Diagnostic performance of Pro-ADM compared with PCT, EASIX and modified EASIX during early complications after pediatric allogeneic HCT

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Background: Early infectious diseases (IDs) and transplant-related complications (TRCs) may resemble uncomplicated febrile neutropenia (FN) after pediatric allogeneic hematopoietic cell transplantation (HCT). Mid-regional proadrenomedullin (Pro-ADM) reflects endothelial stress, whereas procalcitonin (PCT) supports infection assessment. EASIX and modified EASIX (m-EASIX) were developed mainly for longitudinal prognostic stratification; their value for contemporaneous diagnosis is uncertain. Methods: In this prospective multicenter observational study (NCT05523336), 113 first and five second HCTs were evaluated. At episode onset (T1), 105 episodes were classified as TRCs (n=24), IDs (n=26), or FN (n=55). Pro-ADM, PCT, $\log_2$(EASIX), and $\log_2$(m-EASIX) were compared across groups. ROC analyses assessed discrimination of TRCs from FN, alone and in parallel or serial combinations. Results: Median Pro-ADM was 0.93 nmol/L in TRCs, 0.78 in IDs, and 0.59 in FN. Levels differed between TRCs and FN (p=0.00023) and between IDs and FN (p=0.00062), but not between TRCs and IDs (p=0.43). Pro-ADM showed moderate discrimination (AUC 0.76; cutoff 0.70 nmol/L; sensitivity 0.78, specificity 0.77, PPV 0.58, NPV 0.89), numerically similar to PCT (AUC 0.78). EASIX performed poorly (AUC 0.60), while m-EASIX was non-discriminatory (AUC 0.47). Parallel Pro-ADM–PCT positivity increased sensitivity/NPV to 0.83/0.91; serial positivity increased specificity/PPV to 0.88/0.71. Adding EASIX or m-EASIX provided no incremental diagnostic benefit. Conclusions: Pro-ADM and PCT provide complementary early diagnostic information in pediatric HCT. The high NPV of low Pro-ADM, especially with parallel PCT assessment, may support antibiotic stewardship, earlier treatment de-escalation, and avoidance of unnecessary hospitalization in clinically stable children; serial positivity may identify patients requiring intensified evaluation. Prospective validation is required before using these biomarkers to guide discharge or antibiotic withholding. EASIX-based scores did not support acute episode classification, showing that prognostic utility does not necessarily translate into contemporaneous diagnostic value.