SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Peripheral blood biomarkers of malignant melanoma

by Tünde Várvölgyi

Supervisor:
Margit Balázs, DSc

UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF HEALTH SCIENCES

DEBRECEN, 2026

Peripheral blood biomarkers of malignant melanoma

By Tünde Várvölgyi

Supervisor: Margit Balázs, DSc

Doctoral School of Health Sciences, University of Debrecen

Head of the **Defense Committee**: Mariann Harangi, DSc

Reviewers: András Bánvölgyi, PhD
László József Tóth, PhD

Members of the Defense Committee: Norbert Kiss, PhD
Tamás Csonka, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen,
and starts at 1:00 p.m., on the 15th of April, 2026.

Introduction

Malignant melanoma is one of the most aggressive skin tumours and represents a major public health problem worldwide. Although its incidence is relatively lower compared with other skin malignancies, it accounts for the majority of skin cancer-related deaths due to its extremely high metastatic potential, elevated mutation rate and increased resistance to drugs.

The 5-year survival rate of patients with metastatic melanoma has improved substantially over the past 15 years, largely owing to the introduction of targeted therapies (BRAF and MEK inhibitors) and immune checkpoint inhibitors. Nevertheless, despite these therapeutic advances, the survival of patients with advanced-stage and metastatic disease remains limited, barely reaching 50%. In addition to early diagnosis of the primary tumour, timely detection of melanoma relapse significantly improves patient survival. To further reduce mortality rates, there is an increasing demand for easily accessible, rapidly obtainable biomarkers derived from peripheral blood that are suitable for the early detection of relapse. From a clinical perspective, peripheral blood-based assays are less invasive than conventional biopsies and are capable of detecting various proteins, lipids, and cell-free DNA. Ideally, such diagnostic and prognostic serum or plasma biomarkers are useful for monitoring therapeutic efficacy and may also have predictive value for patient survival; moreover, they are more readily and rapidly accessible than certain imaging techniques. However, at present, no valid consensus exists regarding the routine necessity of peripheral blood sampling for diagnostic/prognostic parameters in the follow-up of patients with melanoma. The only meta-analysis conducted in 2008 demonstrated that elevated serum S100B levels are significantly associated with pooerer survival in melanoma patients. Serum lactate dehydrogenase (LDH) is a well-established prognostic marker in patients with advanced-stage melanoma and is also incorporated into the melanoma TNM (tumour size/lymph node involvement/distant metastasis) staging system. In addition to serum LDH and serum S100B, a growing body of literature indicates that plasma osteopontin (OPN) concentrations correlate with melanoma progression. Considerable attention has recently been directed towards investigating altered lipid metabolism in tumour cells, based on the observation that malignant cells actively synthesise and uptake lipids. Such studies may lead to the identification of novel lipid biomarkers capable of providing information on disease stage and response to therapy.

Literature review

Malignant melanoma is a malignant tumour of melanocytes, predominantly arising in the skin; however, in 4-5% of cases, it may also occur in other tissue locations, such as the uvea, mucous membranes or leptomeninges. Its prevalence among Caucasians has increased significantly worldwide over the past four decades. Although it accounts for less than 5% of all skin malignancies, it is responsible for nearly 73% of skin cancer-related deaths. Malignant melanoma is known to carry a high risk of both lymph node and haematogenous metastases. Early metastases develop within 3 years of diagnosis, whereas late metastases can occur even after 10 or more years of asymptomatic disease. The Breslow thickness of the primary tumour and the presence or absence of ulceration represent the two most important histopathological prognostic parameters. Although awareness campaigns and advances in the treatment of metastatic melanoma have improved patient survival, there remains an increasing need for easily accessible biomarkers from peripheral blood to facilitate early detection of relapse and thereby improve mortality rates. Serum or plasma biomarkers may also play an important role in planning the management of metastatic disease, predicting prognosis and monitoring therapeutic efficacy. Not only circulating tumour cells but also various tumour-specific biomarkers can be obtained from peripheral blood.

One well-established biomarker in melanoma patients is serum lactate dehydrogenase (LDH), which is incorporated into the melanoma TNM staging system. LDH has proven to be the most reliable prognostic factor in patients with stage IV melanoma. Elevated LDH levels correlate closely with tumour size and the extent of necrosis; however, this marker is not melanoma-specific, as increased levels may also be observed in other malignancies, in tissue injury independent of malignancy, in patients after myocardial infarction, following haemolysis, or in patients with hepatitis. The sensitivity and specificity of LDH are lower than those of the S100B protein.

S100B, a calcium-binding acidic cytoplasmic protein, is expressed and secreted at significantly higher levels in malignant melanoma tissue than in healthy tissue. Elevated serum S100B levels exhibit greater specificity for disease progression compared with LDH, reflecting tumour burden in metastatic patients; however, serum levels may also be elevated in a variety of other conditions, including cardiovascular disease, liver cirrhosis, previous stroke, breast cancer and SARS-CoV-2 infection. In the only meta-analysis examining the association between serum S100B levels and melanoma, elevated serum S100B was associated with significantly poorer survival in melanoma patients.

Recent studies indicate that elevated plasma osteopontin (OPN) levels are strongly associated with the presence of metastases in multiple malignancies, making OPN a promising biomarker. OPN is a multifunctional extracellular matrix protein composed of approximately 314 amino acids and is encoded on chromosome 4 (also referred to as secreted phosphoprotein 1 [SPP1] or Early T-lymphocyte Activation 1 protein [ETA-1]). The OPN protein is produced by various cell types and demonstrates high expression in numerous cancers, including breast, gastric, colorectal, pancreatic, liver and lung cancers, and melanoma. Detailed microarray analyses suggest a significant role for OPN in melanoma progression. Based on literature data, OPN overexpression is associated with increased tumor invasion and metastasis formation.

In a previous study, Margit Balázs and colleagues demonstrated that OPN expression is elevated at both mRNA and protein levels in thick melanomas, and that increased expression correlates with ulceration of the tumour surface. In a subsequent study, they reported that OPN gene expression is significantly increased in cell lines derived from melanoma metastases compared with those from primary melanomas. In a clinical study, significantly elevated plasma OPN concentrations were found in patients with metastatic melanoma compared with non-metastatic cases.

Serum tumour markers generally exhibit varying prognostic (survival prediction) and diagnostic (relapse prediction) capabilities. From a diagnostic perspective, serum S100B is routinely used in many dermato-oncology centres to detect disease relapse. However, estimates of S100B sensitivity and specificity vary widely (32-94% and 76-97%, respectively). At present, no consensus exists regarding the use of peripheral blood tests for monitoring disease recurrence in patients with high-risk melanoma, or in metastatic cases.

