much greater mortality.

Crush injuries and prolonged compression of limbs are the most important types of trauma encountered in earthquake victims.[1,2] Crush injury results in a characteristic syndrome with rhabdomyolysis inducing myoglobinuric acute renal failure, named crush syndrome.[3]

The Renal Disaster Relief Task Force of the International Society of Nephrology (ISN) arrived at the scene within 24 hours of the disaster. They provided physical and moral support in various ways. This collaboration resulted in an organized approach not only for medical care, but also for the collection of valuable logistic and medical data, the correct analysis of which will be indispensable in planning rescue actions on the occasion of similar disasters in the future. Data collection was organized through the Turkish Society of Nephrology, and an extensive review of this information has been published.[4]

Marmara University Hospital (Istanbul, Turkey) was chosen as a primary reference hospital because of its close proximity to the disaster area. At Marmara Hospital, 476 earthquake victims were admitted, most of whom were severely injured. We believed it would be of interest to report the experience from a single center because it reflects results of a consistent therapeutic policy. In addition, it also was believed that this

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would permit a closer and more detailed examination of data to provide additional information that might get lost in a larger scale multicentric analysis. In the present study, we report the analysis of clinical and laboratory data of 87 patients with crush syndrome admitted and followed up in Marmara University Hospital. The primary aim of the study is to evaluate initial and later clinical and laboratory findings and compare those findings in patients who needed renal replacement therapy (RRT) with those of patients who could be maintained on conservative medical treatment.

## MATERIALS AND METHODS

### *Background*

Marmara University Hospital was the closest reference hospital during the Marmara earthquake of August 17, 1999, with an approximate distance of 100 to 130 km to the disaster region. The hospital has a total capacity of 500 beds. During the immediate aftermath of the earthquake, approximately 90% of these beds were reserved for earthquake victims. Furthermore, the hospital has a well-established hemodialysis center with 17 hemodialysis machines, which serves for patients on chronic maintenance hemodialysis and patients with acute renal failure. An immediate reorganization was made to transfer patients on chronic maintenance hemodialysis therapy to other facilities to offer as many dialysis machines as possible to the injured earthquake victims with acute renal failure. Management of the patient load was made easier by the temporary availability of four additional dialysis machines offered by the Renal Disaster Relief Task Force of the ISN and Doctors Without Borders.

### *Subjects*

Four hundred seventy-six victims (218 men, 258 women) from the Marmara earthquake were admitted to Marmara University Hospital; 87 of these patients had an acute renal problem secondary to traumatic rhabdomyolysis. Acute renal problems caused by crush injury were defined as the presence of at least one of the following: oliguria (urine output $<$ 400 mL/d) and elevated levels of blood urea nitrogen (BUN; $>$40 mg/dL), serum creatinine ($>$2.0 mg/dL), and potassium ($>$6 mEq/L). Eighty-seven patients (52 men, 35 women) conformed to this definition. All these patients experienced traumatic rhabdomyolysis of varying degrees. The age range of patients with renal problems was 35 $\pm$ 19 years for men and 32 $\pm$ 16 years for women.

During this earthquake, 639 patients were registered by the Turkish Society of Nephrology as having acute renal problems caused by crush injury.[4] These 639 patients were treated in 35 hospitals located in such adjacent cities as İstanbul, Bursa, Eskişehir, and Ankara. Patients treated in our hospital represent 13.6% of all victims with acute renal failure caused by traumatic rhabdomyolysis.

### *Clinical and Laboratory Data*

A retrospective analysis of hospital records was performed for all victims of the Marmara earthquake admitted to Marmara University Hospital who had an acute renal problem, defined previously. The following data were recorded: age, sex, systolic and diastolic blood pressure, presence of fever, time under the rubble, clinical data related to extent of the crush injury, and need for surgical intervention (amputations and/or fasciotomy). In addition, the following laboratory data were collected: complete blood count, serum potassium, sodium, BUN, creatinine, calcium, creatine kinase (CK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Initial data recorded on admission and the mean of values for the first 2 weeks of observation were collected. In addition, serum creatinine values on discharge were recorded.

