

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL SCHOOL**

***ETHIOPATHOGENIC AND CLINICAL-IMAGING CORRELATIONS IN THE ASSESSMENT
OF PROGNOSIS IN ACUTE PANCREATITIS***

ABSTRACT

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INTRODUCTION

By the study presented, we addressed a significant public health problem, as acute pancreatitis is a condition with unpredictable evolution, severe in about 20% of cases associated with numerous systemic complications and increased risk of mortality and morbidity. Acute pancreatitis is a pathological entity that raises numerous diagnosis and treatment problems.

In its severe form, it is a challenge for the attending physician, consecutively with the multiple, varied and not always obvious aetiology, complex and incompletely deciphered pathophysiology, the difficult diagnosis, the choice of opportunity for conservative therapy or surgery. The treatment of the disease is most often unspecific, symptomatic and supportive care.

The identification of severe cases and the calculation of various prognostic indicators have constituted the premises of numerous studies carried out so far in an attempt to discern concretely between patients with mild / moderate and severe forms of the disease. They have used the Ranson criteria, Imrie, APACHE II or APACHE-O (associated with body mass index) and severity score based on CT examining –Balthazar score, or various biological markers - C-reactive protein, interleukin 6, tissue activator of trypsinogen, antiproteases, urinary trypsinogen, procalcitonin etc., each with beneficial results variable percentage in assessing severity.

The study conducted was substantiated by the approach of a pathogenic entity that raises numerous diagnosis and treatment problems, which is a challenge both in terms of multiple aetiology, of complex and incompletely elucidated pathophysiology and by choosing appropriate therapeutic measures. The relevance of our study lies in the need for prompt and early diagnosis of acute pancreatitis, and rapid assessment of the severity and prognostic indicators since AP is a condition that can achieve a high percentage of mortality in severe cases.

The rules of a clinical decision, adequate in the management of patients with AP involve the use of assessment scores for the severity and prognosis, in order to choose the therapeutic opportunity and establish proper management of the condition.

STATE OF KNOWLEDGE

Acute pancreatitis (AP), inflammatory disease, clinically characterized by a painful abdominal syndrome and biologically by a serum increase of pancreatic enzymes, with gallstones and alcohol consumption as the most common aetiology in the first attack, accounting for about 75% of cases. Other aetiologies may include metabolic diseases (dyslipidemia, hyperglycaemia, etc.), vascular conditions, injury etc.

The precise assessment of AP incidence is difficult to achieve, considering the subclinical evolution of mild or moderate forms of the disease or the rapid existus in case of fulminant forms. In the United States of America, the annual incidence ranges from 4.9 to 35 reported at 100,000 inhabitants [4-10]. In addition, the incidence of the disease in many European countries is increasing consecutively to the increase of ethanol consumption and means of diagnosis. There is a strong association between gender, age and the incidence of AP, which is more common in men and in older ages. Peak incidence in alcoholic pancreatitis is in the third and fourth decade and for lithiasic aetiology in the seventh decade.

AP related mortality has decreased appreciably due to improved diagnostic and therapeutic means, especially in case of severe forms, hemorrhagic necrotic, the percentage reached in these cases is up to 30%. The cause of deaths in the first two weeks of evolution is usually represented by systemic inflammatory response syndrome (SIRS) and multiple organic failure syndrome (MOFS) and later by sepsis and its complications. A prospective multicenter study that included 1005 subjects, found a mortality of about 5%.

The natural evolution of acute pancreatitis includes several clinical forms, each with specific (clinical, physiological, radiological, biochemical and bacteriological) characteristics, requiring appropriate treatment.

Diagnosis of acute pancreatitis can be difficult because the signs and symptoms present in patients with AP are non-specific and common to other acute medical or surgical conditions. Diagnosis is usually based on personal history, complete physical examination and laboratory and imaging test results. Correct diagnosis implies the presence of at least two of the following: specific abdominal pain, elevated amylase and serum lipids at least 3 times the upper limit of normal and imaging characteristic elements. After the diagnosis of certainty is established, further tests may be applied to determine the cause, establish a prognosis, short and long term evolution, and to apply appropriate therapeutic means.

