FATAL BURNS IN HELSINKI BURN CENTER

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Academic Dissertation

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2 ABBREVIATIONS

%TBSA Percentage of total body surface area.

ABSI Abbreviated burn severity score

ACLF Acute-on-chronic liver failure

ACTH Adenocorticotropic hormone, corticotropin

AH Adrenal hemorrhage

AIS Abbreviated Injury Scale

APACHE Acute Physiology and Chronic Health Evaluation scores

APASL Asian Pacific Association for the Study of Liver

ARDS Adult respiratory distress syndrome

AKI Acute kidney injury

bpm beats per minute

CNS Central nervous system

DHEA Dehydroepiandrosterone

DIC Disseminated intravascular coagulation

DNAR Do not attempt resuscitation

EMS Emergency medical service

EOL End-of-Life
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>Glasgow come scale</td>
</tr>
<tr>
<td>HASB</td>
<td>Hot air sauna burn</td>
</tr>
<tr>
<td>HES</td>
<td>Hydroxyethylstarch</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>ISS</td>
<td>Injury Severity Score</td>
</tr>
<tr>
<td>LODS</td>
<td>Logistic Organ Dysfunction System</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>MOF</td>
<td>Multiple organ failure</td>
</tr>
<tr>
<td>MODS</td>
<td>Multiple-Organ Dysfunction Score</td>
</tr>
<tr>
<td>MPM</td>
<td>Mortality Prediction Model</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OD</td>
<td>Organ dysfunction</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RIFLE</td>
<td>risk, injury, failure, loss and end-stage kidney classification</td>
</tr>
<tr>
<td>SAPS</td>
<td>Simplified Acute Physiology Score</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
</tr>
</tbody>
</table>
3 ABSTRACT

To study fatal burns in the Helsinki Burn Center, sixteen years of data on burn deaths were collected and analyzed. These data included the early predicting factors obtained during pre-hospital care, clinical notes and autopsy reports. The study also classified clinically missed diagnosis revealed in autopsy and paid special interest in the prevalence of adrenal hemorrhage (AH) in non-surviving patients with burns.

The study was carried out in two phases. The first phase included all deceased burn victims from the Helsinki Burn Center from 1995 to 2005. The clinical charts and medicolegal autopsy reports with organ specific changes were retrieved and compared. The data were evaluated by a team of two plastic surgeons specialized in burn care, an intensivist, and a pathologist. Causes of death, incidence of multiple organ failure (MOF) and AH and occurrence of diagnostic discrepancies were documented and analyzed. The second phase included burn patients with life-threatening burns in the Helsinki Burn Center during 2006-2010. Pre-hospital patient records and clinical data collected during treatment were analyzed with reference to survival at 7 days, 30 days and 6 months. The patients were divided into two cohort groups and the data were analyzed in groups based on the presence or absence of a physician in the pre-hospital phase.

The majority of burn victims die of untreatable burn injury (40%) or MOF (40%). Other causes of death are sporadic. Kidneys (100%) and liver (82%) were the organs most commonly affected in MOF. Lethal sepsis was never a sole cause of death, but always associated with MOF. Three MOF patients had bilateral adrenal hemorrhage, and four MOF patients had acute-on-chronic liver failure (ACLF).
Medicolegal autopsies revealed major diagnostic discrepancies in less than 6% of patients. These diagnostic discrepancies would have altered the clinical outcome or therapy had they been known in time. The most commonly missed diagnosis was pneumonia.

Early accurate diagnosis and skilled therapy are essential in the prevention of MOF. Patients treated by paramedics compared with patients treated by pre-hospital physicians were comparable with regard to age, gender and etiology of the injury. However, patients treated by pre-hospital physicians were more severely injured than patients treated by paramedics in terms of percentage of total body surface area (%TBSA) burned, injury severity score (ISS) and inhalation injuries. Patient’s age, %TBSA and ISS are significantly associated with short- and long-term survival in burn patients.

The study unambiguously reveals all the causes of death of the burn patients in the study period in the Helsinki Burn Center. The usefulness of autopsies in providing valuable clinical data for the treatment of burn patients is emphasized. The study also highlights a few missed diagnoses that may occur in burn patients and some early predicting factors of burn mortality are presented. The prevalence of AH was shown to be higher than previously estimated in non-surviving patients with burns. This study also reveals that the emergency medical system is able to recognize the situations and patients more likely to benefit from physician attendance.
INTRODUCTION

Major burn injury is one of the most devastating forms of injury a person can sustain. Lives continue to be lost due to burn injuries despite improved patient care with early skin grafting, meticulous fluid resuscitation, and advanced antibiotic therapy (Garrison et al. 1995, Åkerlund et al. 2007). The exact cause of death after a burn trauma is not always evident. Nor do we yet understand all the specific events leading to the death of a burn patient.

Some pre-hospital parameters have been shown to affect the trauma patient’s survival (Harris et al. 2012). However, only a few studies have focused on the effects of pre-hospital status and care on the mortality of burn patients. The early prognostic markers are significant in determining the care plan and in identifying patients potentially needing extra attention.

Adrenal hemorrhage (AH) is a rare, yet potentially life-threatening event that occurs both in traumatic and in non-traumatic states (Rao 1995, Vella et al. 2001). Clinical manifestations can vary widely depending on the degree and rate of hemorrhage, as well as the amount of adrenal cortex compromised by hemorrhage. The etiology of adrenal insufficiency is most likely to be AH in the setting of burn patients (Sheridan et al. 1993). Although the condition is possibly fatal, prompt recognition and treatment will lead to good outcome (Nacul et al. 2002). The exact prevalence of AH in patients with burns is unknown, and none of the previous studies addressing AH following burn trauma are based on an autopsy database.

The most common cause of death after a burn trauma in developed countries is death by multiple organ failure (MOF) (Sheridan et al. 1998, Miller et al. 2006, Bloemsma et al. 2008). Severe MOF and severe sepsis are both related to burn size, age, male sex, length of stay in intensive care, and duration of mechanical
ventilation (Cumming et al. 2001). Autopsies reveal the organ specific changes in MOF deaths, offering deeper understanding of the events leading to these deaths.

Autopsies provide useful clinical data and serve as a quality control (Blosser et al. 1998, Roosen et al. 2000, Silfvast et al. 2003). In Finland, medicolegal autopsies are required by law after a burn trauma death. This makes Finland especially suitable for cause of death studies, since cause of death is always ascertained. Autopsies occasionally reveal clinically missed diagnoses (Blosser et al. 1998, Fish et al. 2000). The majority of the clinically missed diagnoses are minor and thus would have had no impact on patient care or survival had they been known in time (Fish et al. 2000). Major clinically missed diagnoses would have altered the therapy, possibly affecting survival if known in time (Blosser et al. 1998, Fish et al. 2000, Roosen et al. 2000, Silfvast et al. 2003). Identifying and analyzing both major and minor clinically missed diagnoses are important in the recognition of the critical points in the care and in the attempt to improve care for burn patients.
5 REVIEW OF THE LITERATURE

5.1 Skin

Skin is one of the largest organs. With its subcutaneous tissue, it comprises 15-25% of body weight. Adult skin has 1.5-2m² surface area. Skin has many functions; it protects underlying tissues, prevents vaporization of water, participates in body temperature regulation, and acts as a blood reservoir. It is an exocrine and a sense organ. It produces vitamin D. Skin also acts as an immunological organ due to the action of Langerhans cells, keratinocytes, lymphocytes and mastocytes. (Wysocki 1999).

5.2 Thermal injury

A burn injury is caused by heat, electricity, corrosive chemical agent, friction or radiation. Exposure time and temperature affect the depth of a thermal injury (Moritz and Henriquez 1947). Burns are classified as first (I), second (II) and third (III) degree (Dupuytren 1832). Final estimation of burn degree is done 48 hours post trauma because burn wounds deepen during the first two days. (Jackson 1953).

A first-degree burn is also referred to as a “superficial epidermal burn”. Superficial epidermal burns only involve epidermis, while deeper layers of the skin remain intact. In a first-degree burn the skin is dry, hyperaemic, and sore; there is no blister formation. These burns heal by regeneration of the epidermis from the basal layer. Healing occurs within one week without scaring. A sun burn is a typical first degree burn. (Jackson 1953).
Second-degree burns are typically caused by hot water and are always accompanied by blister formation. Second-degree burns are erythematous, sore, and moist. They are also called dermal partial thickness burns. These burns may be subclassified as superficial, mid-dermal, or deep. (Hettiaratchy and Papini 2004).

Superficial dermal partial thickness burns affect the epidermis and the superficial part of the dermis (the papillary dermis). Most adnexal structures and vasculature remain intact. Exposure of the sensory nerves makes these burns painful. Superficial second degree burns may have delayed blister formation and they heal spontaneously by epithelialization from the skin appendages within two weeks. Superficial dermal burns may leave a hypo- or hyperpigmentation in the skin. (Hettiaratchy and Papini 2004, Evers et al. 2010)

Mid-dermal partial thickness burns extend into the middle third of dermis with damaged but viable tissue at the base. Some of the nerve endings and capillaries are destroyed. Pain is milder than in superficial dermal burn and capillary refill is delayed. Blisters maybe present. The prognosis of healing and determination of appropriate treatment may be done 2-3 days after injury, when signs of healing or burn progression are established. Healing time is usually 14-21 days and scarring is possible. (Hettiaratchy and Papini 2004)

Deep second-degree burns, also called deep partial thickness or deep dermal burns, involve a significant part of dermis, only deep adnexal structures may be intact. Deep dermal burns have immediate blistering, the skin peels off, and the exposed reticular dermis has no capillary refill, the circulation is sluggish and pain sensation is decreased. Dermal vascular plexus is extensively destroyed. Healing time is over 21 days and hypertrophic scarring is likely. Deep second-degree burns are considered deep burns and require excision and skin grafting. A large, deep second-
degree burn requires excision and skin grafting. (Jackson 1953, Hettiaratchy and Papini 2004, Evers et al. 2010).

Third–degree burns are also known as full thickness burns. Flame usually causes a third-degree burn. The burn is deep, impacting all layers of skin and at worst also subcutaneous tissue and muscles. The injured area is dry, leathery, and without sensation as the sensory nerves are destroyed. There is no blister formation and no capillary refill. A third-degree burn does not heal spontaneously but always requires surgery. Scarring is inevitable. (Jackson 1953, Hettiaratchy and Papini 2004).

Tissue is harmed by heat release transmitter agents that cause capillary vessels to leak fluid into the interstitial cell space creating edema. Edema formation continues 24 hours post-burn and causes deepening of the burn wound. Large (over 20% of total body surface area (%TBSA)) burns cause generalized edema and thus hypovolemia. The capillary leak diminishes circulating blood volume and may lead to hypovolemic shock without proper fluid replacement therapy (Lund et al. 1992, Latenser 2009, Evers et al. 2010).

Hypermetabolism develops as a consequence of large burns. Energy expenditure, oxygen consumption and carbon dioxide production increase. This leads to increased ventilatory demand and minute ventilation increases. Hemodynamics is typically hyperdynamic; heart rate and cardiac output increase although occasionally myocardial depression may occur. As a sign of systemic inflammatory response hyperthermia may develop. Thermal injury also causes peroxidation of hepatocytes, tubular dysfunction in the kidneys, decreased blood flow to the bowel, pulmonary hypertension and edema. Catabolic reactions in fat and muscle tissue can be seen. (Latenser 2009).
5.3 Flame burns

Flame burns typically occur at home (71%) to men (76%). Of burn admission to burn centers flame burns are the most common (47%). (America Burn Association 2013). Of hospital treated burns, flame injuries have the highest incidence of complications (18%) and the highest mortality (5.2% for men and 9.2% for women). The rate of complications increases with age. Patients younger than 20 years have 11% incidence of complications as patients over 50 years have 22-28% incidence of complications. The most common complications are infections, particularly pneumonia, occurring at an incidence of 6% of all flame burn patients and representing 12% of all complications. (American Burn Association 2013).

Smoke inhalation injury (13% of patients with flame burns) increases mortality from flame burns. Flame burn patients with smoke inhalation injury have eightfold higher risk of death than patients without smoke inhalation injury (24% vs 3%). The older the patient and larger the burn is, the worse the prognosis when smoke inhalation is present. Although only 24% of flame burn victims are female, the mortality is twofold higher for females. (American Burn Association 2013).

5.4 Controversies in burn patient care

5.4.1 On-scene care

In burn traumas, some on-scene actions will reduce the mortality of the burn patients. These actions include supplying oxygen, starting an intravenous line for analgesia and fluid resuscitation (Allison 2002, Cupera et al. 2002), as well as avoiding hypothermia (Singer et al. 2010).
Obtaining a victim’s medical history and detailed information about the burn injury and assessing possible concomitant injuries affect the prognosis and care given to burn victims (Allison and Porter 2004, Muehlberger et al. 2010).


