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Primary Versus Secondary Warm Autoimmune Hemolytic Anemia: Clinical, Laboratory, and Treatment Outcomes in A 20-Year Retrospective Study

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ABSTRACT

Objective: This study aimed to compare demographic characteristics, laboratory parameters, treatment modalities, and clinical outcomes between adult patients with primary and secondary warm autoimmune hemolytic anemia (wAIHA).

Materials and Methods: This retrospective study included 85 adult patients (57 with primary and 28 with secondary wAIHA) diagnosed between January 2000 and December 2019. Data on baseline hemolytic markers, therapies (corticosteroids, splenectomy, and rituximab), and outcomes were reviewed. The mean age was 53.0±16.2 years, and 74.1% of the patients were female. Patients were assessed for treatment responses and mortality.

Results: No significant differences were observed between the primary and secondary wAIHA groups in terms of baseline hemoglobin, reticulocyte count, lactate dehydrogenase, or bilirubin. However, haptoglobin levels were significantly lower in the primary wAIHA group (p=0.027). Corticosteroid response rates exceeded 90% in both groups, though relapse occurred in 29.4% of responders. Splenectomy led to remission in all secondary and 92% of primary wAIHA cases. Rituximab was administered in only one patient due to reimbursement limitations. Overall mortality was 15.3%, with no significant difference between the primary and secondary groups (p>0.05).

Conclusion: Primary and secondary wAIHA patients show similar clinical and therapeutic profiles. Corticosteroids were highly effective as first-line therapy. Splenectomy showed high response rates, while rituximab usage was limited. Despite clinical differences such as lower haptoglobin in primary wAIHA, mortality rates did not differ significantly.

Keywords: Autoimmune hemolytic anemia, Glucocorticoid, Recurrence, Rituximab, Splenectomy

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INTRODUCTION

Autoimmune hemolytic anemia (AIHA) arises when the immune system produces antibodies directed against the patient's own erythrocytes, resulting in a rare form of anemia. AIHA is a rare anemia caused by autoantibodies against the patient's own erythrocytes.[1] AIHA is subdivided into three main subtypes according to the thermal activity of the autoantibodies: Warm AIHA (wAIHA), cold AIHA (cold agglutinin disease, cAIHA), and mixed/atypical AIHA. wAIHA is the most common, accounting for approximately 60–70% of all AIHA cases; cold AIHA represents about 15–20%, while mixed and atypical forms are considerably less frequent. Based on thermal activity, AIHA is classified into wAIHA, cold agglutinin disease (cAIHA), and mixed/atypical forms; wAIHA accounts for ~60–70% of cases, cold forms for ~15–20%, and mixed/atypical forms are considerably less frequent and comprise the remainder.[2] In wAIHA, the autoantibodies – predominantly of the immunoglobulin (Ig)G class – are active at 37°C and mediate erythrocyte destruction by macrophage phagocytosis via IgG–Fc receptors in the spleen. Some IgG antibodies may also activate the complement cascade, thereby contributing to hemolysis.[3]

AIHA may be classified as primary or secondary. Primary AIHA is diagnosed when no underlying cause is identified in roughly half of adult patients, whereas secondary AIHA is most often associated with hematological malignancies such as chronic lymphocytic leukemia and non-Hodgkin lymphoma, or with autoimmune disorders such as systemic lupus erythematosus (SLE). Less commonly, immunodeficiencies, infections (e.g., Mycoplasma pneumoniae and human mmunodeficiency virus [HIV]), certain medications (e.g., methyldopa and fludarabine), and solid tumors may give rise to secondary AIHA.[2,4] The diagnosis and monitoring of AIHA rely on laboratory markers of hemolysis. Elevations in reticulocyte count, serum lactate dehydrogenase (LDH), total and indirect bilirubin, together with reduced haptoglobin levels, are the principal indicators of active hemolysis. The direct antiglobulin test (DAT) detects IgG, IgM, and/or complement components bound to the erythrocyte surface. Although a positive DAT in the setting of hemolysis suggests an immune-mediated etiology, a definitive diagnosis of AIHA requires integration of DAT results with clinical findings and other laboratory tests.[5] Etiologically, AIHA is defined as primary when no underlying cause is identified and secondary when associated with another condition – most commonly lymphoproliferative malignancies (e.g., chronic lymphocytic leukemia and non-Hodgkin lymphoma) or systemic autoimmune disease such as SLE; less frequently, immunodeficiencies, infections (e.g., *Mycoplasma pneumoniae* and HIV), medications (e.g., methyldopa and fludarabine), and solid tumors are implicated.[2,4] Diagnosis integrates clinical and laboratory evidence of hemolysis – reticulocytosis; elevated LDH and bilirubin; reduced haptoglobin – together with a positive DAT detecting erythrocyte-bound immunoglobulin and/or complement.[5]

