Prognostic nomogram incorporating inflammatory cytokines for overall survival in patients with aggressive non-Hodgkin's lymphoma

Huijuan Zhonga, Jia Chenb, Shuchenga, Suning Chenb, Rong Shenb, Qing Shib, Pengpeng Xua,
Hengye Huangd, Muchen Zhanga, Li Wangac, Depeiwub, Weili Zhaoa,c,*

a State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology, Shanghai Jiao Tong University School of Medicine, 197 Rui Jin Er Road, Shanghai, China
b Jiangsu Institute of Hematology, Institute of Blood and Marrow Transplantation, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China
c Pôle de Recherches Sino-Français en Science du Vivant et Génomique, Laboratory of Molecular Pathology, Shanghai, China
d School of Public Health, Shanghai Jiao Tong University School of Medicine, 227 South Chongqing Road, Shanghai, China

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A B S T R A C T
Background: This study aimed to investigate the association of pre-treatment inflammatory status with survival time and to develop a prognostic nomogram incorporating inflammatory cytokines in non-Hodgkin's lymphoma.

Methods: A total of 228 patients with diffuse large B-cell lymphoma (DLBCL) received R-CHOP-based regimens from a prospective randomized study (NCT01852435) were included as a training cohort. Other cohorts of 886 lymphoma patients were served as validation cohorts. Lymphocyte-monocyte ratio (LMR), serum levels of soluble interleukin s(II)-2R, IL-2, IL-8, IL-10 and tumor necrosis factor-α (TNF-α), were assessed before treatment. Least absolute shrinkage and selection operator (LASSO) regression were used to select variables for nomogram of overall survival (OS). The predictive accuracy of the nomogram was determined by concordance index (C-index).

Findings: The nomogram included lactate dehydrogenase (LDH), sII-2R, TNF-α and decreased LMR. The C-index of the nomogram for OS prediction were range from 0.61 to 0.86 for training cohort of DLBCL and validation cohorts of DLBCL, PTCL, NKTCL and ASCT, which were superior to the predictive power of International Prognostic Index (IPI, 0.67 to 0.84) or NCCN-IPI (0.59 to 0.78), but not in those of indolent lymphoma like FL and MALT.

Interpretations: The nomogram incorporating inflammatory cytokines provides a useful tool for risk stratification in aggressive non-Hodgkin's lymphomas.

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1. Introduction

Non-Hodgkin's lymphomas (NHLs) are the most common hematological malignancies worldwide and represent a heterogeneous entity. Multiple clinical prognostic indexes have been developed and proved helpful for risk stratification. However, predictive value of the clinical indexes may differ from histological subtypes of lymphomas. For example, International Prognostic Index (IPI) [1] and National Comprehensive Cancer Network-IPI (NCCN-IPI) [2] work more efficiently in B-cell lymphomas, while Prognostic Index for PTCL-U (PIT) [3] and Korean Prognostic Index (KPI) [4] in T-cell and natural-killer/T-cell lymphoma (NKTCL). Therefore, it remains great interests to establish a prognostic nomogram easily applicable and well adapted to various lymphomas subtypes.

In addition to lymphoma cells themselves, tumor microenvironment plays an important role on disease progression. Inflammatory status is essential in tumor microenvironment, inducing by antigen stimulation, autoimmunity disorders, or environmental conditions during lymphomagenesis [5]. Inflammatory-IPI model [6] was proposed to predict prognosis in diffuse large B-cell lymphoma (DLBCL) patients treated with rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone, R-CHOP), based on inflammatory factors lactate dehydrogenase (LDH), absolute lymphocyte count (ALC), albumin (ALB), β2-microglobulin (β2-MG), C-reactive protein (CRP), and ferritin. Inflammation-based cumulative prognostic score system (ICPS) [7].
Multiple clinical prognostic indexes have been developed in non-Hodgkin's lymphoma, but predictive value differs from histological subtypes. Inflammatory status plays an essential role on lymphoma progression. No large-scale study on the association of inflammatory status with clinical outcomes has been performed in non-Hodgkin's lymphoma, especially in Chinese patients. Here we used the test and validation cohorts of 1114 lymphoma patients and established a new prognostic nomogram, providing a useful tool of risk stratification for aggressive lymphomas.

