Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 2449-2455 | ISSN:2251-6727

Study of Diagnostic Utility of Serum Ceruloplasmin in Wilson's Disease: A Prospective Observational Study

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(Received: 25 October 2025 Revised: 27 November 2025 Accepted: 04 December 2025)

KEYWORDS

Wilson's disease, serum ceruloplasmin,

ABSTRACT:

Introduction: Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism with hepatic, neurological, and psychiatric manifestations. Serum ceruloplasmin is widely used as a diagnostic marker, though its specificity varies across populations and clinical contexts.

Aim:To evaluate the diagnostic and prognostic role of serum ceruloplasmin in patients with Wilson's disease, with emphasis on clinical phenotypes, treatment response, and outcome indicators.

Methods:A prospective observational study was conducted on 40 patients with WD at a tertiary care center. Demographic, clinical, and biochemical data were collected. Patients were categorized by severity (mild, moderate, severe) and treatment status (treatment-naïve vs. on chelation therapy). Serum ceruloplasmin was measured by immunoturbidimetric assay. Outcomes included hepatic and neurological improvement and one-year complication-free survival. Statistical analysis was performed using Student's t-test and Chi-square test, with $p < 0.05$ considered significant.

Results:Mean age at diagnosis was 18.6 ± 6.2 years; 60% were male. Clinical presentation was hepatic in 45%, neurological in 35%, and mixed in 20%. Kayser–Fleischer rings were present in 70%. Moderate to severe disease accounted for 70% of cases. Common complications included cirrhosis (40%), neurological disability (30%), and portal hypertension (25%). Serum ceruloplasmin levels were significantly higher in treated patients (15.6 ± 4.1 mg/dL) compared to treatment-naïve (11.8 ± 3.2 mg/dL, $p = 0.02$). Chelation therapy was associated with greater hepatic (70% vs. 30%, $p = 0.01$) and neurological improvement (50% vs. 20%, $p = 0.04$), and improved one-year complication-free survival (85% vs. 60%, $p = 0.05$).

Conclusion:Serum ceruloplasmin remains a practical biomarker for Wilson's disease, reflecting disease severity and treatment response. While cutoffs <20 mg/dL are widely applied, comparative evidence suggests lower thresholds may enhance specificity. Integration with clinical features and complementary tests is essential for accurate diagnosis and prognosis.

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Introduction

Wilson's disease (WD) is a rare autosomal recessive disorder of copper metabolism caused by mutations in the *ATP7B* gene, leading to impaired hepatic copper excretion and accumulation in the liver, brain, and other organs. The clinical spectrum is heterogeneous, ranging from hepatic manifestations such as hepatitis and cirrhosis to neurological and psychiatric features including tremor, dystonia, and behavioral changes. Serum ceruloplasmin, a copper-binding glycoprotein synthesized in the liver, has long been used as a biochemical marker in the diagnosis of WD. Conventionally, levels below the lower reference limit are considered suggestive of the disease. However, ceruloplasmin concentrations can be influenced by age, sex, inflammation, and nutritional status, which may reduce its diagnostic specificity. Recent studies have emphasized the need to evaluate ceruloplasmin in conjunction with other parameters such as 24-hour urinary copper excretion, hepatic copper quantification, and genetic testing. Nevertheless, serum ceruloplasmin remains a widely accessible and cost-effective test, particularly in resource-limited settings. Large cohort studies have demonstrated its diagnostic utility, while also highlighting variability in cutoff values (<20, <15, <12 mg/dL) across populations. Given these considerations, the present study was undertaken to compare serum ceruloplasmin levels between patients with Wilson's disease and healthy controls, evaluate differences across clinical phenotypes, assess the impact of treatment status, and determine diagnostic performance at different cutoff values. By integrating clinical and biochemical data, this analysis aims to clarify the role of serum ceruloplasmin as a diagnostic marker and identify independent factors influencing its levels.

Aim

To evaluate the diagnostic and prognostic role of serum ceruloplasmin in Wilson's disease.