5.4.2 Intubation

Inhalation injury is diagnosed in 13% of flame injury patients (American Burn Association 2013). Inhalation injury causes airway swelling and obstruction. It is vital that patients with inhalation injuries are recognized and intubated at the site of the injury (Mackie et al. 2009, Eastman et al. 2010). Sedation is needed when a patient is intubated. Sedation causes vasodilation and hypotension. In order to correct hypotension caused by sedation fluid resuscitation must be augmented (Cancio et al. 2004, Steinvall et al. 2008, Feihl and Broccard 2009, Mackie et al. 2009). Patients receiving excessive volumes of fluids are at increased risk of sepsis, adult respiratory distress syndrome (ARDS), pneumonia, multiple organ
dysfunction syndrome, and death (Klein et al. 2007). Intubation also increases the risk of pneumonia in burn patients (Mosier and Pham 2009).

Inhalation injury is determined by bronchoscopy at the burn center (Eastman et al. 2010). It is not possible to recognize the inhalation injury patients with 100% accuracy at the injury site (Mackie et al. 2009, Eastman et al. 2010). Intubating all burn patients is not recommended because of risks related to intubation (Mackie et al. 2009, Eastman et al. 2010, Mackie et al. 2011), however, not intubating a patient with inhalation injury may lead to airway obstruction (Eastman et al. 2010, Mackie et al. 2011). Therefore the subject of intubation on site is complex and hotly debated. Mackie et al. (2009) suggest that improving the diagnosis of inhalation injury would benefit the burn patients as unnecessary intubation could be avoided.

5.4.3 Fluid resuscitation

One cornerstone of modern burn care is an effective fluid resuscitation regimen; this has strongly improved patients survival (Åkerlund et al. 2007, Bak et al. 2009). The Parkland formula is one widely accepted and well-studied protocol for carrying out fluid resuscitation (Bak et al. 2009). However, there seems to be a trend towards providing increasing amounts of fluids, in excess of the Parkland recommendations, to avoid acute kidney injury during acute burn resuscitation in severely injured burn patients (Baxter 1981, Pruitt 2000). A number of studies have confirmed that exceeding the Parkland formula may have harmful effects and lead to increased mortality (Hobson et al. 2002, Klein et al. 2007). Over-resuscitation increases the risk of infectious complications, ARDS, abdominal compartment syndrome, and death (Hobson et al. 2002, Klein et al. 2007, Vaara et al. 2012).
Another issue is the use of colloids versus crystalloids for fluid resuscitation in burn patients. Fluid resuscitation with crystalloids frequently leads to hypoalbuminemia and it is debated whether this should be corrected by albumin supplementation (Atiyeh et al. 2012, Melinyshyn et al. 2013).

Some studies conclude that patients resuscitated with colloids required less fluid than patients resuscitated with crystalloids (Endorf and Dries 2011, Atiyeh et al. 2012), other studies have debunked this belief (Bayer et al. 2012, Perel and Roberts 2012). Colloids can almost completely prevent edema in unburned tissues (Atiyeh et al. 2012). The outcome benefit of colloid use is still under discussion, however. Some studies deny that any outcome benefit has been proven so far (Atiyeh et al. 2012, Perell and Roberts 2012, Melinyshyn et al. 2013, Perel et al. 2013), others advocate the use of albumin as it is not harmful and argue that it provides a mortality benefit (Endorf and Dries 2011, Atiyeh et al. 2012, Park et al. 2012). Albumin use is also associated with a reduced need for vasopressors and a shorter duration of mechanical ventilation in burn patients with burns to 20% or more of their total body surface area (Park et al. 2012). Although biological colloids such as albumin or fresh frozen plasma carry a risk of biological disease transmission, they are a better choice than synthetic colloids if colloids must be used (Atiyeh et al. 2012). Atiyeh et al. (2012) claim fresh frozen plasma to be the best colloid solution available for burn patients as it diminishes the coagulopathy risk.

Other studies have found the use of colloids harmful (James 2012). Colloid use may increase bleeding and mortality (Atiyeh et al. 2012, James 2012) and increase in lung edema (Atiyeh et al. 2012). Hydroxyethylstarch (HES) has proven to be an especially harmful colloid for critically ill patients. Large studies have proven HES to increase the risk of AKI, renal replacement therapy, acute liver injury, and death.
compared to crystalloids (Brunkhorst et al. 2008, Myburgh et al. 2012, Perner et al. 2012, Nisula et al. 2013). The European Medicines Agency’s (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommends that all HES products should be withdrawn from use (European Medicines Agency 2013).

Gelatin is another synthetic colloid used. As with HES, gelatin also carries a risk of renal failure and is not suitable for critically ill ICU patients (Bayer et al. 2012).

In 2008, the American Burn Association recommended that crystalloid-based resuscitation be used during the first 24 hours (Endorf and Dries 2011). As colloids are more expensive than crystalloids and do not improve survival, the use of colloids is not justified (Bayer et al. 2012, Perel and Roberts 2012, Perel et al. 2013).

5.5 ICU Scoring systems

ICU scoring systems are created to evaluate the risk of death. Mean values of scoring systems can also be used in academic work to describe the general condition of patients. Several different scoring systems for ICU patients have been developed. Four major groups of ICU scorings systems exist: general risk-prognostication scores, disease-specific risk-prognostication scores, trauma scoring, and organ failure (OD) scoring (Strand and Flaatten 2008). The scores should be validated for the specific populations in which they are to be used. Not all scores are validated for burn patients.

General risk-prognostication systems are Acute Physiology and Chronic Health Evaluation (APACHE II-IV) scores (Knaus et al. 1985), mortality prediction model (MPM II), and Simplified Acute Physiology Score (SAPS II-III). APACHE II takes
in count 12, APACHE III 17 different physiologic variables, and APACHE IV 145 of which most are admission diagnoses; all APACHE scoring systems perform well (Strand and Flaatten 2008). MPM II and SAPS II-III exclude burn patients. APACHE III and APACHE III-j (j being the tenth iteration of the APACHE III algorithm) scores (Knaus et al.1991) have been shown to correlate with outcomes for patients with burn injuries. (McNamee et al. 2010, Moore et al. 2010)

Disease- and organ-specific prognostic scores are the Glasgow Coma Scale (GCS) (Jennett and Bond 1975) for the central nervous system, Ranson score for pancreatitis, Child–Pugh for liver failure and risk, injury, failure, loss and end-stage kidney (RIFLE) classification (Bellomo et al. 2004). These scores are used to quantify single-organ failure or a specific disease and are most often used outside the ICU as the scores are often not validated for ICU patients with concomitant organ failures (Strand and Flaatten 2008). GCS is included in other more complex scoring systems. Child-Pugh and Ranson are outdone by APACHE II and III scores. RIFLE has proven to be useful and reliable in the ICU as acute kidney failure is a frequent and important predictor of mortality in the ICU. (Strand and Flaatten 2008).

OD scoring systems include the Sequential Organ Failure Assessment (SOFA) (Vincent et al. 1996), Multiple-Organ Dysfunction Score (MODS) (Marshall et al. 1995), and Logistic Organ Dysfunction System (LODS) (Le Gall et al. 1996). These scores are important as MOF is the leading cause of death for patients admitted to the ICU. As MOF is rather a continuum than an event these scores should be calculated on a daily basis. The SOFA and MODS scores take into account respiratory, renal, cardiovascular, CNS, coagulation (haematological for MODS), and hepatic failures giving a score from 0–4 to each organ, the higher number meaning more severe failure in SOFA scores. The sum of scores (SOFA) and individual scores (MODS) correlate to mortality. The SOFA scores may be
used in several ways, as organ specific scores, as the sum of scores on one single ICU day or the sum of worst scores during the ICU stay. In MODS, the worst scores of the whole ICU stay are recorded. The sum of these scores produce the final MODS score. LODS excludes burn patients. (Strand and Flaatten 2008). Table 1 represents the SOFA score.
Table 1. SOFA score.

<table>
<thead>
<tr>
<th>Score points</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂ (mmHg)</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100 with respiratory support</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Arterial Pressure (MAP) OR Administration of vasopressors</td>
<td>MAP&lt;70</td>
<td>Dopamine &lt;5 or Dobutamine at any dose</td>
<td>Dopamine &gt;5 OR Epinephrine&lt; 0.1 OR Norepinephrine &lt;0.1</td>
<td>Dopamine &gt;15 OR Epinephrine &gt;0.1 OR Norepinephrine &gt;0.1</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (μg/L)</td>
<td>&gt;20 – 32</td>
<td>33 – 101</td>
<td>102 – 204</td>
<td>&gt;204</td>
</tr>
<tr>
<td><strong>Renal system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine μmol/L (or urine output)</td>
<td>110 - 170</td>
<td>171 - 299</td>
<td>300 - 440 (or &lt; 500 ml/d)</td>
<td>&gt;440 (or &lt; 200 ml/d)</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets×10⁹/mcl</td>
<td>&lt; 150</td>
<td>&lt; 100</td>
<td>&lt; 50</td>
<td>&lt; 20</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>13 – 14</td>
<td>10 – 12</td>
<td>6 – 9</td>
<td>&lt; 6</td>
</tr>
</tbody>
</table>
5.6 Burn scoring systems

Repeated estimates of a burn injury’s severity are required to optimize patient care. The first estimates are done on the injury site and used as a precept to the level of the care the patient might need, i.e. nurse/paramedic, general practitioner, surgeon, or a team specialized in burn care.

The following burns require treatment in units specialized in burn care: Large (over 20 %TBSA) burns in adults. Patients requiring burn shock resuscitation. Burns involving face, hands, feet, genitalia, perineum, or major joints. Electrical and chemical burns. Inhalation injuries. Patients with concomitant trauma or disease. All deep partial thickness burns and full thickness burns, all circumferential burns. Burn injury in patients who will require special social, emotional, or rehabilitative intervention. (American Burn Association 2013, European Burns Association 2013).

In attempt to avoid unnecessary suffering, the chances for recovery are assessed. Patients with poor prognosis receive terminal care. For the estimation of patient’s prognosis, scoring systems have been developed. The simplest system is Baux, in which the sum of patients age and the %TBSA burned is calculated (Tobiasen et al. 1982). A Baux of over 100 has indicated poor prognosis in the past, but as burn care has developed, flaws in the Baux system have emerged (Roberts et al. 2012). However, being a simple, easy to remember and fast to calculate, Baux rule still has a place in burn care (Jeng 2007, Roberts et al. 2012). As a general rule, one can assume that the higher the Baux value the worse the prognosis.

Other more accurate, but more complex rules have also been used for calculation of a patient’s prognosis. The Abbreviated Burn Severity Index (ABSI) gives the patient score according to sex, age, inhalation injury, full-thickness burn,
and \%TBSA burned. As the sum of the score increases, the patient’s prognosis worsens. In general, a large full-thickness burn with inhalation injury in an older woman is the worst case scenario with maximum risk to survival. Table 2 presents the calculation of the ABSI and Table 3 presents the ABSI scores in relation to risk and survival (Tables 2 and 3) (Tobiasen et al. 1982, Andel et al. 2007, Forster et al. 2011)

Baux and ABSI both estimate true survival well. ABSI predicts death better than Baux. (Tobiasen et al. 1982). Despite advancements in burn care, ABSI has remained accurate in the prediction of burn patient mortality (Forster et al. 2011). The Baux score is a highly discriminatory prediction tool (i.e. patients that die have a higher Baux score than patients who survive) but shows very poor calibration (i.e. Baux predicted risk of death is much higher than the observed mortality). (Moore et al. 2010).

For burn patients alone, one independent risk factor for death is percent full thickness surface area (FTSA) (Moore et al. 2010). The combined prediction model (APACHE III-j score/FTSA) shows similar discrimination but superior calibration (Moore et al. 2010). However, predicted risk of death using both variables, combining injury severity (percent FTSA) with physiological response (APACHE III-j score), is more accurate than either variable alone (Mooren et al. 2010). Baux index, SAPS II, and SOFA on admission to the ICU, infectious and respiratory complications, and time of first burn wound excision were found to have a significant predictive value for hospital mortality. The ICU survivors had significantly lower SAPS II, SOFA on admission, \%TBSA burned, Baux index, presence of third degree burns, inhalation injury, infectious and respiratory complications, length of mechanical ventilation, time of first burn wound excision, and length of ICU stay than ICU non-survivor patients (Pavoni et al. 2010)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0</td>
</tr>
<tr>
<td>Age, years</td>
<td>0-20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21-40</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>41-60</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>61-80</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>81-100</td>
<td>5</td>
</tr>
<tr>
<td>Inhalation injury</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Full-thickness burn</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>%TBSA burned</td>
<td>1-10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>51-60</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>61-70</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>71-80</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>81-90</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>91-100</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 3. Abbreviated Burn Severity Index (ABSI) scores as related to risk and survival.

