Journal of Autoimmunity 104 (2019) 102316

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Predictive markers of lymphomagenesis in Sjögren's syndrome: From clinical data to molecular stratification

Efstathia K. Kapsogeorgou (PhD)[a,b,*], Michael Voulgarelis (MD)[a,b], Athanasios G. Tzioufas[a,b]

[a] Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Greece
[b] Academic Joint Rheumatology Program, School of Medicine, National and Kapodistrian University of Athens, Greece

ARTICLE INFO

Keywords:
Sjögren's syndrome
Non-hodgkin's lymphoma
Predictive biomarkers
miR200b-5p

ABSTRACT

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease, affecting predominantly the exocrine glands, a large array of systemic manifestations and high risk of lymphoma development. The latter constitutes the major adverse outcome of SS contributing in the increased morbidity and mortality of the disease. The vast majority of lymphomas in SS are B-cell non-Hodgkin's lymphomas (NHL), primarily indolent mucosa-associated lymphoid tissue (MALT) lymphomas, followed by nodal marginal zone lymphomas (NMZL) and diffuse large B cell lymphomas (DLBCL). In the last 3 decades and due to the adverse impact of NHL in disease outcome, an effort has been undertaken to identify markers and models predicting patients with SS at high risk for lymphoma development. Several epidemiological, clinical, laboratory and histological parameters, some of which are evident at the time of SS diagnosis, were proved to independently predict the development of NHL. These include salivary gland enlargement, skin vasculitis/purpura, glomerulonephritis, peripheral neuropathy, Raynaud's phenomenon, lymphadenopathy, splenomegaly, cytopenias, hypocomplementemia, cryoglobulinemia, rheumatoid factor, anti-Ro/La autoantibodies, hypergammaglobulinemia, serum monoclonal gammopathy, biopsy focus score and organization of lymphocytic infiltrates in the salivary glands into ectopic germinal centers. Prediction models combining some of the afore-mentioned predictors have also been described. However, the identification of specific and sensitive molecular biomarkers, related to the process of lymphomagenesis is still pending. Recently, we described a novel biomarker the miR200b-5p micro-RNA. Low levels of this miRNA in the minor salivary glands, appears to discriminate with high specificity and sensitivity the SS patients who have from those who do not have NHL. miR200b-5p, being expressed years before the clinical onset of NHL, independently predicts NHL development with a predictive value higher than the previously published multifactorial models and has a possible role in the monitoring of therapeutic response. Thus, it is a strong candidate for the identification and follow-up of patients at risk.

1. Introduction

Primary Sjögren's syndrome (SS) is a chronic autoimmune disorder affecting mainly middle-aged women. The hallmark of the disease is the dysfunction of the exocrine glands, mainly of the salivary and lacrimal glands (affected in more than 90% of the SS patients), leading to tissue dryness that is expressed as xerostomia and keratoconjunctivitis sicca, respectively. The clinical phenotype of the SS patients is highly heterogeneous, varying from benign, mild exocrinopathy to severe, systemic, disorder with high prevalence (5–10%) of B-cell non-Hodgkin's lymphoma (NHL) [1,2]. In fact, the risk of lymphoma development in SS is the highest among other autoimmune diseases [3,4], representing the major adverse outcome of the disease [5–10]. The observation that NHL lymphoma appears in an autoimmune background, has been attracted the scientific interest over the past decades. The main questions were two: 1. which mechanisms operate at the crossroads of autoimmunity and malignancy and 2. whether there are symptoms, signs and laboratory items present during the benign course of the autoimmune disease, that may herald the development of NHL. To this end, convincing and replicated data demonstrated that patients at high risk

Abbreviations: SS, Sjögren's syndrome; NHL, non-Hodgkin's lymphoma; MZBCL, marginal zone B cell lymphomas; DLCBL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; NMZL, nodal marginal zone lymphomas; ESSDAI, EULAR Sjögren's syndrome Disease Activity Index; OS, overall survival; EFS, event-free survival; IPI, international prognostic index; BAFF, B-cell activating factor; Flt-3, Fms-like tyrosine kinase 3 ligand; TSLP, thymic stromal lymphopoietin; microRNAs, miRNAs

* Corresponding author. Department of Pathophysiology, School of Medicine, National University of Athens, 75 Mikras Asias street, Athens, 11527, Greece.
E-mail addresses: ekapso@med.uoa.gr (E.K. Kapsogeorgou), mvoulgar@med.uoa.gr (M. Voulgarelis), agtzi@med.uoa.gr (A.G. Tzioufas).

https://doi.org/10.1016/j.jaut.2019.102316
Received 2 August 2019; Accepted 3 August 2019
Available online 17 August 2019
0896-8411/

to develop lymphoma constitute a distinct subgroup that can be early identified, even at disease diagnosis. This group of patients display certain clinical, laboratory and histological features, including severe disease, as attested by the presence of systemic manifestations mediated by the deposition of immune complexes, suggestive of vasculitic involvement, aberrant B cell activation, as indicated by the expression of plethora of autoantibodies, as well as massive lymphocytic infiltration in the salivary glands [11–13]. Multivariate analyses of the risk factors identified several independent predictive parameters (mostly clinical and laboratory) [11–13], whereas attempts to create prediction models have also been performed. However, both the predictive factors and models vary, depending mainly, on the type of study and the clinical features of patient cohorts. The readout of this effort was the identification of common predictive factors [13]. However, their predictive value is hampered by the fact that they are rather common clinical or laboratory features with low specificity for lymphoma development in SS. Thus, in recent years and with the introduction of B-cell targeted therapies in SS, the focus of research in SS-associated lymphomas has been directed on the identification of novel specific biomarkers, which serving alone or in combination with the previously recognized predictive clinical and laboratory factors will facilitate the early and precise diagnosis of the SS patients who will develop lymphoma and possibly their follow-up and therapeutic monitoring. In this review, we present a comprehensive analysis of the adverse predictive factors and the prediction models for the development of lymphoma in SS, with an emphasis on a novel molecular biomarker, namely the micro-RNA miR200b-5p, and its predictive value compared to other classical predictive factors and models.

