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Elevated serum concentrations of β-2-microglobulin are often found at the time of diagnosis of hemophagocytic lymphohistiocytosis in adults with lymphoid and myeloid malignancies

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder of immune regulation. In patients over 60 years of age, HLH associated with hematological malignancies (hM-HLH) is the most prevalent. β-2-Microglobulin (B2M) plays an important role in antigen presentation and immunological regulation. Elevated B2M levels reflect T-cell activation. **Objective:** The aim of this study was to determine serum B2M concentrations in adults with hM-HLH and to interpret its significance in the context of overall survival (OS). **Patients and methods:** Serum B2M concentration was determined in 31 adults aged 22–84 years at the time of hM-HLH diagnosis. Lymphoid malignancy was diagnosed in 22 patients and myeloid malignancy in 9 patients. **Results:** The serum concentration of B2M was elevated in 100% of the examined patients. Mean and median serum B2M concentrations were 5.3 and 4.2 mg/L, respectively (range 2–17 mg/L). We have not found any significant differences in terms of the studied serum B2M concentrations between patients with T/NK-cell lymphomas, B-cell lymphomas, and myeloid malignancies. The outcome of HLH was poor in vast majority of patients with the median OS for the entire group of 46 days. **Conclusions:** Elevated serum B2M level is a frequent finding at the time of hM-HLH diagnosis in adults. It seems to be a useful indicator of HLH for its early detection and evaluation afterward, as well as for immediate therapeutic intervention. Further prospective studies answering the question whether serum B2M can be used as a prognostic factor in hM-HLH would be of interest.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a rare disorder with both familial and acquired forms [1, 2]. It is an acute disorder of immune regulation which leads to an exaggerated inflammation. Macrophages and CD8+ cytotoxic T-cells release various pro-inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-8, IL-12, and interferon-γ [3–6]. These cytokines induce immune cells and cytokine production that culminates in cytokine storm and hyperinflammation [3, 4, 7]. In response, anti-inflammatory cytokines (IL-10, IL-18-binding protein) are produced, but they are not sufficient to mitigate the excessive immune activation [8, 9].

In general, HLH is a life-threatening syndrome and has a poor prognosis [1, 10–14]. In adult patients, acquired forms of HLH are the most prevalent [2, 14]. Malignancy-associated HLH (M-HLH) in the patients aged ≥30 years is frequent, and in the group of patients aged ≥60 years, M-HLH is the most frequent form of HLH [10]. Although the clinical presentation of HLH may be variable, the most common signs are unremitting fever, cytopenia, hepatosplenomegaly, jaundice, edema, neurological symptoms and hemophagocytosis in bone marrow (BM), liver or lymph nodes [1, 7, 14]. According to the current HLH-2004 guidelines, the diagnosis of HLH is based on a constellation of clinical and laboratory criteria [15].

β-2-Microglobulin (B2M) is a low-molecular-weight (11.8 kDa) protein synthesized in all nucleated cells and constituting the light chain subunit of the major histocompatibility complex (MHC) class I receptor [5]. B2M plays an important role in antigen presentation and regulation of tumor immunological processes. Approximately 50% of B2M is produced by lymphocytes and is freely filtered through glomerular basement membrane. Under physiological conditions B2M is produced at a constant rate. However, B2M serum levels rise in the presence of glomerular impairment or lymphocyte activation, as well as in patients with hematological malignancy or systemic inflammation [5, 16].

The aim of the present study was to determine serum B2M concentrations in adults with hematologic malignancy-associated HLH (hM-HLH) and to interpret its significance in the context of HLH therapy outcome.

Patients and methods

The study population consisted of 31 adult patients diagnosed with a hematological malignancy and HLH. The enrolled patients were admitted to the Hematology Center Karolinska, Karolinska University Hospital, between January 2009 and December 2016. A hematological malignancy was defined as a neoplasm of lymphoid or myeloid origin and the diagnosis was established according to Swedish national standards and protocols.

In all studied patients, the diagnosis of HLH was based on the criteria proposed by the Histiocyte Society (Table I) [15]. Noteworthy, these criteria were developed based on familial, inherited forms of HLH. Due to the lack of specific guidelines for M-HLH, they are also used to diagnose it.

