Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0089

IgG-defined hypogammaglobulinemia at diagnosis and survival outcomes in diffuse large B-cell lymphoma[a]

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Cite this article: Öztekin S, Ataş Ü, Iltar U, Yücel OK, Salim O, Ündar L. IgG-defined hypogammaglobulinemia at diagnosis and survival outcomes in diffuse large B-cell lymphoma. *J Curr Hematol Oncol Res.* 2026;4(3):93-98. doi:10.51271/JCHOR-0089

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Received: 30/03/2026 ◆ **Accepted**: 22/06/2026 ◆ **Published**: 08/08/2026

ABSTRACT

Aims: To evaluate the prognostic value of hypogammaglobulinemia at diagnosis in patients with diffuse large B-cell lymphoma (DLBCL) and its association with clinical characteristics and survival outcomes.

Methods: A total of 177 adult patients with newly diagnosed DLBCL and available serum immunoglobulin G (IgG) levels were retrospectively analyzed. IgG-defined hypogammaglobulinemia was defined as IgG <700 mg/dl at diagnosis.

Results: IgG-defined hypogammaglobulinemia was identified in 27 patients (15.3%). There were no significant differences between patients with and without IgG-defined hypogammaglobulinemia in terms of age and gender distribution. However, IgG-defined hypogammaglobulinemia was associated with more frequent B symptoms, extranodal involvement, elevated lactate dehydrogenase levels, poor Revised International Prognostic Index (R-IPI) scores, lower serum albumin levels, and a higher rate of infections during follow-up. The median follow-up time was 33 months (range, 0,1-166 months). Patients with IgG-defined hypogammaglobulinemia had significantly shorter progression-free survival (PFS) (p=0.044) and overall survival (OS) (p=0.001). In univariable analysis, IgG-defined hypogammaglobulinemia, ECOG performance status >1, poor R-IPI score, low albumin levels, presence of B symptoms, bone marrow involvement, and infection during follow-up were associated with inferior survival outcomes. In multivariable analysis, IgG-defined hypogammaglobulinemia was not an independent prognostic factor for PFS but remained independently associated with OS in the model including R-IPI.

Conclusion: IgG-defined hypogammaglobulinemia at diagnosis may be associated with inferior survival outcomes in patients with DLBCL. Further prospective multicenter studies are needed to clarify its independent prognostic significance and potential role in risk stratification.

Keywords: Diffuse large B-cell lymphoma, IgG-defined hypogammaglobulinemia, immunoglobulin G, prognosis, survival

Presented as an oral presentation at the 46th Ulusal Hematoloji Kongresi, Turkiye, October 28-31, 2020.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin lymphoma (NHL) and represents a clinically, morphologically, and biologically heterogeneous disease.[1] Prognostic assessment in DLBCL is commonly based on clinical variables such as age, serum lactate dehydrogenase levels, performance status, disease stage, and extranodal involvement, which are incorporated into the International Prognostic Index (IPI), as well as the rituximab-era adaptations including the revised IPI (R-IPI) and NCCN-IPI.[2-4] However, these models still have limitations, particularly in individual risk stratification in the rituximab era.

In this context, molecular features have gained increasing importance. Gene expression profiling has identified germinal center B-cell-like and activated B-cell-like subtypes, while cell-of-origin classification using the Hans algorithm and genetic alterations such as MYC, BCL2, and/or BCL6 rearrangements have been shown to significantly influence prognosis and therapeutic approaches in DLBCL.[5-10] In addition, several other biomarkers, including MYC, TP53, CD5, Ki-67 proliferation index, and beta-2 microglobulin, have also been investigated for their prognostic relevance.[11,12] These findings highlight the ongoing need for novel prognostic markers that are non-invasive, easily accessible, and cost-effective, in addition to existing clinical scoring systems.

