Diagnostic accuracy of serum ascites albumin gradient (SAAG) in a contemporary unselected medical cohort

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Abstract
Objectives: To describe the different aetiologies of ascites and test the validity of serum ascites albumin gradient (SAAG) and cytology in a contemporary unselected medical cohort.

Methods: All adult patients admitted to Nottingham University Hospitals, UK, between 1 May 2013 and 30 April 2018 with new-onset radiologically-confirmed ascites were included. Data were analysed to determine the distribution of different aetiologies of ascites and the diagnostic accuracy of SAAG in portal hypertension and cytology in malignancy as underlying causes of ascites.

Results: Over 5 years, 286 patients presented with new-onset ascites; 122 surgical cases were excluded. Most patients were men (n = 84, 51.2%) over 50 years of age (n = 142, 86.6%). Cirrhosis accounted for 54.9% (n = 90) of the cases of ascites followed by malignancy (n = 48, 29.3%) and cardiac failure (n = 10, 6.1%). SAAG ≥ 11 g/L had a sensitivity of 85.5% and specificity of 60.6% for diagnosing portal hypertension as a cause of ascites (diagnostic accuracy = 78.5%, 95% confidence interval (CI): 69.8–85.5; area under the curve (AUC) = 0.756, 95% CI: 0.652–0.860). Ascitic fluid cytology was positive in 50% of malignant cases and 66% of primary peritoneal carcinomatosis cases.

Conclusion: The underlying aetiology and the validity of available tests varied substantially compared with previous reports.

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Introduction
Ascites is a common presentation to secondary care units. Studies performed over three decades ago in specialist liver centres reported cirrhosis as the main aetiology in the western world (80%–85%) followed by malignancy (10%), heart failure (3%), tuberculosis (2%), pancreatitis (1%) and other rare diseases. In contrast, in the Middle and Far East, cirrhosis accounted for only 69% of cases. The onset of ascites is considered an important landmark in the natural history of liver cirrhosis, with a median decrease in survival ranging from 12 years to 2 years and an associated 50% mortality over 2 years. The key factors in ascites formation are activation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems, causing renal sodium retention and portal (sinusoidal) hypertension.

Guidelines on the investigation of ascites have relied upon historical studies from specialist liver centres. The prioritisation of investigations at the first presentation of ascites is determined by the most prevalent underlying aetiology of the clinical manifestation and potential yield from the diagnostic tests. For example, the reported diagnostic accuracy of serum ascites albumin gradient (SAAG) ≥11 g/L to identify portal hypertension as a cause of ascites is as high as 97%. Kajani et al showed that in alcohol-related liver disease (ArLD), SAAG and portal hypertension correlated significantly (p < 0.05, r = 0.624); however, this relationship was less obvious (r = 0.398) in patients with non-alcoholic fatty liver disease (NAFLD). Furthermore, SAAG is a poor differentiator between ascites due to heart failure or liver disease. The diagnostic yield with cytology if performed with all diagnostic paracenteses of ascites is also low. In contrast, in the context of malignant ascites, the sensitivity of cytology is between 57% and 62% for all cancers and 98% for primary peritoneal carcinomatosis. This issue impacts clinical decision-making, including the cost implications of the yield from each of these tests and which test should be performed routinely.

Imprecise investigations have an associated high cost in overstretched healthcare services and have the potential to cause patients harm. Moreover, imprecise investigations can result in a delay in definitive diagnosis and initiation of appropriate treatments, which in turn impacts patient outcomes. It is pivotal to consider appropriate disease-specific risk factors when requesting any diagnostic workup. We aimed to describe the distribution of different aetiologies of ascites in a contemporary cohort of all medical patients and to test the validity of SAAG and cytology in this unselected cohort.

Material and methods
This retrospective observational study was performed at Nottingham University Hospitals (NUH), United Kingdom. The
NUH serve as secondary care NHS hospitals for a population of 700,000. Local ethical approval was obtained for this study (Registration Number: 18-208c). The requirement to obtain patient consent was waived as this was a retrospective study, done as part of service evaluation, and only anonymized aggregate data were used in the study.