Table I – Diagnostic criteria of HLH-2004

HLH diagnosis if (A) or (B) is met:

(A) The result of molecular diagnostics confirming the presence of mutations typical for HLH

(B) Five of the following eight criteria must be fulfilled for the diagnosis of HLH:

1. Fever
2. Splenomegaly
3. Cytopenias affecting at least two of three cell lineages:
   a. hemoglobin <90 g/L
   b. platelets $<100 \times 10^9$/L
   c. neutrophils $<1.0 \times 10^9$/L
4. Hypertriglyceridemia ≥3.0 mmol/L and/or hypofibrinogenemia ≤1.5 g/L
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent NK-cell activity
7. Hyperferritinemia ≥500 μg/L
8. Elevated concentration of soluble interleukin 2 receptor α (sIL-2Rα/sCD25) ≥2400 U/mL

However, majority of reports published on M-HLH were examined six or less HLH-2004 criteria, and as a rule without sIL-2Rα/sCD25 result and NK cells activity data [11, 14, 17]. Some authors argue that hyperferritinemia ≥10 000 μg/L is a more specific and sensitive HLH criterion [18]. Therefore, we included in this analysis all patients with suspected HLH who fulfilled at least four of six HLH-2004 criteria including at least two of three additional HLH features: sIL-2Rα ≥2400 U/mL, hemophagocytosis in BM, and hyperferritinemia ≥10 000 μg/L.

Fresh blood samples were drawn and directly analyzed at the Karolinska University Laboratory according to standard practice. The Roche B2MG Tina-Quant serum kit was used to measure serum concentrations of B2M immunoturbidimetrically; normal value of serum B2M was <2.0 mg/L. The serum ferritin concentration was assessed using Roche Modular Analyzers (Roche Diagnostics, USA). Serum concentrations of sIL-2Rα were determined by ELISA, using the quantitative 'sandwich' enzyme immunoassay, on the IMMULITE® 1000 Immunoassay System (DPC Siemens).

HLH treatment categories have included proapoptotic chemotherapy (etoposide at 50–150 mg/m^2/dose i.v.) and use of immunosuppressive drugs, targeting hyperactivated macrophages (corticosteroids, IVIG) and T cells (corticosteroids, cyclosporine A). Treatment plan was individually adopted for each patient, based on the protocol HLH-94 [19].

The patients' medical records were reviewed to collect relevant clinical data. The patients provided their informed consent. The study was performed according to the ethical guidelines of the Declaration of Helsinki.

The results are presented as a mean ± standard deviation (SD) or median and variable range. The distribution of continuous values was assessed with the Shapiro–Wilk test. Depending on the variable's distribution, *T* test or Mann–Whitney *U* test was used for comparisons between independent groups. Chi-square Pearson, Yates or Fisher tests were used for nominal values. Overall survival (OS) was estimated by the Kaplan–Meier method and compared with the log-rank test. An α-level of $p < 0.05$ was required for significance. Statistical analysis was performed using *Statistica* version 12.0 PL software.

Results

Twenty-two men (71%) and 9 women (29%), aged 28–84 years (mean and median age 61 years) were enrolled in the study. Lymphoid malignancy was diagnosed in 22 patients and myeloid malignancy in 9 patients. T-cell lymphoid malignancies included anaplastic large cell lymphoma in 2 patients, angioimmunoblastic T-cell lymphoma in 2 patients, enteropathy-associated T-cell lymphoma in 1 patient, and peripheral T-cell lymphoma not otherwise specified in 4 patients. B-cell lymphoid malignancies included follicular lymphoma in 2 patients, chronic lymphocytic leukemia (CLL) in 3 patients, diffuse large B-cell lymphoma in 3 patients, T-cell/histiocyte-rich B-cell lymphoma in 1 patient, and gray-zone diffuse large B-cell lymphoma/Burkitt lymphoma in 1 patient. Hodgkin lymphoma (HL) included lymphocyte depleted in 1 patient, not specified HL in 1 patient, composite EBV-driven HL/non-HL in 1 patient. Patient characteristics are shown in Table II.