Positive diagnosis of AP is based on clinical, laboratory and imaging elements. Common, but at the same time non-specific clinical signs are: abdominal pain, nausea, vomiting, fever, altered mental status, abdominal distension, epigastric tenderness and pasting, slow/absent intestinal transit, jaundice, signs of hypovolemia.

Early identification of severity is a key factor in the approach of acute pancreatitis. The appreciation of pancreatitis severity is made in a standardized way using severity scores, biological markers and imaging findings. **Ranson score**, introduced in 1974, is today the most widespread, although it has the disadvantage of too many parameters and delay by 48 hours of admission for calculations. APACHE II score was also used to quantify the severity of acute pancreatitis, which is a score assessing the severity of patients hospitalized in the Intensive Care Unit. APACHE II score has a better sensitivity than **Ranson score**, but it uses too many variables to be applied routinely to all cases of acute pancreatitis (80% of cases have a benign course and they leave the hospital within 5-10 days).

AIMS AND OBJECTIVES OF THE PAPER

The aim of the study was defined in the first instance by the assessment in the emergency room, of patients with a diagnosis of acute pancreatitis, by the assessment of the evolution and prognosis and the assessment of possible etiopathogenetic, clinical and imaging correlations in the study group.

The study objectives are:

- Anamnesis, clinical and laboratory evaluation of patients with acute pancreatitis
- Quantification of Ranson score
- Assessment of the presence of SIRS
- Assessment of APACHE II severity score
- Assessment of AP severity
- Differentiated analysis of subjects according to the severity
- Differentiated analysis of patients according to the amylasemia level
- Differentiated analysis of patients based on the Ranson score
- Differentiated analysis of patients based on the APACHE II score
- Differentiated analysis of patients according to the presence of SIRS
- Establishing Ranson score correlations with demographic , clinical and laboratory variables of patients with AP

- Evaluation of APACHE II score interrelations with aetiological , clinical and laboratory variables of patients with AP
- Evaluation of the presence of SIRS interrelation with demographic, clinical and laboratory variables of patients with AP
- Risk stratification of the subjects included in the study depending on the risk of developing a severe form of AP according to demographic , clinical, laboratory variables and disease activity scores

MATERIAL AND METHODS

We conducted an observational, prospective study on 207 patients who came in the Emergency Room of the Emergency County Hospital of Craiova in the period January 2013 - December 2014, with a certain diagnosis of acute pancreatitis, according to revised Atlanta criteria, who were hospitalized later in the Gastroenterology ward or the surgical wards of the hospital. The study was conducted in compliance with ethical and moral principles issued by Helsinki "Bill of Rights", it was approved by the local ethics committee and all patients signed the informed consent.

Evaluation of patients included demographic variables (age, gender, area of origin, weight, height, body mass index, behaviours - smoking, alcohol and coffee, previous medical history), clinical examination, biological parameters (determining blood count, urea, creatinine, amylasemia, serum lipase, transaminases, cholestasis enzymes, lactate dehydrogenase – LDH, inflammatory markers- ESR, C-reactive protein, lipid profile, serum ionogram), imaging findings (by performing simple abdominal ultrasound, abdominal ultrasound and CT scanning, in some cases) and assessment of severity and assessment scores of prognosis - the presence of systemic inflammatory response - SIRS, Ranson and APACHE II scores.

RESULTS

I have included in the study 207 patients diagnosed with acute pancreatitis, 35.7% women and 64.73% men. Regarding the distribution of patients by area of residence, there was a predominance of urban areas (55.56% vs. 44.44%). Regarding patients' age, we got an average of 53.44 ± 15.42 years with a minimum of 21 years and a maximum of 88 years. By analyzing the distribution percentage of average age, we note that two-thirds of patients are under 60 years. Aetiological analysis revealed a predominance of ethanol (141; 68.11%) followed by cholelithiasis (47; 22.70%) and other causes in 18 patients (9.18%).