2. Features of SS-associated lymphomas

The lymphomas associated with SS are mainly of B cell origin [11–13], whilst T cell lymphomas have been sparsely reported [14–23]. The vast majority of B cell NHLs in SS are indolent marginal zone B cell lymphomas (MZBCL), followed by high grade diffuse large B cell lymphomas (DLBCL) in 10–20% of patients [2,6,11–13,21,24–30]. On the other hand, DLBCLs (58%) have been reported to predominate in a study of the Swedish SS population that included 11 B cell lymphomas [31]. The MZBCLs arise from memory B cells in the marginal zone of lymphoid tissue and include three subtypes, the extranodal marginal zone or mucosa-associated lymphoid tissue (MALT) lymphomas, the nodal and the splenic marginal zone lymphomas. MALT is the most common type of lymphoma in SS, comprising approximately 60–65% of the SS-associated lymphomas [2,6,11–13,21,24–29]. The major sites affected in SS-associated MALT lymphomas are the parotid and minor salivary glands, whereas other organs involved are the lungs, stomach, skin, liver, kidney, bone marrow, lacrimal glands, thyroid gland, larynx and thymus. Quite often, in approximately 25% of patients, MALT is presented as a multifocal disease, whereas disease stage is rather limited in diagnosis. Thus, in more than half of patients with SS-associated MALT lymphomas staging, according to Ann Arbor [32] is limited to stages I and II and only 35% of patients present with the advanced IV stage. On the contrary, the SS patients with DLBCLs present at diagnosis with advanced III and IV stages being the major contributor for the decreased survival of SS patients with NHL [24]. Nodal marginal zone lymphomas (NMZL) are also rather common in SS (around 15%), whereas other types of lymphomas, such as lymphoplasmacytic and follicular, are rare [2,6,11–13,21,24–29].

In general, the SS patients at high risk to develop NHL or with overt NHL are differentiated from the low risk patients, since they present high disease activity, as assessed by the EULAR Sjögren's syndrome Disease Activity Index (ESSDAI) and manifestations indicative of severe, systemic disease. Thus, SS-associated NHLs have been associated with salivary gland enlargement, skin vasculitis and/or palpable purpura, splenomegaly, lymphadenopathy, peripheral neuropathy, glomerulonephritis and hematologic manifestations, including anemia, neutropenia and/or thrombocytopenia. Additionally, they display aberrant B cell hyperactivity, as indicated by the expression of plethora of autoantibodies, including rheumatoid factor, antibodies against Ro/La ribonucleoproteins and cryoglobulins, as well as the high prevalence of hypergammaglobulinemia, monoclonality in serum and hypocomplementemia [2,6,10–13,21,24–29].

SS has a quite benign prognosis, whereas its reduced survival rates are mainly attributed to the development of NHLs [5–10]. Indeed, the survival of SS patients without lymphoma is similar to general population [29], whereas the 5-year overall (OS) and event-free survival (EFS) rates of the SS patients with NHLs have been reported to be 92% and 57%, respectively [24,29]. Among the patients with SS-associated lymphomas, those with MALT have the most favorable prognosis compared to NMZLs and DLBCLs and DLBCLs the worst. Thus, a 5-year OS of 94% has been described for MALT lymphoma, 87.5% for NMZL and 75% for DLBCL, whereas the respective EFS rates were 86%, 62.5% and 50%. Despite the unfavorable outcome of the DLBCLs associated with SS, this is similar to the observed in the general population [24]. Except the subtype of NHL, the outcome of lymphoma in SS seems to depend on the disease activity score (ESSDAI) [33] and the international prognostic index (IPI) [34] at the time of lymphoma diagnosis [8,24]. Thus, SS patients with NHL and ESSDAI score ≥ 10 or IPI ≥ 3 at lymphoma diagnosis have a higher risk to experience an adverse event or die compared to those with low ESSDAI or IPI [24]. A “wait and watch” policy is recommended for SS patients with MALT lymphoma without dissemination on other hematological sites, whereas rituximab plus chemotherapy can be used in MALT lymphoma patients with disseminated disease. Rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the treatment of choice for SS patients with DLBCLs [24,29].

3. Predictive markers of lymphoma development in SS

During the last decades, a significant number of clinical markers that associate or predict lymphoma development in SS patients has been identified. Some of them are evident since SS disease onset and have been proved strong predictors of SS-associated NHLs in a variety of studies, whereas their value as independent predictor factors has been confirmed by multivariate statistical analyses. Roughly, the factors predicting the development of NHL in SS can be categorized to epidemiological, clinical, laboratory (serological/hematological) and histological markers (Table 1) and will be described thereafter.

3.1. Epidemiological markers

Although age and sex have not been proved independent predictors of lymphoma development in SS, recent data indicate that may be implicated. Patients with disease onset at the age less than 35 years-old have been reported to suffer from a more severe systemic disease [35–39] and have higher incidence of lymphomas [40], compared to SS patients with disease onset at the middle-age. In addition, males seem to suffer from a more severe disease than women, with higher frequency and risk (3.44-fold) of lymphoma, whereas the latter is diagnosed earlier in life compared to women [30,41–47].

3.2. Clinical predictors

Recurrent episodes of unilateral or bilateral salivary gland enlargement is one of the first and strongest predictive markers described, whereas the majority of the studies performing multivariate analyses validated its utility as a strong independent predictive marker of lymphoma development in SS [1,6,9,21,31,46,48–56]. Systemic clinical manifestations indicative of B cell hyperactivity and/or mediated by immunocomplexes have been implicated in lymphoma development. Thus, vasculitic involvement as indicated by palpable purpura and/or skin ulcers is a commonly reported independent adverse risk factor for

Table-1
Epidemiological, clinical, laboratory and histological predictors of NHL development in SS patients.

Epidemiological	Clinical	Laboratory		Histological (*minor salivary glands*)
		Serological	Hematological	
Age Male gender	Salivary gland enlargement Skin Vasculitis/Purpura Glomerulonephritis Peripheral neuropathy Raynaud's phenomenon Lymphadenopathy Splenomegaly ESSDAI	C4 and/or C3 hypocomplementemia Cryoglobulinemia Rheumatoid factor Anti-Ro/La autoantibodies Hypergammaglobulinemia Serum monoclonal gammopathy	CD4+-lymphopenia Low CD4+/CD8+ T cell ratio Lymphopenia Leukopenia Neutropenia	Biopsy focus score Ectopic germinal centers Low miR200b-5p levels

NHL: non-Hodgkin's lymphoma.
ESSDAI: EULAR SS disease activity index.

