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INTEGRATED MICRORNA-MRNA PROFILING IDENTIFIES MOLECULAR BIOMARKERS IN BLADDER OUTLET OBSTRUCTION-INDUCED LOWER URINARY TRACT DYSFUNCTION

Hypothesis / aims of study
Bladder outlet obstruction (BOO) induces significant organ remodelling accompanied by urodynamic changes in bladder function causing lower urinary tract symptoms (LUTS) and dysfunction (LUTD). Early diagnosis of BOO-induced LUTS is complicated by the lack of methods of assessing specific molecular changes in the bladder wall. MicroRNAs (miRNAs) are a class of small noncoding regulatory RNAs altered in patients with LUTD and animal models of partial BOO. Previously we characterized miRNA and mRNA expression profiles associated with different states of BOO-induced LUTD and studied the regulatory role of miRNAs. Here, using RT-qPCR we validated our sequencing results in a bigger cohort of patients and examined diagnostic potential of selected mRNA and miRNAs for distinguishing the BOO states at the molecular level.

Study design, materials and methods
Bladder dome biopsies were collected from controls, and patients with urodynamically established BOO with and without detrusor overactivity (DO and BO groups, respectively) or with detrusor underactivity (UA group). A panel of candidate miRNAs was generated using unsupervised clustering and statistical analysis of differentially expressed miRNAs determined by Next Generation Sequencing (NGS) analysis of 24 samples (n = 6 per group). Receiver operating characteristic curve analysis (ROC) was performed to assess the diagnostic capability of group-specific miRNAs and mRNAs, which were then tested in larger groups of patients to evaluate the specificity and sensitivity of each candidate.

Results
The validation revealed that a combination of 3 miRNAs or mRNAs was sufficient to discriminate each patient group. NRXN3, BMP7 and MYH11 mRNA combination showed to be reliable to segregate each patient group. The DO group was defined by hsa-miR-146b-5p, hsa-miR-142-3p and hsa-miR-374a-5p expression; the BO group by hsa-miR-181a-5p, hsa-miR-212-3p and hsa-miR-146b-5p; and the UA group by hsa-miR-181a-5p, hsa-miR-490-3p and hsa-let-7b-5p.
Using *in silico* analysis of NGS sequencing data, performed on a limited number of biopsy samples, several mRNAs and miRNAs were selected for further RT q-PCR validation. The qPCR successfully validated the clustering of patients in mRNA and miRNA NGS datasets.

Interpretation of results
Testing NGS-based ROC analysis in a bigger sample cohort rejects the potential of using single miRNAs as biomarker determinants for specific BOO states. On the other hand, for precise clustering of patients, our data supports the power of using a group of 3 miRNAs or mRNAs instead of individual miRNAs/mRNAs.

Concluding message
MicroRNA and/or mRNA expression profiles can be used to differentiate different phenotypes of bladder function resulting from BOO. It remains to be determined whether they can also predict the treatment outcome.

Disclosures
Funding: Swiss National Research Foundation **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Cantonal Ethics committee Bern Switzerland **Helsinki:** Yes **Informed Consent:** Yes