CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Bohaček

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Ramic S, Asic K, Balja MP, Paic F, Benkovic V, Knezevic F. Correlation of Phosphorylated HER2 with Clinicopathological Characteristics and Efficacy of Trastuzumab Treatment for Breast Cancer. Anticancer Res. 2013;33(6):2509-15.

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AIM: To determine the correlation of phosphorylated human epidermal growth factor receptor-2 (pHER2) with clinicopathological characteristics of breast cancer (BC) and patients' response to trastuzumab-based therapy. PATIENTS AND METHODS: pHER2 was determinated immuno-histochemically in 88 cases of HER2-positive and 50 cases of HER2-negative BC. All patients with HER2-positive BC received trastuzumab-based therapy and 16 of them (18.2%) had disease progression during therapy treatment (i.e. trastuzumab-resistant). RESULTS: pHER2 was predominantly expressed in HER2-positive BC, with 55 cases (62.5%) of tumours expressing pHER2. Six cases of HER2-negative cancer (12.5%) displayed positive expression of pHER2. Expression of pHER2 correlated with younger age of patients and negative oestrogen receptor status. Acquisition of resistance to trastuzumab correlated with negativity for pHER2 (p=0.028). CONCLUSION: Positive expression of pHER2 may yield additional information regarding the poor prognosis of BC and could be used for pre-selection of patients with HER2-overexpressing BC displaying resistance to trastuzumab treatment.

Gornik I, Gašparović V, Gubarev Vrdoljak N, Haxiu A, Vucelić B. Prior statin therapy is associated with milder course and better outcome in acute pancreatitis - A cohort study. Pancreatology. 2013;13(3):196-200.

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BACKGROUND: Statin treatment was shown to be associated with improved outcomes in several inflammatory conditions. We wanted to evaluate the effects of statin therapy on the course and outcome of acute pancreatitis (AP). METHODS: A prospective cohort study included patients with acute pancreatitis divided into two groups according to statin use prior to hospitalization. Age, sex, etiology of AP, Ranson's score, APACHE II score and maximal CRP were recorded. Outcome measures were hospital length of stay and mortality. Matching of patients for matched analyses was done using individual matching and propensity score matching using variables a priori associated with course and outcome of acute pancreatitis. RESULTS: Inclusion criteria were met for 1062 patients of whom 92 were taking statins. Statin users were older and had higher body mass indexes. Severe disease was more common in the no-statin group than in statin group (20.6% vs. 8.7% respectively). All severity markers were also higher in the no-statin group. All cause mortality was not different, while cardiovascular mortality was higher in the statin group in the cohort analysis. After matching by either method, the severity of disease was greater for the patients without statins treatment. Pancreatitis related mortality was higher in the no-statin group after matching. Among patients who developed severe AP, statin users showed lower Ranson's and APACHE II scores and lower maximal CRP. CONCLUSIONS: Prior statin treatment significantly reduces morbidity and mortality in acute pancreatitis. Further studies are needed to evaluate possible therapeutic use of statins in acute pancreatitis.

Zgaga L, Agakov F, Theodoratou E, Farrington SM, Tenesa A, Dunlop MG, McKeigue P, Campbell H. Model Selection Approach Suggests Causal Association

between 25-Hydroxyvitamin D and Colorectal Cancer. PLoS One. 2013;8(5):e63475.

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INTRODUCTION: Vitamin D deficiency has been associated with increased risk of colorectal cancer (CRC), but causal relationship has not yet been confirmed. We investigate the direction of causation between vitamin D and CRC by extending the conventional approaches to allow pleiotropic relationships and by explicitly modelling unmeasured confounders. METHODS: Plasma 25-hydroxyvitamin D (25-OHD), genetic variants associated with 25-OHD and CRC, and other relevant information was available for 2645 individuals (1057 CRC cases and 1588 controls) and included in the model. We investigate whether 25-OHD is likely to be causally associated with CRC, or vice versa, by selecting the best modelling hypothesis according to Bayesian predictive scores. We examine consistency for a range of prior assumptions. RESULTS: Model comparison showed preference for the causal association between low 25-OHD and CRC over the reverse causal hypothesis. This was confirmed for posterior mean deviances obtained for both models (11.5 natural log units in favour of the causal model), and also for deviance information criteria (DIC) computed for a range of prior distributions. Overall, models ignoring hidden confounding or pleiotropy had significantly poorer DIC scores. CONCLUSION: Results suggest causal association between 25-OHD and colorectal cancer, and support the need for randomised clinical trials for further confirmations.

