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The prognostic significance of TARC in patients with classical Hodgkin lymphoma: a retrospective and prospective study

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Article

Keywords: Classical Hodgkin lymphoma, TARC, CCL17, immunohistochemistry, prognosis, treatment response

Posted Date: September 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10670933/v1

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Additional Declarations: No competing interests reported.

Abstract

Classical Hodgkin lymphoma (cHL) is a highly curable malignancy; however, a subset of patients experience treatment failure or relapse, highlighting the need for reliable predictive biomarkers. Thymus and activation-regulated chemokine (TARC/CCL17), produced by Hodgkin Reed–Sternberg cells, may reflect tumour microenvironment activity. This combined retrospective and prospective cohort study included 113 adults with newly diagnosed cHL treated between 2022 and 2025. Pretreatment tissue TARC expression was assessed by immunohistochemistry in lymph node biopsy specimens, and associations with treatment response and outcomes were analysed. TARC expression was detected in 94.7% of patients and was not significantly associated with treatment response when analysed as a binary variable. In contrast, patients with non-complete response had significantly higher TARC levels than complete responders (83.9% vs 52.3%, $p < 0.001$). A tissue TARC level > 70% predicted non-complete response (AUC = 0.778; sensitivity 71.4%; specificity 75.3%) and was associated with inferior 1-year freedom from progression and overall survival. Pretreatment tissue TARC level, rather than its mere expression, may provide complementary prognostic information in cHL.

Introduction

Classical Hodgkin lymphoma (cHL) is a unique disease characterized by a distinct tumour microenvironment that plays a central role in determining its clinical behaviour and response to treatment.[1, 2] In resource-abundant settings, cHL has an incidence of approximately 2–3 cases per 100,000 persons per year, accounting for around 10% of all lymphomas, 0.5% of all cancers, and 0.2% of cancer-related deaths. The disease demonstrates a bimodal age distribution, with a first peak in adolescents and young adults and a second peak in older individuals.3

Over recent decades, advances in multimodal therapy have resulted in high cure rates exceeding 80–90%, particularly in early-stage disease.[4–8] However, these favourable outcomes are accompanied by significant long-term toxicities, including cardiovascular disease, secondary malignancies and infertility, especially in patients exposed to more intensive treatment strategies.[9–13]

Current therapeutic approaches therefore focus on balancing treatment efficacy with long-term safety through risk-adapted strategies incorporating established prognostic factors and validated scoring systems.[14–16] In this context, there remains a need for reliable biomarkers to refine risk stratification and guide individualized treatment decisions.

Thymus and activation-regulated chemokine (TARC/CCL17) has emerged as a promising biomarker in cHL. It is highly expressed by Hodgkin Reed–Sternberg (HRS) cells and plays a central role in shaping the tumour microenvironment through recruitment of CCR4-positive T-helper 2 and regulatory T cells.[17, 18] This interaction promotes a cytokine-driven feedback loop involving activation of the JAK/STAT signalling pathway, which may contribute to tumour persistence and progression. In this context, the present study was designed to evaluate the prognostic significance of pretreatment TARC expression,

assessed by immunohistochemistry, and to determine its association with established prognostic factors and clinical outcomes in patients with classical Hodgkin lymphoma.

Results

Patient characteristics

A total of 113 patients with classical Hodgkin lymphoma were included. There was a male predominance (74.3%), with a median age of 32 years (IQR: 24–50) and a mean age of 36.8 ± 15.9 years. Lymphocyte-rich classical Hodgkin lymphoma was the most frequent histological subtype (39.8%), followed by mixed cellularity (21.2%), lymphocyte-depleted (20.4%), and nodular sclerosis (18.6%). (Fig. 1) At presentation, 60.1% of patients had early-stage disease (I–II), while 39.8% presented with advanced-stage disease (III–IV). B symptoms were reported in the majority of patients (92.9%). Pretreatment ESR ranged from 10 to 80 mm/hr (normal level: 15–30 mm/hr), while LDH ranged from 100 to 333 U/L (normal level: 100–250 U/L). Adverse prognostic features were frequently observed, including involvement of ≥ 3 lymph node regions (44.2%), bulky mediastinal disease (37.2%), hypoalbuminemia (38.1%) (normal albumin level: 3.5-5 g/dl), anemia (29.2%) (normal haemoglobin level 12-17.5g/dl), and bone marrow infiltration (15%). (Table 1)

Table 1
Distribution of the studied cases according to baseline characteristics.

