Epidemiology and Risk Factors for Pathologic Scarring After Burn Wounds

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Objective: To describe the clinical characteristics of post-burn scars and determine the independent risk factors specific to these patients. While burns may generate widespread and disfiguring scars and have a dramatic influence on patient quality of life, the prevalence of post-burn pathologic scarring is not well documented, and the impact of certain risk factors is poorly understood.

Methods: A retrospective analysis was conducted of the clinical records of 703 patients (2440 anatomic burn sites) treated at the Turin Burn Outpatient Clinic between January 1994 and May 15, 2006. Prevalence and evolution time of postburn pathologic scarring were analyzed with univariate and multivariate risk factor analysis by sex, age, burn surface and full-thickness area, cause of the burn, wound healing time, type of burn treatment, number of surgical procedures, type of surgery, type of skin graft, and excision and graft timing.

Results: Pathologic scarring was diagnosed in 540 patients (77%): 310 had hypertrophic scars (44%); 34, contractures (5%); and 196, hypertrophic-contracted scars (28%). The hypertrophic induction was assessed at a median of 23 days after reepithelialization and lasted 15 months (median). A nomogram, based on the multivariate regression model, showed that female sex, young age, burn sites on the neck and/or upper limbs, multiple surgical procedures, and meshed skin grafts were independent risk factors for postburn pathologic scarring (Dxy 0.30).

Conclusion: The identification of the principal risk factors for postburn pathologic scarring not only would be a valuable aid in early risk stratification but also might help in assessing outcomes adjusted for patient risk.

Arch Facial Plast Surg. 2008;10(2):93-102

Although the modern concepts of burn care date from World War II, major advances in the treatment of massive burn injuries have been made only since the 1960s. Indeed, improved critical care with optimized fluid and electrolyte management combined with new surgical techniques and the use of skin allografts and cultured skin cells have had a strong impact on the natural history of such injuries. Thus, the survival rate of patients with major burns has greatly increased over the last few decades. Unfortunately, humans do not heal through a process of tissue regeneration. Scarring is therefore the rule and remains a lasting reminder of the insult to the patient and the outside world alike. Moreover, minimal scarring, in terms of the quality of the reparative processes and absence of pathologic alterations of the wound healing, is one of the main requirements for recovery. Therefore, care of the burn patient must be oriented toward the best possible functional and cosmetic rehabilitation.

Burn scars have a dramatic influence on a patient’s quality of life. They have been associated with anxiety, social avoidance, depression, a disruption in activities of daily living, the onset of sleep disturbances, and all of the consequent difficulties in returning to normal life after physical rehabilitation. Normotrophic scars, which represent the best clinical end point for treatment, are characterized by minor alterations in skin properties. Perturbations of cutaneous wound-healing mechanisms give rise to the formation of pathologic scars.

There is still much controversy as to the pathophysiology, taxonomy, and clinical course of postburn scarring. Indeed, few epidemiologic observations and data have been published on this question. Furthermore, most of the clinical studies are not homogeneous and often do not include an adjusted population. Thus, the estimates of prevalence determined by these studies vary widely and can be used only as suggestive and advisory data in daily practice. Likewise, knowledge of the risk factors for pathologic scarring is poor, based on supposi-
tions derived from case studies, opinions, and personal expert experiences with no strong statistical correlation. Moreover, in the literature reports, scars have a poorly defined anatomopathologic classification; laboratory markers of induction or remission of abnormality are not reported; and there is a lack of sensitive and specific methods to aid in making an objective evaluation.

Generally, pathologic scarring seems to have a higher prevalence after burns than after surgical procedures or other traumatic lesions. Only a few studies have developed an analysis of prevalence and description of postburn pathologic scarring. Deitch et al.6 analyzed 100 patients with non-surgical burn wounds considering some presumed risk factors. The results showed a 38% prevalence of pathologic scars (hypertrophy and keloid). When the prevalence was calculated for a single anatomic burn area, it dropped to 26%. Stella7 and Bombaro et al.8 describe both type and evolution of the scarring phenomenon in patients with different burn surface areas (BSAs) and report a 70% prevalence of pathologic scars (hypertrophy, hypertrophy with contracture, contracture, and atrophy). Dedovic et al.9 evaluated the cases of more than 700 children 15 years or younger and reported a prevalence of at least 32%. Finally, Spurr and Shakespeare10 investigated the occurrence of scars in children younger than 5 years with the same pattern and nature of burn injury and reported at least 50% pathologic scarring.

The factors involved in pathologic scar formation are still under debate, and their complexity, especially with burns, is well known. Paradoxically, nothing is known of what variables are implicated in the normotrophic scarring process, which interests many patients.7 Deitch et al.6 report a substantial difference between prevalences calculated by single patients vs those calculated by single areas. These data imply that pathologic scarring may involve a local process that depends on the injured site, with the thorax, upper limbs, and feet being at increased risk. Unfortunately, this association has not been confirmed.

