JIM Research Letter

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Temporal trends in guideline-recommended cardiometabolic testing completeness before initiating immune checkpoint inhibitors: A cohort study

Dear Editor,

Immune checkpoint inhibitors (ICIs) are increasingly used but are associated with cardiotoxicity [1–3]. The cardiovascular needs of ICI users were addressed by the European Society of Cardiology's (ESC) 2022 Cardio-Oncology Guidelines [4], with cardiometabolic testing recommended before initiating ICIs (pre-ICI), including glycaemic (HbA1c or fasting glucose), lipid, renal and natriuretic peptide testing, electrocardiogram and echocardiography [4]. However, current practices of pre-ICI cardiometabolic testing are undescribed, and ensuring testing completeness may improve cardiovascular outcomes [5]. We thus examined trends in pre-ICI cardiometabolic testing completeness and explored whether such trends influenced cardiovascular outcomes.

This study was approved by an institutional review board and conducted in accordance with the Declaration of Helsinki. As deidentified data were used, individual consent requirement was waived.

Methods were detailed in the Supporting Information. Data were obtained from a population-based database prospectively recording data of patients attending public hospitals/clinics in Hong Kong, linked to the governmental death registry containing all local citizens' death records. Diagnoses were encoded by the *International Classification of Diseases, Ninth Revision* (ICD-9) codes (Table S1). Mortality causes were encoded using ICD-9/10 (Table S2). This data source was well-published [6, 7].

We included patients with cancer newly initiated on ICI(s) between 1/1/2013 and 31/12/2021, grouped by the year of ICI initiation (2013–2017/2018–2019/2020–2021). Cardiometabolic testing completeness was estimated by numbers of relevant tests (excluding electrocardiogram/echocardiography as data were unavailable, and natriuretic peptide which was then unavailable in Hong Kong's public healthcare system) within 90/180 days pre-ICI. Proportions of patients with each test were reported, per ESC's quality indicators [5].

All patients were followed up from ICI initiation for up to 2 years, until 31/12/2021, or until death, whichever earlier. The outcome was major adverse cardiovascular event (MACE; the composite of myocardial infarction, stroke, heart failure or cardiovascular mortality).

Cardiometabolic testing completeness was modelled using Poisson regression, whereas individual tests were modelled using binary logistic regression. The cumulative incidence of MACE was modelled using Fine-Gray regression, with non-cardiovascular mortality as a competing event. Subgroup and sensitivity analyses were detailed in the Supporting Information.

Altogether, 4324 patients were analysed (baseline characteristics in Table S3). Patients initiated on ICI more recently had more complete cardiometabolic testing within both 90 (2020–2021 vs. 2013–2017: adjusted risk ratio [aRR] 1.10 [95% confidence interval: 1.03–1.18], $p = 0.005$) and 180 (aRR 1.09[1.03–1.16], $p = 0.005$) days pre-ICI (Table S4). Subgrouping mostly produced directionally consistent estimates with overlapping confidence intervals (Tables S5 and S6).

All tests' completeness improved, except cardiac troponin which decreased slightly, and estimated glomerular filtration rate which remained high (Fig. 1, Table S7). Multivariable logistic regression