The cohort was defined as patients admitted to NUH between 1 May 2013 and 30 April 2018. The following inclusion criteria were applied: (a) age ≥18 years, (b) new onset of ascites and (c) diagnosis of ascites confirmed by radiological imaging (computed tomography (CT), abdominal ultrasonography). Patients with peritoneal fluid collection as an immediate or late manifestation of acute surgical abdomen or postoperative complication were excluded.

The underlying cause of ascites was established from the patients’ clinical records. The diagnosis of cirrhosis was confirmed by liver biopsy or standard radiology; that of malignancy was confirmed by histopathology or multidisciplinary team discussion; and that of congestive cardiac failure (CCF) was confirmed by echocardiography and/or elevated serum N-terminal pro-brain natriuretic peptide (NT-proBNP). In the case of end-stage renal disease (ESRD), a nephrologist’s diagnosis was accepted.

Anonymised data for the following variables were collected from the patients’ electronic medical records: age, sex, aetiology (ies) of ascites, serum albumin, ascitic fluid albumin, ascitic fluid cytology, radiological imaging and NT-proBNP. The SAAG value was calculated as the difference between the albumin concentration in the serum and that in the ascitic fluid (SAAG (g/L) = serum albumin – ascitic fluid albumin).16

**Statistical analysis**

The primary outcomes were the distribution of different aetiologies of ascites in a contemporary unselected medical cohort and the diagnostic accuracy of SAAG ≥11 g/L for identifying portal hypertension as a cause of ascites. The secondary outcome was the validity of ascitic fluid cytology in malignancy, as an underlying aetiology of ascites.

Normally-distributed quantitative variables were summarised as mean ± standard deviation (SD), and quantitative variables that did not follow a normal distribution were summarised as median ± interquartile range (IQR). The correlation between normally-distributed quantitative variables was assessed by parametric tests (Pearson’s correlation coefficient, unpaired T-test), and non-normally distributed variables were assessed by non-parametric tests (Spearman’s correlation coefficient, Mann–Whitney U test). Categorical variables were analysed by the Chi-squared test, with results reported as absolute and relative frequencies with/without 95% confidence intervals (CI). The diagnostic performance of SAAG ≥11 g/L was tested by the area under the receiver operating characteristic (ROC) curve (AUC).

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist Version 4 was used for the reporting of this study.17 Statistical analysis was performed using IBM SPSS version 26 (IBM Corp., Armonk, NY, USA).

**Results**

Over five years, 286 patients with a new diagnosis of ascites were identified from the hospital records; 122 patients with ascites due to surgical causes were excluded from the analysis. Over half of the patients were men (n = 84, 51.2%) and the majority were above 50 years of age (n = 142, 86.6%). The baseline characteristics of the cohort are presented in Table 1.
Cirrhosis accounted for over half (n = 90, 54.9%) of the causes of ascites; among these, 58 patients had ArLD, 21 had NAFLD, 3 had chronic viral hepatitis, 1 had hepatitis C with hepatocellular carcinoma, 3 had autoimmune hepatitis and 4 had cryptogenic cirrhosis. Malignancies accounted for 29.3% (n = 48) of the cases of ascites (12 gynaecological, 25 gastrointestinal, 4 cancers of unknown primary origin and 7 other cancers). CCF accounted for 6.1% (n = 10) of the cases of ascites, ESRD for 3.0% (n = 5), chronic pancreatitis for 1.8% (n = 3) and other aetiologies for 4.9% (n = 8) (protein-energy malnutrition, sclerosing mesenteritis, superior mesenteric vein (SMV) thrombosis, human immunodeficiency virus (HIV) with atypical lymphoma and pericardial tuberculosis (TB)).

