# The prevalence and prognosis of hyponatraemia in non-Hodgkin lymphoma-associated hemophagocytic lymphohistiocytosis

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**Research Article**

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# The prevalence and prognosis of hyponatraemia in non-Hodgkin lymphoma-associated hemophagocytic lymphohistiocytosis

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## Abstract

**Background:** Non-Hodgkin lymphoma associated hemophagocytic lymphohistiocytosis (NHL-HLH) in adult secondary HLH (sHLH) is a common and universally highly lethal critical disorder. Hyponatraemia is the most common electrolyte disorder in the critical illness setting and acts as a negative prognostic factor. The aim of our study was to evaluate the prognostic role of hyponatraemia among patients with NHL-HLH.

**Methods:** This retrospective study enrolled 153 newly diagnosed adult NHL-HLH patients, which were divided into 2 groups based on serum sodium concentration on admission, a hyponatraemia and a normonatraemia group. Univariate and multivariate Cox regression analysis were used to identify the prognostic factors associated with worse survival. The overall survival time of all the patients were compared using log rank tests. Restricted cubic splines were conducted to address the association between serum sodium concentration and the risk of mortality.

**Results:** The results showed that 81 (52.9%) patients had hyponatraemia. After a median follow-up of 47 (range 14-180) days, there were 72 (88.9%) cumulative deaths in hyponatraemia group while 50 (69.4%) in normonatremia group. Univariate Cox regression analysis showed that hyponatraemia group demonstrated unfavourable overall survival ($P$ = 0.002). After adjustment for confounders, multivariate analysis revealed that hyponatraemia was an independent prognostic factor for OS (Hazard ratio [HR]:1.51, 95% confidence interval [CI]: 1.03-2.20; $P$ = 0.033). Restricted cubic spline confirmed a linear and positive association between serum sodium and the risk of mortality.

**Conclusions:** Hyponatraemia is relatively frequent in NHL-HLH. As a readily available biomarker in clinical routine, it was a promising prognostic predictor for NHL-HLH.



**Keywords:** Hemophagocytic lymphohistiocytosis, Non-Hodgkin lymphoma, Hyponatraemia, Prognosis, Survival

## Background

Hemophagocytic lymphohistiocytosis (HLH), categorized as genetic or acquired, is considered to be a life-threatening syndrome characterized by aberrant activation and proliferation of polyclonal T lymphocytes and mononuclear macrophages, which leads to an uncontrolled hyperinflammatory response. Adult secondary HLH is commonly triggered by infections, malignancies, autoimmune disorders or unknown aetiologies[1]. Of these, malignancy is the most common trigger identified in adult HLH, especially non-Hodgkin lymphoma-associated sHLH (NHL-HLH), which has a high mortality rate and is considered a major challenge to clinicians due to sHLH and lymphoma share main aspects[2]. NHL-HLH has a progressive course, with mortality rates ranging from 20% to 60% [3, 4]. Early identification of risk factors among NHL-HLH patients is essential for appropriate treatment strategies that rapidly control hyperinflammation and hypercytokine responses.

Hyponatraemia, defined as a serum sodium level<135 mmol/L, is the most common electrolyte disturbance in critically ill patients and cancer patients. Studies have also shown that hyponatraemia is associated with inferior survival of critical illnesses and various types of cancers, including heart failure[5], shock [6], SLE [7], breast cancer (BC), colorectal cancer (CRC), lung cancer and lymphoma [8]. However, no previous literature has investigated the prognostic value of hyponatraemia in NHL-HLH patients on admission.

The purpose of our study was to explore the incidence of hyponatraemia and investigate the relationship between hyponatraemia on admission and overall survival

among adult onset NHL-HLH patients.

## Methods

### Study patients

A total of 153 consecutive patients newly diagnosed between January 1, 2015, and December 28, 2019, at our hospital were included. The inclusion criteria were as follows: 1) patients with an age more than 18 years old; 2) patients for whom the diagnosis of NHL met WHO pathological criteria for biopsy samples [9] or patients for whom the diagnosis of NHL was based on MICM (morphology, flow cytometric immunophenotype, IgH or TCR rearrangement and immunohistochemistry of bone marrow biopsy) criteria [10]; and 3) patients who fulfilled at least 5 of the 8 criteria proposed by the Histiocyte Society in 2004 before treatment [11]. The exclusion criteria were as follows: 1) patients with previous illnesses (i.e. heart, liver or renal diseases); 2) patients with history of medication (i.e. antihypertensives or antidepressants); 3) progressive multiple organ dysfunction (MODS) before treatment; 4) patients with a serum sodium over 145 mmol/L; and 5) patients who acquired HLH during chemotherapy or refused any treatment (Fig. 1).