NHL development in SS [5,6,13,31,50,52,55–57], whereas peripheral neuropathy and glomerulonephritis have been associated and seem to precede lymphoma [2,5,6,46]. Furthermore, Raynaud's phenomenon has also been described to independently predict NHL development in SS [51]. In addition, hematological features associated with aberrant lymphocytic activation, such as lymphadenopathy and splenomegaly, have also been proposed as strong independent predictors of lymphoma in SS [26,46,51,58]. Finally, high disease activity as assessed by ESSDAI score has been reported to independently predict lymphoma in SS patients [21,24,30,52], adverse outcome of MALT lymphoma, as well as of patients (death or event) [24,59].

3.3. Laboratory markers

These include both serological markers, such as complement components, autoantibodies and cytokines, and hematological features. Most of the serological predictors of NHL development in SS reflect the aberrant chronic activation of B cells in this patient subgroup, since they are either directly produced by activated B cells and/or play significant role in immune responses, e.g. autoantibodies and complement consumption, or are critical for B cell survival, activation and differentiation, e.g. cytokines.

3.3.1. Serological markers

Quite early studies, confirmed by future multivariate analyses and prediction models, supported the key predictive role of hypocomplementemia, particularly low serum C4 [5–8,21,26,29,30,50,51,53,54,56], and to a lesser degree C3 levels [9,30,31,54,56], in SS-associated NHLs. Notably, hypocomplementemia has been related to earlier development of NHL and higher mortality [6,56]. Except hypocomplementemia, cryoglobulinemia is another strong predictor of NHL development in SS patients [5,13,21,26,29,30,46,48,52,53,60]. Type II mixed monoclonal cryoglobulinemia with IgMκ monoclonal component bearing rheumatoid factor activity is usually observed in SS patients (20%) and correlates with the infiltration of the minor salivary glands by kappa-positive plasmacytes [60–62]. Of interest, hypocomplementemia and cryoglobulinemia, along with parotid involvement and vasculitis, have been described to be adverse prognostic factors for reduced survival of SS patients [9].

Although there is a dispute about the predicting value of autoantibodies for the development of NHL in SS, there are recent studies identifying anti-Ro/La antibodies and rheumatoid factor as independent predictors of lymphoma. Thus, SS patients expressing anti-Ro/La autoantibodies have significantly less lymphoproliferative manifestations and risk to develop lymphoma than the negative ones [63], whereas the prevalence of anti-Ro/La autoantibodies is significantly higher in SS patients with associated NHLs [63]. Furthermore, anti-Ro/La autoantibodies have been recognized as an independent predictive factor alone [51] or along with parotid gland enlargement [53]. In accordance, rheumatoid factor has been proved an independent predictor of lymphoma in SS in two studies including a large number of SS patients with associated NHLs [21,51].

Although diffuse hypergammaglobulinemia is a common finding reflecting the B cell hyperactivity in SS, it has been reported to be elevated in SS patients who will develop lymphoma and has been also identified as an independent predictor [31,52,53,56]. Moreover, serum monoclonal gammopathy seems to associate with SS-associated NHLs and their prediction [51,64]. Other B cell activation markers that have been associated with NHL in SS are serum-free light chains of immunoglobulins and beta-2 microglobulin, although their utility in lymphoma prediction has not been proved [65].

The levels of serum expression of various cytokines and receptors implicated in B cell activation, survival and differentiation, as well as components and/or resultant products of chronic immune responses, have been associated with SS-associated NHL; however, their predictive value for lymphoma development remains to be validated. These include lower levels of vitamin D and higher levels of B-cell activating factor (BAFF), Fms-like tyrosine kinase 3 ligand (Flt-3), CXCL13, the inflammasome-related molecules IL-18, ASC and cell-free DNA, as well as higher activity of lipoprotein-associated phospholipase A2 (Lp-PLA2) in the sera of SS patients with NHLs compared to those without [66–72]. Recently, a novel promising biomarker predicting the development of severe MALT lymphomas in SS patients has been presented and involves the serum levels of thymic stromal lymphopoietin (TSLP) [73].

3.3.2. Hematological markers

The most commonly reported hematologic predictors of NHL development in SS are various leukopenias. In a study of Swedish SS population with predominant NHL subtype the DLBCLs, $CD4^+$ T lymphocytopenia and low $CD4^+/CD8^+$ T cell ratio (≤ 0.8) were strong predictors of lymphoproliferative disease [31]. In addition, lymphopenia [21,26,29,56], leukopenia [53] and neutropenia [26] have been identified as independent predictors of lymphoma. Although anemia has been reported to predict NHL development in SS, it has not been proved to be an independent predictive factor [56], whereas in another study has been reported as a predictor of non-MALT B-cell lymphomas [30].

Finally, several of the aforementioned laboratory factors have not only been implicated in the prediction of NHL development in SS, but also in the prediction of the NHL subtype. Thus, cryoglobulinemia, neutropenia, low C4 levels, lymphadenopathy and splenomegaly have been shown to independently predict the development of MZBCLs, whereas lymphocytopenia may predict DLBCLs [26]. In addition, it has been reported that SS patients with cytopenias, monoclonal gammopathy and low C4 levels are at high risk to develop non-MALT B-cell lymphoma, whereas those with low C3 levels may predict MALT lymphomas [30].

3.4. Histological markers

It is rather well established that the local immune responses in the salivary glands may dictate the systemic manifestations of SS, including the development of lymphoma. Several decades ago, it became evident that severe lymphocytic infiltration of the salivary glands of SS patients associates with the expression of several extraglandular manifestations and severe systemic disease [74,75]. Furthermore, lymphomagenesis in SS is considered as the result of chronic, aberrant B cell stimulation that mainly takes place in the inflamed salivary glands [11,12]. These initial studies were followed by a more detailed investigation, aiming to find associations between histological parameters and lymphomagenesis. These studies disclosed that the degree of salivary gland infiltration as this depicted by the biopsy focus score [51,76] and the organization of lymphocytic infiltrates to ectopic germinal centers [46,77,78] can serve as predictors of lymphoproliferative disease in SS. Furthermore, lymphoma has been correlated with increased infiltration of salivary glands by macrophages, evident at diagnosis [79,80], as well as IFNγ/IFNα mRNA ratio [81], which possibly reflects the predominance of type-II interferons in heavy infiltrates of salivary glands [82,83].