Patients reaching our hospital within 24 hours were started on vigorous fluid administration, with sequential infusion of normal saline and 5% dextrose reaching up to 10 L/d, forced alkaline diuresis, and mannitol. In patients arriving after the first 24 hours of crush injury, fluid replacement depended on volume status assessment, obtained by clinical examination or invasive monitoring.

Patients with excessive crush syndrome with a potassium level greater than 6 mEq/L and/or daily urinary output less than 250 mL were administered RRT. Intermittent hemodialysis was the preferred procedure for RRT. It was performed using low-flux polysulfone dialyzers and bicarbonate dialysate buffer. Temporary central venous catheters were inserted to obtain vascular access. Potassium values were controlled at least twice daily, and the need for RRT was assessed according to obtained values.

The extent of crush injury was assessed by two different methods: first, as the percentage of total body area crushed calculated by using the rule of nines,[5] and second, by taking into consideration the number of limbs involved. The presence of extremity, thoracic, and/or head trauma also was noted. The main indication for fasciotomy was compartment syndrome, defined as lack of perfusion of a limb and the disappearance of distal pulses. In addition, urinary output during the first 24 hours after admission and the need for RRT were recorded. Data also were collected on amount and type of blood products administered, if any.

### *Statistical Analysis*

Statistical analysis was performed using commercially available software for statistical analysis (ARCUS Quickstat [Biomedical Research Solution, Addison Wesley Longman Ltd, Cambridge, UK] and SPSS, version 10.0 [SPS Inc, Chicago, IL]). Descriptive statistics for clinical and laboratory data are presented as mean $\pm$ SD. Paired *t*-test and chi-square were used, when appropriate, for comparison of quantitative and qualitative data, respectively. Multivariate analysis was performed using logistic regression and discriminant analysis to determine risk factors for dialysis need. Number of transfusions was analyzed by Wilcoxon's test. Statistical significance is accepted for $P$ less than 0.05.

**Table 1. Demographic Characteristics of Patients With an Acute Renal Problem Who Needed Dialysis Therapy Compared With Those Who Responded to Medical Treatment**

| | Patients Requiring Dialysis (n = 59) | Responders to Medical Treatment (n = 28) | *P* |
|---|---|---|---|
| Age (y) | 33.7 ± 13 | 34.5 ± 13 | Not significant |
| Sex (M/F) | 40/19 | 12/16 | 0.02 |
| Time under the rubble (h) | 9.4 ± 6.9 | 19.1 ± 22.5 | 0.003 |

## RESULTS

Demographic characteristics of patients with an acute renal problem who needed dialysis therapy compared with those who responded to medical treatment are listed in Table 1. Among 476 patients admitted to our hospital during the Marmara earthquake, 87 patients (18.2%; 52 men; mean age, 34.4 ± 15 years; 34 women; mean age, 31.9 ± 15.6 years) had an acute renal problem caused by crush injury, defined previously. Fifty-nine patients (68%; 40 men, 19 women) required RRT, whereas 28 patients (32%; 20 men, 16 women) recovered under conservative medical treatment. Mean time to dialysis therapy was 10.5 ± 5.3 hours after the hospital admission in patients who required RRT. Respective mean ages of the two groups were 33.7 ± 13.0 versus 34.5 ± 13.0 years ($P$ = not significant). The number of men was significantly higher in the group that required RRT (68% versus 42%; $P < 0.02$). Interestingly, patients requiring dialysis therapy spent a significantly shorter time under the rubble.

There were no significant differences between the two groups with regard to percentage of body area crushed (Table 2). Patients who required dialysis therapy had significantly less urine output in the first 24 hours, underwent more fasciotomies and amputations, and needed more blood and fresh frozen plasma transfusions compared with patients managed conservatively. Eight patients died during the hospitalization period, seven of these patients belonged to the group requiring RRT versus one patient who needed only conservative medical treatment ($P = 0.04$; Table 2).