Melanoma is currently considered to exhibit the highest mutation rate of all malignancies, resulting in marked metabolic differences between melanoma cells and normal cells. These mutations lead to alterations in metabolic pathways that enable tumour cells to survive in a continuously changing environment. Altered lipid metabolism and the emergence of a lipogenic phenotype represent some of the earliest biochemical characteristics of neoplastic cells. Studies investigating the metabolic behaviour of melanoma have demonstrated that such phenotypic plasticity confers adaptive advantages that promote tumour cell proliferation and survival. Therefore, we aimed to investigate the association between the presence of metastases in melanoma patients and alterations in lipid profiles.

Objectives

Our research focused on the following 3 areas:

- **To evaluate the diagnostic performance of three peripheral blood biomarkers—LDH, S100B, and osteopontin (OPN)—for the detection of metastatic disease in our melanoma patient cohort, in comparison with previously published data.**
- **To systematically review the available literature and perform a meta-analysis comparing the prognostic (survival prediction) and diagnostic (relapse prediction) performance of serum S100B and serum LDH in patients with melanoma.**
- **To investigate associations between plasma lipid profiles and metastatic status in our melanoma patient cohort using state-of-the-art quantitative lipidomic profiling with the Lipidyzer™ platform, covering 13 lipid classes and more than 1,100 lipid species.**

Materials and Methods

Peripheral blood-based biomarkers - S100B, LDH, OPN - in our melanoma patient population

Study population

In one part of our research, we included 206 patients with melanoma in a retrospective study conducted between 4 April 2019 and 22 September 2022. Data for the study were obtained from the clinical databases of the University of Debrecen (MedSolution and UDMED). The study was approved by the Ethics Committee of the Medical Research Council (approval number: IV/1711-4/2021/ECU). Patient data including age and sex, histological subtype of the primary melanoma, Breslow tumour thickness, ulceration status, localisation of the primary tumour, Clark level of invasion, and pathological tumour stage (pT) according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM classification were collected. Serum S100B and LDH levels were also recorded. Peripheral blood samples were collected from 206 patients with melanoma (N=120 without metastasis; N=86 with metastasis). Serum concentrations of S100B (chemiluminescent immunoassay, LIAISON® S100) and LDH (automated colorimetric assay) were routinely measured during patient follow-up. Patients in the metastatic group were diagnosed with metastatic disease by PET-CT or three-region CT ± soft-tissue ultrasonography within one month prior to the date of blood sample collection. The metastatic melanoma group included: 1. patients with confirmed metastasis who had not yet received systemic therapy for metastatic melanoma; 2. metastatic patients receiving BRAF plus MEK inhibitor therapy or immune checkpoint inhibitor therapy. The group without metastases included: 1. patients free of metastasis after removal of the primary melanoma; 2. patients in complete remission after systemic therapy; 3. patients free of metastasis after lymph node block dissection.

Enzyme-linked immunosorbent assays (ELISA)

Plasma osteopontin protein levels were determined by ELISA using the commercially available Human OPN Quantikine ELISA Kit (R&D Systems, Inc., Minneapolis, MN, USA; Catalog No.: DOST00). The assay was performed according to the manufacturer's protocol. Sample absorbance was measured at 540 nm using an Epoch™ microplate spectrophotometer (BioTek Instruments, Winooski, VT, USA).

Statistical analysis

Data normality was assessed using the Shapiro–Wilk test. The χ^2 test or Fisher's exact test was used to analyse categorical variables. In the case of normal distribution, an independent samples t-test (two-sample t-test) was applied to compare continuous variables, whereas in the case of non-normal distribution, the Mann–Whitney U test was used to compare the two groups. Univariate and multivariate logistic regression analyses were performed to develop a model for evaluating diagnostic performance. Odds ratios (ORs) were reported with their corresponding 95% confidence intervals (95% CI). Patients with melanoma were randomly assigned to training and validation groups in a 2:1 ratio. Optimal cut-off values for distinguishing the presence or absence of metastasis in the training and validation groups were determined by receiver operating characteristic (ROC) curve analysis for the variables of interest, both individually and in combination. The optimal cut-off value was defined using the maximum Youden index. The area under the ROC curve (AUC) was calculated with a 95% confidence interval (95% CI). The level of statistical significance was set at $p < 0.05$. Statistically significant differences are denoted as *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) and R software (version 3.6.4; R Foundation for Statistical Computing, Vienna, Austria).

Meta-analysis of the diagnostic and prognostic impact of S100B and LDH

In the meta-analysis section of this research, systematic reviews and meta-analyses were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was registered in the PROSPERO registry (CRD42019137138).

Deviation from the registered protocol

No subgroup analysis was initially planned. However, in one eligible primary study included patients with uveal melanoma, all other patients had cutaneous melanoma, patients with uveal melanoma were included, whereas all other studies involved patients with cutaneous melanoma. As the pathogenesis of uveal and cutaneous melanoma differs, quantitative analyses were performed using only studies that included patients with cutaneous melanoma. In addition, a separate diagnostic impact meta-analysis was conducted including the study that enrolled patients with uveal melanoma.

Eligibility criteria

The review questions were formulated using the PICOTS framework, based on the CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies), adapted for diagnostic impact studies and prognostic factor studies.

Search strategy and selection of studies

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched from database inception to 15 January 2021. Only studies published in English were included. The search strategy used the predictive factors of interest and the target disease as keywords and search terms, including “S100B” or “S100” and “lactate dehydrogenase” or “LDH” and “melanoma” in MEDLINE (via PubMed), and “melanoma” AND “S100B” AND “lactate dehydrogenase” in Embase and the Cochrane Central Register of Controlled Trials.

Data extraction

Data extraction was performed in accordance with the CHARMS recommendations. Items required for meta-analysis, as well as for the assessment of applicability and risk of bias, were collected in Excel spreadsheets. We extracted the first author, study design, country of study, year of publication, population size (with and without metastasis, where applicable), inclusion and exclusion criteria, demographic data (age, sex), methods and cut-off values for S100B and LDH measurement, information on the reference standard, baseline prognostic factors used in Cox models, and outcome data. The literature search, study selection, and data extraction were conducted independently by the investigators, followed by discussion and consensus.

Assessment of applicability and risk of bias (ROB)

The quality of the included studies was assessed independently by the investigators, with consensus facilitated by the flow charts of the primary studies. To assess concerns regarding the applicability of ROB and diagnostic accuracy studies, the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool was used. ROB in prognostic factor studies was assessed using the Quality In Prognosis Studies (QUIPS) tool.

