Case report

Limitations of Transferrin- and UIBC-Based Estimation of Transferrin Saturation in Decompensated Chronic Liver Disease: A Case Series

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Article Info

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Keywords

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Abstract

Case presentation: In this case series, three patients with Decompensated Chronic Liver Disease (DCLD) were admitted to the intensive care unit for management of advanced liver dysfunction. Laboratory investigations revealed anaemia, jaundice and deranged liver function tests. A notable and consistent laboratory finding was an unquantifiably low unsaturated iron-binding capacity (UIBC), which precluded calculation of total iron binding capacity (TIBC) and transferrin saturation (TfSat) by conventional methods. To address this limitation, serum transferrin (Tf) was measured as an alternative approach to calculate TIBC. Serum Tf levels were low in all patients, yielding low calculated TIBC and elevated TfSat. However, the biochemical findings did not provide clear evidence of marked iron overload, highlighting the potential limitations of estimating TIBC from transferrin using a fixed ratio formula and, consequently, calculating TfSat in patients with markedly reduced transferrin concentrations. Therefore, calculated TfSat should be interpreted in conjunction with the clinical context and other laboratory findings when assessing iron status.

Discussion: In DCLD, reduced hepatic synthesis of Tf limits the available iron binding sites. Consequently, during UIBC estimation, minimal binding of added iron occurs, resulting in very low or unquantifiable UIBC. Under these circumstances, the use of transferrin (Tf)-based calculations as an alternative approach yielded a low TIBC and an elevated TfSat, which may not accurately reflect true iron status. Calculated TfSat may increase when the reduction in TIBC is proportionally greater than the reduction in serum iron, or when serum iron concentrations are relatively preserved despite a reduced TIBC. However, in the absence of direct TIBC measurement and an independent reference method for iron status, the relative contributions of biological and methodological factors cannot be determined.

Conclusions: This case series highlights the limitations of Tf- and UIBC-based estimation of TfSat in patients with DCLD and underscores the need for cautious interpretation of calculated iron indices in these patients.

Introduction

Decompensated Chronic Liver Disease (DCLD), also known as decompensated cirrhosis is the advanced stage of liver disease with occurrence of complications, such as ascites, hepatic encephalopathy, gastrointestinal bleeding and portal hypertension [1]. DCLD and iron homeostasis are closely interlinked making interpretation of routine iron status markers particularly challenging and potentially misleading [2].

Iron is essential for the synthesis of heme (a component of hemoproteins) and as a cofactor for enzymes [3]. Markers of body iron status include serum iron, ferritin (Ftn), total iron-binding capacity (TIBC), serum transferrin and transferrin saturation (TfSat) [4]. Serum ferritin is indicative of body iron stores; its concentrations are decreased in the presence of iron deficiency and increased in conditions of iron overload. However, it is also an acute phase reactant, with concentrations being increased in the presence of inflammation [5]. Transferrin (Tf) is the major iron transporter in blood; its capacity to bind iron is expressed as total iron-binding capacity (TIBC). TIBC can be estimated using direct or indirect methods. In labs in India, indirect methods are widely used and formulae were employed to calculate TIBC either by from unsaturated iron-binding capacity (UIBC) or Tf values. The UIBC-based approach is commonly used in diagnostic laboratories in country like India due to its cheaper cost and wide availability. Despite its widespread use, it is subjected to errors. The Tf-based calculation of TIBC is rarely employed due to high cost, inadvertent errors in unit conversion and use of appropriate correction factor [4,5]. Kits are available for direct TIBC estimation, but their widespread use is limited due to a shortage of manufacturers and standardisation.

In this case series, three patients presented with a distinct laboratory finding - their serum unsaturated iron-binding capacity (UIBC) was too low to be quantified; as a result, it was not possible to determine values for TIBC and TfSat. All three patients had chronic liver disease and were advised to undergo liver transplantation.

Case Presentation

The detailed case presentations are as follows.

Case 1

A 51-year-old man, known to have alcohol-related DCLD with portal hypertension, was admitted in the intensive care unit (ICU) due to complaints of fever and drowsiness. He was on the cadaveric liver transplantation list, as part of recommended treatment. He is a non-smoker and does not have any other co-morbidities. Upon examination, he was found to be icteric and pyrexia was observed. Examination of vital signs showed presence of tachycardia (heart rate 138/minute) and hypotension (100/50 mm Hg). The patient was administered intravenous fluids, antibiotics, antifungals and antiemetics. Results of his laboratory investigations are shown in Table 1. He underwent conservative management in the ICU for five days. His general condition improved; he was discharged on sixth day from ICU to ward with the recommendation for follow up in the transplant clinic.

