|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Diseases** | **Sample sizes** |  |  |  |  |  |  |  |  |
| **CRS Type** | **Primary** | **Secondary** | **Number of patients**  | **Number of healthy controls** | **Groups comparison** | **Type of Samples** | **Biomarker validation technique** | **Type of Biomarker** | **AUC** | **Sensitivity**  | **Specificity** | **Reference** |
| Type 1  | ADHF | patients developed CRS type 1 | 111 ADHF patients: 75 patients with CRS 36 patients without CRS | 24 | i.HF patients vs. healthy controls ii.CRS patients vs. non-CRS patients | Urine | ELISA | IGFBP7/TIMP2:predict the development of type I CRS  | TIMP-2: 0.73 IGFBP-7: 0.64KIM-1: 0.54  | NA | NA | [99]Supplementary Table 1: Biomarkers in Cardiorenal Syndrome. |
| NA | ACS | NA | 4947ACSpatients | NA | 4 quartiles based on FGF-23 concentration | Plasma | ELISA | FGF-23 levels are associated to increased risk of CV death or HF hospitalization | NA | NA | NA | [104] |
| Type 1 | STEMI or NSTE-ACS |  AKI | 78 patients:15 patients ACS-AKI63 patients non-AKI | 17 | AKI patients vs. non-AKI patients | Serum | ELISA / magnetic bead-based antibody | IL-1b: found statistically significantly increased in AKI . BUN, IL-1b, NT-ProBNP: significant positive correlation with ΔCr | NA | NA | NA | [108] |
| NA | CKD | HF (HFpEF/ HFrEF) | i.8983 patients without CKDii. 906 patients with CKD: 156 patients with CKD developed HF iii.2413 patients without microalbuminuria:499 patients with mmicroalbuminuria | NA | i.patients with CKD vs. patients without CKD ii.patients without microalbuminuria vs. patients with microalbuminuria | Urine | immunoturbimetry | albuminuria: was associated with incident overall HF | NA | NA | NA | [105] |
| Type 1 | HF | WRF | 908 patients with HF: 4 quartiles based on PENK concentration: 1st:<66.9 pmol/l (n=477) 2nd: 66.9-97.2 pmol/l (n=476), 3rd: 97.2-147 pmol/ l (n=477): 4th: Quartile >4 147 pmol/l (n=478) |   NA | 4 quartiles based on PENKconcentration | Plasma |   ELISA | PENK: i) prognostic value in acute HF. ii) predicting cardiorenal syndrome iii) independent predictive value for death |    0.69 |   NA |   NA |   [107] |
| NA | Hospitalized patients with AHF | WRF | 927 patients | NA | AHF patients with WRF vs. AHF patients without WRF | Plasma | Multiplex magnetic bead-based antibody detection | NGAL: did not predict the development of WRF better than creatinine | 0.637 | eGFR<60/NGAL<150:84.5%eGFR<60/NGAL<109:90.3% | eGFR<60/NGAL<150:41.7%eGFR<60/NGAL<109:26.3% |  [51] |
| NA | CKD | Cardiac events | 252 CKD patients: 36 patients developed CV events | NA | CKD patients with CV events vs. CKD patients without CV events | Plasma | ELISA | NGAL: independent predictor of CV events | 0.801 | NA | NA | [49] |
| NA | ADHF | AKI | 732 ADHF patients: 213 patients developed AKI | NA | i.ADHF patients with AKI vs. ADHF patients without AKI ii. patients with progressive AKI vs. nonprogressors | Urine | ELISA | AGT, NGAL, IL-18: predict AKI progression | AGT:0.78 NGAL: 0.74 IL-18: 0.73 | AGT: 0.78 NGAL:0.76 IL-18: 0.64 | AGT: 0.69 NGAL:0.63 IL-18:0.89 | [48] |
| NA | Acute or chronic HF  | RI | 246 patients: 120 HF patients without RI and 126 CRS patients | 12 | HF patients without RI vs.CRS patients | Plasma | ELISA | NGAL, BUN, TnT , BUN/creat: early diagnosis of RI in acute and chronic HF  | NA | NGAL: 78% BUN:70% TnT:60% BUN/creat: 71% | NGAL: 70% BUN:83% TnT:83% BUN/creat: 80% |  [44] |
| NA | CHF | CKD | 138 patients with heart disease: 26 patients with initial CKD and 82 developed CKD | NA | Patients with initial CKD and CKD progression vs. patients without CKD progression | Urine | ELISA | KIM-1, NAG: predict the progression of CKD in CRS | NAG: 0.72 KIM-1:0.66 NGAL: 0.47 | NAG: 73.1% KIM-1: 66% | NAG:64.3% KIM-1: 61% | [101] |