Sex	**Number**	**Percentage**
Male	84	74.3
Female	29	25.7
Histopathological subtypes		
Nodular sclerosis	21	18.6
Lymphocyte-rich	45	39.8
Mixed cellularity	24	21.2
Lymphocyte-depleted	23	20.4
Staging		
Stage I	38	33.6
Stage II	30	26.5
Stage III	25	22.1
Stage IV	20	17.7
B symptoms		
No	8	7.1
Yes	105	92.9
Established prognostic factors		
Bone marrow (BM) infiltration	17	15.0
Extensive lymphadenopathy (3 or more lymphadenopathy regions)	50	44.2
Bulky mediastinal (med) mass	42	37.2
Albumin < 4 g/dl	43	38.1
HB < 10.5 g/dl	33	29.2
WBCs > 15 × 10^9/L	18	15.9
Lymphocytes < 0.6 × 10^9/L	18	15.9
Age (years)		
Min – Max.	18.0–94.0	

Sex	Number	Percentage
Mean ± SD.	36.80 ± 15.90	
Median (IQR)	32.0 (24.0–50.0)	
ESR (mm/hr)		
Min – Max.	10.0–80.0	
Mean ± SD.	39.82 ± 20.97	
Median (IQR)	30.0 (20.0–50.0)	
LDH (U/L)		
Min – Max.	100.0–333.0	
Mean ± SD.	195.3 ± 52.55	
Median (IQR)	190.0 (150.0–220.0)	

Treatment characteristics and response

Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD) was the most commonly administered regimen in 80 patients (70% of the studied cases), followed by Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine and Prednisolone (BEACOPP) in 27 patients (23.9% of the studied cases), while Adriamycin, Vinblastine and Dacarbazine (AVD) was used in 5 patients (4.4% of the studied cases). Brentuximab Vedotin and Bendamustine (BB) was administered to 1 patient only (0.9% of the studied cases). Complete response was achieved in 85 patients, whereas 28 cases (24.8% of the studied patients) had a non-complete response. The non-complete responders group included those who had either partial response, stable disease or progressive disease. Out of a total of 85 cases, 24 patients experienced relapse, representing 28.2% of the sample, while 61 patients did not experience relapse, accounting for 71.8%. This indicates that the majority of the studied cases remained relapse-free. Regarding the time to relapse among the 24 relapsed cases, 17 cases experienced relapse within 12 months. In contrast, only 7 cases relapsed after 12 months. (Table 2)

Table 2
Distribution of the studied cases according to the initial chemotherapy protocol and treatment response.

Protocol of initial chemotherapy	No.	%
ABVD	80	70.8
AVD	5	4.4
BB	1	0.9
BEACOPP	27	23.9
Brentuximab Vedotin as salvage therapy		
No	99	87.6
Yes	14	12.4
Complete Response (CR)		
Yes	85	75.2
No	28	24.8
Non-complete Response		
Partial response	10	35.8
Stable disease	6	21.4
Progressive disease	12	42.8
Total	28	100
Relapse		
Yes	24	28.2
No	61	71.8
Total	85	100
Time to relapse		
Less than 12 months	17	70.8
More than 12 months	7	29.2
Total	24	100

Tissue TARC expression and treatment response

TARC expression was detected in 94.7% of patients, with levels ranging from 0 to 100% (mean 60.1 ± 33.5%). Binary TARC expression (present vs absent) was not significantly associated with treatment response. In contrast, quantitative analysis demonstrated significantly higher mean TARC levels in patients with non-complete response compared to complete responders (83.9 ± 23.8 vs 52.3 ± 32.6; $p < 0.001$). Receiver operating characteristic (ROC) curve analysis identified a tissue TARC cut-off value > 70% for predicting non-complete response, with an area under the curve (AUC) of 0.778, sensitivity of 71.4%, and specificity of 75.3%. Patients with tissue TARC level > 70% were significantly more likely to exhibit non-complete response compared to those with lower levels ($p < 0.001$) (Table 3 and Fig. 2).

Table 3
Relation between tissue TARC expression and level and treatment response.