4. Models predicting lymphoma development in SS

The effort for the identification of the SS patients who will develop lymphoma was not restricted by the discovery of predictors. The later were combined to facilitate a sensitive and specific identification of SS patients at risk, resulting in the development of four distinct multifactorial predictive models (Table 2). More analytically, Ioannidis et al. [6] defined as high risk, the SS patients that present at least one of the following risk factors: parotid enlargement, palpable purpura and low C4 levels. Baimpa et al. [26] defined five risk factors, namely neutropenia, cryoglobulinemia, splenomegaly, lymphadenopathy and low C4 levels. The statistical analysis revealed that the proportion of the SS patients who developed lymphoma by the number of risk factors was 3.62%, 11.96%, 34.78%, 80% and 100% for patients with 0, 1, 2, 3 and 4 risk factors, respectively (the study did not include any patient with all 5 risk factors). Thus, the patients can be roughly categorized in those expressing at least 1, at least 2 or ≥3 of the five independent risk factors (model 1, 2 and 3, respectively). Quartuccio et al. [53] defined the group of SS patients at high-risk to develop lymphoproliferative disease as those who suffer persistent glandular swelling and express at least two of the following: low C4 levels, cryoglobulinemia, anti-La antibodies and leukopenia. Finally, Fragkioudaki et al. identified seven independent predicting factors, including salivary gland enlargement, lymphadenopathy, Raynaud phenomenon, anti-Ro/SSA and/or anti-La/SSB antibodies, rheumatoid factor positivity, monoclonal gammopathy and C4 hypocomplementemia. Patients carrying two or less risk factors had 3.8% probability to develop lymphoma, those with 3–6 factors 39.9% and patients fulfilling all seven predictors will all develop lymphoma. Thus, according to this model the high-risk group can be defined as the patients expressing three or more risk factors.

Table-2
Models predicting lymphoma development in SS.

Model	Risk Factors	Criteria	Reference
Ioannidis et al.	Salivary gland enlargement C4 hypocomplementemia Palpable purpura	≥1	[6]
Baimpa et al., model 1	C4 hypocomplementemia Cryoglobulinemia	1	
Baimpa et al., model 2	Neutropenia Splenomegaly	2	[26]
Baimpa et al., model 3	Lymphadenopathy	≥3	
Quartuccio et al.	Salivary gland enlargement C4 hypocomplementemia Cryoglobulinemia anti-La autoantibodies Leukopenia	Salivary gland enlargement + ≥2	[53]
Fragkioudaki et al.	Salivary gland enlargement C4 hypocomplementemia Lymphadenopathy Raynaud phenomenon, anti-Ro and/or anti-La Rheumatoid factor Monoclonal gammopathy	≥3	[51]

The generation of a universal prediction model is up-to-date hampered by the low incidence of the disease and the even lower prevalence of NHLs in SS, the heterogeneity of the cohorts studied and the clinical data recorded, the lack of multicentered studies of predicting factors specific for the disease. Novel analytical approaches based on machine learning and big data analysis is anticipated to overcome these obstacles and permit the harmonization of patients and development of universal algorithms for their classification and follow up. This is the aim of HarmonicSS project, a European-funded multicentric protocol (H2020-SC1-2016; grant agreement no: 731944). Furthermore, studies are focused in the identification of novel specific predictive biomarkers that will facilitate the early and specific identification of the SS patients who will develop lymphoproliferative disease and possibly their follow up and response to treatment. In this context, we recently presented a novel molecular biomarker that covers most of these aspects and involves the low expression of the micro-RNA (miRNA) miR200b-5p in the minor salivary glands of SS patients who will develop or have NHL [52].

Low levels of miR200b-5p in the minor salivary glands of SS patients: a novel strong molecular biomarker for lymphoma development.

Although the role and function of miR200b-5p miRNAs has not been studied, it is considered to act synergistically with miR200b-3p in the regulation of epithelial-to-mesenchymal transition and as such it has been implicated in the oncogenesis of solid tumors [84–90]. The levels of miR200b-5p expression in the minor salivary glands were significantly downregulated in the SS patients who will develop or have overt NHL compared to low-risk patients. This reduced expression was evident years before clinical lymphoma onset and did not change over lymphoma transformation. Furthermore, they were found to strongly discriminate the SS patients who have NHL versus those who do not, as well as those who will develop NHL versus those who will not. More importantly, miR200b-5p levels predicted the development of lymphoma independently from other known predicting factors. In fact, multivariate analysis revealed that miR200b-5p levels were independent predictors of NHL development in SS along with high ESSDAI, salivary gland enlargement, purpura, vasculitis, splenomegaly, cryoglobulinemia and hypergammaglobulinemia [52]. The comparison of its predictive utility over that of the previously published multifactorial models revealed its superiority in predicting NHL development in SS (Table 3) [91], strengthening its value as a predictive marker. Furthermore, preliminary data indicate that it might have a role in the monitoring of the therapeutic response since it remained stable in patients that did not respond to treatment, increased in those that succeeded complete remission and was reduced in those that relapsed [52]. All these features make miR200b-5p a promising candidate for the identification and follow-up of the SS patients who will develop NHL and its utility remains to be validated in large-scale, multicentric studies.

5. Future perspectives

The findings of the last decades and the progress in the identification of specific biomarkers support that the early and specific prediction of lymphoma development in SS is a feasible goal. Future perspectives involve the development of precision medicine approaches for both the identification and the treatment of SS patients with associated NHLs. However, to achieve this, there are some prerequisites: a) efficient and

Table-3
Comparison of the utility of the various multifactorial prediction models and miR200b-5p for the prediction of NHL development in SS patients.

Prediction Model	ROC		KM p value	PPV	NPV	PSEP	Se	Sp	Se + Sp
	AUC	p value							
Ioannidis et al.	0.748	0.006	0.006	0.57	0.94	0.51	0.94	0.56	1.50
Baimpa et al., model 1	0.775	0.002	0.003	0.63	0.90	0.53	0.88	0.67	1.55
Baimpa et al., model 2	0.687	0.038	0.006	0.88	0.72	0.60	0.41	0.96	1.37
Baimpa et al., model 3	0.647	0.104	0.008	1.00	0.69	0.69	0.29	1.00	1.29
Quartuccio et al.	0.794	0.001	**≤0.0001**	1.00	0.79	**0.79**	0.59	1.00	1.59
Fragkioudaki et al.	**0.830**	**≤0.0001**	**≤0.0001**	0.71	0.91	0.63	0.88	0.78	1.66
Low miR200b-5p levels	**0.863**	**≤0.0001**	**≤0.0001**	0.87	0.86	**0.73**	0.76	0.93	**1.69**

AUC: Area Under the ROC curve.
KM: Kaplan-Meier lymphoma-free survival curves compared by the log-rank test.
PPV: positive predictive value.
NPV: negative predictive value.
Se: sencitivity
Sp: specificity.
PSEP: index of the model intrinsic prognostic value [26,92].

early stratification of SS patients based on both clinical and molecular features, which requires multicentric, large-scale cohort studies, as mentioned afore, and b) in-depth understanding of the pathogenetic mechanisms underlying the distinct clinical phenotypes of the disease and especially those associated with lymphomagenesis. This will permit both the development of targeted therapies and their educated use in the appropriate subgroup of SS patients.