Diagnosis of HLH criteria

Fever (median 39 °C; range 38.2–40.6 °C) was present in 28 (90%) patients. The remaining three patients had median body temperature of 37.4 °C (range 36.9–37.8 °C).

Splenomegaly occurred in 17/28 (61%) patients; one patient had earlier undergone splenectomy and in two patients a spleen size was not determined.

Examination of fine needle BM aspirates disclosed hemophagocytosis in 22/30 (73%) patients. BM examination was not performed in 1 patient.

Whole blood hemoglobin concentration (Hb) ranged from 69 to 129 g/L (ref.: 134–170 g/L). Thus, anemia was found in all patients and mean Hb was 88.6 ± 12.5 g/L. HLH-2004 criterion of Hb <90 g/L was fulfilled in 17/31 (55%) patients.

Neutropenia with neutrophils $<1.0 \times 10^9$/L was present in 12/31 (39%) patients.

Thrombocytopenia (platelets /PLT/ ref.: 145–348 $\times 10^9$/L) was revealed in 30/31 (97%) patients. Mean PLT count was 44.1 ± 46.7 $\times 10^9$/L, median PLT was 28 $\times 10^9$/L, and PLT range was 5–344 $\times 10^9$/L. HLH-2004 criterion of PLT $<100 \times 10^9$/L was fulfilled in vast majority (29/31, 93%) of studied patients.

Serum triglyceride level ≥3.0 mmol/L (ref.: 0.45–2.6) was found in 35% (11/31) of patients. Serum fibrinogen concentration (ref.: 2.0–4.2 g/L) was decreased ≤1.5 g/L in 29% (9/31) patients. However, HLH-2004 criterion of hypertriglyceridemia ≥3.0 mmol/L and/or hypofibrinogenemia ≤1.5 g/L was fulfilled in 48% (15/31) patients.

Serum ferritin concentration (ref.: 30–350 μg/L) at the time of hM-HLH diagnosis was elevated in all but one patient. Mean ferritinemia was 48 635 ± 119 886 μg/L (median 14 727 μg/L, range 96–645 291 μg/L). HLH-2004 criterion, hyperferritinemia ≥500 μg/L was met in 97% (30/31) of patients at the time of HLH diagnosis.

The level of sIL-2Rα in serum was measured in 30/31 patients and in 97% (29/30) of cases it was elevated ≥2400 U/mL.

Twenty-one patients fulfilled at least five HLH-2004 criteria and 10 patients fulfilled at least four HLH-2004 criteria (all of them presenting at least two of the following features: sIL-2Rα ≥2400 U/mL, hemophagocytosis in BM, and hyperferritinemia ≥10 000 μg/L) (Fig. 1). The incidences of tested HLH-2004 criteria for the study group are shown in Fig. 2.

Serum B2M in newly diagnosed hM-HLH

The serum concentration of B2M was elevated in all of the examined hM-HLH patients at the time of diagnosis of hM-HLH. Mean and median serum B2M concentrations were 5.3 and 4.2 mg/L, respectively (range 2–17 mg/L). We have not found any significant differences in terms of the studied serum B2M concentrations between patients with T/NK-cell lymphomas, B-cell lymphomas, and myeloid malignancies (Fig. 3).

Table II – Patient characteristics

Characteristic	Number of patients (%)
Gender	
Male	22 (71%)
Female	9 (29%)
Age at the time of HLH diagnosis (years)	
Mean ± SD	60.7 ± 14.3
Median (range)	61 (22–84)
Hematological malignancies	
Lymphoid	22 (71%)
Myeloid	9 (29%)
Lymphoid malignancies	
NK/T-cell lymphoma	9 (29%)
B-cell lymphoma	10 (32%)
Hodgkin lymphoma	3 (10%)
Myeloid malignancies	
AML	4 (13%)
MDS-AML	2 (6%)
MDS	2 (6%)
Polycythemia vera	1 (3%)

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; SD, standard deviation.

