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ORIGINAL ARTICLE

Elevated serum soluble interleukin-2 receptor levels increase malignancy-related risk in patients on chronic hemodialysis

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Abstract

Background Patients on chronic hemodialysis (HD) have an increased incidence of malignancy due to decreased immunity. Soluble interleukin-2 receptor (sIL-2R), as an immunomodulator, seemed to have an effect in the process of malignancy. In this study, we aimed to evaluate the clinical significance of increased sIL-2R in the course of malignancy among HD patients.

Methods Patients who undergoing chronic hemodialysis were followed for 24 months. Risk factors for malignancy events and malignancy-related mortality during the 2-year follow-up period were investigated among various clinicopathological variables.

Results Of the 363 patients included in this research, 47 patients (12.95%) had a prior history of treated malignancy. During the 2-year follow-up period, malignancy events were detected in 15 (4.12%) patients. Sixty-seven patients died during the study period, of which nine patients (13.43%) were died of malignancy. Malignancy events reduced 2-year mortality significantly (log-rank = 23.02, $P < 0.0001$). Both high sIL-2R levels ($\geq$2-fold upper limit of the normal value) (OR 6.6, $P = 0.006$) and a prior history of treated malignancy (OR 4.12, $P = 0.018$)were identified by multivariate logistic analysis as independent determinants for malignancy events. However, only the levels of sIL-2R (used as a continuous variable) had the significantly predictive effect on malignancy events and malignancy-related mortality in the following 2 years.

Conclusions Elevated sIL-2R levels was commonly seen in serum of HD patients. And this elevated level increased the risk of malignancy. Aside from its role as a biomarker, sIL-2R may also exert biological effects in the course of malignancy.

Keywords Soluble interleukin-2 receptor · Hemodialysis · Malignancy event · Malignancy-related mortality

Abbreviations

IL-2	Interleukin-2
IL-2R	Interleukin-2 receptor
sIL-2R	Soluble interleukin-2 receptor
HD	Hemodialysis
ESRD	End-stage renal disease
CVD	Cardiovascular disease
BMI	Body-mass index
ESA	Erythropoietin-stimulating agent
spKt/V	Single-pooled Kt/V
TNF-α	Tumor necrosis Factor α
RDW	Red blood cell distribution width
hsCRP	High-sensitivity C-reactive protein
AKP	Alkaline phosphatase

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GGT	γ-Glutamyl transferase
LDH	Lactate dehydrogenase
SCr	Serum creatinine
UA	Uric acid
β2-MG	Beta-2-microglobulin
iPTH	Intact parathyroid hormone
HbA1c	Glycosylated hemoglobin
SD	Standard deviation
IQR	Interquartile range
ROC	Receiver operating characteristic
OR	Odds ratio
CI	Confidence interval

Introduction

More and more evidences have proved that end-stage renal disease (ESRD) patients undergoing hemodialysis (HD) present a higher-than-normal cancer risk [1–4]. Both uremic-related and dialysis-related immune dysfunction may contribute to cancer susceptibility in these subjects. Despite this, the issue of malignancy is usually ignored due to its small portion contributing to incidence and mortality among ESRD patients on HD. And much less attention and resources have been allocated to cancer management compared to other complications, such as cardiovascular disease (CVD). However, with the improvement of survival in HD patients, cancer incidence increases obviously in recent years, which impose a large disease burden and an additional financial burden on ESRD patients receiving HD. Though the exact mechanisms responsible for this increased incidence of malignancy have not been completely understood, immune dysfunction related to uremia and dialysis plays an important part in promoting malignancy formation and progression [5].

Interleukin-2 (IL-2) signaling, by binding to its receptor—IL-2R, has an essential role in regulating immune functions during various pathophysiological processes [6]. IL-2R consists of three chains, termed alpha, beta and gamma chains, respectively. Both IL-2R beta and gamma chains are constitutively expressed, while IL-2R alpha chain is expressed only after immunocyte activation. Soluble IL-2R (sIL-2R) is a soluble form of IL-2R alpha chain cleaved by proteolytic enzymes and shed from the cell surface into circulation [7, 8]. Thus, the levels of sIL-2R may reflect the status of immunity responses. Elevated sIL-2R levels have been detected in a variety of diseases, such as autoimmune and inflammatory disorders, transplant rejections, as well as cancer (including leukemias, lymphomas, and malignant solid tumors) [7].

Due to the pre-activated immune cells under the conditions of uremic and dialysis [9–15], HD patients also present a significantly higher level of sIL-2R by nearly 3–30 folds compared with the general population [9–15]. However, the presence of a large amount of sIL-2R in serum of HD patients is just an immune biomarker or may exert some biological effects remains unknown. In this study, we aimed to access whether this increase in sIL-2R levels has a role in the course of malignancy among ESRD patients treated with chronic HD.

Methods and materials

Patient selection

ESRD patients receiving chronic HD treatment in Blood Purification Center, Zhongshan Hospital, Fudan University, were enrolled. Patients were excluded if they had the following situations prior to the enrollment: (1) < 18 years of age, (2) hematologic disease, (3) human immunodeficiency virus infection, (4) autoimmune disease, (5) use of immunosuppressive agents, (6) history of transplantation, (7) recent infections within 3 months before enrolling into the study, and (8) patients without a prior history of malignancy showed evidence of cancer, or patients with a prior history of malignancy after radical resection showed recurrence or metastasis of their disease.

This study was started from September 2016, and since then cytokines tests have been routinely performed in our blood purification. All eligible patients were followed prospectively until October 2018. The follow-up program included chest X-ray and ultrasonography every 6 months. Patients transferred to other centers or received kidney transplantation during the follow-up period were not included in the final analysis. This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (Approval Number: B2013-139). Written informed consents were obtained from all eligible patients.

End-point and its evaluation

The primary end-point was malignancy events during the 2-year follow-up period. Malignancy events were defined as follow: (1) new-onset cancer in patients without a prior history of malignancy; or (2) cancer recurrence or metastasis in patients with a prior history of treated malignancy. Evidence of malignancy was identified by radiological investigations or histological examinations if necessary. Once evidence of malignancy was confirmed, malignancy events free time was defined as the time from enrollment to malignancy events detected. Deaths during follow-up period without evidence of malignancy were censored. Patients alive at the end of this study were also censored.