Acknowledgements

EKK and AGT have been funded by grants of the Research Grant from the Greek Rheumatology Society and Professional Association of Rheumatologists and the European-funded multicentric protocol 'HARMONIzation and integrative analysis of regional, national and international Cohorts on primary Sjögren's Syndrome (pSS) towards improved stratification, treatment and health policy making' (HARMONICSS; H2020-SC1-2016; grant agreement no: 731944).

References

[1] S.S. Kassan, T.L. Thomas, H.M. Moutsopoulos, R. Hoover, R.P. Kimberly, D.R. Budman, et al., Increased risk of lymphoma in sicca syndrome, Ann. Intern. Med. 89 (1978) 888–892.
[2] M. Voulgarelis, U.G. Dafni, D.A. Isenberg, H.M. Moutsopoulos, Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjogren's Syndrome, Arthritis Rheum. 42 (1999) 1765–1772.
[3] C. Tarella, A. Gueli, M. Ruella, A. Cignetti, Lymphocyte transformation and autoimmune disorders, Autoimmun. Rev. 12 (2013) 802–813.
[4] E. Zintzaras, M. Voulgarelis, H.M. Moutsopoulos, The risk of lymphoma development in autoimmune diseases: a meta-analysis, Arch. Intern. Med. 165 (2005) 2337–2344.
[5] F.N. Skopouli, U. Dafni, J.P. Ioannidis, H.M. Moutsopoulos, Clinical evolution, and morbidity and mortality of primary Sjogren's syndrome, Semin. Arthritis Rheum. 29 (2000) 296–304.
[6] J.P. Ioannidis, V.A. Vassiliou, H.M. Moutsopoulos, Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome, Arthritis Rheum. 46 (2002) 741–747.
[7] E. Theander, R. Manthorpe, L.T. Jacobsson, Mortality and causes of death in primary Sjogren's syndrome: a prospective cohort study, Arthritis Rheum. 50 (2004) 1262–1269.
[8] P. Brito-Zeron, B. Kostov, R. Solans, G. Fraile, C. Suarez-Cuervo, A. Casanovas, et al., Systemic activity and mortality in primary Sjogren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients, Ann. Rheum. Dis. 75 (2016) 348–355.
[9] P. Brito-Zeron, M. Ramos-Casals, A. Bove, J. Sentis, J. Font, Predicting adverse outcomes in primary Sjogren's syndrome: identification of prognostic factors, Rheumatology 46 (2007) 1359–1362.
[10] M. Ramos-Casals, P. Brito-Zeron, J. Yague, M. Akasbi, R. Bautista, M. Ruano, et al., Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjogren's syndrome, Rheumatology 44 (2005) 89–94.
[11] A.V. Goules, A.G. Tzioufas, Lymphomagenesis in Sjogren's syndrome: predictive biomarkers towards precision medicine, Autoimmun. Rev. 18 (2019) 137–143.
[12] A. Papageorgiou, M. Voulgarelis, A.G. Tzioufas, Clinical picture, outcome and predictive factors of lymphoma in Sjgren syndrome, Autoimmun. Rev. 14 (2015) 641–649.
[13] S. Retamozo, P. Brito-Zeron, M. Ramos-Casals, Prognostic markers of lymphoma development in primary Sjogren syndrome, Lupus 28 (2019) 923–936.
[14] M. Saito, T. Fukuda, T. Shiohara, M. Homori, Angioimmunoblastic T-cell lymphoma: a relatively common type of T-cell lymphoma in Sjogren's syndrome, Clin. Exp. Rheumatol. 23 (2005) 888–890.
[15] P.G. van der Valk, H. Hollema, P.C. van Voorst Vander, M.G. Brinker, S. Poppema, Sjogren's syndrome with specific cutaneous manifestations and multifocal clonal T-cell populations progressing to a cutaneous pleomorphic T-cell lymphoma, Am. J. Clin. Pathol. 92 (1989) 357–361.
[16] A. Fredenrich, J.G. Fuzibet, M. Lasserre, B. Taillan, S. Raynaud, N. Gratecos, et al., [Non-Hodgkin's malignant T-cell lymphoma in Gougerot-Sjogren syndrome], Ann. Med. Interne 140 (1989) 428.
[17] S. Ros, C. Gomez, J.M. Nolla, D. Roig-Escofet, [Angiocentric pulmonary T-cell lymphoma associated with primary Sjogren syndrome], Med. Clínica 107 (1996) 117–118.
[18] T. Yamamoto, M. Ohi, K. Nishioka, Lymphomatoid papulosis associated with Sjogren's syndrome, J. Dermatol. 29 (2002) 174–177.
[19] X. Chevalier, P. Gaulard, M.C. Voisin, J. Martigny, J.P. Farcet, B. Larget-Piet, Peripheral T cell lymphoma with Sjogren's syndrome: a report with immunologic and genotypic studies, J. Rheumatol. 18 (1991) 1744–1746.
[20] W.S. Wilke, R.R. Tubbs, R.M. Bukowski, T.E. Currie, L.H. Calabrese, R.A. Weiss, et al., T cell lymphoma occurring in Sjogren's syndrome, Arthritis Rheum. 27 (1984) 951–955.
[21] G. Nocturne, A. Virone, W.F. Ng, V. Le Guern, E. Hachulla, D. Cornec, et al., Rheumatoid factor and disease activity are independent predictors of lymphoma in primary Sjogren's syndrome, Arthritis & rheumatology 68 (2016) 977–985.
[22] D. Khanna, H.V. Vinters, E. Brahn, Angiocentric T cell lymphoma of the central nervous system in a patient with Sjogren's syndrome, J. Rheumatol. 29 (2002) 1548–1550.
[23] R. Godinho, P.V. de Oliveira, D.G. Schmoeller, H.L. Staub, Hepatosplenic gamma-delta T-cell lymphoma and Sjogren's syndrome, Reumatol. Clínica 10 (2014) 264–265.
[24] A. Papageorgiou, D.C. Ziogas, C.P. Mavragani, E. Zintzaras, A.G. Tzioufas, H.M. Moutsopoulos, et al., Predicting the outcome of Sjogren's syndrome-associated non-hodgkin's lymphoma patients, PLoS One 10 (2015) e0116189.
[25] L.A. Anderson, S. Gadalla, L.M. Morton, O. Landgren, R. Pfeiffer, J.L. Warren, et al., Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies, Int. J. Cancer 125 (2009) 398–405.
[26] E. Baimpa, I.J. Dahabreh, M. Voulgarelis, H.M. Moutsopoulos, Hematologic manifestations and predictors of lymphoma development in primary Sjogren syndrome: clinical and pathophysiologic aspects, Medicine 88 (2009) 284–293.
[27] K. Ekstrom Smedby, C.M. Vajdic, M. Falster, E.A. Engels, O. Martinez-Maza, J. Turner, et al., Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium, Blood 111 (2008) 4029–4038.
[28] B. Royer, D. Cazals-Hatem, J. Sibilia, F. Agbalika, J.M. Cayuela, T. Soussi, et al., Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses, Blood 90 (1997) 766–775.
[29] M. Voulgarelis, P.D. Ziakas, A. Papageorgiou, E. Baimpa, A.G. Tzioufas, H.M. Moutsopoulos, Prognosis and outcome of non-Hodgkin lymphoma in primary Sjogren syndrome, Medicine 91 (2012) 1–9.
[30] P. Brito-Zeron, B. Kostov, G. Fraile, D. Caravia-Duran, B. Maure, F.J. Rascon, et al., Characterization and risk estimate of cancer in patients with primary Sjogren syndrome, J. Hematol. Oncol. 10 (2017) 90.
[31] E. Theander, G. Henriksson, O. Ljungberg, T. Mandl, R. Manthorpe, L.T. Jacobsson, Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors, Ann. Rheum. Dis. 65 (2006)