Case 2

A 43-year-old man was admitted in the emergency room with complaints of fever, loss of weight for the past one week. Upon examination, he was found to be icteric and pyrexia was observed. He was diagnosed to have type-2 diabetes mellitus a month ago. He is a smoker and has been an alcoholic for a decade and does not have any other co-morbidities. Examination of vital signs revealed a heart rate of 90/minute and a blood pressure reading of 110/60 mm Hg. Ultrasound and computed tomography scans showed evidence of chronic liver disease with portal hypertension and right pyelonephritis. Results of his laboratory investigations are shown in Table 1. He was managed conservatively with antacids, antiemetics, and antibiotics. He was diagnosed to have DCLD with portal hypertension and advised to undergo liver transplantation as the further course of management. His general condition improved, and he was discharged with the recommendation for follow up in the transplant clinic.

Case 3

A 48-year-old man, known to have DCLD, was admitted in the intensive care unit (ICU) with presenting complaints of abdominal distension, decreased urine output, itching and constipation. He had raised similar complaints two years ago and was advised regular follow-up for further management. However, he was irregular with follow-up and also attempted native medicines for medical management for three months. He is a alcoholic for two decades and does not have any other co-morbidities. Upon examination, he was found to have bilateral pitting pedal edema and a moderate degree of ascites with distended veins in the abdomen. Examination of vital signs revealed a heart rate of 80/minute and blood pressure of 110/70 mm Hg. He was administered intravenous fluids, antibiotics, antifungals and antiemetics. Results of his laboratory investigations are shown in Table 1. He was advised to undergo liver transplantation as the further course of management.

Table 1: Laboratory investigations.

	Reference range	Case 1	Case 2	Case 3
Hemoglobin, g/dL	13-17	9.1 ↓	9.2 ↓	9.4 ↓
Mean corpuscular volume (MCV), fL	83-101	99.9	98.3	99.5
Mean corpuscular hemoglobin (MCH), pg	27-32	37.7 ↑	35.2 ↑	36.2 ↑
Mean corpuscular hemoglobin concentration (MCHC), g/dL	31-34	37.7 ↑	35.8 ↑	36.4 ↑
Red cell distribution width (RDW), %	11-14	13.8	13.1	14.3 ↑
Total bilirubin, mg/dL	0.3-1.2	37.41 ↑	2.22 ↑	7.92 ↑
Indirect Bilirubin, mg/dL	0.2-1	18.87 ↑	0.72	7.13 ↑
Direct Bilirubin, mg/dL	0-0.3	18.54 ↑	1.50 ↑	6.19 ↑
Total protein, g/dL	6-7.8	5.1 ↓	7.1	6.3
Albumin, g/dL	3.5-5.5	2.5 ↓	3.1 ↓	2.7 ↓
Globulins, g/dL	2.5-3.5	2.6	4	3.6
A:G ratio	1.2-1.5:1	0.96 ↓	0.77 ↓	0.75 ↓
AST, IU/L	10-40	263 ↑	43 ↑	42 ↑
ALT, IU/L	10-40	189 ↑	26	19
ALP, IU/L	36-92	118 ↑	57	133 ↑
Prothrombin time (PT), in seconds	10-13	38 ↑	18 ↑	22 ↑
PT-INR	0.8-1.1	3.2 ↑	1.5 ↑	1.9 ↑
MELD 3.0 Score	6–40 (higher scores indicate worse prognosis)	38	18	27
Child Pugh Score	5-15 Class A (5–6), Class B (7–9), and Class C (10–15)	11	7	12
Serum urea, mg/dL	17-43	104 ↑	31	19
Serum creatinine, mg/dL	0.7-1.4	1.4	0.7	0.9
Hepatitis B Surface Antigen (HBsAg)	Signal-to-cutoff (S/CO) ratio: <1.0 - Negative, ≥1.0 - Positive	Negative	Negative	Negative
Anti-Hepatitis B Surface Antibody titre, mIU/mL (Anti-HBs)	<10 - Non-protective >10 - Protective	Not done	Not done	0.1
Anti-Hepatitis C Virus Antibody (Anti-HCV)	Signal-to-cutoff (S/CO) ratio: <1.0 - Negative, ≥1.0 - Positive	Negative	Negative	Negative
Hepatitis B Core Antibody (Anti-HB Core)	Signal-to-cutoff (S/CO) ratio: <1.0 - Negative, ≥1.0 - Positive	Not done	Not done	Negative
HIV-1 and 2 (Antigen and Antibody)	Signal-to-cutoff (S/CO) ratio: <1.0 - Non-reactive, ≥1.0 - Positive	Non-reactive	Non-reactive	Non-reactive
Serum iron, µg/dL	59-158 (males) 37-145 (females)	55 ↓	174 ↑	150
Unsaturated iron-binding capacity (UIBC), µg/dL	112-347	<17	<17	<17
Serum total iron-binding capacity (TIBC), µg/dL (calculated from UIBC)	250-400	Indeterminable	Indeterminable	Indeterminable
Serum ferritin, ng/mL	20-250 (males) 10-120 (females)	475 ↑	924 ↑	159
Transferrin saturation (TfSat), % (calculated using iron and TIBC)	14-50	Indeterminable	Indeterminable	Indeterminable