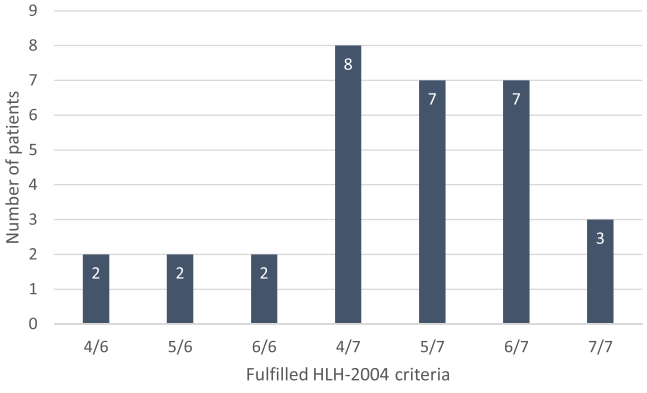

Fig. 1 – The number of examined and fulfilled HLH-2004 criteria at the time of HLH diagnosis in 31 patients with hematological malignancies

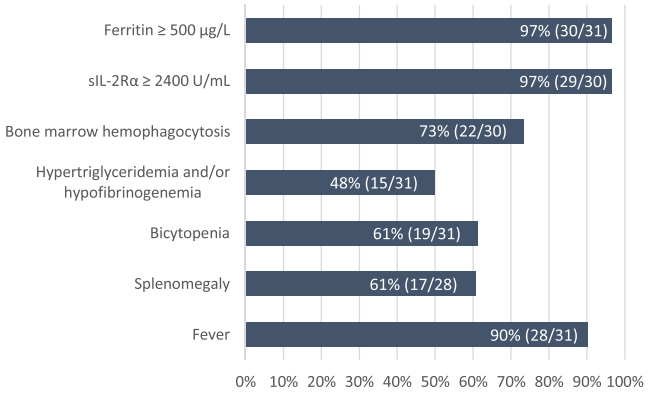

Fig. 2 – The incidence of clinical and laboratory HLH-2004 criteria in 31 patients with newly diagnosed HLH and hematological malignancy

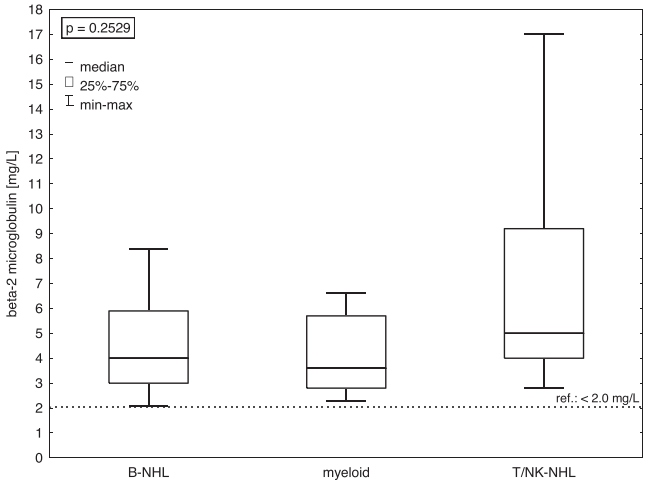

Fig. 3 – Serum B2M concentration in hM-HLH depending on background malignancy

Therapy and Outcome of HLH

In 10 patients HLH therapy started before confirmation of HLH diagnosis, based on clinical suspicion of HLH. Eight patients started HLH therapy on the day of HLH diagnosis. In 13 patients, HLH therapy started in median 4 days after the HLH diagnosis.

The median OS for the entire studied group was 46 days (Fig. 4). Probably due to the small subgroups, we have not found any significant difference in terms of survival among patients depending on their background malignancy. However, the median OS for patients with hM-HLH and B-cell lymphoma was 228 days compared with 44 days for T/NK-cell lymphoma and 40 days for myeloid malignancy (Fig. 5).

Discussion

M-HLH can occur as the first manifestation of an occult malignancy, before the start or during treatment of a known malignancy, or as the sign of a malignancy relapse or transformation to a more aggressive disease form [7, 14]. There is a rising body of evidence that M-HLH can occur in the course of all hematological malignancies, and not mainly in T/NK-cell lymphomas as it was thought previously [2, 10–14, 17, 20]. The association between serum B2M levels and HLH has previously rarely been reported, and we were able to find only a few such studies in the literature [5, 16, 21–23].