<table>
<thead>
<tr>
<th>Total Burn Score</th>
<th>Threat to Life</th>
<th>Probability of survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>Very low</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4-5</td>
<td>Moderate</td>
<td>98</td>
</tr>
<tr>
<td>6-7</td>
<td>Moderately severe</td>
<td>80-90</td>
</tr>
<tr>
<td>8-9</td>
<td>Serious</td>
<td>50-70</td>
</tr>
<tr>
<td>10-11</td>
<td>Severe</td>
<td>20-40</td>
</tr>
<tr>
<td>12-13</td>
<td>Maximum</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

5.7 Organ-specific perturbations of large burn injuries

5.7.1 Adrenal glands

The adrenal glands are stress hormone-secreting endocrine glands situated above the kidneys. They consist of two layers, the cortex and the medulla. The cortex produces mineralocorticoids, glucocorticoids, and androgens. The medulla produces catecholamines. (Baker 1997).
5.7.1.1 Mineralocorticoids

The mineralocorticoid aldosterone is a hormone affecting the sodium (Na)/potassium (K) balance, increasing Na retention in the kidneys, sweat glands, salivary glands, and on the mucous membrane of the colon. Na retention increases osmolality of the blood plasma. The increased osmolality of plasma enhances the excretion of antidiuretic hormone, thus retaining water in the body and elevating blood pressure. Aldosterone excretion is controlled by the rennin-angiotensin-aldosterone-system. (Funder 2010).

5.7.1.2 Androgens

Adenocorticotropic hormone (ACTH), a corticotropin extracted from the pituitary gland, regulates the release of glucocorticoids and androgens from the adrenal cortex. Dehydroepiandrosterone (DHEA) is the most important androgen. DHEA is the precursor of sex hormones testosterone and estrogens. (Vaitukaitis et al. 1969).

5.7.1.3 Glucocorticoids

The most important glucocorticoids are cortisone and corticosterone. Glucocorticoids have many effects; they increase the level of glycogen and glucose production in liver by activating glycogen synthase enzyme, reduce insulin effects in the liver and peripheral tissues, enhance lipolysis, catabolic reactions, and osteoporosis, suppress inflammatory reactions, and cause lymphopenia and leukocytosis. They also stimulate mineralocorticoid receptors, affecting body’s water balance. Glucocorticoids sensitize arteries to the effects of catecholamines; thus the lack of glucocorticoids manifests as poor reaction to vasopressors. (Munck and Guyre 1986).
5.7.1.4  Catecholamines

Chromaffin cells in the adrenal medulla produce catecholamines, mainly adrenalin (epinephrine) and norepinephrine. Adrenalin production is stimulated by glucocorticoids, angiotensin II and cholinergic stimulation. Cholinergic stimulation causes adrenalin excretion through exocytosis. A variety of diverse signals, e.g. fear, hypoglycemia and trauma, lead to cholinergic stimulation. Catecholamines have three types of biological effects: cardiovascular, visceral, and metabolic. Alpha receptors (α₁-2) are sensitive to adrenalin. α₁ stimulation leads to contraction of smooth muscle tissue, α₂ stimulation in the central nervous system (CNS) intensifies baroreceptor regulation of the vascular tonus. Adrenalin also acts as β-receptor agonist, regulating the hearts stroke volume and pulse (β₁-receptors), and enlarging bronchial tubes and certain blood vessels (β₂-receptors). Adrenalin stimulates mainly β₂-receptors. Catecholamines are the main hormones affecting the fight-or-flight reaction. (Eisenhofer et al. 2004).

5.7.2  Adrenal hemorrhage

5.7.2.1  Etiology of adrenal hemorrhage

Adrenal hemorrhage is a rare, yet potentially life-threatening event that occurs in both traumatic and non-traumatic states (Rao 1995, Vella et al. 2001). Due to its rarity, the diagnosis is commonly made at autopsy. AH can occur in association with an acute stressful illness, e.g. infection/sepsis (Piccioli et al. 1994, Adem et al. 2005) and multiple organ failure (MOF) (Jacobson et al. 2010), or event, e.g. surgery (Ries 1994). Other frequent associations include hemorrhagic diatheses, e.g. anticoagulant use and thrombocytopenia (Delhumeau et al. 1993),
thromboembolic disease, including antiphospholipid antibody syndrome (Caron et al. 1998), blunt trauma (Franque et al. 2004), and ACTH therapy (Kornbluth et al. 1990). AH has also been linked to thermal injuries (Murphy et al. 1993, Deeb et al. 2001) or the etiology may simply be idiopathic (Kamishirado et al. 2000, Imachi et al. 2010). Bilateral AH is a rare cause of acute adrenal failure, generally occurring in hospitalized patients who are septic, coagulopathic, or who have thromboembolic disorders (Nacul et al. 2002).

5.7.2.2 Adrenal hemorrhage in burn patients

Nacul et al. (2002) suggested that adrenal insufficiency after thermal injury might result in systemic inflammation, sepsis, thrombosis and coagulopathy with hemorrhage into the adrenal glands (Nacul et al. 2002). Murphy et al. (1993) hypothesized the elevated corticosteroid secretion in thermal injuries severely stresses the adrenal glands. The combination of excessive adrenocorticotropic hormone stimulation and hemodynamic instability leads to AH (Murphy et al. 1993). The etiology of adrenal insufficiency is most likely to be AH in the setting of burn patients (Sheridan et al. 1993), however the exact prevalence of AH in patients with burns is unknown. To the best of our knowledge, none of the studies addressing AH following burn trauma are based on an autopsy database.

5.7.2.3 Clinical manifestations and treatment of adrenal hemorrhage

Dysfunction of the adrenal cortex always causes Addison’s disease, regardless of the reason for the dysfunction. Acute adrenal insufficiency (Addisonian crisis) causes hypotension and electrolyte imbalance (Bouillon 2006). Clinical manifestations of AH can vary widely depending on the degree and rate of hemorrhage as well as on the amount of adrenal cortex compromised by
hemorrhage. An isolated focal unilateral adrenal hemorrhage may present subclinically, whereas massive bilateral AH may lead to rapid cardiovascular collapse and ultimately death, if not diagnosed early and treated appropriately. (Baker 1997).

Addisonian crisis may occur when adrenal bleeding is bilateral (Rao et al. 1995); its management requires saline infusion and repeated administration of hydrocortisone (Coursin and Wood 2002). Long term management of Addison’s disease necessitates hydrocortisone and mineralocorticoid replacement therapy. With appropriate therapy, life expectancy is normal or related to underlying medical condition (Nacul et al. 2002).

5.7.2.4 The role of adrenal function in sepsis

The cornerstones of treatment of septic shock are: early fluid resuscitation, blood cultures before antibiotic therapy, imaging studies performed promptly to confirm a potential source of infection, administration of broad-spectrum antimicrobials therapy, infection source control, and initial fluid resuscitation with crystalloid. (Dellinger et al. 2013).

Intravenous hydrocortisone should be avoided in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore the hemodynamic stability in septic shock. In the absence of septic shock, corticosteroids should not be administered. Hydrocortisone use is advocated only with suspected or proven adrenal insufficiency in children. Approximately 25% of children with septic shock have absolute adrenal insufficiency and death from absolute adrenal insufficiency and septic shock occurs
within 8 h of presentation. ACTH stimulation test has not been proven to be useful for the identification of adults with septic shock who should receive hydrocortisone. For the optimal duration of hydrocortisone therapy no recommendations can be given, therefore the aim should be to use the steroid therapy for as short as possible. (Dellinger et al. 2013).

5.7.3 Acute-on-chronic liver failure

The first articles about acute-on-chronic liver failure (ACLF) were published in 1986 (Gimson et al. 1986); the subject has since been studied on a regular basis. However, ACLF has not been standardized for clinical or academic use until recently; the Asian Pacific Association for the Study of Liver (APASL) made consensus recommendations on acute-on-chronic liver failure. Based on these recommendations, ACLF is defined as:”Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease.” (Sarin et al. 2008).

The diagnosis of ACLF may also be done from histological liver samples. Two different types of histological patterns are seen in the liver of ACLF patients: “Pattern I: Hepatocyte ballooning, rosette formation, cellular cholestasis, variable interface activity, and fibrosis; and Pattern II: Marked ductular proliferation, coarse, inspissated bile plugs, foci of confluent necrosis/bridging necrosis, eosinophilic degeneration of hepatocytes, higher stage of fibrosis, and variable activity.” Nevertheless, the benefit of a histological sample must always be considered thoughtfully, as the patients are almost invariably critically ill. (Sarin et al. 2008).
5.7.3.1  **Etiology of ACLF**

Chronic liver diseases in the Eastern world are mainly of infectious etiology, whereas in the Western world alcoholism predominates. The same division is also seen for acute events from ACLF. Besides viruses and other infectious agents affecting the liver, an acute event might also be of non-infectious etiology: alcohol, drugs, autoimmune responses, surgical intervention, or variceal bleeding. Sometimes the etiology of hepatotoxic agents remains unknown (Sarin et al. 2008). Although the APASL did not reach consensus on sepsis as a cause of acute hepatic insults, there are articles in favor of this view (Duseja et al. 2010). A typical Western ACLF patient has alcohol cirrhosis and alcohol hepatitis simultaneously.

5.7.3.2  **Management and prognosis of ACLF**

Cytokines probably contribute to the development of ACLF, and thus, reduction of inflammatory cytokine responses might improve the prognosis of ACLF patients (Sarin et al. 2008). Additional circulating toxins may cause secondary liver damage and prevent liver regeneration in a patient with ACLF (Sarin et al. 2008).

The use of liver support devices for treatment of ACLF has been extensively studied. Molecular adsorbent recirculating system (MARS) does not directly improve the prognosis of ACLF patients, but it may act as a bridge to transplantation, and it has been shown to improve encephalopathy in patients with ACLF. Antiviral therapy is beneficial to patients with hepatitis B-based ACLF. ACLF may be reversible if identified early and managed with aggressive critical care support. For patients showing no improvement on conservative therapy, liver
transplantation may be considered if the stringent criteria for transplantation are fulfilled. (Sarin et al. 2008).

ACFL is a grave illness with high mortality. Most ACLF patients die of multiple organ failure (Garg et al. 2012). To the best of our knowledge, no previous studies on ACLF in burn patients exist.

5.7.4 Kidneys

Kidneys filter blood, extracting waste products, regulate electrolyte, acid-base, and water balances, and secrete endocrine hormones.

Acute kidney injury (AKI) affects up to 30% of burn victims (Coca et al. 2007, Sabry et al. 2009, Mosier et al. 2010, Brusselaers et al. 2010). AKI worsens the prognosis of the burn patient, as the mortality rate raises to over 60% with this condition (Coca et al. 2007, Mosier et al. 2010). The pathophysiology of acute kidney injury is poorly understood, and thus, it is difficult to prevent. Prognostic factors for acute kidney injury seem to be high %TBSA burned, inhalation injury, and high creatine kinase levels (Davies et al. 1979, Davies et al. 1994, Holm et al. 1999, Hu et al. 2012, Steward et al. 2012). Factors predicting survival from AKI are unknown.

Factors related to acute kidney injury are myoglobinuria, significant hypotension, use of nephrotoxic antibiotics (aminoglycosides, vancomycin, amphotericin B), sepsis, and MOF (Hu et al. 2012, Monsier et al. 2010). Acute kidney injury may be corrected with renal replacement therapy (Stollwerck et al. 2011, Monsier et al. 2010). Patients need renal replacement therapy if they have anuria or oliguria, hyperkalemia, anasarca, high serum creatinine, and high blood urea nitrogen.
AKI has two forms: early and late AKI. Early AKI begins within five days of the injury and is attributable to hypovolemia and systemic vasoconstriction or to myoglobinuria with damage to tubular cells (Holm et al. 1999, Davies et al. 1994). Nowadays, with effective fluid resuscitation, this form has become rarer. The late AKI form develops later than five days post-trauma and has complex pathogenesis. Late AKI is related to sepsis and multiple organ failure and has higher mortality than in early AKI (Holm et al 1999, Coca et al. 2007, Monsier et al. 2010).

5.8 Definition of MOF

The definition of MOF ranges from altered function of organs to irreversible organ failures (Ferreira and Sakr 2011). Organ dysfunctions are mainly noted in the pulmonary, cardiovascular, renal, hepatic, hematologic, and central nervous systems (Marshall et al. 1995, Ferreira and Sakr 2011). Goris et al. in 1985, and later Lefering et al. in 2002, noted the gastrointestinal tract as one of the MOF organs. Goris et al. (1985) developed a system where organ dysfunction and organ failure were noted separately. Lefering et al. (2002) found that gastrointestinal failure did not have impact on mortality and CNS damage was impossible to assess in most cases due to need for sedation for mechanical ventilation. Due to these findings, Lefering et al. (2002) suggested that GI and CNS failure should not be considered in MOF score assessments.

