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Evaluation of the performance of biochemical ratios and albumin's gradient in the etiological exploration of ascitic fluid

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KEY WORDS

Ascites, Exsudat, Transsudat, Light Criteria, Ratios biochimiques, Gradient albumine serum-ascite

Abstract

Biochemical exploration of effusion fluids plays a crucial role in the diagnosis of underlying pathologies. This study aimed to evaluate the performance of biochemical ratios and the albumin gradients in the diagnostic process of ascitic fluids.

Methods-The study was prospective, involving 56 samples from ascitic patients. For each patient, five biochemical parameters (glucose, protein, albumin, LDH, and total amylase) were performed in ascites and plasma samples. The ascites/plasma protein, LDH ratios, and serum-ascites albumin gradients (SAAG), were calculated to evaluate their diagnostic relevance.

Results - Twenty-eight adult patients presenting ascites were included in this study,18 women (64.28%) and 10 men (35.71%) with an M/F sex ratio of 0.55. The most efficient parameters to distinguish the transudate/exudate concept were: Ascitic proteins (p =0.01), ascitic/plasma proteins (p =0.004), ascitic LDH (p =0.011), ascitic/plasma LDH ratio (p =0.013), ascitic albumin (p = 0.012), ascitic albumin/plasma ratio (p = 0.002) and ascitic glucose/plasma ratio (p = 0.02). A threshold of 14 g/L of Albumine had a better positive predictive value than a threshold set at 20 g/L (73 vs 46%). The sensitivity, specificity, diagnostic efficiency,and positive and negative predictive values for SAAG were 100%, 64%, 78%, 64%, and 100% respectively, and for the modified Light's criteria 78%, 86%, 82%, 80%, and 82% which hadbetter diagnostic efficiency and specificity than the classic Light's criteria with the respective comparative value 82 vs 78% and 86 vs 57% but less sensitivity (78 vs 100%). The criteria H20-30, H25, and TAL had good diagnostic efficiency with 75%, 75%, and 78% respectively.

Conclusion -The integration of biochemical ratios and the albumin's gradient significantly improves the differential diagnosis of ascites. It is essential to promote the use of these parameters in clinical practice to improve the treatment of patients with ascites.

1. Introduction

The biochemical analysis of body fluids is essential for the diagnosis of medical conditions that lead to fluid effusion (1). Ascites is the accumulation of fluid in the peritoneal cavity caused by serious underlying diseases (2) and is among the most common effusions submitted to the medical laboratory. It is classified according to the underlying pathophysiological process, either as an exudate or a transudate, by the presence or absence of portal hypertension. Liver cirrhosis is the most common cause (75%) of ascites in adults in the Western world, followed by cancer (10%), heart failure (3%), tuberculosis (2%), and pancreatitis (1%). The establishment of an etiological diagnosis is necessary to guide treatment decisions(3). The biochemical analysis of ascitic fluid is commonly used for diagnostic orientation.

Usually, it is possible to distinguish the mechanism of ascite formation, meaning exudate from transudate, using the total protein concentration in ascitic fluid (TPasc), with a cut-off value of 25 g/L. However, this approach does not provide good diagnostic performance (diagnostic accuracy 56%) (4). To improve the diagnostic effectiveness, the criteria of Light et al. (LC) previously used for pleural effusion fluid, were adapted for ascites. An exudate is defined by the presence of 2 of the following criteria: a TPasc/TPserum ratio(TP ratio) > 0.5, an LDH level> 165 IU/l, or an LDH asc/LDH serum ratio (LDH ratio) > 0.6 (5).

In addition, the use of serum-ascites albumin gradient (SAAG) can differentiate ascites caused by portal hypertension (hepatic cause) from other non-hepatic causes, providing a better diagnostic approach. Indeed, an SAAG of 11g/l indicates cirrhotic ascites associated with portal hypertension, while an SAAG < 11g/l could be in favor of a non-hepatic cause: peritoneal carcinomatosis, peritoneal tuberculosis, pancreatic disease, or nephrotic syndrome(6).

These measurements proved to be more reliable than the quantification of biochemical markers only in ascitic fluid, allowing a better characterization of ascites and providing more importantinformation. The importance of biochemical analysis in the diagnostic approach of ascites still raises a scientific debate.