Biochemical data on admission for both groups are listed in Table 3. The mean of values from the first 2 weeks is listed in Table 4. BUN, creatinine, potassium, and AST levels, both on admission and later, were significantly greater in patients requiring RRT. The initial CK value was greater in patients needing RRT; however, this difference was not maintained during further follow-up. The graphic demonstration of initial CK and AST values in patients requiring RRT, as well as the group managed conservatively, is shown in Figs 1 and 2. There were no statistically significant differences for hematocrit or leukocyte levels on admission (Table 3), but a statistically significant decrease in hematocrit and increase in leukocyte count was observed during the follow-up period in patients requiring hemo-

**Table 2. Clinical Characteristics of Patients With an Acute Renal Problem Who Required Dialysis Therapy Compared With Those Who Responded to Medical Treatment**

| | Patients Requiring Dialysis (n = 59) | Responders to Medical Treatment (n = 28) | *P* |
|---|---|---|---|
| Urine output in 1st 24 h (mL) | 453 ± 489 | 1,484 ± 1,382 | <0.0001 |
| Body area crushed (%) | 14 ± 8 | 13 ± 10 | NS |
| Presence of amputations | 10 | 2 | <0.01 |
| Presence of fasciotomy | 34 | 5 | 0.0003 |
| Patients administered blood transfusions | 41 (69.5) | 8 (28.6) | 0.04 |
| Blood transfusion (bags/patient) | 4.7 ± 6.5 | 1.9 ± 4.4 | 0.05 |
| Patients administered fresh frozen plasma | 23 (39) | 4 (14.3) | 0.001 |
| Fresh frozen plasma (bags/patient) | 3.5 ± 4.9 | 0.4 ± 1.1 | 0.002 |
| Deaths | 7 (11.8) | 1 (3.5) | 0.04 |

NOTE. Values expressed as mean ± SD or number (percent).
Abbreviation: NS, not significant.

**Table 3. Initial Laboratory Data for Patients With an Acute Renal Problem Who Required Dialysis Therapy Compared With Those Who Responded to Medical Treatment**

| Laboratory Values on Admission | Patients Requiring Dialysis (n = 59) | Responders to Medical Treatment (n = 28) | *P* |
|---|---|---|---|
| Hematocrit (%) | 35.2 ± 10.8 | 35.7 ± 7.4 | NS |
| Leukocytes (/μL) | 16,488 ± 9,156 | 13,620 ± 5,135 | NS |
| Platelets (/μL) | 172,206 ± 88,160 | 189,150 ± 61,977 | NS |
| BUN (mg/dL) | 69 ± 55 | 44 ± 28 | 0.02 |
| Creatinine (mg/dL) | 5.1 ± 3.8 | 2.2 ± 1.7 | 0.0002 |
| Potassium (mEq/L) | 5.5 ± 1.3 | 4.6 ± 0.8 | 0.004 |
| Calcium (mg/dL) | 7.5 ± 1 | 8.3 ± 0.7 | NS |
| CK (IU) | 4,977 ± 8,264 | 1,341 ± 1,843 | 0.02 |
| AST (IU) | 906 ± 721 | 425 ± 444 | 0.002 |
| ALT (IU) | 382 ± 448 | 222 ± 232 | NS |
| Albumin (mg/dL) | 2.6 ± 0.5 | 2.3 ± 0.5 | NS |

Abbreviation: NS, not significant.

dialysis therapy. All patients who were treated by RRT and survived recovered renal function and were free of dialysis therapy at discharge. Creatinine values at discharge were greater in patients who had required RRT: 1.9 ± 1.3 versus 1.3 ± 1.2 mg/dL, respectively ($P = 0.02$).

To analyze the initial positive and negative predictive factors for the later need for dialysis therapy, multivariate analysis was performed, entering age; sex; time under the rubble; number of injured limbs; need for fasciotomy; need for amputation; systolic blood pressure; presence of fever; percentage of crushed body surface; initial CK, ALT, and AST levels; and number of transfusions. Using a step-forward logistic regression, only need for fasciotomy (odds ratio [OR], 6.075; 95% confidence interval [CI], 1.82 to 20.1; $P = 0.001$) and time spent under the rubble (OR, 0.94/h; 95% CI, 0.88 to 1.00; $P = 0.05$) were retained in the model. The other parameters not included are listed in Table 5.