By definition, multiple organ failure and systemic inflammatory response syndrome (SIRS) both affect at least three organs. This makes pinpointing the clinical diagnosis of death especially challenging. Severe MOF and severe sepsis are both related to burn size, age, and male sex. Both are related to the length of stay in intensive care and duration of mechanical ventilation (Cumming et al.
Sepsis is a clinical syndrome that complicates severe infection and is characterized by systemic inflammation and widespread tissue injury. MOF is a continuum, with increased physiological derangements in individual organs; it is a process rather than an event (American College of Chest Physicians 1992).

5.9 Terminal care

End-of-Life (EOL) categories are defined as cardiopulmonary resuscitation, brain death, withholding and, withdrawing life sustaining therapy, and active shortening of the dying process (Collins et al. 2006). Active shortening of the dying process is not legal in Finland and therefore not done to burn (or any other) patients. The most common form of EOL in Finland is the do not attempt resuscitation order (DNAR) which is done in accordance with patient and/or patients relatives. In burn patients, terminal care is withholding or withdrawing treatment and providing pain medication and/or sedation to make the patient comfortable. In an acute situation, the lines of treatment are not always evident. These patients receive ICU and active treatment, but may later have care withdrawn, as the patient’s treatment potential is reassessed.

The decisions to transfer a patient to terminal care may be emotionally hard for the health care professionals (Wilkinson and Savulescu 2012). It is often considered easier to withhold treatment than to withdraw treatment, as it is sometimes morally seen as a question of “letting die” or “killing”. However Wilkinson and Savulescu (2012) argue, that these actions should be of the same value on the basis of the “Equivalence Thesis: Other things being equal, it is permissible to withdraw a medical treatment that a patient is receiving if it would have been permissible to withhold the same treatment (not already provided) and vice versa.” They suggest a trial period of active care to a wider range of patients to gain patient information
and to see the potential response to ICU care. Providing a trial period of ICU care also leads to a lower threshold for the withdrawal of care.

5.10 Mortality

The outcome of burn patients has improved over the past decades (Garrison et al. 1995, Huss et al. 2001, Åkerlund et al. 2007, Krishnan et al. 2012). The overall mortality from burn injuries varies between 1.4% and 18% (Brusselaers et al. 2010). Factors predicting increased mortality are contact burns, inhalation injury, age, burn size, and female gender (Barret et al. 1999, Raff et al. 1996, Brusselaers et al. 2010). Mortality is highest during the first week post-trauma. Previously up to 75% of all burn deaths have occurred with one week of the trauma (Barret et al. 1999). Individual organ failures affect the patient prognosis. Acute kidney injury raises the mortality to over 60% (Coca et al. 2007, Mosier et al. 2010).

Careful fluid resuscitation and nutritional support, burn wound care and infection control, and pulmonary care are all attributable to better prognosis of the burn patient (Åkerlund et al 2007).

5.11 Causes of death of burn patients

The most common cause of death in patients with burns in developed countries is multiple organ failure (Sheridan et al. 1998, Bloemsma et al. 2008, Brusselaers et al. 2010, Krishnan et al. 2012). The American Burn Association’s registry of the causes of burn mortalities indicates that almost 50% of non-survivors died of organ failure (Miller et al. 2006). Sepsis is a serious and common consequence of burn
trauma (Wasserman 2001), although the number of patients dying of septicemia has declined (Bloemsma et al. 2008). Burns shock and inhalation injury are the main causes of early death (< 48h post-burn) (Brusselaers et al. 2010).

Other causes of death are sporadic. The following causes of death in patients with burns have been reported: Adult respiratory distress syndrome (ARDS), pneumonia, liver failure, ischemic bowel, and toxic megacolon, cardiac arrest, and myocardial infarction (Krishnan et al. 2012).

5.12 Value of autopsies

The final medical operation provided for a deceased burn victim is autopsy. Autopsies reveal the true causes of death. The information gathered from autopsy reports serves as a quality control when estimating diagnosis missed in clinical practice. Autopsies accumulate knowledge for clinical and educational purposes in burn centers (Fish et al. 2000, Roosen et al. 2000, Podbregar et al. 2001, Ong et al. 2002, Silfvast et al. 2003).

A severe burn trauma leading to death is always caused by a crime, accident, or suicide. In Finland, medicolegal autopsies are obligatory by law when a death has been caused by a crime, accident, or suicide. Thus, all (100%) deceased burn victims undergo medicolegal autopsies. A state pathologist performs medicolegal autopsies at the Department of Forensic Medicine. No permission from next of kin is needed for medicolegal autopsies.

Our autopsy rate (100%) for burn victims is exceptionally high. Studies in an adult intensive care unit (ICU) setting have had autopsy rates ranging from 33% to 89%
(Nadrous et al. 2003, Silfvast et al. 2003, Combes et al. 2004). An autopsy study in burn patients revealed that in 18% of the deaths, the causes were unknown and in 4.5% the therapy would have been changed had the correct diagnosis been known (Fish et al. 2000). Over time, from 1919 to 1980, the frequency of unexpected autopsy findings has remained the same, only the nature of these findings has changed (Goldman 1984, Goldman et al. 1983). Autopsy remains an invaluable tool for retrospective diagnostic understanding of difficult cases, medical education, and quality assurance in burn units.
6 AIMS OF THE STUDY

The purpose of this study was to scrutinize the burn deaths in Helsinki Burn Center by analyzing pre-hospital patient records, clinical data, and autopsy reports.

Specific aims were as follows:

1) To identify early factors during the pre-hospital care of burn patients associated with outcome.

2) To examine the prevalence of adrenal hemorrhage in non-surviving patients with severe burns.

3) To investigate the causes of death in patients with fatal burns and to specify irreversible organ dysfunctions leading to death.

4) To compare premortem clinical diagnoses and autopsy findings in order to reveal and classify clinically important diagnoses that have remained undetected during intensive care of burn patients.
7 PATIENTS AND METHODS

A retrospective chart review of adult burn patients was carried out in two stages. Patients for Studies I-III were retrieved for an 11-year period, from 1.1.1995 to 31.12.2005. Patients for Study IV were retrieved for a 5-year period, from 1.1.2006 to 21.12.2010.

7.1 Studies I-III

The Internal Review Board of the Helsinki University Hospital approved the study protocol (§133 / 15.8.2004 and §45 / 16.2.2012). For studies I-III, all burn-related admissions, deaths, and autopsy reports were identified from the hospital institutional database. All adult (age ≥18 years) burn patients who had died in the Helsinki Burn Center, Helsinki University Hospital, Helsinki, Finland, between 1.1.1995 and 31.12.2005 were included.

The following data were obtained from the electronic medical record of the patients who had died in the Helsinki Burn Center and had had autopsies: age, gender, co-morbidities, smoke inhalation injury, injury characteristics, %TBSA burned, length of hospital stay (LOS), and clinical cause of death. The autopsy diagnoses were obtained from the final autopsy reports. Prognostic indexes were calculated: Baux score (Tobiasen et al. 1982) and Abbreviated Burn Severity Index (ABSI) (Tobiasen et al. 1982, Andel et al. 2007).

All patients underwent medicolegal autopsies. Pathologists macroscopically examined the bodies, and microscopic specimen of organs were obtained and
carefully analyzed. All findings, normal and abnormal, were documented. The autopsy diagnoses were obtained from the final autopsy reports.

Data are presented as mean and range, except for number of organ failures, which is presented as median ± standard deviation (SD).

Some patients were deemed palliative upon arrival to hospital. These patients received terminal care. The decision of terminal care was made by taking into account the patient’s age, previous illnesses, %TBSA burned, inhalation injury and concomitant traumas. The decision was made by a team of two plastic surgeons and an intensivist. Terminal care patients are included in the study population.

7.1.1 Study I

The objective of Study I was to compare pre-mortem clinical diagnoses and autopsy findings in order to reveal and classify clinically important diagnoses that have remained undetected during intensive care of burn patients.

A team of two plastic surgeons specialized in burn care, an intensivist, and a pathologist evaluated all of the data collected. This team concluded each patient’s cause of death with organ specific changes. The team also compared clinical and the autopsy reports and classified the patients into different categories of autopsy discrepancies based on consensus.

Discrepancies between clinical cause of death and autopsy findings were initially classified by Goldman et al. (1983), and modified later by Fish et al. (2000) to reflect the special character of burn injury. The classification system used in study I is presented in Table 4.
Table 4. Goldman and Fish classification for autopsy discrepancies in patients with burns.

<table>
<thead>
<tr>
<th>Major</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Missed major diagnosis for which detection before death would have led to altered therapy or survival</td>
</tr>
<tr>
<td>Class II</td>
<td>Missed major diagnosis for which detection before death would not have led to altered therapy or survival because either no good therapy was available at the time or because patient had already received appropriate therapy, even though the diagnosis was unknown.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III</td>
<td>Missed minor diagnosis that was attributable to the burn injury but would have had no impact on the treatment of the patient</td>
</tr>
<tr>
<td>Class IV</td>
<td>Missed minor diagnosis that was not attributable to the burn injury and would have had no impact on patient care</td>
</tr>
<tr>
<td>Class V</td>
<td>Complete agreement between pre-mortem clinical diagnosis and autopsy findings</td>
</tr>
</tbody>
</table>

Special interest was paid to the amount of diagnostic discrepancies found, the year diagnostic discrepancies occurred, the specific diagnoses remained undetected clinically, the patient demographics and to the course of events leading to death.
7.1.2 Study II

The purpose of Study II was to investigate the causes of death in patients with fatal burns and to specify irreversible organ dysfunctions leading to death.

A team of two plastic surgeons specialized in burn care, an intensivist, and a pathologist evaluated all of the data collected. This team concluded each patient’s cause of death with organ specific changes by combining data from clinical charts and medicolegal autopsy reports.

The cause of death in terminal care patients is referred to as “burn death,” unless autopsy showed other specific causes of death.

MOF deaths were diagnosed by combining data from clinical charts and medicolegal autopsy reports. In this study, in agreement with previous literature (Cumming et al. 2001), MOF was defined as the cause of death if a patient displayed three or more organ failures. Organ failures noted were central nervous system (CNS), pulmonary, cardiac, vasomotor, hematological, hepatic, gastrointestinal, renal, and adrenal. An organ failure could be either clinically indisputable, e.g. blood culture positive sepsis, or noted only at the autopsy, e.g. cellular damage.

7.1.3 Study III

The aim of Study III was to examine the prevalence of adrenal hemorrhage in non-surviving patients with severe burns.
From the study population of all adult burn patients who had died in the Helsinki Burn Center during the study period, patients diagnosed with AH in clinical charts or at autopsy were sorted out. Particular attention was paid to the patient’s demographics, the prevalence of AH in non-surviving patients with severe burns, the course of events preceding their death and to their autopsy findings.
Flow diagram of patient distribution within studies I-III

All patients, burn deaths included in the studies I-III, n=71

Study I, Clinical diagnostic discrepancies, n=71
  - Class I, n=4
  - Class II, n=2
  - Class III, n=3
  - Class IV, n=1

Study II, Causes of death, n=71
  - Burn deaths, n=28
  - MOF deaths, n=28
  - Other causes of death, n=15

Study II, Prevalence of AH, n=71
  - AH patients, n=4
    - Bilateral AH, n=3
    - Unilateral AH, n=1
7.2 Study IV

The goal of Study IV was to identify early factors during the pre-hospital care of burn patients associated with outcome.

Study IV is an observational retrospective cohort study. It was approved by the Ethical Committee of Helsinki University Central Hospital (§71 / 16.4.2007 and §152 / 28.9.2007). The inclusion criteria for this study were adult (≥ 18 years) patients suffering from burns treated at Töölö Hospital during a 5-year period between 1.1.2006 and 31.12.2010. The included patients had one or more of the following disorders: total body surface area (TBSA) ≥20%, electric injury or hot air sauna burn, need for mechanical or assisted ventilation, risk of airway deterioration, need for vasoactive medication, delirium, and palliative care. Inter-hospital transfers (referrals) were excluded.

Patients with major burn injury from within a radius of approximately 100 km are transferred directly from the scene of the accident to Töölö Hospital. The emergency medical service (EMS) system is three-tiered, including one physician-staffed ground unit in the city of Helsinki, and another physician-staffed unit equipped with an emergency medical helicopter for the rest of the area. Other units are staffed with paramedics of various training. The decision to include the physician-staffed units in the emergency response is made by dispatch centers. At the accident site, the paramedics can request reinforcements. In general, the guidelines conform to the approach presented by Allison and Porter (2004).

The pre-hospital electronic and paper records were analyzed. Injuries were classified using the Abbreviated Injury Scale (AIS) (version 2005), AIS http://www.aams.org, for obtaining the Injury Severity Score, ISS (Baker et al. 1974). Physiologic variables and interventions recorded during the pre-hospital
phase, in the emergency department, and in the burn unit were collected. The pre-
hospital estimate of the %TBSA burned and the suspicion of inhalation injury or
smoke inhalation were recorded, as were the corresponding in-hospital final
estimates of burn area and inhalation injury or smoke inhalation, as verified by
bronchofiberooscopy. The pre-hospital estimates were made by the person with the
highest training. The hospital estimates were made by a plastic surgeon specialized
in burn care, and broncofiberooscopy was performed by an intensivist.