Hemodialysis protocol

Our blood purification center has a leading position in China as described elsewhere [16]. ESRD patients in our blood purification center received HD three times/week for 4 h/session or two times/week for 5 h/session depending on their residual renal function. Patient were treated with standard bicarbonate dialysate (Na^+: 138.0 mmol/L, K^+: 2.0 mmol/L, Ca^{2+}: 1.2 5 mmol/L, Mg^{2+}: 0.5 mmol/L, HCO_3^-: 32.0 mmol/L) by low-flux dialyzers (membrane area: 1.4 m^2) with synthetic membranes [17]. The dialysis water quality met the standards required by Association for the Advancement of Medical Instrumentation and was examined every month.

Data collection

Demographic characteristics including age, gender, body-mass index (BMI), primary kidney disease, vascular access for dialysis, dialysis vintage, daily urine volume and erythropoietin-stimulating agent (ESA) dosage per week were collected for all patients. BMI was defined as the weight in kilograms divided by the height in meters squared. Dialysis vintage was calculated from the date of the first dialysis and the onset of data collection. Single-pooled Kt/V (spKt/V) was calculated based on the reduction in the serum urea concentration during dialysis and calculated by the Daugirdas formula [18].

Blood samples were obtained at the beginning of the study. Laboratory indexes including cytokines [tumor necrosis Factor α (TNF-α), IL-1β, sIL-2R, IL-6, IL-8, IL-10], blood cell counts (neutrophils, lymphocytes and monocytes), hemoglobin, red blood cell distribution width (RDW), high-sensitivity C-reactive protein (hsCRP), albumin, globulin, alkaline phosphatase (AKP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH), serum creatinine (SCr), uric acid (UA), beta-2-microglobulin (β2-MG), intact parathyroid hormone (iPTH), iron, ferritin, epoetin, vitamin B_{12}, folic acid and glycosylated hemoglobin (HbA1c) were measured. Cytokines in our hospital were determined by chemiluminescent quantitative measurement using the IMMULITE 1000 kits (Siemens Healthcare Diagnostics, UK) on the IMMULITE 1000 analyzer. The reference value of serum sIL-2R level in our hospital was 223–710 U/mL.

Patient grouping and stratification

In our previous study, we showed that sIL-2R had potential value in patient outcomes, and the optimal cut-off value was nearly twofold of the normal upper limit value. So, patients were stratified into 2 groups, that is, high sIL-2R group with sIL-2R ≥ twofold of the normal upper limit value (710 U/mL), and low sIl-2R group with sIL-2R < twofold of the normal upper limit value.

Statistical analyses

Quantitative data were expressed as means ± standard deviations (SDs) or medians with interquartile ranges (IQRs). Differences in continuous variables were assessed by Student's *t* test if normally distributed or Mann–Whitney rank sum test if skewed. Categorical data were presented as numbers and percentages (%). Differences between categorical variables were compared by Pearson's Chi-square analysis or Fisher's exact test if necessary. Risk factors related to malignancy were estimated by logistic regression model. Receiver operating characteristic (ROC) plots were used to evaluate the predictive performance among variables of interest. Overall survival was calculated from the date of enrollment to death or the last date of follow-up. Survival distribution of patients was estimated by the Kaplan–Meier method and compared by the log-rank test.

All analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX). P values < 0.05 denoted statistical significance.

Results

Study population

363 patients (221 males and 142 females) undergoing chronic hemodialysis were included in the study. All surviving patients had a follow-up period of 24 months. None was lost during this period. The average age was 61.12 ± 13.55 (range 26–88) years with a median dialysis duration of 4.63 (2.39, 7.47) years prior to the study.

Table 1 The underlying causes of kidney disease

Disease causes	Patient number (%)
Glomerulonephritis	191, 52.62%
Nephrosclerosis	8, 2.20%
Diabetes mellitus	72, 19.83%
Hypertension	29, 7.99%
Polycystic kidney disease	35, 9.64%
Urolithiasis	5, 1.38%
Gouty nephropathy	4, 1.10%
Obstructive uropathy (irrelevant to malignancy)	3, 0.83%
System disease (e.g., vasculitis, amyloidosis)	3, 0.83%
Nephrotoxic substance induced nephropathy	3, 0.83%
Single kidney after nephrectomy	10, 2.75%

The underlying causes of kidney disease are listed in Table 1. The first three main causes of kidney diseases in this study were glomerulonephritis (52.62%), diabetes mellitus, (19.83%) and polycystic kidney disease (9.64%). There were 47 patients (12.95%) had a prior history of malignancy, and 40.43% (19 patients) of which were urologic tumors. The median level of sIL-2R in this study was 1277 (1061, 1555) U/mL. 353 patients (97.25%) had a higher level of sIL-2R than the upper limit of the normal range (223–710 U/mL).

Malignancy events and its prognosis

During the 2-year follow-up period, malignancy events were detected in 15 patients (4.12%). Of these 15 patients, six patients (40%) had a prior history of malignancy. Patients with a prior history of malignancy had a higher incidence of malignancy events compared to those without a prior history of malignancy (12.77% vs. 2.85%, $\chi^2 = 10.16$, $P = 0.001$). The median malignancy events free time was 11.43 (8.73, 18.63) months. There was no significant difference between patients with [11.77 (7.86, 18.80) months] or without [11.43 (8.76, 17.73) months] a prior history of malignancy in terms of malignancy events free time ($P = 0.8137$). Details of malignancy events are listed in Table 2.

Demographic and laboratory characteristics were compared between patients with or without malignancy events (Table 3). In the group of patients developed malignancy events, more patients had a prior history of malignancy ($P = 0.001$). The dosages of ESA provided were larger ($P = 0.0479$). The levels of sIL-2R ($P = 0.0002$) and GGT ($P = 0.0017$) were also higher as compared with patients had no malignancy events during the same follow-up period. However, there were no significant differences in terms of other clinical parameters.

67 patients died during the study period. 13.43% (9 patients) of these deaths were due to malignancy. Of them, three cases had a prior history of malignancy. Patients had malignancy event during the follow-up period were at a higher risk of death as compared with those had no such experience. Two-year mortality was significantly reduced in patients with malignancy events (log-rank = 23.02, $P < 0.0001$) (Fig. 1).

