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Research Article

Prognostic and Predictive Value of Baseline Hypogammaglobulinemia for Chronic Lymphocytic Leukemia Prognosis and Complications

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Abstract

Objectives: Hypogammaglobulinemia has been reported to predispose to infectious complications and is associated with poor prognosis. Therefore, we aimed to evaluate the predictive value of hypogammaglobulinemia for infectious complications by revealing the frequency, prognostic value in newly diagnosed CLL patients.

Methods: We retrospectively analyzed 74 CLL patients. Electronic medical records, as well as patients' files, were screened to collect the presented data. Risk assessment was performed using current Rai and Binet staging systems.

Results: Among 74 patients included in this study, 52 (70.3%) were male and 22 (29.7%) female. The most common chromosomal abnormalities was the 13q deletion (27.0%). Hypogammaglobulinemia was found in 24.3% (n=18) of the patients. The overall survival was 54,1 months. Most patients had advance disase. In our study, the incidence of infection was determined as 13.5% (n=10), and the mortality incidence was 8.1% (n=6). A positive correlation was detected between IgA levels and mean survival time (p=0.022). The mean IgG levels of patients with 17p deletion were found significantly decreased (p=0,015). Furthermore, frequency of infection in patients with hypogammaglobulinemia (33,3% vs. 7,3%; p=0.005) and mortality rate in patients with infection (50,0% vs. 3,8%; p=0.002) were found to be significantly increased.

Conclusion: We detected significantly increased infection frequency associated with hypogammaglobulinemia in addition to increased infection-related mortality rates. A significant correlation between increased IgA levels and prolonged survival was shown. Moreover, significantly decreased IgG levels were found in patients with 17p deletion, which is a well-known poor prognostic factor.

Keywords: Chronic lymphocytic leukemia, hypogammaglobulinemia, prognosis

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Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by the accumulation and proliferation of non-functional, mature B lymphocytes in the peripheral blood, bone marrow, spleen, liver, and lymphoid tissues.[1] CLL is a typical disease of advanced age with a median age at diagnosis of 70 years. The male pa-

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tients are at higher risk than female patients with poorer survival rates and treatment responses.[2] CLL is the most common leukemia in western countries with unknown etiology. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), approximately 20,940 new cases were reported in 2018 in the United States.[3]

The clinical course of this CLL is heterogeneous, ranging from indolent to fatal-aggressive forms. Numerous prognostic factors such as advanced age, gender, stage, lymphocyte count, lymph node involvement, chromosome abnormalities (trisomy 12, 11q deletions and 17p deletions), β2-microglobulin level (β2 M), thymidine kinase, mutation status (IgVH, TP53 mutations) have predictive value in treatment response and overall survival.[4] In addition, infections are the leading cause of morbidity and mortality in CLL patients.5 Although widely accepted conventional Rai and Binet staging systems are valuable tools to predict prognosis in patients, novel prognostic markers may contribute.[4]

Hypogammaglobulinemia (<700 mg/dL), chemo-immunotherapy, dysfunction in T cells, complement system and neutrophils have been reported to predispose to infectious complications.6 The frequency of hypogammaglobulinemia in CLL ranges from 20% to 70%. Moreover, hypogammaglobulinemia has been controversially associated with poor prognosis and survival rates.[7] Therefore, we aimed to evaluate the predictive value of hypogammaglobulinemia for infectious complications by revealing the frequency, prognostic value, and effect on overall survival rates in newly diagnosed CLL patients. As a secondary aim we wanted to assess if chromosomal abnormalities affected hypogammaglobulinemia seen in these patients.

