

# The relationship between clinical factors and high ferritin in metabolic surgery patients with hepatic iron overload

Hamzah Shariff<sup>1</sup>, Craig Wood<sup>2</sup>, Peter Benotti, M.D.<sup>2</sup>, Glenn Gerhard, M.D.<sup>3</sup>, Jon Hayes<sup>2</sup>, Matthew Still<sup>2</sup>, Christopher D. Still, D.O.<sup>2</sup>

<sup>1</sup>Geisinger Commonwealth School of Medicine, Scranton, PA

<sup>2</sup>Geisinger Obesity Institute, Danville, PA

<sup>3</sup>Lewis Katz School of Medicine at Temple University, Philadelphia, PA

# Geisinger

## Introduction

Increased serum ferritin is a commonly used blood test that reflects iron stores including liver iron overload. However, the interpretation of ferritin levels is influenced both by iron stores and its role as an acute phase reactant in inflammation, infection, and malignancy.<sup>1</sup> In patients with obesity, it has been demonstrated that a positive relationship between ferritin and C-reactive protein exists, suggesting underlying inflammation.<sup>2</sup> However, iron overload in the setting of obesity can present with normoferritinemia, thus complicating the interpretation of ferritin levels in patient care. This study investigated the clinical factors associated with hyperferritinemia in patients with hepatic iron overload and severe obesity undergoing metabolic surgery.

Study aims:

- Determine the frequency of elevated ferritin in metabolic surgery patients with hepatic iron overload
- Identify factors associated with elevated ferritin for patients with hepatic iron overload

## Methods and materials

- 4359 metabolic surgery patients with wedge liver biopsy were selected between 2004 and 2021
  - pre-operative serum ferritin was documented at time of surgery
  - Perls' Prussian blue stain was used to diagnose hepatic iron overload
- Exclusion criteria:
  - Patients with iron deficiency (ferritin <30 ng/mL)
  - Patients with extremely high ferritin levels (ferritin >1000 ng/mL)
- Elevated ferritin was defined as 300-999 ng/ml in males and 200-999 ng/ml in females
- Clinical data collected included demographics, chronic medical conditions, and pathologic findings on liver biopsy
- Statistical analysis:
  - Stratified patients by iron overload subtype (Kupffer, hepatocyte, both) to assess for relationship between subtype and elevated ferritin
  - Performed bivariate analysis followed by multiple logistic regression to determine which clinical factors were independently associated with elevated ferritin
  - All tests were two-sided and p-values <0.05 were considered significant

## Results

- 703 of 4359 patients (16%) were found to have hepatic iron overload
- Patient demographics (Table 1) and grading of liver pathology (Table 2) were collected