796–803.
[32] P.P. Carbone, H.S. Kaplan, K. Musshoff, D.W. Smithers, M. Tubiana, Report of the committee on hodgkin's disease staging classification, Cancer Res. 31 (1971) 1860–1861.
[33] R. Seror, P. Ravaud, S.J. Bowman, G. Baron, A. Tzioufas, E. Theander, et al., EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome, Ann. Rheum. Dis. 69 (2010) 1103–1109.
[34] P. International Non-Hodgkin's Lymphoma Prognostic Factors, A predictive model for aggressive non-Hodgkin's lymphoma, N. Engl. J. Med. 329 (1993) 987–994.
[35] C. Anquetil, E. Hachulla, F. Machuron, X. Mariette, V. Le Guern, O. Vittecoq, et al., Is early-onset primary Sjogren's syndrome a worse prognosis form of the disease? Rheumatology 58 (2019) 1163–1167.
[36] E. Theander, R. Jonsson, B. Sjostrom, K. Brokstad, P. Olsson, G. Henriksson, Prediction of Sjogren's syndrome years before diagnosis and identification of patients with early onset and severe disease course by Autoantibody profiling, Arthritis & rheumatology 67 (2015) 2427–2436.
[37] M. Ramos-Casals, R. Cervera, J. Font, M. Garcia-Carrasco, G. Espinosa, S. Reino, et al., Young onset of primary Sjogren's syndrome: clinical and immunological characteristics, Lupus 7 (1998) 202–206.
[38] H.J. Haga, R. Jonsson, The influence of age on disease manifestations and serological characteristics in primary Sjogren's syndrome, Scand. J. Rheumatol. 28 (1999) 227–232.
[39] M. Tishler, I. Yaron, I. Shirazi, M. Yaron, Clinical and immunological characteristics of elderly onset Sjogren's syndrome: a comparison with younger onset disease, J. Rheumatol. 28 (2001) 795–797.
[40] O. Argyropoulou, A. Goules, E. Zampeli, M. Mavromati, C.P. Mavragani, F. Skopouli, et al., Analysis of clinical and serological picture of patients with primary Sjögren's syndrome and an early disease onset at age before 35 years, Ann. Rheum. Dis. 78 (2019) 790–791.
[41] L. Chatzis, A. Venetsanopoulou, M. Pappa, A.G. Tzioufas, A. Goules, Comparison of clinical phenotype, serological characteristics and histologic features of males vs females patients with primary Sjögren's syndrome (pSS), Ann. Rheum. Dis. 78 (2019) 141.
[42] G. Gondran, A. Fauchais, M. Lambert, K. Ly, D. Launay, V. Queyrel, et al., Primary Sjogren's syndrome in men, Scand. J. Rheumatol. 37 (2008) 300–305.
[43] J.I. Ramirez Sepulveda, M. Kvarnstrom, P. Eriksson, T. Mandl, K.B. Norheim, S.J. Johnsen, et al., Long-term follow-up in primary Sjogren's syndrome reveals differences in clinical presentation between female and male patients, Biol. Sex Differ. 8 (2017) 25.
[44] J.M. Anaya, G.T. Liu, E. D'Souza, N. Ogawa, X. Luan, N. Talal, Primary Sjogren's syndrome in men, Ann. Rheum. Dis. 54 (1995) 748–751.
[45] P. Ansell, J. Simpson, T. Lightfoot, A. Smith, E. Kane, D. Howell, et al., Non-Hodgkin lymphoma and autoimmunity: does gender matter? Int. J. Cancer 129 (2011) 460–466.
[46] D. Sene, S. Ismael, M. Forien, F. Charlotte, R. Kaci, P. Cacoub, et al., Ectopic germinal center-like structures in minor salivary gland biopsy tissue predict lymphoma occurrence in patients with primary Sjogren's syndrome, Arthritis & rheumatology 70 (2018) 1481–1488.
[47] A. Flores-Chavez, B. Kostov, R. Solans, G. Fraile, B. Maure, C. Feijoo-Masso, et al., Severe, life-threatening phenotype of primary Sjogren's syndrome: clinical characterisation and outcomes in 1580 patients (GEAS-SS Registry), Clin. Exp. Rheumatol. 36 (Suppl 112) (2018) 121–129.
[48] S. De Vita, S. Gandolfo, S. Zandonella Callegher, A. Zabotti, L. Quartuccio, The evaluation of disease activity in Sjogren's syndrome based on the degree of MALT involvement: glandular swelling and cryoglobulinaemia compared to ESSDAI in a cohort study, Clin. Exp. Rheumatol. 36 (Suppl 112) (2018) 150–156.
[49] N. Sutcliffe, M. Inanc, P. Speight, D. Isenberg, Predictors of lymphoma development in primary Sjogren's syndrome, Semin. Arthritis Rheum. 28 (1998) 80–87.
[50] A.P. Risselada, A.A. Kruize, J.W. Bijlsma, Clinical features distinguishing lymphoma development in primary Sjogren's Syndrome–a retrospective cohort study, Semin. Arthritis Rheum. 43 (2013) 171–177.
[51] S. Fragkioudaki, C.P. Mavragani, H.M. Moutsopoulos, Predicting the risk for lymphoma development in Sjogren syndrome: an easy tool for clinical use, Medicine 95 (2016) e3766.
[52] E.K. Kapsogeorgou, A. Papageorgiou, A.D. Protogerou, M. Voulgarelis, A.G. Tzioufas, Low miR200b-5p levels in minor salivary glands: a novel molecular marker predicting lymphoma development in patients with Sjogren's syndrome, Ann. Rheum. Dis. 77 (2018) 1200–1207.
[53] L. Quartuccio, M. Isola, C. Baldini, R. Priori, E. Bartoloni Bocci, F. Carubbi, et al., Biomarkers of lymphoma in Sjogren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study, J. Autoimmun. 51 (2014) 75–80.
[54] C. Baldini, P. Pepe, N. Luciano, F. Ferro, R. Talarico, S. Grossi, et al., A clinical prediction rule for lymphoma development in primary Sjogren's syndrome, J. Rheumatol. 39 (2012) 804–808.
[55] M.B. Nishishinya, C.A. Pereda, S. Munoz-Fernandez, J.M. Pego-Reigosa, I. Rua-Figueroa, J.L. Andreu, et al., Identification of lymphoma predictors in patients with primary Sjogren's syndrome: a systematic literature review and meta-analysis, Rheumatol. Int. 35 (2015) 17–26.
[56] R. Solans-Laque, A. Lopez-Hernandez, J.A. Bosch-Gil, A. Palacios, M. Campillo, M. Vilardell-Tarres, Risk, predictors, and clinical characteristics of lymphoma development in primary Sjogren's syndrome, Semin. Arthritis Rheum. 41 (2011) 415–423.
[57] E. Abrol, C. Gonzalez-Pulido, J.M. Praena-Fernandez, D.A. Isenberg, A retrospective study of long-term outcomes in 152 patients with primary Sjogren's syndrome: 25-year experience, Clin. Med. 14 (2014) 157–164.