Methods

Patients

Two hundred patients diagnosed with CLL, between January 1991 and April 2020 according to the NCIWG / IWCLL criterias were screened. Subjects with known immunodeficiency and <18 years old were excluded. A total of 74 patients whose immunoglobulin subgroup test results were available were enrolled in the study. In addition to the physical examination findings and demographic characteristics of patients, the results of laboratory tests such as complete blood count, routine biochemistry, peripheral smear, presence of B symptoms, as well as findings of imaging, cytogenetic examination, flow cytometry, histopathological evaluation, treatment regimens and survival data obtained during the application, follow-up and treatment period were recorded. Risk assessment was performed using current Rai and Binet staging systems. Some of the patients (n=42) were decided to be followed without treatment after the staging and evaluation at the time of diagnosis. Fludarabine-Cyclophosphamide-Rituximab (FCR), Ibrutinib, Endoxan, Cyclophosphamide-Oncovin-Prednisone (COP) and Rituximab-bendamustine protocols were administered in patients (n=27) who received therapy. The study was approved by Istanbul Medical Faculty Ethical Committee (11.09.2018 nr141-2018).

Serum Immunoglobulin Level Analysis

An immunological autoanalyser performed the analysis of serum IgG, IgA, IgM levels via a nephelometric method (Beckman Coulter Unicel DXI 800, Brea, CA, USA). IgG <700 mg/dL level was accepted as hypogammaglobulinemia.

Statistical Analysis

Individual and aggregate data were summarized using descriptive statistics, including mean, standard deviations, medians (min-max), frequency distributions and percentages. The Kolmogorov-Smirnov test verified the normality of data distribution. A comparison of the variables with normal distribution was made with the Student's t-test. For the variables which were not normally distributed, the Mann Whitney and Kruskal Wallis tests were conducted to compare between groups. Evaluation of categorical variables was performed by Chi-Square test. The presence of correlation was analysed with Spearman's Rho or Pearson tests. P-Values of less than 0.05 were considered statistically significant. SPSS (Statistical Package for the Social Sciences) software for Windows (v21.0; IBM, Armonk, NY, USA) was used.

Results

Seventy-four patients were included in this study. Fifty-two (70.3%) were male and 22 (29.7%) were female. The mean age was 60,4 (Range: 38-84) years. Fifty cases (67.5%) were in the 50-70 aged group. The clinical characteristics of CLL patients were presented in Table 1. According to the evaluation of immunodeficiency state; the mean values of IgG, IgA, and IgM in patients were 924.13 (Range: 115,0-2250,0) mg/dl, 136.57 (Range: 0,2-456,0) mg/dl and 126.53 (Range: 3,0-2131,0) mg/dl respectively and hypogammaglobulinemia (IgG <700 mg/dl) was detected in 24.3% (n=18) of patients.

The follow-up time of patients was 54,1 months (Range = 0,47-347,5 months) in our study. The incidence of infection was 13.5% (n=10) and 80% (n=8) of the infections were reported as pneumonia. The mortality rate was 8.1%

Table 1. Clinical characteristics of CLL patients

	Clinical Variables	n	%
Age	Mean±SD	-	60.43±10.09
Gender	Female	22	29.7
	Male	52	70.3
Rai Staging	Stage 0	33	44.6
	Stage 1	18	24.3
	Stage 2	15	20.3
	Stage 3	3	4.1
	Stage 4	1	1.4
Binet Staging	A	46	62.2
	B	10	13.5
	C	14	18.9
CD20	Negative	3	4.1
	Positive	34	45.9
CD19	Negative	1	1.4
	Positive	48	64.9
CD5	Negative	4	5.4
	Positive	40	54.1
CD23	Negative	4	5.4
	Positive	38	51.4
Del-13q	Negative	18	24.3
	Positive	20	27.0
Del-17p	Negative	39	52.7
	Positive	2	2.7
Del-11q	Negative	31	41.9
	Positive	5	6.8
Trizomi 12	Negative	19	25.7
	Positive	4	5.4
B symptom	Absent	54	73.0
	Present	20	27.0
Baseline Lymphocyte ($x10^9$/L)	Mean±SD	-	43.2±58.8

(n=6). In 32.4% (n=24) of the patients, a chromosomal abnormality was reported. The mean survival time for cases with 13q deletion (74,8 months) was found to be significantly longer than patients without 13q deletion (40,8 months) (p=0.011). There were no statistically significant differences found in survival time according to the gender, Binet-Rai staging, presence of B symptoms, del-17p, del-11q, trisomy 12, initial leukocyte counts, hypogammaglobulinemia, treatment and infection status (p>0.05) (Table 2).