TARC Parameter		Complete Response (n = 85)	Non-Complete Response (n = 28)	Statistical test	p-value
TARC expression	Absent	5 (5.9%)	1 (3.6%)	2 = 0.224	1.000
TARC expression	Present	80 (94.1%)	27 (96.4%)		
TARC level (continuous)	Min – Max	0.0-100.0	0.0-100.0	U = 528.5	< 0.001*
TARC level (continuous)	Mean SD	52.29 32.62	83.93 23.78		
TARC level (continuous)	Median (IQR)	50.0 (20.0–70.0)	90.0(70 − 0–100.0)		
TARC level (cut-off)	≤ 70%	64 (75.3%)	8 (28.6%)	2 = 19.888	< 0.001*
TARC level (cut-off)	> 70%	21 (24.7%)	20 (71.4%)		

Kaplan–Meier analysis further confirmed significantly inferior 1 year freedom from progression and 1 year overall survival among patients with elevated TARC levels (Fig. 3a,b).

Predictors of non-complete response

Univariate analysis demonstrated that multiple clinical and laboratory variables were significantly associated with non-complete response, including bone marrow infiltration, extensive nodal involvement, bulky disease, anemia, hypoalbuminemia, leukocytosis, lymphopenia, and elevated TARC levels (all $p < 0.001$) (Table 4). In multivariate analysis, only bulky mediastinal mass (AOR = 7.0; $p = 0.015$) and hemoglobin < 10.5 g/dL ($p = 0.008$) remained independent predictors of non-complete response. (Table 4)

Table 4
Univariate and multivariate analysis of predictors of non-complete response.

Non-complete response Vs Complete response	**Univariate**	**Univariate**	**Multivariate**	**Multivariate**
Non-complete response Vs Complete response	p	OR (95%C.I)	p	AOR (95%C.I)
Bone marrow (BM) infiltration	< 0.001*	112.000 (13.594–922.775)	0.104	8.181 (0.651–102.783)
3 or more nodes regions	< 0.001*	33.042 (7.272–150.136)	0.150	4.112 (0.601–28.120)
Bulky mediastinal mass	< 0.001*	15.979 (5.354–47.691)	0.015*	7.009 (1.466–33.505)
Albumin < 4 g/dl	< 0.001*	14.950 (5.030–44.432)	0.116	3.440 (0.738–16.041)
HB < 10.5 g/dl	< 0.001*	34.500 (10.700–111.243)	0.008*	0.155 (0.039–0.620)
WBCs > 15 109 /L	< 0.001*	55.333 (11.287–271.266)	0.086	0.180 (0.026–1.274)
Lymphocyte < 0.6 109 /L	< 0.001*	55.333 (11.287–271.266)	0.086	5.544 (0.785–39.167)
TARC level (> 70%)	< 0.001*	7.619 (2.927–19.832)	0.435	1.696 (0.451–6.383)

Discussion

In this study, the clinical significance of pretreatment tissue TARC expression in patients with classical Hodgkin lymphoma and its association with treatment response and survival outcomes were evaluated. The findings of the present study demonstrated that while tissue TARC expression was highly prevalent, its quantitative level rather than its mere presence carried significant prognostic value. Unlike most previous studies that focused primarily on serum TARC levels, the present study specifically assessed TARC expression by immunohistochemical staining of lymph node tissue, providing direct evaluation of the tumour microenvironment.

TARC expression was detected in 94.7% of the patients, similar to previous reports. Driessen et al. [26] reported immunohistochemical positivity in approximately 86% of cases, while Kilsdonk et al. [20] observed positivity in up to 92%, with strong staining in 77% of Hodgkin Reed–Sternberg cells. However, this high prevalence limits its discriminatory and prognostic value when assessed qualitatively, supporting the need for quantitative evaluation.

Moreover, the results of the present study showed that quantitative TARC levels were significantly higher in patients with non-complete response. This is consistent with findings by Sauer et al. [27] who demonstrated that elevated pretreatment serum TARC levels were significantly associated with an unfavorable response to therapy. In addition, Plattel et al. [28] showed that combining serum TARC with interim FDG-PET improves response evaluation compared to PET alone, supporting its added value in early treatment assessment. Similarly, Kopińska et al. [29] reported that TARC levels are elevated at diagnosis, decline with treatment, and higher baseline levels are associated with poorer outcomes, supporting its role as a marker of disease activity and treatment response.