Statistical analysis

Between-study heterogeneity was assessed using the I^2 statistic, calculated as $I^2 = 100\% \times (Q - df)/Q$, which reflects the magnitude of heterogeneity (moderate: 30-60%; substantial: 50-90%; significant: 75-100%). Pooled estimates (AUROC with 95% confidence interval, sensitivity, specificity, adjusted HR (hazard ratio) with 95% confidence interval, survival rates (at 1 and 2 years) with 95%

confidence interval) were calculated using a DerSimonian-Laird random-effects model. Funnel plots and Egger's test were used to assess potential publication bias. Statistical analyses were performed using Stata version 16.1 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA) and the R package version 4.0.3 (R Foundation for Statistical Computing).

Analysis of plasma lipidomic abnormalities in a melanoma patient population

In the third part of our research, 151 patients were included in a plasma lipidomic study of melanoma. 83 patients were classified as metastasis-free, as CT or PET-CT scans within one month prior to blood sampling showed no evidence of metastasis. In addition, 68 patients had metastatic melanoma at the time of blood sampling. Patients in the metastatic group were diagnosed by PET-CT or three-region CT scans ± soft tissue ultrasonography within one months prior to blood sampling. The metastatic melanoma group included: 1. patients with confirmed metastasis who had not yet received therapy for metastatic melanoma, 2. metastatic patients receiving BRAF plus MEK inhibitor or immune checkpoint inhibitor therapy. The group without metastases included: 1. patients free of metastases after removal of the primary melanoma, or 2. patients in complete remission after drug treatment, or 3. patients free of metastases after lymph node block dissection. Distant metastases most commonly involved the lung, brain, liver, or kidney. Metastatic melanoma patients were classified into two groups according to the route of metastatic spread: lymphogenic and haematogenous. Regional lymph node metastasis was present in 19 patients, while distant metastases were detected in 49 patients at the time of blood sampling. The primary melanoma types in patients considered tumour-free at the time of blood sampling were predominantly cutaneous (98.7%); two primary tumours were choroidal melanomas. It is important to note that patients with advanced metastatic disease almost always also exhibited regional lymph node involvement, which made complete separation of the two metastatic pathways challenging.

Peripheral blood samples

Blood samples were collected at the Department of Dermatology, Faculty of General Medicine, University of Debrecen. Sampling was performed at least one month after surgical removal of the primary tumour. All samples were processed within one hour of collection. Blood samples were handled in accordance with the institutional regulations of the University of Debrecen, with approval from the Scientific and Research Ethics Committee of the Health Science Council (TUKEB 17876-2018/EKU and BMEÜ/715-1/2022/EKU).

Standards and extraction of lipids

Methanol, 2-propanol, dichloromethane, HPLC-grade water (H_2O), and ammonium acetate were purchased from VWR International, LLC (Radnor, PA, USA). All solvents were of HPLC grade. Internal standard (ISTD) kits for quantitative lipidomic analysis of human samples were purchased from AB Sciex Germany GmbH (Darmstadt, Germany). The kits contained internal standards covering 13 lipid classes.

Lipidomic analysis

Lipid samples were analysed using high-performance liquid chromatography coupled with electrospray ionisation tandem mass spectrometry (HPLC-ESI-MS/MS), as previously described. Lipidomic analyses were performed using a Lipidyzer platform consisting of a Nexera X2 HPLC system (Shimadzu Germany GmbH, Duisburg, Germany) coupled to a Sciex QTRAP 5500 mass spectrometer equipped with SelexION technology (AB Sciex Germany GmbH, Darmstadt, Germany). NanoViper capillary tubes (750 × 0.05 mm and 350 × 0.05 mm; Thermo Fisher Scientific Inc., Waltham, MA, USA) were used to connect the HPLC autosampler valve to the grounding connection of the ESI ionisation source, and the grounding connection to the ESI electrode (65 µm inner diameter), respectively.

Nomenclature of lipids

In this study, lipid nomenclature proposed by the Lipid Maps Consortium was used. Triacylglycerol (TG) species containing three fatty acid chains were denoted by the number of carbon atoms and double bonds in one fatty acid chain, followed by the sum of the number of carbon atoms and double bonds in the remaining two fatty acid chains (e.g. TG 20:4_33:1). Other lipids containing one or two fatty acid chains were denoted by the number of carbon atoms and double bonds in each fatty acid chain (e.g. CE 14:0, containing one fatty acid chain without double bonds, and PC 18:1_18:1, containing two fatty acid chains, each with one double bond).

Statistical analysis

The Shapiro–Wilk test was used to assess data normality. Non-parametric methods and logistic regression models were applied for data analysis. Binary logistic regression modelling was used to evaluate the association between lipid species levels and prognostic factors (presence or absence of metastasis, mortality, and localisation of metastasis) as dichotomous covariates, with adjustment for age and sex. Odds ratios were calculated with corresponding 95% confidence intervals. Logistic regression analysis was performed to identify lipid panels showing significant associations with prognostic factors after adjustment for age and sex. Receiver operating characteristic (ROC) curves were generated based on the logistic regression models, and the area under the curve (AUC) was used to evaluate model performance. ROC analyses were also used to determine optimal cut-off values. The Youden index (J statistic) was used to optimise sensitivity and specificity. To determine the optimal cut-off values, the maximum Youden index based on the combined concentrations of lipid species was selected. Comparisons of lipid levels were performed using the Mann–Whitney–Wilcoxon test or the Kruskal–Wallis test, followed by Dunn's post hoc test where appropriate. Statistical analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered statistically significant.

Results

Results of peripheral blood biomarkers - S100B, LDH, OPN - in our melanoma patient population

A total of 206 melanoma patients were included in the study, comprising 120 non-metastatic and 86 metastatic cases. Regarding primary tumour characteristics, the most common histological subtype in both groups was nodular melanoma. Furthermore, more invasive tumours (Clark level V) and ulcerated primary tumours (pT4b) with a Breslow thickness > 4 mm were significantly more frequent in the metastatic group ($p = 0.012$ and $p < 0.001$, respectively). The prevalence of BRAF mutation did not differ significantly between the groups ($p = 0.375$). Serum S100B and plasma OPN levels were significantly higher in the metastatic group ($p < 0.001$ and $p = 0.002$, respectively), whereas serum LDH levels did not differ significantly between the non-metastatic and metastatic melanoma patient groups ($p = 0.107$).

Univariate and multivariate logistic regression

Logistic regression models were used to assess factors associated with the presence of metastasis in melanoma patients.