Increased concentrations of B2M were observed in patients with hematopoietic malignancies, such as multiple myeloma, CLL, and HL. Moreover, serum concentration of B2M has been shown to be an independent prognostic factor for these diseases [24–26], as well as a predictor of total mortality in a general population of older adults [27].

Elevated levels of serum B2M reflect T-cell activation [5]. In this study, we have found that serum concentrations of B2M were elevated in 100% of adult patients with hM-HLH,

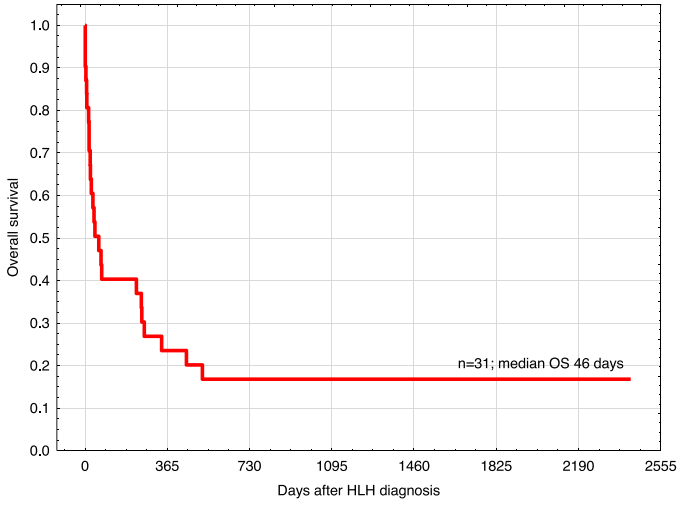

Fig. 4 – Overall survival of patients with hematological malignancies and HLH

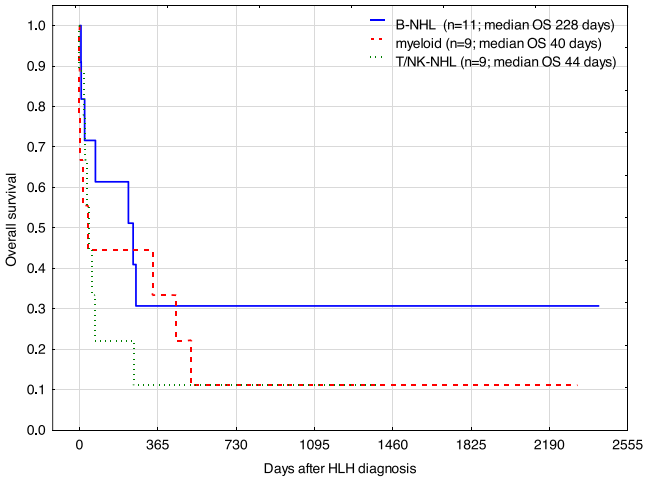

Fig. 5 – Overall survival of patients with hM-HLH depending on malignancy type

whereas their kidney functions were normal (data not shown).

Similarly, in the study by Jiang et al. the serum levels of B2M were markedly high in almost all patients with HLH, especially those with lymphoma-associated HLH (LAHS) [21]. The authors have also found that OS was significantly shorter in LAHS patients with serum B2M levels ≥4.03 mg/L compared to <4.03 mg/L ($p < 0.001$). However, we could not confirm the aforementioned results using the above cutoff for serum B2M in our cohort (Fig. 6). Based on their study, Jiang et al. proposed that serum B2M concentration was a powerful and independent prognostic factor for OS in patients with LAHS [21].