The objective of this study is to evaluate the performance of different biochemical ratios and SAAG in the diagnostic approach of ascites and to propose other diagnostic criteria.

2. Materials & Methods

This prospective study evaluated the biochemical ascites/plasma ratios and SAAG for the etiological diagnosis of ascites. The study was conducted in 12 weeks on hospitalized patients with ascites from February 12 to May 3, 2023. The inclusion criteria were: patients over 18 years old with clinically confirmed ascites and patients who gave informed consent to participate in the study. The criteria for non-inclusion were patients withcontraindications to ascitic tap (paracentesis), patients requiring ultrasound-guided paracentesis, patients with refractory or septated ascites that make sampling impossible, and patients with insufficient blood samples. The samples were collected in grey sodium fluoride tubes to inhibit glycolysis. The ascitic tap and blood sampling were performed at the same time to avoid any temporal differences in the sampling conditions. The macroscopic analysis of ascites was performed for each sample.

Biochemical analysis was performed on the RESPONS 920 DiaSys® analyzer after centrifugation of samples for 10 minutes at a speed of 2290 rotations per minute (RPM); the following parameters were measured: Glucose (Hk/G6PD FS Method), Protein (BIURET FS Method), Albumin (BCG FS Method), LDH (Lactate/Pyruvate IFCC FS Method) and Total Amylase (EPS-G7 IFCC FS Method).

We proposed five criteria for diagnosis improvement: modified light's criteria (LC'), H20-30 and H25criteria, TAL criteria, and finally the albumin cut-off value. LC' suggests that the presence of one positive criterion among LC, such as LDHasc > 165 IU/L, LDH ratio > 0.6, or TP ratio > 0.5, is enough to discriminate exudativeascites. The H20-30 criterion is based on two parameters: TP and LDH asc. A TP level below 20 g/l and an LDHasc above 165 IU/L would indicate an exudate. A TP greater than 30 g/l confirms the presence of an exudate, regardless of LDHasc level. However,if the TP concentration is between 20 and 30 g/l, only the LDH asc level would be considered for diagnosis (Table 1).

The third criterion proposed is H25, including the following criteria: if the TP is less than 25 g/l and the LDH asc is greater than 165 IU/L, the ascites is considered as an exudate. As far as, if the TP is greater than 25 g/l and the LDH asc is less than 165 IU/L. conversely if the TP is < 25 g/l with an LDH asc level<165 IU/L, or a TP greater than 25 g/l and an LDH asc > 165 IU/L. the ascites is a transudate. The fourth criterion is the Albumin cut-off valueof 14 g/l which classifies ascites,as exudate or transudate, but also according to the presence or absence of portal hypertension (PHT). A value below 14 g/l is in favor of transudative effusions and leads to the diagnosis of PHT, while a value above 14 g/l is in favor of exudative effusions and excludes PHT.

The TAL criteria are based only on the levels of TP, LDH, and Albumin in ascitic fluid (Albasc). The cut-off values were respectively: 25 g/l, 165 IU/l, and 14 g/l. If only one of these criteria is positive, the pathophysiological mechanism of ascite formation is exudative. The data was analyzed by the IBM® SPSS statistics version 21. The Student's t-test for independent samples and the ANOVA one-way test were used to compare the means.

The p-values less than 5% were considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic effectiveness were calculated as shown in Table 2.

Table 1. Differential diagnosis of ascites based on H20-30 criteria

H20 30	TP<20g/l		20 g/l >TP ≥ 30 g/l		TP ≥ 30 g/l	
	LDH <165 UI/ l	LDH >165 UI/ l	LDH <165 UI/ l	LDH >165 UI/ l	LDH <165UI/l	LDH >165UI/l
Clinical diagnosis	Transudate	Exsudate	Transudate	Exsudate	Exsudate	Exsudate
The positive criterion is taken into account	/	LDH	LDH	LDH	TP	/

