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Interpretable tumor risk stratification via surrogate decision tree analysis of machine learning models: Case study on biliary tract cancer

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Early detection of biliary tract cancer (BTC) is hindered by overlap with benign biliary tract disease (BTD). We present a deployable pipeline coupling a CA19-9–agnostic tabular classifier with a Surrogate Decision Tree (SDT) that yields transparent, protocol-ready rules. This single, deployable framework is designed for bedside use and integration into routine workflows. Trained on multicenter PHR data, the model maintained high discrimination across CA19-9 strata (AUROC 0.893 [95% CI 0.863–0.920]; sensitivity 0.784 [0.727–0.827]) and outperformed the diagnostic performance of CA19-9 itself, enabling use in Lewis antigen–negative patients and in those with normal CA19-9 (<37 U/mL). The rules derived from the SDT recovered clinically coherent patterns: ALP >311.5 U/L signaled high risk (~77.8%), further heightened by extreme hyperbilirubinemia (>6.02 mg/dL; ~94.4%). Unexpectedly, in high-ALP patients, moderately elevated bilirubin (1.15–6.02 mg/dL) mapped to lower risk (~34.9%) than near-normal bilirubin (≤1.15 mg/dL; ~73.0%), consistent with differing phenotypes (e.g., intrahepatic disease vs benign partial obstruction). With ALP ≤311.5 U/L, CEA stratified risk (≥9.69 ng/mL ≈86.4%; 3.31–9.69 ng/mL plus bilirubin >5.28 mg/dL ≈84.8%). In older adults (>56.5 years) with otherwise unremarkable markers, isolated marked hyperbilirubinemia (>8.90 mg/dL) remained a strong red flag (~73.5%). Together, a CA19-9-independent model and SDT provide accurate, explainable BTC screening across benign biliary tract disease presentations, particularly when CA19-9 is non-informative. These results underscore the robustness of our framework and its potential for protocolized deployment as a frontline clinical decision-support tool in healthcare.