In warm AIHA, corticosteroids remain the standard first-line therapy.[6] Adult patients typically commenced on oral prednisolone at 1–1.5 mg/kg daily; those who respond are usually weaned over 2–3 weeks and the course discontinued within 3–6 months. Lack of a meaningful response by week 3 is considered an indication to discontinue steroids.[4,7,8] Although around 80% of patients initially respond to corticosteroids, more than 50% experience relapse within the 1st year.[9] For patients who are refractory to or dependent on steroids, splenectomy has long been the conventional second-line option in wAIHA, particularly in primary cases, yielding response rates of 60–70% and complete remission in up to 40% of patients. Despite risks of post-operative infection and thrombosis, splenectomy remains a valuable intervention when appropriately selected.[4,10] Since the early 2000s, rituximab – an anti-CD20 monoclonal antibody – has emerged as an alternative to splenectomy in secondline therapy for wAIHA. Studies by Birgens et al.[7] in 2013 and Michel et al.[8] in 2017 demonstrated that adding rituximab to first-line glucocorticoids prolongs remission and improves response rates compared with glucocorticoids alone. Current guidelines recommend rituximab for patients unresponsive to steroids, whilst tailoring the decision for splenectomy based on individual clinical factors. No controlled trials have directly compared rituximab and splenectomy.[4,10] Other immunosuppressants such as azathioprine, ciclosporin, and mycophenolate mofetil may be employed following failure of second-line therapy.[11,12]

Most data on treatment responses and clinical courses in primary versus secondary wAIHA derive from retrospective series with limited patient numbers. In the secondary setting, the heterogeneity of underlying conditions – ranging from hematological malignancies to autoimmune diseases such as SLE – hampers standardization of therapeutic strategies and prediction of clinical outcomes.[4,6,13]

The aim of this study was to compare the demographic, clinical, and laboratory features as well as treatment responses of adult patients diagnosed with warm AIHA of primary versus secondary etiology, thereby elucidating potential differences in management and outcomes.

Adults typically start oral prednisolone 1–1.5 mg/kg/day with early assessment for response and tapering in responders; lack of meaningful improvement by week 3 supports discontinuation.[4,7,8] Initial responses approach 80%, yet >50% relapse within the 1st year.[9] For steroid-refractory or -dependent disease, splenectomy has historically yielded

60–70% responses (complete remission up to 40%) but carries infectious and thrombotic risks.[4,10] Since the early 2000s, rituximab has become a widely used second-line option and, when added to first-line glucocorticoids, can improve response rates and prolong remission;[7,8] other immunosuppressants (azathioprine, cyclosporine, and mycophenolate mofetil) are considered after failure of second-line therapy.[11,12]

Despite these options, comparative evidence for primary versus secondary wAIHA remains limited and largely retrospective, with heterogeneous secondary etiologies complicating standardization and prognostication.[4,6,13] Accordingly, this study compares the demographic, clinical, and laboratory features, as well as treatment responses, of adult patients with primary versus secondary wAIHA to delineate differences in disease behavior and management outcomes.

