

## Original Research Article

# A study of clinicopathological profile and treatment outcomes in patients with autoimmune hemolytic anaemia

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**Received:** 24 January 2019

**Accepted:** 14 February 2019

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## ABSTRACT

**Background:** Autoimmune haemolytic anaemia (AIHA) is relatively uncommon condition with grave consequences, if not diagnosed and treated early. The literature on the clinical outcome and response to treatment is relatively scarce. Aim was to study the clinic-pathological profile and the treatment outcomes in patients with AIHA.

**Methods:** Around 25 patients with AIHA attending a tertiary care hospital over a period of one year were included in the study. The patients were divided based on severity of anaemia and etiology. All the patients data were analysed for the demographic data, clinico-pathological findings and the response to treatment. All the patients data were analysed using SPSS software (version 22).

**Results:** Out of 25 patients, 76% were females and 24% were males. Based on severity of anaemia, 60%, 28% and 8% had severe, moderate and mild anaemia. Around 48% of the patients had thrombocytopenia along with anaemia. 8 (32%) and 17 (68%) patients have primary and secondary AIHAs respectively. In our study the commonest cause for the secondary AIHA was Systemic Lupus Erythematosus (SLE) followed by haematological malignancy, primary Sjogrens, Anti-phospholipid antibody (APLA) syndrome, carcinoma colon and Wilsons disease. Hepatosplenomegaly and lymphadenopathy were present in 36% and 4% respectively. Out of 22 (88%) patients on corticosteroid therapy, 15 (60%) patients responded to corticosteroids alone and 6(24%) patients required corticosteroid plus immunosuppressive therapy.

**Conclusions:** AIHA has to be ruled out in all anaemia patients with indirect hyperbilirubinemia and abnormal peripheral smear. Secondary AIHA is more common than primary. Corticosteroids and immunosuppressive agents are the mainstay of treatment of AIHA.

**Keywords:** AIHA, DAT, Haemolytic anaemia, Primary AIHA, Secondary AIHA, SLE

## INTRODUCTION

Autoimmune haemolytic anaemia (AIHA) is a potentially fatal condition which is recognised less often.<sup>1</sup> The severity of AIHA depends on the onset of haemolysis (gradual or abrupt) and the extent of erythrocyte destruction. Mild haemolysis is usually asymptomatic while severe haemolysis can be life threatening.<sup>2</sup>

The incidence of AIHA in western world is 1-3 per 100,000 per year and its prevalence is 17:100,000.<sup>1</sup> The AIHA is sub-classified based on the presence or absence of underlying diseases. In the absence of an underlying disease, AIHA is termed as primary or idiopathic. When AIHA occurs as a manifestation or complication of

another disease, the term secondary AIHA is used. Systemic lupus erythematosus (SLE) accounts for a large number of secondary AIHA. Certain drugs, infections and tumors also cause immune mediated injury to RBCs.<sup>3</sup>

The diagnosis of AIHA is made using the direct antiglobulin test (DAT) along with the other laboratory findings: normocytic or macrocytic anaemia, reticulocytosis, low serum haptoglobin levels, elevated lactate dehydrogenase (LDH) level, increased indirect bilirubin level.<sup>2</sup> The first option for treatment of AIHA is usually corticosteroids.<sup>1</sup> An initial dose of 10-15mg/kg/day methyl prednisolone intravenously followed by 1mg/kg/day prednisone (PDN) is given orally.<sup>4</sup> Second-line treatment is started if response is not obtained in 3 weeks. According to the recommendation of the American College of Rheumatology (ACR), all patients on steroid therapy should receive vitamin D, bisphosphonates, and calcium supplements from the beginning. Folic acid supplementation is also recommended.<sup>2</sup> Azathioprine, cyclosporine, mycophenolate mofetil (MMF) and rituximab are used in relapse or steroid non responders.<sup>1</sup>

## METHODS

The study was initiated after getting institutional ethical committee approval and informed consent from the patients. This is a facility based cross sectional study conducted among patients attending Saveetha Medical College and Hospital, Chennai.