Factors related to malignancy risk

Risk factors for malignancy events were evaluated among patient demographic characteristics and several laboratory factors. sIL-2R ≥ twofold of the normal upper limit value (710 U/mL) was regarded as high sIL-2R, whereas it was regarded as low sIL-2R. Univariate analysis revealed that high sIL-2R (used as a dichotomous variable), hemoglobin, GGT and a prior history of malignancy were significant predictors for malignancy events. However, only high sIL-2R level (OR 6.6, $P = 0.006$) and a prior history of malignancy (OR 4.12, $P = 0.018$) were identified as independent determinants in multivariate analysis (Table 4).

ROC analyses were used to access the performances of sIL-2R and a prior history of malignancy in predicting malignancy events and malignancy-related mortality in the following 2 years. Only sIL-2R (used as a continuous variable) showed the significantly predictive effect on these two outcomes (Fig. 2). The AUC for malignancy

Table 2 Malignancy events in patients with or without a prior history of treated malignancy

Malignancy events ($N = 15$)	Time to malignancy events (month)
Malignancy events in patients with a prior history of treated malignancy ——cancer history before enrolment ($N = 6$, 12.77%)	11.77 (7.86, 18.80)
Hepatic metastasis——1.24 years after colon cancer ($n = 1$)	19.30
Lung metastasis——1.75 years after colon cancer ($n = 1$)	8.73
Recurrence——7.34 years after bladder cancer ($n = 1$)	9.20
Recurrence——8.85 years after liver cancer ($n = 1$)	14.33
Secondary bladder cancer——7.50 years after renal caner ($n = 1$)	18.63
Secondary thyroid cancer——12.32 years after renal cancer ($n = 1$)	5.23
Malignancy events in patients without a prior history of malignancy ($N = 9$, 2.85%)	11.43 (8.76, 17.73)
Lung cancer ($n = 2$)	10.63/16.30
Mediastinal tumor ($n = 1$)	12.23
Leukemia ($n = 1$)	19.17
Lymphoma ($n = 1$)	22.83
Renal carcinoma ($n = 1$)	9.57
Colon adenocarcinoma ($n = 1$)	7.17
Breast cancer ($n = 1$)	11.43
Brain cancer ($n = 1$)	7.97

Table 3 Comparisons between patients with or without malignancy events

	Total ($N=363$)	With malignancy event ($N=15$, 4.13%)	Without malignancy event ($N=348$, 95.87%)	P value
Demographic characteristics				
A prior history of malignancy, *N* (%)	47 (12.95%)	6 (40%)	41 (11.78%)	0.001
Age (years)	62 (53, 70)	65 (58, 74)	61 (53, 70)	0.2419
Male, *N* (%)	221 (60.88%)	9 (60.00%)	212 (60.92%)	0.943
BMI (kg/m^2)	22.49 (20.70, 24.84)	22.36 (20.67, 24.40)	22.50 (20.67, 24.85)	0.9561
Infection of hepatitis, *N* (%)	29 (7.99%)	1 (6.67%)	28 (8.05%)	1.000
Diabetes, *N* (%)	103 (28.37%)	3 (20.00%)	100 (28.74%)	0.570
ESRD due to CGN, *N* (%)	191 (52.62%)	8 (53.33%)	183 (52.59%)	0.955
Presence of anuria, *N* (%)	261 (71.90%)	12 (80.00%)	249 (71.55%)	0.571
HD three times/week, *N* (%)	337 (92.84%)	14 (93.33%)	294 (92.82%)	0.939
Dialysis vintage, years	4.63 (2.39, 7.47)	3.45 (2.93, 4.70)	4.66 (2.38, 7.49)	0.3227
AVF access use, *N* (%)	297 (81.82%)	14 (93.33%)	283 (81.32%)	0.324
spKt/V	1.29 (1.14, 1.46)	1.29 (1.16, 1.33)	1.28 (1.14, 1.47)	0.8052
ESA dosage (units/week)	11,343. 67 ± 5592.76	14,138.93 ± 5355.55	11,223.18 ± 5578.67	0.0479
Laboratory characteristics				
sIL-2R (U/ mL)	1277 (1061, 1555)	1650 (1432, 2020)	1261.5 (1055.5, 1534)	0.0002
TNF-α (pg/mL)	33.4 (22.8, 59.3)	44.2 (29.8, 58.4)	32.95 (22.6, 59.45)	0.1934
IL-1β (pg/mL)	19 (5, 81.9)	22.1 (14, 160)	18.55 (5, 79.43)	0.2855
IL-6 (pg/mL)	9.8 (4.4, 41.4)	13.2 (6.2, 98.7)	9.7 (4.23, 39.33)	0.2440
IL-8 (pg/mL)	141 (27.1, 979)	228 (94.7, 2844)	138 (25.8, 956.25)	0.1371
IL-10 (pg/mL)	5 (5, 5)	5 (5, 5)	5 (5, 5)	0.0606
Neutrophil count (1×10^9/L)	4.2 (3.3, 5.2)	4.2 (2.9, 5.4)	4.2 (3.3, 5.18)	0.8801
Lymphocyte count (1×10^9/L)	1.2 (1, 1.6)	1.1 (0.7, 1.7)	1.2 (1, 1.6)	0.4035
Monocyte count (1×10^9/L)	0.51 (0.39, 0.67)	0.61 (0.35, 0.67)	0.51 (0.39, 0.67)	0.6294
Hemoglobin (g/L)	115 (105, 123)	110 (104, 117)	115 (105, 123)	0.1508
RDW (%)	14.1 (13.3, 15)	14.2 (13.7, 16.1)	14 (13.3, 14.9)	0.2170
hsCRP (mg/L)	3.9 (1.4, 10.3)	4.7 (2.5, 15.7)	3.8 (1.4, 10.3)	0.1477
Albumin (g/L)	39 (37, 41)	39 (36, 42)	39 (37, 41)	0.2821
Globulin (g/L)	32 (29, 35)	32 (31, 35)	32 (29, 35)	0.4369
AKP (U/L)	72 (57, 92)	92 (59, 115)	71 (57, 91)	0.0775
GGT (U/L)	20 (13, 33)	35 (19, 64)	20 (13, 31)	0.0017
LDH (U/L)	345 (277, 456)	397 (319, 474)	344 (277, 454)	0.2446
SCr (μmol/L)	1000.93 ± 273.80	1027.93 ± 274.70	999.77 ± 274.10	0.6971
UA (μmol/L)	436 (382, 496)	455 (425, 501)	436 (382, 495.75)	0.4389
β2-MG (mg/L)	38.96 (32.99, 43.18)	38.64 (38, 46.89)	38.97 (32.89, 43.09)	0.1531
iPTH (pg/mL)	264.2 (150.7, 408.1)	230.5 (79.4, 281.6)	268.6 (151.33, 408.33)	0.3676
Iron (μmol/L)	12.1 (8.63, 16.3)	11.5 (8.2, 14.4)	12.1 (8.65, 16.4)	0.3548
Ferritin (ng/mL)	248.4 (89.8, 446.5)	112.4 (54.2, 499.3)	250.6 (93.93, 434.44)	0.3548
Epoetin (mIU/mL)	19.1 (13.3, 33.1)	16.2 (14.9, 48.8)	19.1 (13.18, 33.03)	0.5366
Vitamin B_{12} (pg/mL)	574.1 (426.6, 1020)	604.7 (459.8, 2000)	571.4 (423.85, 1016.25)	0.5520
Follic acid (ng/mL)	5.6 (4.1, 8.8)	4.6 (4, 10.6)	5.6 (4.1, 8.78)	0.7362
HbA1c (%)	5.6 (5.28, 6.1)	5.8 (5.1, 6.3)	5.6 (5.3, 6.1)	0.7276
Prognosis				
All-cause death, *N* (%)	67 (18.46%)	9 (60.00%)	58 (16.67%)	< 0.0001
2-Year mortality (%)	82.64%	40%	84.48%	< 0.0001