Training group and validation group

The 206 melanoma patients were randomly divided in a 2:1 ratio into a training cohort (N = 138) and a validation cohort (N = 68) to evaluate the diagnostic model. No significant differences were observed between metastatic and non-metastatic patients in terms of age, sex, histological subtype, or BRAF mutation status in either the training or validation cohort. Primary tumour localisation, Clark level, and pT stage differed significantly between metastatic and non-metastatic melanoma patients in the training cohort but not in the validation cohort. Significant differences between metastatic and non-metastatic patients were observed in both cohorts for serum S100B and plasma OPN levels, whereas no significant differences were found for serum LDH levels.

Diagnostic impact of biomarkers and their combinations

Receiver operating characteristic (ROC) analysis was used to determine optimal cut-off values for the biomarkers and to calculate the area under the curve (AUC). The optimal cut-off value for serum S100B was 0.085 µg/L, with an AUC of 0.671 (95% CI: 0.598–0.752) in the training cohort and 0.682 (95% CI: 0.547–0.817) in the validation cohort. For serum LDH, the optimal cut-off value was 220.5 U/L, and the AUC was 0.575 (95% CI: 0.477–0.674) in the training cohort and 0.563 (95% CI: 0.424–0.703) in the validation cohort. For OPN, an optimal cut-off value of 80.09 ng/mL was determined based on the Youden index, yielding an AUC of 0.616 (95% CI: 0.518–0.715) in the training cohort and 0.643 (95% CI: 0.500–0.786) in the validation cohort. The combination of individual blood biomarkers resulted in comparable AUC values. The combined model including all three biomarkers (LDH, S100B, and OPN), primary tumour localisation, and the AJCC 8th edition pT category yielded the highest AUC values (0.803; 95% CI: 0.729–0.878 in the training cohort and 0.822; 95% CI: 0.726–0.919 in the validation cohort). Exclusion of OPN from the combined model still resulted in high AUC values in both the training and validation cohorts: 0.791 (95% CI: 0.713–0.869) and 0.812 (95% CI: 0.712–0.911), respectively.

The prognostic and diagnostic abilities of serum S100B and serum LDH

Selection of studies and characteristics of the studies included in the analysis

The literature search yielded 478 records. After removal of duplicates and exclusion of non-English language publications, 389 studies remained for screening. Based on titles and abstracts, 92 studies were selected for full-text review. Thirteen publications were not available in full text, and 62 did not meet the predefined inclusion criteria. Finally, 7 primary studies evaluating diagnostic impact (6 involving cutaneous melanoma and 1 involving uveal melanoma) and 10 studies investigating prognostic factors were included in the qualitative and quantitative synthesis.

Qualitative assessment of the studies included in the study

The qualitative assessment indicated that several studies were at risk of bias, with the highest risk observed in relation to the reference standards used. Imaging techniques with varying sensitivity and specificity were applied as reference standards for detecting disease relapse, and their diagnostic accuracy differed depending on disease stage across studies. As not all domains could be classified as having a low risk of bias, broad generalisation of the findings was avoided. According to the funnel plot for AUROC, publication bias appeared unlikely. Funnel plot assessment and Egger's test did not demonstrate evidence of publication bias for hazard ratios derived from Cox models ($p = 0.245$ for S100B; $p = 0.344$ for LDH).

Meta-analysis of diagnostic impact

Six studies including 1033 patients with cutaneous melanoma were included in the meta-analysis. Quantitative synthesis demonstrated that the discriminative ability of S100B to correctly identify patients with or without melanoma relapse was significantly greater than that of LDH ($p = 0.013$). Sensitivity and specificity were also analysed using predefined cut-off values for dichotomised continuous serum concentrations of S100B and LDH. The pooled sensitivity of S100B was significantly higher than that of LDH ($p = 0.017$), whereas pooled specificity did not differ significantly between the two biomarkers ($p = 0.557$). The ROC-optimised cut-off value for serum S100B was higher than the manufacturer-recommended predefined cut-off and was associated with higher specificity but lower sensitivity. Quantitative analysis of data from seven eligible studies included a total of 1167 participants (n = 1033 with cutaneous melanoma and n = 134 with uveal melanoma). In this broader analysis, the discriminative ability of serum S100B to correctly identify patients with or without disease relapse was not significantly different from that of serum LDH ($p = 0.061$). However, the pooled sensitivity of serum S100B remained significantly higher than that of LDH ($p = 0.024$), while the overall specificity was similar between the two biomarkers ($p = 0.643$).

Meta-analysis of prognostic impact

Ten studies including 1987 participants were included in the analysis of adjusted hazard ratios for overall survival derived from multivariate Cox proportional hazards models. No significant difference was observed between the hazard ratios associated with elevated serum S100B levels and elevated serum LDH levels ($p = 0.389$). Both elevated serum S100B and elevated LDH levels were associated with an increased risk of death in patients with metastatic melanoma. Four studies including 1940 participants were included in the analysis of one- and two-year survival rates. The one-year survival rate of patients with normal serum S100B levels was significantly higher than that of patients with elevated serum S100B levels ($p = 0.033$). A similar trend was observed for the two-year survival rate (normal serum S100B: 32.51%; elevated serum S100B: 14.68% [95% CI: 5.77–23.58]), although the difference did not reach statistical significance ($p = 0.082$). The one-year survival rate of patients with normal serum LDH levels was higher than that of patients with elevated serum LDH levels; however, the difference was not statistically significant ($p = 0.152$). Similar findings were observed for two-year survival (normal serum LDH: 26.94%; elevated serum LDH: 13.39%; $p = 0.207$).

Analysis of plasma lipidomic abnormalities in a melanoma patient population

Distribution of lipid classes between patients without and with metastasis

A total of 151 peripheral plasma samples from melanoma patients were analysed using the Sciex Lipidyzer™ platform. Clinical characteristics of the patients and tumour samples are summarised in the Materials and Methods section. Our initial observation was that the overall lipid content among the quantified lipid species (n = 802) was significantly lower in plasma samples from patients with metastatic disease compared with those without metastasis ($p \leq 0.05$). The distribution across the 13 lipid classes also differed between the two patient groups, with the most pronounced change being a reduction in free fatty acid (FFA) levels in patients with metastasis. Comparison of total lipid class levels between patients with and without metastasis revealed significant decreases in two lipid classes (FFA and LCER) in plasma samples from patients with metastatic melanoma.