### Study period and population

Present study was conducted for a period of one year (2017-2018). A total of 31 patients aged more than 16 years, either attending OPD or to admitted were included in the study after they were screened using the exclusion and inclusion criteria.

### Inclusion criteria

Patients with DAT positive AIHA age more than 16 years and patients with hyperbilirubinemia, reticulocytosis and raised LDH.

### Exclusion criteria

Patients with DAT negative and patients on drugs known to cause haemolysis.

### Methodology

Out of 31 patients, 6 patients who had DAT negative were excluded. A total of 25 patients satisfied inclusion criteria were included in the study. We performed the direct Coombs test with gel Coombs cards (Biorad Diamed GmbH, Switzerland) and polyspecific anti-human globulin (AHG) serum containing anti-IgG and C3d. A 0.8% red cell suspension was used for testing as

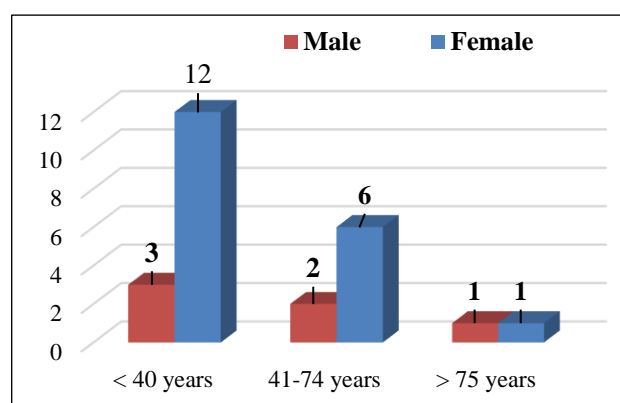
per the manufacturer's instructions. These 25 patients were classified based on severity of anaemia into mild anaemia, moderate anaemia, and severe anaemia according to their haemoglobin levels of 9-10.9g/dl, 7-8.9g/dl and <7g/dl respectively. The etiological workup to find out the cause of anaemia were done which include rheumatological workup, bone marrow biopsy, tissue biopsy, serum ceruloplasmin, urine copper, KF ring, blood culture, urine culture, endotracheal tube culture were done. Based on which AIHA patients were classified into primary and secondary types. Both primary and secondary AIHA patients were analysed for the demographic features, presenting complaints, clinical/pathological findings at diagnosis and associated diseases, types of therapy given and response to therapy.

### Statistical analysis

The study data was converted into Microsoft excel format and analysed using SPSS 22 software and results were obtained which are depicted in form of pie charts and bar diagrams.

## RESULTS

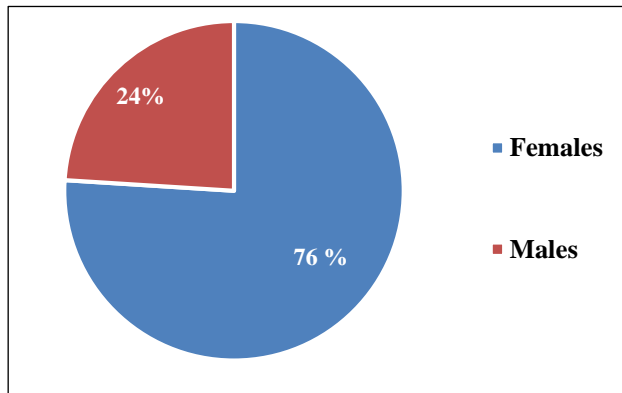
In present study based on the age distribution, 15 (60%) patients were less than 40 years of which 3 (12%) were males and 12 (48%) were females which shows that AIHA is more prevalent in young aged females. Around 8 (32%) were between 41-74 years of which 2 (8%) were males and 6 (24%) were females which also shows female predominance. In present study group only 2 (8%) patients were more than 75 years of which 1 (4%) patient was male and 1 (4%) patient was female (Figure 1). Out of 25 patients in the study, 19 (76%) were females and 6 (24%) were males which shows a female predominance. Around three-fourth of the patients were females as depicted in (Figure 2).