↑ and ↓ denote values above and below the respective reference ranges. Complete blood count (CBC) was performed using the Beckman Coulter DxH 800 analyzer. PT-INR was measured using the ACL Elite Pro analyzer. Serum iron and UIBC were measured by the ferrozine colorimetric method, in which UIBC was determined from the difference between added and unbound ferrous iron, using a Mindray UIBC reagent kit on a Mindray BS-430 autoanalyzer. Serum liver function tests, urea, and creatinine were measured using colorimetric assays with Agappe reagents on a Toshiba 120-FR autoanalyzer. Serum ferritin was measured by latex-enhanced immunoturbidimetry using Agappe ferritin reagent on a Toshiba 120-FR autoanalyzer. Viral serology (HBsAg, anti-HBs, anti-HBc, anti-HCV, and HIV-1/2 antigen/antibody) was performed using a chemiluminescence immunoassay on the Vitros 3600 analyzer.

Case work-up

Firstly, pre-analytical errors such as timing of sample collection, HIL (hemolysis, icterus, lipemia) indices of sample was documented and recent intake of iron supplementation and intravenous iron administration were ruled out. Each sample was rerun after serial pre-dilution and re-analysed to rule out any matrix effect, results of UIBC were unchanged. In addition, according to the manufacturer's specifications, the UIBC assay is not affected by bilirubin concentrations up to 40 mg/dL. The highest bilirubin concentration observed in this case series was 37.4 mg/dL, indicating that bilirubin interference was unlikely.

In routine lab practice, TIBC and TfSat are calculated using serum iron and UIBC, using mathematical formulae shown below [4]. Since the value of UIBC was not quantifiable, it was not possible to use these formulae to calculate values for TIBC and TfSat.

$$TIBC, \mu g/dL = Serum\ iron\ (in\ \mu g/dL) + Serum\ UIBC\ (in\ \mu g/dL)$$

$$TfSat, \% = \left(\frac{Serum\ iron\ (in\ \mu g/dL)}{Serum\ TIBC\ (in\ \mu g/dL)}\right) * 100$$

An alternative method to calculate TIBC and TfSat is by using serum transferrin [4]. Therefore, serum transferrin was directly measured, and TIBC and TfSat were subsequently calculated in these three patients, using the following formulae:

$$TIBC, in\ \mu g/dL = 1.41 * Serum\ transferrin\ (in\ mg/dL)$$

$$TfSat, \% = \left(\frac{Serum\ iron\ (in\ \mu g/dL)}{Serum\ transferrin\ (in\ mg/dL) * 1.41}\right) * 100$$

The calculated values for TIBC and TfSat are shown in Table 2. All three patients had low transferrin and total iron-binding capacity; however, their TfSat values were very high (Table 2).

Table 2: Transferrin-based TIBC and TfSat.

	Reference range	Case 1	Case 2	Case 3
Serum transferrin, mg/dL	200-360	42 ↓	98 ↓	131 ↓
Serum TIBC, µg/dL (calculated from transferrin)	250-400	59 ↓	137 ↓	184 ↓
Serum TfSat, % (calculated using iron and transferrin)	14-50	93 ↑	126 ↑	81 ↑

↑ and ↓ denote values above and below the respective reference ranges. Serum Transferrin was measured using immunoturbidimetric method using Roche e411autoanalyser.

Case discussion

UIBC-based approach

The method used to estimate UIBC explains the low values seen in patients with chronic liver disease. UIBC is measured by saturating transferrin in serum at an alkaline pH through addition of known excess amount of iron. The unbound ferrous ions were subsequently measured using the ferrozine method. The difference between the amount of iron added and the unbound iron measured is taken as the UIBC of the sample.

UIBC,(g/dL)= Amount of ferrous iron added -Amount of unbound ferrous iron

TIBC is then calculated as described earlier by adding the UIBC to the serum iron concentration. This approach is widely used in labs, and does not require a separation step to remove non-transferrin bound iron, unlike direct TIBC estimation methods [4]. However this method is prone to analytical variability arising from iron contamination, as well as differences in calibrators and control materials [6]. A previous study have demonstrated a negative bias in the estimation of both TIBC and TfSat using this method [7].