In the current literature, hypogammaglobulinemia has been well characterized in chronic lymphocytic leukemia and certain indolent lymphoma subtypes, where it is primarily associated with an increased risk of infections

and adverse clinical outcomes.[13-15] More recently, there has been growing interest in the role of immune dysfunction and immunoglobulin levels in B-cell lymphomas. In patients with NHL, low pre-treatment immunoglobulin levels have been associated with increased mortality and hospitalization rates.[16]

In DLBCL, however, data remain limited. Earlier studies have mainly focused on secondary hypogammaglobulinemia following rituximab-based therapy and its association with infections.[17,18] In contrast, a limited number of recent studies defining hypogammaglobulinemia as a decrease in any immunoglobulin class at diagnosis have reported a prevalence of approximately 20% and suggested an association with inferior progression-free and overall survival (OS).[19-21]

In this study, we aimed to evaluate the prognostic value of IgG-defined hypogammaglobulinemia, whose role in DLBCL remains incompletely defined, in conjunction with other clinical and laboratory parameters.

METHODS

The study was approved by the Clinical Researches Ethics Committee of Akdeniz University Faculty of Medicine (Date: 04.03.2020, Decision No: 245). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Adult patients (≥18 years) diagnosed with DLBCL and treated with rituximab-based first-line immunochemotherapy (R-CHOP or R-mini-CHOP) at the Hematology Department of Akdeniz University Faculty of Medicine Hospital between October 2007 and December 2019 were retrospectively evaluated. To maintain a relatively homogeneous treatment cohort, patients with primary mediastinal B-cell lymphoma, primary bone lymphoma, central nervous system involvement, or other high-risk subtypes requiring alternative frontline treatment approaches (e.g., DA-R-EPOCH) were excluded from the study. Eligible patients with complete clinical and laboratory data were included in the study.

Data were collected from patient records, the electronic hospital database, hematology clinic records, the central laboratory database, the pathology archive system, and the National Death Notification System. Demographic and clinical characteristics of patients with DLBCL were recorded, including gender, age, Eastern Cooperative Oncology Group (ECOG) performance status, date of diagnosis, presence of bulky disease, bone marrow involvement, Ann Arbor stage, B symptoms, presence and number of extranodal sites, and serum levels of lactate dehydrogenase (LDH), albumin, and beta-2 microglobulin. Serum immunoglobulin G (IgG) levels at diagnosis were also recorded.

The R-IPI score was calculated using baseline clinical data. Treatment regimens, response to first-line therapy according to the International Working Group response criteria, presence and timing of relapse, date of last follow-up, and final status (remission, relapse, or death) were documented.

IgG-defined hypogammaglobulinemia was defined as a serum IgG level below the lower limit of normal (<700 mg/dl). Progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death from any cause. OS was defined as the time from diagnosis to death from any cause or last follow-up. During follow-up, a total of 63 progression events and 37 deaths were observed and constituted the events for the PFS and OS analyses, respectively.

Statistical Analysis

All data analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as frequencies and percentages for categorical variables, and as mean±standard deviation or median (minimum–maximum) for continuous variables, as appropriate. Associations between categorical variables were evaluated using the Chi-square test or Fisher's exact test, as appropriate. Comparisons of continuous variables between groups were performed using parametric or non-parametric tests according to data distribution.

Survival analyses were conducted using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to identify prognostic factors associated with PFS and OS. The proportional hazards assumption was assessed for all Cox regression models and was found to be satisfied. Model adequacy was assessed during construction of the Cox regression models and was considered acceptable. Two separate multivariable models were constructed. Model 1 included age, ECOG performance status, serum albumin level, and IgG-defined hypogammaglobulinemia. Potential collinearity was evaluated during model construction. Because the R-IPI score incorporates age, serum LDH level, performance status, disease stage, and extranodal involvement, these variables were not entered simultaneously into the same model to minimize collinearity. Therefore, model 2 included the R-IPI risk group, serum albumin level, and IgG-defined hypogammaglobulinemia. Variables were selected based on clinical relevance and the results of univariable analyses. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 210 patients screened, 33 were excluded because of missing baseline IgG measurements, incomplete clinical data, or treatment other than rituximab-based first-line immunochemotherapy (R-CHOP or R-mini-CHOP), resulting in a final cohort of 177 patients. Among the included patients, IgG-defined hypogammaglobulinemia (IgG <700 mg/dl) was identified in 27 (15.3%), whereas 150 (84.7%) had normal IgG levels. Detailed demographic, clinical, and laboratory characteristics of the patients are summarized in **Table 1**.