The pathologic scar seems to have the same prevalence in both sexes. Borsini et al.11 show that hypertrophy is more common in young patients and that evolution seems to be longest in children. On the contrary, scarring often evolves more rapidly in elderly patients.11 Hypertrophy is directly correlated with burn extension and occurs more frequently when the burn is caused by flame. The literature has documented race as a risk factor for pathologic scarring, particularly keloids, with black patients bearing a 2-fold risk compared with Hispanic and Asian patients.6,12 These data suggest that genetics play an important role in the pathogenesis of scarring; indeed, some articles seem to support this hypothesis.13-15 It seems that such local factors as burn depth, the presence of infection in the wound bed, and healing delay have a relevance.6

Few studies consider the type of surgical treatment: generally, treatment with a full-thickness skin graft leads to a lower prevalence of contracture than treatment with a partial-thickness skin graft or spontaneous healing.16 On the contrary, Yannas17 suggests that treatment of the excised burn with biological or biosynthetic cutaneous substitutes improves scar quality, possibly because these treatment techniques allow for regeneration rather than repair of the normal skin layers.

Herein, we describe the clinical characteristics and evolution of postburn scarring in a wide population, determine the factors associated with an increased risk of pathologic scarring, and establish useful guidelines for determining a reliable prognosis and the best treatment options.

### METHODS

Beginning in January 1994, The Department of Plastic and Reconstructive Surgery–Burn Center of The Turin Traumatologic Hospital has made use of a standard form for the collection of data regarding the scarring process. Clinical histories are compiled by consulting the patient’s clinical notes during their initial hospitalization as well as the details recorded during outpatient clinic visits and/or subsequent hospitalizations for corrective surgery.

The present cohort was made up of 703 patients and included a total of 2440 anatomic burn sites. All patients were enrolled into a surveillance program after the completion of the burn wound healing phase to control and/or treat the post-burn scarring as necessary. During this study, the type of scar was defined on the basis of the morphologic classification described by Magliacani et al.18 and the scar evolution was evaluated according to the classification groups described by Muir19 (ie, in days from manifestation until complete remission) (Table 1).

Patients were given a weekly clinical examination until the second month after complete reepithelialization, and from the third month, on average, they were visited monthly until the sixth month (more frequently if deemed necessary). Throughout this period a number of characteristics were evaluated (Table 2): sex, age, total burn surface and full-thickness area, cause of the burn, and wound healing time. If the burn involved more than 1 anatomic area, each burn site (Figure 1) was evaluated individually for type of burn treatment (medical or surgical), number of surgical procedures, type of surgical approach (excision and coverage with autologous skin grafts, Alexander technique, dermal abrasion, or another technique), type of skin graft (sheet or meshed), and excision and graft timing.

The diagnosis of pathologic or normotrophic scarring was based on the clinical evaluation. Our primary objective was to describe the severity and characteristics of pathologic scarring as it presents in the clinical environment.

The scars were classified as normotrophic (1) when they assumed characteristics similar to those of the surrounding healthy skin in terms of thickness, color, and pliability; (2) when they were only slightly hypopigmented or hyperpigmented; or (3) when any erythema, with or without itching, disappeared within

### Table 1. Clinical Classification of Pathologic Postburn Scars

<table>
<thead>
<tr>
<th>Scar Typea</th>
<th>Scar Diffusion</th>
<th>Scar Evolutionb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotrophy</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>Generalized, localized</td>
<td>Short-term, intermediate, long-term</td>
</tr>
<tr>
<td>Hypertrophy and contracture</td>
<td>Generalized, localized</td>
<td>Short-term, intermediate, long-term</td>
</tr>
<tr>
<td>Contracture</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Atrophy</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

a Type classification as described by Magliacani et al.18

b Scar evolution was evaluated according to the groups described by Muir.19

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Pathologic scars (hypertrophy, contracture, and/or atrophy) were diagnosed on the basis of the presence of typical signs and symptoms (Table 3). Medical treatment was started for pathologic scars, and the checkups were repeated every 30 to 40 days. When scarring began to enter into the remission phase, clinical controls were reduced to every 2 months, followed by every 6 months after complete remission.

