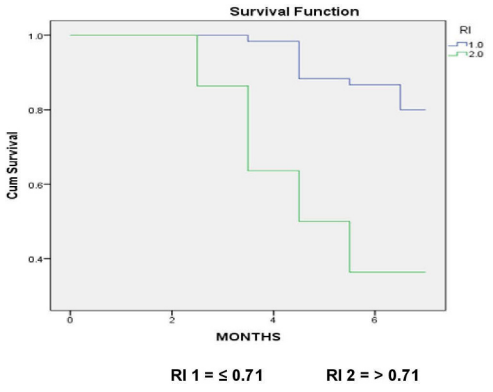

Kaplan Meir survival analysis of the study population

Su1558

METABOLOMICS REVEALS DIFFERENCES IN METABOLIC PATHWAYS PREDICTIVE OF RECOVERY OF RENAL FUNCTION AFTER LIVER TRANSPLANTATION

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Background: Acute kidney injury (AKI) is common in patients with cirrhosis, and impacts pre and post liver transplant (LT) outcomes. In our previous study, examination of known urinary protein biomarkers of AKI among urine samples collected prior to LT did not predict recovery of renal function after LT. In the present study, untargeted metabolomics analysis was applied to the urines, to determine whether metabolite biomarkers/pathways were capable of distinguishing recovery versus non-recovery of renal function after LT alone among patients with liver cirrhosis. Methods: Metabolites in deproteinized urines of 29 patients (16 F) were analyzed by nanoLC-MS/MS on an Eksigent C_{18} ChipLC column (15 cm x 200 µm ID) using a 20 min 0-95% linear gradient of acetonitrile on 0.1% formic acid at 45ºC. Data were recorded in negative ion and positive modes. each cycle consisted of a 250 ms hi-res TOF-MS, followed by twenty 50 ms MSMS selected precursor ions. Collected data were processed using XCMSonline. Aligned metabolite ions and their peaks were subjected to statistical analysis with Metaboanalyst 3.0 with total ion current normalization and Pareto scaling. Normalized data were also subjected to pathway and module analysis with Mummichog 1.0.9. Results: Initial multivariate Partial Least Squares Discriminant Analysis (PLSDA) on recovery versus non-recovery of renal function demonstrated two groups to be well separated. Mummichog analysis showed statistical differences in steroid metabolism, oxidized fatty acids and squalene biosynthesis. In women, metabolites in the lysine metabolism pathway, trimethylammoniobutanal, trimethylammoniobutanoate and carnitine were observed. Two enzymes in carnitine pathway (N ε-Trimethyllysine hydroxylase and γ-butyrobetaine hydroxylase) are alpha-ketoglutarate (αKG)-dependent. A second key metabolite was thiamine, which as pyrophosphate is an essential cofactor for 2-oxoglutarate dehydrogenase, to produce αKG. The metabolies in the squalene pathway were farnesyl diphosphate, geranyl diphosphate and geranylgeranyl diphosphate. The latter forms covalent adducts with Cys residues on the Rho GTPases, RhoA and Rac1, and causes mitochondrial dysfunction which may lead to αKG deficiency. These data suggest that an αKG deficiency may be a rationale for the onset of AKI. Other metabolic pathways affected in women were in estrogen quinone formation. In men, principal pathways affected were in steroid metabolism (negative and positive modes) and fatty acid oxidation (positive mode). Conclusion: Kidney among cirrhosis patients is vulnerable to modifications to key pathways, which may be distinctive among patients who recover their renal function after LT alone compared to those who are unable to recover the renal function. These biomarkers may have clinical utility as basis for optimal allocation of simultaneous liver kidney transplants.

Su1559

TISSUE RENIN-ANGIOTENSIN SYSTEM IN THE KIDNEY OF ASCITIC CIRRHOSIS: AN INNOCENT BYSTANDER OR A PROTAGONIST?