Analysis of *biological parameters* in patients included in the study started by determining the complete blood count, which revealed the following data: mean Hb value of 12.34 ± 5.73 g/dl (minimum 7.23g/dl, the maximum 18.01g/dl), an Le average of 10.292 ± 4000.66 /mmc (min 3400 / mmc, max 25700 / mmc). 142 patients (68.59%) were above the upper limit of normal (> 8000 / mmc) and 25 (%) values over 16000 / mmc, composite item of Ranson score for prognostic assessment of patients with AP at baseline. The mean platelet count was $186,434 + 60711.32$ / mmc. *Serum transaminases* evaluation showed a mean GOT of 118.04 ± 128 U/l with a minimum of 7.4, and a maximum of 670U/l. 80.19% (166) patients were above the upper limit of normal and 25 patients had a value above 250U / l, composite item of Ranson score. For GPT, an average of 117.77 ± 133.92 U/l was obtained, minimum 8U/l, maximum 749 U/l. For 83.57% (173) of patients, a value above the upper limit of normal was achieved. Analysis of biological parameters of patients in the study continued by assessing and stratifying serum amylase, certain diagnostic and prognostic marker in patients with AP. (below 150 IU and over 150 IU). Regarding the values recorded, we note that nearly 20% of patients (18.84%) had normal serum levels below 150 IU.

Evaluation of prognostic scores of AP

In order to assess prognosis, we used APACHE II score, Ranson score and we evaluated the presence of SIRS. APACHE II score, calculated at the time the patient came at the emergency room, recorded an average value of 5.831 + -2.133, with a maximum of 11 and a minimum of 3 (95% CI 5.53-6.12). Regarding the distribution of APACHE II values in the patients with AP in the study, according to research published to date, a value over 8 is associated with increased mortality of patients, so we considered it to be a threshold value in order to constitute the 2 groups: patients with APACHE II score > 8 and a second group with an APACHE II score < 8.

Depending on the AP aetiology, we got different values of APACHE II score: in those with ethanolic aetiology, the average value recorded was 5.342+2.004, significantly statistically different (p <0.0001) from the value recorded in the group with AP of biliary aetiology

Patient characteristics according to the APACHE score

	APACHE>8	APACHE<8	p
Age (years)	68.15±12.57	48.12±12.67	0.002
Sex	29 M 26 F	105B 37F	0.154
Severity	23 severe AP 27 moderate AP 5 mild AP	0 severe AP 12 moderate AP 140 mild AP	<0.0001
BMI(kg/m ²)	23.69±4.76	22.22±3.457	0.103
L(nr/mm ^c)	14296±4006	8843±2872	0.001
Ht			
Blood sugar (mg/dl)	242.9±59.54	187.34±34.45	<0.001
Creatinine (mg/dl)	1.33±0.09	0.87±0.62	<0.0001
Urea (mg/dl)	54.32±4.76	45.76±36.37	0.002
Total serum amylase	1513±171.3	854.1±2060	<0.001
Pancreatic amylase	1380±64.3	612.6±812.4	<0.0001
GOT (U/l)	176±157.3	91.09±110.2	<0.0001
GPT (U/l)	189±178.9	91.94±103	<0.0001
Aetiology	14 biliary 5 other causes 36 alcoholic	33 biliary 13 other causes 105 alcoholic	<0.0001

Regarding the interrelationship of the APACHE II score with the variables that characterize the patients studied, we obtained the following data:

	Age	BMI	Le	Urea	Cr	Blood sugar	GOT	GPT	Pancreatic amylase	Ht
r	0.368	0.140	0.597	0.516	0.368	0.141	0.176	0.211	0.3167	0.459
p	0.0057	0.305	<0.0001	<0.0001	0.005	0.100	0.002	<0.0001	<0.0001	<0.0001

I C 9 5 %	0.114- 0.577	-0.129- 0.391	0.395- 0.745	0.405 3 - 0.612	0.114 - 0.577	-0.026 - 0.250	0.011	0.073- 0.341	0.184- 0.437	0.3405 - 0.563
R 2	0.135	0.019	0.357	0.221	0.135	0.562	0.082	0.109	0.112	0.321

Regarding the severity of AP for patients with a severe form, we obtained a mean value of 9.47 ± 1.20 of APACHE II score, 7.82 ± 1.31 in those with a moderate form of the disease and 4.72 ± 1.19 in those with mild AP, the differences between groups are statistically significant ($p < 0.0001$). The results are similar to those published in the literature, a recent report published in 2011 in *Journal of Clinical and Diagnostic Research* by Suvarna et al [149] providing similar data, as well as those reported by Wilson et al in *Br.J.Surg* [150] and Wahab et al in *Acta Gastroenterologica Latinoamericana* [151].