2. Methods and materials

2.1. Patients and treatments

A total of 1114 patients were enrolled in this study, including 990 de novo cases (DLBCL, n = 538, PTCL, n = 134, NKTCL, n = 105, FL, n = 151, MALT, n = 62) and 124 cases undergone autologous stem cell transplantation (ASCT) (DLBCL, n = 77, PTCL, n = 38, NKTCL, n = 9). The historical diagnosis was established according to World Health Organization (WHO) classification [17]. Among DLBCL patients, 228 patients were enrolled in a randomized controlled phase III trial (NCT01852435) who received six courses of R-CHOP, at either standard regimens, and 124 patients with ASCT. Patients were stratified according to IPI [1], NCCN-IPI [2], inflammatory-IPI [6], ICPS [7], PIT [3] or KPI [4] as necessary. The study was approved by the Institutional Review Board with informed consent obtained in accordance with the Declaration of Helsinki.

2.2. Inflammatory factors and cytokines assessment

Serum specimens were collected at diagnosis or before ASCT. β2-MG was detected using chemiluminescence immunoassay and CRP using rate nephelometry method. As for cytokines, sIL-2R, IL-8, IL-10 and TNF-α were assessed by IMMUNITE 1000 chemiluminescence analyzer (Siemens), and IL-6 by IMMUNITE 2000 chemiluminescence analyzer (Siemens). Lower limit of detection (LOD) for sIL-2R, IL-8, IL-10 and TNF-α were 5 U/ml, 2 pg/ml, 5 pg/ml, 5 pg/ml and 4 pg/ml, respectively. Upper LOD for sIL-2R, IL-6, IL-8, IL-10 and TNF-α were 7500 U/ml, 1000 pg/ml, 7500 pg/ml, 1000 pg/ml and 1000 pg/ml, respectively. T-cell subsets containing CD3+, CD3 + CD4+, CD3 + CD8+, CD4 + CD28+, CD8 + CD28+, CD4 + CD45RA+, CD4 + CD45RO+, CD4 + CD25+, CD4 + CD25 + CD127(low), CD3 + HLA-DR+, CD3 + CD69+, NK (CD56 + CD16+) and absolute count of CD3+, CD4+, CD8 + T cells were detected in DLBCL patients of the training and validation cohorts by flow cytometry (BD FACSCanto II).

2.3. Construction and validation of the nomogram

In the design of the nomogram, we incorporated clinical features and inflammatory factors as prognostic features. These factors included age, gender, performance status (ECOG), Ann Arbor stage, extranodal involvement, LDH, LMR, ALB, β2-MG, CRP, sIL-2R, IL-8, IL-10 and TNF-α. We used least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation to select the most useful predictive variables via minimum criteria for nomogram of overall survival (OS) from the training cohort. Nomogram validation comprised several stages. Internal validation was first undertaken, with a concordance index (C-index) being estimated. Next, calibration curves were plotted to determine whether the predicted and observed probabilities for survival time were in concordance. Bootstrap resampling (1000 resamples) was used for this plot. Finally, external validation was performed, in which the nomogram was used to assess each patient in the validation cohorts, and Cox regression analysis in total score of each patient as an independent factor. The regression analysis was then carried out to derive the C-index and the calibration curve. Comparisons between nomogram and other prognostic models were evaluated by C-index.

2.4. Statistical analysis

All statistical analysis was carried out using R software (version 3.4.3: http://www.R-project.org) and Statistical Package for the Social Sciences (SPSS) 20.0 software (SPSS Inc., Chicago, IL, USA). Association between clinical characteristics and inflammatory factors/cytokines, or between disease progression and T-cell subsets were assessed using independent-sample t-test. OS was measured from the date of diagnosis to the date of death or the last follow-up. Survival functions were estimated using the Kaplan-Meier method and compared by the log-rank test.

3. Results

3.1. Clinical characteristics

Clinical characteristics of the training and validation cohorts were shown in Table S1. Serum levels of inflammatory factors were well balanced among histological subtypes, including LMR, ALB, β2-MG, CRP, cytokines sIL-2R, IL-8, IL-10 and TNF-α. All the patients were categorized according to IPI and NCCN-IPI, and patients with available data categorized according to inflammatory-IPI and ICPS.