BMI body-mass index, *ESRD* end-stage renal disease, *CGN* chronic glomerulonephritis, *HD* hemodialysis, *AVF* arteriovenous fistula, *ESA* erythropoietin-stimulating agent, *sIL-2R* soluble interleukin-2 receptor, *TNF-α* tumor necrosis Factor α, *IL* interleukin, *RDW* red blood cell distribution width, *hsCRP* high-sensitivity C-reactive protein, *AKP* alkaline phosphatase, *GGT* γ-glutamyl transferase, *LDH* lactate dehydrogenase, *SCr* serum creatinine, *UA* uric acid, *β2-MG* beta-2-microglobulin, *iPTH* intact parathyroid hormone, *HbA1c* glycosylated hemoglobin

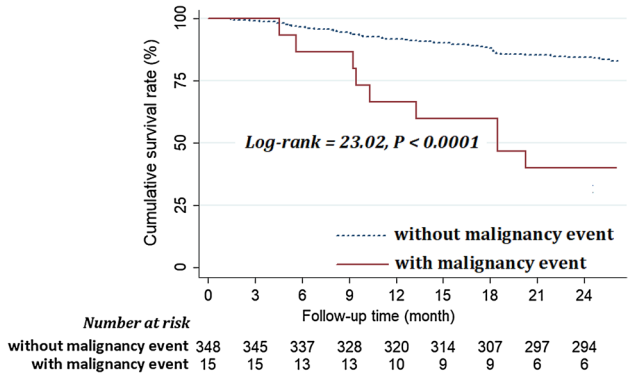

Fig. 1 Kaplan–Meier survival curves for patients with or without malignancy events during the 2-year follow-up period. Patients with malignancy events exhibited a significantly decreased survival compared to those without malignancy events (log-rank = 23.02, $P < 0.0001$)

events was 0.7889 (95% CI 0.6996, 0.8782), and the optimal cut-off value was 1539 U/mL with a sensitivity of 73.33% and specificity of 75.29%. The AUC for malignancy-related mortality was 0.8544 (95% CI 0.7787, 0.9300), and the optimal cut-off value was 1648 U/mL with a sensitivity of 88.89% and specificity of 81.36%.

There was no significant difference in the baseline level of sIL-2R between patients with [1340 (1093, 1637) U/mL] or without [1268 (1059.5, 1550.5) U/mL] a prior history of malignancy ($P = 0.4532$). In patients suffered from malignancy events, the baseline level of sIL-2R also was comparable between patients with [1591 (1417, 1787.5) U/mL] or without [1796 (1475, 2055.5) U/mL] a prior history of malignancy ($P = 0.4094$). However, patients suffered from malignancy events or died of malignancy were at a significantly higher baseline level of sIL-2R than those had no such experience. And this conclusion remained unchanged, no matter in patients with or without a prior history of malignancy (Fig. 3).

Discussion

Malignancy is a global issue. According to the Cancer statistics in China, the incidence rate in 2015 was 201.1 per 100,000 [19, 20]. In patients on chronic HD, this incidence is increased. Several studies have reported a higher risk of malignancy in HD patients than that in the general population [4, 21, 22]. In this study, we also observed the incidence of malignancy events during the 2-year follow-up period was extremely high (4.12%) compared to the general population, especially in those with a prior history of malignancy (12.77%). Even in those without a prior history of malignancy, this incidence was not rare and was nearly 1.5% per year, which was comparable to other studies [3, 23]. About 13.43% of deaths were related to malignancy. In patients who suffered from malignancy events during the follow-up period, overall survival was significantly decreased as compared to that in those had no such experience. Obviously, malignancy events will significantly reduce patient survival. In patients on dialysis, cancer contributes to an increased risk of non-vascular death [24] and has become the third leading cause of death next to CVD and infection in some district [25].

Cancer is an important cause of morbidity and mortality worldwide. It is wildly acknowledged that cancer–immune interactions play a crucial role in malignancy occurrence and progression. Cancer cell may make use of some regulative mechanisms to evade immune response and assure it has an optimal environment for growth [7]. Failure of the host immune system to detect and destroy transformed cells timely may result in uncontrollable proliferation and cancer progression [26]. Some immunological conditions may promote malignancy growth by inhibiting anticancer responses of the immune system [27, 28]. As described in several studies, immune dysfunction is a remarkable character of ESRD patients treated with HD due to the presence of persistent uremia status and the dialysis treatment itself [29–32]. This weakened immune system may result in reduced host immune surveillance and favor cancer initiation and progression [5].