There were no significant differences between patients with and without IgG-defined hypogammaglobulinemia in terms of age and sex distribution. However, the proportion of patients with ECOG performance status >1 and poor R-IPI scores, as well as the presence of B symptoms, extranodal involvement, and elevated LDH levels, were higher in the IgG-defined hypogammaglobulinemia group. In addition,

Table 1. Baseline characteristics according to IgG-defined hypogammaglobulinemia (IgG <700 mg/dl)

Variable	Non-HG (n=150)	HG (n=27)	p
Age, years, median (IQR)	58 (21)	64 (26.8)	0.290
Female gender, n (%)	70 (46.7%)	12 (44.4%)	0.831
ECOG >1, n (%)	26 (17.3%)	11 (40.7%)	0.006
Stage III–IV, n (%)	88 (59.1%)	22 (81.5%)	0.082
B symptoms, n (%)	66 (44.0%)	19 (70.4%)	0.012
Extranodal involvement, n (%)	81 (54.0%)	21 (77.8%)	0.021
Elevated LDH, n (%)	101 (67.3%)	24 (88.9%)	0.024
Poor R-IPI, n (%)	63 (42.0%)	17 (63.0%)	0.044
Albumin, g/dl, median (IQR)	4.0 (0.8)	3.2 (1.0)	<0.001
Beta-2 microglobulin, mg/L, median (IQR)	3.0 (2.4)	3.25 (2.7)	0.095
Total protein, g/dl, median (IQR)	6.8 (1.0)	5.0 (1.3)	<0.001
Globulin, g/dl, median (IQR)	2.8 (0.8)	1.9 (0.6)	<0.001
Ki-67 ≥80%, n (%)	50 (33.3%)	11 (40.7%)	0.814
Non-GCB subtype, n (%)	32 (21.3%)	7 (25.9%)	0.881
Febrile neutropenia, n (%)	39 (26.0%)	9 (33.3%)	0.442
≥1 Infection episode, n (%)	29 (19.3%)	14 (51.9%)	<0.001
R-min-CHOP, n (%)	6 (4.0%)	3 (11.1%)	0.110
Treatment response, n (%)			0.028*
CR	101 (67.3)	10 (37.0)	
PR	25 (16.6)	6 (22.2)	
PD	11 (7.3)	5 (18.5)	

IgG: Immunoglobulin G, HG: Immunoglobulin G-defined hypogammaglobulinemia, IQR: Interquartile range, ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase, R-IPI: Revised International Prognostic Index, Non-GCB: Non-germinal center B-cell, CR: Complete response, PD: Progressive disease, PR: Partial response
*Fisher exact test used for treatment response comparison.

albumin, total protein, and globulin levels were significantly lower in patients with IgG-defined hypogammaglobulinemia. Although the frequency of stage III–IV disease was higher in this group, the difference did not reach statistical significance. Patients with IgG-defined hypogammaglobulinemia had higher frequency of ≥1 infection episode during follow-up. There were no significant differences between the groups regarding beta-2 microglobulin levels, Ki-67 index, non-germinal center B-cell (non-GCB) subtype, incidence of febrile neutropenia, or use of R-mini-CHOP.

During follow-up, the rate of experiencing at least one infection episode was significantly higher in the IgG-defined hypogammaglobulinemia group. Although the complete response (CR) rate after first-line therapy was lower and the rate of progressive disease (PD) was higher in patients with IgG-defined hypogammaglobulinemia, these differences did not reach statistical significance.

The median follow-up time was 33 months (range, 0.1-166 months). Kaplan–Meier survival analysis demonstrated that the presence of IgG-defined hypogammaglobulinemia at diagnosis was associated with inferior PFS and OS. Patients with IgG-defined hypogammaglobulinemia had significantly shorter PFS compared to those without IgG-defined hypogammaglobulinemia (log-rank p=0.044) (**Figure 1a**). Similarly, OS was significantly shorter in the IgG-defined hypogammaglobulinemia group (log-rank p=0.001) (**Figure 1b**).