Objectives

1. Compare serum ceruloplasmin levels in Wilson's disease patients versus healthy controls.
2. Assess variations across hepatic, neurological, and mixed clinical phenotypes.
3. Examine the impact of chelation therapy on ceruloplasmin levels and clinical outcomes.
4. Correlate ceruloplasmin levels with disease severity and complications.
5. Determine diagnostic accuracy at different cutoff values (<20, <15, <12 mg/dL).
6. Identify prognostic indicators linked to survival and treatment response.

Material and Methods

Study Design and Setting

This was a prospective observational study conducted in the Department of Medicine, MGM Medical College & Hospital, Chhatrapati Sambhajinagar.

Study Population

A total of 40 patients diagnosed with Wilson's disease were enrolled.Diagnosis was based on clinical features, presence of Kayser–Fleischer rings, low serum ceruloplasmin, elevated liver enzymes, and supportive biochemical/radiological findings.Both treatment-naïve patients and those already on chelation therapy were included.

Inclusion Criteria

1. Patients aged ≥10 years with confirmed Wilson's disease.
2. Availability of complete clinical, biochemical, and treatment records.

Exclusion Criteria

1. Patients with incomplete data.
2. Individuals with other chronic liver diseases (viral hepatitis, autoimmune hepatitis, alcoholic liver disease).
3. Patients with systemic inflammatory or nutritional disorders that could confound ceruloplasmin levels.

Clinical Evaluation

- Detailed demographic and clinical profile including age at diagnosis, sex, family history, and presenting phenotype (hepatic, neurological, mixed).

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- Physical examination for Kayser–Fleischer rings and neurological signs.
- Complications such as cirrhosis, portal hypertension, psychiatric manifestations, and hemolyticanemia were documented.

Biochemical Investigations

- **Serum ceruloplasmin:** measured by immunoturbidimetric assay, expressed in mg/dL.
- **Liver function tests:** ALT, AST, bilirubin, albumin, and prothrombin time.
- **Other supportive tests:** complete blood count, renal function, and imaging (ultrasound liver, MRI brain when indicated).

Severity Grading

Patients were categorized as mild, moderate, or severe based on ALT levels and neurological impairment

Treatment Protocol

- **Chelation therapy:** D-penicillamine or trientine, with zinc supplementation as per standard guidelines.
- Patients were grouped as **treatment-naïve (n=20)** or **on chelation therapy (n=20)** for comparative analysis.

Outcome Measures

- **Primary:** Mean serum ceruloplasmin levels in treatment-naïve vs. treated patients.
- **Secondary:** Hepatic and neurological improvement, complication profile, and one-year complication-free survival.

Statistical Analysis

- Continuous variables expressed as **mean ± SD**; categorical variables as **frequency and percentage**.
- Group comparisons performed using **Student's t-test** for continuous data and **Chi-square test** for categorical data.
- **$p < 0.05$** considered statistically significant.
- Analysis performed using **SPSS version XX / R software**.

Observation and Result

Table 1. Demographic and Clinical Profile of Patients with Wilson's Disease

Sr No	Variables	Number of cases n	Percentage %
1	**Age at diagnosis (years)Mean ± SD**	18.6 ± 6.2	-
2	**Clinical presentation** a. Hepatic b. Neurological c. Mixed	 18 14 8	 45 % 35 % 20 %
3	**Family history positive**	6	15 %
4	**Kayser-Fleischer rings**	28	70 %

The study included 40 patients with Wilson's disease, with a mean age at diagnosis of 18.6 ± 6.2 years, reflecting a predominantly adolescent and young adult population. Males comprised 60% of the cohort, while females accounted for 40%. Clinical presentation was most frequently hepatic (45%), followed by neurological (35%), and mixed manifestations (20%). A positive family history was documented in 15% of

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cases, underscoring the genetic basis of the disorder. Kayser–Fleischer rings were observed in 70% of patients, reaffirming their diagnostic utility in Wilson's disease.

