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Ascitic fluid to serum bilirubin ratio for differentiation of exudates from transudates

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Abstract

Background: Regarding the diagnostic errors of the classic criteria including serum ascites albumin gradient (SAAG), total protein concentration and the adapted Light et al's criteria in distinguishing transudate versus exudates, we evaluated the ascitic fluid to serum bilirubin ratio as a new criteria in this regard. We also evaluated whether the combination of bilirubin ratio with each of these classic criteria improves the diagnostic accuracy.

Methods: One-hundred ascitic fluid specimens were analysed prospectively whereas the category of fluid was assessed according to the clinical diagnosis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall accuracy, positive likelihood ratio (LR^+), negative likelihood ratio (LR^-) and the Youden's index of each criterion alone and in combination with the bilirubin ratio were calculated.

Results: SAAG seems to be the best criterion (specificity = 0.9090, PPV = 0.97, LR^+ = 8.03, Youden's index = 0.64). Bilirubin and LDH ratio criteria had equivalent specificity (0.8333 and 0.8205, respectively), accuracy (0.80 and 0.81, respectively), PPV (0.54 and 0.55, respectively), NPV (0.90 and 0.93, respectively) and LR^+ (4.09 and 4.30, respectively) which generally were better than fluid total protein and total protein ratio but not as predictive as SAAG. The addition of bilirubin ratio to any criterion did not make any improvement.

Conclusion: Ascitic fluid to serum bilirubin ratio, although not more predictive than SAAG, can be used as an alternative criterion in distinguishing exudative versus transudative ascitic fluid as it is more cost-effective in terms of laboratory processing and also more available.

Keywords: Bilirubin gradient, ascites, transudative, exudative.

Introduction

Ascites is defined as the pathologic accumulation of free fluid in the peritoneal cavity [1]. This condition develops most frequently as part of the decompensation of previously asymptomatic chronic liver disease. Abdominal paracentesis with careful analysis of the ascitic fluid to classify it as exudate or transudate should be a very early step in evaluating patients with ascites [2]. This fluid is usually a transudate in patients with acute or chronic liver failure, massive liver metastasis, hypoalbuminemia, or heart failure, whereas it is an exudate in those with peritoneal carcinomatosis, peritonitis or pancreatic ascites [3].

There are multiple methods being used to classify the ascitic fluid as either exudate or

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transudate. These include the serum-ascites albumin gradient (SAAG), total protein concentration of the ascitic fluid, the adapted Light et al's criteria for classifying pleural fluid including fluid to serum protein ratio, fluid lactate dehydrogenase (LDH) concentration and fluid to serum LDH ratio [4].

In view of the high protein concentration of normal peritoneal fluid and cardiac ascites, the low protein concentration of most infected specimens, and the disappointing overall accuracy of the total protein level in classifying specimens of ascitic fluid, the entire exudate-transudate concept has been called into question [2]. Therefore, looking for an alternative criterion without such problems seems rational. Following studies conducted by Meisel et al. [5] and Elis et al. [3] in using fluid to serum bilirubin concentration as an alternative criterion for the classification of exudative vs. transudative plural and ascitic fluid respectively, and also controversy exists as to which method is more accurate, we conducted this study to compare sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall accuracy, positive likelihood ratio (LR^+), negative likelihood ratio (LR^-) and the Youden's index of this criterion with other above-mentioned criteria. We also evaluated the added value of this criterion to other routine criteria for separating transudates from exudates.

Methods

One-hundred ascitic fluid specimens from consecutive patients admitted to Rasoul Akram General Hospital, Tehran, Iran, were studied prospectively between March 2006 and June 2007. All patients were diagnosed with only one etiology for their ascites and there was no concurrence of etiologies in any of the patients. Biochemical parameters were determined using a multichannel analyser (Synchron LX20). Total protein levels were measured by the modified biuret method. Albumin levels were measured using bromcresol green by spectrophotometric method. The concentration of total bilirubin was determined by measurement of azobilirubin after reaction with diazotised sulfanilic acid and addition of an accelerator. LDH levels were measured using a kinetic UV optimised standard method (the upper normal limit for serum is defined at 460 IU/l). Etiology was considered as the gold standard for the classification of ascitic fluid.

The diagnosis of the disease causing the effusion was considered to be confirmed when the following conditions were met:

Liver cirrhosis was diagnosed by the combination of impaired liver function tests, evidence of portal hypertension and decreased or patchy uptake with preferential uptake by the bone marrow and spleen of the radiocolloid on the liver scan, or liver biopsy findings of cirrhosis.