Topić I, Ikić M, Ivčević S, Kovačić N, Marušić A, Kušec R, Grčević D. Bone morphogenetic proteins regulate differentiation of human promyelocytic leukemia cells. Leuk Res. 2013;37(6):705-12.

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We investigated the role of bone morphogenetic proteins (BMPs) in suppression of all-trans retinoic acid (ATRA)-mediated differentiation of leukemic promyelocytes. In NB4 and HL60 cell lines, BMPs reduced the percentage of differentiated cells, and suppressed PU.1 and C/EBPε gene expression induced by ATRA. BMP and ATRA synergized in the induction of ID genes, causing suppression of differentiation. In primary acute promyelocytic leukemia bone-marrow samples, positive correlation of PML/RARα and negative of RARα with the expression of BMP-4, BMP-6 and ID genes were found. We concluded that BMPs may have oncogenic properties and mediate ATRA resistance by a mechanism that involves ID genes.

Dedić Plavetić N, Jakić-Razumović J, Kulić A, Vrbanec D. Prognostic value of proliferation markers expression in breast cancer. Med Oncol. 2013 Jun;30(2):523.

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In this study, immunohistochemical expression of five proliferation markers: Ki-67, aurora-A kinase, survivin, B-Myb and cyclin B1, was analyzed. Consecutive 215 tumor samples from breast cancer patients operated from 2002 to 2003 were analyzed using the TMA ("tissue microarray") method. The median follow-up was 95 months (from 7.8 to 107 months). Statistically significant correlations between expression levels in five proliferation markers, and correlations between some of the proliferation markers and traditional prognostic factors were found. Statistically significant prognostic influence of aurora-A kinase, survivin and B-Myb expression levels on overall and disease-free survival was found, and cyclin B1 expression level on disease-free survival. A multivariate analysis confirmed survivin and B-Myb expression as independent prognostic factors of overall (p = 0.0195; p = 0.0004) and disease-free survival (p = 0.0107 and p = 0.0205) in breast cancer patients.

Gotovac N, Išgum I, Viergever MA, Biessels GJ, Fajdić J, Velthuis BK, Prokop M. Calcium at the carotid siphon as an indicator of internal carotid artery stenosis. Eur Radiol. 2013;23(6):1478-86.

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OBJECTIVES: Carotid siphon calcification is often visible on unenhanced head CT (UCT), but the relation to proximal carotid artery stenosis (CAS) is unclear. We investigated the association of carotid siphon calcification with the presence of CAS. METHODS: This IRB-waived retrospective study included 160 consecutive patients sus-

pected of stroke (age 64 ± 14 years, 63 female) who underwent head UCT and CTA of the head and neck. CAS was rated on CTA as not present or present with non-significant (<50 %), moderate (50-69 %) or significant (≥70 %) stenosis. Presence, shape (on UCT) and volume (on CTA) of carotid siphon calcifications were related to CAS. RESULTS: Carotid siphon calcification was absent in 41 % of patients and bilateral in 94 % of those with calcifications. Presence, shape and volume of calcification resulted in odds ratios for having significant CAS of 10.1, 3.9 and 8.4, with 95 % CIs of 1.3-79.6, 1.1-14.1 and 2.6-26.8, respectively. Corresponding NPVs were 0.98, 0.98 and 0.96, while PPVs were 0.14, 0.07 and 0.29, respectively. CONCLUSION: Absence of calcification in the carotid artery siphon on UCT has high negative predictive value for carotid artery stenosis in patients with suspected stroke. However, siphon calcification is not a reliable indicator of significant carotid artery stenosis.

Jeric M, Roje D, Medic N, Strinic T, Mestrovic Z, Vulic M. Maternal pre-pregnancy underweight and fetal growth in relation to institute of medicine recommendations for gestational weight gain. Early Hum Dev. 2013;89(5):277-81.