Table 4 Logistic regression analysis of risk factors related to malignancy events

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
sIL-2R (high = 1; low = 0)	7.14 (1.98, 25.77)	0.003	6.6 (1.71, 25.77)	0.006
A prior history of malignancy (yes = 1; no = 0)	4.99 (1.69, 14.75)	0.004	4.12 (1.27, 13.30)	0.018
Hemoglobin per 1 g/L increase	0.97 (0.94, 0.99)	0.024	0.99 (0.96, 1.02)	0.384
GGT per 1 U/L increase	1.01 (1.00, 1.01)	0.012	1.01 (1.00, 1.02)	0.055

sIL-2R soluble interleukin-2 receptor, *GGT* transglutaminases, *OR* odds ratio, *CI* confidence interval

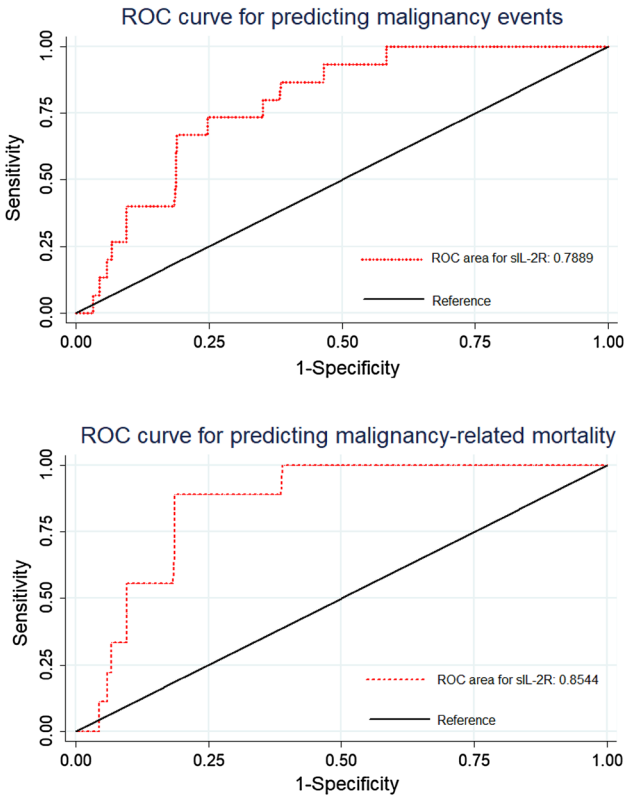

Fig. 2 ROC curves for sIL-2R in predicting malignancy events and malignancy-related mortality in HD patients. The AUC for malignancy events was 0.7889 (95% CI 0.6996, 0.8782), and the optimal cut-off value was 1539 U/mL with a sensitivity of 73.33% and specificity of 75.29%. The AUC for malignancy-related mortality was 0.8544 (95% CI 0.7787, 0.9300), and the optimal cut-off value was 1648 U/mL with a sensitivity of 88.89% and specificity of 81.36%

Elevated sIL-2R levels have been noted in a variety of disorders, including autoimmune diseases, inflammatory diseases, graft-versus-host diseases and cancers [7]. ESRD patients treated with chronic HD also presented a higher level of sIL-2R. Several researches have proven that elevated sIL-2R is prevalent among HD patients. Over 95% of HD patients have increased levels of sIL-2R by nearly 3–30 folds as compared to those in healthy individuals [9–15]. Elevation of sIL-2 levels in HD patients is related not only with the decreased renal clearance, but more importantly with the increased production [33]. As showed in previous studies, several factors may lead to an increase of sIL-2R in uremic patients treated with HD, such as patient-related factors, including patient characteristics, concomitant illnesses, inflammatory-nutritional status and the degree of immune activation. Besides, treatment-related factors, including exposure to cytokine-inducing substances in impure dialysate, as well as the bio-incompatibility of dialyzer and its pipeline during the dialysis session, also contribute to the increase in sIL-2R production [34, 14, 11, 35]. These abnormal amounts of sIL-2R in circulation may induce an

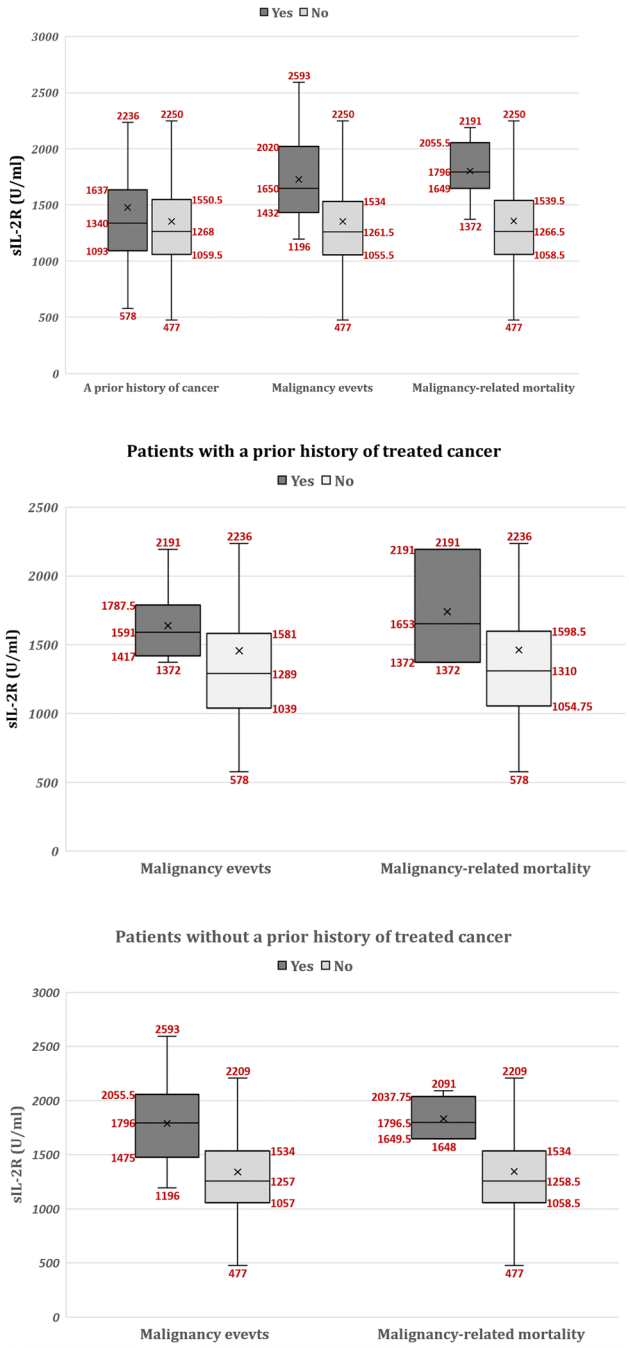

Fig. 3 Comparisons of the baseline sIL-2R levels in patients with different situations. The baseline levels of sIL-2R were comparable between patients with or without a prior history of malignancy ($P=0.4532$). However, patients suffered from malignancy events or died of malignancy always showed a significantly higher baseline level of sIL-2R. The boxes depicted the means (cross lines), medians (middle lines), 25th (bottom lines) and 75th (top lines) percentiles values; whereas the bars represented the intervals between the maximum and minimum values

imbalance of the IL-2/IL-2R system and interfere with IL-2-dependent functions.