Giovanni Sansoe, Manuela Aragno, Raffaella Mastrocola, Maurizio Parola

Introduction. In liver cirrhosis, kidney local renin-angiotensin system (RAS) deserves scrutiny and includes: conversion of angiotensin I into angiotensin II (Ang-II) by ACE and chymase; binding of renin and prorenin to their tissue receptor (RPR), leading to local generation of angiotensin I and Ang-II; conversion of Ang-II by ACE2 into natriuretic peptide angiotensin1-7; degradation of the latter to angiotensin1-4 by neprilysin. Changes in expression of these enzymes and receptors may affect renal levels of sodium-retentive (Ang-II) and natriuretic (angiotensin1-7) peptides. **Aims.** To assess, in ascitic rats' kidney, content and immunolocation of RPR, ACE, chymase, neprilysin, Ang-II and angiotensin1-7. **Methods.** Healthy rats (group G1) and rats with ascitic cirrhosis due to CCl_4 (G2) were studied. Kidney content of ACE, chymase, RPR, ACE2, neprilysin, Ang-II, angiotensin1-7 and plasma levels of Ang-II, direct renin (DR), plasma renin activity (PRA) were measured. DR is quantified through monoclonal antibodies that bind both active renin and prorenin, and therefore plasma concentrations of prorenin can be derived from the ratio DR/PRA. **Results.** DR/PRA ratios were 3.3 ± 0.8 and 7.9 ± 1.6 in healthy and ascitic rats, respectively (P<0.03), showing more prorenin in ascitic rats. In G2, Ang-II was higher than normal in plasma (P<0.01) but especially in renal tissue (1150 ± 199 vs. 78 ± 22 pg/mg kidney protein, P<0.001). Kidney content of ACE, chymase, ACE2 and neprilysin was significantly higher, but RPRrs significantly lower, in ascitic than in healthy rats. The ratio Ang-II/Angiotensin1-7 in kidneys rose from 1.3 ± 0.2 in G1 to 5.3 ± 0.4 in G2 (P<0.03). **Conclusions.** In ascitic cirrhosis: a) the contribution of ACE and chymase to renal Ang-II synthesis seems stronger than that of RPRs, despite increased plasma prorenin; b) the kidney shows an imbalance in favour of the production of anti-natriuretic Ang-II because overexpressed neprilysin finally degrades ACE2-generated angiotensin1-7.

Su1560

TRENDS IN THE PREVALENCE OF PORTAL VEIN THROMBOSIS AND ASSOCIATED MORTALITY IN CIRRHOSIS: ANALYSIS OF A NATIONALLY REPRESENTATIVE INPATIENT COHORT

Josephine Cool, Russell Rosenblatt, Sonal Kumar, Catherine Lucero, Brett Fortune, Carl V. Crawford, Arun Jesudian

BACKGROUND Portal vein thrombosis (PVT) is common in cirrhosis and has been associated with poor survival. Increased recognition of the associated clinical consequences has led providers to more aggressively identify and treat PVT in these patients in recent years. To date, no study has analyzed the trend of the prevalence of PVT and its effect on mortality in hospitalized decompensated cirrhotics. METHODS This study was performed using the Nationwide Inpatient Sample (NIS) from 1998-2014, a large, nationally-representative database of hospital discharges. All inpatients older than 18 years of age with decompensated cirrhosis or evidence of clinically-significant portal hypertension were identified using a validated algorithm. Those with hepatocellular carcinoma were excluded. The primary outcomes were the trend in prevalence and mortality associated with PVT. The secondary outcomes were the identification of risk factors in the development of PVT and its effect on acute kidney injury and hepatorenal syndrome. Multivariate logistic regression was used to correct for conditions known to affect mortality in cirrhotics. RESULTS We identified 3,045,098 patients, of which 48,438, 1.6%, had PVT. PVT prevalence increased from 0.7% in 1998 to 2.4% in 2014. Mortality in cirrhotics with PVT fluctuated but overall declined over the same time period, decreasing from 11.9% in 1998 to 9.1% in 2014. In univariate analysis, PVT was associated with increased risk of mortality (OR 1.24, 95% CI 1.11-1.39, p<0.001). PVT was associated with an increased mortality even when controlling for age, gender, ascites, infection, encephalopathy, and Elixhauser comorbidity index (OR 1.17, 95% CI 1.10-1.25, p<0.001). Multivariate logistic regression demonstrated that PVT significantly increased the risk of acute kidney injury (OR 1.69, 95% CI 1.61-1.77, p<0.001) and hepatorenal syndrome (OR 1.56, 95% CI 1.45-1.66, p<0.001). CONCLUSIONS Our findings demonstrate that while the prevalence of PVT is rising in hospitalized cirrhotics, mortality in patients with cirrhosis and PVT is decreasing despite increased risk of acute kidney injury and hepatorenal syndrome. Decreased mortality over time might be related to more aggressive anticoagulation of PVT and/or improved inpatient care of decompensated cirrhotics. The causes underlying these trends warrant further study.
Mortality