### Parameters associated with NHL-HLH

Clinical parameters assessed at the first admission included fever, complete blood cell counts, blood biochemical tests including triglycerides (TG), lactate dehydrogenase (LDH), albumin (ALB), fibrinogen (FIB), ferritin, and serum soluble interleukin-2 receptor (sIL-2R, sCD25). Hscore criteria were further applied to support the diagnosis of HLH based on HLH-2004 criteria [12]. We did not evaluate natural killer (NK) cell cytotoxic activity. EBV was evaluated by both serology and EBV DNA real-time

quantitative polymerase chain reaction (RQ-PCR) analysis. Bone marrow aspiration and biopsy samples were reviewed at the first diagnosis. The type of initial therapy was also reviewed. For this analysis, patients were divided into two groups: hyponatraemia was defined as below 135 mmol/L; normonatraemia between 135 and 145 mmol/L. Hypernatraemia was excluded from the analysis because there were only two patients (147.5 mmol/L and 156 mmol/L) in our collected clinical data.

**Statistical analysis**

Data analysis was performed using SPSS version 23.0 (Chicago, IL, USA) and MedCalc (version 15.6.1, Ostend, Belgium). To determine the equality of variances, Levine's test was used. Continuous variables are presented as the means ± standard deviations or the medians (with interquartile ranges, IQR). We used Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical data are presented as frequencies and percentages using Pearson's $\chi 2$ test. Overall survival (OS) was the primary outcome and was defined as the time from the first day of diagnosis to the date of death due to any cause or last follow-up. The association between hyponatraemia and overall survival was examined using Kaplan-Meier estimators and the log-rank test. To identify predictors of death, a Cox proportional hazards regression analysis was performed. Continuous variables (absolute neutrophil count, hemoglobin, platelet, fibrinogen, TG, triglyceride) optimal cut-off values of patients' clinical parameters were dichotomized applying usual clinical thresholds according to HLH-2004 protocol of the International Histiocyte Society in Univariate and multivariate Cox regression analyses. Optimal cut-

off values of ALB and ferritin were dichotomized according to the serum albumin level and previous literature[13, 14]. Receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of sCD25 to discriminate between survivors and non-survivors and to find the ideal cut-off value of sCD25. Variables ($P < 0.05$ in univariate analysis) were entered into a Cox proportional hazards regression model with a stepwise variable elimination procedure in the multivariate model. Restricted cubic splines with three knots placed at the $10^{th}$, $50^{th}$ and $90^{th}$ percentiles were generated to examine the nonlinear relationships of serum sodium with the risk of mortality after adjusting for confounding factors, and the tests for nonlinearity were calculated by Wald $\chi^2$ tests[15]. Moreover, we performed subgroup analyses to assess the interaction between hyponatraemia and clinically related and valuable variables by means of Cox proportional hazards analysis. A two-sided $P < 0.05$ was used to define statistical significance for all comparison.

## Results

### Serum sodium levels in NHL-HLH patients and correlations with patient clinical parameters

One hundred and fifty-three patients with detailed serum sodium profiles at diagnosis of NHL-HLH were recruited in our study, with a median age of 54 years (range, 41.5–64.5 years). The majority of sHLH patients were male (71.9%). Hyperferritinaemia, elevated sCD25, fever, splenomegaly and lymphadenopathy were present in more than 95% of patients, whereas hepatomegaly and bone marrow hemophagocytosis were present in 36.6% and 86.3% of patients, respectively (Supplementary file1). All

recruited patients were categorized as having B cell lymphoma-triggered HLH (BCL-HLH) (n = 62, 40.5%), of which the most frequent histopathological subtype was B cell lymphoma, unclassified, followed by diffuse large B cell lymphoma (DLBCL); T cell lymphoma-triggered HLH (TCL-HLH) was observed in 91 (59.5%) patients, consisting of aggressive NK/T cell lymphoma and T cell lymphoma, unclassified.