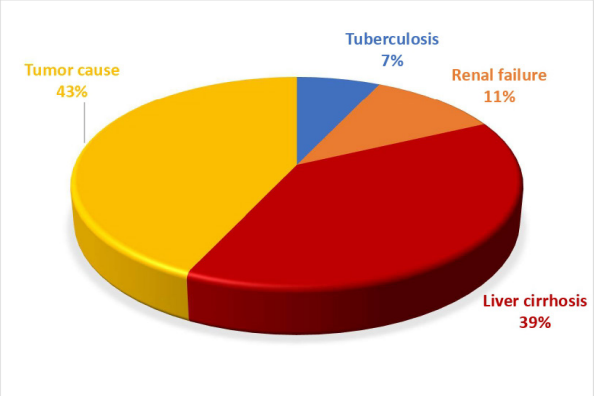
Table 2. Contingency table

	Reference test		
Test result	Presence of disease	Absence of disease	
Positive test	True positives (a)	False positives (b)	VPP = a/ (a + b)
Negative test	False positives (c)	True negatives (d)	VPN = d/(c + d)
	Sensitivity = a / (a +c)	Specificity =d / (b + d)	Total = N
Diagnostic effectiveness = (a + d) / N			

3. Results

Sixty samples were collected (30 ascites samples and 30 blood samples). However, two samples were excluded due to insufficient collection. A total of 28 patients with ascites were included in this study. There were 18 women (64.28%) and 10 men (35.71%) with an M/F sex ratio of 0.55. The average age of the patients was 57.5 ±15.69 years with extremes ranging from 21 to 86 years. The different causes of ascites are shown in figure 1.

Figure 1. Distribution of the sample according to etiology



Macroscopic analysis of the samples showed that the most common appearance is that of a citrine yellow liquid found in 82% of cases (23 patients). Three samples had an icteric appearance (11%). On the other hand, the least common appearance is that of a dark brown liquid, which was observed in only one patient (3.5%), as well as the haematic appearance (3.5%).

Seventeen patients had a SAAG ≥ 11g/l (60.71%) against 11 patients (39.29%) with a gradient < 11 g/l. According to protein rates, 18 samples were transudates and 10 exudates, however according to the light criteria 20 were transudates and 8 were exudates.

The analysis of the performance of the biochemical parameters showed that the ratios and the SAAG were the most significant in the distinction between an exudative and transudative process (**Table 3**).The tie-in calculation showed that the CLs accord in 86% with the TP, and in 100% with the LDH asc and the LDH's ratio.

Table 3. Expression of the parameters measured as average ± standard deviation depending on the transudate/ exudate's concept

	Transudate	Exsudate	
	Average ± standard deviation	Average ± standard deviation	P
TPasc	15.17 ± 8.41	26.04 ± 11.96	0.01 S
TPplasma	54.35 ±5.24	52.00 ± 7.91	0.36 NS
Ratio TP	0.28 ± 0.15	0.50 ± 0.20	0.004 S
LDHasc	66.08 ± 36.37	380.85 ± 395.78	0.011 S
LDHplasma	262.50 ± 94.31	408.21 ± 254.86	0.06 NS
Ratio LDH	0.30 ± 0.15	1.04 ± 0.96	0.013 S
Albasc	9.30 ± 5.64	16.10 ± 7.54	0.012 S
Albplasma	27.86 ± 4.61	26.48 ± 4.92	0.44 NS
Ratio Alb	0.32 ± 0.17	0.60 ± 0.24	0.002 S
SAAG	18.50 ± 5.18	10.37 ± 6.85	0.002 S
Glucoseasc	1.19 ± 0.59	1.14 ± 0.52	0.82 NS
Glucoseplasma	1.01 ± 0.42	1.19 ± 0.52	0.34 NS
Ratio Glucose	1.15 ± 0.11	0.97 ± 0.23	0.02 S
Amylaseasc	32.22 ± 16.19	38.69 ± 39.32	0.57 NS
Amylaseplasma	50.71 ± 24.79	43.35 ± 25.16	0.44 NS
Ratio Amylase	0.69 ± 0.31	0.78 0.41	0.51 NS

The tie-in calculation showed that the CLs accord in 86% with the TP, and in 100% with the LDHasc and the LDH's ratio. On the other hand, with the TP's ratio, the agreement was 75%. Table 4 summarizes the results of the evaluation of the threshold of distinction, specificity, sensitivity, PPV, NPV, and diagnostic effectiveness of the biochemical parameters and the criteria that we proposed according to the exudate/ transudate concept. Table 5summarizes the results of the evaluation of specificity/sensitivity, PPV/NPV, and the diagnostic effectiveness of SAAG, Albumin, and albumin ratio according to the presence or absence of PHT.