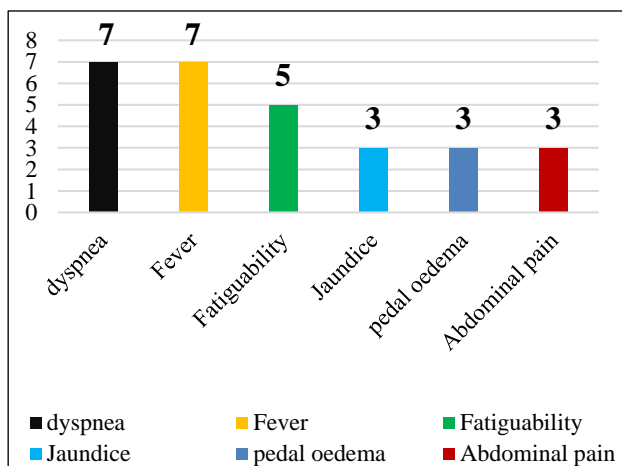
**Figure 1: The age and sex wise distribution in patients with autoimmune hemolytic anaemia.**

Most common presenting complaints were dyspnoea and fever which are present in 7 (28%) and 7 (28%) patients respectively. Easy fatigability was seen in 5 (20%) of patients. Jaundice in 3 (12%) patients, pedal oedema in

another 3 (12%) patients and abdominal pain in another 3 (12%) patients. One patient has presented with more than one symptom at time of presentation. Hence the (Figure 3) shows the most common clinical presentation in present study group.



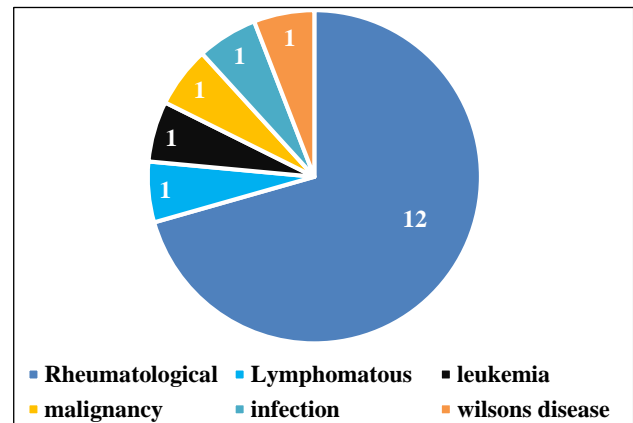
**Figure 2: Percentage of males and females with autoimmune hemolytic anaemia in study group.**



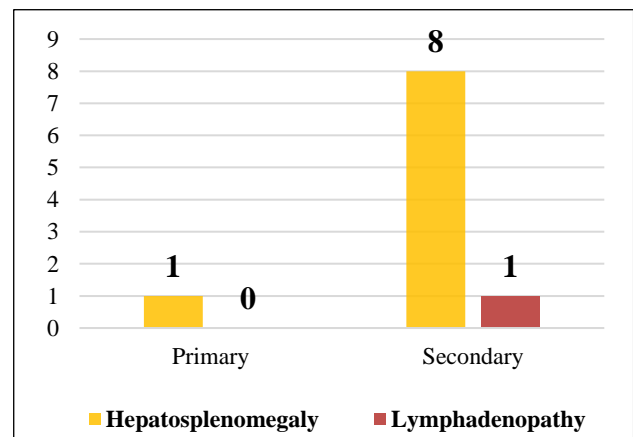
**Figure 3: The common clinical presentations in patients with autoimmune hemolytic anaemia.**

The etiological workup to find out the cause of anaemia were done which include rheumatological workup, bone marrow biopsy, tissue biopsy, serum ceruloplasmin, urine copper, KF ring, blood culture, urine culture, endotracheal tube culture was done. Based on etiological workup, 8 (32%) patients had primary AIHA and 17(68%) patients had secondary AIHA. Majority of the patients had secondary AIHA. The commonest cause of secondary AIHA was rheumatological disorders which is seen in 12 (48%) patients. Out of 12 (48%) patients 10 (40%) patients had SLE, 1 (4%) patient had primary Sjogren's and 1 (4%) patient had anti-phospholipid antibody syndrome. Myelodysplastic syndrome was present in 1 (4%) patient, acute lymphoblastic leukemia was present in 1 (4%) patient, carcinoma colon was present in 1 (4%) patient, Wilson's disease was present in 1 (4%) patient and Burkholderia cepacia infection was present in 1 (4%) patient. Out of 25 patients in present

study only 1 patient has infectious AIHA (Figure 6). On physical examination, 1 patient (4%) with primary AIHA and 8 patients (32%) with secondary AIHA had hepatosplenomegaly. Lymphadenopathy was present in 1 patient (4%) with secondary AIHA. Hence hepatosplenomegaly and lymphadenopathy were more common in secondary AIHA compared to primary AIHA as show in figure (Figure 5).