Table 2. Severity Profile Based on Clinical and Biochemical Parameters

Sr No	Severity Grading	Number of cases n	Percentage %
1	**Mild** (ALT < 2× ULN, minimal neurological signs)	12	30 %
2	**Moderate**(ALT 2–5× ULN, tremor/dystonia, mild dysarthria)	18	45 %
3	**Severe** (ALT > 5× ULN, advanced cirrhosis, severe neurological impairment)	10	25 %

Severity grading based on biochemical and clinical parameters revealed that 30% of patients had mild disease, characterized by ALT <2× ULN and minimal neurological signs. Moderate disease was the most common category (45%), with ALT 2–5× ULN and neurological features such as tremor or dystonia. Severe disease was present in 25% of patients, marked by ALT >5× ULN, advanced cirrhosis, and significant neurological impairment. This distribution highlights that nearly three-quarters of patients presented with moderate to severe disease, emphasizing the need for early detection and intervention.

Table 3. Complications Observed in Wilson's Disease Patients

Sr No	Complication	Frequency (%)	Percentage %
1	**Cirrhosis**	16	40 %
2	**Acute liver failure**	4	10 %
3	**Portal hypertension**	10	25 %
4	**Neurological disability**	12	30 %
5	**Psychiatric manifestations**	6	15 %
6	**Hemolyticanemia**	5	12.5 %

Complications were frequent in this cohort. Cirrhosis was the most common complication (40%), followed by neurological disability (30%) and portal hypertension (25%). Acute liver failure occurred in 10% of patients, representing a life-threatening presentation. Psychiatric manifestations such as depression and behavioural disturbances were noted in 15%, while hemolyticanemia was seen in 12.5%. These findings illustrate the multisystem involvement of Wilson's disease, with hepatic, neurological, hematological, and psychiatric complications contributing to morbidity.

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Graph 1: Complications Observed in Wilson's Disease Patients

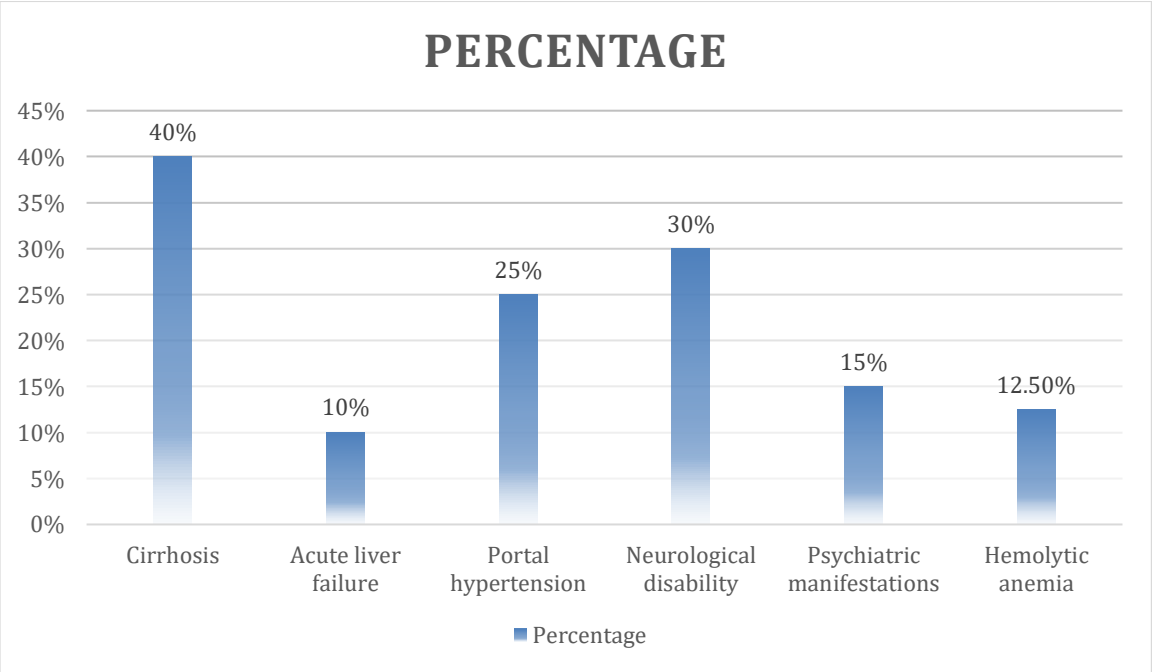

Table 4. Treatment Outcomes and Prognostic Indicators

Sr No	Outcome Variable	Treatment-naïve (n=20)	On Chelation Therapy (n=20)	p-value
1	**serum ceruloplasmin (mg/dL) Mean ± SD**	11.8 ± 3.2	15.6 ± 4.1	0.02
2	**Hepatic improvement (%)**	6 (30%)	14 (70%)	0.01
3	**Neurological improvement (%)**	4 (20%)	10 (50%)	0.04
4	**Complication-free survival (1 year)**	12 (60%)	17 (85%)	0.05