Emerging evidence suggests that TARC may serve as a biomarker beyond initial response assessment. Lawrence [30] demonstrated that serum TARC levels can be elevated years prior to clinical diagnosis, indicating a potential role in early disease detection. Likewise, Teesink et al. [31] reported that rising TARC levels during follow-up may precede clinical relapse, supporting its utility as a dynamic marker for disease monitoring. Collectively, these findings highlight that TARC reflects disease burden and treatment response in a dynamic manner and may have greater clinical relevance when assessed longitudinally rather than as a static parameter. Furthermore, Weihrauch et al. [32] demonstrated that TARC levels in patients with progressive disease (PD) were higher than those in patients with continuous complete remission (CCR) both at baseline and after therapy. Baseline TARC levels also showed significant correlations with disease stage, erythrocyte sedimentation rate, leukocyte count, and lymphocyte count. In addition, post-treatment TARC levels > 2,000 pg/mL were associated with significantly poorer survival, supporting the potential role of TARC monitoring in evaluating treatment success and disease progression in Hodgkin lymphoma.

In contrast, Prochazka et al. [33] found that TARC did not show any significant correlation with complete response, highlighting inconsistencies in the literature and suggesting that its predictive value may depend on the method and timing of assessment.

The ROC analysis in the present study identified an initial tissue TARC expression cut-off value > 70% with a predictive accuracy of 74.34%. Similarly, Guidetti et al. [34] identified a serum TARC cut-off level of 800 pg/ml prior to treatment to discriminate between normal and abnormal values, with elevated baseline levels observed in the majority of patients. They further demonstrated that TARC levels significantly decrease during treatment, and that lower interim TARC (iTARC) levels are associated with treatment success and negative interim PET/CT after 2 cycles (PET-2). To the best of our knowledge, the present study is the first study to define a cut-off level of TARC expression for prognostic stratification based on immunohistochemical staining of lymph node specimens.

From a prognostic standpoint in this study, higher pretreatment TARC levels were associated with significantly inferior 1 year freedom from progression (FFP) and 1 year overall survival ($p < 0.001$). These findings are supported by previous studies demonstrating that elevated or persistently high interim TARC (iTARC) levels are associated with inferior progression-free survival (PFS). Bachanova et al. [35] showed that PFS at 12 months decreases progressively with increasing iTARC levels, while Viviani et al. [36] reported that higher iTARC levels (> 800 pg/ml) were associated with significantly worse PFS, even among patients with negative PET-2. Furthermore, a retrospective Egyptian study from Ain Shams University Hospitals identified advanced stage at presentation, B symptoms, ECOG performance status, interim PET/CT findings, and radiotherapy as significant prognostic factors affecting survival outcomes and event-free survival in Hodgkin lymphoma patients [37].

Another Egyptian study also demonstrated that advanced disease stages, high ESR, hypoalbuminemia, and B symptoms were more prevalent in Egyptian patients compared with the worldwide reports, with lower complete response rates after initial treatment. The study further highlighted that Hodgkin lymphoma in Egypt may exhibit a distinct regional pattern characterized by earlier age of presentation, male predominance, and higher burden of adverse prognostic factors, emphasizing the need for optimized risk stratification and individualized treatment approaches in the Egyptian population [38].

In the present study multivariate regression analysis demonstrated that TARC did not remain an independent predictor, while bulky mediastinal disease and anemia retained their significance. The apparent effect of TARC might therefore reflect its association with these underlying disease characteristics rather than acting as an independent driver. In contrast, Sauer et al. [27] showed that elevated baseline serum TARC remained an independent predictor of treatment response in multivariate regression analysis, with levels ≥ 10,000 pg/ml associated with an approximately threefold higher risk of treatment failure. Similarly, Guidetti et al. [34] demonstrated that lower interim TARC (≤ 800 pg/ml) was associated with significantly improved 5-year PFS (90.1% vs 55.6%) and remained an independent predictor of PFS in multivariable regression analysis.

Strengths and limitations

The present study has several strengths, including the integration of clinical, laboratory, and biomarker data in a well-defined cohort of patients with Classical Hodgkin Lymphoma, the use of standardized diagnostic and PET-based response assessment, and the evaluation of TARC as a quantitative biomarker with identification of a clinically relevant cut-off. Notably, to the best of our knowledge, this is the first Egyptian study, and among the very few worldwide, to evaluate TARC expression using immunohistochemical assessment of lymph node tissue rather than serum-based analysis alone, providing direct tissue-based prognostic insight. In addition, the analysis of TARC in relation to established prognostic factors enhances the clinical applicability of the findings. However, limitations include the inclusion of a partially retrospective component, the lack of serial TARC assessments, and the relatively short follow-up duration. These factors may limit broader generalisation and long-term interpretation of the findings.