Relationship between lipids and the presence of metastases in melanoma patients

A logistic regression model adjusted for age and sex was used to examine the association between lipid species levels and the presence or absence of metastasis. This analysis identified 19 lipid species with significant prognostic relevance. Patients with lower levels of 18 lipid species and higher levels of PE(18:0/20:2) were more likely to have metastatic melanoma. Binary logistic regression analysis was subsequently applied to determine which of these 19 lipid species showed the strongest independent association with metastatic status. This analysis yielded a panel of three lipid species (CE(12:0), FFA(24:1), and TAG 47:2–FA16:1) whose associations remained independent of age and sex. This lipid panel may be useful for predicting the probability of metastatic disease. ROC analysis demonstrated that this lipid panel achieved an AUC of 0.753. The potential predictive value of this panel was further evaluated in combination with serum LDH and serum S100B levels. The combined biomarker model yielded an AUC of 0.811, whereas the conventional model based on serum S100B and LDH alone showed an AUC of 0.715.

Lipids associated with the lymphogenic and haematogenic pathway of melanoma metastasis

To investigate the relationship between lymphogenic and haematogenous pathways of melanoma metastasis, plasma samples from metastatic patients were divided into two groups. The first group consisted of patients with regional lymph node metastasis (N = 19), while the second group comprised patients with distant metastasis (N = 49). The total concentration of lysophosphatidylcholine (LPC) and seven individual lipid species (including five LPC species: LPC(16:0), LPC(18:0), LPC(18:1), LPC(18:2), and LPC(20:4)) showed a negative association with the haematogenous pathway, indicating that reduced levels of these lipids were associated with distant metastatic spread. To develop a quantitative approach for estimating the individual probability of lymph node metastasis, we further evaluated five LPC species (LPC(16:0), LPC(18:0), LPC(18:1), LPC(18:2), and LPC(20:4)) associated with metastatic pathway classification. The combined concentrations of these five lipid species were analysed using ROC analysis, which identified a plasma concentration cut-off value of 202.46 µmol/L, corresponding to a sensitivity of 0.895 and a specificity of 0.510. Samples were stratified according to this cut-off value, and logistic regression analysis demonstrated that patients with a total plasma concentration of the five LPC species > 202.46 µmol/L had a significantly higher probability of lymph node metastasis compared with haematogenous metastasis ($p = 0.004$; odds ratio: 0.093; 95% confidence interval: 0.018–0.477). Further logistic regression analysis identified a two-lipid panel consisting of

LPC(16:0) and LPC(20:4), which showed strong predictive ability for distinguishing metastatic pathways, with an AUC of 0.841 based on ROC analysis. The predictive performance of this two-lipid panel did not improve with the addition of further LPC species.

In addition, differences in the levels of the five LPC species were examined among patients without metastasis, patients with regional lymph node metastasis, and patients with distant metastasis.

Lipids associated with melanoma patient outcome

Despite the relatively low number of deaths in the study cohort (22 deaths compared with 129 patients who were alive at the time of analysis), we also examined lipidomic "fingerprints" associated with patient outcome. Reduced levels of seventeen lipid species were associated with mortality.

Logistic regression analysis identified a single lipid species, CE(14:0), which demonstrated the highest AUC among all analysed lipids, including when evaluated in combination with other lipid species. Based on plasma concentrations of CE(14:0) in melanoma patients, an optimal threshold value of 18.03 µmol/L was determined. Analysis indicated that patients with CE(14:0) levels above this threshold had a significantly higher probability of survival (Mann–Whitney test, $p < 0.002$), corresponding to an approximately eleven-fold increase in survival likelihood.

Discussion

Diagnostic efficacy of peripheral blood biomarkers, LDH, S100B and OPN in metastasis and relapse

In patients with advanced melanoma, elevated serum LDH levels are primarily attributed to increased release from glycolytically active tumour cells (particularly LDH isoenzymes 3 and 4). In a study involving 121 patients, LDH demonstrated a specificity of 92.2% and a sensitivity of 41.9% for detecting regional or distant metastases in stage III–IV melanoma. However, because LDH levels may also be elevated in a range of non-malignant and malignant conditions, false-positive results may occur. In our study, serum LDH levels were significantly associated with the presence of metastasis in univariate logistic regression analysis ($p = 0.019$); however, this association was not retained in the multivariate model. Intracellular S100 proteins function as Ca^{2+}- and Zn^{2+}-binding sensors involved in numerous protein interactions and regulate several cellular processes, including transcription, protein phosphorylation, cell motility, and energy metabolism, all of which may influence tumour growth. In melanoma patients, elevated serum S100B levels are thought to result from tumour cell death and protein degradation associated with apoptosis and necrosis. Serum S100B concentrations correlate with melanoma stage, with lower levels typically observed in stages I–II and higher levels in more advanced disease. Moreover, a significant association between Breslow tumour thickness and serum S100B levels has been reported in patients with stage III melanoma. S100B has also been shown to be useful for detecting disease progression in asymptomatic patients during follow-up. It is noteworthy that, although S100B demonstrates higher specificity for melanoma compared with LDH, elevated S100B levels may also occur in various other conditions, including cardiovascular diseases, liver cirrhosis, migraine, breast cancer, vitiligo, and SARS-CoV-2 infection. In 2011, a study comparing the diagnostic value of serum S100B measurement with PET-CT imaging in patients with metastatic melanoma was published. These observations collectively suggest that serum S100B assessment represents a valuable tool in the follow-up of melanoma patients, particularly for detecting disease progression in asymptomatic individuals.

In our study, serum S100B levels were significantly associated with the probability of metastasis in both univariate ($p < 0.001$) and multivariate ($p = 0.020$) logistic regression analyses. The discriminative performance of serum S100B for identifying metastatic disease was superior to that of serum LDH; however, the AUC did not exceed 0.7 even for serum S100B. Notably, the ROC-optimised cut-off value for serum S100B was lower than the manufacturer's recommended cut-off. This finding is clinically relevant, as the choice of cut-off directly influences the sensitivity and specificity of a diagnostic test. In contrast, the ROC-optimised cut-off value for serum LDH corresponded to the upper limit of normal (ULN) established by the local laboratory. Collectively, our results support the need to identify additional complementary peripheral biomarkers to improve the detection of metastasis and relapse in melanoma patients.

Previous studies have demonstrated that osteopontin (OPN) expression is elevated at both mRNA and protein levels in thick and ulcerated melanomas. In a recent study by Margit Balázs and colleagues, significantly increased OPN mRNA expression was observed in melanoma cell lines derived from metastatic lesions compared with those derived from primary tumours. Furthermore, elevated OPN gene expression was reported in melanoma cell lines harbouring the BRAFV600E mutation. Consistent with these findings, we observed significantly higher plasma OPN levels in the metastatic group ($p = 0.002$) compared with the non-metastatic group. Moreover, plasma OPN levels were significantly associated with the probability of metastasis in both univariate ($p < 0.001$) and multivariate ($p < 0.001$) logistic regression analyses. However, the discriminative ability of plasma OPN for identifying metastatic disease was not superior to that of serum S100B, and comparable AUC values were observed for serum S100B and plasma OPN.

