

CROATIAN INTERNATIONAL PUBLICATIONS

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Bačić I^{1,2}, Karlo R^{1,2}, Zadro AŠ³, Zadro Z⁴, Skitarelić N^{2,5}, Antabak A⁶. Tumor angiogenesis as an important prognostic factor in advanced non-small cell lung cancer (Stage IIIA). *Oncol Lett.* 2018;15:2335-2339.

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The aim of the present study was to evaluate angiogenesis by determining the micro vascular density (MVD) and the expression of vascular endothelial growth factor (VEGF-A) in advanced non-small cell lung cancer (NSCLC) tumor samples, and to analyze their associations with clinical parameters and survival. Tumor tissue specimens of fifty patients (41 males and 9 females), who underwent radical surgical treatment for NSCLC in stage IIIA (T1-3N2) were collected for immunohistochemical analysis. MVD evaluation was performed using an anti-CD31 monoclonal antibody and VEGF-A expression using a polyclonal anti-VEGF-A antibody. The results were associated with two-year survival. Statistical analysis revealed significant associations in the level of angiogenesis (high MVD) and shorter survival of patients with NSCLC (P=0.0007). VEGF-A expression showed no association with micro vascular density (P=0.51) or survival (P=0.68). There was no significant association between MVD and VEGF-A. The measurable, clinical MVD parameters could be used as a reliable prognostic factor for the survival of patients with advanced NSCLC.

Lucijanac M¹, Prka Z², Pejsa V^{1,2}, Stoos-Veic T³, Lucijanac J⁴, Kusec R^{1,2,5}. Prognostic implications of low transferrin saturation in patients with primary myelofibrosis. *Leuk Res.* 2018;66:89-95.

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OBJECTIVES: Transferrin saturation (TSAT) 20% or less is considered to represent functional iron deficiency in the context of malignant disease, phenomenon mediated through inflammatory changes of iron homeostasis. We aimed to investigate clinical and prognostic significance of low TSAT in patients with primary (PMF) and secondary myelofibrosis (SMF), malignant diseases characterized by strong inflammatory milieu. **METHODS:** We retrospectively analyzed 87 patients with myelofibrosis and compared TSAT with disease specific parameters. **RESULTS:** One-third of patients had TSAT ≤20%. Lower TSAT was significantly associated with Janus-kinase-2 (JAK2) mutation (P = 0.007), transfusion independency (P = 0.003), higher platelets (P = 0.004), lower mean-corpuscular-volume (P < 0.001), lower ferritin (P < 0.001), higher absolute-neutrophil-count (P = 0.027), lower absolute-lymphocyte-count (P = 0.041) and lower albumin (P = 0.018). PMF patients presenting with low TSAT (≤20%) experienced significantly shorter overall-survival (OS) (HR = 2.43; P = 0.017), whereas TSAT did

not affect OS of SMF patients (HR = 1.48; P = 0.623). Low TSAT remained significantly associated with inferior OS in PMF in a series of multivariate Cox regression models comparing its properties to anemia, transfusion dependency, ferritin and Dynamic-International-Prognostic-System (DIPSS). CONCLUSIONS: Low TSAT has detrimental effect on survival of PMF patients. This effect is independent of anemia and of ferritin levels that seem to be better at representing iron overload in PMF patients.

Bosnjak J¹, Butkovic SS², Miskov S¹, Coric L¹, Jadrijevic-Tomas A¹, Mejaski-Bosnjak V³. Epilepsy in patients with pineal gland cyst. Clin Neurol Neurosurg. 2018;165:72-75.

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OBJECTIVE: The aim of the study is to describe types of epileptic seizures in patients with pineal gland cyst (PGC) and their outcome during follow up period (6-10 years). We wanted to determine whether patients with epilepsy differ in PGC volume and compression of the PGC on surrounding brain structures compared to patients with PGC, without epilepsy. **PATIENTS AND METHODS:** We analyzed prospectively 92 patients with PGC detected on magnetic resonance (MR) of the brain due to various neurological symptoms during the period 2006-2010. Data on described compression of the PGC on surrounding brain structures and size of the PGC were collected. **RESULTS:** 29 patients (16 women, 13 men), mean age 21.17 years had epilepsy and PGC (epilepsy group). 63 patients (44 women, 19 men), mean age 26.97 years had PGC without epilepsy (control group). Complex partial seizures were present in 8 patients, complex partial seizures with secondary generalization in 8 patients, generalized tonic clonic seizures (GTCS) in 10 and absence seizures in 3 patients. Mean PGC volume in epilepsy group was 855.93 mm³, in control group 651.59 mm³. There was no statistically significant difference between epilepsy and control group in PGC volume. Compression of PGC on surrounding brain structures was found in 3/29 patients (10.34%) in epilepsy group and in 11/63 patients (17.46%) in control group with no statistically significant difference between epilepsy