In our previous study, we have evaluated the potential value of increased sIL-2R in HD patients. Results revealed that this increased level of sIL-2R had potential value in patient outcomes. Since sIL-2R is an immunomodulatory cytokine, in the present study, we aimed to further explore the effects of increased sIL-2R in the course of malignancy among HD patients. Our results showed that several factors may predispose HD patients to malignancy events. A prior history of malignancy is the main risk, largely due to the presence of undetected residual disease. Besides, patients suffered from malignancy events during the follow-up period seemed to have received a larger dosage of ESA treated for anemia and present a higher baseline level of GGT. ESA, as a pleiotropic growth factor, has an anti-apoptotic action on both normal and malignant cells [36]. Chronic ESA treatment may exhibit an adverse effect of on the management of cancer growth and progression. As for GGT, which is a marker of oxidative stress, also has been reported to be relevant to cancer risk [37]. However, among a variety of clinical parameters, only sIL-2R was identified as an independent determinant for malignancy events and showed a predicting power in malignancy-related mortality for patients treated with HD.

During the past 30 years, sIL-2R has gained much interest in cancer [7]. The concentrations of sIL-2R are significantly higher in patients with hematological and non-hematological malignancy, compared to those in general population [38]. In hematological disorders, sIL-2R is predominantly of lymphoproliferative origin [39, 40]. In patients with solid tumors, its source is more complex. It may be the consequence of augmented release from activated immune cells in response to malignant transformed cells; or may be shed from the surface of cancer cells themselves, such as melanoma cells [41], lung cancer cell [42], esophageal squamous cell [43], and colorectal cancer cells [44], etc. Moreover, some proteinases, such as matrix metalloproteinase (MMP)-9 in cancer microenvironment seem to have the ability of cleaving IL-2R alpha chain, thus contributing to the increased production of sIL-2R in circulation [45]. sIL-2R levels increase in patients with disseminated cancers, whereas keep in a stable range in those with locally limited lesions [46]. Hence, the level of sIL-2R may be helpful to reflect disease burden, activity and progression [7]. Numerous studies have regarded sIL-2R as a valuable cancer-related biomarker for various types of malignant disorders [47, 7]. However, considering the immunological effect of sIL-2R, it is possible that sIL-2R may have a biological role in cancer process.

Theoretically, sIL-2R may present inhibitory effects, immunostimulatory effects or no effect on immune response. The possible underlying mechanisms of the above functional effects can be summarized as follow: sequestration of IL-2 from the membrane receptor [8], protection of IL-2 from degradation [48] and induction of conformational change in IL-2 [49]. In the process of cancer immunoediting, suppression of IL-2R signaling [8], activation of cancer-friendly CD4 + Treg cells [50, 51], inhibition of anticancer activity of cytotoxic CD8 T cells [50], as well as stimulation of cancer cell proliferation [7, 40, 52, 53] were reported to be associated with sIL-2R release, which suggested that increased sIL-2R promoted immunosuppression and immune tolerance to malignant transformed cells [50, 54]. Our study also showed that elevated sIL-2R was commonly seen in serum of HD patients with a median level of 1277 (1061, 1555) IU/mL. And this elevated level of sIL-2R was significantly related to an increased risk of malignancy in the following days. In patients with a prior history of malignancy, sIL-2R seemed to facilitate cancer relapse and metastasis. And in those without a prior history of malignancy, sIL-2R also seemed to have created a suitable environment for cancer cells to settle. Though the exact role of sIL-2R in the course of malignancy is not yet fully be elucidated, it is most likely to block IL-2- dependent anticancer immunity by binding it.

Since increased IL-2R level in HD patients is correlated with the degree of uremia, anemia, nutrition and inflammatory as showed in previous study [12, 55], efforts on eliminating risk factors that probably influence the level of sIL-2R, such as correcting nutritional-inflammatory abnormalities, as well as improving the quality of dialysis therapy (e.g., increasing the dose of dialysis, using high-flux dialyzer with more biocompatible membrane and providing ultrapure dialysate for dialysis) may lead to a fall in sIL-2R concentration. However, whether these improvements can reverse the impaired immune response remains unclear.

In this study, patients who had a prior history of malignancy after radical resection but showed no evidence of recurrence or metastasis at the enrollment were enrolled. It was possible that recurrences or metastases already existed in some of these patients before the enrollment, since they presented a higher baseline level of sIL-2R. But this level was comparable to that in patients without a prior history of malignancy. Potential lesions probably existed in both groups, but these lesions might be too small to be detected by the routine cancer screenings, such as physical examinations, X-ray and ultrasound tests. At least, we did not find any malignant lesions at the sites of liver, lung, urinary tract, etc., before the enrollment in this study. Thus, all patients were included and analyzed to detected "clinically apparent" malignancy events during the follow-up period.

Increased sIL-2R was not just an indicator for potential lesions, more importantly, the its persistent existence in serum presented an ideal environment for cancer growth, relapse and metastasis, thus leading to an increased risk of malignancy in the following days, especially in patients with

a prior history of malignancy. Cancer screening bias could exist in this group, despite the uniform follow-up programs for all patients. Nevertheless, sIL-2R consistently showed the effects on malignancy risk, no matter in patients with or without a prior history of malignancy. In view of the effect of sIL-2R on malignancy-related risk, a more frequent observation and a selective cancer screening are recommended for patients at a high level of sIL-2R, especially those had a prior history of malignancy. Since this study is limited by the small sample size from a single institution, further validation from multicenter with a larger cohort and a longer follow-up is warranted to confirm the significance of sIL-2R in the course of malignancy. Besides, whether elevated sIL-2R has different effects on oncogenesis and metastasis; or whether it plays a different role in hematological and non-hematological malignancies also need further investigations.