The association between serum sodium ($S\text{-}Na^{+}$) concentration on admission and baseline clinical parameters of 153 NHL-HLH patients is summarized in Table 1. Four parameters were significantly elevated in patients with hyponatraemia compared with normonatraemia: ferritin levels ($P < 0.001$), the proportion of patients with EBV infection and the proportion of patients with TCL- HLH ($P = 0.034$ and $P = 0.01$, respectively). Only serum chlorine ($S\text{-}Cl^{-}$) was significantly decreased in patients with hyponatraemia ($P < 0.001$). In addition, no significant difference was detected in the distribution of NHL-HLH therapies between the two groups.

Among these 153 patients, 110 patients (71.9%) had received various kinds of chemotherapy, including 70 patients treated with a CEOP±R-based regimen (cyclophosphamide, vincristine, etoposide, prednisone, and/or rituximab), 14 treated with the LMED regimen (methotrexate, etoposide, L-asparaginase, and dexamethasone), 13 treated with the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), 6 treated with the DEP regimen (liposomal doxorubicin, etoposide, and methylprednisolone), 4 treated with the P-GemOx±R regimen (pegaspargase, gemcitabine, oxaliplatin and/or ruxolitinib), 2 treated with anti-programmed death 1 antibody, and 1 treated with a modified R-hyper-CVAD regimen

(rituximab, cyclophosphamide, doxorubicin, vincristine and dexamethasone alternating with rituximab, high-dose methotrexate and cytarabine). A median of 1 cycle (range 1–6 cycles) was given. The other 43 patients received only the HLH-94 protocol or steroid and/or etoposide therapies. Patients did not receive lymphoma-specific therapy is that early death while receiving HLH directed therapy, not suitable for intensive treatment due to MODS.

**Hyponatraemia and overall survival**

The median survival was 47 (16-180) days in all evaluable patients. A total of 122 (79.7%) subjects died until the end of follow-up. The Kaplan-Meier method was employed to estimate the prognostic significance of S-$Na^+$ levels in NHL-HLH (Fig. 2A). Compared to normonatraemia, patients with hyponatraemia on admission showed evidently worse overall survival (median: 92 days *vs* 30 days, $P$=0.0018). In the Cox multivariate analysis, hyponatraemia (HR:1.51, 95% CI: 1.03-2.20; $P$ = 0.033) remained independently associated with poor survival (Table 2). Restricted cubic spline regression models revealed a significant linear relationship between serum sodium and risk of mortality after adjusting for potential confounding factors (Fig. 2B). The effect was flat when serum sodium was more than 135mmol/L concentrations and was sharply increased when less than 135mmol/L.

**Subgroup evaluation of hyponatraemia in NHL-HLH**

In the subgroup analysis, etiologies-stratified models suggested that the association of hyponatraemia with worse survival was significant among TCL-HLH but not BCL-HLH (Fig. 3A, 3B). Effects were similar across most subgroups (Fig. 3), however,

there were significant interactions between hyponatraemia and ferritin, TG with respect to poorer overall survival.

## Discussion

To the best of our knowledge, this is the first study to probe into the prognostic effect of serum sodium concentration on the survival of patients with NHL-HLH. we showed that a low level of serum sodium was positively associated with increased mortality, resulting in a linear dose–response relationship.

Hyponatraemia is a common electrolyte disturbance in critical illness and malignancies. Many prospective and retrospective studies have indicated the occurrence of hyponatraemia and its importance as a prognostic factor in ICU patients [16], acute-on-chronic liver failure [17], glioblastoma [18], and lung cancer [19]. Nevertheless, hyponatraemia has rarely been reported during the course of lymphoma, especially NHL-HLH, which has mostly been presented in case reports [20-22]. In this study, we discovered for the first time that the prevalence of hyponatraemia in sHLH patients on admission for NHL was 52.9%, which was higher than that mentioned above, and moderate to severe hyponatraemia occurred in 20.9% of patients. Consistent with our results, Zeinah et al discovered that hyponatraemia occurred in 60% of patients with lymphoma and moderate to severe hyponatraemia occurred in 19% of patients with lymphoma [23].