**Figure 4: The etiological distribution of secondary autoimmune hemolytic anaemia in terms of percentage.**

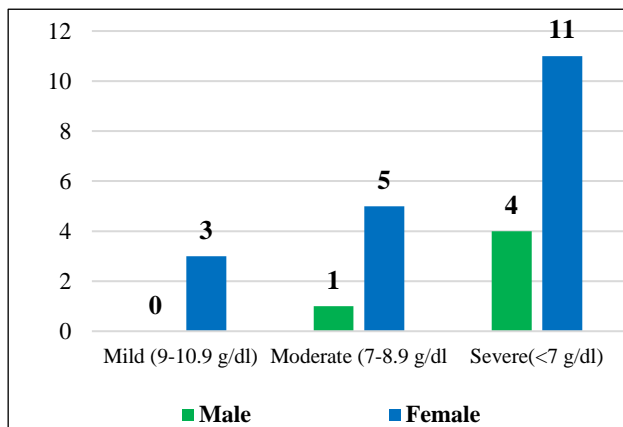


**Figure 5: The number of autoimmune hemolytic anaemia patients with hepatosplenomegaly and lymphadenopathy.**

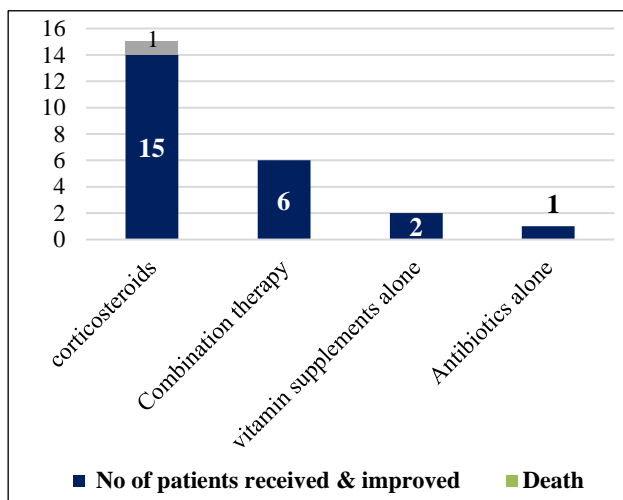
On the basis of severity of anaemia, 15 patients (60%) had severe, 6 patients (24%) had moderate and 3 patients (12%) had mild anaemia respectively one (4%) patient has normal haemoglobin which shows that most of the patients in present study have severe anaemia (Figure 6). In current study 12 (48%) of patients had simultaneous immune thrombocytopenia called Evans syndrome of which 4 (16%) patients had primary AIHA and 8 (32%) patients had secondary AIHA.

Out of 22 (88%) patients on corticosteroids therapy alone-injection methylprednisolone 500mg-1gm IV OD for 3 days followed by Tab prednisolone in dose of 30-

60mg for 2 weeks and gradually tapered over 4 weeks duration, 15 (60%) patients improved and are on regular follow up and 1 (4%) patient expired, 6 (24%) patient required immunosuppressive agent along with corticosteroids. Immunosuppressive agents used are cyclophosphamide, methotrexate, mycophenolate mofetil, 6-mercaptopurine, etoposide. All 6 (24%) patients on combination therapy (corticosteroid and immunosuppressive agents) improved and are on regular follow up. One patient (4%) with *Burkholderia cepacia* infection improved with intravenous antibiotics alone and another 2 (8%) patients improved with vitamin supplementation alone. In present study, 1 patient (4%) expired due to sepsis while others were on regular follow up (Figure 7).