Discussion

In this study, we evaluate the relevance of some biochemical parameters, their ratios, and the Albumin gradient in the process diagnostic of ascites. results allowed us to propose diagnostic criteria that increase the performance of distinction between exudative and transudative liquids to guide the etiological diagnosis of ascites.

Our results were consistent with the majority of studies; female predominance was observed. These results are consistent with previous observations by Sidibé et al. 2009 (7) and Adhemar et al. 2016 (8) which reported proportions of 54.1% and 66% of women respectively. In a memory work carried out in the Médéa region in 2017 (9), the frequency found was also similar to ours (64%).

This predominance could be explained by the fact that women are more likely to develop ascites than men. Indeed, a study conducted in the United States in 2020 (10) showed that women had a significantly higher susceptibility than men for most chronic diseases other than cirrhosis, such as cancers (ovarian cancer, breast cancer). breast and cervix), diabetes, high blood pressure, congestive heart failure, and stroke. In our study, the most common etiology of ascites was cancers, followed by cirrhosis, contrary to the studies of Yousouf et al. 2017 (11), Sastry et al. 2017 (12), Sidibe et al (2009) (7), Chikyala 2023 (13) and Khan F.Y et al 2007 (14), where it represented the first etiology. This difference could be attributed to the limited number of patients included in our sampling.

The macroscopic appearance of samples revealed that the majority of cases presented a citrine color of ascitic fluid. Similar results were reported in the study of I. Chaouch and M. Ettahri in Médéa 2017 (9), and Yousouf et al. 2017 (11) revealed a rate of 80 %, while no chylous appearance was observed. In the literature, CL and SAAG (albumin-serum ascites gradient) are recognized as keys of the diagnostic strategy for the effusions classification into transudates and exudates. However, in current clinical practice, biochemical exploration of ascites focuses on the measure of parameters in ascites fluid but in this study, we included calculations of ratios and SSAG, then we classified the parameters in two categories: useful and useless for the discrimination between exudate and transudate. This approach highlighted the importance and usefulness of measuring TP and SAAG. Our results agree with those reported by Cabantous P 2021 (15) and we also found that measuring glucose in ascites was useless. Nevertheless, it is important to note that statistical significance was noted in the glucose ratio, suggesting that its assessment could be relevant to detect possible metabolic activity in ascites.

for amylase, contrary to the reference study we observed, that its dosage was useless. This difference could be attributed to the fact that we did not have ascites with pancreatic origin, which explains the lack of significant correlation. Similarly, Cabantous P et al (15) found that the LDH assay was useless, while our results showed that its assay was very useful. In addition, our results showed that the Albasc dosage and the calculation of the ratios: TP, Alb, LDH, and glucose were significant and useful to guide the diagnosis, except the amylase ratio which was not significant. The study of concordance of the different parameters with Light's criteria allowed us to note that the TP measurements are more in agreement with the CL than the TP ratio in the physiopathological classification.

diagnostic markers the most correlated with Light's criteria, in comparison with TP and its corresponding ratio.The results also revealed that the TP ratio is more reliable and precise for the classification of ascites into transudates and exudates. Indeed, the TP ratio presented better sensitivity/ specificity and better diagnostic efficiency than the ascites concentration of total proteins. This could be explained by analytical variability and systemic errors that can occur during the analysis. However, these variation factors are largely eliminated and switched by the calculation of the TP ratio. According to the study by Kahn AM et al. (16), LDH levels in transudate ascites are typically around 200 IU/L. Additionally, for clinical presentation of patients with exudative ascites primarily due to a malignant cause, LDH levels are greater than 250 IU.

Our observations are in agreement with these results, because we obtained an average of 66.08 ± 36.37 IU/L for transudate ascites, while the average for exudative ascites was 350.85 ± 395.78 IU. Furthermore, the application of this parameter and its ratio demonstrates a sensitivity of 100% and a specificity of 57%, with a diagnostic efficiency of 78%. We also observed a similarity in sensitivity and diagnostic efficiency between CL and SAAG, however, SAAG presents higher specificity compared to CL. Our results are consistent with the study conducted by BURGESS et al. (17), who compared the accuracy of CL, cholesterol level, cholesterol ratio, bilirubin level, and SAAG in distinguishing exudates from transudates in 393 patients. They found that CLs were the most accurate criteria (93%), with a sensitivity of 98% and a specificity of 83%.