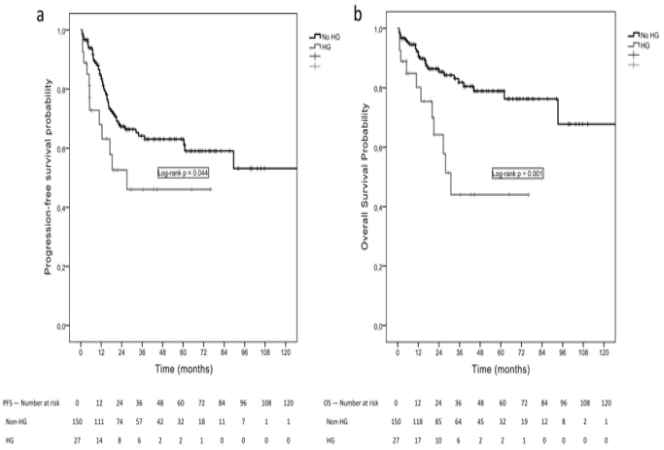

Figure 1. Kaplan–Meier curves of progression-free survival (PFS) **(a)** and overall survival (OS) **(b)** according to baseline IgG-defined hypogammaglobulinemia status (IgG <700 mg/dl).
IgG: Immunoglobulin G, HG: Hypogammaglobulinemia, PFS: Progression-free survival, OS: Overall survival

In univariable Cox regression analysis, IgG-defined hypogammaglobulinemia was associated with inferior PFS and OS. ECOG performance status >1, poor R-IPI score, low serum albumin levels, presence of B symptoms, and bone marrow involvement were also associated with adverse survival outcomes. Elevated LDH levels were significantly associated with OS but not with PFS. Increasing age was associated with PFS, whereas its association with OS did not reach statistical significance. The results of the univariable analyses are summarized in **Table 2**.

In multivariable analysis, IgG-defined hypogammaglobulinemia was not an independent prognostic factor for either PFS or OS in model 1, which included age, ECOG performance status, serum albumin, and IgG-defined hypogammaglobulinemia. In this model, only ECOG performance status >1 remained an independent adverse predictor for both PFS and OS. In model 2, which included the R-IPI risk group (a composite score incorporating age, serum LDH, performance status, disease stage, and extranodal involvement), serum albumin, and IgG-defined hypogammaglobulinemia, IgG-defined hypogammaglobulinemia was not independently associated with PFS but remained an independent adverse prognostic factor for OS. In the same model, poor R-IPI was significantly associated with both PFS and OS, while higher serum albumin levels were associated with improved OS. The results of the multivariable analysis are presented in **Table 3**.

DISCUSSION

In our study, patients with IgG-defined hypogammaglobulinemia at diagnosis had significantly shorter PFS and OS. In addition, these patients more frequently exhibited B symptoms, extranodal involvement, elevated LDH levels, poor R-IPI scores, and lower serum albumin levels, as well as a higher rate of infections during follow-up. These findings suggest that IgG-defined hypogammaglobulinemia may be associated with more aggressive disease characteristics.

DLBCL is a clinically and biologically heterogeneous disease, and prognostic assessment is commonly based on established scoring systems such as the IPI, R-IPI, and

Table 2. Univariable Cox regression analysis for PFS and OS

Variable	PFS HR (95% CI)	p value	OS HR (95% CI)	p value
IgG-defined HG	1.90 (1.01–3.57)	0.048	3.18 (1.56–6.49)	0.001
ECOG >1	4.67 (2.80–7.75)	<0.001	7.14 (3.70–13.67)	<0.001
R-IPI poor risk	2.35 (1.40–3.92)	0.001	3.53 (1.74–7.14)	<0.001
Elevated LDH	1.49 (0.82–2.71)	0.188	2.62 (1.02–6.71)	0.046
Albumin (per 1 g/dl increase)	0.61 (0.42–0.89)	0.009	0.39 (0.24–0.62)	<0.001
Age (per year increase)	1.02 (1.00–1.04)	0.025	1.02 (1.00–1.05)	0.062
B symptoms	2.59 (1.52–4.42)	<0.001	4.22 (1.93–9.26)	<0.001
Bone marrow involvement	1.86 (1.06–3.26)	0.031	2.54 (1.27–5.12)	0.009
Infection during follow-up	3.38 (2.03–5.62)	<0.001	6.67 (3.44–12.99)	<0.001