In our study, we demonstrated that primary tumour location in the lower limbs is an independent predictor of an increased probability of metastasis. Results previously published by our group in 2024 indicated that, within our melanoma patient population, melanomas located on the limbs carried a significantly higher risk of progression compared with those on the trunk. To enhance diagnostic performance for metastasis detection, we examined a model combining the three peripheral biomarkers with primary tumour location and AJCC 8th edition pT category. Our findings showed that incorporating tumour location and pT category significantly improved the discriminative ability of all biomarkers for identifying metastatic disease, yielding an AUC of approximately 0.8. The highest AUC was observed in the model combining serum S100B, LDH, OPN, tumour location, and pT category. However, while serum S100B measurement is routinely available in most clinical laboratories, plasma OPN assessment is not. Notably, omission of OPN from the combined model resulted in similarly strong discriminative performance.

Meta-analysis of the literature to compare the prognostic and diagnostic ability of serum S100B and serum LDH in patients with melanoma.

In a subgroup of patients with metastatic melanoma, serum S100B levels were not consistently elevated, and several studies have examined its prognostic impact. Given the strong discriminative ability of serum S100B in identifying metastatic disease, we selected only studies including metastatic patients for the analysis of prognostic impact. Surprisingly, very few suitable studies were identified, as multivariate analyses in this area are rare, patient selection is often biased, and significant reporting bias exists in prognostic studies regarding outcomes. Our results showed that the overall adjusted hazard ratio (HR) of S100B was similar to that of LDH, indicating that serum S100B has comparable prognostic value to serum LDH in patients with metastatic melanoma. Importantly, in line with the distinct biology associated with elevated serum LDH and S100B levels, the studies included in the meta-analysis suggested that the prognostic ability of the two markers is independent. Quantitative analysis of data from six studies including 1,033 patients with cutaneous melanoma demonstrated that the discriminative ability of serum S100B to identify disease relapse was significantly greater than that of serum LDH. Ten studies encompassing 1,987 patients were included in the analysis of mortality risk, which showed that the prognostic ability of serum S100B (pooled estimate of adjusted HR) was independent but not superior to that of serum LDH. The novelty of our meta-analysis lies in its comparative approach, the evaluation of multiple outcomes, and the inclusion of logistic regression models. Furthermore, the results were based on analyses of patient populations exceeding 1,000 individuals for each outcome studied.

Searching additional biomarkers in the plasma lipidome.

Plasma of patients with malignancies often shows reduced HDL levels and elevated LDL levels, which are associated with an increased risk of metastasis. Our lipidomic data indicate a significant decrease in total plasma lipids in metastatic melanoma patients, accompanied by changes in the percentage distribution among the 13 lipid classes. Among these classes, we observed significant decreases in FFA and LCER in patients with metastatic melanoma. The decrease in FFA levels may seem surprising, as several studies have reported elevated FFA levels in various cancers, including prostate cancer, lung cancer, gastric cancer, thyroid cancer, colon cancer, ovarian cancer, B-cell lymphoma, and breast cancer. We also observed a significant reduction in lactosylceramide levels in the plasma of patients with metastatic melanoma. This class of sphingolipids is known to promote tumour progression by supporting cell survival, proliferation, adhesion, and invasion.

Functionally, lipids play a role in several stages of the metastatic cascade. In various cancers, overexpression of genes related to fatty acid uptake, lipid accumulation, and other aspects of fatty acid metabolism has been associated with increased invasiveness, enhanced migration properties, and the ability of tumour cells to metastasise to distant organs. These alterations are linked to metastatic progression and poor prognosis across multiple tumour types.

Our results are consistent with the literature, where reduced plasma levels of cholesterol esters such as CE(12:0), CE(14:0), and CE(15:0) were associated with an increased risk of metastasis and, correspondingly, an increased risk of disease-related mortality. This phenomenon aligns with our observations regarding other lipids. Notably, we also observed a significant reduction in several TAG lipids in plasma samples from metastatic melanoma patients, similar to the reduced serum TAG levels seen in hepatocellular carcinoma. This decrease may result from tumour-produced pro-inflammatory cytokines such as interleukin-1 (IL-1), which can delay intestinal absorption and reduce tissue lipid uptake. Additionally, interleukin-2 (IL-2) may induce hypocholesterolaemia by inhibiting the activity of lecithin–cholesteryl acyltransferase (LCAT).

In our study, we observed that the total levels of LPCs in patients with lymphatic metastasis were higher than in patients without metastasis, whereas the lowest levels were detected in the plasma of patients with distant metastasis. These prominent LPC species—palmitoyl, oleoyl, linoleoyl, and arachidonoyl-lysophosphatidylcholine (LPC 16:0, 18:1, 18:2, and 20:4)—serve as predictive markers of regional lymph node metastasis rather than hematogenous metastasis. These LPCs are among the most abundant in human plasma and are all capable of inducing COX-2 expression, which has been associated with lymph node metastasis in multiple cancers. This lymph node involvement can be explained by the differential regulation of cyclooxygenase isoforms: COX-1 maintains constant, housekeeping-level expression, whereas COX-2 is rapidly inducible, tightly regulated, and markedly upregulated during inflammatory processes.

Furthermore, decreased CE(14:0) levels were associated with a significantly higher risk of death, consistent with findings for other cholesteryl esters such as CE(12:0) and CE(15:0), which also differed when comparing patients without metastases to those with metastases.

Summary

In the first part of our research in our melanoma patient population, our results suggested that the combined assessment of primary tumor location, AJCC 8th edition pT category, and serum S100B and LDH levels may serve as reliable markers for predicting metastases. Plasma osteopontin (OPN) levels showed a significant and independent effect on the probability of metastasis, similar to serum S100B levels. Additionally, lower limb localization of the primary tumor was associated with an increased likelihood of metastasis. Importantly, combining the three peripheral blood biomarkers with primary tumor localization and AJCC pT category resulted in excellent discriminative ability (AUC: training set 0.803; validation set 0.822). While plasma OPN can be considered a melanoma biomarker, incorporating clinicopathological prognostic variables can further improve the diagnostic impact of peripheral blood biomarkers for predicting metastasis.