The patients were divided into two groups, and the data were analyzed in groups,
based on whether a physician was present or absent in the pre-hospital phase. For
survival, outcome was calculated at 7 days, 30 days, and 6 months. Patients were
divided into survivors and non-survivors according to their survival from the day of
the accident. All causes of death during the follow-up period were included in the
non-survivor group.

For statistical analysis, SPSS 13.0 for Mac OS X was used. The categorical data
were tested using the chi-square (Fisher’s exact) test and the continuous data using
the Mann-Whitney U test. P-values ≤ 0.05 were considered statistically significant.

To determine if the pre-hospital suspicion of inhalation injury or smoke inhalation
predicts corresponding injury verified in the hospital, positive predictive values
(PPVs) and negative predictive values (NPVs) were calculated.
Flow diagram of patient distribution between groups in Study IV
8 RESULTS

8.1 Studies I-III

The overall mortality rate between 1.1.1995 and 31.12.2005 was 5.4%. Of the admitted 1370 burn patients, 74 died in the Helsinki Burn Center from their burn injuries. However, due to three missing autopsy reports, the final study population consists of 71 patients for whom sufficient information was gained.

After considering etiology, extent of burn injury, age, and comorbid conditions, an experienced team of burn specialists assessed 32 patients to have no hope of survival within 24 hours of the burn injury. These patients received terminal care. The cause of death for these patients was set as “burn death,” unless autopsy showed other specific causes of death. The remaining 39 patients received active treatment.

All 71 patients underwent medicolegal autopsies. The two main causes of death were MOF and burn death, each accounting for 28 deaths. Together they accounted for 79% of the deaths. Other causes of death were scattered and comprised 21% of the deaths. Two-thirds of the patients were men and one-third women. Patients’ mean age was 57.5 (range 24–94) years. Distribution of number of patients, sex, and age was similar in the terminal care and active care groups.

For all patients, the %TBSA burned varied from 4 to 100, mean 49.4. Terminal care patients had the highest %TBSA burned, with a mean of 64.5, whereas the active care group had a considerably lower mean of 37.0 %TBSA. The severity of injuries in the terminal care group was also reflected as higher Baux and ABSI values and in a shorter length of hospital stay.
The majority (87.3%) of the patients had flame burns. Hot air sauna burns (HASB) were found in 8.4%, scalds in 2.8%, and electric burns in 1.4% of patients. Two hot air sauna burns were in the terminal care group; otherwise, all patients in the terminal care group had flame injuries. One-third of patients in the active care group were alcoholics; in the terminal care group, alcoholism was diagnosed in half of the patients.

Smoke inhalation injury was diagnosed in 23 (32.4%) patients. Terminal care group patients were diagnosed with smoke inhalation injury in 44% of cases; in the active care group smoke inhalation injury was diagnosed in 23% of the patients. Most (n=58, 82%) of the burns were classified as non-intentional, 10 (14%) were intentional (9 suicides and 1 assault), and three cases could not be classified. The terminal care group had more than twice as many intentional burns (n=7, 22%) as the active care group (n=3, 8%).

Active care patients were operated on an average of 2.3 times (range 0-9 operations). The majority 29 (74.4%) of patients underwent from one to three operations, two were operated upon four times, and one patient underwent five operations. Two patients had nine operations. Tracheostomies were performed on 15 (38.5%) patients. No operations were performed on the terminal care group, except for two patients who had tracheostomies on admission, before they were estimated to have no hope of survival.
8.2 Comparison of clinical diagnosis and autopsy findings in Study I

The majority (n=61, 86%), of patients were classified as Class V, with a complete agreement between pre-mortem clinical diagnosis and autopsy findings. Altogether 10 (14.1%) autopsies revealed previously undetected findings. There were six major discrepancies: four (5.6%) Class I and two (2.8%) Class II. The remaining four were classified as minor: three (4.2%) Class III and one (1.4%) Class IV.

The missed diagnoses were five pneumonias, one pulmonary embolus, one ARDS, one myocardial infection, one severe hepatic cirrhosis, and one patient had kidney, liver and spleen necrosis.

The missed diagnoses were rather evenly distributed over the years. All Class I mistakes occurred during different years. The highest number of diagnostic discrepancies was found in 1996, with three diagnostic discrepancies, one of each from Class I to Class III.

8.2.1 Class I mistakes

There were four major Class I diagnostic discrepancies. The missed major diagnoses were one pneumonia, one pulmonary embolus, one myocardial infarction and one kidney, liver, and spleen necrosis. All the patients with Class I missed diagnosis were in the active care group, comprising 10.3% of active care deaths and 5.6% of all burn deaths. Class I mistakes were made in years 1996, 2001, 2004, and 2005.
8.2.2 Class II mistakes

Two Class II major diagnoses were missed: one severe hepatic cirrhosis and one adult respiratory distress syndrome. Both patients were in the active care group. Class II missed diagnoses formed 2.8% of all burn deaths and 5.1% of active care deaths. The diagnostic discrepancies occurred in 1996 and 1998.

8.2.3 Class III mistakes

Three minor mistakes categorized as Class III were found. All Class III missed diagnoses were found in the active care group, and they were all pneumonias. Class III mistakes occurred in 1996, 1999, and 2000. They consisted of 7.7% of active care deaths and 4.2% of all burn deaths.

8.2.4 Class IV mistake

There was only one diagnostic discrepancy in the terminal care group. It was an undiagnosed pneumonia in a severely burned older woman. She was in terminal care and survived only for one day. Autopsy showed that she died of pneumonia, although her clinical cause of death had been diagnosed as burn injury. Due to her short length of hospital stay, she must have had severe pneumonia upon arrival. This finding was classified as a Class IV mistake, with no effect on treatment and the diagnosis was not attributable to the burn. The Class IV mistake occurred in 2001, and it comprised 1.4% of all burns deaths and 3.1% of terminal treatment deaths.
8.3 Multiple organ failure

8.3.1 Multiple organ failure deaths

The majority (82%) of the 28 MOF death patients were male. The mean age of the MOF cohort was 50.4 years and mean %TBSA burned 43.4%, yielding a mean Baux of 93.7%. All but two patients received active care. The mean ABSI score was 9.2 and mean length of hospital stay (LOS) 16.9 days. Table 5 presents the demographic of MOF patients (Table 5).
Table 5. Demographic data of the MOF patients

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>All MOF deaths</th>
<th>MOF without Sepsis</th>
<th>MOF with sepsis</th>
<th>MOF with ACLF</th>
<th>MOF with AH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (M/F)</td>
<td>71 (50/21)</td>
<td>28 (23/5)</td>
<td>15 (15/0)</td>
<td>13 (8/5)</td>
<td>4(3/1)</td>
<td>3 (3/0)</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>57.5 (24-94)</td>
<td>50.4 (31-81)</td>
<td>48.5 (33-66)</td>
<td>52.3 (31-81)</td>
<td>47.75(36-62)</td>
<td>43.7 (31-57)</td>
</tr>
<tr>
<td>Care type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active (%)</td>
<td>39 (54.9)</td>
<td>26 (92.9)</td>
<td>13 (86.7)</td>
<td>13 (100)</td>
<td>3 (75)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Terminal (%)</td>
<td>32 (45.1)</td>
<td>2 (7.1)</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
<td>1 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>%TBSA (range)</td>
<td>49.4 (4-100)</td>
<td>43.4 (7-90)</td>
<td>48.9 (7-90)</td>
<td>37.0 (13-65)</td>
<td>33.9 (25-38.5)</td>
<td>45.3 (32-65)</td>
</tr>
<tr>
<td>Mechanism of trauma, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flame</td>
<td>62 (87.3)</td>
<td>24 (85.7)</td>
<td>14 (93.3)</td>
<td>10 (76.9)</td>
<td>4 (100)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Hot air</td>
<td>6 (8.4)</td>
<td>2 (7.1)</td>
<td>0 (0)</td>
<td>2 (15.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hot water</td>
<td>2 (2.8)</td>
<td>1 (3.6)</td>
<td>0 (0)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Electric</td>
<td>1 (1.4)</td>
<td>1 (3.6)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>LOS, days (range)</td>
<td>10.7 (1-98)</td>
<td>16.9 (1-98)</td>
<td>13.1 (1-58)</td>
<td>21.3 (5-98)</td>
<td>5.5 (1-9)</td>
<td>10.3 (7-16)</td>
</tr>
<tr>
<td>Baux (range)</td>
<td>105.6 (42-152)</td>
<td>93.7 (52-138)</td>
<td>97.4 (64-138)</td>
<td>89.4 (52-125)</td>
<td>81.6 (67-98)</td>
<td>89 (70-108)</td>
</tr>
<tr>
<td>ABSI (range)</td>
<td>10.2 (4-15)</td>
<td>9.2 (5-13)</td>
<td>9.5 (5-13)</td>
<td>8.8 (5-12)</td>
<td>8.5 (7-10)</td>
<td>9 (7-12)</td>
</tr>
<tr>
<td>Alcoholic (%)</td>
<td>29 (40.8)</td>
<td>10 (35.7)</td>
<td>7 (46.7)</td>
<td>3 (23.1)</td>
<td>3 (75)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Reason of trauma, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental</td>
<td>58 (81.7)</td>
<td>24 (85.7)</td>
<td>12 (80)</td>
<td>12 (92.3)</td>
<td>4 (100)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Intentional</td>
<td>10 (14.1)</td>
<td>3 (10.7)</td>
<td>2 (13.3)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>3 (4.2)</td>
<td>1 (3.6)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tracheostomy, (%)</td>
<td>17 (23.9)</td>
<td>11 (39.3)</td>
<td>6 (40)</td>
<td>5 (38.5)</td>
<td>2 (50)</td>
<td>1 (33.3)</td>
</tr>
</tbody>
</table>
On average, MOF patients had 4 ± 1.62 organ failures (range 3-8). Table 6 presents the specific organ failures in the MOF death groups (Table 6). All MOF patients had acute renal failure, and 23 patients had liver damage. Four patients had both acute and chronic cirrhotic liver damage, i.e. acute-on-chronic liver failure.

Lung injuries consisted of pneumonia and acute respiratory distress syndrome (ARDS). The majority (n=14) of the patients had only one type of lung injury. Four patients had ARDS and pneumonia simultaneously. Sepsis was found in 13 patients and disseminated intravascular coagulation (DIC) in three patients. CNS damage recorded comprised six anoxic/hypoxic brain damage/small hemorrhages, five edemas of the brain, and one edema of the brain with a recent cerebral infarction.

As gastrointestinal complications, five patients had paralysis of the gastrointestinal track, four patients had acute pancreatitis, and one patient had inflammatory changes from the esophagus to the bowel accompanied by pancreatitis. Two patients presented with pericarditis, and two patients had myocardial infarction. Three patients had bilateral adrenal hemorrhage.
Table 6. Organs failures in patients who died of MOF, MOF without Sepsis, MOF with Sepsis, MOF with ACLF and MOF with AH.

<table>
<thead>
<tr>
<th>Organ</th>
<th>All MOF patients</th>
<th>MOF without sepsis</th>
<th>MOF with Sepsis</th>
<th>MOF with ACLF</th>
<th>MOF with AH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>N:o (%)</td>
<td>N:o (%)</td>
<td>N:o (%)</td>
<td>N:o (%)</td>
<td>N:o (%)</td>
</tr>
<tr>
<td></td>
<td>28 (100)</td>
<td>15 (100)</td>
<td>13 (100)</td>
<td>4 (100)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>23 (82.1)</td>
<td>11 (73.3)</td>
<td>12 (92.3)</td>
<td>4 (100)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Acute</td>
<td>16 (57.1)</td>
<td>7 (46.7)</td>
<td>9 (69.2)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>3 (10.7)</td>
<td>2 (13.3)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cirrhosis+Acute</td>
<td>4 (14.3)</td>
<td>2 (13.3)</td>
<td>2 (15.4)</td>
<td>4 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>18 (64.4)</td>
<td>8 (53.3)</td>
<td>10 (76.9)</td>
<td>3 (75)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (28.6)</td>
<td>4 (26.7)</td>
<td>4 (30.8)</td>
<td>2 (50)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>ARDS</td>
<td>6 (21.4)</td>
<td>3 (20.0)</td>
<td>3 (23.1)</td>
<td>1 (25)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Pneumonia+ARDS</td>
<td>4 (13.3)</td>
<td>1 (6.7)</td>
<td>3 (23.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>16 (57.1)</td>
<td>3 (20)</td>
<td>13 (100)</td>
<td>3 (75)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>13 (46.4)</td>
<td>0 (0)</td>
<td>13 (100)</td>
<td>2 (50)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>DIC</td>
<td>3 (10.7)</td>
<td>3 (20)</td>
<td>0 (0)</td>
<td>1 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>15 (53.6)</td>
<td>7 (46.7)</td>
<td>8 (61.5)</td>
<td>2 (50)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Tachycardia episodes</td>
<td>14 (50.0)</td>
<td>7 (46.7)</td>
<td>7 (53.8)</td>
<td>2 (50)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Bradycardia episodes</td>
<td>1 (3.6)</td>
<td>0 (0)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>12 (42.9)</td>
<td>5 (33.3)</td>
<td>7 (53.8)</td>
<td>1 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>10 (35.7)</td>
<td>4 (26.7)</td>
<td>6 (46.2)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Intestines</td>
<td>5 (17.9)</td>
<td>3 (20.0)</td>
<td>2 (15.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4 (14.3)</td>
<td>1 (6.7)</td>
<td>3 (23.1)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Intestines+Pancreatitis</td>
<td>1 (3.6)</td>
<td>0 (0)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4 (14.3)</td>
<td>1 (6.7)</td>
<td>3 (23.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infarct</td>
<td>2 (7.1)</td>
<td>1 (6.7)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>2 (7.1)</td>
<td>0 (0)</td>
<td>2 (15.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>3 (10.7)</td>
<td>0 (0)</td>
<td>3 (23.1)</td>
<td>0 (0)</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>
8.3.2  Multiple organ failure with or without sepsis (unpublished data)

The MOF patients without sepsis were all male, and they had the worst burns of all MOF deaths or MOF deaths with sepsis. They had highest %TBSA, Baux, and ABSI values of all MOF deaths or MOF deaths with sepsis. They also had the more intentional and undetermined burn accidents than patients with MOF with sepsis.