In addition, there was a positive statistically significant correlation detected between IgA levels and mean follow-up time (r=0.269, p=0.022). Similarly, there was a positive, statistically significant correlation between CD23 levels and mean follow-up time (r=0.439, p=0.007). There was also a negative statistically significant correlation between patients' age and survival time (r=-0.266, p=0.024). In our study, no statistically significant correlation was found between follow-up time and initial lymphocyte levels, IgM, IgG, percentages of CD5, CD19, CD20, and CD38 (Fig. 1).

Hypogammaglobulinemia was found in 50% of the patients (n=6) who died during follow-up. Additionally, 23.1% of patients with hypogammaglobulinemia and 6.4% of patients without hypogammaglobulinemia died (p=0,109) (Fig. 2). In addition, 33.3% of the patients with hypogammaglobulinemia were complicated with an infection during the follow-up time. Therefore, the frequency of infections in patients with hypogammaglobulinemia was found to be significantly higher compared to patients without infection (7,3%) (p=0,005). Moreover, mortality rates were found to be statistically significantly higher in cases with infection (50.0%) compared to cases without infection (3.8%) (p=0,002) (Log Rank=0,008). However, staging at the time of diagnosis was not significantly associated with hypogammaglobulinemia (p>0.05) (Table 3). Furthermore, the mean IgG levels of patients with 17p deletion (521,50±mg/dl) was found to be significantly lower than patients without 17p deletion (988,20±mg/dl) (p=0,015) (Table 4).

Discussion

CLL is a heterogeneous disease and it may remain asymptomatic for decades or show rapid and fatal clinical progression. CLL is accepted as an advanced age disease, and the male/female ratio is reported as 1.7/1; moreover, the incidence of the disease increases rapidly after the fourth decade.[2,3] It was reported that half of the 15,000 new cases annually in the USA are older than 71 years. In addition, more than 70% of the newly diagnosed cases are aged over 65 years.[8] Similarly, Kumar et al. reported 59.26% male, 40.74% female, and the mean age of 69 in a study consisting of 38,754 CLL patients.[9] By these data, the 74 patients included in our study were 70.3% male, 29.7% female, and the mean age of patients was 60,43±10,09 years. It was also determined that 67.5% of the cases were in the 50-70 aged group. In addition, there was a negative statistically significant correlation found between age and survival time.

One of the significant issues in the management of the CLL is to predict the highly heterogeneous characteristics of prognosis and follow-up at diagnosis.10 In addition, the most common chromosome abnormalities identified in CLL cases is 13q deletion with a rate of 40-50%, followed by 11q deletion (17-20%) 17p deletion (7-10%) in the literature.[4] When the survival data were evaluated regarding chromosome abormalities, the median life expectancy is 2-3 years in patients with del17p, 6-7 years in patients

Table 2. Comparison of patients' clinical characteristics and survival times

	Clinical Variables	n (%)	Survival (month) (Mean±SD)	p
Gender	Female	22 (29.7)	63.87±57.80	0.280
	Male	52 (70.3)	50.02±64.35	
Binet Staging	A	46 (62.2)	67.68±72.47	0.098
	B	10 (13.5)	30.14±23.97	
	C	14 (18.9)	34.75±36.62	
Rai Staging	Stage 0	33 (44.6)	70.07±80.46	0.591[a]
	Stage 1	18 (24.3)	49.90±46.66	
	Stage 2	15 (20.3)	37.79±36.33	
	Stage 3	3 (4.1)	31.00±21.07	
	Stage 4	1 (1.4)	31.00	
B symptom	Absent	26 (35.1)	42.65±38.40	0.160
	Present	20 (27.0)	63.22±52.01	
Del-13q	Negative	18 (24.3)	40.89±50.87	0.011*
	Positive	20 (27.0)	74.83±61.50	
Del-17p	Negative	39 (52.7)	57.42±58.29	0.585
	Positive	2 (2.7)	24.91±8.60	
Del-11q	Negative	31 (41.9)	55.94±50.50	0.563
	Positive	5 (6.8)	89.74±102.7	
Trizomi 12	Negative	19 (25.7)	55.99±64.86	0.620
	Positive	4 (5.4)	31.00±24.35	
Baseline Lymphocyte	5-20.000/10^9/L	13 (17.6)	43.30±49.10	0.329
	20-50.000/10^9/L	34 (45.9)	50.60±50.90	
	50-100.000/10^9/L	10 (13.5)	93.94±101.1	
	>100.000/10^9/L	11 (14.9)	54.18±73.36	
Hypogammaglobulinemia	Negative	55 (74.3)	59.34±84.15	0.781
	Positive	18 (24.3)	53.42±54.51	
Treatment	Absent	42 (56.8)	54.26±66.99	0.302
	Present	27 (36.5)	58.48±60.06	
Infections	Absent	64 (86.5)	52.70±64.63	0.274
	Present	10 (13.5)	63.37±47.36	