**Table 1.** Metabolic Surgery Patient Demographics

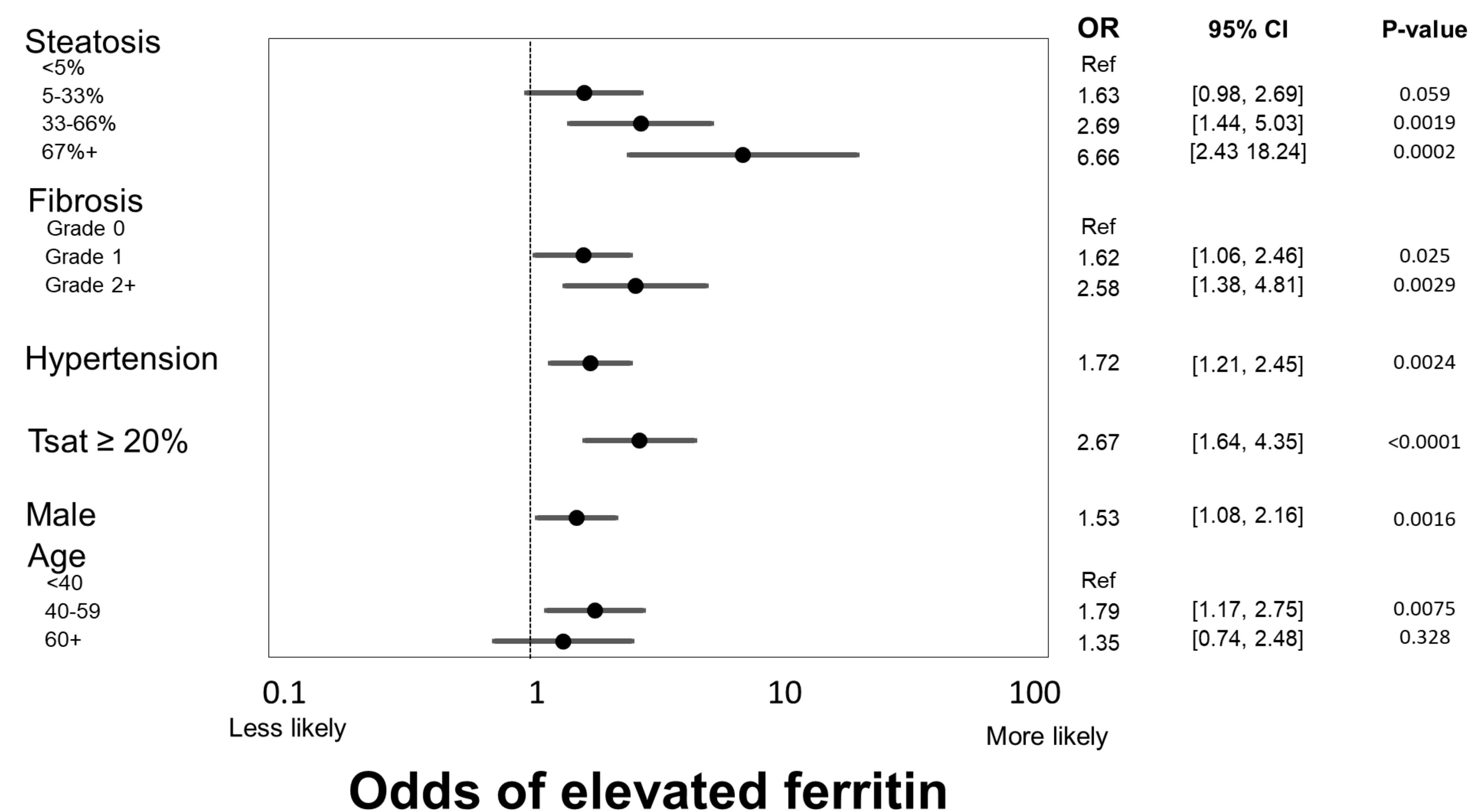
|                        | Percentage or Mean (SD) |
|------------------------|-------------------------|
| Sex                    |                         |
| Male                   | 37% (N=262)             |
| Female                 | 63% (N=441)             |
| Age, years             | 47.8 (SD=10.6)          |
| BMI, kg/m <sup>2</sup> | 47.1 (SD=8.1)           |
| Smoking history        | 46% (N=326)             |
| Diabetes               | 37% (N=259)             |
| Hypertension           | 54% (N=379)             |
| Hyperlipidemia         | 44% (N=306)             |

**Table 2.** Pathology from liver biopsy

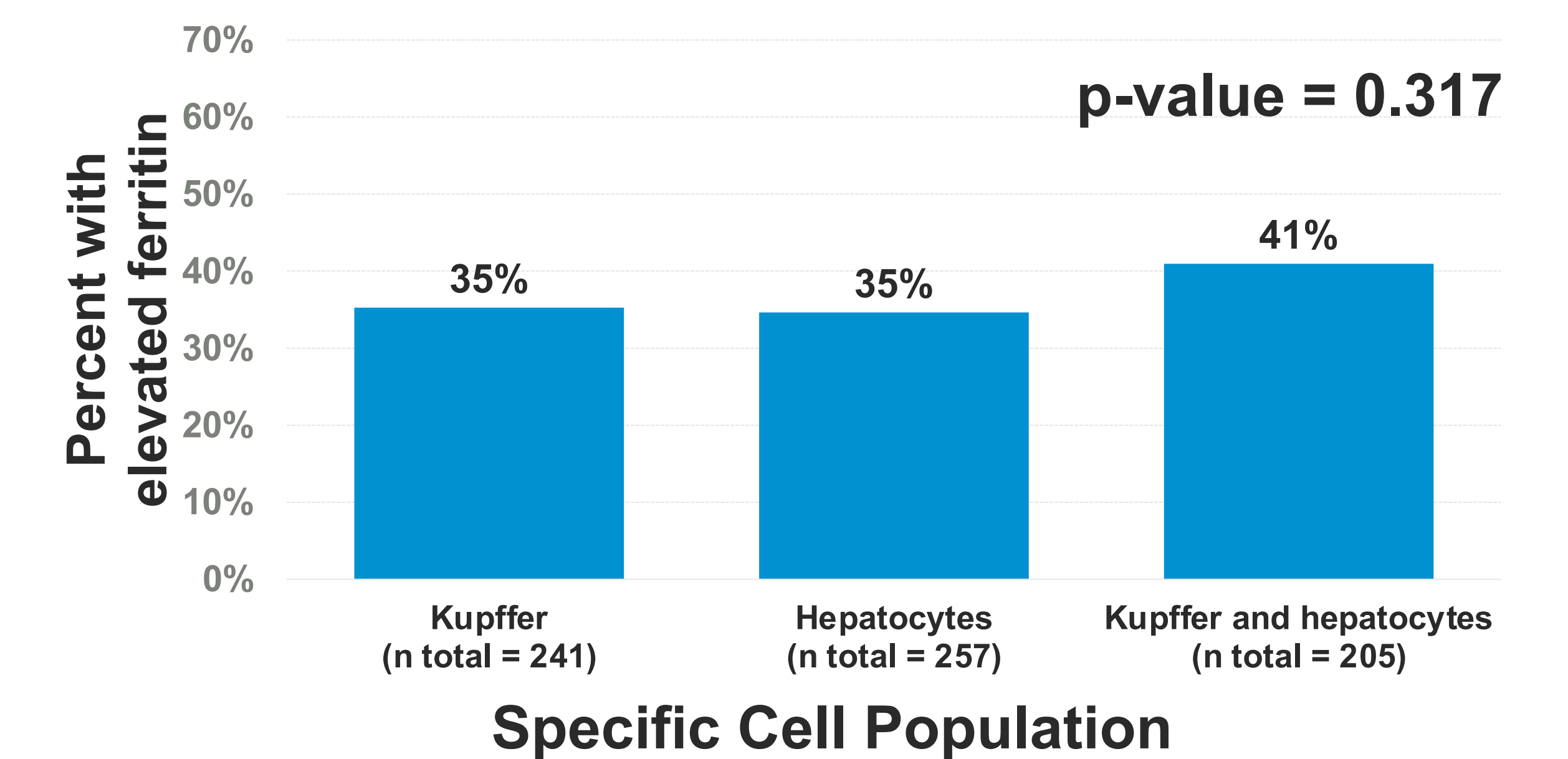
| Liver pathology and grade | Percentage  |
|---------------------------|-------------|
| Liver Steatosis           |             |
| <5%                       | 17% (N=121) |
| 5-33%                     | 59% (N=413) |
| 34-66%                    | 20% (N=140) |
| >67%                      | 4% (N=29)   |
| Liver Fibrosis            |             |
| Grade 0                   | 67% (N=465) |
| Grade 1                   | 26% (N=181) |
| Grade 2                   | 4% (N=25)   |
| Grade 3                   | 4% (N=29)   |
| Grade 4                   | <1% (N=3)   |

