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Letters

RESEARCH LETTER

High-Sensitivity Cardiac Troponin I for Long-Term Cardiovascular Risk Stratification in a Cancer Clinic Population

Potentially cardiotoxic therapies are commonly used in the management of patients with cancer.[1-3] Our objective was to assess the utility of the high-sensitivity cardiac troponin I (hs-cTnI) cardiovascular risk stratification cutoffs proposed for the general population in a large outpatient cancer population for future myocardial infarction (MI) or heart failure (HF) admission.[4]

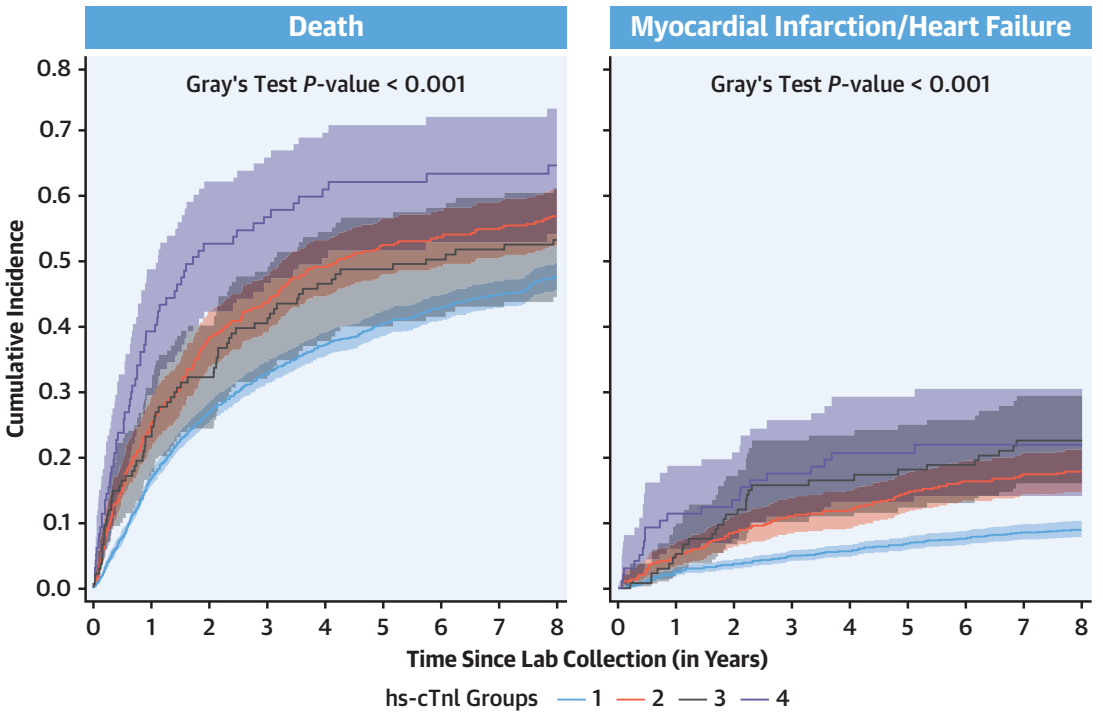
After ethics approval (Hamilton Integrated Research Ethics Board #4717), over a 6-week period (March through April) in 2013, every clinically ordered lithium heparin plasma sample (used for clinical chemistry testing) obtained from ambulatory patients at the Juravinski Cancer Center (ie, cancer clinic patients) was tested using the Abbott hs-cTnI assay.[2,3] In total, 4,817 samples were tested for hs-cTnI. The results were not reported to the ordering clinicians (ie, not used for clinical purposes). We obtained clinical outcomes via linkage to provincial databases housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences) (Registered Persons Database for mortality and Canadian Institute for Health Information Discharge Abstract Database for hospital discharges associated with MI or HF).[5] These data sets were linked using unique encoded identifiers and analyzed at ICES with the outcome approach having been validated.[5] We excluded samples drawn from patients previously diagnosed with HF (n = 383). If more than 1 sample was obtained during the accrual period, we used only the first sample per unique patient for analysis (n = 1,316 excluded). We further excluded patients with histories of MI, percutaneous coronary intervention, coronary artery bypass graft surgery (n = 109) and those for whom the exact cancer diagnoses date was not in the Ontario Cancer Registry database (n = 300). We assessed the final cohort (n = 2,709 unique patients, 50.1% men) for future MI or HF (composite outcome over 8 years, as previously described in another population).[5]

We used the following risk stratification cutoffs: group 1 consisted of patients with hs-cTnI <4 ng/L (female) and <6 ng/L (male), group 2 included patients with hs-cTnI 4 to 10 ng/L (female) and 6 to 12 ng/L (male), group 3 included patients with hs-cTnI 11 to 16 ng/L (female) and 13 to 34 ng/L (male), and group 4 consisted of patients with hs-cTnI above the sex-specific 99th-percentile upper reference limits (>16 ng/L in women, >34 ng/L in men).[4] We used outcome rates per 1,000 person-years in constructing Cox models (cause-specific hazard model with death as a competing risk) and produced cumulative incidence function curves as part of the competing risk analysis (death as a competing risk, Gray's test) to assess the composite outcome over 8 years across different hs-cTnI groups. We adjusted the Cox model for age, sex, medical history (diabetes, arrhythmia, hypertension, stroke, angina, stress test, peripheral vascular disease, liver disease, and dementia), presence of metastases, cancer site, the Charlson comorbidity index, and time from cancer diagnosis to hs-cTnI measurement. We performed all statistical analyses using SAS (SAS Institute) and present the results from the Cox model as HRs with corresponding 95% CIs; $P < 0.05$ were considered to indicate statistical significance.