*= p<0.05 statistically significant; a= Stage 4 (n=1) excluded. Kruskal Wallis analysis.

with del11q, 9 years in patients with trisomy 12, and 11 years in patients with del13q alone in CLL cases.[11] On the other hand, detecting monoallelic or biallelic 13q deletion alone is associated with a good prognosis.[4] Glassman et al. reported 28% of chromosomal abnormalities in 100 patients diagnosed with CLL11. Additionally, the most common chromosome abnormalities reported are 13q deletion with a rate of 40%, followed by 11q deletion (23%) and 17p deletion (12%) in these cases. The researchers significantly associated the presence of 11q (mean 79 months) and 17p (mean 32 months) deletions with rapid progression and short survival and the presence of 13q deletion (mean 133 months) with prolonged survival and good prognosis.[11] Similarly, in a study consisting of 86 CLL patients, Giertlova et al. reported del13q as the most frequent chromosome abnormality with a rate of 31%. The researchers also documented significantly shorter survival times in cases with del17p, del11q and trisomy 12 abnormalities (10, 12 and 14 months, respectively) and significantly longer survival time in cases with del13q (p=0.027).[12] By published data, the chromosomal abnormality incidence was 32.4% in our study. The most common chromosome abnormalities detected in our study were 13q deletion with a rate of 27,0%, followed by 11q deletion (6,8%) and trisomy 12 (5,4%). The mean survival time was significantly longer in patients with 13q deletion than patients without 13q. Furthermore, the mean IgG levels of patients with 17p deletion significantly decreased than patients without 17p deletion. Considering the increase of hypogammaglobulinemia-associated infection and

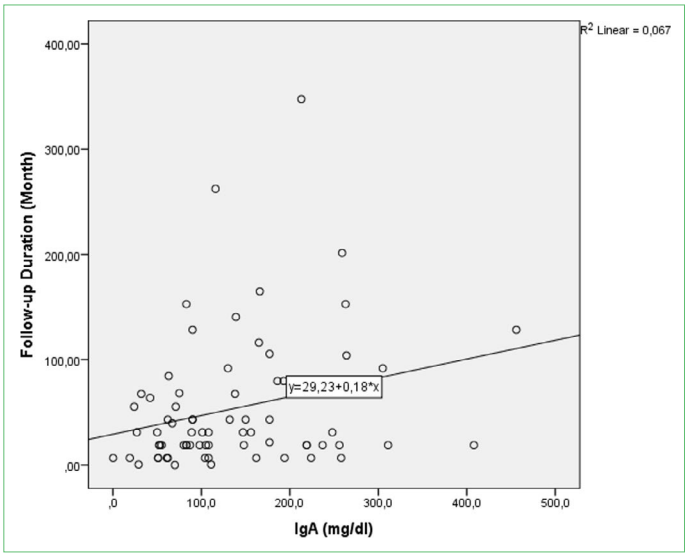

Figure 1. Correlation between IgA and survival time in patients.