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PURPOSE: Maternal nutritional status is one of the most important factors of fetal growth and development. Consequently, the currently increasing prevalence of underweight women worldwide has come in the focus of interest of perinatal medicine. The aim of the study was to assess the effect of low pre-pregnancy body mass index (BMI) on fetal growth. MATERIALS AND METHODS: Data on 4678 pregnant women and their neonates were retrospectively analyzed. Pre-pregnancy BMI of study women was categorized according to the WHO standards. Fetal growth was assessed by birth weight and birth length, birth weight for gestational age, and ponderal index. RESULTS: Study group included 351 (7.6%) women with pregestational BMI<18.5kg/m(2), while all women with pregestational BMI 18.5-25kg/m(2) (n=3688; 78.8%) served as a control group. The mean birth weight and birth length of neonates born to underweight mothers were by 167g and 0.8cm lower in comparison with the neonates born to mothers of normal nutritional status, respectively (P<0.001 both). The prevalence of small for gestational age (SGA) births was twofold that found in the control group of mothers of normal nutritional status (9.7% vs. 4.9%; P<0.001). The inappropriately low gestational weight gain additionally increased the rate of SGA infants in the group of mothers with low pre-pregnancy BMI (21.4% vs. 10.4%; P=0.02). Pre-pregnancy BMI category did not influence neonatal growth symmetry. CONCLUSION: Low maternal pregestational BMI is associated with fetal growth assessment. Improvement of the maternal nutritional status before pregnancy can increase the likelihood of perinatal outcome.

Hudolin T, Kastelan Z, Ilic I, Levarda-Hudolin K, Basic-Jukic N, Rieken M, Spagnoli GC, Juretic A, Mengus C. Immunohistochemical analysis of the expression of MAGE-A and NY-ESO-1 cancer/testis antigens in diffuse large B-cell testicular lymphoma. J Transl Med. 2013;11:123.

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BACKGROUND: Primary testicular lymphoma (PTL) is a rare and lethal disease. The most common histological subtype is diffuse large B-cell lymphoma (DLBCL). Standard treatments are frequently ineffective. Thus, the development of novel forms of therapy is urgently required. Specific immunotherapy generating immune responses directed against antigen predominantly expressed by cancer cells such as cancer-testis antigens (CTA) may provide a valid alternative treatment for patients bearing PTL, alone or in combination with current therapies. METHODS: Three monoclonal antibodies (mAbs), 77B recognizing MAGE-A1, 57B recognizing an epitope shared by multiple MAGE-A CTA (multi-MAGE-A specific) and D8.38 recognizing NY-ESO-1/LAGE-1 were used for immunohistochemical staining of 27 PTL, including 24 DLBCL. RESULTS: Expression of MAGE-A1 was infrequently detectable in DLBCL specimens (12.50%), whereas multi-MAGE-A and NY-ESO-1/LAGE-1 specific reagents stained the cytoplasms of tumor cells in DLBCL specimens with higher frequencies (54.17% and 37.50%, respectively) with different expression levels. CONCLUSIONS: These results suggest that MAGE-A and NY-ESO-1/LAGE-1, possibly in combination with other CTA, might be used as targets for specific immunotherapy in DLBCL.

Reiner Z. Statins in the primary prevention of cardiovascular disease. Nat Rev Cardiol. 2013 Jun 4. doi: 10.1038/nrcardio.2013.80.

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Statins are widely used in the evidence-based lowering of cardiovascular disease (CVD) risk. The use of these drugs for secondary prevention of CVD is well founded, but their expanding use in primary prevention-in individuals without documented CVD-has raised some concerns. Firstly, evidence suggests that, in primary prevention, statins substantially decrease CVD morbidity, but only moderately reduce CVD mortality. Secondly, long-term statin use might cause adverse effects, such as incident diabetes mellitus. Thirdly, the cost-effectiveness of such a strategy is unclear, and has to be balanced against the risk of 'overmedicating' the general population. Data clearly support the use of statins for primary prevention in high-risk individuals, in whom the strategy is cost-effective and the benefits exceed the risks. Whether primary prevention is beneficial in individuals at low or moderate risk is not certain. Therefore, the prescription of statins for primary prevention should be individualized on the basis of clinical judgment, particularly for low-risk individuals. In appropriately selected individuals, statins should also be used for primary prevention of ischaemic stroke and transient ischaemic attack.