Methods

This was a combined retrospective and prospective cohort study of patients with classical Hodgkin lymphoma. A total of 113 adult patients were managed at the Haematology Unit and Outpatient Haematology Clinic, Internal Medicine Department, Alexandria Main University Hospital, and Damanhour Oncology Center between June 2022 and June 2025. 70 patients were prospectively enrolled, while 43 patients were retrospectively identified from archived records.

Sample size was calculated using Epi Info software [19] assuming a power of 80% and a confidence level of 95%, based on a reported TARC prevalence of 92% in Hodgkin lymphoma [20], yielding a minimum required sample of 113 patients.20

Eligible patients were aged ≥ 18 years with newly diagnosed classical Hodgkin lymphoma according to the WHO 2022 classification [21] and eligible for treatment. Patients with prior therapy, severe comorbidities precluding treatment, pregnancy, age < 18 years, or nodular lymphocyte-predominant Hodgkin lymphoma were excluded.

Ethics

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Alexandria University (ethical approval number: 0201989). Written informed consent was obtained from all prospectively enrolled patients. For the retrospectively identified patients, the requirement for informed consent was waived by the Research Ethics Committee, and retrospective data were obtained from archived medical records in accordance with the approved institutional ethical protocol, with strict confidentiality of patient records maintained.

Baseline Assessment, Diagnosis and Immunohistochemical staining of TARC

All patients underwent standardized baseline evaluation including detailed history taking, comprehensive clinical examination, and routine laboratory investigations.

Diagnosis was established by histopathological and immunohistochemical examination of lymph node biopsy specimens, including CD3, CD20, CD15 and CD30 [22].

Assessment of pretreatment TARC expression was done using formalin-fixed, paraffin-embedded tissue sections (4 μm thick) from Hodgkin lymphoma patients which were deparaffinised, rehydrated, subjected to immunostaining using an automated immunostainer (DAKO Autostainer Link 48, Agilent Technologies, Denmark) with rabbit rapid polyclonal anti-TARC (CCL17) antibody (orb522171, Biorbyt; 1:200 dilution) and detected using a polymer-based system with DAB chromogen. Sections were counterstained with haematoxylin. TARC expression in Reed–Sternberg cells was evaluated semi-quantitatively by a

pathologist blinded to clinical data using a Zeiss light microscope, and the percentage of positive cells was recorded [17].

Staging and Risk Stratification

Baseline staging was performed using FDG-PET/CT imaging. Patients were stratified according to Ann Arbor staging into early-stage (I–II) and advanced-stage (III–IV) disease [14].

Early-stage patients were further classified into favorable and unfavorable groups based on the presence of B symptoms, bulky mediastinal disease, or lymphadenopathy > 10 cm [23].

Treatment

Treatment was administered according to disease stage and patient fitness. Early-stage patients received Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD) chemotherapy, while advanced-stage patients were treated with Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine and Prednisolone (BEACOPP). Patients unfit for intensive therapy received Adriamycin, vinblastine and Dacarbazine (AVD)

One patient received BB (Brentuximab Vedotin and Bendamustine) as a part of individualized treatment approach.

Patients with relapsed or refractory disease received salvage therapy with Brentuximab vedotin-based protocols followed by autologous stem cell transplantation in eligible cases [23].

Response Assessment and Study Variables

Treatment response was assessed using PET/CT [24]. Clinical, laboratory, and treatment-related variables were collected, including demographic data, disease characteristics, prognostic factors, treatment modalities, and outcomes (response, relapse, and survival).

The association between pretreatment TARC expression and level, treatment response, and established prognostic factors was evaluated.

Statistical analysis

Data were analysed using SPSS software [25] (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation or median (interquartile range) as appropriate, while categorical variables were presented as frequencies and percentages.

Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and the Chi-square test or Fisher’s exact test for categorical variables, as appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value of tissue TARC for predicting treatment response.

Survival outcomes, including overall survival (OS) and free-from-progression (FFP), were analysed using the Kaplan–Meier method and compared using the log-rank test.