In our meta-analysis, we investigated the applicability of serum S100B and serum LDH for predicting melanoma progression from both diagnostic and prognostic perspectives. We found that the discriminative ability of serum S100B to identify disease relapse was greater than that of serum LDH. Because melanoma relapse is associated with elevated serum S100B levels in only a subset of patients, S100B should be considered in combination with additional serum biomarkers within a multivariate diagnostic predictive model. Furthermore, serum S100B demonstrated prognostic power similar to and independent of serum LDH in metastatic melanoma, suggesting that using both markers would be beneficial in developing a multivariate prognostic predictive model.

In the third part of our research, we analysed lipid abnormalities in plasma samples from our melanoma patient population. Our aim was to identify additional biomarkers that, alone or in combination, may

improve early detection of disease relapse. The lipid content of samples from metastatic patients was significantly lower than that of plasma samples from patients without metastases. We found significantly lower levels of lipids in two lipid classes (FFA, LCER) in plasma samples from metastatic patients. Specifically, a lipid panel consisting of three lipids (CE(12:0), FFA(24:1), TAG47:2-FA16:1), when combined with elevated S100B and LDH levels, may be useful for predicting the probability of metastasis.

New findings

Our results show that the combined assessment of primary tumor location, AJCC 8th edition pT category, and serum S100B and LDH levels is a reliable marker for predicting metastases. Plasma OPN levels had a significant and independent effect on the probability of metastasis. The combination of the three peripheral blood biomarkers with primary tumor location and AJCC pT category demonstrated excellent discriminatory power. Plasma OPN can therefore be considered a melanoma biomarker.

According to our meta-analysis, the discriminative power of serum S100B in identifying melanoma relapse is greater than that of serum LDH. Serum S100B also exhibits prognostic power in metastatic melanoma that is similar to and independent of serum LDH.

In our melanoma patient population, we observed lipid content of samples from metastatic patients was significantly lower than that of plasma samples from patients without metastases. We found significantly lower levels of lipids in two lipid classes (FFA, LCER) in plasma samples from metastatic patients. Specifically, a lipid panel consisting of three lipids (CE(12:0), FFA(24:1), TAG47:2-FA16:1), when combined with elevated S100B and LDH levels, may be useful for predicting the probability of metastasis.

UNIVERSITY of DEBRECEN

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Registry number: DEENK/34/2026.PL
Subject: PhD Publication List

Candidate: Tünde Várvölgyi
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Várvölgyi, T.**, Janka, E. A., Szász, I., Koroknai, V., Toka-Farkas, T., Szabó, I. L., Ványai, B., Szegedi, A., Emri, G., Balázs, M.: Combining Biomarkers for the Diagnosis of Metastatic Melanoma.
   J Clin Med. 13 (1), 1-13, 2024.
   DOI: http://dx.doi.org/10.3390/jcm13010174
   IF: 2.9

2. Szász, I., Koroknai, V., **Várvölgyi, T.**, Pál, L., Szűcs, S., Pikó, P., Emri, G., Janka, E. A., Szabó, I. L., Ádány, R., Balázs, M.: Identification of Plasma Lipid Alterations Associated with Melanoma Metastasis.
   Int. J. Mol. Sci. 25 (8), 1-15, 2024.
   DOI: http://dx.doi.org/10.3390/ijms25084251
   IF: 4.9

3. Janka, E. A., **Várvölgyi, T.**, Sipos, Z., Soós, A., Hegyi, P. J., Kiss, S., Dembrovszky, F., Csupor, D., Kéringer, P., Pécsi, D., Solymár, M., Emri, G.: Predictive Performance of Serum S100B Versus LDH in Melanoma Patients: a Systematic Review and Meta-Analysis.
   Front Oncol. 11, 1-11, 2021.
   DOI: http://dx.doi.org/10.3389/fonc.2021.772165
   IF: 5.738

List of other publications

4. Szász, I., Koroknai, V., **Várvölgyi, T.**, Pál, L., Szűcs, S., Pikó, P., Emri, G., Janka, E. A., Szabó, I. L., Ádány, R., Balázs, M.: Association of Plasma Lipid Patterns and LDL Cholesterol Levels with Breslow Thickness and Ulceration in Melanoma Patients.
   Int. J. Mol. Sci. 26 (4), 1-11, 2025.
   DOI: http://dx.doi.org/10.3390/ijms26041716
   IF: 4.9 (2024)

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

5. Szász, I., Koroknai, V., **Várvölgyi, T.**, Emri, G., Szabó, I. L., Balázs, M.: Circulating Calprotectin Distinguishes Metastatic Melanoma and Predicts Liver Metastasis.
   Int. J. Mol. Sci. 26 (16), 1-9, 2025.
   DOI: http://dx.doi.org/10.3390/ijms26168028
   IF: 4.9 (2024)

6. Koroknai, V., Szász, I., **Várvölgyi, T.**, Emri, G., Fodor, Á., Balázs, M.: Cytokine and Chemokine-Associated Signatures Underlying Dermal Invasion and Skin Metastasis in Melanoma.
   Int. J. Mol. Sci. 26 (19), 1-14, 2025.
   DOI: http://dx.doi.org/10.3390/ijms26199334
   IF: 4.9 (2024)

7. Janka, E. A., Szabó, I. L., Toka-Farkas, T., Soltész, L., Szentkereszty-Kovács, Z., Ványai, B., **Várvölgyi, T.**, Kapitány, A., Szegedi, A., Emri, G.: Development of Nomograms to Predict the Probability of Recurrence at Specific Sites in Patients with Cutaneous Melanoma.
   Cancers. 17 (18), 1-21, 2025.
   DOI: http://dx.doi.org/10.3390/cancers17183080
   IF: 4.4 (2024)

8. **Várvölgyi, T.**, Szegedi, A., Töröcsik, D.: JAK gátlás alopecia areataban.
   Bőrgyógyász. venerol. szle. 101 (2), 98-105, 2025.
   DOI: http://dx.doi.org/10.7188/bvsz.2025.101.2.6

9. Tósaki, Á., Remenyik, É., Veres, I., Szegedi, A., **Várvölgyi, T.**: Mucin a dermisben.
   Bőrgyógyász. venerol. szle. 100 (6), 293-298, 2024.
   DOI: http://dx.doi.org/10.7188/bvsz.2024.100.6.2

10. Janka, E. A., Szabó, I. L., Kollár, S., Toka-Farkas, T., Ványai, B., **Várvölgyi, T.**, Kapitány, A., Shabu, H., Szegedi, A., Emri, G.: Prognostic Role of Clinicopathological Characteristics and Serum Markers in Metastatic Melanoma Patients Treated with BRAF and MEK Inhibitors.
   Cancers (Basel). 16, 1-18, 2024.
   DOI: http://dx.doi.org/10.3390/cancers16172981
   IF: 4.4