Table 2. Clinical Characteristics of the Study Population by Burn Scar Type

<table>
<thead>
<tr>
<th>Characteristicb</th>
<th>Overall Study Population</th>
<th>NS (n=1058)</th>
<th>HS (n=905)</th>
<th>HS + C (n=385)</th>
<th>C (n=88)</th>
<th>AS (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>1526 (63) 692 (65)</td>
<td>551 (61)</td>
<td>227 (59)</td>
<td>53 (60)</td>
<td>3 (75)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age</td>
<td>914 (37) 366 (35)</td>
<td>354 (39)</td>
<td>158 (41)</td>
<td>35 (40)</td>
<td>1 (25)</td>
<td>1.24 (0.99-1.56)</td>
</tr>
<tr>
<td>Cause of burn</td>
<td>38 (25-54) 38 (25-54)</td>
<td>38 (24-54)</td>
<td>36 (24-52)</td>
<td>41 (22-59)</td>
<td>31 (15-51)</td>
<td>0.94 (0.81-1.10)</td>
</tr>
<tr>
<td>FT BSA, median (IQR), %</td>
<td>20 (10-35) 18 (10-35)</td>
<td>20 (10-35)</td>
<td>30 (15-45)</td>
<td>15 (10-30)</td>
<td>10 (8-14)</td>
<td>1.15 (0.97-1.36)</td>
</tr>
<tr>
<td>Cause of burn</td>
<td>10 (0-25) 8 (0-20)</td>
<td>10 (4-20)</td>
<td>20 (10-30)</td>
<td>10 (5-25)</td>
<td>10 (7-11)</td>
<td>1.54 (1.22-1.94)</td>
</tr>
<tr>
<td>Cause of burn</td>
<td>(n=2334)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical</td>
<td>50 (2) 22 (2)</td>
<td>21 (3)</td>
<td>5 (1)</td>
<td>1 (1)</td>
<td>1 (50)</td>
<td>0.91 (0.43-1.95)</td>
</tr>
<tr>
<td>Contact</td>
<td>36 (2) 18 (2)</td>
<td>10 (1)</td>
<td>6 (2)</td>
<td>2 (3)</td>
<td>0</td>
<td>0.72 (0.27-1.91)</td>
</tr>
<tr>
<td>Electrical</td>
<td>36 (2) 29 (3)</td>
<td>6 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>0.17 (0.06-0.49)</td>
</tr>
<tr>
<td>Flame</td>
<td>1:4 (67) 62 (64)</td>
<td>561 (67)</td>
<td>262 (76)</td>
<td>43 (58)</td>
<td>0</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Scald</td>
<td>297 (13) 140 (14)</td>
<td>125 (15)</td>
<td>18 (5)</td>
<td>14 (19)</td>
<td>0</td>
<td>0.80 (0.59-1.10)</td>
</tr>
<tr>
<td>Pressure</td>
<td>5 (&lt;1) 0</td>
<td>3 (&lt;1)</td>
<td>2 (1)</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Flash</td>
<td>299 (13) 128 (13)</td>
<td>104 (12)</td>
<td>54 (16)</td>
<td>13 (18)</td>
<td>0</td>
<td>0.96 (0.65-1.41)</td>
</tr>
<tr>
<td>Sunburn</td>
<td>12 (1) 10 (1)</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.14 (0.04-0.58)</td>
</tr>
<tr>
<td>Steam</td>
<td>13 (1) 6 (1)</td>
<td>6 (1)</td>
<td>0</td>
<td>0</td>
<td>1 (50)</td>
<td>0.84 (0.20-3.49)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>170 (7) 98 (9)</td>
<td>67 (7)</td>
<td>5 (1)</td>
<td>0</td>
<td>0</td>
<td>0.41 (0.30-0.58)</td>
</tr>
<tr>
<td>Lower limb</td>
<td>606 (25) 234 (22)</td>
<td>321 (35)</td>
<td>48 (12)</td>
<td>1 (1)</td>
<td>2 (50)</td>
<td>0.90 (0.70-1.16)</td>
</tr>
<tr>
<td>Upper limb</td>
<td>834 (34) 301 (28)</td>
<td>308 (34)</td>
<td>185 (48)</td>
<td>39 (44)</td>
<td>1 (25)</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Neck</td>
<td>166 (7) 71 (7)</td>
<td>26 (3)</td>
<td>49 (13)</td>
<td>16 (18)</td>
<td>0</td>
<td>0.72 (0.51-1.03)</td>
</tr>
<tr>
<td>Perineum</td>
<td>77 (3) 50 (3)</td>
<td>24 (3)</td>
<td>3 (1)</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>290 (12) 199 (19)</td>
<td>61 (7)</td>
<td>20 (5)</td>
<td>9 (10)</td>
<td>1 (25)</td>
<td>0.26 (0.19-0.34)</td>
</tr>
<tr>
<td>Chest</td>
<td>301 (12) 105 (10)</td>
<td>98 (11)</td>
<td>75 (19)</td>
<td>23 (26)</td>
<td>0</td>
<td>1.05 (0.80-1.39)</td>
</tr>
<tr>
<td>Burn treatment</td>
<td>Medical</td>
<td>1106 (45) 678 (64)</td>
<td>336 (37)</td>
<td>65 (17)</td>
<td>25 (28)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Surgical</td>
<td>1334 (55) 380 (36)</td>
<td>569 (63)</td>
<td>320 (83)</td>
<td>63 (72)</td>
<td>2 (50)</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>No. of surgical procedures (n=2301)</td>
<td>1105 (48) 677 (67)</td>
<td>336 (39)</td>
<td>65 (18)</td>
<td>25 (32)</td>
<td>2 (50)</td>
<td>2.10 (1.73-2.56)</td>
</tr>
<tr>
<td>Type of surgical approach (n=1330)</td>
<td>Alexander</td>
<td>15 (1) 4 (1)</td>
<td>7 (1)</td>
<td>4 (1)</td>
<td>0</td>
<td>0.05 (0.13-0.83)</td>
</tr>
<tr>
<td>Dermal abrasion</td>
<td>34 (3) 14 (4)</td>
<td>14 (2)</td>
<td>4 (1)</td>
<td>2 (3)</td>
<td>0</td>
<td>0.55 (0.26-1.16)</td>
</tr>
<tr>
<td>Flap</td>
<td>6 (&lt;1) 6 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Excision</td>
<td>43 (3) 7 (2)</td>
<td>23 (4)</td>
<td>12 (4)</td>
<td>1 (2)</td>
<td>0</td>
<td>1.97 (0.82-4.69)</td>
</tr>
<tr>
<td>Excision and autograft</td>
<td>1211 (91) 335 (89)</td>
<td>515 (91)</td>
<td>299 (93)</td>
<td>60 (95)</td>
<td>2 (100)</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Excision and xenograft</td>
<td>6 (&lt;1) 5 (1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Excision and allograft</td>
<td>15 (1) 7 (2)</td>
<td>7 (1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Type of skin graft (n=847)</td>
<td>1:2</td>
<td>229 (27) 59 (27)</td>
<td>114 (30)</td>
<td>44 (21)</td>
<td>12 (31)</td>
<td>NA</td>
</tr>
<tr>
<td>1:4</td>
<td>450 (53) 113 (51)</td>
<td>218 (58)</td>
<td>108 (51)</td>
<td>11 (28)</td>
<td>0</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>1:6</td>
<td>8 (1) 3 (1)</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Sheet</td>
<td>160 (18) 47 (21)</td>
<td>40 (11)</td>
<td>57 (27)</td>
<td>16 (41)</td>
<td>0</td>
<td>0.81 (0.49-1.33)</td>
</tr>
<tr>
<td>Wound healing time, median (IQR), d+</td>
<td>40 (25-67) 35 (20-60)</td>
<td>40 (27-62)</td>
<td>55 (35-67)</td>
<td>57 (51-100)</td>
<td>19 (10-28)</td>
<td>1.15 (1.02-1.29)</td>
</tr>
<tr>
<td>Excision and grafting time, median (IQR), d+ (n=1102)</td>
<td>10 (5-17) 10 (5-19)</td>
<td>10 (6-17)</td>
<td>7 (3-16)</td>
<td>10 (4-16)</td>
<td>9</td>
<td>0.90 (0.79-1.02)</td>
</tr>
</tbody>
</table>