Hyponatraemia has been identified as a negative prognostic factor in critical illness and malignancies. A multicentre cohort study between 2005 and 2012 including 7067 participants from 18 ICUs discovered that hyponatraemia was independently associated

with increased day 28 mortality (OR:1.31, 95% CI: 1.06 - 1.61) [6]. Jorge and his group showed that compared with normonatraemia, hyponatraemia was associated with significantly worse OS in breast cancer (HR: 3.7, 95%, CI: 1.9–7.2; $P < 0.01$), non-small-cell lung carcinoma (HR: 2.8, 95%, CI: 2.0–3.9; $P<0.01$) and lymphoma (HR: 4.5, 95%, CI: 1.8–11.5; $P < 0.01$) [8]. In keeping with previous results in cancer patients. our present study showed a linear relation between serum sodium and risk of mortality. Hyponatremia on admission were significantly associated with unfavourable OS in NHL-HLH patients (adjusted HR: 1.51, 95% CI: 1.03-2.20; $P = 0.033$).

The pathophysiology of hyponatraemia in critical illness as well as haematological malignancies is still not fully understood. Most studies of the occurrence of hyponatraemia and its prognostic value performed to date have been related to central nervous system (CNS) disorders [24], drugs [25], and pulmonary diseases [26], which is usually caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH) and driven by ectopic secretion of arginine vasopressin (AVP) [8, 27]. Nevertheless, in our NHL-HLH cohort, primary CNS lymphoma was not seen in the study; in addition, hyponatraemia occurred prior to treatment. Such high rates of hyponatraemia might also be associated with inflammation. To our knowledge, HLH is characterized by excessive pro-inflammatory cytokines and chemokines, such as IFN-γ, IL-6, interleukin (IL)-1 and TNF-α [28]. There is a possibility that elevated cytokines could be implicated in the pathogenesis of hyponatraemia in NHL-HLH patients. First, several studies pointed out that high cytokines, such as IL-1 and TNF-α, reduce sodium transport by reducing the expression and function of apical epithelial sodium channels

and/or the sodium-potassium ATPase (Na/K ATPase) at the basolateral membrane, accompanied by increased levels of natriuresis [29, 30]. Second, other studies have revealed that IL-1β and IL-6 injection or elevated levels of IL-6 might increase antidiuretic hormone (ADH) secretion in both animal experiments and human studies, leading to hyponatraemia [31, 32]. This explanation was verified by SLE patient who improved of hyponatraemia after treatment with tocilizumab (an IL-6 receptor antibody) [33].

Several limitations exist in this study regarding the prognostic impact of serum sodium concentration in NHL-HLH. First, serum sodium concentrations were not corrected for glucose concentrations in this study, while, the impact of this limitation is likely to be small, as diabetes mellitus (DM) patients were documented in only 1.6% of our patients. Second, cytokine profiles were not available in all patients, and the severity of hyponatraemia and cytokine levels were not verified. Third, we had no information on volume status or measurement of urine electrolytes and urea or diuretic therapy before admission at our hospital. Despite these limitations, the current data are noteworthy because this is the first study, focusing specifically on hyponatraemia at sHLH admission, demonstrating that hyponatraemia is common and is an independent risk factor for a high mortality rate. Therefore, clinicians should recognize hyponatraemia in sHLH.

## Conclusion

We identified that hyponatremia is relatively frequent in patients admitted for NHL-HLH, and it has prognostic implications. Therefore, patients with hyponatremia

should be carefully monitored.

**Abbreviations**

Non-Hodgkin lymphoma-associated hemophagocytic lymphohistiocytosis, NHL-HLH; sHLH, secondary hemophagocytic lymphohistiocytosis; BC, breast cancer; CRC, colorectal cancer; DM, diabetes mellitus; TG, triglycerides; LDH, lactate dehydrogenase; ALB, albumin; FIB, fibrinogen; sCD25, soluble interleukin-2 receptor;ANC, absolute neutrophil count; HB, hemoglobin; PLT, platelet; ALT, alanine transaminase; AST, aspartate transaminase; $\beta_2$-MG, beta$_2$-microglobulin; EBV, Epstein-Barr virus; MHLH, malignancy-associated hemophagocytic lymphohistiocytosis; Non-MHLH, non-malignancy associated hemophagocytic lymphohistiocytosis; GC, glucocorticoid; IVIG, intravenous immunoglobulins; CsA, cyclosporine; VP16, etoposide; HR, hazards ratio; 95% CI, 95% confidence interval; CNS, central nervous system; SIADH, syndrome of inappropriate antidiuretic hormone secretion; AVP, arginine vasopressin; ADH, antidiuretic hormone

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**Author contributions**

GLY and HXQ designed the experiments. GLY performed the experiments. GLY, CFM and HXQ organized the clinical materials. GLY and CFM performed the data analysis. GLY and CFM wrote the paper. All authors contributed to the final approval of the manuscript.