and control group. All patients with epilepsy were put on antiepileptic therapy (AET). During the follow up period, 23 patients (79.31%) were seizure free, 3 patients (13.04%) had reduction in seizure frequency, whereas 3 patients had no improvement in seizure frequency. Two patients from epilepsy group and 3 patients from control group were operated with histologically confirmed diagnosis of PGC in 4, and pinealocytoma in 1 patient. CONCLUSIONS: In patients with PGC, epileptic seizures were classified as: complex partial seizures (with or without secondary generalization), GTCS and absence seizures. All patients were put on AET. During follow up period 79.31% patients were seizure free. There was no difference in PGC volume, nor in described compression of the PGC on surrounding brain structures between epilepsy and control group. Based on our findings, pathomechanism of epileptic seizures in patients with PGC cannot be attributable solely to PGC volume or described compression on surrounding brain structures based on MRI findings.

Henigsberg N¹, Šarac H², Radoš M^{1,2}, Radoš M¹, Ozretić D^{1,2}, Foro T¹, Erdeljić Turk V², Hrbač P¹, Bajš Janović M², Rak B³, Kalember P⁴. Lower choline-containing metabolites/creatine (Cr) rise and failure to sustain NAA/Cr levels in the dorsolateral prefrontal cortex are associated with depressive episode recurrence under maintenance therapy: a proton magnetic resonance spectroscopy retrospective cohort study. Front Psychiatry. 2017;8:277.

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BACKGROUND: The aim of this study was to evaluate the relationship between changes in proton magnetic resonance spectroscopy (1H-MRS) parameters at the start of the index episode recovery phase and at recurrence in patients with recurrent depression who were treated with prolonged maintenance therapy. **METHODS:** 1H-MRS parameters were analyzed in 48 patients with recurrent depression who required maintenance therapy with antidepressant medication prescribed by a psychiatrist and who continued with the same antidepressant during the maintenance phase, either to recurrence of depression, completion of the 10-year observation period, or the start of the withdrawal phase (tapering-off antidepressant). N-

acetylaspartate (NAA), choline-containing metabolites (Cho), creatine (Cr), and glutamine/glutamate were measured at the start of the recovery phase and 6 months later. RESULTS: Recurrent depressive episodes occurred in 20 patients. These individuals had a smaller increase in Cho/Cr after the beginning of the recovery phase compared to the non-recurrent patient group and also exhibited a decreased NAA/Cr ratio. CONCLUSION: Sustainable NAA and increased Cho levels at the onset of the recovery phase of the index episode are early markers of antidepressant effectiveness associated with a lower risk of major depressive disorder recurrence. The NAA and Cho changes in the non-recurrent group may be attributable to increased brain resilience, contrary to the transient temporal effect observed in subjects who experienced a depressive episode.

Kust D, Staničić J, Mateša N. Bethesda thyroid categories and family history of thyroid disease. Clin Endocrinol (Oxf). 2018;88:468-472.

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OBJECTIVE: Thyroid cancer is the most common type of endocrine-related cancer worldwide. The aim of this article was to assess the relationship between thyroid diseases diagnosed by fine needle aspiration (FNA) and family history of thyroid disease. DESIGN: The study was conducted in a tertiary high-volume thyroid cancer centre. Fine needle aspiration (FNA) of a thyroid nodule detected on neck ultrasound for any reason was performed in all included patients. PATIENTS: A total of 10 709 patients were included in the study. MEASUREMENTS: Correlation of cytological findings classified according to the Bethesda system and family history was calculated using Fisher's exact test. RESULTS: There were 2580 (24.09%) patients with non-malignant thyroid diseases in the family and 198 (1.85%) patients who had a history of thyroid cancer in the family. A total of 2778 (25.94%) patients had positive family history of thyroid diseases, and 7931 (74.06%) patients had negative family history. In patients with papillary thyroid carcinoma in family history, the difference between those with benign (Bethesda 2) and malignant thyroid FNA diagnosis (Bethesda 6) was found to be statistically significant ($P = .0432$). CONCLUSIONS: Family history plays a significant role in the development of thyroid cancer, and having first-degree relatives with not only medullary, but also papillary thyroid cancer strongly predicts the risk of developing the

malignant thyroid disease. In contrast, benign thyroid disorders in family history do not lead to the development of thyroid cancer.

Premuzic V¹, Batinic J², Roncevic P², Basic-Jukic N¹, Nemet D², Jelakovic B¹. Role of plasmapheresis in the management of acute kidney injury in patients with multiple myeloma: should we abandon it? Ther Apher Dial. 2018;22:79-86.