Abbreviations: AS, atrophic scars; BSA, burn surface area; C, contractures; CI, confidence interval; FT, full thickness; HS, hypertrophic scars; IQR, interquartile range; NA, not applicable; NS, normotrophic scars; PS, pathologic scars.

a Unless otherwise indicated, data are reported as number (percentage) of patients.
b Unless otherwise indicated, the total number of patients included in the analysis of a given group is 2440.
c Unless otherwise indicated, odds ratios apply (1) to the effect of an interquartile difference for continuous variables (eg, age interquartile difference, 29 years; therefore, for every increase of 29 years in age, the odds ratio is 0.94) or (2) to the category with the highest observed frequency (reference) for categorical variables (eg, male sex is the highest observed category; therefore, the 1.24 odds ratio is interpreted for female vs male). Boldface type indicates a statistically significant finding.
d Odds ratio applies to the effect of difference in 1 surgical procedure.

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In the case of hypertrophy, the diffusion (localized or generalized) was evaluated. To evaluate the hypertrophic scar evolution, we considered (1) the type of treatment applied to every location (medical and/or surgical), (2) latency of appearance (from induction to initial remission), (3) activity duration (from induction to complete remission), (4) remission time (from initial remission to complete remission), and (5) total duration of hypertrophic scarring (from induction to complete remission).

For contracted scars, only the latency of appearance and type of treatment were considered.

Surgical indications included scar retraction or hypertrophic scarring associated with contractures that could not be managed by the conventional use of physiotherapeutic rehabilitation. While surgery was indicated for hypertrophy, it was used only in the case of stable scars, ie, those in complete remission.

Continuous data are expressed as medians with interquartile ranges (IQRs) as a measure of variability. Scar evolution was expressed by the time before the onset of scarring and was estimated using the Kaplan-Meier curve and 95% confidence interval (CI).

The individual effects of patient characteristics and clinical and instrumental variables on the risk of pathologic postburn scarring (vs normotrophic scarring) were evaluated by a logistic regression model and a univariate estimate of the odds ratios (ORs) presented along with their 95% CIs. No P values are presented.

A total of 540 of 703 patients were classified as having pathologic scars, for an overall prevalence of 77%. The development of hypertrophy was observed in 310 (44%) (Figure 2A-C), hypertrophy with contracture in 196 (28%) (Figure 2B), and pure contracture in 24 (5%) (Figure 2D). A localized form of hypertrophic scarring was observed in 372 (69%), while scarring was generalized to all burn locations in 168 (31%).

The prevalence of pathologic scarring decreased to 57% when the cohort was considered according to the anatomic burn sites (1382 of 2440). However, hypertrophy with and without contracture remained the most common type of scar (28% [385 of 1382] and 65% [905 of 1382], respectively).

As to scar evolution, 403 of 506 burn patients with hypertrophic scars (80%) completed the surveillance program, with 986 of 1290 hypertrophic scar areas healed (77%) (ie, with complete remission of clinical signs of scar abnormality), 199 lost to follow-up (16%), and 105 still in evolution (8%) at the end of the study (May 15, 2006).

The percentage of hypertrophic scars increased, with a median latency of 23 days (IQR, 11-45 days) from com-

### Table 3. Clinical Presentation of Pathologic Postburn Scars

<table>
<thead>
<tr>
<th>Scar Type</th>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophy</td>
<td>Raised, erythematous, or fibrous skin</td>
<td>Pain, itching, dysesthesias</td>
</tr>
<tr>
<td>Contracture</td>
<td>Skin coarctation or deformity</td>
<td>Reduced range of motion in involved joints, subjective sensation of constriction</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Thinned or fragile skin</td>
<td>Itching</td>
</tr>
</tbody>
</table>

*Induction characterized by the onset of the listed signs and symptoms and remission by a gradual decrease in intensity.
complete burn healing. The total median length of the scar process was 15 months (IQR, 10-23 months) divided into an activity phase of 23 weeks (IQR, 15-36 weeks) and a remission phase of 40 weeks (IQR, 24-67 weeks) (Table 4).