| NA | HF | RI | 908 patients with a discharge diagnosis of HF | NA | HF patients with renal dysfunction vs. HF patients without renal dysfunction | Serum | NA | BNPand BUN/creat: stratifies patients with RI | BNP and BUN/creatHR=1.8, 95% CI 1.2-2.7,p=0.008 | NA | NA | [84] |
| NA | AHF  | WRF | 427 AHF patients: patients were divided into 4 groups based on RAAS biomarkers | NA | 4 groups of patients  | Plasma | ELISA | High levels of RAAS biomarkers are associated with WRF | NA | NA | NA | [16] |
| Type 1 and 2 | HF | WRF | 179 patients with acute HF: 87 had CRS and 92 patients had preserved renal function | NA | i.Patients with WRF vs. patients without WRFii. Patients with CRS vs. patients without CRS | Plasma | ELISA | NGAL: early diagnosis of WRF during hospitalization | Recognition of CRS:NGAL: 0.68 BUN:0.80 Prediction of WRF: NGAL:0.82 BUN:0.66 Predict mortality: NGAL: 0.72 | Recognition of CRS:NGAL:70% BUN:70% Prediction of WRF: NGAL:92% BUN:73%Predict mortality: NGAL: 72 % | Recognition of CRS:NGAL: 52% BUN:82% Prediction of WRF: NGAL:71% BUN:54%Predict mortality: NGAL: 72 % | [46] |
| NA | ADHF | Impaired Kidney Function | 96 hospitalized patients with ADHF: 11 patients with cystatin C≥0.4 mg/l and 85 patients with cystatin-C <0.4 mg/l | NA | patients with cystatin C ≥0.4 mg/l vs. patients with cystatin-C <0.4 mg/l | NA | NA | **i.Cystatin-C: independent predictor of prognosis in AHF patients with renal dysfunction****ii. BNP: is associated with short term outcome in AHF patients with renal dysfunction** | Prediction of cardiac death: cystatin-C: 0.68 and BNP: 0.66 | NA | NA | [24] |
| NA |  ADHF |  WRF | 87 ED patients with ADHF:23 patients with WRF and 64 without WRF | NA | Patients with WRF vs. patients without WRF | Urine | multiplex magnetic bead-based antibody detection | urine biomarkers of renal injury did not predict WRF in ED patients with ADHF | KIM-1: 0.49 NAG: 0.46 cystatin-C: 0.46 NGAL: 0.61 BUN: 0.57 |  NA | NA | [50] |
| NA | CHF | NA | 24 CHF patients without primitive renal disease  | 25 controls |  CHF patients vs.marathones | Plasma | ELISA | b2M and TIMP1: are independently associated with GFR values | NA | NA | NA |  [100] |
| Type 2 | PD | CHF | 129 patients: 66 lost RRF and 63 preserved RRF | 25 | Patients with lost RRF vs. Patients with preserved RRF | Blood | ELISA and nephelometry | IL-6, NT-proBNP and CRP: independent risk factors for RRF | NA | NA | NA |  [109] |
| Type 1 | patients with AKI who underwent CRRT | acute cardiorenal syndrome | 708 patients with CRRT:223 AKI patients receiving CRRT,35: patients with ACRS receiving CRRT | NA | i.survivors vs. nonsurvivorsii. early intervention patients vs. late-intervention patients | Blood | Automated hematology analyzer | MPV: predictive value for in-hospital mortality | 0.735 | NA | NA | [51] |

AKI: Acute Kidney Injury, CRRT: Renal Replacement Therapy, ACS: Acute Cardiorenal Syndrome, MPV: Mean Platelet Volume, ADHF: Acute decompasated heart failure, CRS: Cardiorenal Syndrome, IGFBP-7: Insulin-like growth factor-binding protein 7, TIMP-2: Tissue inhibitor of metalloproteinases 2, FGF-23:Fibroblast growth factor 23, STEMI: ST-elevation myocardial infarction, NSTE-ACS: non-ST elevation acute coronary syndrome, IL-10: Interleukin 10, ET-1: Endothelin -1, IL-1β: Interleukin 1 beta, TnI: Troponin I, ACS-AKI: Acute Coronary Syndrome-Acute Kidney Injury, CKD: Chronic Kidney Disease, HF: Heart Failure, HFrEF: HF with reduced ejection fraction,HFpEF: HF with preserved ejection fraction, PENK: Proenkephalin, WRF: Worse Renal Function, AHF: Acute Heart Failure, eGFR: estimated GFR, NGAL: Neutrophil gelatinase-associated lipocalin, CV: Cardiovascular, BNP: Brain Natriuretic Peptide, AGT: Angiotensinogen Protein, RI: Renal Impaired, BUN: Blood Urea Nitrogen, TnT:Troponin T,IL-18: Intereleukin-18, ED: emergency department patients, CHF: Chronic Heart Failure, PD: Peritonreal dialysis,RRF: Residual renal function, NT-proBNP: N-terminal pro b-type natriuretic peptide, IL-6 : Interleukin-6 NA: Not Available.