Congestive heart failure (CHF) was diagnosed with the presence of an enlarged heart with clinical or echocardiographic evidence of cardiac dysfunction, and one or more of the following alterations: pulmonary venous congestion on radiography, peripheral edema, tachycardia, or ventricular gallop.

Hypoalbuminemia was defined as serum albumin level <25 g/L, with no evidence of cirrhosis.

Massive metastatic liver disease was identified by liver biopsy or cytopathological findings demonstrating malignant cells, or a documented primary tumor and unequivocal CT scan demonstration of liver metastasis without peritoneal involvement.

Malignant ascites was diagnosed by performing peritoneal biopsy or cytopathological findings of malignant tissue, or unequivocal CT scan finding of a malignant process involving the peritoneum.

Pancreatic ascites was identified by the elevated serum and ascitic fluid amylase level and demonstration of contrast material passage from a major pancreatic duct or a pseudocyst into the peritoneal cavity.

Fluid type	Etiology	n	Relative frequency
Transudates		78	0.78
	Liver cirrhosis	38	0.38
	Congestive heart failure	25	0.25
	Hypoalbuminemia	13	0.13
	Massive liver metastasis	2	0.02
Exudates		22	0.22
	Malignant ascites	18	0.18
	Tuberculous peritonitis	3	0.03
	Pancreatic ascites	1	0.01
Total		100	1.00

Table 1. The type and cause of ascites.

Tuberculous peritonitis was diagnosed by identifying bacilli in ascitic fluid or biopsy specimen cultures or by the presence of caseous granulomas in peritoneal biopsy tissue.

SAAG > 1.1 g/dL was considered as transudative [6]. Ascitic fluid protein > 2.5 g/dL [4], total protein ratio > 0.5 (4), LDH ratio > 0.6 [4], and total bilirubin ratio > 0.6 [3] were considered as exudative. Ascitic fluids associated with liver cirrhosis, CHF, hypoalbuminemia and massive metastatic disease were considered as transudates and the rest as exudates. The ascitic fluid to serum ratio of total protein, LDH and bilirubin, and also the SAAG, were calculated.

Statistical analysis and ethical consideration:

Statistical studies were carried out using SPSS program (version 11.5, SPSS, Chicago, Illinois, USA). The diagnostic accuracy of each criterion and of the combination of bilirubin ratio with each criterion, with reference to contended etiology, was evaluated using Bayesian methods to measure the following: sensitivity, TP/TP+FN; specificity, TN/TN+FP; accuracy, TP+TN/TP+TN+FP+FN; PPV, TP/TP+FP; NPV, TN/TN+FN; where TP is the number of true positive diagnoses, TN the number of true negative diagnoses, FP the number of false positive diagnoses, and FN the number of false negative diagnoses. We also calculated positive diagnostic likelihood ratio (LR^+), negative diagnostic likelihood ratio (LR^-) and also Youden's index for each criterion or their combination. McNemar's nonparametric test was used to evaluate the incompatibilities between clinical and laboratory criteria. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

A total of one-hundred consecutive patients affected by ascites were included. The study population comprised 64 men and 36 women, with a mean age of 48.1±10.3 years. Seventy-eight specimens were determined as transudates and twenty-two as exudates. The type and etiology of ascites are depicted in Table 1.

Sensitivity, specificity, accuracy, PPV, NPV, LR^+, LR^- and Youden's index of each criterion with respect to the etiology are summarized in Table 2. It is evident that SAAG with the highest specificity, PPV, LR^+ and Youden's index is the best predictor. Fluid total protein and total protein ratio are the poorest criteria regarding

Criterion	Sensitivity	Specificity	Accuracy	PPV	NPV	LR^+	LR^-	Youden's index
SAAG > 1.1g/dL = transudate	0.731	0.9090	0.77	0.97	0.49	8.03	0.29	0.64
Fluid total protein >2.5 g/dL=exudate	0.8181	0.6794	0.71	0.42	0.93	2.55	0.26	0.49
Total protein ratio > 0.5 = exudate	0.7727	0.7692	0.77	0.49	0.92	3.35	0.29	0.54
LDH ratio > 0.6 = exudate	0.7727	0.8205	0.81	0.55	0.93	4.30	0.27	0.59
Total bilirubin ratio > 0.6 = exudate	0.6818	0.8333	0.80	0.54	0.90	4.09	0.38	0.51

PPV: positive predictive value, NPV: negative predictive value, LR^+: positive likelihood ratio, LR^-: negative likelihood ratio, SAAG: serum-ascites albumin gradient, LDH: lactate dehydrogenase.