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### Availability of data and materials

The data of our patients is available in the Department of Medical Records at Jiangsu Province Hospital and the First Affiliated Hospital of Nanjing Medical University. These data can be released with consent from the patients and are available from the corresponding author upon reasonable request.

## Declarations

### Ethics approval and consent to participate

Our study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University and registered on the Chinese Clinical Trial Registry (ChiCTR2000032421). All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all patients or legal trustee.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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## Figure legends

**Fig. 1** Flowchart of this study.

**Fig. 2 A**. Crude survival in 153 evaluable patients with NHL-HLH according to the initial value of serum sodium on admission;

**Fig. 2 B**. Cubic spline plot of the association between serum sodium and the risk of mortality among NHL-HLH. The solid line and dashed line represent the estimated hazard ratios and their corresponding 95% CIs. Analyses were adjusted for fibrinogen (FIB), ferritin, sCD25 and treatment strategies.

**Fig. 3** Overall survival analyses of subgroups of different etiologies, TG, ferritin, FIB, and sCD25 values. TG, triglyceride; FIB, fibrinogen; sCD25, Soluble IL-2 receptor.

# Figures

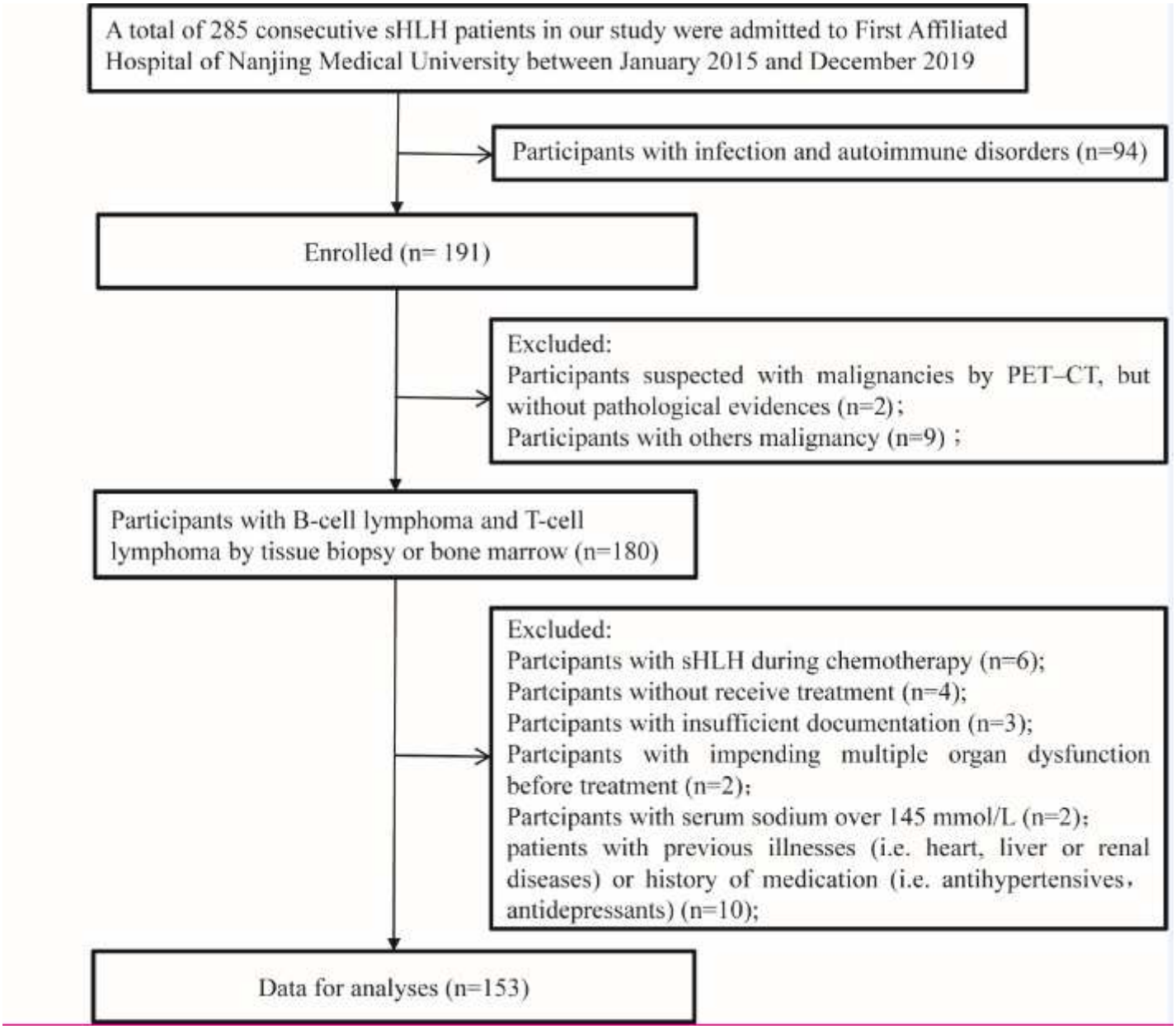
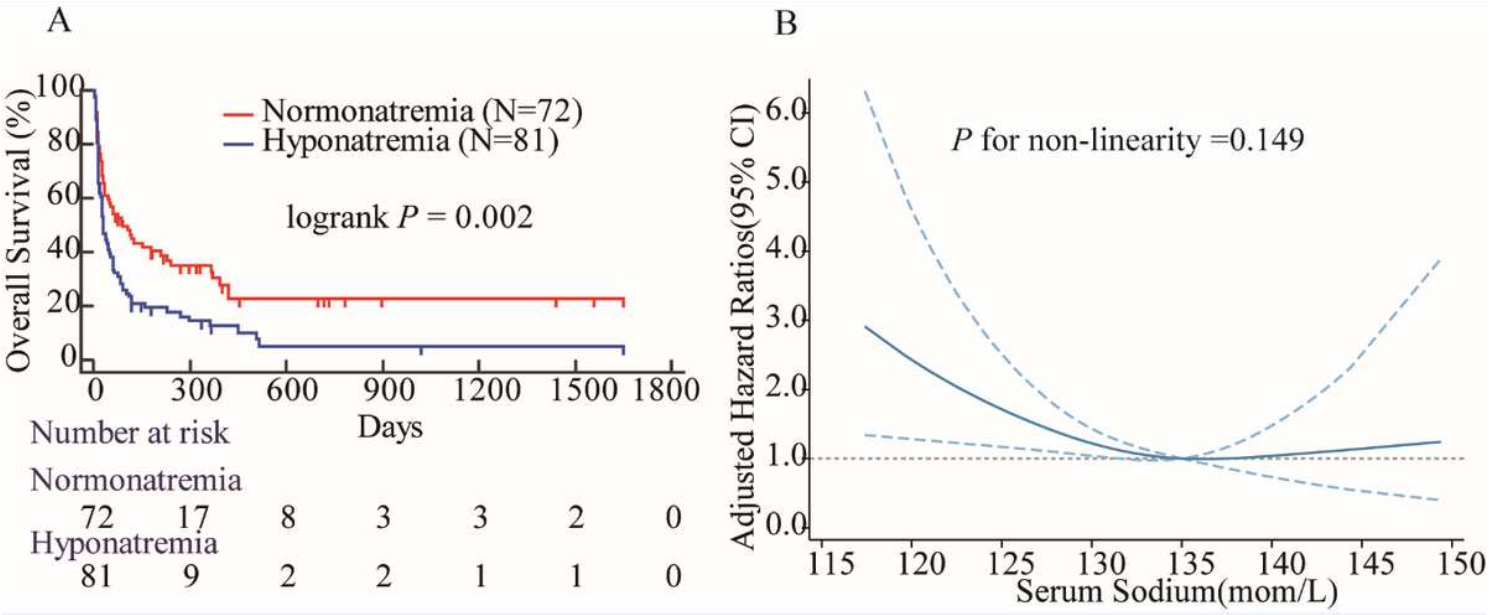



**Figure 1**

Flowchart of this study.




## Figure 2

Fig. 2 A. Crude survival in 153 evaluable patients with NHL-HLH according to the initial value of serum sodium on admission; Fig. 2 B. Cubic spline plot of the association between serum sodium and the risk of mortality among NHL-HLH. The solid line and dashed line represent the estimated hazard ratios and their corresponding 95% CIs. Analyses were adjusted for fibrinogen (FIB), ferritin, sCD25 and treatment strategies.