When stratified according to the Muir classification chart, 153 hypertrophic scars regressed within 1 year and were considered to undergo short-term evolution (38%). The same percentage became normotrophic within 2 years (intermediate-term evolution), and 98 remained active for many years (24%) (long-term evolution) (Table 4). When the cohort was evaluated according to the anatomic scar areas, the percentages were similar to those found in the Muir scar classification analysis (Figure 3). The remission period could be considered the crucial phase for the classification of the evolution term because it lasted for a median period of 5 months (IQR, 3.5-6.5 months) in short-term scars, 10.5 months (IQR, 8-13 months) in intermediate-term scars, and 23 months (IQR, 18-29 months) in long-term scars. On the contrary, the median length of the activity phase was quite similar in all 3 different evolution types (6 months; IQR, 4-8 months) (Table 4).

Hypertrophic scars with contracture developed earlier than did pure hypertrophic scars (19 days [IQR, 10-34 days] vs 26 days [IQR, 12-50 days]), and a median of 2 months more was required to reach complete remission (16 months [IQR, 11-24 months] vs 14 months [IQR, 10-23 months]).

RISK FACTOR ANALYSIS

A univariate analysis of predictors of postburn pathologic scarring is summarized in Table 2, while a univariate analysis of the predictors of postburn hypertrophic scarring and postburn contracted scarring is summarized in Table 5.

SEX AND AGE AT BURN TRAUMA

The study population was made up of 412 men (59%) and 291 women (41%). As summarized in Table 2, women were more prone to postburn pathologic scarring than men (OR, 1.24; 95% CI, 0.99-1.56). The median age at initial burn injury was 38 years (IQR, 25-54 years). Older subjects had a significantly lower risk of pathologic scarring (OR, 0.64; 95% CI, 0.45-0.90), both for hypertrophy (OR, 0.55; 95% CI, 0.36-0.82) and for contracture (OR, 0.68; 95% CI, 0.44-1.05) at multivariate analysis (Table 6).

BURN SEVERITY

The median BSA was 18% (IQR, 10%-35%) in patients with normotrophic scars, while it was 30% (IQR, 15%-
45%) in those burn patients who developed hypertrophic-contracted scars. The same difference was observed in the full-thickness BSA analysis: 8% (IQR, 0%-20%) for patients without pathologic scars and 20% (IQR, 10%-30%) for those with hypertrophy and contracture. The risk of postburn pathologic scarring was significantly higher among those with a high percentage of BSA (OR, 1.15; 95% CI, 0.97-1.36) and full-thickness BSA (OR, 1.54; 95% CI, 1.22-1.94).

**BURN CAUSE**

The prevailing burn cause was the flame, primed most commonly by alcohol, gasoline, or solvents. Scalds (prevalently by hot water) were the second most frequent cause, followed by flash flame caused usually by flammable gases. Less common among the evaluated burns were electrical burns, chemical burns (usually by acids), contact burns, steam burns, pressure burns, and sunburns. A total of 620 of the 1058 normotrophic scar areas were caused by flame burns (64%) compared with 262 of the 385 hypertrophic-contracted scar areas (76%). Compared with flame burns, electrical burns (OR, 0.17; 95% CI, 0.06-0.49) and sunburns (OR, 0.14; 95% CI, 0.04-0.58) were significantly more likely to result in normotrophic scarring, while scalds had significantly less risk for contracted scarring (OR, 0.46; 95% CI, 0.27-0.80).

**BURN LOCATION**

More than 50% of the 2440 burn sites involved the 4 limbs, with the upper limbs being the most commonly injured area (34%). Distal segments of affected anatomic sites were the most involved (eg, wrist and hand), especially in association with head burns (12%), which were mainly on the nose, ears, and the cheeks.

Burns on the abdomen (OR, 0.41; 95% CI, 0.30-0.58), perineum (OR, 0.30; 95% CI, 0.19-0.50), and head (OR, 0.26; 95% CI, 0.19-0.34) had a significantly lower risk of pathologic scarring than burns of the upper limb. Of the 834 burns of the upper limb and of the 301 chest burns, respectively, 533 (64%) and 196 (65%) generated pathologic scars. Burns of the lower limb often generated hypertrophic scars (OR, 1.34; 95% CI, 1.03-1.74) rather than contractures (OR, 0.28; 95% CI, 0.18-0.44). In contrast, burns on the neck generated more hypertrophic and contracted scars than they did pure hypertrophy (OR, 0.36; 95% CI, 0.22-0.58).

**BURN TREATMENT**

The aim of this study was not to evaluate the efficacy of one specific burn treatment over another on the scar outcome. The strategies applied were not selected before starting but rather followed those standard indications that had produced the most evidence in literature. Therefore, the associations obtained were the result of a simple retrospective observation of the study cohort.

Surgical indications were present for 1334 burn sites (55%). It was necessary to perform 2 or more surgical procedures in 31% of the surgical burns (366 of 1196), commonly in massive burns for multiple excisions and in deep burns for temporary coverage with alloplastic skin grafts to prepare the wound bed. When burn surgery was evaluated, only the last operation was taken into consideration as a presumed risk factor.

The type of surgical approach most commonly used was excision and coverage with autologous skin grafts (91%; 1211 of 1330). The most common type of skin graft applied was 1:4 meshed (53%), while the sheet skin graft was used in 78% of neck burns and in 26% of upper limb burns, particularly for those on the dorsal sur-
face of fingers and hands. Dermal abrasion was used most frequently in the treatment of head burns (3%; 34 of 1330), while local and regional flaps were used for the coverage of deep electrical necrosis (6 of 1330).