Regarding the distribution of APACHE II values in patients with AP included in the study, according to research published to date, a value over 8 is associated with an increased mortality of patients, in 11-18%, so we considered it to be a threshold value, in order to establish the 2 groups: patients with APACHE II score > 8 and a second group with a value of APACHE II score < 8 . 55 patients with AP had an APACHE score > 8 (26.53%). The analysis of the two groups of patients showed statistically significant differences between the two groups. Depending on the AP aetiology, we got different values of APACHE II score: in those with ethanolic aetiology, the average value recorded was 5.342 ± 2.0045 , significantly statistically different ($p < 0.0001$) from the value recorded in the group with AP of biliary aetiology.

The analysis of correlation of APACHE II score with AP severity has identified a strong correlation variables, with a Spearman correlation coefficient of 0.807, $p < 0.0001$, also supported by the linear regression analysis with an r of 0.6519, $p < 0.0001$, according to data provided by other significant scientific reports.

Ranson score, upon presentation, recorded an average value of 1.18 ± 1.11 . Depending on the value considered as early predictive marker of severe pancreatitis (3), we divided the subjects included into two groups: Ranson score < 3 (29 subjects) and > 3 (178 patients). Comparing the two groups revealed statistically significant differences:

	RANSON>3	RANSON<3	p
Age (years)	71.44 ± 10.89	48.12 ± 12.67	< 0.0001
Sex	17 B 12 F	119 B 61 F	0.398
Severity	14 grade 3 12 grade 2 2 grade 1	6 grade 3 25 grade 2 148 grade 1	0.001
BMI(kg/m ²)	23.96 ± 4.43	22.38 ± 0.297	0.039
L(nr/mm ^c)	13582.76 ± 4748	9715 ± 270.7	< 0.0001
Ht (%)			
Blood sugar (mg/dl)	139.9 ± 38.32	141.3 ± 4.616	0.013
Creatinine (mg/dl)	1.36 ± 0.80	0.93 ± 0.04	0.001
Urea (mg/dl)	72.28 ± 44.10	45.73 ± 2.40	0.0001

Total serum amylase	1726±1324	908.8±148.2	0.003
Pancreatic amylase	1553±1336	687.4±65.65	<0.0001
GOT	227.7±174.2	100.6±8.36	<0.0001
GPT	208.1±188.3	103.6±8.89	<0.001
Aetiology	8 biliary 2 other causes 18 alcoholic	37 biliary 16 other causes 126 alcoholic	

Analysis of Ranson score correlation with the variables of patients revealed the following data:

	Age (years)	BMI (kg/m ²)	Ht (%)	Le (no/mc)	Urea (mg/dl)	Creatinine (mg/dl)	Blood sugar (mg/dl)	GOT (U/l)	GPT (U/l)	Total amylase (U)	Pancreatic amylase (U/l)	APACHE
R	0.6251	0.2305	0.5558	0.444	0.411	0.3034	0.0116	0.3142	0.3161	0.2131	0.3908	0.717
IC 95%	0.534-0.701	0.097-0.355	0.453-0.643	0.534-0.547	0.291-0.518	0.174-0.422	-0.020-0.248	0.1858-0.432	0.187-0.433	0.078-0.339	0.269-0.500	0.644-0.779
P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.095	P<0.0001	P<0.0001	P<0.0001	P<0.0001	<0.0001
R ²	0.1976	0.005	0.3089	0.197	0.169	0.092	0.013	0.098	0.099	0.045	0.152	0.013

Assessment of disease severity

Assessment of AP severity, according to Atlanta criteria, revealed 23 (11.11%) patients with severe AP, 39 (18.84%) with moderate AP and 145 (70.04%) patients with a mild form of the disease.