Wakabayashi et al. analyzed serum B2M levels in 23 females (aged 39 ± 16.4 years, range 16–75 years) with autoimmune-associated HLH. Sixteen patients had systemic lupus erythematosus (SLE) and 7 patients had adult-onset Still's disease (AOSD) [16]. Serum B2M concentration was

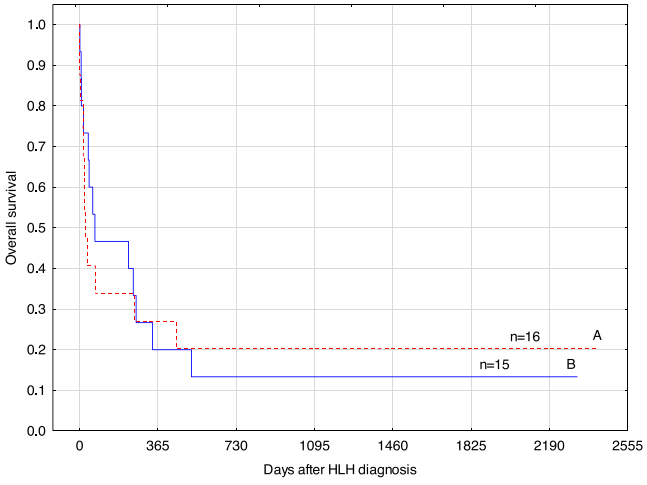

Fig. 6 – Overall survival of patients with hM-HLH in subgroups with serum B2M concentration ≥4.03 mg/L (curve A) and <4.03 mg/L (curve B)

compared between the active and inactive statuses of SLE and AOSD. The serum B2M level was high in the active status of underlying diseases and decreased significantly after the therapy (3.5 ± 1.4 vs. 2.1 ± 0.8 mg/L, $p < 0.001$). Among patients with active disease status, the B2M level was higher in 5 patients with HLH than in patients without HLH (4.9 ± 1.8 vs. 3.3 ± 1.4 mg/L, $p < 0.05$). These authors conclude that serum B2M concentration would be a useful indicator of disease activity and development of HLH in patients with SLE and AOSD [16].

In another study Kaito et al. analyzed 34 patients with HLH (5 patients had hematological malignancy; 6 patients had infections; 1 patient had SLE, AOSD, and chronic renal failure each; and 20 patients had no obvious underlying disease) [28]. They concluded that the risk factors associated with death were age >30 years, DIC, increased ferritin and B2M concentrations, and anemia accompanied by thrombocytopenia and jaundice.

In the abstract, Machowicz et al. showed that 12 of 13 patients with unspecified forms of HLH (median age 30 years, range 17–80 years) had elevated serum B2M concentrations (median 5.1 mg/L, range 1.83–15.3 mg/L) [23]. The authors speculate whether B2M could be useful as a marker of HLH activity.

The mechanism inducing secondary HLH, including M-HLH, is not fully understood. It is believed that immunological dysregulation associated with an underlying disease might be crucial [16]. It has been suggested that the levels of sIL-2Rα, which is reflective of T-cell activation, and soluble CD163, which is related to activation of phagocytic macrophages, might be useful as diagnostic markers of HLH and helpful in monitoring disease activity and response to treatment. Measurements of the levels of these factors or of cytokines such as IFN-γ, TNF-α, and IL-18 may not be easily available in a timely fashion to aid in the early diagnosis of HLH [1, 3, 4, 7]. In contrast, serum B2M concentration can be measured in common clinical laboratories of hospitals and the result can be obtained in a timely fashion [16]. Serum B2M level would be a useful indicator of HLH for its early detection and evaluation afterward, as well as for immediate therapeutic intervention.

M-HLH is a highly lethal disorder in the adult population and has the worst outcome in comparison with any other form of HLH [10, 28–32]. The present study showed that OS of adults with hM-HLH is particularly dismal. It is possible that high serum B2M concentrations indicated a high HLH and/or malignancy activity, which was responsible for a poor outcome in the present study. Although in many patients poor outcome depends on malignancy progression, in some patients the lack of effective M-HLH therapy may further impede adequate treatment of malignancy. Further prospective investigations focusing on the question whether serum B2M can be used as a marker and prognostic factor in M-HLH or generally in HLH would be of interest.

Authors' contributions/Wkład autorów

ES – assisted in study planning, gathered the clinical and laboratory data, analyzed the data, drafted the manuscript;

EP – performed statistical analysis, drafted the manuscript; CKB – assisted in study planning, drafted the manuscript; MM – planned the study, gathered the clinical and laboratory data, analyzed the data, drafted the manuscript.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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