Table 2. Summary of statistical results for each criterion of ascites.

Criterion	Sensitivity	Specificity	Accuracy	PPV	NPV	LR^+	LR^-	Youden's index
SAAG > 1.1g/dL + Bilirubin ratio > 0.6	0.6818	0.5897	0.61	0.32	0.87	1.66	0.54	0.27
Fluid total protein >2.5 g/dL + Bilirubin ratio > 0.6	0.5	0.5769	0.56	0.25	0.80	1.18	0.87	0.08
Total protein ratio > 0.5 + Bilirubin ratio > 0.6	0.4090	0.6282	0.58	0.24	0.79	1.1	0.94	0.04
LDH ratio > 0.6 + Bilirubin ratio > 0.6	0.5	0.6538	0.62	0.29	0.82	1.44	0.76	0.15

PPV: positive predictive value, NPV: negative predictive value, LR^+: positive likelihood ratio, LR^-: negative likelihood ratio, SAAG: serum-ascites albumin gradient, LDH: lactate dehydrogenase.

Table 3. Summary of statistical results in patients with ascites after combining albumin gradient with each of the accepted criteria.

the lowest specificity, accuracy, PPV, LR^+, LR^- and also Youden`s index, but with considerable sensitivity and NPV. Bilirubin ratio (accuracy: 0.80, NPV: 0.90) and LDH (accuracy: 0.81, NPV: 0.93) ratio criteria have, to some extent, equivalent specificity, accuracy, PPV, NPV and LR^+ with almost the highest accuracy and NPV and are better predictors than fluid total protein or total protein ratio but still poorer than SAAG.

Table 3 summarizes all the previously mentioned statistical results after combining bilirubin gradient with each of the accepted criteria. It is clear that the combination of bilirubin ratio with each of the accepted criteria will not improve any of the statistical results measured here.

Using McNemar's exact test reveals that, clinical and laboratory diagnosis were not compatible in only a few cases. These discrepancies were found in each of the laboratory criteria with no statistically significant difference between them.

Discussion

Abdominal paracentesis should be performed as the first diagnostic step in all patients presenting with ascites. It is generally accepted that an effusion due to peritoneal diseases more closely resembles plasma (exudate), whereas accumulation of fluid secondary to hemodynamic aberrations or oncotic changes is an ultrafiltrate of plasma (transudate). However, numerous exceptions have been noted in using classic criteria for the interpretation of ascitic fluid as exudate or transudate. For instance, cardiac ascites or even normal peritoneal fluid may have a high protein concentration and also most infected specimens may have a low protein concentration [7,8].

Regarding the limitations found in the diagnostic accuracy of classically used criteria such as SAAG and total protein, looking for new criteria with greater diagnostic accuracy seems logical. Following the serendipitous discovery of pleural fluid to serum bilirubin concentration ratio as a useful diagnostic criterion to distinguish exudates from transudates with a sensitivity and specificity of 96% and 83%, respectively, [5] and its acquisition as an alternative criterion, Elis et al [3] found a sensitivity and specificity of 72% and 86%, respectively, for this criterion in distinguishing exudative versus transudative ascitic fluid. They also found that a bilirubin ratio > 0.6 has a highly statistically significant association with exudates.

In the current study we compared the ascitic fluid to serum bilirubin ratio to the other accepted criteria. We also evaluated whether the combination of this criterion and one of the classically used criteria has additional value for the distinction of transudates from exudates. We found that specificity, accuracy, PPV, NPV and LR^+ of the bilirubin ratio were similar to those of fluid to serum LDH ratio. These two criteria are better than both fluid-serum protein ratio and ascitic total protein concentration for distinction of exudates from transudates. These findings are in line with what Elis et al found [3]. However, as previous studies mentioned, we found that SAAG is the best predictor for

distinction of exudative versus transudative ascitic fluid [3, 8-10]. We also found that the addition of bilirubin ratio to any of the classic criteria, including the SAAG, did not improve the diagnostic accuracy or the predictive values. Therefore, these combination criteria do not seem to be useful in clinical practice but bearing in mind what Light et al [4] concluded that no single or several chemical tests are absolutely accurate in distinguishing exudates from transudates and that increasing the number of tests results in a more reliable separation are still valid, it seems rational to look for more accurate diagnostic modalities.

In conclusion, ascitic fluid to serum bilirubin ratio, although not more predictive than SAAG, can be used as an alternative criterion in distinguishing exudative versus transudative ascitic fluid and be more cost-effective in terms of laboratory processing and also its availability.

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