Evaluation of Recovery in Iatrogenic Evoked Acute Mediastinitis

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Abstract—This study attempts to find a prediction method of death risk in patients with acute mediastinitis (AM). There is no such tool described in available literature for this serious disease. The study comprised 37 consecutive cases of iatrogenic AM. General anamnesis and biochemical data were included. Factor analysis was used to extract the risk characteristic for the patients. The most valuable results were obtained for eight parameters, which were selected for further statistical analysis (all collected during a few hours after admission). Three factors reached eigenvalue>1. Clinical explanations for these combined statistical factors are as follows: Factor 1—proteinic status (serum total protein, albumin, and hemoglobin level), Factor 2—inflammatory status (white blood cells, C-reactive protein, and procalcitonin), and Factor 3—general risk (age and number of coexisting diseases). Threshold values of prediction factors were estimated using statistical analysis (factor analysis, Statgraphics Centurion XVI). The final prediction result for the patients is constructed as simultaneous evaluation of all factor scores. High probability of death should be predicted if factor 1 value decreases with simultaneous increase of factors 2 and 3. The diagnostic power of the proposed method was revealed to be high [sensitivity=100 %, specificity=69.2 %]; Factor 1 [SNC=95.8 %, SPC=76.9 %]; Factor 2 [SNC=100 %, SPC=53.8 %]; and Factor 3 [SNC=75 %, SPC=76.9 %]. The described method may turn out to be a valuable prognostic tool for patients with AM.

KEY WORDS: acute mediastinitis; prediction method; inflammatory status; proteinic status.

INTRODUCTION

Iatrogenic acute mediastinitis (IAM), defined as an infection of organs and tissues within mediastinal space with accompanying sepsis following medical procedures, is one of the most dangerous complications in thoracic surgery. The death rate in acute mediastinitis (AM) remains at a difficult-to-accept level of 14 % to 47 % [1, 2]. Modern diagnostics, antibacterial therapy, supporting treatment, and early qualification for aggressive surgery have not contributed to significant improvement of the treatment. The authors of this study made an attempt to identify the most important risk factors and to work out a prognostic scale called “AM risk calculator.”

Our fundamental assumption was to create a simple and useful prognostic scale allowing early categorization of patients requiring special management and urgent surgery. The initial results of the application of this scale in patients with AM of diverse etiology (descending, posttraumatic, iatrogenic, and neoplastic) seemed encouraging, and they were the subject of earlier publications [3]. The scale sensitivity was...
90 %, and specificity was 64 %; however, the series was heterogenic, considering the origin. With experience as our basis, we decided to check its diagnostic value in a more homogeneous group of patients with AM of only iatrogenic origin. To date, no method has been available for evaluating the probability of recovery if a patient has AM.

MATERIALS AND METHODS

Causes of IAM

In the years 1998–2011, at the Department of Thoracic Surgery, General and Oncological Surgery of the Medical University of Lodz, 37 consecutive patients, in whom infection of mediastinum was the consequence of complications following endoscopy and surgical procedures mainly on the esophagus and the trachea, were treated. The patients fulfilled the modified criteria of mediastinitis diagnosis worked out by Esterra et al. [6], which, in the original version, were related to descending necrotizing mediastinitis: (1) clinical manifestation of severe infection; (2) demonstration of AM etiological factors; (3) characteristic radiological picture of mediastinitis; (4) isolation of the pathogen in microbiological cultures from the mediastinal area; and (5) intraoperative or postmortem documentation of mediastinitis. IAM patients fulfilling all the above criteria were included into the study group. Exponents of sepsis in the form of fever, tachycardia, hyperventilation, and leukocytosis were observed in all patients.

The study was approved by the Ethics Committee of the Medical University in Lodz, Poland.

Surgical Management

All 37 patients with IAM underwent surgery. Surgical strategy was determined to be individually dependent on the etiology, delay from the diagnosis establishment, local conditions, and the patient’s general state. The surgery, first of all, aimed at controlling the infection source and at limiting local inflammation by means of a wide cervical and/or mediastinal drainage through various surgical approaches. Most procedures concerned the esophagus and the trachea. Different surgeries were performed, such as primary repair with flapping or wrapping, drainage only, esophageal exclusion or diversion, and esophageal or tracheal resections.