3.2. Inflammatory factors and cytokines

In the training cohort of DLBCL, serum levels of LDH, β2-MG, CRP, sIL-2R, IL-8, IL-10 and TNF-α were significantly elevated, while LMR and ALB reduced, as compared to healthy volunteers (Table S2). Meanwhile, association of inflammatory factors with clinical characteristics was analyzed. Patients ≥60 years had higher levels of β2-MG than those of patients ≤60 years. Decreased levels of LMR, ALB, but increased...
Fig. 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) cox regression model. (a) LASSO coefficient profiles of the 15 features for OS. (b) Tuning parameter (λ) selection in the LASSO model used 10-fold cross-validation via minimum criteria for OS.
levels of LDH, β2-MG, CRP, sIL-2R, IL-6, IL-10 and TNF-α were closely related to advanced Ann Arbor stage and poor performance status. Increased levels of sIL-2R were observed in patients with bone marrow or liver involvement, and increased levels of TNF-α in patients with lung involvement.

### 3.3. Nomogram development and internal validation

The median OS of the training cohort of DLBCL was 32.8 (2.6–57.6) months, with 4-year OS rate of 83.9%. The 2-year OS of the validation cohorts of DLBCL, PTCL, NKTCL, FL, MALT and ASCT were 79.6%, 42.7%, 76.9%, 96.5%, 98.2% and 78.1%, respectively.

For the development of nomogram, we incorporated clinical features and inflammatory factors as prognostic features: age, gender, performance status, Ann Arbor stage, extranodal involvement, LDH, LMR, ALB, β2-MG, CRP, sIL-2R, IL-6, IL-8, IL-10 and TNF-α. All these parameters were reduced to the most useful 4 potential predictors for OS in the training cohort, with nonzero coefficients in the LASSO cox regression model (Fig. 1). Nomogram to predict 4-year OS was developed using the results from the LASSO cox regression model. sIL-2R, TNF-α, LMR ≤ 2.7 and elevated LDH were independent risk factors (Fig. 2 and Table 1). The predictive accuracy for OS as measured by C-index was 0.78 in the internal validation. The calibration plot for the probability of 4-year OS showed a good correlation between the actual observed outcome and the prediction by the nomogram (Fig. 3a).

### 3.4. External validation of nomogram

The nomogram was externally validated in the DLBCL, PTCL, NKTCL, FL, MALT and ASCT validation cohorts. The C-index of the nomogram for the prediction of 2-year OS was 0.81 in DLBCL. The models also showed a good level of discriminative ability to predict 1-year OS in PTCL (0.68) and NKTCL (0.86). However, the nomogram was not effectively significant in FL and MALT. In the ASCT group, the nomogram significantly predicted prognosis, but C-index (0.61) was lower. The nomogram was well calibrated as revealed by the calibration curves (Fig. 3b to e) and performed well in predicting OS of patients with aggressive NHLs at diagnosis or after ASCT.

### 3.5. Comparison of nomogram with clinical prognostic indexes

IPI, NCCN-IPI and inflammatory-IPI showed good levels of risk stratification both in training cohort (0.72, 0.72, 0.69) (Fig. 4) and validation cohorts of DLBCL (0.77, 0.76, 0.74), PTCL (0.67, 0.67, 0.68) and NKTCL (0.84, 0.78, 0.82), as well as ICPS in DLBCL (0.69 both in training and validation cohort), PIT (0.67) in PTCL and KPI (0.76) in NKTCL, NCCN-IPI (0.59) in ASCT (Table 2). The nomogram displayed the highest levels of accuracy to predict OS in all cohorts. Therefore, the prognostic nomogram works accurately and well adapted for patients with aggressive NHLs.