Regardless the limitations, our data suggests that elevated level of sIL-2R was prevalent in HD patients, which provided an optimal environment for cancer formation and progression. sIL-2R is not just a biomarker, it may also exert biological effects in the course of cancer and contributed to an increased risk for malignancy. So, sIL-2R may be used as a therapeutic target. Efforts on correction of sIL-2R levels may be helpful but need evaluated by further studies.

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Compliance with ethical standards

Conflict of interest We declare no conflict of interest.

Informed consent Informed consents were obtained from all individual participants included in the study.

References

1. Chien CC, Han MM, Chiu YH et al (2017) Epidemiology of cancer in end-stage renal disease dialysis patients: a national cohort study in Taiwan. J Cancer 8(1):9–18. https://doi.org/10.7150/jca.16550
2. Cheung CY, Chan GC, Chan SK et al (2016) Cancer incidence and mortality in chronic dialysis population: a multicenter cohort study. Am J Nephrol 43(3):153–159. https://doi.org/10.1159/000445362
3. Butler AM, Olshan AF, Kshirsagar AV et al (2015) Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996–2009. Am J Kidney Dis 65(5):763–772. https://doi.org/10.1053/j.ajkd.2014.12.013
4. Maisonneuve P, Agodoa L, Gellert R et al (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet (London, England) 354(9173):93–99
5. Vamvakas S, Bahner U, Heidland A (1998) Cancer in end-stage renal disease: potential factors involved—editorial. Am J Nephrol 18(2):89–95. https://doi.org/10.1159/000013314
6. Bayer AL, Pugliese A, Malek TR (2013) The IL-2/IL-2R system: from basic science to therapeutic applications to enhance immune regulation. Immunol Res 57(1–3):197–209. https://doi.org/10.1007/s12026-013-8452-5
7. Bien E, Balcerska A (2008) Serum soluble interleukin 2 receptor alpha in human cancer of adults and children: a review. Biomarkers Biochem Indic Expo Response Susceptibility Chem 13(1):1–26. https://doi.org/10.1080/13547500701674063
8. Rubin LA, Kurman CC, Fritz ME et al (1985) Soluble interleukin 2 receptors are released from activated human lymphoid cells in vitro. J Immunol (Baltimore, Md: 1950) 135(5):3172–3177
9. Memoli B, Libetta C, De Nicola L et al (1996) Hemodialysis related interleukin-2 receptor release by peripheral blood mononuclear cells. ASAIO J (Am Soc Artif Intern Org: 1992) 42(1):60–63
10. Daichou Y, Kurashige S, Hashimoto S et al (1999) Characteristic cytokine products of Th1 and Th2 cells in hemodialysis patients. Nephron 83(3):237–245
11. Beaurain G, Naret C, Marcon L et al (1989) In vivo T cell preactivation in chronic uremic hemodialyzed and non-hemodialyzed patients. Kidney Int 36(4):636–644
12. Sennesael JJ, Demanet CG, Verbeelen DL (1995) Serum soluble interleukin 2 receptor in hemodialysis patients treated with recombinant human erythropoietin. Blood Purif 13(6):347–356. https://doi.org/10.1159/000170219
13. Mehta R, Shah G, Adler W et al (2004) Soluble interleukin 2 receptor (sIL-2R) levels in renal transplant recipients. Clin Transpl 18(Suppl 12):67–71. https://doi.org/10.1111/j.1399-0012.2004.00221.x
14. Shu KH, Lu YS, Cheng CH et al (1998) Soluble interleukin 2 receptor in dialyzed patients. Artif Org 22(2):142–144
15. Holtkamp W, Brodersen HP, Stollberg T et al (1993) Zinc supplementation stimulates tetanus antibody formation and soluble interleukin-2 receptor levels in chronic hemodialysis patients. Clin Investig 71(7):537–541
16. Ding X (2016) SIKD is on the road. Blood Purif 42(1):I–vi. https://doi.org/10.1159/000442281
17. Cao XS, Chen J, Zou JZ et al (2015) Association of indoxyl sulfate with heart failure among patients on hemodialysis. Clin J Am Soc Nephrol 10(1):111–119. https://doi.org/10.2215/cjn.04730514
18. Daugirdas JT (1993) Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol JASN 4(5):1205–1213
19. Chen W, Zheng R, Baade PD et al (2016) Cancer statistics in China, 2015. CA Cancer J Clin 66(2):115–132. https://doi.org/10.3322/caac.21338
20. Chen WQ, Zheng RS, Zeng HM et al (2012) Trend analysis and prediction of cancer incidence in China. Zhonghua yu fang yi xue za zhi [Chin J Prev Med] 46(7):581–586
21. Matas A, Simmons R, Kjellstrand C et al (1975) Increased incidence of malignancy during chronic renal failure. Lancet (London, England) 1(7912):883–886
22. Cengiz K (2002) Increased incidence of neoplasia in chronic renal failure (20-year experience). Int Urol Nephrol 33(1):121–126
23. Lin HF, Li YH, Wang CH et al (2012) Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. Nephrol Dial Transpl 27(4):1585–1590. https://doi.org/10.1093/ndt/gfr464
24. Wong G, Staplin N, Emberson J et al (2016) Chronic kidney disease and the risk of cancer: an individual patient data meta-analysis of 32,057 participants from six prospective studies. BMC Cancer 16:488. https://doi.org/10.1186/s12885-016-2532-6