Sarac H, Markeljevic J, Erdeljic V, Josipovic-Jelic Z, Hajnsek S, Klapan T, Batinica M, Barsic I, Sertic J, Dobrila Dintinjana R. Signal Hyperintensities on Brain Magnetic Resonance Imaging in Patients with Primary Sjogren Syndrome and Frequent Episodic Tension-type Headache: Relation to Platelet Serotonin Level and Disease Activity. J Rheumatol. 2013 Jun 1. [Epub ahead of print]

From the Department of Neurology, University Hospital Zagreb; Croatian Institute for Brain Research, Medical School Zagreb; Medical School, University of Zagreb, Department of Internal Medicine, University Hospital Sisters of Mercy; Division of Clinical Pharmacology, Department of Medicine, University Hospital Zagreb; Diagnostic Centre Medikol, Zagreb; Department of Laboratory Diagnostic, University Hospital Zagreb, Zagreb; and Medical School University of Rijeka, University Hospital Rijeka, Department of Oncology, Rijeka, Croatia.

OBJECTIVE: To examine differences in number and size of signal hyperintensities (SH) on magnetic resonance imaging (MRI) between patients with primary Sjögren syndrome (pSS) and controls who all had frequent episodic tension-type headache (FETH), and to investigate their relation to platelet serotonin level (PSL), patient age, disease duration, and activity. METHODS: SH in 22 pSS patients with FETH were compared to 20 aged-matched controls with FETH, using the modified semiquantitative rating scale. Spectrofluorimetry was used for determination of PSL, and the European League Against Rheumatism SS Disease Activity Index (ESSDAI) for disease activity assessment. RESULTS: Statistically significant differences in the total number of SH were noted infratentorially (p = 0.025) and in the basal ganglia for lesions of diameter > 5 mm (p = 0.048). Significant correlations were found between disease duration and number of overall lesions > 5 mm (p = 0.04) and subcortical lesions of diameter 2-5 mm (p = 0.035). Number of periventricular SH inversely correlated to PSL (p = 0.019) and to patient age (p = 0.004), without association with markers of immunoinflammation and ESSDAI. CONCLUSION: Our study showed that SH on brain MRI are more common in specific regions of the brain in pSS patients with FETH than in controls with FETH, signifying a more widespread cerebral vasculopathy in SS patients with FETH. Periventricular SH seem to be associated to increased platelet serotonin release in pSS patients with FETH and correlated with disease duration, without correlation to the actual ESSDAI and markers of immunoinflammation, and might be linked with chronic immunoinflammation of low-grade intensity and vasculitis in pSS.

Markic J, Jeroncic A, Polancec D, Bosnjak N, Markotic A, Mestrovic J, Culic VC. CD15s is a potential biomarker of serious bacterial infection in infants admitted to hospital. Eur J Pediatr. 2013 Jun 1. [Epub ahead of print]

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Early recognition of serious bacterial infection (SBI) in children is essential for better treatment outcome. Flow cytometry analysis of neutrophil surface molecules has been more frequently utilized as a tool for diagnosis of infection. The infants (n = 105) under 6 months of age presenting to the pediatric emergency department with fever without apparent source who were hospitalized with suspicion of having SBI were enrolled in this prospective study. Sixty-nine infants were included into the training pool and were classified into bacterial or viral infection group. Validation pool consisted of 36 infants. The values of white blood cells counts, absolute neutrophil count (ANC), C-reactive protein (CRP), procalcitonin (PCT), neutrophil CD11b, CD15s and CD64 expression, and the percentage (%CD15s+) and absolute count (AC-CD15s+) of CD15s+ neutrophils were determined. In infants with SBI, %CD15s+ was 10.5 times more likely to be higher than the cut-off value. ANC, CRP, PCT, CD64, and AC-CD15s+ were also found as

useful biomarkers for differentiation between bacterial and viral infection. The best fit multivariate logistic regression model included CRP, PCT, and %CD15s+ as strong predictors of SBI. The model's sensitivity (87 %) and specificity (83 %) indicated high model's accuracy. After validation on independent dataset, model's accuracy maintained high: 86 % sensitivity and 93 % specificity, confirming its reliability and supporting CRP, PCT, and %CD15s+ as real predictors. The findings of this study support assumption made in the literature on significance of CD15s in inflammation processes. Also, this study demonstrated for the first time that CD15s is potentially valuable biomarker of SBI in infants.