The SAAG was the second-best performing test, with an accuracy of 89%, sensitivity of 87%, and specificity of 92%. Among the 19 transudates misclassified by CL in this study, 13 were correctly classified by SAAG. The results demonstrated that SAAG presents both better sensitivity and specificity compared to TPasc for the diagnosis. These findings are consistent with several previous studies (12,18,19).

Our study also showed that the diagnostic accuracy of SAAG is better than that of TP (78 vs 71%), which is in agreement with several studies: Runyon et al. (20) (USA) (96.7 vs 55.6%), Akriviadis et al. (21) (Greece) (98 vs 52%), Younas et al. (18) (Pakistan) (96 vs 56%),AL-knawye et al.(22) (Saudi Arabia) (94 vs 81%).Unlike previous studies, our study observed a lower PPV for SAAG compared to TPasc, with rates of 64% and 66% respectively. It is important to note that PTs can be influenced by other factors and are not specific to a single cause of ascites, which may confound the etiological diagnosis and result in false-positive results, thereby affecting sensitivity and specificity measurement & therefore The PPV of the TP asc. However, regarding NPV, SAAG showed superior performance compared to protein rates, with rates of 100% and 80% respectively. Our results are consistent with several previous studies (14, 18, 23).

The difference in accuracy between SAAG and TP in diagnosing ascites may be explained by the misclassification of ascites according to the transudate and exudate concepts based on total proteins. In our study, we found that 5 patients with malignant ascites were misclassified as transudates, as well as 1 patient with tuberculosis and 2 patients with renal failure who were misclassified as exudates. These classification errors may influence the diagnostic performance of PT compared to SAAG. In this study, we demonstrated that the TP measure in ascites alone is not sufficient to classify the physiopathological process in exudate/transudate, so it is recommended to replace it with SAAG which presents a better sensitivity, specificity, and diagnostic effectiveness. Or to use it in the second line. On the other hand, measurements of LDH and albumin in ascites provide a piece of important additional information to improve diagnostic accuracy. Additionally, the inclusion of biochemical ratios adds diagnostic value, with similar efficacy to SAAG, whichoffers better assessment and diagnostic guidance of ascites.

The ascites and blood samples are essential for calculating the different biochemical ratios and SAAG, but it is not always possible to do it for both at the same time. Thus, the introduction of other criteria can be necessary to evaluate the diagnosis. Indeed,we proposed CH20-30 and CH25 criteria that are mainly based on TPasc and LDHasc, while the TAL criteria take into account TPasc, Albasc, and LDHasc, and finally, Albasc with a threshold of 14 g/ L.

Our data showed that TAL criteria have the best performance in diagnostic efficiency, sensitivity, and precision. The CL', H20-30, and H25 criteria, for their part, have a better capacity to avoid false positives. Conversely, only the CL criteria offered the best liability, reliability, and precision to correctly identify true positives and true negatives samples.

These proposed criteria constitute an acceptable alternative to improve diagnostic performance when it is impossible to take both samples simultaneously. However, given the small number of our sample, which constitutes the main limitation of this study, it is desirable to validate these criteria through studies including a larger cohort to strengthen their reliability.

Conclusion

This study highlights the importance of a global and integrated approach to the biochemical exploration of ascites. We demonstrated that biochemical ratios and albumin gradients have an important role in understanding the physiopathological mechanism of ascites, and in making a precise clinical diagnosis. These measurements offer better performance than simple measures of biochemical markers in ascites and provide valuable information for diagnosis and patient management. Criteria that we proposed led to a significant improvement in diagnostic accuracy. Furthermore, the combination of LDHasc, Albasc, and TPasc offers an interesting alternative when taking ascites and blood samples simultaneously is difficult, also the LDH ratio offers a relevant alternative when other measures are not available. These different tests will contribute to better quality of care by providing precise information concerning the differential diagnosis of ascites; and by guiding appropriate therapeutic decisions to optimize the management of patients with ascites and improve their prognosis.

Conflicts of interest

The authors have no conflicts of interest to declare.

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