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Original Article

Development and validation of a scoring system for the identification of pleural exudates of cardiac origin☆

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ABSTRACT

Background: Light's criteria misclassify about 30% of cardiac effusions as exudates, possibly leading to unnecessary testing. Our purpose was to derive and validate a scoring model to effectively identify these falsely categorized cardiac effusions, in the setting of natriuretic peptide lacking data.

Methods: We retrospectively analyzed data from 3182 patients with exudative pleural effusions based on Light's criteria, of whom 276 had heart failure (derivation set). A scoring model was generated with those variables identified as independent predictors of cardiac effusions in a logistic regression analysis, and further evaluated in an independent population of 1165 patients.

Results: The score consisted of age ≥ 75 years (3 points), albumin gradient > 1.2 g/dL (3 points), pleural fluid lactate dehydrogenase < 250 U/L (2 points), bilateral effusions on chest radiograph (2 points), and protein gradient > 2.5 g/dL (1 point). At the best cutoff of ≥ 7 points, the score yielded 92% diagnostic accuracy, a likelihood ratio positive of 12.7 and a likelihood ratio negative of 0.39 for labeling cardiac effusions in the derivation sample. The respective figures in the validation sample were 87%, 6.5 and 0.33. Notably, the score had higher discriminatory properties than protein and albumin gradients in both the derivation (respective area under the curve – AUC – of 0.925, 0.825, and 0.801) and validation (respective AUC of 0.908 0.862 and 0.802; all $p \leq 0.01$) cohorts.

Conclusions: A simple scoring system can assist clinicians in accurately identifying false cardiac exudates when natriuretic peptides are not available.

1. Introduction

Pleural effusions are common in patients with decompensated heart failure (HF). The identification of cardiac effusions is usually considered to be an easy task and the performance of a pleural tap is unnecessary in most clinical situations. However, the diagnosis of cardiac effusions is not always straightforward, even when pleural fluid data are available [6]. For example, one study called into question the physicians' ability to correctly identify transudates prior to thoracentesis by showing that the initial clinical presumption failed 44% of the time [13]. In addition, Light's criteria [4], which are considered the gold standard for transudate-exudate differentiation in every-day practice, leave nearly 30% of cardiac effusions erroneously labeled as exudates [1,10]. No consensus exists on the best way to reclassify the latter as true transudates [7]. Although the identification of cardiac effusions, in general, and false cardiac exudates, in particular, may be greatly improved with the measurement of natriuretic peptides [9], these biomarkers of HF are not always used as an initial diagnostic test for the work-up of pleural effusions and variabilities in laboratory methodologies and proper cutoffs should be considered.

The goal of this study was to provide a practical tool based on the combination of simple clinical, radiological and pleural fluid biochemical findings for the accurate identification of exudative effusions (according to Light's criteria) secondary to HF, when natriuretic peptides are not immediately available. To this end, an easily applicable scoring model was devised and validated.

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2. Methods

2.1. Study population

A retrospective review was done of the medical charts of all consecutive patients who were subjected to a diagnostic thoracentesis at the Arnau de Vilanova University Hospital (Lleida, Spain) from 1994 to 2016, and whose pleural fluids met Light's criteria for exudates [4]. This 450-bed tertiary care facility serves a population of approximately 450,000 people. Recruited patients from this hospital aided in the generation of a scoring system for discriminating between cardiac and non-cardiac effusions (derivation set), which was subsequently validated in an independent sample of patients who were also retrospectively identified at the Santiago de Compostela Hospital (Spain) during the 1995–2015 period. This 1300-bed tertiary hospital serves 385,000 people. The local ethics committee approved the study protocol (CEIC-1814).

The following data were recorded, when available, in the derivation sample: demographics (sex, age), size and laterality of pleural effusions on chest radiographs, pleural fluid biochemistries (red blood cell count, leukocytes and differential, protein, lactate dehydrogenase — LDH, glucose, adenosine deaminase — ADA, pH, albumin, cholesterol, C-reactive protein), pleural fluid cultures, pleural cytohistological studies, serum chemistries (protein, LDH, albumin), and final diagnoses. In cases of repeated thoracenteses, only the results of the first procedure were considered. Two physicians in each of the participating hospitals simultaneously reviewed radiological data and final diagnoses and, in case of discrepancy, reached an agreement.