MATERIALS AND METHODS

This single-center retrospective study was conducted at the Departments of Internal Medicine and Hematology of Prof. Dr. Cemil Taşçıoğlu, City Hospital, affiliated with the University of Health Sciences, between January 2000 and December 2019. Medical records of 85 adult patients diagnosed with warm AIHA were reviewed. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, with approval from the Clinical Research Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (approval no: 2020/212; decision date: June 02, 2020; document no: 48670771514.10).

Demographic and clinical data recorded included age, sex, primary or secondary AIHA classification, concomitant diseases, baseline hemoglobin (Hb), reticulocyte percentage, LDH, total and indirect bilirubin, alanine and aspartate transaminases, haptoglobin, DAT results, and anticardiolipin IgM status. Data on specific antibody isotypes and complement binding were unavailable, as only a polyspecific anti-human globulin reagent is used in our institution's blood bank.

First-line therapy consisted of methylprednisolone or prednisolone. Patients who failed to respond or relapsed proceeded to second-line treatment, which comprised splenectomy or rituximab. Two patients were lost to follow-up before the first-line response could be assessed; hence, response analysis was performed on 83 patients. Complete response was defined as Hb ≥12 g/dL with resolution of hemolytic markers (normalization of bilirubin, LDH, and haptoglobin). Partial response was defined as Hb ≥10 g/dL with at least a 2 g/dL increase over baseline, despite persistence of mild hemolysis. Refractory disease was defined as failure to achieve the expected Hb rise by week 2 and absence of significant improvement by week 3. Relapse was defined as a drop in Hb and recurrence of hemolytic markers after initial complete or partial response.[5]

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics 22 (IBM SPSS, Türkiye). Normality was tested by the Shapiro–Wilk test. Continuous variables are presented as mean±standard deviation. Comparisons between two groups used Student's *t*-test for normally distributed parameters and the Mann–Whitney U test otherwise. Categorical variables are expressed as numbers and percentages and compared using Fisher's Exact test, the Fisher–Freeman–Halton test, or the Chi-square test with Yates' correction as appropriate. $P<0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of Patients

A total of 85 patients met the inclusion criteria. Ages ranged from 18 to 87 years, with a mean of 53.0±16.2 years. 65 (74.1%) patients were female, with no appreciable difference in sex distribution between the primary and secondary AIHA groups. Of the cohort, 57 patients (67.1%) had primary AIHA and 28 (32.9%) had secondary AIHA. In the secondary group, underlying hematological malignancies were most common (46.4%), followed by autoimmune diseases (28.6%), solid tumors (14.3%), drug-related AIHA (7.1%), and infection-related AIHA (3.6%) (Table 1).

Table 1. Underlying conditions associated with secondary AIHA.

	n	%
Hematologic malignancy	13	46.4
Chronic lymphocytic leukemia	6	21.4
Hodgkin lymphoma	3	10.7
Non-Hodgkin lymphoma	2	7.1
Multiple myeloma	1	3.6
Acute myeloid leukemia	1	3.6
Solid tumors	4	14.3
Autoimmune diseases	8	28.6
Systemic lupus erythematosus	5	17.9
Rheumatoid arthritis	2	7.1
Primary biliary cholangitis	1	3.6
Other causes	3	10.7
Drugs	2	7.1
Infection	1	3.6

AIHA: Autoimmune hemolytic anemia

Comorbidities were present in 45 patients (52.9%), most frequently hypertension (27%), diabetes mellitus (9.4%), and chronic kidney disease (10.6%). 85% of patients exhibited at least one symptom at presentation, most commonly fatigue (64.7%), palpitations (12.9%), and dizziness (17.6%) (Table 2). No significant differences in demographics or symptom frequency were observed between primary and secondary groups (p>0.05).

Laboratory comparisons revealed that haptoglobin levels were significantly lower in primary AIHA (90.9%) than in secondary AIHA (54.5%) (p=0.027). Other hemolytic markers did not differ significantly between groups (p>0.05) (Table 3).