Collected Data

The following clinical risk characteristics were evaluated: age, gender, etiology, number of coexisting diseases, delay in surgical treatment, isolated pathogens, type of surgical procedure, the number and kind of postoperative complications, and the number of transfused blood units. An association between the selected clinical risk factors and mortality was investigated. Two groups of patients were compared to estimate the effect of the diagnosis-to-surgery delay: surgery <24 h after IAM diagnosis [S<24 h] and ≥24 h [S≥24 h]. Then, the association between mortality rate and selected biochemical risk factors was investigated by analyzing the following parameters: hemoglobin level [HGB], hematocrit, red blood cell count, white blood cell count [WBC], platelet count, serum sodium [Na] and potassium level [K], protein and albumin level, C-reactive protein (CRP), and procalcitonin (PCT). In the case of three inflammation markers: WBC, CRP, and PCT, their levels were estimated in the preoperative period (pre) and on day 3 postoperatively (post). The factors for which, in statistical analysis, no association was found with the prognosis were excluded from further studies.

Statistical Methods

Exploratory factor analysis (EFA) was used to uncover the underlying structure of a relatively large set of variables (i.e., eight in this study). The researcher’s a priori assumption was that any indicator may be associated with any factor. This is the most common form of factor analysis. There is no prior theory, and one uses factor loadings to intuit the factor structure of the data.

Statistical methods were used to select eight patient features [age, coexisting diseases, HGB, WBC_pre, CRP_pre, PCT_pre, proteins, and albumins], which were included into the construction of prognostic factors (Table 1). With a known statistical method (EFA) as basis, three factors were extracted to cumulate prediction power of collected patient features and to lower the number of factors interpreted. Their equations were calculated as follows:

Factor1 = 0.712131HGB + 0.854481Proteins
− 0.131796Coex_diseas
+ 0.00534419WBC_pre − 0.141942 Age
+ 0.908303Albumins − 0.651832CRP_pre
− 0.560482PCT_pre
In Factor 1, the value is higher than the threshold [intuitive interpretation of the value obtained for each factor. Factor 1 has positive meaning (high level of serum proteins is promising for a patient). Factors 2 and 3 have negative meaning—high level of inflammation markers, high white blood cell count, older patients, and more coexisting diseases are serious risk for IAM survival. Thus, because it is the prediction of survival, it will look for an intuitive “better” result:

- In Factor 1, the value is higher than the threshold [intuitive general “better” is when proteinic status is higher],
- In Factors 2 and 3, the value is lower than the threshold [intuitive “better” is when inflammatory status and general risk are lower].

Thresholds for prediction were established according to the previous study [3], i.e., authors predicted recovery when proteinic status was higher than −1.4 (i.e., the caesura in the distribution between dead and recovered cases), inflammatory status was less than 1.0 (the same caesura as in factor 1), and general risk was less than 0.4 (the same caesura as in Factor 1) (Fig. 1; Table 3). Prediction power and interpretation reliability of the calculated factors are variable among cases and that is why the authors looked for average prediction way as below.

The final prediction was established as cumulated results of three factors: when two of three indicated recovery, then recovery was the final result of the treatment, and when two of three factors indicated lethal outcome, then death was the final outcome of the treatment.

Specificity (SPC) and sensitivity (SNC) coefficients of the prognostic method were calculated for IAM to check the prediction power of the proposed method. The method was designed for the prediction of recovery; thus, the result of the test is positive [P] as the test predicts the recovery and negative [N] as the test does not predict the recovery, that is, “death.” The result of the test is true [T] as the test predicts recovery when the observed result was “recovery,” and the result of the test is negative [N] as the test does not predict the recovery (TP—patient recovered predicted as “recovery,” TN—patient died predicted as “death,” FP—patient died predicted as “recovery,” and FN—patient recovered predicted as “death”).

With the above-mentioned definitions as bases, sensitivity and specificity coefficient equations are proposed as follows:

Sensitivity coefficient: \( SNC = \frac{TP}{TP+TN} \times 100\% \)

Specificity coefficient: \( SPC = \frac{TN}{TN+FP} \times 100\% \)

The relation of the prediction factors to other collected patient parameters was analyzed by simple regression. Results were considered as significant for \( p<0.05 \).