11. Ványai, B., Szabó, I. L., Veres, I., Soltész, L., **Várvölgyi, T.**, Emri, G.: Lentigo maligna melanoma.
   Bőrgyógyász. venerol. szle. 99 (4), 293-297, 2023.
   DOI: http://dx.doi.org/10.7188/bvsz.2023.99.4.7

12. Janka, E. A., Ványai, B., Szabó, I. L., Toka-Farkas, T., **Várvölgyi, T.**, Kapitány, A., Szegedi, A., Emri, G.: Primary tumour category, site of metastasis, and baseline serum S100B and LDH are independent prognostic factors for survival in metastatic melanoma patients treated with anti-PD-1.
   Front Oncol. 13, 1-11, 2023.
   DOI: http://dx.doi.org/10.3389/fonc.2023.1237643
   IF: 3.5

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

13. Ványai, B., Chien, Y. C. C., Beke, L., Szabó, I. L., Péter, Z., Steuer-Hajdu, K., **Várvölgyi, T.**, Méhes, G., Emri, G.: Cutaneous metastases at the sites of pembrolizumab-induced bullous pemphigoid lesions in a patient with melanoma.
Immunotherapy. 14 (17), 1377-1382, 2022.
DOI: http://dx.doi.org/10.2217/imt-2022-0113
IF: 2.8

14. Emri, G., Ványai, B., Soltész, L., Szabó, I. L., **Várvölgyi, T.**, Janka, E. A., Oláh, J.: Melanoma kezelés: merre tovább?
Bőrgyógyász. venerol. szle. 98 (5), 256-262, 2022.
DOI: http://dx.doi.org/10.7188/bvsz.2022.98.5.3

15. Janka, E. A., Ványai, B., Dajnoki, Z., Szabó, I. L., Reibl, D., Komka, I., Blasszauer, C., **Várvölgyi, T.**, Szegedi, A., Emri, G.: Regional variability of melanoma incidence and prevalence in Hungary. Epidemiological impact of ambient UV radiation and socioeconomic factors.
Eur. J. Cancer Prev. 31 (4), 377-384, 2022.
DOI: http://dx.doi.org/10.1097/CEJ.0000000000000716
IF: 2.4

16. Soltész, L., Urbán, P., **Várvölgyi, T.**, Lajszné Tóth, B., Szegedi, A.: Skin lesions of primary immunodeficiency diseases.
Bőrgyógyász. venerol. szle. 98 (2), 56-63, 2022.
DOI: http://dx.doi.org/10.7188/bvsz.2022.98.2.2

17. Steuer-Hajdu, K., **Várvölgyi, T.**, Szegedi, A.: Új típusú terápiák gyulladásos bőrbetegségekben.
Immunol. Szle. 4, 51-62, 2021.

18. **Várvölgyi, T.**: Vírusos eredetű bőrbetegségek gyermekkorban.
Bőrgyógyász. venerol. szle. 97 (2), 100-106, 2021.
DOI: http://dx.doi.org/10.7188/bvsz.2021.97.2.5

19. **Várvölgyi, T.**, Szegedi, A.: Vitiligo.
Bőrgyógyász. venerol. szle. 97 (3), 158-166, 2021.
DOI: http://dx.doi.org/10.7188/bvsz.2021.97.3.5

20. **Várvölgyi, T.**: Vitiligo.
Orvostovábbk. szle. 28 (6), 14-17, 2021.

21. **Várvölgyi, T.**, Szegedi, A.: Csecsemőkori gyakoribb, nem fertőző bőrbetegségek.
Gyermekorv. Továbbképz. 19 (3), 124-130, 2020.

22. Janka, E. A., Kékedi, K., **Várvölgyi, T.**, Gellén, E., Kiss, B. K., Remenyik, É., Emri, G.: Increasing melanoma incidence in the elderly in North-East Hungary: is this a more serious problem than we thought?
Eur. J. Cancer Prev. 28 (6), 544-550, 2019.
DOI: https://doi.org/10.1097/CEJ.0000000000000489
IF: 2.413

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

23. Juhász, I., **Várvölgyi, T.**: Diagnosztikai lehetőségek és jelentőségük a sebkezelésben.
Sebkezelés-Sebgyógyulás. 21 (1), 5-11, 2018.

24. Nagy, E., Erdei, I., Farkas, M., Péter, Z., **Várvölgyi, T.**, Király, G., Juhász, I.: A sejtterápia lehetőségei az égés kezelésében: debreceni tapasztalatok.
Bőrgyógyász. Venerol. Szle. 93 (3), 114-118, 2017.

25. Szabó, I. L., Ócsai, H., Kiss, B. K., Kékedi, K., Kósa, P., **Várvölgyi, T.**, Kun, E., Kenyeres, A., Szöllősi, A. G., Remenyik, É., Emri, G.: BRAF-mutáció pozitív áttétes melanoma célzott gyógyszeres kezelése.
Bőrgyógyász. Venerol. Szle. 93 (4), 160-167, 2017.
DOI: http://dx.doi.org/10.7188/bvsz.2017.93.4.4

26. Emri, E., Egervári, K., **Várvölgyi, T.**, Rózsa, D., Mikó, E., Dezső, B., Veres, I., Méhes, G., Emri, G., Remenyik, É.: Correlation among metallothionein expression, intratumoural macrophage infiltration and the risk of metastasis in human cutaneous malignant melanoma.
J. Eur. Acad. Dermatol. Venereol. 27 (3), e320-e327, 2013.
DOI: http://dx.doi.org/10.1111/j.1468-3083.2012.04653.x
IF: 3.105

Total IF of journals (all publications): 51,256
Total IF of journals (publications related to the dissertation): 13,538

The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

29 January, 2026

Acknowledgements

I would like to thank my supervisor, Professor Margit Balázs, for her professional guidance, support, and the opportunity to work in her research group.

I would like to thank Dr. Gabriella Emri for her advice, and I am grateful for her dedicated teaching, both past and present.

I would like to thank Dr. Eszter Anna Janka for her comprehensive statistical analysis and assistance, which constituted a significant part of the work.

I would like to thank Professor Andrea Szegedi for her advice and support.

I would like to thank Professor Éva Remenyik for her encouragement.

I would like to thank Professor Róza Ádány for her support during my work.

I would like to thank Dr. Viktória Koroknai, Dr. István Szász, Dr. Sándor Szűcs and Dr. László Pál for the lipidomic measurements and analysis.

I would like to thank Tünde Toka-Farkas, Szilvia Tóthné Molnár, and Annamária Váradi for collecting peripheral blood samples.

I would like to thank my colleagues and friends for their encouragement.

I would like to thank my family for their support.