Treatment and response rates

First-line corticosteroid therapy was administered to 85 patients (97.6% received methylprednisolone; 2.4% prednisolone) for a duration of 1–58 months (mean 6.46±6.8 months). However, treatment response could be evaluated in only 83 patients because two were lost to follow-up before response assessment. Seventy-eight patients (94%) responded; 58 (69.9%) with complete and 20 (24.1%) with partial responses; five patients (6%) were refractory. Response rates did not differ significantly between primary (52/56; 92.8%) and secondary (26/27; 96.2%) AIHA (p>0.05). Treatment responses to corticosteroids and splenectomy are summarized in Table 4. Relapse occurred in 23 of 78 responders (29.4%); relapse rates were similar in primary (28.8%) and secondary (30.8%) groups. Of relapsed patients, 12 restarted steroids, and 11 underwent splenectomy. Among refractory cases, three had splenectomy, and one received rituximab; one secondary AIHA patient with concomitant acute myeloid leukemia died before second-line therapy.

Splenectomy was performed in 14 patients (16.4%) as second-line therapy – 12 primary (21%) and two secondary (7.1%) AIHA cases (P=0.027). Eleven primary patients achieved complete and one partial remission; both secondary patients attained complete remission. No refractory cases were noted in either subgroup (p>0.05). Rituximab was used in only one primary AIHA patient, who did not respond; reinitiation of corticosteroids achieved complete remission.

Mortality

During follow-up, 13 patients (15.3%) died; Seven with primary AIHA (12.3%) and six with secondary AIHA (21.4%), with no significant difference in mortality between groups (p>0.05).

DISCUSSION

In this retrospective single-center series of 85 adults with warm AIHA, 67% had primary disease and 33% secondary. Whereas most series report an even distribution of primary

Table 2. Demographic and clinical characteristics of primary and secondary wAIHA patients.

	Primary OIHA (n=57) (%)	Secondary OIHA (n=28) (%)	p
Demographic characteristics			
Age (mean±SD)	52.59±15.91	53.93±16.98	[1]0.723
Gender *n* (%)			
Male	13 (22.8)	9 (32.1)	[2]0.509
Female	44 (77.2)	19 (67.9)	
Comorbidity			
Yes	27 (47.4)	18 (64.3)	[1]0.216
No	30 (52.6)	10 (35.7)	
Hypertension			
Yes	16 (28.1)	7 (25)	[1]0.968
No	41 (71.9)	21 (75)	
Chronic kidney disease			
Yes	7 (12.3)	2 (7.1)	[2]0.711
No	50 (87.7)	26 (92.9)	
Diabetes mellitus			
Yes	6 (10.5)	2 (7.1)	[2]1.000
No	51 (89.5)	26 (92.9)	
Hypothyroidism			
Yes	3 (5.3)	4 (14.3)	[2]0.211
No	54 (94.7)	24 (85.7)	
Presenting symptoms			
Yes	41 (71.9)	17 (60.7)	[1]0.426
No	16 (28.1)	11 (39.3)	
Fatigue			
Yes	39 (68.4)	16 (57.1)	[1]0.435
No	18 (31.6)	12 (42.9)	
Palpitation			
Yes	7 (12.3)	4 (14.3)	[2]1.000
No	50 (87.7)	24 (85.7)	
Dizziness			
Yes	13 (22.8)	2 (7.1)	[2]0.128
No	44 (77.2)	26 (92.9)	
Dyspnea			
Yes	12 (21.1)	2 (7.1)	[2]0.129
No	45 (78.9)	26 (92.9)	

Table 2. Continue.