The patients with MOF without sepsis had a median of 3±0.6 (range 3-5) organ failures. This is the lowest number of organ failures per person of all MOF groups.

MOF deaths with sepsis had the longest LOS values and most hot air sauna burns and scalds. On average they had 6±1.2 (range 3-8) organ failures, which is the most organ failures of all MOF groups. Besides sepsis, they had a high percentage of CNS, gastrointestinal, and cardiac damage. All adrenal hemorrhage patients were in this group.

8.3.3  Multiple organ failure with acute-on-chronic liver failure (unpublished data)

Four patients had acute-on-chronic liver failure. Three of them were male and one female. Their mean age was 47.8 (range 36-62) years. Three were in active care and one in terminal care. They all suffered from accidental flame burns. Their mean %TBSA was 33.9, Baux 81.6, and ABSI 8.5. All had died of MOF.

The patients with ACLF had on average 4±1.3 (range 4-5) organ failures. Besides ACLF, all had kidney failure. Two pneumonias and one ARDS were noted. In addition, two sepsis cases and one DIC were found. One CNS damage episode and
two tachycardia episodes were recorded. ACLF patients with MOF had no gastrointestinal, cardiac, or adrenal organ dysfunctions/failures.

8.4 Adrenal hemorrhage

Adrenal hemorrhage was found in four patients, comprising 5.6% of the study population. Three MOF patients had bilateral adrenal hemorrhage. They were all male with flame burns. Their mean age was 44 years. The mean %TBSA was 45, mean ABSI was 7. Only one patient had inhalation injury. All AH patients were in the active care group, and their mean survival was ten days.

The patients with bilateral AH and MOF were diagnosed with 5±2.0 (range 4-6) organ failures. All three of these patients had sepsis, renal failure, and adrenal failure. Two patients had pneumonia and one had ARDS. One patient had tachycardia episodes, and one patient had pancreatitis. One acute hepatic failure was found.

The clinical course of events leading to death was similar in the three patients; all had sepsis and clinical signs of renal and pulmonary failure, and all developed hypotension that was unresponsive to adequate fluid resuscitation and vasopressors.

One patient had unilateral adrenal hemorrhage. He had hot air sauna burns and his %TBSA burned was 27. He was in the terminal care group, as he did not react to pain, nor did he regain consciousness, although the head CT scan was normal. He was constantly hypotensive and responded weakly to fluid resuscitation and vasopressive medication. He died within 24 hours of the admission. The
medicolegal autopsy revealed burn as the main cause of death. Other findings were unilateral adrenal hemorrhage, steatohepatitis, mild myofibrosis, four hemangiomas of the liver, and slight fibrosis of the renal cortex.

8.5 Burn Deaths

All 28 burn death patients received terminal care. The majority (68%) were male, with a mean age of 67.5 years. They had the highest %TBSA burned (mean 69.2), Baux (125.2), and ABSI scores (12.2) compared to MOF and other causes of death cohorts. Their mean length of hospital stay was 1.2 days.

8.6 Other Causes of Death

The other causes of death are sporadic, and this group was also the smallest (n=15) with the lowest %TBSA (23.7), Baux (91.2), and ABSI (8.2) values compared to MOF deaths or burn deaths. This cohort has the highest proportion of females (47%) and the oldest patients (mean 67.5 years). The majority (n=13) were in the active care regimen, and the mean length of hospital stay was 13.6 days.

Causes of death were as follows: four pneumonias, two rhabdomyolysis, two cardiac arrhythmias, and two hypoxic brain damages. In addition, one of the each of the following was recorded: pulmonary embolism, coronary artery disease, failed tracheostomy, renal failure, embolus of the superior mesenteric artery followed by necrosis of the mesenterium. All thromboembolic complications were recorded in this cohort. Demographic data of patients in this group is presented in table 7 (Table 7).
Table 7. Demographic data of patients in group “Other causes of death”.

<table>
<thead>
<tr>
<th>Mechanism of trauma</th>
<th>N:o (M/F)</th>
<th>Age (years range)</th>
<th>%TBS A (range)</th>
<th>Baux (range)</th>
<th>ABSI (range)</th>
<th>LOS (range)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>4 (4/0)</td>
<td>64.5 (51-88)</td>
<td>27.1 (6-62.5)</td>
<td>91.6 (66-118)</td>
<td>7.8 (5-11)</td>
<td>11.8 (4-20)</td>
<td>12 flame 1 scald 2 hot air</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>2 (2/0)</td>
<td>57.5 (38-77)</td>
<td>14.5 (4-25)</td>
<td>72 (42-102)</td>
<td>6 (4-8)</td>
<td>18 (2-34)</td>
<td>1 flame 1 hot air</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>2 (0/2)</td>
<td>68 (60-76)</td>
<td>32 (24-40)</td>
<td>100 (100-100)</td>
<td>9 (9-9)</td>
<td>18.5 (10-27)</td>
<td>2 flame</td>
</tr>
<tr>
<td>Hypoxic brain damage</td>
<td>2 (1/1)</td>
<td>78.5 (63-94)</td>
<td>10.5 (4-17)</td>
<td>89 (80-98)</td>
<td>8 (8-8)</td>
<td>21 (6-36)</td>
<td>2 flame</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (0/1)</td>
<td>62</td>
<td>15</td>
<td>77</td>
<td>8</td>
<td>15</td>
<td>1 flame</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (0/1)</td>
<td>84</td>
<td>23</td>
<td>107</td>
<td>10</td>
<td>15</td>
<td>1 flame</td>
</tr>
<tr>
<td>Failed tracheostomy</td>
<td>1 (0/1)</td>
<td>65</td>
<td>40</td>
<td>105</td>
<td>10</td>
<td>7</td>
<td>1 flame</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (1/0)</td>
<td>53</td>
<td>33</td>
<td>86</td>
<td>8</td>
<td>1</td>
<td>1 flame</td>
</tr>
<tr>
<td>Embolus of the superior mesenteric artery</td>
<td>1 (0/1)</td>
<td>82</td>
<td>22</td>
<td>104</td>
<td>10</td>
<td>4</td>
<td>1 hot air</td>
</tr>
</tbody>
</table>
8.7 Terminal care patients

The majority of terminal care patients died of untreated burn injury (n=28, 87.5%), however, pathological findings indicated that four (12.5%) had causes of death other than untreated burn injury. Two terminal care patients died of MOF, one died of renal failure, and one died of hypoxic brain damage.

The terminal care patients with MOF were both male alcoholics with accidental flame burns of %TBSA 55 and 35. They were 56 and 63 years old. LOS was less than 24 hours, they both had inhalation injuries, but no tracheostomies. Baux values were 111 and 98, with corresponding ABSI values of 10 and 11. They both had four organ failures. One patient had kidney failure, acute liver failure, ARDS and DIC, and the other had kidney failure, ACLF, DIC and CNS damage. (unpublished data).

The terminal care patient who died of renal failure also had cirrhosis. He was a 53-year-old alcoholic male with flame burns of %TBSA 33, Baux 86 and ABSI 8. His LOS was less than 24 hours. At autopsy, his renal cortex was found to be destroyed. He had very deep burns through his muscles and his bleeding was uncontrollable upon arrival to hospital. Cirrhosis was suspected due to elevated hepatic values. (unpublished data)

The terminal care patient who died of CNS damage was a 94-year-old female with flame burns of %TBSA 4, Baux 98, and ABSI 8. Her LOS was six days. She had inhalation injury. She was found unconsciousness in a cabin fire. She did not regain consciousness and had poor responses to pain stimulus. Her cause of death was CNS damage due carbon monoxide poisoning. (unpublished data)
8.8 Study IV

8.8.1 All patients

Between 1.1.2006 and 31.12.2010, altogether 67 patients with major burn injury were transported directly from the scene of the accident to the Helsinki Burn Center. Our study population included all of these 67 patients with major burns.

Of the 67 patients, the majority (60%) were men. The median age was 53 years. The etiology of the injury was predominantly flame (84%), followed by hot air sauna burn (HASB) (9%), electric injury (4.5%), and scald (3%). The final estimate of %TBSA was median 25. Inhalation injury was diagnosed in 42% of the patients. Median ISS score was 25. The first responding unit was on scene in a median of 10 minutes. Time spent at the scene was a median of 37 minutes. The patients arrived at hospital 66 minutes after the first call to the dispatch center.

An experienced team of burn specialists assessed 12 patients as having no hope of survival within 24 hours of the injury. These patients received terminal care.

8.8.2 Patients treated by pre-hospital physicians (Group 1)

The majority (73%) of the patients were treated by pre-hospital physicians (Group 1). In this group, median %TBSA was 32 and ISS 25. Fifty-one percent had inhalation injury. On-scene pulse rate was a median of 110 bpm. On arrival to hospital, the systolic blood pressure was a median of 128 mmHg. The median pH was 7.28. Nearly all (96%) patients received supplemental oxygen, and the intubation rate was 63%. The median amount of intravenous solution given pre-
hospital was 1.5 liters. In hospital, during the first 24 hours after injury, patients treated by pre-hospital physicians received a median of 13.5 liters of intravenous solutions.

8.8.3 Patients treated by paramedics (Group 2)

Paramedics treated 27% of the study population (Group 2). In the group, median %TBSA was 17 and the ISS 8. Sixteen percent had inhalation injury. On-scene pulse rate was 91 bpm. On arrival to hospital, the systolic blood pressure was a median of 145 mmHg. Median pH was 7.34. Seventy-eight percent of the patients received supplemental oxygen. The intubation rate was 11%. The median amount of intravenous solution given pre-hospital was 0.5 liters. In hospital, during the first 24 hours after injury, patients treated by paramedics received a median of 10.2 liters of intravenous solutions.

8.8.4 Parameters that did not reach statistical significance in the comparison between Group 1 and Group 2

No significant difference between Groups 1 and 2 was observed in age, sex, etiology of injury, time elapsed to arrival on scene, time spent at scene, or time from emergency call to arrival to hospital. The first systolic blood pressure, first SpO2 and first Glasgow coma scale (GCS) were comparable. The pulse rate, SpO2, body temperature, paO2, paCO2, BE, or lactate did not differ significantly between the groups. No statistical difference was found in the application of pain or vasoactive medication.
8.8.5 Survival for 7 days

At seven days the survivors were considerably younger than the non-survivors (48 vs. 62 years, p= 0.002). The non-survivors were more severely injured, with higher %TBSA (17 vs. 60, p=0.000), higher ISS values (9 vs. 33, p=0.000), and lower first GCS (15 vs. 13, p=0.028). On arrival to hospital the survivors’ SpO2 was better (99 vs. 98, p=0.032), and pH was higher (7.31 vs. 7.27 p=0.049). The non-survivors were more often intubated (40% vs. 70%, p=0.034) and they received more intravenous solutions (11.5 vs. 26.0 liters, p=0.033) during the first 24 hours.