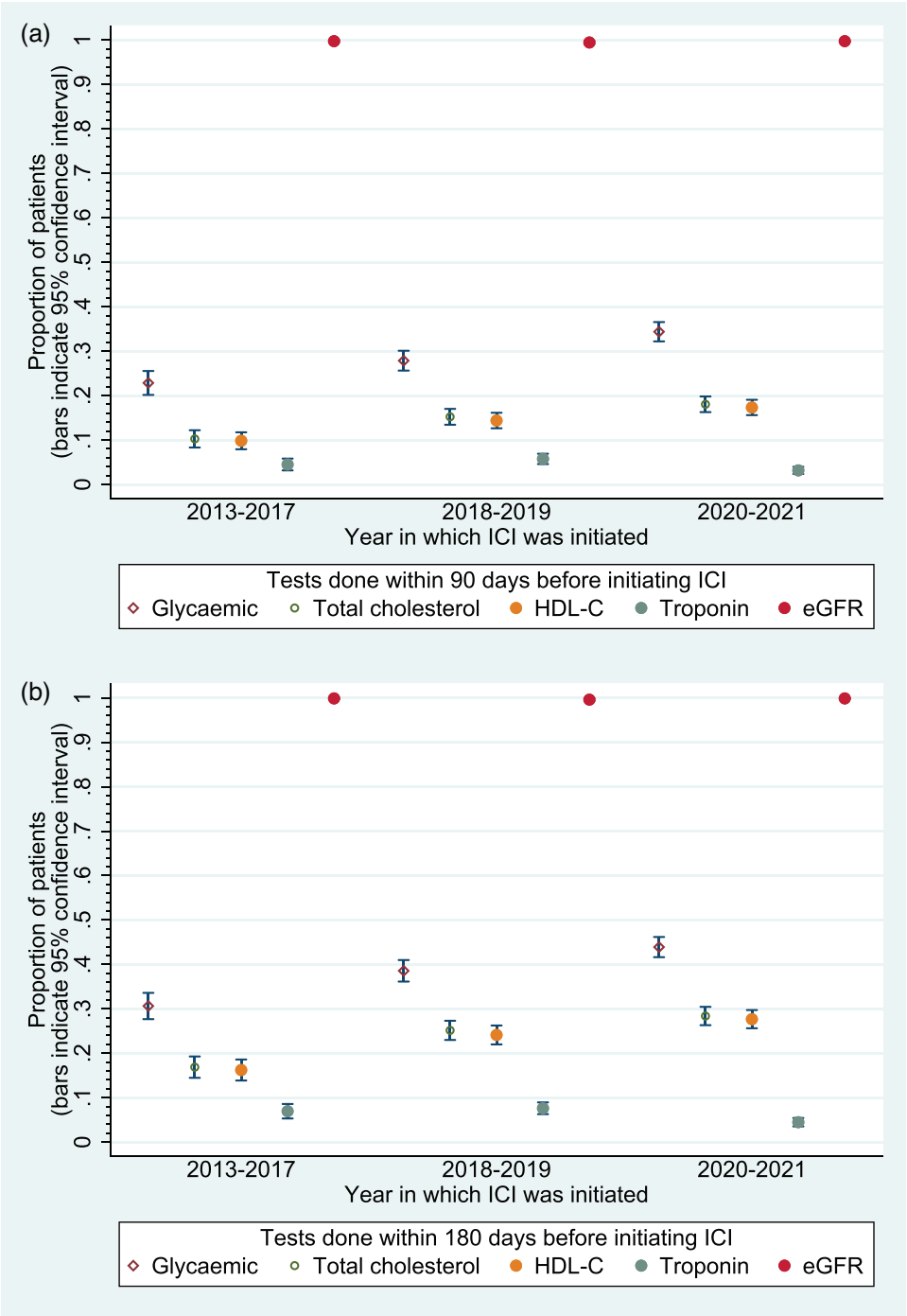

Fig. 1 *Respective proportions of patients who underwent the cardiometabolic tests of interest within (A) 90 and (B) 180 days before initiating immune checkpoint inhibitor(s) (ICIs) throughout the study period. Bars indicate 95% confidence intervals. eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol.*

confirmed such findings (Table S4). Nonetheless, testing completeness remained poor overall (Fig. 1, Table S7). Figures S1 and S2 show the number of tests within 90/180 days pre-ICI. Figures S3–S7 show the time between the most recent pre-ICI tests and ICI initiation.

Over a 0.9-year median follow-up [interquartile range: 0.4–2 years], 130 patients (3.0%) had MACE; 2185 had non-cardiovascular mortality (50.5%). Unadjusted Fine-Gray regression found no significant differences in MACE cumulative incidence between years of ICI initiation (Fig. S8, Table S8). Although adjusted analysis found those initiated on ICI more recently having lower 2-year MACE cumulative incidence (possibly due to shorter follow-up in these patients), no significant 1-year differences were observed. Additional adjustment for 180-day testing completeness did not meaningfully modify these associations (Table S8). Sensitivity analysis produced similar results as unadjusted regression (Table S9).

This was one of the first studies examining cardiometabolic testing completeness in patients with cancer receiving ICIs. Improving testing completeness likely reflected increasing awareness of the cardiometabolic impacts of ICI and other cancer therapies, with similar observations for other therapies [8]. Nonetheless, most tests were still only performed for selected patients, and the degrees of improvements were likely insufficient to influence outcomes. Cardiometabolic testing completeness remains a potential opportunity for bettering cardiovascular outcomes in these patients, possibly with dedicated cardio-oncology services [9].

Using population-based data, our findings were representative and generalizable to many Asian metropolitans. Although data for some cardiometabolic testing components were unavailable, most were included, and echocardiography was only recommended for patients at high cardiovascular risks [4]. Some cardiovascular variables/risk factors were unavailable, for example blood pressure, but numerous covariates were considered and should cover most confounders. Furthermore, individual outcome adjudication was impossible, and misdiagnosis/miscoding of ICI-related cardiovascular sequelae was possible. Lastly, Hong Kong's healthcare system is heavily subsidized. Our findings may have limited applicability to countries/regions with different medical financing systems [10].

Briefly, although cardiometabolic testing completeness in patients with cancer being initiated on ICI was improving, completeness remained poor. Such improvements probably did not meaningfully influence cardiovascular outcomes.

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Conflict of interest statement

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Data availability statement

All underlying data are available upon reasonable request to the corresponding authors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supporting Information