**Figure 6: The severity grading of anaemia in patients with autoimmune hemolytic anaemia.**



**Figure 7: The various therapeutic modalities used in treatment of autoimmune hemolytic anaemia and response to them.**

## DISCUSSION

Autoimmune haemolytic anaemia is a very rare disease which is potentially fatal condition. The diagnosis is delayed generally due to varied presentation of this

disease which makes its recognition difficult. Female predominance was found in this study which was similar to previous GIMEMA study.<sup>4</sup> But in contrast to GIMEMA study, most of the patients in present study were below 40 years which is in accordance with Prabhu R et al, study.<sup>1</sup> In contrast to previous studies, 60% of present patients had severe anaemia at presentation.<sup>5</sup>

Dyspnoea, easy fatigability and hepatosplenomegaly were the most common presenting features which was similar to Zulfiqar et al study.<sup>6</sup> SLE was the leading cause of secondary AIHA in present study as seen in Zulfiqar et al study.<sup>6</sup> 4 in primary AIHA and 8 in secondary AIHA had simultaneous immune thrombocytopenia called Evans syndrome which is combination of both AIHA and immune primary thrombocytopenia. Evans syndrome is mainly caused by systemic lupus erythematosus and other lymphoproliferative syndromes.<sup>7</sup>

Out of 22 patients on steroid therapy, 15 patients improved and are on regular follow-up which concurred with Prabhu R et al study.<sup>1</sup> Zupanska et al demonstrated similar results with the most of patients responding initially, but only 19 (46%) patients of the 41 continued to respond after 3 weeks to treatment.<sup>8</sup> These studies suggested that 80% of patients respond to corticosteroids promptly; however, a proportion of responders relapse after the steroid-induced remission. Petz observed that about 50% of responders to corticosteroid therapy require maintenance therapy.<sup>9</sup> Six patients required steroid plus immunosuppressive therapy.<sup>1</sup> One patient with *Burkholderia cepacia* infection was given intravenous antibiotic based on culture sensitivity who improved and DAT testing was negative on his follow up. This indicates the role of this organism in causing AIHA as showed by Thomson ELS et al and Hutchison et al.<sup>10,11</sup> One elderly male AIHA patient diagnosed to have unilineage MDS which was in accordance with Zulfiqar, et al study which states that lymphoproliferative disorders are the main cause for AIHA in elderly patients.<sup>6</sup>

More than 60% of current patients have severe anaemia, but none received blood transfusion which was in contrast to Prabhu R et al study where 21 out of 33 patients required transfusion.<sup>1</sup> 60% were on steroids alone, 24% were on immunosuppressive plus steroid therapy and 4% of patients with *Burkholderia cepacia* infection improved and are on regular follow up. None of the patients in present study had undergone splenectomy which was in accordance with Prabhu R et al study.<sup>1</sup> Further studies with long term follow up are required to prove efficacy of corticosteroids and immunosuppressive therapy and to establish treatment guidelines for AIHA in future.

## CONCLUSION

Present study is one among very few south Indian studies to assess the clinico-pathological profile and treatment outcomes in AIHA patients. AIHA has good prognosis if

diagnosed early. Blood transfusion is not indicated in all patients with anaemia. DAT is indicated in patients with anaemia, indirect hyperbilirubinemia and abnormal peripheral smear especially in females. AIHA may be the first manifestation of underlying disease which is treatable.

Incidence of secondary AIHA is more than primary AIHA in present study. Prevalence of AIHA is predominantly seen in young females. Nearly 50% patients with AIHA have associated immune thrombocytopenia. SLE (40%) was found to be most common cause of secondary AIHA. 60% patients responded well to steroid therapy alone. It is important for the treating physician to keep in mind the various etiologies for AIHA to differentiate between primary and secondary. Corticosteroids and immunosuppressive agents are mainstay of treatment.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Sri LI, Jagadeesan M, Nithyananthan P, Karthik PS, Kannan R, Rajendran K, et al. A study of clinicopathological profile and treatment outcomes in patients with autoimmune hemolytic anaemia. *Int J Adv Med* 2019;6:201-5.