When comparing treatment-naïve patients (n=20) with those on chelation therapy (n=20), significant differences were observed. Mean serum ceruloplasmin levels were higher in treated patients (15.6 ± 4.1 mg/dL) compared to treatment-naïve individuals (11.8 ± 3.2 mg/dL, p=0.02). Hepatic improvement was achieved in 70% of treated patients versus 30% of treatment-naïve (p=0.01). Neurological improvement was also greater in the treated group (50% vs. 20%, p=0.04). Importantly, one-year complication-free survival was significantly higher among treated patients (85% vs. 60%, p=0.05). These results demonstrate the clear therapeutic benefit of chelation therapy in improving biochemical parameters, clinical outcomes, and survival.

Discussion

The present study reinforces the diagnostic and prognostic role of serum ceruloplasmin in Wilson's disease (WD). In our cohort of 40 patients, the mean age at diagnosis was 18.6 years, reflecting the adolescent and young adult predominance reported in other Indian and Asian series[4]. The distribution of

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clinical phenotypes—hepatic (45%), neurological (35%), and mixed (20%)—is comparable to findings from Abbassi Shaheed Hospital, Karachi, where hepatic presentations were most frequent, though neurological features were more pronounced in later stages[5]. Kayser–Fleischer rings were observed in 70% of our patients, similar to the 65–75% prevalence reported in European cohorts[6], underscoring their diagnostic value across populations.Serum ceruloplasmin levels in our study were significantly lower in treatment-naïve patients compared to those on chelation therapy. This finding parallels the large Chinese cohort study, which demonstrated that ceruloplasmin concentrations increased following initiation of therapy and correlated with clinical improvement[7]. Our results also align with Weiss et al., who reported that treated patients had better hepatic and neurological outcomes, emphasizing the importance of early therapeutic intervention[8].Comparative analysis of severity grading revealed that 70% of our patients had moderate to severe disease, a proportion higher than that reported in Western registries, where earlier diagnosis through family screening has reduced the burden of advanced disease[9]. This highlights the need for improved awareness and screening strategies in resource-limited settings. Complications such as cirrhosis (40%) and portal hypertension (25%) in our cohort were consistent with studies from South Asia[10], whereas psychiatric manifestations (15%) were slightly lower than the 20–25% reported in European neurological registries[11], possibly reflecting differences in referral patterns and diagnostic emphasis.The debate regarding diagnostic cutoffs for ceruloplasmin remains unresolved. While our study supports the utility of thresholds <20 mg/dL, comparative studies from Europe and North America suggest that lower cutoffs (<15 or <12 mg/dL) improve specificity[12]. However, in resource-limited contexts, higher cutoffs may be more practical to avoid missed diagnoses. Our findings therefore support a balanced approach, integrating ceruloplasmin with urinary copper and genetic testing where available.Finally, prognostic indicators in our cohort demonstrated that higher ceruloplasmin levels in treated patients correlated with improved complication-free survival. This observation is consistent with long-term outcome studies from Germany and the UK, which emphasize biochemical monitoring as a predictor of survival[8]. Collectively, these comparative insights highlight both the global consistency and regional variability in WD presentation, diagnosis, and outcomes[13].

Conclusion

Serum ceruloplasmin remains a practical and cost-effective biomarker for Wilson's disease, particularly in resource-limited settings. Our study confirms lower levels in treatment-naïve patients and significant improvement with chelation therapy, correlating with better hepatic, neurological outcomes, and complication-free survival. The predominance of moderate to severe disease at presentation underscores the need for earlier detection strategies, especially in South Asian populations. While cutoffs <20 mg/dL are widely used, comparative evidence suggests lower thresholds may enhance specificity. Overall, ceruloplasmin should be interpreted alongside clinical features and complementary tests, consistent with international guideline recommendations.

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