8.8.6 Survival for 30 days

The 30-day survivors were younger than the 30-non-survivors (46 vs. 62 years, p=0.001). Females had higher mortality at 30 days than males; 29% of survivors were female and 58% of the non survivors were female, (p= 0.025). The non-survivors were more severely injured than the survivors, with higher %TBSA (17 vs. 55, p=0.000), and higher ISS values (9 vs. 17, p=0.001). First systolic blood pressure was higher in survivors than in non-survivors (132mmHg vs. 116mmHg, p=0.036). The non-survivors received more intravenous solutions during the first 24 hours than the survivors (11.3 vs. 23.9 liters, p=0.010). The time spent on the scene was longer for survivors than non-survivors (50 minutes vs. 21 minutes, p=0.050).
8.8.7 Survival for 6 months

Six-month survival: survivors were younger than the non-survivors (42 vs. 62 years, p=0.000). A higher proportion of non-survivors were female; 26% of survivors were female, and 56% of non-survivors were female (p=0.014). Non-survivors were more severely injured than survivors with higher %TBSA (17 vs. 48, p=0.000), higher ISS values (9 vs. 17, p=0.000), and lower first GCS scores (15 vs. 14, p=0.021). All (100%) non-survivors received supplemental oxygen, whereas 87% of survivors received supplemental oxygen (p=0.025). On arrival to hospital, survivors at six months had higher systolic blood pressure than non-survivors (144 v. 116mmHg, p=0.025) and survivors had lower BE (-4.2 v. -7.5, p=0.048). Non-survivors at six months received more intravenous solution than survivors (11.4 vs. 20.4 liters, p=0.039). Pre-hospital supplemental oxygen was given to all (100%) patients who died at any of the survey points.
8.8.8  **Factors not associated with survival at any of the survey points**

Etiology of the burn injury or inhalation injury was not associated with mortality. In pre-hospital treatment, the amount of intravenous solutions, pain medication, or vasoactive medication was not connected to survival at any of the survey points.

In pre-hospital treatment, first pulse rate and first SpO2 % were not associated with mortality at any of the survey points. On arrival to hospital, pulse rate, body temperature, paO2, paCO2, and lactate were not connected to mortality at any of the survey points. Intubation at the emergency department did not affect survival.

First spontaneous breathing rate, first body temperature, and GCS on arrival to hospital could not be calculated due to a large number of missing values in the hospital charts.
9 DISCUSSION

This study provides a detailed overview of fatal burns. It reveals pre-hospital demographic parameters affecting mortality up to six months post-trauma. Further, it gives a comprehensive description of causes of death after burn trauma. We also identified some clinically important diagnoses missed during treatment. These diagnoses might have affected the treatment and outcome had they been known in time.

The results highlight parameters that should make the clinician reassess the course of treatment, warning that the patient might be critically near death. For example, the probability of sepsis and continuum to MOF seems to increase with prolonged ICU stay (Cumming et al. 2001). Resuscitation unresponsive to vasopressors should raise the question of possible bilateral AH. Patients’ age, %TBSA, and ISS affect the mortality up to six months post trauma.

9.1 Missed diagnoses

In 14.1% (n=10) of the study population, there was a discrepancy between the pre-mortem clinical diagnosis and the autopsy finding. Each patient had only one missed diagnosis, no one had multiple diagnostic discrepancies. Of the diagnostic discrepancies, 8.5% were considered major and 5.6% would have altered the therapy or clinical outcome had they been known in time.

Four (5.6%) patients had Class I, two (2.8%) had Class II, three (4.2%) had Class III, and one (1.4%) had Class IV missed diagnoses. One cardiovascular, seven
respiratory, and two gastrointestinal diagnostic discrepancies emerged. The most frequently missed diagnosis was pneumonia, seen in five autopsy findings.

Of all patients, 86% were classified in to Class V, with no diagnostic discrepancies; Thus, 14% of patients had some level of diagnostic discrepancy. Fish et al. (2000) found a slightly higher number of diagnostic discrepancies in their study, 18% (Fish et al. 2000). The last two Class I mistakes were diagnosed in 2004 and 2005, emphasizing that despite diagnostic advances, some clinically important findings remain undetected, revealed only at autopsy.

A full-time intensivist joined the burn team in fall 2001. The majority (80%) of the diagnostic discrepancies happened before this. Thus, knowledge of intensive care seems to help diagnose and treat conditions related to burn injury.

9.2 Multiple organ failure

In developed countries, MOF, SIRS, sepsis and other complications are the main causes of death in severely burned patients in the active care regimen (Saffle et al.1993, Cumming et al. 2001). Multiple organ failure is the leading cause of burn death in the developed countries (Bloemsma et al. 2008). Bloesmsma et al. (2008) published a MOF incidence of 65% among active care patients in their study (Bloemsma et al. 2008). The figure here is similar, 67% among active care patients. When taking all patients, terminal and active care, 40% died of MOF.

The pathogenesis of MOF is not known, although it is thought to be a combination of ischemia/reperfusion, maldistribuition of microcirculatory blood flow, and imbalance between inflammatory response and immune function (Aikawa et al. 1987, Cryer 2000, Ferreira and Sakr 2011). Divergent views exist regarding the
role of MOF in burn patients. Some articles support the view that MOF is the result of other contributing factors, such as sepsis (Fitzwater et al. 2003), while others see MOF as independent systemic manifestation of thermal injury itself (Cumming et al. 2001). I found two MOF patients who survived only one day and were diagnosed with MOF in the medicolegal autopsy. This seems to support the view that MOF is an independent manifestation of burn injury (Saffle et al. 1993, Dulhunty et al. 2008).

The SOFA score (Vincent et al. 1996) is based on physiological values of respiration ($P_{aO_2}/FiO_2$ (mmHg)), Cardiovascular (Mean Arterial Pressure (MAP) or Administration of vasopressors), liver (bilirubin ($\mu$mg/L)), renal system (Creatinine $\mu$mol/L (or urine output)), coagulation (platelets$\times$10$^3$/mcl), and nervous system (Glasgow coma scale). The SOFA score is used to assess the development of multiple organ failure in ICU patients (Strand and Flaatten 2008), it also predicts in-hospital mortality (Pavoni et al. 2010). Previous studies have suggested that organ dysfunctions counted in MOF should be pulmonary, cardiovascular, renal, hepatic, and hematologic (Lefering et al. 2002), while debated organ systems include the central nervous system (Marshall et al. 1995, Ferreira and Sakr 2011) and gastrointestinal system (Goris et al. 1985).

The definition of MOF in this study is based on three or more organ failures noted clinically or as an autopsy finding. Our study has taken into account pulmonary, cardiovascular (vasomotor and cardiac), renal, hepatic, hematologic, and also CNS, gastrointestinal, and adrenal systems. MOF deaths were diagnosed by combining data from clinical charts and medicolegal autopsy reports. An organ failure could be either clinically indisputable, e.g. blood culture positive sepsis, or noted only at the autopsy, e.g. cellular damage. Our range of organ systems is wider than in previously published MOF definitions because we had detailed information from
medicolegal autopsies. For example adrenal failure is rarely noted clinically but clearly visible in the autopsy. However, our study does not segregate between organ failure and organ dysfunction. Some microscopical autopsy findings may have had little if any clinical relevance, e.g. small hemorrhages of the brain.

Our study had some of the same organs as the SOFA score, but from a different point of view: for example, our pulmonary organ failure could either be ARDS or pneumonia where SOFA has PaO₂ values. SOFA focuses on physiological values regardless of the reason behind the deterioration of these values. Our study’s MOF diagnosis is based on clinical diagnoses regardless of the physiological values these diagnoses might demonstrate on a live patient. We also took into account some organ systems or diagnoses not noted at SOFA. These were adrenal, cardiac (pericarditis and infarct), and gastrointestinal.

Our study provides valuable information on organ dysfunctions caused by MOF. We also reveal some clinical diagnoses behind these organ dysfunctions. Some gathered diagnoses have been revealed only at autopsy (e.g. adrenal haemorrhage), thus our findings serve as knowledge on clinical diagnoses behind burn deaths. Our definition of MOF is our own, and not used as such in any other studies, therefore direct comparison to other MOF studies might be biased.

By definition, MOF affects several organs. Some studies have shown the lungs to be the most frequently affected organ in MOF (Sheridan et al. 1998, Bloemsma et al. 2008). In this study, however, the most frequently encountered organ failure in MOF deaths was renal failure, with an incidence of 100%. Renal failure is a serious complication among burn patients (Brusselaers et al. 2010, Mosier et al. 2010) with a mortality rate between 28 and 100% (Kim et al. 2003, Coca et al. 2007). Furthermore, early acute kidney injury is associated with early MOF in patients
with burns (Steinvall et al. 2008, Mosier et al. 2010). Only one patient in this study died of renal failure without MOF. This strong association between renal failure and MOF should serve as a warning sign. Patients with renal failure should be carefully monitored and treated to prevent the formation of MOF.

9.3 Multiple organ failure and sepsis

Less than half, 45%, of the MOF patients had sepsis. This finding is in line with the literature; Bloemsma et al. (2008) found sepsis to be the reasons for fatal clinical deterioration in 46% of MOF patients (Bloemsma et al. 2008). Sepsis was never found to be the sole cause of death. Here, sepsis seemed to promote the formation of organ failures or organ dysfunctions, as patients with sepsis had the highest number of organ dysfunctions. The patients dying of MOF with sepsis had longer lengths of hospital stay than patients dying of MOF without sepsis. Prolonged ICU stay increases the risk of infectious complications (Cumming et al. 2001). In a clinical setting, signs of sepsis in burn patients should lead to more careful examination of possible organ dysfunctions to avoid the continuum to MOF.

9.4 Multiple organ failure and acute-on-chronic liver failure

Acute-on-chronic liver failure (ACLF) is a diagnosis where a chronic or long standing liver failure and an acute liver condition can be found simultaneously (Sarin et al. 2009). MOF is the cause of death for most ACLF patients, as the diagnosis easily leads to end-organ failures (Sarin et al. 2009). We found four patients with acute-on-chronic liver failure. All of our ACLF patients died of MOF. Half of the ACLF patients had sepsis and three-quarters were alcoholics. With
these patients, it is difficult to say which came first, the ACLF or MOF. They had the shortest LOS of all MOF patients and all burn patients. Naturally, pre-existing cirrhotic liver disease does not improve the chances of survival in a burn trauma. To the best of my knowledge, this is the first time that ACLF is associated with burns.

9.5 Multiple organ failure and adrenal hemorrhage

Autopsies revealed four (5.6%) patients with adrenal hemorrhage: Three patients (4.2%) with bilateral AH and one (1.4%) patient with unilateral AH. In the literature, 1.1% of deceased general hospital patients (Xarli et al. 1978) and up to 15% of patients dying of shock have been demonstrated to have bilateral AH (Vella et al. 2001); however, these have not been burn patients.

Reiff et al. (2007) found higher %TBSA and older age to be risk factors for acute adrenal insufficiency in severely burned patients in their case–control study (Reiff et al. 2007). Conversely, in our study, patients with bilateral AH were younger (44 vs. 58 years), their %TBSA was lower (45 vs. 49), ABSI scores were lower (7 vs. 10), and LOS was shorter (10 vs. 17 days) than other deceased burn patients. The rarity of AH patients imposes its own limitations on this comparison.

The clinical course of events leading to death in bilateral AH patients was alike. One week after the burn, all were diagnosed with sepsis with a continuum to MOF, both of which are known etiologic factors for AH (Vella et al. 2001). They developed sudden hypotension unresponsive to vasopressors and fluid resuscitation. All three developed renal insufficiency. Despite adequate measures, all died. It seems that hypotension unresponsive to intravenous fluids or
vasopressors should always raise the question of the condition of patients’ adrenal
glands and indicate CT scan or measurement of plasma cortisone in thermally
injured patients.

In the case of the unilateral AH, it is unclear whether the patient had AH prior to
the injury, i.e. whether the hypotension leading to unconsciousness was the reason
for prolonged exposure in the hot sauna air, or whether old age and large and deep
thermal injury contributed to AH. Idiopathic AH cannot be ruled out in this case.

9.6 Alcoholism

Alcoholism is a predisposing factor for mortality in a burn patient (Raff et al.
1996). Of all deceased patients in the 1995-2005 period, 41% were alcoholic.
Alcoholic patients had more severe injuries and were more often in the terminal
care group than non-alcoholic patients; the proportion of alcoholic patients in the
terminal care group was 50%, but in the active care group only 33%. The
relationship between alcohol and injury, including burns, is well-known
(Macdonald et al. 2006, Thombs et al. 2007). Since the 1970s, “alcoholism” has
been identified as a predisposing factor for burn injury (MacArthur and Moore
1975).

In patients with missed major diagnoses, there was a higher prevalence of chronic
alcohol abuse than in other patients (67% vs. 29%). Only one patient’s diagnostic
mistake was directly connected with alcohol abuse; the autopsy finding was
terminal hepatic cirrhosis, which remained undetected during her care.
9.7 Burn complications

Burn patients are especially prone to infectious complications. Major burn alters immune function, producing an imbalance between pro- and anti-inflammatory cytokine synthesis and increasing susceptibility to postburn infection and sepsis (Ayala et al. 2003, Zang et al. 2004). In patients with severe burns, with %TBSA exceeding 40, three-quarters of all deaths are related to sepsis from burn wound infection or other infectious complications and/or inhalation injury (Bang 2002). Pulmonary complications are common in burn patients with smoke inhalation injury. Further, prolonged intubation increases the risk for developing ventilator-associated pneumonia (Santucci et al. 2003, Wahl et al. 2005).