Using a step-forward discriminant analysis to predict the need for dialysis therapy, again, only need for fasciotomy ($P = 0.001$) and time spent under the rubble ($P = 0.001$) were retained in the model. This model predicted the need for dialysis therapy with a specificity of 87% and sensitivity of 57%. If all mentioned variables were entered for prediction, specificity increased to 96%, and sensitivity, to 78%.

Analysis of data for the 59 patients requiring RRT showed that these patients overall required

**Table 4. Average of First 2 Weeks' Laboratory Data for Patients With an Acute Renal Problem Who Required Dialysis Therapy Compared With Those Who Responded to Medical Treatment**

| Average of Laboratory Values During the First 2 Weeks | Patients Requiring Dialysis (n = 59) | Responders to Medical Treatment (n = 28) | *P* |
|---|---|---|---|
| Hematocrit (%) | 20.3 ± 4 | 26.1 ± 11 | 0.009 |
| Leukocytes (/μL) | 24,795 ± 12,079 | 16,396 ± 6,657 | 0.002 |
| Platelets (/μL) | 162,117 ± 78,140 | 178,577 ± 74,330 | NS |
| BUN (mg/dL) | 97 ± 51 | 44 ± 28 | <0.0001 |
| Creatinine (mg/dL) | 7.5 ± 3 | 2.2 ± 1.6 | <0.0001 |
| Potassium (mEq/L) | 5.9 ± 1.1 | 4.8 ± 0.7 | <0.0001 |
| Calcium (mg/dL) | 7.3 ± 1 | 8.3 ± 0.6 | NS |
| CK (IU) | 5,151 ± 11,907 | 4,734 ± 3,357 | NS |
| AST (IU) | 963 ± 706 | 612 ± 512 | 0.03 |
| ALT (IU) | 334 ± 228 | 255 ± 263 | NS |
| Albumin (mg/dL) | 2.3 ± 0.5 | 2.3 ± 0.4 | NS |

Abbreviation: NS, not significant.

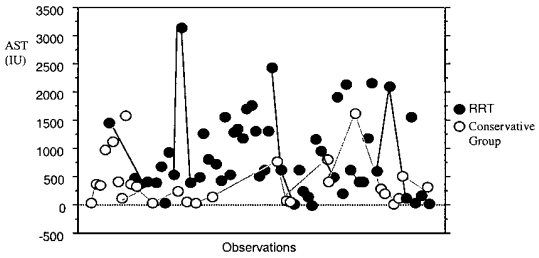


**Fig 1. Initial AST levels in patients on RRT and the conservative-therapy group.**

537 hemodialysis sessions. Of patients requiring RRT, 12 patients (20.3%) needed greater than 14 sessions, whereas 47 patients (79.7%) needed less than 14 dialysis sessions.

## DISCUSSION

To our knowledge, this study is the first comparing large-scale data from patients with crush syndrome who needed RRT with those who could be maintained on conservative medical treatment.

Earthquakes are the most unpredictable and potentially hazardous type of disaster. Throughout the world each year, an average of 16 earthquakes occur that lead to fatalities.[6] The major earthquakes of recent years that have led to massive loss of life have been associated with a variable incidence of acute renal failure.[7-10]

Sixty years ago, Bywaters[11] first defined crush syndrome as the clinical picture of acute renal failure developing in war victims who experienced crush trauma and subsequently died. Widespread use of dialysis with improved technology showed that when this opportunity can be offered, in appropriate cases, lives can be saved and renal function recovers completely within a brief delay.[6-13]