Milošević D, Trkulja V, Turudić D, Batinić D, Spajić B, Tešović G. Ultrasound bladder wall thickness measurement in diagnosis of recurrent urinary tract infections and cystitis cystica in prepubertal girls. J Pediatr Urol. 2013 May 29. doi: 10.1016/j.jpurol.2013.04.019.

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OBJECTIVE: To evaluate urinary bladder wall thickness (BWT) assessed by ultrasound as a diagnostic tool for cystitis cystica. PATIENTS AND METHODS: This was a 9-year prospective study comprising 120 prepubertal girls. Sixty subjects of whom half underwent cystoscopy represented cases while the other 60 (those with a single urinary tract infection and healthy subjects) represented controls. RESULTS: Based on receiver operating characteristics (ROC) analysis, BWT discriminated very well between cases and controls with area under the ROC curve close to 1.0. At the optimum cut-off defined at 3.9 mm, negative predictive value (NPV) was 100% leaving no probability of cystic cystitis with BWT <3.9 mm. Positive predictive value (PPV) was also very high (95.2%), indicating only around 4.82% probability of no cystic cystitis in patients with BWT values ≥3.9 mm. BWT could also distinguish between healthy subjects and those with a cured single urinary tract infection, although discriminatory properties were moderate (area under ROC 86.7%, PPV 78.8%, NPV 85.2%). CONCLUSION: Ultrasound mucosal bladder wall measurement is a non-invasive, simple and quite reliable method in diagnosis of cystitis cystica in prepubertal girls with recurrent urinary tract infections.

Banac S, Rožmanić V, Manestar K, Korotaj-Rožmanić Z, Lah-Tomulić K, Vidović I, Serer M, Svraka N, Petrić T. Rising trends in the prevalence of asthma and allergic diseases among school children in the north-west coastal part of Croatia. J Asthma. 2013 May 13. [Epub ahead of print].

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OBJECTIVE. To estimate time trends in prevalence of symptoms and reported diagnosis related to asthma, allergic rhinitis/conjunctivitis and eczema among school children in the north-west coastal part of Croatia. METHODS. Results of two identical cross-sectional surveys conducted on the same area 8 years apart (school years 2001/02 vs. 2009/10) in complete adherence to the protocol of the International Study of Asthma and Allergies in Childhood were compared. Surveyed population comprised two age groups: 6-7 (n=1634 vs. n=1052) and 13-14 (n=2194 vs.1181) year olds. RESULTS. Significant (p<0.001) increases in prevalence (%) of symptoms related to asthma (8.4 vs. 14.0), allergic rhinitis (17.5 vs. 25.6), allergic rhinoconjunctivitis (6.7 vs. 15.3) and eczema (3.4 vs. 5.9) were observed in the 13-14 year olds. In the 6-7 year olds there were observed significant (p< 0.001) increases in prevalence of symptoms of eczema (5.4 vs. 8.7) and allergic rhinitis (16.9 vs. 22.1) whereas prevalence of symptoms related to asthma (9.7 vs. 9.4; p=0.398) and allergic rhinoconjunctivitis (5.6 vs. 6.8; p=0.102) showed to be stable. Significant increases in prevalence of reported diagnosis were observed for asthma (5.2 vs. 6.9; p=0.02) and hay fever (10.5 vs. 14.6; p<0.001) in the older, and for eczema (10.6 vs. 14.1; p<0.001) in the younger age group. CONCLUSION. Prevalence of asthma and allergic diseases among the school children living on the surveyed area showed a rising trend.