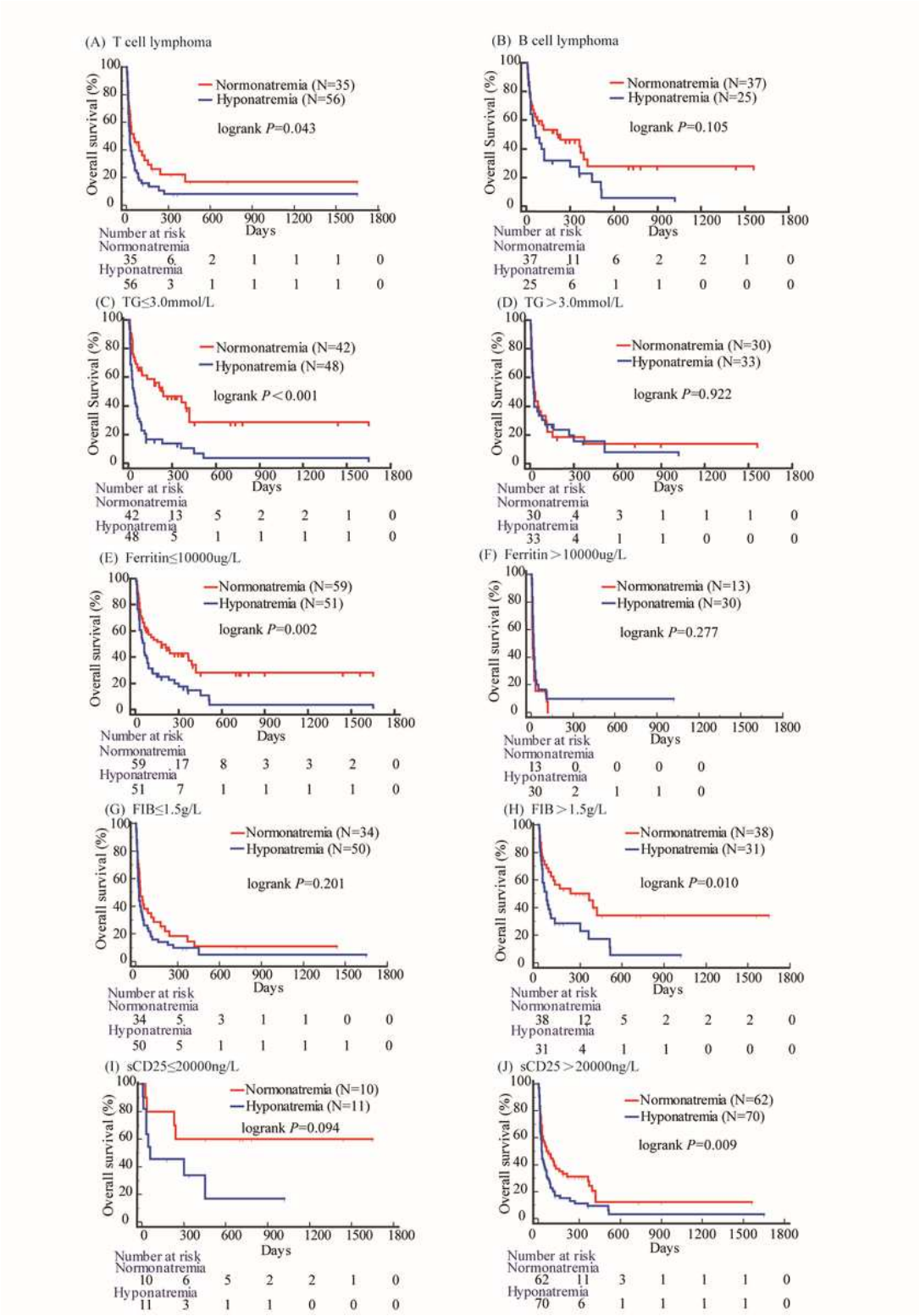



**Figure 3**

Overall survival analyses of subgroups of different etiologies, TG, ferritin, FIB, and sCD25 values. TG, triglyceride; FIB, fibrinogen; sCD25, Soluble IL-2 receptor.

# Supplementary Files

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