	Primary OIHA (*n*=57) (%)	Secondary OIHA (*n*=28) (%)	*p*
Jaundice			
Yes	9 (15.8)	5 (17.9)	[2]1.000
No	48 (84.2)	23 (82.1)	
Angina			
Yes	3 (5.3)	0 (0)	[2]0.548
No	54 (94.7)	28 (100)	

Data are presented as *n* (%) for categorical variables and as mean±SD for continuous variables. SD: Standard deviation, wAIHA: Warm autoimmune hemolytic anemia

and secondary AIHA, the predominance of primary cases in our cohort likely reflects underrecognition of secondary etiologies over the 20-year study period.[4,14] Consistent with previous studies, hematological malignancies (46.4%) and autoimmune diseases (28.6%) were the leading secondary etiologies.[15,16] No significant age difference was observed between subgroups, though larger cohort studies have reported older age at onset in secondary AIHA.[17] Female predominance in both primary and secondary groups aligns with existing literature.[18,19]

In our series, the mean Hb level at diagnosis was lower in the secondary AIHA group, reflecting a tendency toward more pronounced anemia at presentation. A similar study reported mean Hb concentrations of 6.3 g/dL in secondary warm AIHA patients versus 7.1 g/dL in primary cases.[16] Although we observed a numerical difference between the two groups, it did not reach statistical significance. No significant differences were identified between primary and secondary AIHA in Hb and reticulocyte counts.[16,20] In our study, haptoglobin levels were the only parameter that differed between the two groups; low haptoglobin was significantly more frequent in the primary warm AIHA cohort. No previous studies have reported such a discrepancy. Although this finding is noteworthy, its interpretation must be cautious given the small sample size and the absence of a clear mechanistic rationale.[15,16]

Corticosteroids remain the cornerstone of first-line therapy in warm AIHA, and in our study, more than 90% of patients in both cohorts responded to prednisolone. Overall, initial response rates were high, with no statistically significant difference between primary and secondary AIHA. Our findings align with numerous reports indicating that 80–90% of wAIHA cases respond to firstline steroids.[17] For example, Rattarittamrong et al.[21] observed a 96% response rate – regardless of whether AIHA was primary or SLEassociated secondary – whereas

Table 3. Laboratory findings of patients with primary and secondary wAIHA.

	Primer OIHA (*n*=57)	Sekonder OIHA (*n*=28)	*p*
Hemoglobin (g/dL)	7.35±2.02	6.63±1.91	0.121
Hematocrit (%)	21.96±6.29	20.45±5.58	0.306
Reticuloscyte percentage	10.72±7.44	9.72±9.28	0.268
LDH (U/L).	679.93±754.69	600.4±561.45	0.720
Total bilirubin (mg/dL)	2.94±2.79	2.45±2.27	0.440
İndirect bilirubin (mg/dL)	2.47±2.47	2.7±1.85	0.281
ALT (U/L).	60.8±239.55	24.27±22.66	0.812
000.812AST (U/L).	44.88±78.18	36±41.63	0.410
Haptoglobin (%)			0.027*
Low	20 (90.9)	6 (54.5)	
High	2 (9.1)	5 (45.5)	
Direct coombs test (%)			0.256
Positive	48 (84.2)	27 (96.4)	
Negative	9 (15.8)	1 (3.6)	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DAT: Direct antiglobulin (Coombs) test; Hb: Hemoglobin; Hct: Hematocrit; LDH: Lactate dehydrogenase; wAIHA: Warm autoimmune hemolytic anemia.
Data are presented as *n* (%) for categorical variables and as mean±standard deviation for continuous variables. Haptoglobin levels were measured in 22 patients with primary AIHA and 11 patients with secondary AIHA, with values <30 mg/dL considered low. Direct and indirect Coombs tests were reported as positive or negative. Student's *t*-test or Mann–Whitney U test was used for continuous variables, and Fisher's exact test was applied for categorical variables.

Table 4. Treatment responses to first- and second-line therapy in primary and secondary wAIHA patients.