Nonsurgical burn healing was significantly more protective in terms of scar outcome than surgical burn treatment (OR, 0.25; 95% CI, 0.20-0.31). In fact, the risk of pathologic scarring significantly doubled for every surgical operation performed (OR, 2.2; 95% CI, 1.73-2.56). No substantial difference was evidenced by the analysis of the type of surgical technique used.

More interesting were the results obtained from skin grafting analysis. Sheet skin grafts were significantly more prone to hypertrophic scarring (OR, 0.44; 95% CI, 0.25-0.78) and more prone to contracture, although not significantly (OR, 1.47; 95% CI, 0.85-2.56) than 1:4 meshed skin grafts.

Finally, a delayed wound healing time was a significant risk factor for pathologic scarring (OR, 1.15; 95% CI, 0.85-1.57) while local and regional flaps were used for the cover-

## POSTBURN SCAR TREATMENT

Seventy-nine percent of all pathologic postburn scar locations were treated with medical and rehabilitative therapy (1097 of 1382): 82% of hypertrophic scars (n = 742), 35% of pure contractures (n = 31), and 84% of hypertrophic and contracted scars (n = 324). On the contrary, there were indications for reconstructive surgery in 233 of 1382 pathologic scar locations (17%).

The most commonly prescribed therapy was a compressive elastic garment (46%), especially for limb and chest scars. Contact media (20%), represented by silicone gel sheeting and adhesive microporous hypoallergenic paper tape, were used on scars of limited extension, often in partial remission and sometimes in association with pressure therapy. Other treatment included rehabilitation (17%), thermal cures and massages (10%), splints, LPG System Bodywear (Valencia, France), laser therapy, and corticosteroid injections.

Surgical treatment was indicated mainly for contracted scars (87%; 196 of 233). Multiple reconstructive procedures were often necessary to obtain a complete correction of skin coarctation. Hypertrophic scars were always operated on after complete remission and mainly for aesthetic reasons (4%; 37 of 1058). The most commonly corrected scar sites were the neck, hand, mouth, eyelid, elbow, and axilla.

Surprisingly, medical treatment did not significantly improve time to complete remission (hazard ratio, 0.79; 95% CI, 0.57-1.11).

## PREDICTION OF OUTCOME

Multivariate analysis results based on each prognostic model are summarized in Table 6.

Sex, age, anatomic burn site, number of surgical procedures, and type of skin graft were selected as independent predictors of pathologic postburn scarring. However, when hypertrophic and contracture scarring were considered as single outcomes, the addition of full-thickness BSA to the other variables was significantly associated with scar outcome.

Finally, to estimate the risk of developing a pathologic postburn scar in the individual patient, a nomogram was generated (Figure 4). On the basis of the multivariate model for pathologic scarring, specific points relative to the effect on the risk of the categorical variables were as-

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### Table 5. Univariate Analysis of Predictor Characteristics

<table>
<thead>
<tr>
<th>Predictor Characteristic</th>
<th>Hypertrophy vs Normotrophy</th>
<th>Contracture vs Normotrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (vs male)</td>
<td>1.21 (0.94-1.57)</td>
<td>1.30 (0.96-1.77)</td>
</tr>
<tr>
<td>Age (IQD, 29 y)</td>
<td>0.95 (0.79-1.13)</td>
<td>0.93 (0.76-1.14)</td>
</tr>
<tr>
<td>BSA (IQD, 25%)</td>
<td>0.95 (0.78-1.16)</td>
<td>1.53 (1.27-1.85)</td>
</tr>
<tr>
<td>FT BSA (IQD 25%)</td>
<td>2.48 (1.80-3.41)</td>
<td>5.76 (3.77-8.79)</td>
</tr>
<tr>
<td>Burn cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flame</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Chemical</td>
<td>1.05 (0.47-2.38)</td>
<td>0.55 (0.18-1.67)</td>
</tr>
<tr>
<td>Contact</td>
<td>0.61 (0.19-1.95)</td>
<td>0.90 (0.32-2.55)</td>
</tr>
<tr>
<td>Electrical</td>
<td>0.23 (0.08-0.65)</td>
<td>0.07 (0.01-0.52)</td>
</tr>
<tr>
<td>Scald</td>
<td>0.90 (0.70-1.39)</td>
<td>0.46 (0.27-0.80)</td>
</tr>
<tr>
<td>Pressure</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Flash</td>
<td>0.90 (0.56-1.43)</td>
<td>1.06 (0.69-1.65)</td>
</tr>
<tr>
<td>Sunburn</td>
<td>0.22 (0.05-0.89)</td>
<td>NA</td>
</tr>
<tr>
<td>Steam</td>
<td>1.11 (0.25-4.80)</td>
<td>NA</td>
</tr>
<tr>
<td>Burn anatomic site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.67 (0.48-0.94)</td>
<td>0.87 (0.63-1.17)</td>
</tr>
<tr>
<td>Lower limb</td>
<td>1.34 (1.03-1.74)</td>
<td>0.28 (0.18-0.44)</td>
</tr>
<tr>
<td>Neck</td>
<td>0.36 (0.22-0.58)</td>
<td>1.23 (0.83-1.82)</td>
</tr>
<tr>
<td>Perineum</td>
<td>0.47 (0.28-0.79)</td>
<td>0.08 (0.02-0.26)</td>
</tr>
<tr>
<td>Head</td>
<td>0.30 (0.22-0.41)</td>
<td>0.20 (0.13-0.30)</td>
</tr>
<tr>
<td>Chest</td>
<td>0.91 (0.67-1.25)</td>
<td>1.25 (0.91-1.73)</td>
</tr>
<tr>
<td>Surgical (reference) vs medical treatment</td>
<td>3.02 (2.40-3.81)</td>
<td>1.40 (1.16-1.68)</td>
</tr>
</tbody>
</table>