In the cohort, the median time from cancer diagnosis to sample collection for hs-cTnI testing was 1.7 years (Q1-Q3: 0.5-4.4 years). Hematological cancers were the most prevalent (29%), followed by colorectal cancers (12%). Approximately 27% of the visits were related to chemotherapy, 3% were related to radiotherapy, and the remainder were follow-up or monitoring visits (70%). The median follow-up time for the MI and HF outcome was 4.1 years (Q1-Q3: 1.1-8.0 years), with the total number of events being 90 MIs, 263 episodes of HF, and 1,582 deaths over the 8 years. In the time-to-event models, only first events were considered, and accordingly, there were 80 MIs, 238 HF, and 1367 deaths.

A total of 96 patients (3.5%) had hs-cTnI concentrations exceeding the 99th percentile (ie, myocardial

FIGURE 1 Survival Curves According to hs-cTnI Risk Thresholds for MI and HF



Cumulative incidence function curves as part of the competing risk analysis (death as a competing risk, Gray's test) to assess the composite outcome of myocardial infarction (MI) and heart failure (HF) over 8 years across different high sensitivity cardiac troponin I (hs-cTnI) groups.

injury was present), with 25 patients on treatment (mean hs-cTnI 117 ± 285 ng/L). Both age ($P < 0.001$) and the MI and HF rate per 1,000 person-years ($P < 0.001$) were different among the groups: in group 1, the median age was 61 years (Q1-Q3: 52-70 years), and the outcome rate was 19 (95% CI: 16-22); in group 2, the median age was 71 years (Q1-Q3: 62-78 years), and the outcome rate was 51 (95% CI: 41-62); in group 3, the median age was 69 years (Q1-Q3: 63-78 years), and the outcome rate was 66 (95% CI: 46-94); and in group 4, the median age was 66 years (Q1-Q3: 58-78 years), and the outcome rate was 104 (95% CI: 68-159). Cumulative incidence function curves demonstrated a stepwise increase in event rates with increasing hs-cTnI levels (Figure 1).

During the 8 years of follow-up, relative to group 1 (low risk), the HR was 1.54 (95% CI: 1.17-2.03) for group 2, 2.20 (95% CI: 1.47-3.29) for group 3, and 4.01 (95% CI: 2.50-6.43) for group 4. In sensitivity analyses evaluating visit type and metastatic disease status, only the HRs for group 4 remained significant ($P < 0.05$) in patients at follow-up visits (n = 71; HR: 4.58; 95% CI: 2.68-7.85), at treatment-related visits (n = 25; HR: 3.22; 95% CI: 1.09-9.50), and in patients with (n = 21; HR: 19.72; 95% CI: 4.56-85.28) and without (n = 75; HR: 3.63; 95% CI: 2.18-6.04) metastatic disease.

The other significant covariates in the overall Cox model were age (HR per year increase: 1.04; 95% CI: 1.03-1.05), male sex (HR: 1.42; 95% CI: 1.08-1.85), history of diabetes (HR: 1.39; 95% CI: 1.07-1.80), hypertension (HR: 1.55; 95% CI: 1.18-2.02), and liver disease (HR: 3.77; 95% CI: 1.15-12.42). Excluding patients with hospital admissions within 2 weeks prior to blood collection (n = 49), the HRs remained similar for the aforementioned covariates and for group 2 (HR: 1.58; 95% CI: 1.19-2.08), group 3 (HR: 2.19; 95% CI: 1.46-3.29), and group 4 (HR: 4.11; 95% CI: 2.56-6.61).

This study provides important long-term cardiovascular risk stratification information regarding hs-cTnI in a large cancer clinic population. Specifically, these data pertain to hs-cTnI measurements performed both during cancer treatment and in

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survivorship (ie, remote from cancer therapy completion). Limitations include the lack of documentation of specific cancer treatments and cancer stage in the ICES database, as well as assessing all-cause death as opposed to cardiovascular death (not available in the data set) in this cohort. Notwithstanding these limitations, these data indicate that cancer clinic patients with hs-cTnI concentrations <4 ng/L (women) and <6 ng/L (men) are at lowest cardiovascular risk, with concentrations above the 99th percentile (group 4) representing a high-risk group that warrants further clinical and laboratory investigations.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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