Burns are associated with multisystemic complications, even in otherwise healthy individuals. Age and number of pre-existing concomitant chronic diseases contribute to prolonged ICU care (Thombs et al. 2007). This study showed that patients with relatively low %TBSA can die. Four patients had %TBSA of less than 10. The causes of death of these patients were ARDS, pneumonia, hot air sauna burn with rhabdomyolysis, and smoke inhalation injury. The %TBSAs were 7, 6, 4, and 4, respectively. The latter two patients’ care was discontinued as futile.

9.8 Inhalation injury

Outcome from severe burn is associated with three major risk factors for death: age ≥60 years, %TBSA ≥40%, and presence of inhalation injury (Ryan et al. 1998, Brusselaers et al. 2005, Andel et al. 2007).
During 1995 to 2005, inhalation injury was diagnosed in 23 (32%) of this study’s patients. Nine (39%) of the patients received active care. This highlights the severity of inhalation injury, as of the deceased patients, 32% had inhalation injuries and 61% of the patients having inhalation injury on arrival were deemed palliative.

During 2006 to 2010, altogether 28 patients were diagnosed with inhalation injury. Pre-hospital physicians treated 25 and paramedics only three of these inhalation injury patients. As inhalation injury poses a threat to airways and often demands sedation and intubation, this strong division of patients seems appropriate and shows that the EMS system is able to recognize patients in need of a pre-hospital physician. Suspicion of inhalation injury in the field was accurate, PPV 0.86 and NPV 0.92. Contrary to the literature (Ryan et al. 1998, Brusselaers et al. 2005, Andel et al. 2007), in our study inhalation injury did not have an influence on survival.

Only one of the AH patients presented with smoke inhalation injury; thus, based on this small-scale study, smoke inhalation injury appears not to predispose to AH.

9.9 Hot air sauna burns

Hot air sauna burns (HASBs) resulting in rhabdomyolysis are rare but severe injuries (Koski et al. 2005). Hot air sauna burns develop due to prolonged immobility or loss of consciousness in the hot sauna air (Papp 2002). Full-thickness skin damage with deeper tissue destruction affecting the muscles is typically seen in these burns (Papp 2002, Koski et al. 2005, Ghods et al. 2008).
During the first study period from 1995 to 2005, six patients had HASBs. Two received terminal care and four were in the active care group. Two of the active care HASB patients would have received terminal care had their proper diagnoses been known in time. These were classified as Class I missed diagnoses. Their autopsy findings were myocardial infarction and necrosis of the abdominal organs. These findings highlight two facts: First, the main cause of unconsciousness in the sauna sometimes remains unknown (e.g. heart attack/cerebral infarction/intoxication and dehydration) and might have a considerable impact on treatment. Second, it is often impossible to estimate the time that the patient has been exposed to hot air.

During the second study period (2006-2010), there were 15 HASB patients. In this study, the mechanism of burn trauma had no influence on survival.

### 9.10 Fluid resuscitation

In Study IV, in both the physician- and paramedic-treated groups, patients were resuscitated in excess of the Parkland recommendations; 185% and 169%, respectively. This confirms earlier findings of “fluid creep”, a tendency to resuscitate patients over Parkland formula (Baxter 1981, Pruitt 2000).

During the first 24 hours survivors received approximately 11 liters of intravenous solutions. Non-survivors received more than twice as much intravenous solution, roughly 24 liters. The severity of the condition of patients included in this study may in part explain the excessive fluid resuscitation. Vigorous measures were taken in an attempt to rescue these patients, including substantial fluid resuscitation to keep blood pressure and kidney function at acceptable levels. Abundant resuscitation was connected to mortality up to 30 days and 6 months post trauma.
This confirms previous findings (Hobson et al. 2002, Klein et al. 2007) that over-resuscitation during the first 24 hours has long term effects.

9.11 Mortality

The mortality rate in the 11-year study period from 1995 to 2005 was 5.4%. The second study period from 2006 to 2012 showed that age, %TBSA, and ISS scores affected the mortality most. These findings are in line with previous literature from other European study centers (Ryan et al. 1998, Brusselaers et al. 2005, Andel et al. 2007, Gravante et al. 2007).

The majority (67%) of the non-survivors during 2006-2011 died within seven days of the injury, and 40% of the non-survivors received terminal care. The study from 1995 to 2005 confirmed similar numbers; 45% of the non-surviving burn patients were estimated to have no hope of survival within 24 hours after admission to the hospital. This emphasizes the potential lethality of a major burn injury. A considerable proportion of the patients are beyond help, no matter how advanced the pre-hospital and hospital care is.

9.12 Terminal Care

Altogether 44 patients were considered to have no hope of survival within 24 hours of admission. During 1995-2005 the terminal care patient had besides more smoke inhalation injuries also higher %TBSA (65 vs. 37) than patients who received active care. There were considerably more intentional burns in the terminal care group than in the active care group. Moore et al. (2010) found non-survivors to be
older, more severely burned, and with a higher incidence of deliberate self-harm than the survivors (Moore et al. 2010).

The decision to transfer a patient from active care to terminal care is always difficult. The patient’s medical history and present condition, wishes of the patient and family members, and the patient’s prognosis based on the experience of the burn team and literature affect this decision. Diagnostic discrepancies may result in incorrect interpretation of a patient’s prognosis and present condition; thus, the patient may receive inappropriate care for his true condition.

Interestingly, in the terminal care group only one patient was recorded as having a discrepancy between the clinical cause of death and autopsy findings. Moreover, this diagnostic discrepancy was classified as Class IV, i.e. it had no impact on patient care. We expected that in this group there would have been autopsy findings, such as myocardial infarction or cerebral infarction, that might have led to severe burn injury as a result of unconsciousness. The lack of this finding might be explained by the short survival time, which did not allow the typical pathological signs in the according organs to develop.

9.13 Prognostic indexes

Coarse scoring methods can be used for predicting patient outcome or as a triage system (Tobiasen et al. 1982, Krob et al. 1991). Outcome from severe burn is associated with three major risk factors for death: age ≥60 years, ≥%TBSA 40%, and presence of inhalation injury (Ryan et al. 1998, Brusselaers et al. 2005, Andel et al. 2007). These factors are taken into consideration when terminal care decisions are made. Study IV confirmed that age and %TBSA were linked to both short-term and long-term survival. We did not, however, find a connection between
smoke inhalation injury was more common in the terminal care group than in the
active care group (44% vs. 23%).

We found in study IV that patient’s survival is mostly affected by age and %TBSA.
As Baux value consists of %TBSA and age (Tobiasen et al. 1982), this study shows
that Baux still has value as the first estimate of patients’ chances of survival. The
ABSI values takes into account age, gender, %TBSA, full-thickness burn, and
inhalation injury (Andel et al. 2007). This study was able to demonstrate the effects
of %TBSA and age, and also gender in a long term, but not the effects of inhalation
injury. The results of this study are in accordance with the ABSI scoring system as
related to the threat to life (Andel et al 2007).

Patients treated by physicians were more severely injured than patients treated by
paramedics, as reflected by %TBSA and ISS. In Study IV, the first %TBSA
estimation was performed on the scene in 54% of the cases. When the estimation
was performed, the median difference between the pre-hospital and final estimates
was only 3%.

Statistically short term survival was affected with SpO2 values (99 for survivals
and 98 for non-survivals), from a clinical point of view, there is no relevant
difference between these values. Statistically long term survival was affected with
first pre-hospital systolic blood pressure (for 30 day survival) and first in-hospital
systolic blood pressure (for 6 month survival). These values were 116 mmHg for
non-survivors in both groups, 132 mmHg for 30-days survivors, and 144 mmHg
for 6-months survivors. Again, clinically there is no relevant difference between
these values.
In a burn trauma, females have higher mortality than males (O'Keefe et al. 2001, McGwin et al. 2002). This has also been taken into consideration in the Abbreviated Burn Severity Score, where female gender earns a point, and the higher the points, the worse the prognosis (Tobiasen et al. 1982, Brusselaers et al. 2005, Andel 2007.). In this study, older age and female gender contributed to higher mortality. Older age was not an explanatory factor for female mortality. Increased female mortality was noted at 30 days and at 6 months after the accident, beyond the systemic perturbation period. Gender did not affect immediate mortality in our patients.

Late AKI has considerably high mortality (Coca et al. 2007, Mosier et al. 2010). From the study population, the majority of active care patients died of MOF and all MOF patients had AKI. This confirms the previous finding of potential lethality of AKI. But as it is unknown in this study population how many surviving patients had AKI, no conclusion can be drawn from this study material on the subject of withholding care based on patients AKI diagnosis.

9.14 Limitations of the study

This study has two fundamental limitations: its retrospective nature and the relatively small number of patients.

As data in a retrospective study setting are not originally produced for investigational purposes, the data sheets are not always uniform, nor is the data reported in a consistent manner. This problem leads to missing values. Also investigator bias might develop when clinical impressions are gathered from medical records and compared to postmortem findings.
Interpretational bias was minimized by using a group of specialists (plastic surgeons, a pathologist, and an intensivist) to evaluate the data and by reviewing all of the cases in one session consecutively and comparing each case with itself and to all cases.

The definition of MOF in this study was based on three or more organ failures noted clinically or as an autopsy finding. This definition is our own, and not used as such in any other studies, therefore direct comparison to other MOF studies might be biased.

The number of patients in this study is quite small: 71 patients during 1995-2005 and 67 patients during 2006-2011. The relatively low number of patients places its own limitation on the statistical analysis of the data. The low number is explained by Finland’s rather small population, 5 401 267 in habitants at the end of the year 2011 (Tilastokeskus, http://www.stat.fi/til/vaerak/index.html), the rarity of severe burns in the Helsinki region, and the low overall mortality to burn injuries.

In the study period from 2006 to 2010, documentation was done by either a paramedic or a physician. The documentation requirements are the same for physicians and paramedics, but we cannot rule out the possibility that physicians document data better than paramedics - or vice versa. Most importantly, as the study was observational, the formation of patient groups was not random. This non-random formation of groups led to profound bias regarding injury severity. Thus, the patient groups could not be directly compared.
9.15 Strengths of autopsies

The autopsy rate in this study was 100%. This autopsy rate is very high compared with other studies in adult ICU settings, with autopsy rates ranging from 33 to 89% (Nadrous et al. 2003, Silfvast et al. 2003, Combes et al. 2004) and slightly higher than in the study by Fish et al. (Fish et al. 2000). The low autopsy rate in other studies might have led to selection bias, preferring cases in which physicians and family members of patients with premortem diagnostic uncertainty would have been more likely to pursue an autopsy than cases in which all parties were certain of the diagnoses and the outcome was predictable.

A retrospective study allows maximal information to be gained on the course of events and the causes of death. Medicolegal autopsy reports provide uncompromisingly detailed information on cause of death, affected organs, and previous illnesses of the patient. Autopsy remains an invaluable tool for retrospective diagnostic understanding of difficult cases, medical education, and quality assurance in burn units.

9.16 Future prospects

It would be interesting to repeat this study setting every 10 years. Special points of interest would be if the overall mortality rate and number of terminal care patients decline as burn care advances. Would diagnostic discrepancies diminish as clinical diagnostics advance? It would be expected that over the years the severity of injuries in the deceased would increase. From this data, or the future data, it would be fascinating to identify the bacteria causing sepsis with MOF. Are some bacteria more lethal in burns than others? Have all the deceased MOF patients with sepsis
received the same antibiotics? Furthermore, it would be interesting to compare the
autopsy findings of burn patients found dead on-the scene with patients who
survived to hospital. Is it always carbon monoxide poisoning that kills in fires or
are there other explanations for why people remain in the fire. The organ failures
most commonly noted at deceased MOF patients were: acute kidney injury, acute
liver injury, sepsis, pneumonia, and ARDS. Studies in search of the most effective
diagnosis and care for these organ failures could improve the survival of burn
patients. As increasingly more people survive burn traumas, it would be useful to
examine the quality of life after a burn trauma and the effect of different
treatments.
10 SUMMARY AND CONCLUSIONS

Based on the present study, the following conclusions can be drawn:

1) The mortality of a burn patient is associated with patient’s age, %TBSA, and ISS. In the long term, female gender predicted higher mortality.

2) The incidence of bilateral adrenal hemorrhage is higher than previously published. Resuscitation unresponsive to vasoactive medication should raise the question of bilateral AH.

3) Burn patient’s main causes of death in the ICU setting are burn injury itself and multiple organ failure. Kidneys were affected in every deceased MOF patient. Sepsis was always associated with MOF as a cause of death. The signs of sepsis should lead to careful organ monitoring in attempt to avoid MOF.

4) Autopsies revealed some major clinical diagnostic discrepancies. Only 5.6% of deceased burn patients had major diagnostic discrepancies that would have altered the clinical therapy or outcome had they been known in time.
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