Treatment	Response	Primary wAIHA (*n*=56) (%)	Secondary wAIHA (*n*=27)	Total wAIHA (*n*=83)	*p*
Corticosteroid	Complete response	40 (71.4)	18 (66.6)	58 (69.9)	
	Partial response	12 (21.4)	8 (29.6)	20 (24.1)	0.62
	Refractory to treatment	4 (7.2)	1 (3.8)	5 (6.0)	
Splenectomy	Complete response	11 (91.7)	2 (100)	13 (92.9)	1.00
	Partial response	1 (8.3)	0	1 (7.1)	
	Refractory to treatment	0	0	0	

wAIHA: Warm autoimmune hemolytic anemia

Sudulagunta et al.[16] reported response rates of approximately 97% in primary wAIHA and 87% in secondary wAIHA. In our cohort, the vast majority of both primary and secondary cases responded to steroids, and refractory rates were low. This concordance demonstrates that secondary AIHA patients can achieve outcomes comparable to those with primary AIHA, supporting guideline recommendations to employ the same initial treatment strategy in both subtypes.[4,22]

Among patients who initially responded to steroids, relapse occurred in roughly 30–28.8% in the primary group and 30.8% in the secondary group. In the series by Rattarittamrong et al.[21] involving 101 warm AIHA patients, the overall relapse rate after steroids was 49.5% (50% in primary; 48.7% in secondary).[21] It is generally understood that while about 80% of patients respond to steroids initially, only 30–40% maintain durable remission at 1 year.[9] Our observed relapse rates were lower, likely owing to attrition in long-term follow-up over the 20-year period, which may have led to underestimation of true relapse frequency.

In our study, splenectomy was performed as second-line therapy in 14 patients, 12 of whom had primary AIHA and 2 of whom had secondary AIHA. The rate of splenectomy was significantly higher in the primary AIHA group (21%) compared with the secondary group (7.1%). Among those who underwent splenectomy, 11 primary AIHA patients achieved complete remission, and 1 achieved a partial response, whereas both secondary AIHA patients attained complete remission. Although response rates were high in both cohorts, splenectomy was significantly favored for primary AIHA patients in our series. International consensus reports indicate that response to splenectomy in secondary AIHA may be comparable to that in primary cases; however, they emphasize that splenectomy should be avoided where possible in secondary AIHA because of the increased risk of infectious and thrombotic complications associated with comorbid conditions.[4] Conversely, splenectomy remains a well-established secondline option in primary AIHA, with literature reporting 60–70% response rates. Our results are consistent with these data, and the wider adoption of laparoscopic techniques has further reduced operative risks, underscoring splenectomy's continued role in appropriately selected patients.[11,23,24]

Rituximab has been used since the early 2000s as a second-line therapy for steroid-refractory or -dependent wAIHA and, in some studies, in combination with steroids as first-line treatment.[7,8,10] However, in our series, rituximab was administered to only one primary AIHA patient, who did not respond. This low utilization likely reflects the drug's recent introduction into practice during the study period and restrictive reimbursement policies that limited access.

In our cohort, mortality occurred in 13 of the 85 patients: Seven in the primary AIHA group and six in the secondary AIHA group. This difference did not reach statistical significance. Although some series report higher mortality in secondary AIHA, others have found no significant difference between primary and secondary cases. Our data demonstrate that the numerically greater death rate in the secondary subgroup was not statistically significant.[16,19]

Limitations include the retrospective design, potential incomplete evaluation of secondary causes, variable follow-up durations, and missing data for certain laboratory parameters. Despite these constraints, our findings support comparable treatment responses in primary and secondary warm AIHA and underscore the need for standardized evaluation and management protocols tailored to underlying etiologies.

CONCLUSION

In this retrospective study of 85 adults with wAIHA, primary and secondary subgroups exhibited comparable demographic characteristics, laboratory profiles, and treatment responses. First-line corticosteroid therapy produced high initial

response rates (>90%) in both cohorts, with relapse occurring in approximately 30%. Splenectomy demonstrated robust efficacy as a secondline intervention, while rituximab use was minimal due to reimbursement constraints. Mortality rates did not differ significantly between subgroups, despite a numerically higher rate in secondary cases. These findings suggest that primary and secondary wAIHA follow similar clinical courses and respond similarly to current treatment algorithms.

DECLARATIONS

Ethics Committee Approval: The study was approved by Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Committee (No: 48670771 514.10, Date: 02/06/2020).

Conflict of Interest: The authors declare that there is no conflict of interest.

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