	Age	BMI	Le	Cr	Urea	Blood sugar	GOT	GPT	Total Amylase	Pancreatic amylase	APACHE	Ranson
r	0.704	0.1332	0.582	0.421	0.590	0.134	0.2067	0.2426	0.4417	0.4643	0.7442	0.686
IC 95%	0.625-0.768	0.007-0.268	0.481-0.668	0.299-0.530	0.490-0.674	-0.006-0.269	0.068-0.337	0.105-0.370	0.320-0.548	0.3465-0.567	0.674-0.800	0.604-0.754
p	<0.0001	0.0557	<0.0001	<0.0001	<0.0001	0.054	0.0028	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

The age of patients was significantly different in the three forms of the disease: 75.35 ± 7.31 years for the severe form, 66.13 ± 10.01 years for the moderate one and 46.24 ± 11.47 years for the mild form, $p < 0.001$. The influence of age and sex on the prognosis of patients with AP has been assessed in other studies that revealed a significant correlation between age and male gender and severe disease [141, 143, 144]. By the Spearman coefficient calculation, we obtained a value of 0.704, < 0.0001 between age and severity consistent with the results published by Lankisch et al in *The Pancreas* and Bota et al in *Annals of Gastroenterology* [141, 144].

Numerous studies and meta-analyses have reported a poorer prognosis in obese and overweight patients [97, 144-147]. Regarding the study group, we did not obtain significant correlation of variables, but we found a statistically significant difference in BMI between the group with severe disease and the one with a mild form of AP (26.10 ± 5.60 kg/mp vs. 22.21 ± 3.44 kg/mp, $p < 0.001$).

Regarding the biological parameters, we obtained a statistically significant correlation between severity and WBC, $r = 0.582$ (IC 0481 -0.668, $p < 0.001$), creatinine, $r = 0.421$ (95% CI 0.299 -0.530, $p < 0.0001$), total amylase $r = 0.4417$ (95% CI 0.32-0.54, $p < 0.0001$), pancreatic amylase $r = 0.463$ (95% CI 0.34-0.56, $p < 0.0001$). Similar data were published in 2008 in *World J Gastroenterology* by Ibrahim et al [143] in *Annals of Gastroenterology*, 2013 by Bota et al and 2007 [144] in *Surgery* by Ueda et al [148].

Risk stratification sample size depending on the risk of developing a severe form of AP according to demographic variables, clinical, laboratory and disease activity scores revealed the following data: an APACHE II score of at least 8 predicted 77.69% of cases with severe AP, with a 87% specificity and a 95% sensitivity; the positive predictive value recorded was 51.11% , and the negative predictive value was 99.34%.

Ranson score, upon presentation, recorded an average value of 1.18 ± 1.11 . Depending on the value considered as early predictive marker of severe pancreatitis (3), we divided the subjects included into two groups: Ranson score < 3 (29 subjects) and > 3 (178 patients). Comparing the two groups revealed statistically significant differences: the age of patients was 71.44 ± 10.89 years in the first group (> 3), compared to 48.12 ± 12.67 years in those with Ranson score < 3 ($p < 0.0001$), the number of patients with severe AP was statistically ($p = 0.001$) significantly higher in the first group; statistically significant differences were found for the leukocytes ($13582.76 + 4748 / \text{mmc}$ vs. $9715 + 270.7 / \text{mmc}$, $p < 0.0001$), creatinine ($1.36 + 0.80 \text{ mg / dl}$ vs. $0.93 + 0.04 \text{ mg / dl}$, $p = 0.001$), urea ($p = 0.0001$), total amylase ($p = 0.003$) and pancreatic amylase < 0.0001 , transaminases: GOT $P < 0.0001$ and GPT $p < 0.001$.

Regarding the aetiology, of the 29 patients with a score Ranson of at least 3, in 19 (64.28%) we have identified alcohol in anamnesis, in 8 (28.57%) the AP aetiology was represented by gallstone disease and in 2 (7.14%) patients, triggering causes were identified.

The correlation analysis of Ranson score with the AP severity identified a strong correlation of variables, with a Spearman correlation coefficient of 0.6867, $p < 0.0001$, supported by linear regression analysis, $r^2 = 0.5236$ $p < 0.000$. Ranson score over 3 predicted 46.6% of the cases of severe AP, with a specificity of 91.16% and a sensitivity of 53.81%. The value calculated by the ROC curve was 0.8279, 95% CI 0.7479 -0.9078. Similar data were reported by other studies published in the literature [144, 152, 153].