Participants with paired serum and ascitic albumin data were further divided into two groups based on the absolute SAAG values using a cut off of ≥11 g/L. Paired albumin samples were available for 116 patients of which 72.4% (n = 84) were categorised as the high SAAG (>11 g/L) group, which comprised patients with liver cirrhosis (77.4%, n = 65), cardiac failure (7.1%, n = 6), underlying malignancy (10.7%, n = 9) and other diseases (4.8%, n = 4). In comparison, in the low SAAG group (SAAG <11 g/L), 28.1% (n = 9) of the patients had cirrhosis, 9.4% (n = 3) had cardiac failure, 15.6% (n = 5) had ESRD, 40.6% (n = 13) had underlying malignancy and 6.3% (n = 2) had other diseases. A detailed distribution of the aetiologies based on the SAAG cut off is presented in Table 2. Of the eight patients with malignant ascites and SAAG >11 g/L, two had liver metastases and none had cirrhosis.

A 2 by 2 contingency table revealed that SAAG ≥11 g/L was 85.5% (95% CI: 76.1–92.3) sensitive and 60.6% (95% CI: 42.1–77.0) specific, with a diagnostic accuracy of 78.5% (95% CI: 69.8–85.5) for identifying portal hypertension as the cause of ascites. The positive predictive value of SAAG ≥11 g/L was 84.5% (95% CI: 78.0–89.4), the negative predictive value was 62.5% (95% CI: 47.9–75.1) and the AUC was 0.756 (95% CI: 0.652–0.860; p < 0.001) (Figure 1 and Supplemental Table 1).

Results for ascitic fluid cytology were available for 116 patients in the entire

| Table 1. Baseline characteristics of the cohort. |
|-----------------------------------------------|
|                                | Liver disease (n = 90) | Non-liver disease (n = 74) | p   |
|-----------------------------------------------|
| Age (years)                                 | 0.01                     |
| 18–49                                        | 18 (20.0)                | 4 (5.4)                     |
| ≥50                                          | 72 (80.0)                | 70 (94.6)                   |
| Sex                                          | 0.124                    |
| Female                                       | 39 (43.3)                | 41 (55.4)                   |
| Male                                         | 51 (56.7)                | 33 (44.6)                   |
| SAAG                                         | <0.001                    |
| >11 g/L                                      | 9 (12.2)                 | 23 (54.8)                   |
| <11 g/L                                      | 65 (87.8)                | 19 (45.2)                   |
| Missing data                                 | 16                       | 32                          |

Data are presented as number (%) or number.
SAAG, serum ascites albumin gradient.

| Table 2. Distribution of aetiologies for ascites as per serum ascites albumin gradient (SAAG). |
|-----------------------------------------------|
|                                | SAAG >11 g/L | SAAG <11 g/L |
| Cirrhosis                      | 65 (77.4)    | 9 (28.1)     |
| ArLD                           | 43 (87.8)    | 6 (12.2)     |
| Other                          | 22 (88.0)    | 3 (12.0)     |
| Congestive cardiac failure     | 6 (7.1)      | 3 (9.4)      |
| End-stage renal disease        | 0            | 5 (15.6)     |
| Malignancy                     | 9 (10.7)     | 13 (40.6)    |
| Other                          | 4 (4.8)      | 2 (6.3)      |

Data are presented as number (%) or number.
Other aetiologies comprised chronic pancreatitis (n = 2), superior mesenteric vein (SMV) thrombosis (n = 1), tuberculosis (n = 1), protein-energy malnutrition (n = 1) and sclerosing mesenteritis.
ArLD, alcohol-related liver disease.
cohort and for 41 of 48 patients with malignant ascites. Positive cytology was present in 50.0% of the patients with underlying malignancy, with a sensitivity of 51.2% (95% CI: 35.1–67.12), specificity of 100% (95% CI: 96.1–100) and diagnostic accuracy of 85.3% (95% CI: 78.2–90.8) to identify malignancy as a cause of ascites. The yield with positive cytology was higher (66.0%) in cases of primary peritoneal carcinomatosis.