[58] M. Fallah, X. Liu, J. Ji, A. Forsti, K. Sundquist, K. Hemminki, Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study, Ann. Oncol. 25 (2014) 2025–2030.
[59] R.P. Pollard, J. Pijpe, H. Bootsma, F.K. Spijkervet, P.M. Kluin, J.L. Roodenburg, et al., Treatment of mucosa-associated lymphoid tissue lymphoma in Sjogren's syndrome: a retrospective clinical study, J. Rheumatol. 38 (2011) 2198–2208.
[60] A.G. Tzioufas, D.S. Boumba, F.N. Skopouli, H.M. Moutsopoulos, Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjogren's syndrome, Arthritis Rheum. 39 (1996) 767–772.
[61] A.G. Tzioufas, M.N. Manoussakis, R. Costello, M. Silis, N.M. Papadopoulos, H.M. Moutsopoulos, Cryoglobulinemia in autoimmune rheumatic diseases. Evidence of circulating monoclonal cryoglobulins in patients with primary Sjogren's syndrome, Arthritis Rheum. 29 (1986) 1098–1104.
[62] H.M. Moutsopoulos, A.G. Tzioufas, M.K. Bai, N.M. Papadopoulos, C.S. Papadimitriou, Association of serum IgM kappa monoclonicity in patients with Sjogren's syndrome with an increased proportion of kappa positive plasma cells infiltrating the labial minor salivary glands, Ann. Rheum. Dis. 49 (1990) 929–931.
[63] L. Quartuccio, C. Baldini, E. Bartoloni, R. Priori, F. Carubbi, L. Corazza, et al., Anti-SSA/SSB-negative Sjogren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution, Autoimmun. Rev. 14 (2015) 1019–1022.
[64] A.L. Tomi, R. Belkhir, G. Nocturne, F. Desmoulins, E. Berge, S. Pavy, et al., Brief report: monoclonal gammopathy and risk of lymphoma and Multiple myeloma in patients with primary Sjogren's syndrome, Arthritis & rheumatology 68 (2016) 1245–1250.
[65] J.E. Gottenberg, R. Seror, C. Miceli-Richard, J. Benessiano, V. Devauchelle-Pensec, P. Dieude, et al., Serum levels of beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjogren's syndrome. Data at enrollment in the prospective ASSESS cohort, PLoS One 8 (2013) e59868.
[66] G. Nocturne, R. Seror, O. Fogel, R. Belkhir, S. Boudaoud, A. Saraux, et al., CXCL13 and CCL11 serum levels and lymphoma and disease activity in primary Sjogren's syndrome, Arthritis & rheumatology 67 (2015) 3226–3233.
[67] L. Quartuccio, S. Salvin, M. Fabris, M. Maset, E. Pontarini, M. Isola, et al., BLyS upregulation in Sjogren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal expansion in the salivary glands, Rheumatology 52 (2013) 276–281.
[68] G.J. Tobon, A. Saraux, J.E. Gottenberg, L. Quartuccio, M. Fabris, R. Seror, et al., Role of Fms-like tyrosine kinase 3 ligand as a potential biologic marker of lymphoma in primary Sjogren's syndrome, Arthritis Rheum. 65 (2013) 3218–3227.
[69] A. Papageorgiou, C.P. Mavragani, A. Nezos, E. Zintzaras, L. Quartuccio, S. De Vita, et al., A BAFF receptor His159Tyr mutation in Sjogren's syndrome-related lymphoproliferation, Arthritis & rheumatology 67 (2015) 2732–2741.
[70] A.G. Vakrakou, S. Boiu, P.D. Ziakas, E. Xingi, H. Boleti, M.N. Manoussakis, Systemic activation of NLRP3 inflammasome in patients with severe primary Sjogren's syndrome fueled by inflammagenic DNA accumulations, J. Autoimmun. 91 (2018) 23–33.
[71] E. Kotsifaki, A. Nezos, A. Psarrou, P. Garantziotis, M. Koutsilieris, C.P. Mavragani, The role of the phospholipase LP-PLA2 activity in Sjögren's syndrome related lymphomagenesis: a new serum biomarker? Ann. Rheum. Dis. 78 (2019) 1549.
[72] N. Agmon-Levin, S. Kivity, A.G. Tzioufas, M. Lopez Hoyos, B. Rozman, I. Efes, et al., Low levels of vitamin-D are associated with neuropathy and lymphoma among patients with Sjogren's syndrome, J. Autoimmun. 39 (2012) 234–239.
[73] S. Gandolfo, C. Fabro, M. Bulfoni, E. Doriguzzi Breatta, D. Cesselli, C. DI Loreto, et al., Serum thymic stromal lymphopoietin (TSLP) as a biomarker of B-cell lymphoproliferation in Sjögren's syndrome, Ann. Rheum. Dis. 78 (2019) 387.
[74] R. Gerli, C. Muscat, M. Giansanti, M.G. Danieli, M. Sciuto, A. Gabrielli, et al., Quantitative assessment of salivary gland inflammatory infiltration in primary Sjogren's syndrome: its relationship to different demographic, clinical and serological features of the disorder, Br. J. Rheumatol. 36 (1997) 969–975.
[75] S. Nakamura, A. Ikebe-Hiroki, M. Shinohara, Y. Ohyama, T. Mouri, M. Sasaki, et al., An association between salivary gland disease and serological abnormalities in Sjogren's syndrome, J. Oral Pathol. Med. : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology 26 (1997) 426–430.
[76] A.P. Risselada, A.A. Kruize, R. Goldschmeding, F.P. Lafeber, J.W. Bijlsma, J.A. van Roon, The prognostic value of routinely performed minor salivary gland assessments in primary Sjogren's syndrome, Ann. Rheum. Dis. 73 (2014) 1537–1540.
[77] E. Theander, L. Vasaitis, E. Baecklund, G. Nordmark, G. Warfvinge, R. Liedholm, et al., Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjogren's syndrome, Ann. Rheum. Dis. 70 (2011) 1363–1368.
[78] S.J. Johnsen, E. Berget, M.V. Jonsson, L. Helgeland, R. Omdal, R. Jonsson, Evaluation of germinal center-like structures and B cell clonality in patients with primary Sjogren syndrome with and without lymphoma, J. Rheumatol. 41 (2014) 2214–2222.
[79] M.I. Christodoulou, E.K. Kapsogeorgou, H.M. Moutsopoulos, Characteristics of the minor salivary gland infiltrates in Sjogren's syndrome, J. Autoimmun. 34 (2010) 400–407.
[80] E.K. Kapsogeorgou, M.I. Christodoulou, D.B. Panagiotakos, S. Paikos, A. Tassidou, A.G. Tzioufas, et al., Minor salivary gland inflammatory lesions in Sjogren syndrome: do they evolve? J. Rheumatol. 40 (2013) 1566–1571.
[81] A. Nezos, F. Gravani, A. Tassidou, E.K. Kapsogeorgou, M. Voulgarelis, M. Koutsilieris, et al., Type I and II interferon signatures in Sjogren's syndrome