### Table 1. Selected Eight Clinical Parameters Included to Prediction Schema

| Case      | Age   | HGB   | WBC_pre | CRP_pre | PCT_pre | Proteins | Albumins | Coex_Diseas |
|-----------|-------|-------|---------|---------|---------|----------|----------|-------------|
| Average   | 57.68 | 12.40 | 16.91   | 209.45  | 2.12    | 58.38    | 30.75    | 3.41        |
| Minimum   | 23.0  | 8.3   | 4.9     | 96.4    | 0.53    | 38.3     | 20.6     | 1           |
| Maximum   | 83.0  | 19.5  | 36.3    | 459.2   | 10.3    | 73.6     | 35.1     | 6           |
| Median    | 58.0  | 12.2  | 16.3    | 201.6   | 1.76    | 59.5     | 31.9     | 3.0         |
| Standard deviation | 11.18 | 2.18  | 4.88    | 78.86   | 1.57    | 2.42     | 3.71     | 3.0         |
RESULTS

The age of the patients was from 23 to 83 years (Table 1), mean 57.67 years (median 58.00). There were 21 men, with mean age of 57.52 years (median 58.00), and 16 women, with mean age of 57.87 years (median 58.00). The average time of hospitalization was 22.13 (±10.48) days, with median of 19.00. The time from the establishment of the diagnosis of IAM to the introduction of surgical treatment ranged from 2 to 120 h (Table 1), with mean of 1.22 days (±1.12) and median of (1.0).

Survival rate was 64.87 % in the published series. Thirteen IAM patients died; the total death rate was 35.13 % (38.09 % in male subjects and 31.25 % in female subjects).

The etiology of IAM was differentiated. There were 17 patients (45.95 %) after esophageal and tracheal major surgical procedures (morality, 47.06 %) and 20 (54.05 %) with injuries of these organs during endoscopy or intubation (morality, 25.00 %). Among the isolated bacterial strains, there were 24 (64.86 %) dominated aerobes, including 13 Gram negatives and 11 Gram positives. Anaerobes were detected in eight patients (21.62 %) and mixed bacteria in five patients (13.51 %). Streptococci (5), staphylococci (5), Klebsiella (4), and Pseudomonas (3) were the most prevalent bacterial strains.
The diagnosis-to-surgery delay was demonstrated to decide about the prognosis. The group exposed to surgery earlier [S<24] included 22 patients, and three of them died (13.67 %); the group operated on later [S>24] included 15 patients, and ten of them died (66.67 %).

Next, coefficients of sensitivity and specificity were calculated for each factor: proteinic status [SNC=95.80 %, SPC=76.90 %], inflammatory status [SNC=100 %, SPC=53.80 %], and general risk [SNC=75 %, SPC=76.9 %]. Later prevalence test classification [TP, TN, FP, and FN] was taken to establish the whole prognostic power of the method among patients with IAM—SNC=100 %, SPC=69.20 %.

**DISCUSSION**

AM is one of the most severe complications, which remains a great challenge for thoracic surgeons. High death rate in patients with AM motivates to seek early detection methods and monitoring, which may contribute to more effective management of this severe disease. In the sequence of developing events, the patient’s clinical picture and evaluation of laboratory tests, which are the base for introducing further radiological and endoscopic diagnostics and for qualification for surgery, provide the key data. Early aggressive surgical treatment, selection of antibiotic therapy, and maintenance treatment in the intensive care unit decide about the success of the treatment [1, 2, 4]. Age, etiology, coexisting diseases, delay in surgery, the kind of procedure and time of its duration, the type of isolated pathogen, blood transfusions, postoperative complications, and others are listed among clinical risk factors in patients with AM [2–4, 9]. Biochemical parameter monitoring provides important data concerning the developing septic state. Deviation from their values often anticipates clinical symptoms. Systematic analysis of biochemical parameters revealed significant importance of detailed examination of patients in AM [5].