**Discussion**

This study investigated the utility and diagnostic accuracy of SAAG in a contemporary secondary care cohort presenting with ascites for the first time. The results showed that the diagnostic accuracy of SAAG, with a cut off of ≥11 g/L, for differentiating portal hypertension-related ascites from other causes was lower than that previously described in the literature. In the largest study to date of 901 paired ascitic fluid and serum samples from 330 patients, SAAG ≥11 g/L had a sensitivity and specificity of 97% and 90%, respectively, for identifying portal hypertension as the cause of ascites. The results from this landmark study were the basis for the recommendations in international guidelines for using SAAG to classify the cause of ascites. However, patients in the landmark study were recruited from hepatology inpatient and outpatient services, which reflects a large proportion of patients with underlying cirrhosis (81.2%). Additionally, multiple samples from the same patients were used in the cohort, enhancing the performance characteristics of SAAG. The diagnostic value of SAAG in identifying the underlying aetiology of ascites is less relevant in individuals for whom the diagnosis has been established. Furthermore, the diagnostic accuracy of SAAG is influenced
by the varying prevalence of the target condition. In our study, all patients presenting to the hospital with new-onset ascites were included, and only 54.9% had cirrhosis. The sensitivity and specificity of SAAG in our cohort of patients were 86% and 61%, respectively, as we used the SAAG value from each patient only once: that obtained at the time of initial admission. This reflects the context of the use of SAAG more accurately.

Cardiac failure was responsible for 6.1% of the ascites cases in our cohort. Both heart failure and cirrhosis cause hepatic sinusoidal hypertension.19,20 Moreover, hepatic sinusoids are more permeable in heart failure, which allows leakage of protein-rich lymph into the abdominal cavity. The total protein concentration in ascitic fluid is high with a SAAG of ≥11 g/L, which makes it difficult to distinguish between ascites due to heart failure or cirrhosis. The measurement of BNP in serum and/or ascitic fluid has proven useful in this context.19,20 The evidence shows that ascitic fluid total protein concentration >2.5 g/dL and serum BNP >364 ng/L is suggestive of underlying or additional cardiac disease, whereas serum BNP values <182 ng/L and ascitic fluid total protein concentration <2.5 g/dL suggest cirrhosis as the most likely cause of ascites.19–21

Pancreatic ascites is a rare complication of pancreatitis as well as chronic alcoholism; however, pancreatic ascites is more common when pancreatic necrosis and pseudocyst are present.22 Pancreatic ascites is characterised by ascitic fluid amylase concentrations >1000 IU/L and SAAG <11 g/L, and the condition is suspected when the ascitic fluid amylase value is greater than half of the serum amylase value.22,23

Ascitic fluid cytology data were available in 86% of the patients with malignant ascites, in this study. The yield for positive cytology in the context of malignancy was low as malignant cells were identified in only 50% of the cases. Among the patients with malignancy, the yield was better in patients with primary peritoneal carcinomatosis, where 66% had positive cytology results. The literature reports rates of positive cytology in malignant ascites ranging from 0% to 96.7%, which is partly determined by the site of the tumour.24,25 Combining cytology with tumour marker concentrations in the ascitic fluid has been reported to increase the positive predictive value in malignant ascites.24

The limitations of this study are its retrospective design and missing data for paired serum ascitic and albumin concentrations. The risk of selection bias was mitigated by including all medical cases of newly-diagnosed ascites that presented during the study period. Additionally, complete case analysis was performed to address missing data. The use of data from an unselected contemporary cohort provided good insight into the cause of ascites in patients presenting to secondary care facilities, which can be used when prioritising diagnostic investigations.

**Conclusion**

In a contemporary medical cohort of patients with ascites, the underlying aetiology and the validity of currently available tests (SAAG, cytology) varied substantially from those described in the literature. Liver cirrhosis accounted for just over half of the cases and malignancies accounted for a third of the cases in this study. Consideration of the incidence of different aetiologies causing ascites should inform clinical practice, particularly regarding the prioritisation of diagnostic tests.

**Data availability**

The data underlying this article will be shared on reasonable request to the corresponding author.
Declaration of conflicting interests
The authors declare that there is no conflict of interest.

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