Death	Odds Ratio (95% Confidence Interval)	P value
Portal Vein Thrombosis (PVT)	1.17 (1.10-1.25)	<0.001
Infection (SBP, Cdiff, PNA, UTI)	1.70 (1.66-1.73)	<0.001
Age	1.01 (1.00-1.01)	<0.001
Female	0.85 (0.84-0.87)	<0.001
Ascites	1.27 (1.25-1.30)	<0.001
PSE (Hepatic Encephalopathy)	1.87 (1.83-1.90)	<0.001
Elixhauser Comorbidity Index	1.066 (1.061-1.077)	<0.001

Su1561

THE ASSOCIATION BETWEEN PORTAL VEIN THROMBOSIS AND OTHER VENOUS THROMBOEMBOLISM IN CIRRHOSIS: ANALYSIS OF A NATIONALLY REPRESENTATIVE INPATIENT COHORT

Josephine Cool, Russell Rosenblatt, Sonal Kumar, Catherine Lucero, Brett Fortune, Carl V. Crawford, Arun Jesudian

BACKGROUND Patients with cirrhosis are known to be at increased risk of portal vein thrombosis (PVT) in the setting of portal hypertension. Recent data suggest that rebalanced hemostasis also places cirrhotics at an almost two-fold increased risk of additional venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). As there is little evidence identifying the association between PVT and VTE in decompensated cirrhotics, this study examined this interaction, and the outcomes related to multiple thrombotic events in this population. METHODS This study was performed using the Nationwide Inpatient Sample (NIS) from 1998-2014, a large, nationally-representative database of hospital discharges. All patients older than 18 years of age with decompensated cirrhosis or evidence of clinically-significant portal hypertension were identified using a validated algorithm. Those with hepatocellular carcinoma were excluded. The primary outcome was the association between PVT and DVT/PE. The secondary outcomes were the effect of DVT/PE on mortality in cirrhotics with PVT and identification of risk factors in the development of PVT and DVT/PE. Multivariate logistic regression was employed to control for conditions known to affect outcomes in cirrhosis. Disease states were identified using ICD-9 codes. RESULTS We identified 3,045,098 patients with cirrhosis excluding hepatocellular carcinoma (HCC), of which 48,438, or 1.6%, had PVT. Patients with PVT were more likely to have an underlying DVT or PE than patients without PVT (2.5% vs. 0.9%, p<0.001). In univariate analysis, PVT was associated with an increased risk of DVT/PE (OR 2.93, 95% CI 2.57-3.34, p<0.001). This association persisted in multivariate analysis controlling for age, gender, race, hypercoagulable state such as pregnancy or myeloproliferative disorder, recent major operation or non-primary liver cancer (OR 2.16, 95% CI 1.81-2.59, p<0.001). In multivariate analysis, patients with PVT did not have a significantly higher inpatient mortality if they had a DVT/PE. Patients with PVT were more likely to have DVT/PE if they had a hypercoagulable disorder (OR 4.05, 95% 2.56-6.42, p<0.001), recent major operation (OR 3.47, 95% CI 2.58-4.66, p<0.001), and acute kidney injury (OR 1.48, 95% CI 1.10-1.99, p=0.01). CONCLUSIONS Our study noted that VTE is more common in hospitalized