The Marmara earthquake was one of the most

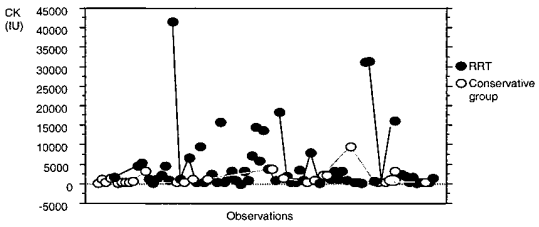


**Fig 2. Initial CK levels of patients on RRT and the conservative-treatment group.**

**Table 5. Logistic Regression Analysis of Factors Affecting RRT Requirement; Variables Not in the Equation for Prediction of Dialysis**

| Variables | OR | *P* |
|---|---|---|
| Age | 0.762 | 0.383 |
| No. of injured limbs | 2.027 | 0.154 |
| Need for amputation | 1.068 | 0.301 |
| Systolic blood pressure | 0.395 | 0.530 |
| Presence of fever | 0.066 | 0.797 |
| Crushed body surface (%) | 0.394 | 0.530 |
| Initial CK | 1.426 | 0.232 |
| Initial ALT | 1.969 | 0.161 |
| Initial AST | 1.761 | 0.185 |
| No. of transfusions | 16.815 | 0.266 |

NOTE. *P* to enter $< 0.05$.

catastrophic events of the last century. The Marmara region of Turkey is a densely populated area, and overall, cities of this region have approximately 20,000,000 inhabitants. Because of the destruction of most hospitals in the disaster region per se, victims were followed up in 35 hospitals that were as close as possible to the epicenter of the earthquake. Among these hospitals, Marmara University Hospital was one of the closest centers; therefore, it was accepted as the primary reference hospital by the Turkish Society of Nephrology. Our center had the largest number of admissions and the largest number of patients with acute renal failure caused by crush syndrome.

Among patients admitted to our hospital, 18.3% developed renal problems. The reported incidence of crush syndrome until the present seems to vary among different locations: 2% to 5% in Tangshan, China[14]; 7.4% in Hanshin-Awai, Japan[9]; and 25% in Mexico City.[15] These variations could be related to differences in climate, construction material, time under the rubble, availability and efficacy of rescue teams and medical support, distance to reference hospitals from the earthquake epicenter, and imperfections in data collection caused by disaster conditions.[13,16,17]

Ron et al[18] recommended aggressive fluid treatment at the location of the catastrophe, even before victims had been rescued. Myoglobinuric renal injury probably occurs after reperfusion of the trapped limb, releasing free myoglobin into the circulation.[19-22] The Marmara earthquake struck a very large area, and victims were res-

cued by many teams with variable technical facilities and even by amateur efforts. Furthermore, because local health infrastructures also were seriously damaged, only a limited number of victims could receive on-site fluid replacement therapy. Nevertheless, efforts were made to distribute pamphlets in the damaged area, giving concise information about the attitude to be taken.[23]

Conversely, during the Marmara earthquake, combined efforts of the Turkish army, civil organizations (medical and nonmedical), and the Renal Disaster Relief Task Force of the ISN saved many lives.[23] In addition to their extensive aid on the scene, the presence of the Renal Disaster Relief Task Force of the ISN also resulted in organized data collection with the intention to obtain better organization in the future. Therefore, data reported here may be of supplementary interest because of the systematic approach for data collection.

Demographic data show a male predominance in patients requiring dialysis therapy compared with those responding to conservative medical treatment (Table 1). However, sex difference was not a positive predictive factor of the need for dialysis therapy.

Time under the rubble was longer in patients responding to medical treatment compared with patients requiring dialysis (Table 1), and also in multivariate analysis, longer time under the rubble decreased the OR for dialysis therapy. It has been claimed that a minimum of 4 hours of muscle contusion is required to result in crush syndrome.[24] Therefore, a shorter time under the rubble seems to be contradictory to what is expected. However, most patients with severe muscle injury also had head trauma and thorax compression leading to lung contusion; therefore, these patients probably died before they could reach a hospital unless they were rescued very fast. Conversely, victims rescued only after a long delay had less severe injury and thus a lower risk for dialysis therapy. Therefore, longer time under the rubble in the medically managed group could be related to less severe injury. This also is reflected in the greater OR in patients who needed fasciotomy, as an indicator of severity of injury.