### 3.6. Association of inflammatory cytokines with T-cell subsets

T-cell subsets were assessed in peripheral blood of 518 DLBCL patients. Patients were divided into the group with early death (OS ≤ 6 months) and with non-early death (OS > 6 months). In early death group, absolute count of CD3 + T and CD4 + T cells, as well as

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**Table 1**

| Risk factors for the nomogram of overall survival in DLBCL. |
|-----------------------------------------------|
| β\(\) | Overall survival HR (95% CI) | p value |
| sIL-2R | -0.001 | 1.000 | <0.001 |
| TNF-α | 0.029 | 1.030 (1.025 to 1.035) | <0.001 |
| LMR ≤ 2.7 | 1.530 | 4.610 (4.250 to 4.970) | <0.001 |
| Elevated LDH | 1.720 | 5.590 (5.230 to 5.950) | <0.001 |

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**Fig. 2.** Nomogram of OS in aggressive non-Hodgkin’s lymphomas.
Fig. 3. Calibration curves of the nomogram in training cohort and validation cohorts of lymphoma. (a) Prediction of 4-year OS in training cohort of DLBCL. (b) Prediction of 2-year OS in validation cohort of DLBCL. (c) Prediction of 1-year OS in PTCL validation cohort. (d) Prediction of 1-year OS in NKTCL validation cohort. (e) Prediction of 2-year OS in ASCT validation cohort.
percentage of functional subset of inductor/helper T cells (CD4 + CD28+) and cytotoxic T cells (CD8 + CD28+) were significantly decreased, while early-activated T cells (CD3 + CD69+) and late-activated T cells (CD3 + HLA-DR+) were significantly increased, as compared to non-early death group (Table S3).

4. Discussion

Inflammatory status provoked by tumor microenvironment plays an important role in disease progression of NHLs. Aiming to establish a prognostic system independent on histological subtypes of lymphoma, and possibly independent on therapeutic strategies (chemotherapy, ASCT, etc.). We performed assessment on multiple inflammatory factors, as well as serum cytokines closely related to host immunity status. Meanwhile, both training and validation cohorts were applied to further improve the accuracy of the prognostic index. LMR, as a routinely available index which reflects host systemic immunity, predicts survival in DLBCL [18], NKTCL [19], and FL [20]. For cytokines, sIL-2R is critically involved in T-cell activation. Pretreatment serum sIL-2R is associated with inferior outcomes of DLBCL both in pre-rituximab and rituximab era [8], PTCL [9], NKTCL [10] and FL [11]. TNF-α acts as a tumor-promoting factor and contributes to aggressive clinical behavior in DLBCL [8] and PTCL [16]. To our knowledge, this is the largest study on the association of inflammatory status with clinical outcomes in NHLs. Using a randomized study to define the possible role of serum cytokines in the prospective setting, a nomogram incorporating with inflammatory factors was set up and appeared more effective than clinical prognostic index. Therefore, in addition to tumor-associated LDH, immune response to tumor burden such as LMR, sIL-2R and TNF-α are valuable prognostic biomarkers, reflecting the combined effect of tumor and microenvironment on lymphoma progression.

Decreased LMR represents an imbalance between immuno-surveillance and immunosuppression in lymphomas. Lymphopenia is

| Table 2 | The C-index of the nomogram in DLBCL training cohort and DLBCL, PTCL, NKTCL, ASCT validation cohorts. |
|---------|---------------------------------------------------------------|
|         | Training cohort (n = 228) | DLBCL validation cohort (n = 310) | PTCL validation cohort (n = 134) | NKTCL validation cohort (n = 105) | ASCT validation cohort (n = 124) |
| Nomogram | 0.78 | 0.81 | 0.68 | 0.86 | 0.61 |
| IPI      | 0.72 | 0.77 | 0.67 | 0.84 | NA |
| NCCN-IPI | 0.72 | 0.76 | 0.67 | 0.78 | 0.59 |
| Inflammatory-IPI | 0.69 | 0.74 | 0.68 | 0.82 | NA |
| ICPS     | 0.69 | 0.69 | NA  | NA  | 0.59 |
| PIT      | 0.67 | 0.67 | NA  | NA  | 0.59 |
| KPI      | 0.76 | 0.76 | NA  | NA  | 0.59 |
considered as a poor prognostic factor in DLBCL [21, PTCL [22] and NKTCL [23], at diagnosis and after ASCT [24]. Monocytes promote tumor angiogenesis and metastasis via tumor-associated macrophages [25]. In our study, decreased LMR was resulted from lymphopenia and increased monocytes, which negatively regulated host immunity and contributed to lymphoma progression. IL-2R, a membrane receptor for IL-2, expressed on the surface of activated T-cells and shed into the circulation in a soluble form as sIL-2R [26]. sIL-2R was associated with increased late-activated T-cells [27] and decreased cytotoxic T-cells [28]. Here we showed that early-death group presented with significant elevation of late-activated T-cells and reduction of cytotoxic T-cells, which correspond to the immunosuppressive effect of sIL-2R on patients with extreme poor prognosis. TNF-α is a pro-inflammatory cytokine that has both anti-inflammatory and immunosuppressive effect. Positively correlated with late-activated T-cells [27], chronic stimulation with TNF-α may induce CD4 + T-cell exhuastion and impairs CD4 + T cell-mediated immunological control [29]. Meanwhile, TNF-R1-dependent TNF-α signaling triggered CD8 + T-cell death and inhibited accumulation of tumor-infiltrating CD8 + T cells [30]. Thus, in addition to sIL-2R, TNF-α induced suppression of CD4 + effer-ct T-cells and cytotoxic T-cells, and served as another important com-ponent of prognostic nomogram incorporating with inflammatory status.