PFS: Progression-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, HG: Hypogammaglobulinemia, ECOG: Eastern Cooperative Oncology Group, R-IPI: Revised International Prognostic Index, LDH: Lactate dehydrogenase

Table 3. Multivariable Cox regression analysis for PFS and OS

Variable	PFS HR (95% CI)	p value	OS HR (95% CI)	p value
Model 1				
IgG-defined HG	1.27 (0.65–2.49)	0.476	1.69 (0.79–3.63)	0.170
ECOG >1	3.85 (2.17–6.67)	<0.001	4.63 (2.17–10.00)	<0.001
Albumin (per 1 g/dl increase)	0.85 (0.57–1.27)	0.434	0.66 (0.39–1.12)	0.121
Age (per year increase)	1.01 (0.99–1.03)	0.160	1.01 (0.99–1.04)	0.310
Model 2				
IgG-defined HG	1.58 (0.81–3.06)	0.176	2.29 (1.09–4.85)	0.030
R-IPI poor risk	2.14 (1.24–3.68)	0.006	2.73 (1.29–5.75)	0.008
Serum albumin (per 1 g/dl increase)	0.80 (0.53–1.20)	0.283	0.57 (0.34–0.96)	0.034

PFS: Progression-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, HG: Hypogammaglobulinemia, ECOG: Eastern Cooperative Oncology Group, R-IPI: Revised International Prognostic Index
Model 1 included age, ECOG performance status, serum albumin, and hypogammaglobulinemia.
Model 2 included the R-IPI risk group (which incorporates age, serum LDH, performance status, disease stage, and extranodal involvement), serum albumin, and hypogammaglobulinemia.
Variables were selected based on clinical relevance and results of univariable analysis.

NCCN-IPI.[2-4] However, the association between IgG-defined hypogammaglobulinemia and clinical outcomes observed in our study, beyond these conventional prognostic factors, suggests that existing models may be insufficient in certain patient subgroups and highlights the need for additional prognostic biomarkers.[11,12]

In chronic lymphocytic leukemia (CLL), hypogammaglobulinemia at diagnosis has been reported with variable frequencies (15-70%) and is well established to be associated with an increased risk of infections. However, its relationship with prognosis remains controversial, with some studies reporting no significant association and others identifying hypogammaglobulinemia as an independent adverse prognostic factor.[13-15,22-25] In patients with NHL, data on hypogammaglobulinemia are more limited, and most studies have focused on secondary hypogammaglobulinemia following rituximab-based therapy and its association with infection risk. These studies have demonstrated an increased risk of infections and infection-related mortality; however, the impact on survival remains largely unclear.[17,18] Notably, a recent study suggested that low pre-treatment immunoglobulin levels in NHL patients may be associated with increased mortality and hospitalization.[16] In addition, hypogammaglobulinemia in DLBCL has been shown to occur not only during treatment but also at diagnosis, where it may have clinical relevance, particularly in relation to infection risk.[26] Similarly, in our study, IgG-defined hypogammaglobulinemia at diagnosis was also associated with a higher rate of infections during follow-up.