Presence of SIRS was identified in 58 of the 207 patients (28.01%). Severe AP statistically significantly correlated with the presence of SIRS $r = 0.6810$, $p < 0.0001$. The presence of systemic inflammatory response syndrome (SIRS) is associated with high mortality, so it was necessary to create a score for its assessment [100]. Studies based on its use have reported increased reliability in predicting AP severity and a significant feasibility and may be performed daily or as often as necessary [101]. A significant study reported a mortality rate of 25% in those with persistent SIRS at the moment of presentation, 8% in patients with SIRS present at baseline but not persisting and 0% in those without the presence of SIRS [102]. Another significant report, published in 2009 in *Clinical Gastroenterology Hepatology*, reported a greater severity of AP in the patients with SIRS from the baseline, especially those with 3 or 4 of the criteria compared with those without the presence of SIRS [103]. Thus, the assessment of SIRS is inexpensive, accessible and comparable in terms of usefulness to other prognostic scores.

CONCLUSIONS

- The study conducted was substantiated by the approach of a pathological entity that raises numerous diagnosis and treatment problems, which is a challenge both in terms of multiple aetiology, of complex and incompletely elucidated pathophysiology and by choosing appropriate therapeutic measures.
- The relevance of our study lies in the need for prompt and early diagnosis of AP, and rapid assessment of the severity and prognostic indicators since AP is a disease accompanied by high mortality rate.
- Regarding the aetiology, gallstone disease is the most common cause, with a percentage between 30 and 40; the emphasized results of the study conducted reveals a 23% rate for biliary aetiology; in a rate of 68 of cases, the incriminated etiological factor was the use of ethanol.
- Peak incidence in alcoholic pancreatitis is in the third and fourth decade of age, and in case of lithiasic aetiology in the seventh decade; in the group studied, we achieved an average of 53.44 ± 15.42 years with a minimum of 21 years and a maximum of 88 years, and in the percentage distribution analysis of the average age of patients, we see that two thirds are under 60; in patients with ethanolic aetiology, the average was 41.04 ± 0.34 years and in the biliary aetiology, we recorded an average of 69.18 ± 12.21 years
- Assessment of AP severity, according to Atlanta criteria, identifies in the literature a 15-25 percentage of patients who develop severe disease; our results have identified a similar percentage, 11.11% of patients with severe AP.
- Alcohol consumption, with a major role in the onset of a severe form of the disease was present in a significant percentage in patients with AP, 61%; gallstones have been identified at a rate of 26 and other causes in 13% of patients.
- Although it has been previously shown that overweight or obese patients fall into a group of high risk for severe disease, with regard to the study group, by calculating the Spearman correlation coefficient, we obtained an r value of 0.13, statistically insignificant, $p = 0.055$; however, we identified significant differences in the BMI between the group of patients with severe AP and those with mild disease.
- Patient age, significant item for AP severity was different among groups of patients with severe, moderate and mild AP: 75.35 ± 7.31 years, respectively 66.13 ± 10.01 years and 46.24 ± 11.47 years, $p < 0.001$; between the two variables, we calculated a correlation coefficient of 0.704.
- Males were also more frequently incriminated to associate with a severe form of PA; in the patients included in the study we observed a slight predominance of male subjects (60.86% vs. 39.14%).
- Analysis of biological parameters interrelation with the AP severity, has detected a statistically significant correlation for the WBC, urea and creatinine.
- The presence of SIRS significantly correlated with a severe form of AP, thus constituting an inexpensive method, accessible and with a usefulness comparable to other prognostic scores.
- The presence of SIRS predicted 82.60% with 86.36% sensitivity, 79.35% specificity, and the negative predictive value was 97.99%.
- Risk stratification of subjects included in the study to develop a severe form of AP, using the APACHE II score revealed the following data: an APACHE II score of at least 8 predicted 77.69% of cases with severe AP, with a 87% specificity and a 95% sensitivity; the positive predictive value recorded was 51.11% , and the negative predictive value was 99.34%.

- more than 3 Ranson score of 46.6% of predicted cases of severe AP, with a specificity of 91.16% and a sensitivity of 53.81%.
- Rules of adequate clinical decisions in the management of patients with AP involve the use of assessment scores severity and prognosis, the election of therapeutic opportunity and establish correct management of the condition.
- Our study materializes direct interrelation of Ranson and APACHE II scores, as well as the presence of SIRS with AP severity, which emphasizes the inclusion of these items in the standard evaluation of patients.

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