The nomogram is useful to conduct risk-adapted therapeutic strategies. Efficient in aggressive subtype DLBCL, PTCL and NKTCL, the nomogram is not suitable for indolent subtype FL and MALT, probably due to the very good prognosis achieved upon R-CHOP-based chemotherapy. ASCT is considered as an important therapeutic strategy in high-risk patients with age-adjusted-IPI (aa-IPI) score 2–3 [31,32]. However, the indication for front-line ASCT is controversial. Accordingly, using our prognostic nomogram, we also identified a subset of the patients with aa-IPI 2–3, but presented with a long-term survival without ASCT. For these patients, ASCT may not be necessary as front-line therapy. Meanwhile, there were still patients suffered from relapse or progression after ASCT. For these patients, instead of ASCT, novel therapeutic strategies should be applied, for example, ibrutinib targeting MYD88 L265P/CD79B mutant [33], lenalidomide targeting MYC-translocation [34], and chimeric antigen receptor therapy (Car-T) directly targeting immune dysregulation. Further studies should be conducted to validate the potential application of nomogram in patients treated with Car-T.

In conclusion, the nomogram proposed in this study incorporates inflammatory factors and cytokines, reflecting tumor burden and immunosuppressive microenvironment in lymphoma. It predicted the overall survival time more accurately than clinical prognostic index, providing a useful tool for risk stratification in aggressive NHLs.

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Conflicts of interests

All authors declare no potential conflict of interest

Author contributions

HJZ, J.C and SC performed the project, collected and analyzed the data, and wrote the article. SNC provided material support. RS, QF and MCZ collected the data. PX, HYH and LW provided statistical analyses and support. DPW and WLZ designed and supervised the study, and wrote the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2019.02.048.