Our prognostic method consists of three factors, the results of which decide about the prognosis. Two parameters were taken into account to evaluate the general risk: age and the number of coexisting diseases. They are often listed among the factors related to poor prognosis in critically ill patients with sepsis [6]. They had been used in already existing prognostic scales for the determination of long-term survival, such as Charlson comorbidity index (CCI), Davies (Stokes) score, and index of coexistent diseases (ICED) [7–9]. CCI is used most frequently and consists of 19 coexisting diseases, which are assigned with a score. The age scores are counted according to the following manner: one score for each decade over 40 years of age. The scores are summed up and give a total score, which enables to predict mortality [7]. In our method, Factor 3,
| Case | Proteinic status | Inflammatory status | General risk | Real Treatment | Prediction of survive as ≥ 1.4 | Prediction of survive as < 1.0 | Prediction of survive as < 0.4 | At least two predictions are consistent with outcome |
|------|------------------|---------------------|--------------|----------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------------------------|
| 1    | −9.38045         | 2.075432            | 1.254755     | Death          | TN                          | FP                          | TN                          | TN                                               |
| 2    | −0.9354          | 0.351968            | −0.58566     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 3    | 2.518824         | −0.40282            | −0.70039     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 4    | 0.973319         | −0.36334            | −0.18624     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 5    | 0.276415         | −0.40874            | −1.80834     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 6    | 1.060506         | −0.09981            | −0.16861     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 7    | −2.33128         | −0.14447            | −0.7557      | Recovery       | FN                          | TP                          | TP                          | TP                                               |
| 8    | 5.431153         | −1.60496            | −4.63741     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 9    | −1.50054         | −0.39738            | 0.26658      | Death          | TN                          | FP                          | FN                          | FP                                               |
| 10   | −2.56223         | 2.052345            | 0.865421     | Death          | TN                          | TN                          | TN                          | TN                                               |
| 11   | 2.19273          | −0.42608            | 1.409769     | Recovery       | TP                          | TP                          | FN                          | TP                                               |
| 12   | −4.63438         | 0.4127              | −0.25291     | Death          | TN                          | FP                          | FP                          | FP                                               |
| 13   | 1.120934         | −2.03625            | −0.87172     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 14   | 3.436513         | −1.88757            | −3.41403     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 15   | −2.88121         | 0.438392            | 0.735355     | Death          | TN                          | FN                          | TN                          | TN                                               |
| 16   | 1.705809         | −0.66294            | −0.35677     | Recovery       | TP                          | TP                          | FN                          | TP                                               |
| 17   | −0.14001         | 0.375695            | 0.704417     | Recovery       | TP                          | TP                          | FN                          | TP                                               |
| 18   | −0.18777         | −2.91853            | −2.62223     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 19   | 2.399365         | −1.219              | −0.46791     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 20   | 2.425412         | 0.259163            | 0.921801     | Recovery       | TP                          | TP                          | FN                          | TP                                               |
| 21   | −1.25105         | 0.958045            | 1.881383     | Death          | FP                          | TP                          | FN                          | TP                                               |
| 22   | −0.45735         | 0.021338            | 1.810612     | Recovery       | TP                          | TP                          | FN                          | TP                                               |
| 23   | 1.013204         | −1.14899            | 0.144194     | Recovery       | TP                          | TP                          | TN                          | TN                                               |
| 24   | 3.604206         | −0.76206            | −1.13215     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 25   | 3.299378         | −1.21632            | −1.68195     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 26   | −0.86946         | 0.254306            | 1.227232     | Death          | FP                          | TP                          | TN                          | TN                                               |
| 27   | 2.986857         | −1.06319            | 1.088926     | Recovery       | TP                          | TP                          | FN                          | TP                                               |
| 28   | −1.42868         | 1.340042            | 1.650665     | Death          | TN                          | TN                          | TN                          | TN                                               |
| 29   | −0.14795         | 1.598835            | 2.343811     | Death          | FP                          | TN                          | TN                          | TN                                               |
| 30   | −6.28117         | 2.259139            | 3.195265     | Death          | TN                          | TN                          | TN                          | TN                                               |
| 31   | 4.589195         | −1.34128            | −2.29581     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 32   | −3.5547          | 3.030246            | 2.114995     | Death          | TN                          | TN                          | TN                          | TN                                               |
| 33   | 1.346878         | 0.323035            | 0.035438     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 34   | −1.68553         | 1.593065            | 0.596345     | Death          | TN                          | TN                          | TN                          | TN                                               |
| 35   | −2.63384         | 1.605091            | 0.332041     | Death          | TN                          | TN                          | FP                          | TN                                               |
| 36   | 1.543068         | −0.49518            | −1.25009     | Recovery       | TP                          | TP                          | TP                          | TP                                               |
| 37   | 1.018834         | −0.45824            | 0.594206     | Recovery       | TP                          | FN                          | TP                          | TP                                               |

TN patient dead predicted as death, TP patient recovered predicted as recovery, FP patient dead predicted as recovery, FN patient recovered predicted as death
responsible for general condition, demonstrated a relatively high value in predicting the prognosis (SNC=75 %, SPC=76.9 %). Many authors emphasize the importance of early qualification for surgery in regard to the prognosis [2, 10]. In our patients, we observed nearly five times lower death rate if the surgery was performed within the first 24 h. However, this parameter showed no statistical significance in relation to the three factors of our scale. We suspect that surgical delay is not a parameter to be measured objectively. Diagnosis of IAM in patients after major thoracic surgeries receiving antibiotics and strong analgesics is, as a rule, delayed for a few hours. Wang et al. think that, in the era of advanced intensive care capabilities, delay in primary repair of the esophagus does not have to be associated with worse result in some patients [11]. Because of that, we have not included this parameter into the suggested scale.