25. Yoo KD, Lee JP, Lee SM et al (2017) Cancer in Korean patients with end-stage renal disease: a 7-year follow-up. PLoS ONE 12(7):e0178649. https://doi.org/10.1371/journal.pone.0178649
26. Igney FH, Krammer PH (2002) Immune escape of tumors: apoptosis resistance and tumor counterattack. J Leukoc Biol 71(6):907–920
27. Poggi A, Zocchi MR (2006) Mechanisms of tumor escape: role of tumor microenvironment in inducing apoptosis of cytolytic effector cells. Arch Immunol Ther Exp 54(5):323–333. https://doi.org/10.1007/s00005-006-0038-7
28. Chouaib S, Thiery J, Gati A et al (2002) Tumor escape from killing: role of killer inhibitory receptors and acquisition of tumor resistance to cell death. Tissue Antigens 60(4):273–281
29. Xiang FF, Zhu JM, Cao XS et al (2016) Lymphocyte depletion and subset alteration correlate to renal function in chronic kidney disease patients. Ren Fail 38(1):7–14. https://doi.org/10.3109/0886022x.2015.1106871
30. Xiang F, Chen R, Cao X et al (2018) Monocyte/lymphocyte ratio as a better predictor of cardiovascular and all-cause mortality in hemodialysis patients: a prospective cohort study. Hemodial Int Int Symp Home Hemodial 22(1):82–92. https://doi.org/10.1111/hdi.12549
31. Guo M, Chen R, Xiang F et al (2018) Decreased percentage of memory B cells is independently associated with increased susceptibility to infection in patients on maintenance hemodialysis. Int Urol Nephrol. https://doi.org/10.1007/s11255-018-1977-8
32. Chen R, Xiang F, Hu J et al (2017) Factors associated with the elevated percentage of CD4CD69 T cells in maintained hemodialysis patients. Ren Fail 39(1):547–554. https://doi.org/10.1080/0886022x.2017.1349672
33. Descamps-Latscha B, Herbelin A, Nguyen AT et al (1995) Balance between IL-1 beta, TNF-alpha, and their specific inhibitors in chronic renal failure and maintenance dialysis Relationships with activation markers of T cells, B cells, and monocytes. J Immunol (Baltimore, Md: 1950) 154(2):882–892
34. Chatenoud L, Dugas B, Beaurain G et al (1986) Presence of preactivated T cells in hemodialyzed patients: their possible role in altered immunity. Proc Natl Acad Sci USA 83(19):7457–7461
35. Schiffl H, Lang SM, Stratakis D et al (2001) Effects of ultrapure dialysis fluid on nutritional status and inflammatory parameters. Nephrol Dial Transpl 16(9):1863–1869
36. Debeljak N, Solar P, Sytkowski AJ (2014) Erythropoietin and cancer: the unintended consequences of anemia correction. Front Immunol 5:563. https://doi.org/10.3389/fimmu.2014.00563
37. Fentiman IS (2012) Gamma-glutamyl transferase: risk and prognosis of cancer. Br J Cancer 106(9):1467–1468. https://doi.org/10.1038/bjc.2012.128
38. Nakase K, Tsuji K, Tamaki S et al (2005) Elevated levels of soluble interleukin-2 receptor in serum of patients with hematological or non-hematological malignancies. Cancer Detect Prev 29(3):256–259. https://doi.org/10.1016/j.cdp.2005.03.001
39. Nakase K, Kita K, Nasu K et al (1994) Differential expression of interleukin-2 receptors (alpha and beta chain) in mature lymphoid neoplasms. Am J Hematol 46(3):179–183
40. Nakase K, Kita K, Shirakawa S et al (1994) Induction of cell surface interleukin 2 receptor alpha chain expression on non-T lymphoid leukemia cells. Leuk Res 18(11):855–859
41. Rimoldi D, Salvi S, Hartmann F et al (1993) Expression of IL-2 receptors in human melanoma cells. Anticancer Res 13(3):555–564
42. Yano T, Fukuyama Y, Yokoyama H et al (1996) Interleukin-2 receptors in pulmonary adenocarcinoma tissue. Lung Cancer (Amst, Neth) 16(1):13–19
43. Wang LS, Chow KC, Li WY et al (2000) Clinical significance of serum soluble interleukin 2 receptor-alpha in esophageal squamous cell carcinoma. Clin Cancer Res 6(4):1445–1451
44. Huang A, Quinn H, Glover C et al (2002) The presence of interleukin-2 receptor alpha in the serum of colorectal cancer patients is unlikely to result only from T cell up-regulation. Cancer Immunol Immunother CII 51(1):53–57. https://doi.org/10.1007/s00262-001-0250-6
45. De Paiva CS, Yoon KC, Pangelinan SB et al (2009) Cleavage of functional IL-2 receptor alpha chain (CD25) from murine corneal and conjunctival epithelia by MMP-9. J Inflamm (Lond, Engl) 6:31. https://doi.org/10.1186/1476-9255-6-31
46. Berghella AM, Pellegrini P, Piancatelli D et al (1994) Progression mechanisms in colon cancer: soluble interleukin-2 (IL-2) receptor, IL-2 plus anti-CD3 proliferative response and tumour stage correlations. Cancer Immunol Immunother CII 38(3):160–166
47. Murakami S (2004) Soluble interleukin-2 receptor in cancer. Front Biosci J Virtual Libr 9:3085–3090
48. Kobayashi H, Tagaya Y, Han ES et al (1999) Use of an antibody against the soluble interleukin 2 receptor alpha subunit can modulate the stability and biodistribution of interleukin-2. Cytokine 11(12):1065–1075. https://doi.org/10.1006/cyto.1999.0509
49. Wang X, Rickert M, Garcia KC (2005) Structure of the quaternary complex of interleukin-2 with its alpha, beta, and gammac receptors. Science (New York, NY) 310(5751):1159–1163. https://doi.org/10.1126/science.1117893
50. Yang ZZ, Grote DM, Ziesmer SC et al (2011) Soluble IL-2Ralpha facilitates IL-2-mediated immune responses and predicts reduced survival in follicular B-cell non-Hodgkin lymphoma. Blood 118(10):2809–2820. https://doi.org/10.1182/blood-2011-03-340885
51. Brivio F, Lissoni P, Fumagalli L et al (2008) Correlation between soluble IL-2 receptor serum levels and regulatory T lymphocytes in patients with solid tumors. Int J Biol Mark 23(2):121–122
52. Kasprzak A, Olejniczak K, Przybyszewska W et al (2007) Cellular expression of interleukin 2 (IL-2) and its receptor (IL-2R, CD25) in lung tumours. Folia Morphol 66(3):159–166
53. Kuhn DJ, Dou QP (2005) The role of interleukin-2 receptor alpha in cancer. Front Biosci J Virtual Libr 10:1462–1474
54. Nukui A, Masuda A, Abe H et al (2017) Increased serum level of soluble interleukin-2 receptor is associated with a worse response of metastatic clear cell renal cell carcinoma to interferon alpha and sequential VEGF-targeting therapy. BMC Cancer 17(1):372. https://doi.org/10.1186/s12885-017-3369-3
55. Zaoui P, Green W, Hakim RM (1991) Hemodialysis with cuprophane membrane modulates interleukin-2 receptor expression. Kidney Int 39(5):1020–1026