Univariate and multivariate logistic regression analyses were conducted to identify predictors of non-complete response. A p-value < 0.05 was considered statistically significant.

Conclusion

In conclusion, pretreatment TARC expression is highly prevalent in classical Hodgkin lymphoma but lacks prognostic value when assessed qualitatively. In contrast, quantitative TARC levels provide clinically prognostic information, with a defined cut-off (> 70%) identifying patients at increased risk of suboptimal response and inferior survival. The lack of independent significance in multivariate analysis supports TARC as a surrogate marker of tumour burden. These findings position TARC as a clinically applicable, complementary biomarker within risk-adapted strategies, warranting further validation in prospective studies.

Declarations

Acknowledgements

Not applicable

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions

Soha A. ElHakim contributed to the investigation, data curation, formal analysis, data interpretation, and writing of the original draft. Mohamed H. Nafea contributed to the methodology, supervision, data interpretation, and writing—review and editing. Aida A. Nazier contributed to the methodology, supervision, data interpretation, and writing—review and editing. Marwa M. Abd ElAziz contributed to the investigation, methodology, formal analysis, data interpretation, validation, and writing—review and editing. Nadia E. Zaki contributed to the conceptualization, methodology, supervision, project administration, investigation, and writing—review and editing. All authors read and approved the final manuscript.

Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Alexandria University (ethical approval number: 0201989).

Consent for publication

Not applicable.