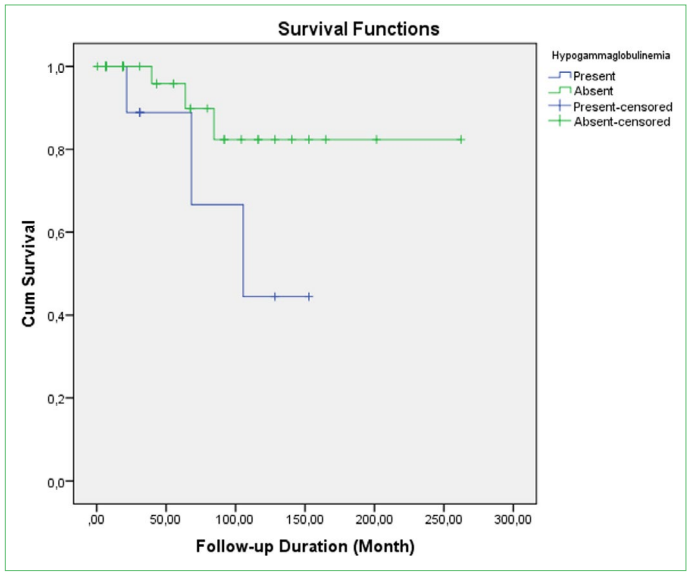

Figure 2. Hypogammaglobulinemia associated survival data (Log Rank=0,095).

mortality rates, it has been confirmed that 17p deletion has a predictive value for a poor prognosis.

Hypogammaglobulinemia is known as the most common immune deficiency documented in CLL cases. However, the relationship between hypogammaglobulinemia-related infection and infection-related mortality is controversial in published data.[12] The hypogammaglobulinemia incidence was reported 26% in a study conducted by Parikh et al. with 1485 CLL patients. Researchers significantly associated hypogammaglobulinemia with advanced stage at the time of diagnosis and decreased overall survival.[13] Similarly, Umit et al. documented significantly decreased overall survival times in the presence of hypogammaglobulinemia (42,2 months vs 61.3 months) in their study consisting of 104 CLL patients aged 65 and older.[14] Murru et al. detected at least one infection in 60% of 211 randomly selected CLL patients. Researchers reported that IgA levels decreased significantly in patients with infection. Moreover, researchers also noted that in patients with important infection history (24%), both IgA and IgG levels were significantly lower at the time of diagnosis (p-values = 0.01 and 0.006, respectively).[15]

On the contrary, Svensson et al. concluded that hypogammaglobulinaemia did not cause a significant increase in infection rates (79.5% vs 79.1%, p=0.706) and may not contribute as a routine predictive marker for infection risk in a study that included 111 CLL patients.[16] Similarly, Parikh et al. detected hypogammaglobulinemia in 26% of 1485

Table 3. Comparison of the prognostic factors associated with hypogammaglobulinemia

	Clinical Variables	Hypogammaglobulinemia (-) n (%)	Hypogammaglobulinemia (+) n (%)	p
Exitus	Alive	44 (93.6)	10 (76.9)	0.109
	Exitus	3 (6.4)	3 (23.1)	
İnfection	Absent	51 (92.7)	12 (66.7)	0.005*
	Present	4 (7.3)	6 (33.3)	
Binet Staging	A	37 (68.5)	9 (56.3)	0.667
	B	7 (13.0)	3 (18.8)	
	C	10 (18.5)	4 (25.0)	
Rai Staging	0	27 (50.0)	6 (37.5)	0.451
	1	14 (25.9)	4 (25.0)	
	2	11 (20.4)	4 (25.0)	
	3	1 (1.9)	2 (12.5)	
	4	1 (1.9)	0 (0.0)	

*= p<0.05 statistically significant.