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The aim of the current study was to determine whether plasmapheresis in combination with chemotherapy could significantly remove free light chains (FLC) in multiple myeloma (MM) patients with acute kidney injury (AKI) and therefore improve renal recovery and patient survival. During the study period, 29 patients with MM and AKI presented to our unit and were treated with two different therapy modalities (plasmapheresis with chemotherapy or bortezomib). At the end of treatment, a significant decrease of FLCs was present in the group treated with plasmapheresis compared to the bortezomib group. Patients treated with plasmapheresis had similar survival compared to patients treated with bortezomib. There was a significantly higher decrease of FLCs and longer survival in patients treated with three or more plasmapheresis sessions than in patients treated with two plasmapheresis sessions. Plasmapheresis therapy still remains a useful and effective method in the treatment of AKI in MM patients. Plasmapheresis significantly reduces FLCs compared to bortezomib especially with higher number of plasma exchange sessions but it must be combined with other chemotherapy agents in order to prolong renal recovery and therefore patient survival.

Krbot Skorić M¹, Crnošija L², Gabelić T¹, Adamec I¹, Habek M^{1,2}. Relationship between sensory dysfunction and walking speed in patients with clinically isolated syndrome. J Clin Neurophysiol. 2018;35:65-70.

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PURPOSE: The aim of this study was to investigate a relationship between sensory dysfunction examined with somatosensory-evoked potentials of the posterior tibial nerve (tSSEP) and walking speed in patients with clinically isolated syndrome. **METHODS:** In 120 patients (mean age 32.2 ± 8.7 years, 84 females), Expanded Disability Status Scale (EDSS), timed 25-foot walk test (T25FW), brain and spinal cord MRI, and tSSEP were performed. P40 latencies and N22a-P40 interlatencies were analyzed, and the z-score for each latency was calculated and combined into total tSSEP z-score. **RESULTS:** T25FW significantly correlated with total tSSEP z-score ($r_s = 0.211$; $P = 0.021$). When looking at each component of the tSSEP separately, T25FW significantly correlated with z-scores of P40 wave latencies ($r_s = 0.223$; $P = 0.014$) and N22a-P40 interlatencies ($r_s = 0.241$; $P = 0.008$) of the left side. There were no significant correlations with N22a wave latencies. Patients who presented with transverse myelitis ($N = 41$) and patients who had spinal cord lesions on MRI ($N = 53$) had significantly higher total tSSEP z-score compared with other patients (0.07 vs. -0.28 , $P = 0.019$ and -0.02 vs. -0.38 , $P = 0.023$; respectively). Somatosensory-evoked potentials of the posterior tibial nerve z-score corrected for age, sex, cervical spinal cord MRI lesions, and total number of supratentorial T2 lesions was a statistically significant predictor for T25FW ($B = 0.267$, $P = 0.023$). **CONCLUSIONS:** Spinal somatosensory dysfunction is one of the factors associated with reduction in walking speed in early patients with multiple sclerosis. Somatosensory-evoked potentials of the posterior tibial nerve may potentially be useful in identifying patients at higher risk for the development of walking impairment in the future.

OBJECTIVE: Studies show high comorbidity of mood disorders in asthma. As asthma is a highly heterogeneous disease with different phenotypes it can be expected that there is a difference in this association with different asthma phenotypes. The aim of our cross-sectional study was to assess the association of specific asthma phenotypes with anxiety and/or depression and their impact on asthma control. **METHODS:** A cross-sectional study in 201 consecutive adult outpatients with asthma (≥ 18 years of age) was conducted. Each patient underwent physical examination, detailed medical history, Hospital Anxiety and Depression Scale, Asthma Control Questionnaire, Asthma Control Test, together with measurements of lung function and fraction of exhaled nitric oxide. Phenotypes were assessed using cluster analysis, and a multivariate analysis was used to identify associations of mood disorders with different phenotypes. **RESULTS:** Five asthma phenotypes were identified: allergic (AA, 43.8%), aspirin-exacerbated respiratory disease (AERD, 21.9%), late-onset (LOA, 18.9%), obesity-associated (OAA, 10.0%), and respiratory infections associated asthma (RIAA, 5.5%). A multivariate analysis showed a significant association of anxiety with LOA and comorbid hypertension (LOA, odds ratio (OR) = 2.12; hypertension, OR = 2.37, $p = 0.012$), and depression with AA, RIAA, hypertension, and ACQ score (AA, OR = 6.07; RIAA, OR = 4.73; hypertension, OR = 5.67; ACQ, OR = 1.87; $p < 0.001$). Comorbid anxiety/depression was associated with AA, LOA, RIAA, hypertension, and ACQ score (AA, OR = 10.15; LOA, OR = 2.98; RIAA, OR = 6.29; hypertension, OR = 5.15; ACQ, OR = 1.90; $p < 0.001$). **CONCLUSION:** Mood disorders were significantly associated with AA, LOA, and infection-associated asthma, together with comorbid hypertension and the level of asthma control.

Labor M^{1,2}, Labor S^{1,2}, Jurić I³, Fijačko V^{1,2}, Grle SP⁴, Plavec D^{2,5}. Mood disorders in adult asthma phenotypes. *J Asthma*. 2018;55:57-65.

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