### Abbreviations
- BSA: burn surface area
- CI: confidence interval
- FT: full thickness
- IQD: interquartile difference
- NA: not applicable
- OR: odds ratio

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signed. The patient’s values on each predictor are located, and a line is drawn upward to determine how many points the patient receives for each variable value. A point scale was used for the continuous variable. Thus the points are summed, and the result is located on the “total points” axis. A line is drawn downward to then determine the risk of developing a pathologic postburn scar.

**Table 6. The Results of the Multivariable Analysis of Predictor Characteristics**

<table>
<thead>
<tr>
<th>Predictor Characteristic</th>
<th>Postburn Scarring Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pathologic</td>
</tr>
<tr>
<td>Female sex (vs male)</td>
<td>1.28 (0.82-2.00)</td>
</tr>
<tr>
<td>Age (IQD 29 y)</td>
<td>0.64 (0.45-0.90)</td>
</tr>
<tr>
<td>FT BSA (IQD 25%)</td>
<td>0.63 (0.43-0.94)</td>
</tr>
<tr>
<td>Burn anatomic site</td>
<td>[Upper limb] 1.00 [Reference]</td>
</tr>
<tr>
<td></td>
<td>[Abdomen] 0.18 (0.10-0.32)</td>
</tr>
<tr>
<td></td>
<td>[Lower limb] 0.66 (0.40-1.11)</td>
</tr>
<tr>
<td></td>
<td>[Neck] 3.27 (1.01-10.54)</td>
</tr>
<tr>
<td></td>
<td>[Perineum] 0.16 (0.06-0.39)</td>
</tr>
<tr>
<td></td>
<td>[Head] 0.82 (0.26-2.60)</td>
</tr>
<tr>
<td></td>
<td>[Chest] 0.80 (0.45-1.41)</td>
</tr>
<tr>
<td>No. of surgical procedures</td>
<td>1.00 (0.87-1.39)</td>
</tr>
<tr>
<td>Type of skin graft</td>
<td>[1:4] 1.00 [Reference]</td>
</tr>
<tr>
<td></td>
<td>[1:2] 0.95 (0.57-1.59)</td>
</tr>
<tr>
<td></td>
<td>[1:6] 0.42 (0.07-2.57)</td>
</tr>
<tr>
<td></td>
<td>[Sheet] 0.47 (0.26-0.84)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FT BSA, full-thickness burn surface area; IQD, interquartile difference.

a. For pathologic postburn scars altogether, D and Dxy were 0.05 and 0.30, respectively. When hypertrophy and contracture were considered separately, D and Dxy became 0.08 and 0.30 for the first model and 0.24 and 0.53 for the second model.

b. Unless otherwise indicated, odds ratios apply (1) to the effect of an IQD for continuous variables (eg, age IQD, 29 years; therefore, for every increase of 29 years in age, the odds ratio for pathologic postburn scarring is 0.64) or (2) to the category with the highest observed frequency (reference) for categorical variables (eg, male sex is the highest observed category; therefore, the 1.28 odds ratio for pathologic postburn scarring is interpreted for female vs male). Boldface type indicates a statistically significant finding.

c. Odds ratios apply to the effect of difference in 1 surgical procedure.

Scar formation is the natural final step of wound healing. The problem of pathologic scarving is severe for patients and difficult for clinicians, especially in the case of burn injuries, because no reliable satisfactory meth-
ods exist for its alleviation. Therefore, experts recommend that follow-up treatment of burn patients be carried out by the highly specialized medical personnel in outpatient clinics located within burn centers.

Following the maxim that prevention of complications is preferable to treatment of an established problem, burn care specialists are searching for clinical criteria to identify patients who might benefit from prophylactic programs. To our knowledge, the present study is the first to investigate risk prediction models for pathologic postburn scarring. Indeed, the data analyzed herein probably represent the largest cohort published on this open question.

These data show that postburn pathologic scarring is extremely common (a prevalence of 77%) and that hypertrophy and contracture should be classified separately if we are to understand these phenomena better. Hypertrophy is the most frequently encountered pathologic feature, either alone (44%) or in combination with contracture (28%) at the same time in the same patient. Moreover, it was observed that most patients who developed a pathologic scar in 1 anatomic area had normotrophic outcomes in other burn sites (69%) and localized diffusion of hypertrophy.

Hypertrophic scars had an early appearance from complete reepithelialization (3.5 weeks; IQR, 1.5-6.5) (Table 4), reaching at least a steady state after an initial activation phase followed by a regression phase (total duration, 15 months). The remission phase persisted for long periods but varied considerably from individual to individual. Consequently, remission might be considered the most important period on which the research should be focused. Five percent of the cohort had pure contractures, which were usually diagnosed late owing to their having a longer latency period of manifestation (27 days; IQR, 10-55 days). Atrophy is rare (4 of 2440 anatomic burn sites), and it could be considered, especially in older subjects, a late outcome of different types of scars that finally evolve into areas of poor extracellular matrix synthesis. The epidemiologic data confirm the classification charts proposed by Magliacani et al and Muir as reliable stratification methods.