Recent studies have suggested that hypogammaglobulinemia in treatment-naive, newly diagnosed DLBCL patients may be associated with inferior PFS and OS.[19-21] The relationship between hypogammaglobulinemia, defined as a decrease in any immunoglobulin class (IgG, IgA, or IgM), and prognosis was first evaluated by Singh et al.[19] in a cohort of approximately 200 newly diagnosed DLBCL patients. In that study, IgG-defined hypogammaglobulinemia was observed in 22% of patients, while IgG deficiency (<700 mg/dl) was reported in approximately 13.5%, and was associated with inferior survival outcomes. These findings were subsequently supported by Pan et al.[20] in a larger cohort of 553 patients, in which hypogammaglobulinemia was reported in 19% of cases and IgG-defined hypogammaglobulinemia (<700 mg/dl) in 5.0%. In that study, hypogammaglobulinemia was associated with both inferior PFS and OS. More recently, Lindberg et al.,[21] in a study including 585 patients, reported hypogammaglobulinemia in 24% and IgG-defined hypogammaglobulinemia (<700 mg/dl) in 18% of patients, demonstrating an association not only with survival outcomes but also with an increased risk of infections.

In our study, IgG-defined hypogammaglobulinemia was defined solely based on serum IgG levels, using a similar cutoff value (<700 mg/dl) as in previous studies. According to this definition, the prevalence of IgG-defined hypogammaglobulinemia was 15.3%, which is consistent with reported rates of IgG deficiency in the literature. Furthermore, we similarly demonstrated that IgG-defined hypogammaglobulinemia was associated

with inferior survival outcomes. However, patients with IgG-defined hypogammaglobulinemia also had a higher frequency of adverse baseline clinical characteristics, including poor ECOG performance status, B symptoms, extranodal involvement, elevated LDH levels, poor R-IPI scores, and lower albumin levels. Therefore, IgG-defined hypogammaglobulinemia may partly reflect higher tumor burden, systemic inflammation, or poorer general condition rather than representing a purely independent prognostic factor. Consistent with this interpretation, IgG-defined hypogammaglobulinemia was not retained as an independent predictor across all multivariable models and remained independently associated only with OS in one model. Accordingly, our findings support an association between baseline IgG-defined hypogammaglobulinemia and adverse outcomes, although causality and independent prognostic significance require further validation.

Limitations

This study has several limitations. First, the retrospective single-center design and relatively limited sample size may have affected the statistical power of some analyses and restricted the availability of certain prognostic variables. In particular, molecular markers such as MYC, BCL2, and double-hit/triple-hit status were not consistently available because of the long study period and retrospective nature of the study and therefore could not be incorporated into the multivariable analyses. Furthermore, despite efforts to minimize heterogeneity through strict inclusion criteria, temporal differences in patient management over the study period cannot be excluded. Second, hypogammaglobulinemia was defined solely based on serum IgG levels, while other immunoglobulin isotypes and subclasses were not evaluated. Therefore, our findings should be interpreted as reflecting baseline IgG deficiency rather than global hypogammaglobulinemia. Furthermore, primary immunodeficiencies were not systematically excluded in patients with hypogammaglobulinemia and changes in immunoglobulin levels during the course of treatment were not assessed. Third, infection was not a baseline variable and may have been influenced by treatment course, disease progression, and survival duration; therefore, its association with survival outcomes should be interpreted with caution. Finally, detailed data regarding salvage therapies and transplantation were not available for all patients, and their potential effect on OS cannot be excluded.

CONCLUSION

As a result, our findings support an association between IgG-defined hypogammaglobulinemia at diagnosis and inferior survival outcomes in patients with DLBCL. However, patients with IgG-defined hypogammaglobulinemia also exhibited a higher frequency of adverse baseline clinical characteristics, and our multivariable analyses did not consistently support its role as an independent prognostic factor. Therefore, larger prospective multicenter studies with more comprehensive adjustment for established prognostic variables are needed to clarify its independent prognostic significance and potential role in risk stratification.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Clinical Researches Ethics Committee of Akdeniz University Faculty of Medicine (Date: 04.03.2020, Decision No: 245).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: SÖ, OS, LÜ; Design: SÖ, ÜA, UI, OS; Control: ÜA, UI, OKY, OS; Data Collection and/or Processing: SÖ, ÜA, UI; Analysis and/or Interpretation: SÖ, ÜA, UI, OKY; Literature Review: SÖ, ÜA, UI; Article Writing: SÖ, ÜA, UI; Critical Review: OKY, OS, LÜ.

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