pathogenesis: Contributions in distinct clinical phenotypes and Sjogren's related lymphomagenesis, J. Autoimmun. 63 (2015) 47–58.
[82] J.C. Hall, L. Casciola-Rosen, A.E. Berger, E.K. Kapsogeorgou, C. Cheadle, A.G. Tzioufas, et al., Precise probes of type II interferon activity define the origin of interferon signatures in target tissues in rheumatic diseases, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 17609–17614.
[83] J.C. Hall, A.N. Baer, A.A. Shah, L.A. Criswell, C.H. Shiboski, A. Rosen, et al., Molecular subsetting of interferon Pathways in Sjogren's syndrome, Arthritis & rheumatology 67 (2015) 2437–2446.
[84] B. Humphries, C. Yang, The microRNA-200 family: small molecules with novel roles in cancer development, progression and therapy, Oncotarget 6 (2015) 6472–6498.
[85] D. Senfter, S. Madlener, G. Krupitza, R.M. Mader, The microRNA-200 family: still much to discover, Biomol. Concepts 7 (2016) 311–319.
[86] M. Ragusa, A. Majorana, B. Banelli, D. Barbagallo, L. Statello, I. Casciano, et al., MIR152, MIR200B, and MIR338, human positional and functional neuroblastoma candidates, are involved in neuroblast differentiation and apoptosis, J. Mol. Med. 88 (2010) 1041–1053.
[87] T.S. Lee, H.W. Jeon, Y.B. Kim, Y.A. Kim, M.A. Kim, S.B. Kang, Aberrant microRNA expression in endometrial carcinoma using formalin-fixed paraffin-embedded (FFPE) tissues, PLoS One 8 (2013) e81421.
[88] M.F. Chen, F. Zeng, L. Qi, X.B. Zu, J. Wang, L.F. Liu, et al., Transforming growth factorbeta1 induces epithelialmesenchymal transition and increased expression of matrix metalloproteinase16 via miR200b downregulation in bladder cancer cells, Mol. Med. Rep. 10 (2014) 1549–1554.
[89] Y.X. Cheng, G.T. Chen, C. Chen, Q.F. Zhang, F. Pan, M. Hu, et al., MicroRNA-200b inhibits epithelial-mesenchymal transition and migration of cervical cancer cells by directly targeting RhoE, Mol. Med. Rep. 13 (2016) 3139–3146.
[90] L.V. Rhodes, E.C. Martin, H.C. Segar, D.F. Miller, A. Buechlein, D.B. Rusch, et al., Dual regulation by microRNA-200b-3p and microRNA-200b-5p in the inhibition of epithelial-to-mesenchymal transition in triple-negative breast cancer, Oncotarget 6 (2015) 16638–16652.
[91] E. Kapsogeorgou, A. Protogerou, A. Papageorgiou, M. Voulgarelis, A.G. Tzioufas, Predictive value of mir200b-5p in the lymphomagenesis in Sjögren's syndrome (SS): comparison with the published prediction models. Preliminary results, Ann. Rheum. Dis. 78 (2019) 1725–1726.
[92] D.G. Altman, P. Royston, What do we mean by validating a prognostic model? Stat. Med. 19 (2000) 453–473.