Noteworthy are the data on sex, age, anatomic burn site, number of surgical procedures, and type of skin graft that allow for a significant prediction of postburn pathologic scarring. Moreover, they provide additional prognostic information and indicate interesting directions for biological research.

Concerning the causes of postburn pathologic scarring, it has been hypothesized that hypertrophy is a systemic inflammatory disease of central origin, regulated by local influencing factors. Indeed some results of the present study seem consistent with this hypothesis. Numerous studies have pointed out the key role played by lymphocytes and the skin's immune system in general in the maintenance of a continuous inflammatory activated state of hypertrophic tissue.

Our data seem to support the role of the immune system for a number of reasons. First, female sex carries a higher risk for pathologic postburn scarring, as it does for most diseases of immunologic pathogenesis (eg, rheumatoid arthritis, Sjogren syndrome, and systemic lupus erythematosus). Second, burn patients who presented with pathologic scars were significantly younger than those with normotrophic scarring. Organs and systems, particularly the immune system, are less functional in older persons, in whom autoimmune diseases have hazy and insidious signs and symptoms. On the contrary, children have a strong anabolic basal activity that often generates an unbalance in the remodeling phase of wound healing.

Finally, according to the results obtained from our analysis of burn severity, it is also likely that hormonal context (eg, stress index) during the acute phase of burns could play a role in scar alterations. In fact, a positive correlation has been noted between the levels of serum inflammatory molecules (eg, prolactin and cytokines) at early time points and burn severity as expressed by BSA. Indeed this correlation suggests that burn injury mediates a systemic response, independent from the site, continuing from the acute to the postburn phase, as demonstrated in the multicenter study of the genomic and proteomic response to burn injury. While our findings are not evidence based, our analysis of the recommended medical topical treatment of scars indicates that pressure garments and silicone gel sheeting could help to alleviate symptoms and improve body homeostasis. However, there is no clear evidence that these local aids influence either scar evolution or the need for secondary scar correction, further supporting the idea that hypertrophic scars are sustained by a systemic inflammatory mechanism.

As to local variables, the role of the single anatomic site has a strong risk-prediction significance, thus being implicated in the pathogenesis of pathologic scarring. The neck and upper limb are sites at higher risk than the abdomen and perineum. Surely each specific region has different histomorphologic characteristics that could be crucial in the wound healing processes. Interestingly, it has been suggested that hypertrophic scars occur in sites characterized by cones, localized in the deep dermis and containing skin appendages and fat domes that perforate the dermis matrix. Moreover, an imbalance in skin tension after healing could give rise to contractures. Indeed, it has been observed that myofibroblasts in these scars fail to undergo apoptosis because there are incorrect stimulations.

When dealing with the role of burn treatment and its efficacy on the scar outcome, a burn without surgical indications might be reasonably defined as superficial or of moderate partial thickness. The analysis of surgical burn treatment emphasizes that burn depth is an important risk factor: destruction of the dermal or hypodermal layer could create serious repair problems, which may often induce pathologic scarring. The type of skin graft is also significant, with sheet skin grafts being more protective than other types from the risk of pathologic scarring. It has been suggested that the sheet skin graft bears new epithelium and new dermal fibroblasts, while with meshed skin grafts, the healing process is also sustained by the fibroblasts coming from the injured area, which have a profibrotic phenotypic pattern.

In addition, a delay in reepithelialization increases the risk of wound infection and prolongs the inflammatory phase, consequently leading to scar abnormalities. A less important role seems to be played by the surgical tech-
niques used to resurface third-degree burns. Moreover, new biological or biosynthetic cutaneous substitutes have offered promising improvement in scar quality, although their role should be investigated in large case series. On the whole, the results of the present study may have relevant clinical implications and could be used to improve the approach to postburn pathologic scars, in particular in view of the findings from the multivariate analysis and its use through the application of a nomogram (Figure 4). Risk information may be easily integrated into routine clinical practice for early risk stratification, thus facilitating optimal medical prevention and helping physicians adopt follow-up timing and more aggressive or experimental therapies for subjects likely to be at high risk.

We would welcome the validation of our prediction model in other cohorts worldwide to provide us the opportunity to adjust for any variations found and thus set up a risk-prediction instrument that might easily be applied to most situations with a high degree of accuracy.

Accepted for Publication: June 26, 2007.

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Author Contributions: Drs Gangemi and Stella had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Gangemi and Stella. Acquisition of data: Gangemi, Zingarelli, Cairo, Bollero, Ganem, Capocelli, Cuccuru, Cassano, Risso, and Stella. Analysis and interpretation of data: Gangemi, Gregori, Berchialla, and Stella. Drafting of the manuscript: Gangemi, Gregori, Zingarelli, Cairo, Bollero, Ganem, Capocelli, Cuccuru, Cassano, Risso, and Stella. Critical revision of the manuscript for important intellectual content: Gangemi, Gregori, Berchialla, and Stella. Statistical analysis: Gregori and Berchialla. Administrative, technical, and material support: Zingarelli, Cairo, Bollero, Ganem, Capocelli, Cuccuru, Cassano, and Risso. Study supervision: Stella.

Financial Disclosure: None reported.

Previous Presentation: This article was presented at the 13th International Society for Burn Injuries Congress; September 25, 2006; Fortaleza, Brazil.

Additional Contributions: Simone Teich Alasia, MD, provided continuing support and collaboration.

REFERENCES