Time under the rubble does not give an ideal reflection of the possible severity of the crush injury because it is the magnitude of pressure in a given time that is important, not only the time itself. Percentage of crushed body area and number of fasciotomies therefore could be better predictors of the severity of crush injury. We used the rule of nines currently applied to measure body surface area involved in burns to measure the percentage of body area crushed and found no difference between the two groups. However, crushed body surface area is merely a measure of body surface and does not reflect the depth and/or mass of crushed muscles. Therefore, the authors believe the lack of statistically significant difference between the two groups cannot be interpreted as similarity in the severity of crush injury.

Although the percentage of body area crushed is similar in the two groups, the number of fasciotomies and amputations was higher in patients requiring dialysis therapy (Table 2). Fasciotomy was the most powerful predictive factor for the later need for dialysis therapy in multivariate analysis. Patients who underwent fasciotomy had an approximately 10 times increased risk for dialysis requirement. The impact of all other factors, such as sex; age; number of injured limbs; need for amputation; systolic blood pressure; presence of fever; percentage of body surface crushed; initial CK, ALT, and AST levels; and number of transfusions, was covered in the multivariate model by the need for fasciotomies. The need for fasciotomy thus can be considered a good indicator of the severity of the crush.

Fasciotomy was the most frequent surgical intervention among the presently evaluated patients and is associated with significant blood and fluid loss from the wound. More importantly, it significantly increases the risk for life-threatening infections and deterioration of renal function in patients with crush syndrome.

Despite vigorous fluid replacement, forced alkaline diuresis, and mannitol administration, urine output in the first 24 hours was significantly lower in the group of patients requiring dialysis therapy compared with the other group (Table 2). Although this parameter did not appear a strong predictor in logistic regression, this probably reflects that some patients may develop nonoliguric renal failure. The authors still believe that patients with urine output less than 400 mL

during the first 24 hours need to have priority in referral to centers with dialysis facilities.

CK and AST levels, accepted markers of muscle damage, were significantly greater on admission in patients requiring dialysis therapy. However, these two biochemical markers did not have a major impact on increasing the risk for dialysis therapy in multivariate logistic analysis (Table 5). During the follow-up period, AST levels remained significantly greater in patients requiring RRT, whereas the difference between CK levels became insignificant.

Despite the similarity of hematocrit and leukocyte levels on admission (Table 4), a statistically significant decrease in hematocrit and increase in leukocyte count were observed during the follow-up period in patients requiring hemodialysis therapy. Both differences can be attributed, at least in part, to a higher number of fasciotomies and amputations in this group. Surgical interventions are a common source of blood loss, and in addition, fasciotomies are a common source of infection and sepsis.[24,25]

The favorable outcome of renal function in patients requiring RRT suggests that dialysis requirement is not necessarily a bad prognostic predictor for recovery of renal function.

The present study also offers logistic information regarding the use of technical and human resources. Analysis of logistic data for the 59 patients requiring dialysis therapy showed that these patients overall required 537 hemodialysis sessions. The majority of these patients (80%) required dialysis therapy for less than 14 days. These data suggest that the need for such technical support as dialysis machines, dialyzers, and dialysis fluid and professional help offered by nephrologists, dialysis nurses, and technicians is greatest during the first 2 weeks. The same is true for the need for blood and blood products because patients requiring dialysis therapy also had an increased requirement for the use of these products (Table 2).

In conclusion, patients with crush syndrome who require dialysis therapy most frequently also have severe trauma of the extremities necessitating fasciotomies, and fasciotomies seem to be the strongest predictor of later need for RRT. These patients also have a greater requirement for blood and/or blood products. Our data suggest that patients with crush syndrome fulfilling the conditions stated should have priority in referral to medical centers with dialysis facilities in the occurrence of a similar disaster in the future.

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