There are several prognostic scales using the evaluation of protein metabolism and the severity of the infection based on laboratory parameters. Among biochemical markers, protein and albumin levels are most frequently used in nutritional status assessment [12, 13]. In 1988, Buzby et al. first described the NRI to score the severity of postoperative complications [14]. It combines two nutritional indicators (albumin and weight loss), which are strictly correlated with higher morbidity and mortality risk. GNRI is a similar but more objective scale, devoid of the need for calculating the ideal body weight [15]. With the conducted factor analysis as our basis, we have demonstrated that there is also a need for inclusion of the level of hemoglobin (among other blood proteins) into the proteicin status. The presence of preoperative anemia and high intraoperative blood loss is a known factor affecting poor prognosis, particularly in combination with other diseases [16, 17].

We are convinced that limitation to the assessment of the nutritional status itself does not provide satisfactory information for the prediction of the prognosis. It seems that, in the case of an infectious disease, the scales analyzing nutritional status in combination with biochemical parameters of inflammation have greater diagnostic value.

Prognostic inflammatory and nutritional index (PINI), worked out by Ingenbleek and Carpentier, is one of the most frequently used prognostic scales in critically ill patients, an index, which takes into account the above parameters [18]. The scale is based on the evaluation of four parameters: two markers of nutritional (albumin and prealbumin) and two markers of inflammatory CRP and AAG states. PINI has been found to be a reliable indicator of both nutritional status and prognosis in trauma, burns, infection [19], and lately, in cancer [20]. PINI is the closest scale to that proposed by us, comprising two of three analyzed groups of risk factors.

It is commonly accepted that CRP and PCT are markers of high sensitivity and specificity in sepsis, septic complications, and cancers [21–23]. The statistical analyses performed earlier demonstrated higher mean number of WBC in the group of patients with AM who died [5]. Therefore, inclusion of this parameter into the group of factors determining “inflammatory status” seems to be appropriate, not purely from the mathematical point of view. It should be reminded that the WBC value is one of the criteria of SIRS and sepsis diagnosis [24]. It should be emphasized that the patients’ nutritional status can affect CRP and PCT values. According to Ballou and Kushner, the level of CRP is prognostically more important in the monitoring of the patient’s condition in malnutrition than other acute phase proteins, and it increases significantly [21]. Other authors also confirm that nutritional status can affect inflammatory response in patients with advanced carcinoma and the results of PINI prognostic scale [25, 26]. Therefore, in these cases, the concentration of CRP alone may be a sufficient indicator of the inflammatory response [26].

Wunder et al. presented an interesting attempt of working out an independent indicator of early prediction of death in sepsis [27]. The authors, analyzing 33 patients with sepsis of different etiology, noticed that the deviations of PCT values and Acute Physiology and Chronic Health Evaluation (APACHE II) were correlated with poor prognosis. Novotny et al. [28] carried out similar studies on a larger group of 160 patients with sepsis resulting from peritonitis or mediastinitis after an anastomotic leak or perforation of a hollow organ. It should be emphasized that the clinical material presented in this study was greatly similar to our material. The authors combined both indicators and calculated a prognosis score using binary logistic regression analysis, which allowed the identification of groups with high and low risk of death. In a multivariate analysis, both PCT values and the APACHE III score were identified as independent, early predictive indicators of sepsis lethality.

We think that the use of three markers for the assessment of inflammatory status allows more precise and complex evaluation of this status and prognosis,
eliminating errors resulting from heterogeneity of the investigated group and known deviations in the behavior of the selected markers in some severe morbid states.

The final diagnostic value of AM risk calculator turned out to be high in relation to other discussed scales. We think that the construction of our prognostic tool based on the evaluation of three groups of risk factors determining inflammatory, proteinic, and general status will be less sensitive to difficult-to-foresee deviations of the values of biochemical markers associated with the impact of factors such as malnutrition, bacteriological etiology, comorbidities, and surgical complications. Thus, the described method is a promising prognostic tool for patients with IAM. AM risk calculator can be prepared in a user-friendly electronic version in which, after introduction of the required data, the predicted prognosis will be obtained automatically. The categorization of the patients most at risk will enable early intensification of the medical management.

CONCLUSIONS

We do hope that the proposed AM risk calculator will be introduced into the clinical practice, which can contribute to the modification of the treatment of patients with AM. It is based on mathematical assessment of our own material and devoid of subjective interpretation. Inclusion into the assessment of two simple clinical data and six biochemical tests, which can be obtained within the first 1–2 h after the patient’s admission to hospital (duration of laboratory investigations); low costs; and simple interpretation of the results are the most important advantages.

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