2.2. Diagnostic criteria

Following current guideline recommendations [5], the diagnosis of HF relied on clinical grounds (i.e., history, physical examination, chest-X ray, echocardiogram – if performed – and response to diuretics). Patients were given a definitive diagnosis of malignant effusion if malignant cells were detected on pleural fluid or biopsy specimens. A diagnosis of probable malignancy was accepted for patients with a known primary tumor or extra-pleural metastases of undetermined origin and cytology-negative exudates, in whom other potential causes for the fluid accumulation had been ruled out. A definitive diagnosis of tuberculous pleuritis was established by the identification of bacilli in pleural fluid, sputum or pleural biopsy specimens (using auramine stain and/or solid culture media). Tuberculosis was considered probable in patients with lymphocytic exudates, high pleural ADA levels (> 35 U/L), negative cytological fluid results, and resolution of the effusion in response to anti-tuberculous therapy. Parapneumonic effusions referred to those associated with bacterial pneumonia. Empyema was defined as pus in the pleural space. Patients were labeled as having an idiopathic pleural effusion if they met the following: 1) an exudate with low ADA levels and negative cytological studies, 2) an uninformative chest computed tomography or, when performed, pleural biopsy, and 3) resolution of the pleural effusion without specific therapy during follow-up. Other causes of pleural effusion were determined by well-established clinical criteria. Patients were excluded from the analysis if: 1) there could be more than one potential cause for the effusion, or 2) there was insufficient pleural fluid testing, imaging and clinical follow-up to establish a presumptive diagnosis, or label the effusion as idiopathic.

2.3. Pleural fluid measurements

In both derivation and validation cohorts, biochemical measurements on pleural fluid samples were conducted with discrete analyzers (Hitachi models 717, 917, or modular DP, Roche Diagnostics, Mannheim, Germany) using standard photometric methodologies and according to the manufacturer's instructions. Specifically, the pH was measured in a blood-gas analyzer and the ADA by an automated ultraviolet kinetic assay (Roche Diagnostics, Barcelona, Spain). In our center, the normal upper limit of serum LDH is 378 U/L; so, two-thirds of this figure was rounded down to 250 U/L. In the other hospital which recruited the validation cohort, even though the normal upper limit of the serum LDH value was 320 U/L, pleural fluid concentrations representing two-thirds of this figure (213 U/L) were matched with the corresponding cutoff of the derivation sample (250 U/L).

2.4. Statistical analysis

Non-normally distributed continuous variables (according to the Kolmogorov-Smirnov test) were reported as median (25th–75th percentiles), whereas categorical variables were reported as numbers (percentages). The Mann-Whitney U and Chi-square tests were used for comparison of continuous and categorical data, respectively, between cardiac and non-cardiac effusions. A receiver operating characteristic (ROC) curve analysis selected the best cutoff values for labeling HF-related effusions, while aiming for a sensitivity $> 90\%$ in the case of protein and albumin gradients (that value being selected to counteract the relatively low sensitivity of Light's criteria for identifying transudates). A logistic regression analysis with a backward conditional method chose those variables that were statistically significant, thus allowing the generation of a scoring system for discriminating between cardiac and non-cardiac effusions. Weight values to each variable were assigned proportionally to the magnitude of the logistic equation's coefficients. The diagnostic performance of the derived score in the derivation and validation cohorts was expressed in terms of sensitivity, specificity, diagnostic accuracy (i.e., proportion of correct results), likelihood ratios (LR), and area under the curve (AUC), along with their 95% confidence intervals (CI). For comparisons of AUC, the Hanley & McNeil method was used, while comparisons of diagnostic accuracy measurements between the scoring system and other variables, such as the protein and albumin gradients (i.e., serum minus pleural fluid values), were performed using the McNemar test. Finally, between-group comparisons of LR were tested with bootstrap methodologies. The level of significance was set at 0.05 (two-tailed). Analyses were performed with SPSS Statistics version 24.0 (IBM) and, for AUC comparisons, with Epidat version 3.1 (Xunta de Galicia, Spain).

3. Results

3.1. Patients characteristics

A total of 3182 adult patients with exudative pleural effusions, of which 276 (8.7%) were related to HF, composed the derivation sample. The validation sample was comprised of 1165 patients with a similar proportion of cardiac (107, 9.2%) and non-cardiac effusions (1058, 90.8%) as the derivation set ($p = 0.60$). Also, the median age and sex of cardiac and non-cardiac effusions were comparable between both cohorts. These and other baseline characteristics are displayed in Tables 1 and 2.

3.2. Diagnostic accuracy of individual findings for cardiac effusions (derivation set)

The individual findings that increased the probability of cardiac effusions the most were the presence of a bilateral effusion on a chest radiograph (LR = 4.3), a serum to pleural fluid protein gradient $>$ 3.1 g/dL (LR = 3.9), and a pleural fluid LDH concentration $<$ 250 U/L (LR = 3.5). Conversely, the findings that decreased the probability of HF-related effusions the most were a protein gradient ≤ 2.5 g/dL (LR = 0.30), an albumin gradient ≤ 1.2 g/dL (LR = 0.33) and aged $<$ 75 years (LR = 0.34) (Table 3).