Table 4. Comparison of IgG levels and clinical characteristics

	Clinical characteristics	n (%)	IgG (Mean±SD)	p
Gender	Female	22 (29.7)	981.4±265.9	0.327
	Male	52 (70.3)	899.8±346.5	
B symptom	Absent	26 (35.1)	962.6±228.4	0.444
	Present	20 (27.0)	904.7±279.9	
CD20	Negative	18 (24.3)	1001.3±88.9	0.665
	Positive	20 (27.0)	925.05±297.4	
CD5	Negative	18 (24.3)	732.00±343.6	0.145
	Positive	20 (27.0)	941.00±261.6	
CD23	Negative	18 (24.3)	1034.2±452.3	0.438
	Positive	20 (27.0)	920.00±257.9	
Del-13q	Negative	18 (24.3)	949.72±265.5	0.761
	Positive	20 (27.0)	975.80±258.3	
Del-17p	Negative	39 (52.7)	988.20±257.4	0.015*
	Positive	2 (2.7)	521.50±36.06	
Del-11q	Negative	31 (41.9)	976.25±249.0	0.845
	Positive	5 (6.8)	951.00±370.7	
Trizomi 12	Negative	19 (25.7)	984.36±212.9	0.788
	Positive	4 (5.4)	1023.2±444.7	
Treatment	Absent	42 (56.8)	918.3±352.1	0.721
	Present	27 (36.5)	947.7±298.8	
Exitus	Alive	64 (86.5)	950.03±334.6	0.172
	Exitus	10 (13.5)	750.50±345.87	

*= p<0.05 statistically significant.

a= Stage 4 (n=1) excluded. Kruskal Wallis analysis.

CLL patients and concluded that the presence of hypogammaglobulinemia did not have a significant effect on overall survival.[7] Andersen et al. reported infection in 16% of 159 newly diagnosed CLL patients, but they could not establish a significant relationship between hypogammaglobulinemia and infectious complications.[17] On the other hand, Visentin et al. highlighted that immunoglobulin replacement therapy (IgRT) significantly decreased the incidence of major infections of patients with high-risk major infection findings in their study, including 706 CLL cases.[18] Correlated with these published data, the hypogammaglobulinemia incidence was 24,3%, and infection incidence was 13.5% in our study. Additionally, 23.1% of patients with hypogammaglobulinemia and 6.4% of patients without hypogammaglobulinemia died (p=0,109). Hypogammaglobulinemia was found in 50% of the patients that died. Of the patients, 33.3% with hypogammaglobulinemia were found to be complicated with an infection. Therefore, the frequency of infections in patients with hypogammaglobulinemia was significantly higher than in patients without infection (7,3%). Moreover, mortality rates were found to be statistically higher in cases with infection (50.0%) compared to cases without infection (3.8%). Furthermore, the mean IgG levels of patients with 17p deletion were found as significantly lower than patients without 17p deletion (p=0.015).

In addition to decreased IgG levels, decreased IgA and IgM levels have also been associated with poor prognosis and shorter survival time in the literature. Decreased IgA and IgM level incidence has been reported between 12%-68% and 4%-56% respectively in the literature. Ishdorj et al. noted that decreasing levels of both IgG and IgA are independent prognostic markers for infection. Additionally, researchers concluded that IgG and IgA have predictive value for disease progression and survival in their study involving 511 CLL patients.[19] Čolović et al. reported decreased IgG levels in 21.2%, IgA in 31% and IgM in 24.2% of 66 CLL patients in their study.[20] Supportively, in our study, there was a positive statistically significant correlation detected between IgA levels and mean survival time.

In conclusion, significantly increased infection frequency associated with hypogammaglobulinemia and also increased infection-related mortality rates have been found in our study. Additionally, a significant correlation was assessed between increased IgA levels and prolonged survival times. Moreover, significantly decreased IgG levels were found in the presence of 17p deletion, which is well known as a poor prognostic factor. Thus, the predictive biomarker value of hypogammaglobulinemia on infection complications, infection-related mortality risk, poor prognosis, and survival rates has been demonstrated in patients diagnosed with CLL. Therefore, we can conclude that the addition of serum immunoglobulin tests to the routine initial workup of CLL patients may contribute to predict survival and infectious complications.

Limitations

In our study, we have examined a limited number of samples and conducted a retrospective study. Thus, some patients serum immunoglobulin subgroup tests and cytogenetic examinations were missing in our study sample group.

Disclosures

Ethics Committee Approval: The study was approved by Istanbul Medical Faculty Ethical Committee (11.09.2018 nr141-2018).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – F.K.; Design – F.K., M.B.; Supervision – M.N.; Materials – M.H., Y.C.; Data collection and/ or processing – F.K., S.G., F.A., A.A.; Analysis and/or interpretation – M.B., N.S., M.H.; Literature search – F.K., A.A.; Writing – F.K., M.B.; Critical review – M.N.

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