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Figures

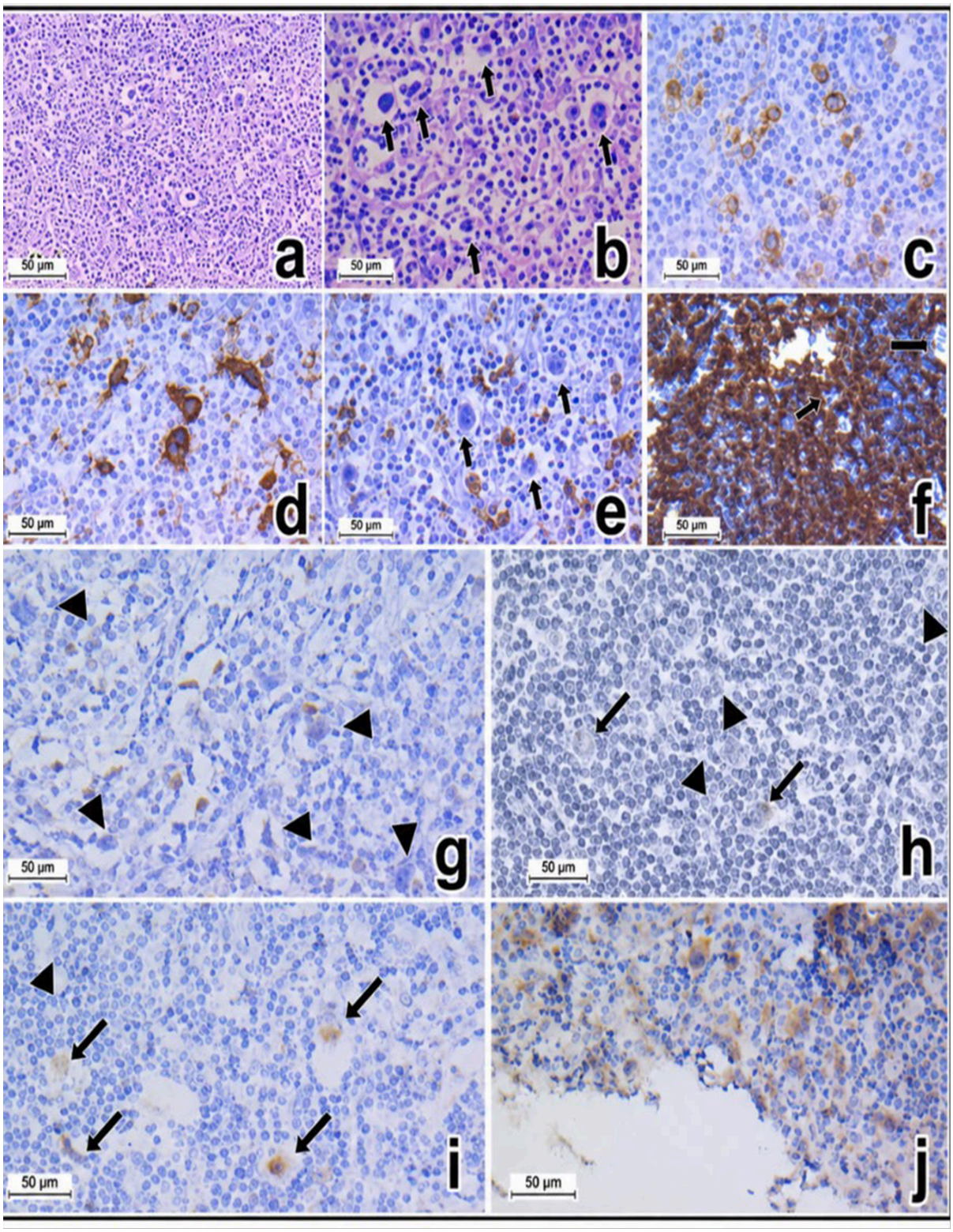


Figure 1

Classical Hodgkin lymphoma: a: Low power shows few scattered large neoplastic cells in a background of inflammatory cells [H&E x200]. b: High power showing neoplastic Reed Sternberg (RS) cells (arrows) including binucleated and mononuclear forms, in a background of small mature lymphocytes and few eosinophils [H&E x400]. c: The RS cells show positive staining for CD30. d: The RS cells are positive for CD15. e: The RS cells (arrows) are negative for CD20 which stains only few scattered small mature

lymphocytes. f: The RS cells (arrows) are negative for CD3 which stains most of the small mature lymphocytes in the background. TARC immunohistochemical staining in Classical Hodgkin lymphoma (CHL). g: A case of CHL showing negative staining for TARC in Reed Sternberg (RS) cells (arrowheads), with positive staining in some eosinophils serving as positive internal control. h: A case of CHL showing positive staining for TARC in very few RS cells (arrows), with negative staining in most of the RS cells (arrowheads). i: A case of CHL showing positive staining for TARC in most of the RS cells (arrows), with negative staining in only one RS cell (arrowhead). j: A case of CHL showing positive staining for TARC in all RS cells. [IHC x400].