In those with advance chronic liver disease, transferrin concentrations are reduced due to impaired synthetic function of liver. The reduced transferrin results in diminished capacity to bind the added iron. Consequently, the calculated difference between the added and unbound iron—that is, the UIBC—is markedly low. Given the analytical reporting range of the assay (17–558 µg/dL), UIBC values in these patients were reported as <17 µg/dL. As the UIBC was below the quantifiable range and an absolute value could not be obtained, TIBC and transferrin saturation could not be reliably calculated in these cases. By substituting the UIBC value as "17 µg/dL", TfSat would be approximately 76%, 91% and 90% suggesting the possibility of iron overload.

Tf-based approach

This is an alternative, less widely employed approach to calculate TIBC and TfSat and formula has been described earlier [4]. The serum TfSat calculated by Tf-based approach were higher in all three patients, suggesting the possibility of iron overload, if interpreted in isolation (Table 2).

Transferrin (Tf), predominantly synthesised in the liver is a major iron transporter. It carries two iron atoms in ferric state (di-ferric Tf) and its levels are determined by the systemic iron status and largely by the biosynthetic function of the liver. Hence, in patients with DCLD due to impaired synthetic function, transferrin and UIBC levels were decreased. As TfSat is calculated using serum iron as the numerator and TIBC as the denominator, a disproportionate reduction in TIBC may result in elevated calculated TfSat despite the absence of convincing biochemical evidence of marked iron overload. This may occur when the reduction in TIBC is proportionally greater than the reduction in serum iron or when serum iron concentrations remain relatively preserved despite reduced TIBC.

Among the three patients, serum iron levels were below the reference range in patient 1, mildly increased in patient 2, and within the reference range in patient 3. Serum ferritin levels were elevated in patients 1 and 2, while remaining within the reference range in patient 3. In DCLD, as hepatic transferrin synthesis declines, iron exceeds the reduced binding capacity of transferrin and shifts into the non-transferrin bound iron (NTBI) pool. The standard ferrozine colorimetric assay for serum iron measures both iron bound to transferrin (TBI) and NTBI [8], hence serum iron concentrations may remain relatively preserved or elevated despite reduced transferrin levels.

Alcohol-related decompensated liver disease was the underlying etiology in all three patients, and alcohol consumption has been shown to perturb iron homeostasis [9]. The Child-Pugh score classified Patient 1 and 3 as Class C (decompensated cirrhosis) and Patient 2 as Class B (significant functional compromise). The high MELD 3.0 scores further indicate advanced liver disease and a poorer prognosis. These findings reemphasise the marked impairment of hepatic synthetic function, resulting in reduced transferrin production and consequently lower UIBC/TIBC levels. A study have shown low transferrin correlated with poor outcome and predict survival in patients with liver disease awaiting transplantation [10]. All three patients in this case series were awaiting liver transplantation. Therefore, in patients with advanced DCLD, calculated TIBC and TfSat should be interpreted together with serum iron, ferritin, and the overall clinical context, rather than in isolation, when assessing iron status.

There are other markers that can be employed to assess iron status in those with DCLD. The studies have reported the diagnostic utility of soluble transferrin receptor (sTfR):log ferritin ratio in differentiating iron deficiency anemia (IDA) and anemia of chronic disease (ACD) [11].

Limitations

A major limitation of this study was direct TIBC estimation was not done, hence a method specific bias cannot be excluded. Hence, it is not possible to determine whether the observed elevation in TfSat is attributable to the underlying disease process, limitations of the UIBC methodology, or the mathematical conversion factors used to derive TIBC and TfSat. Furthermore, the absence of an independent reference method, such as MRI-based liver iron quantification or liver biopsy, limits our ability to definitively establish the true iron status of these patients. Inflammatory markers such as C-reactive protein and procalcitonin were not measured; therefore, the potential contribution of inflammation to the observed ferritin levels could not be assessed.

Conclusion

This case series highlights the limitations of transferrin- and UIBC-based estimation of transferrin saturation (TfSat) in patients with decompensated chronic liver disease (DCLD). These patients may present with low transferrin concentrations, low UIBC/TIBC values, and elevated calculated TfSat. In this setting, elevated TfSat should be interpreted cautiously and in conjunction with supportive clinical and laboratory evidence, as it may not accurately reflect true iron status. Overall, an integrated approach to iron evaluation is essential in DCLD to avoid diagnostic errors and support appropriate clinical decision-making.

Statement and Declarations

Funding sources

This study does not require any funding.

Declaration of interests

None.

Ethical Approval

This case series utilized anonymized patient data and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was waived by the Institutional Ethics Committee.

Credit Author Statements

JR: Study Design, Conceptualization, Writing – Original Draft, Reviewing And Editing, Data Visualization, Validation, Methodology, Formal Analysis And Supervision.

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