References

[1] International Non-Hodgkin’s Lymphoma Prognostic Factors P. A predictive model for aggressive non-Hodgkin’s lymphoma. N Engl J Med 1993;329(14):987–94.
[2] Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced international prognostic index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;124(3):119–23.
[3] Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004;103(7):2474–9.
[4] Lee J, Suh C, Park YH, et al. Extramedullary natural killer-T cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol 2006;24(14):612–8.
[5] Baccaloni E, Smedby KE, Sutton LA, Askling J, Rosenquist R. Lymphoma develop-ment in patients with autoimmune and inflammatory disorders— what are the driv- ing forces? Semin Cancer Biol 2014;24:61–70.
[6] Kim C, Lee H, Jo J, et al. Clinical usefulness of inflammatory factors based modified international prognostic index in diffuse large B cell lymphoma treated with rituxi-mab combined chemotherapy. Blood 2016;128:4220.
[7] Sun F, Zhu J, Lu S, et al. An inflammation-based cumulative prognostic score system in patients with diffuse large B cell lymphoma in rituximab era. BMC Cancer 2018;18:173.
[8] Druyhuy I, Fillela X, Rovira J, et al. High serum levels of soluble interleukin-2 receptor (sIL2-R), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF) are associated with adverse clinical features and predict poor outcome in diffuse large B-cell lymphoma. Leuk Res 2017;59:20–5.
[9] Gupta M, Stenson M, O’Byrne M, et al. Comprehensive serum cytokine analysis iden-tifies IL-1RA and soluble IL-2Ralpha as predictors of event-free survival in T-cell lymph-oma. Ann Oncol 2016;27(1):165–72.
[10] Wang L, Liao DZ, Zhang J, Xia ZJ, Peng XW, Lu Y. Clinical significance of serum soluble interleukin-2 receptor-alpha in extranodal natural killer/T-cell lymphoma (ENKTL): a predictive biomarker for treatment efficacy and prognostic factor. Med Oncol 2013;30(4):723.
[11] Kusunou Y, Yokoyama M, Terui Y, et al. High pretreatment level of soluble interleukin-2 receptor is a robust prognostic factor in patients with follicular lymphoma treated with R-CHOP-like therapy. Blood Cancer J 2017;7(9):e614.
[12] Manfroi B, McKee T, Mayof JF, et al. CCLI-8/18 produced by diffuse large B-cell lymphoma cells recruits neutrophils expressing a proliferation-inducing ligand APRIL. Cancer Res 2017;77(5):1097–107.
[13] Miyata-Takata T, Takata K, Toji T, et al. Elevation of serum interleukin-8, 4, and 1beta levels in patients with gastrointestinal low-grade B-cell lymphoma. Sci Rep 2015;5:18434.
[14] Roncarolo MG, Gregori S, Battaglia M, Bachetta R, Fleischhauer K, Levings MK. Inter-leukin-10–secreting type 1 regulatory T cells in rodents and humans. Immunol Rev 2006;212:28–50.
[15] Wang H, Wang L, Wuxiao Z, et al. Increased serum levels of interleukin-10 predict poor prognosis in extranodal natural killer/T-cell lymphoma patients receiving asparaginase-based chemotherapy. Onco Targets Ther 2015;8:2589–99.
[16] Heemann C, Kreuz M, Stoller I, et al. Circulating levels of TNF receptor II are prognostic for patients with peripheral T-cell non-Hodgkin lymphoma. Clin Cancer Res 2012;18(13):3637–47.
[17] Svedlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Orga-nization classification of lymphoid neoplasms. Blood 2016;127(20):2375–90.
[18] Wilcox RA, Ristow K, Habermann TM, et al. The absolute monocyte and lymphocyte index, providing a useful tool for risk stratification in aggressive NHLs.
Huang JJ, Jiang WQ, Lin TY, et al. Absolute lymphocyte count is a novel prognostic indicator in extranodal natural killer/T-cell lymphoma, nasal type. Ann Oncol 2011;22(1):149–55.

Porrata LF, Inwards DJ, Ansell SM, et al. New-onset lymphopenia assessed during routine follow-up is a risk factor for relapse postautologous peripheral blood hematopoietic stem cell transplantation in patients with diffuse large B-cell lymphoma. Biol Blood Marrow Transplant 2010;16(3):376–83.

Dirix AE, Oude Egbrink MG, Wagstaff J, Griffioen AW. Monocyte/macrophage infiltration in tumors: modulators of angiogenesis. J Leukoc Biol 2006;80(6):1183–96.

Rubin LA, Kurman CC, Fritz ME, et al. Soluble interleukin 2 receptors are released from activated human lymphoid cells in vitro. J Immunol 1985;135(5):3172–7.

Rea IM, McNerlan SE, Alexander HD. CD69, CD25, and HLA-DR activation antigen expression on CD3+ lymphocytes and relationship to serum TNF-alpha, IFN-gamma, and sIL-2R levels in aging. Exp Gerontol 1999;34(1):79–93.

Gooding B, Riches P, Dadian G, Moore J, Gore M. Increased soluble interleukin-2 receptor concentration in plasma predicts a decreased cellular response to IL-2. Br J Cancer 1995;72(2):452–5.

Beyer M, Abdallah Z, Chemnitz JM, et al. Tumor-necrosis factor impairs CD4(+) T cell-mediated immunological control in chronic viral infection. Nat Immunol 2016;17(5):593–603.