- The study sample included 63% (n=445) with normal ferritin and 37% (n=258) with elevated ferritin
- In multiple logistic regression, items significantly associated with greater odds of elevated ferritin included higher steatosis grade, higher fibrosis stage, hypertension, transferrin saturation ≥20%, male sex, and age 40-59 (Figure 1)
- There was no significant difference in percentage of elevated ferritin between iron overload subtypes (Figure 2)

**Figure 1.** Clinical factors associated with supranormal levels of serum ferritin



**Figure 2.** Proportion of cell-specific iron overload in patients with elevated ferritin



## Discussion

- The histopathological and demographic parameters significantly associated with hyperferritinemia in metabolic surgery patients with hepatic iron overload suggest the role of ferritin in clinical evaluation
- Significant odds of elevated ferritin in patients with increased steatosis, increased fibrosis, and presence of hypertension may reflect underlying inflammatory processes in obesity with iron overload<sup>3</sup>
- Lack of difference in proportion of cell-specific iron overload rules out cell-specific contribution to increased serum ferritin
- Aging immunosenescence may explain significant odds ratio in 40-59 range, but remains unclear for 60+ range<sup>4</sup>
- Higher odds of elevated ferritin in males compared to women may be related to testosterone-dependent suppression of hepcidin leading to increased systemic iron<sup>5</sup>
- Future studies should evaluate ferritin changes based on effect of PCOS status and heavy menstrual bleeding

## Conclusion

Hyperferritinemia and normoferritinemia can be present in patients with concurrent obesity and hepatic iron overload. This study supports a supranormal level of ferritin is likely indicative of systemic inflammation and its associated disorders. Further work is necessary to elucidate the relationship between ferritin levels and age and sex hormonal changes in the patient population of this study.

## References

1. Wang, W., Knovich, M. A., Coffman, L. G., Torti, F. M. & Torti, S. V. Serum ferritin: Past, present and future. *Biochim. Biophys. Acta BBA - Gen. Subj.* **1800**, 760–769 (2010).
2. Khan, A., Khan, W. M., Ayub, M., Humayun, M. & Haroon, M. Ferritin Is a Marker of Inflammation rather than Iron Deficiency in Overweight and Obese People. *J. Obes.* **2016**, 1–7 (2016).
3. Kowdley, K. V. *et al.* Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology* **55**, 77–85 (2012).
4. Sanada, F. *et al.* Source of Chronic Inflammation in Aging. *Front. Cardiovasc. Med.* **5**, 12 (2018).
5. Bachman, E. *et al.* Testosterone Suppresses Hepcidin in Men: A Potential Mechanism for Testosterone-Induced Erythrocytosis. *J. Clin. Endocrinol. Metab.* **95**, 4743–4747 (2010).