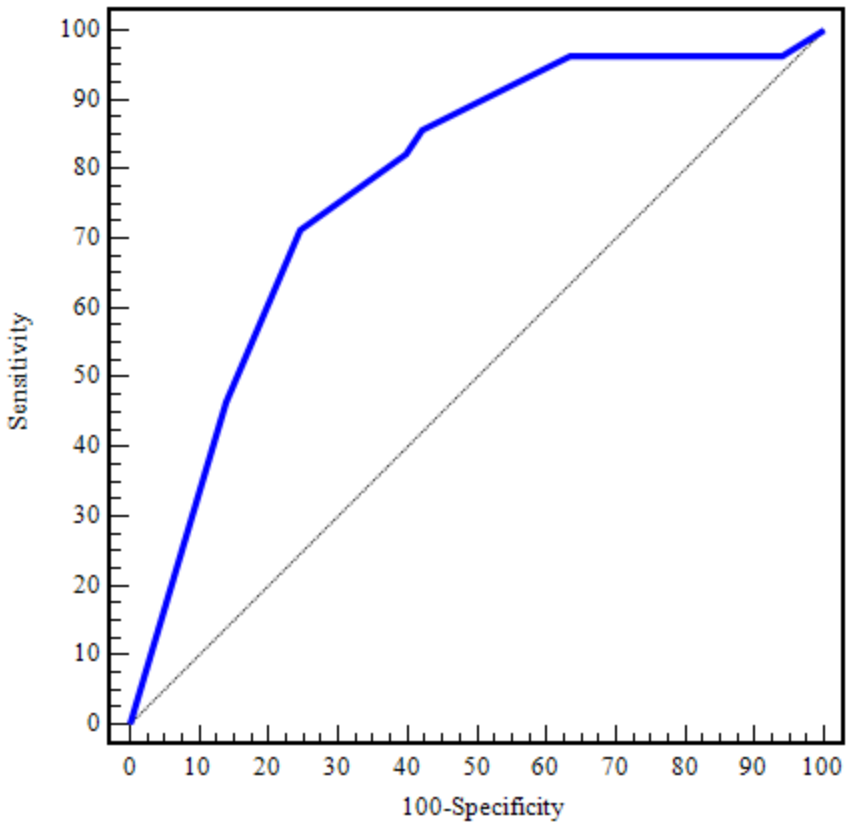


Figure 2

ROC curve of pretreatment tissue TARC level for predicting non-complete response

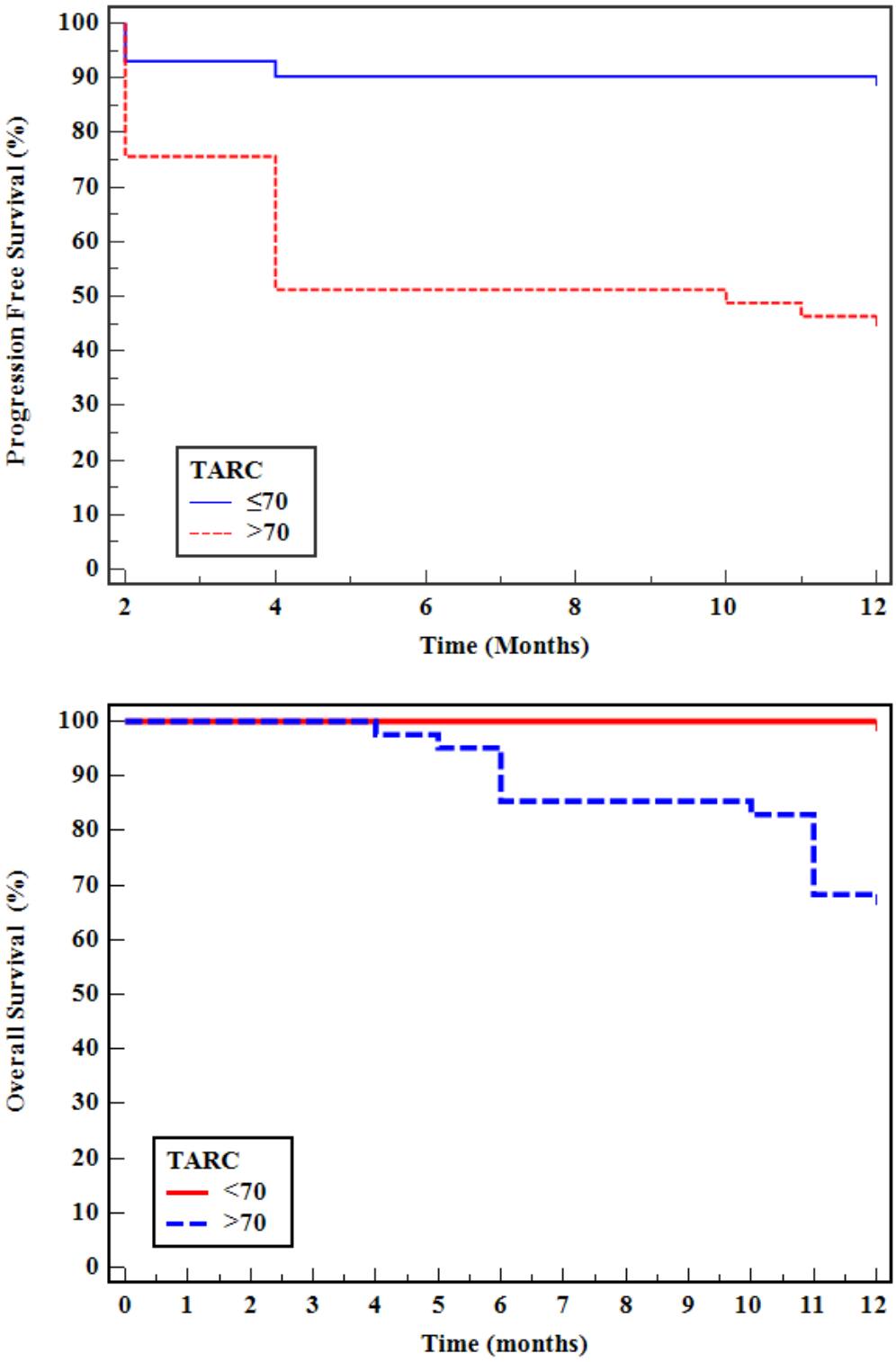


Figure 3

a,b): Kaplan-Meier survival curve for 1 year overall survival (OS) and 1 year freedom from progression FFP with tissue TARC level