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Prognostic Significance of Routine Cardiac Biomarkers in Hypertension When Heart Failure Is Excluded: A Real-World Analysis of the TriNetX Database

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Abstract

The use of biomarkers in heart failure (HF) is long established; however, little is known about the prognostic significance of these biomarkers in hypertension when HF has been excluded. This study examined the prognostic significance of routine cardiac biomarkers (natriuretic peptides and cardiac troponins) in hypertensive patients when HF has been excluded. We analyzed electronic medical records from a global federated research network TriNetX. Cohorts were built based on biomarker-specific thresholds with 1:1 propensity-score matching. Cox proportional models were used to estimate hazard ratios with 95% confidence interval for 5-year incident major adverse cardiac events (MACE). Our analysis identified four biomarker cohorts: (a) B-type natriuretic peptide (BNP)-80,740 patients (b) N-terminal pro B-type natriuretic peptide (NT-proBNP)-46,164 patients (c) cardiac troponin T-13,785 patients, and (d) cardiac troponin I-183,346. Elevated NT-proBNP had an increased risk for MACE (HR 1.9, 95% CI 1.86, 1.96 $p < 0.0001$) and all-cause mortality (HR 2.13 95% CI 95% CI 2.07, 2.18 $p < 0.0001$) compared to those with lower levels. Similarly, hs-cTnT showed significant association with MACE (HR 1.53 95% CI 1.46, 1.61 $p < 0.0001$). Elevated natriuretic peptides and cardiac troponins in hypertensive patients without HF demonstrate significant risk of MACE and its individual components.

Keywords: biomarkers; major adverse cardiovascular events (MACE); risk factors; hypertension; heart failure

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1. Introduction

Globally, hypertension is the leading most preventable risk factor for cardiovascular disease (CVD) all-cause mortality [1,2]. It remains a significant risk factor for heart failure (HF) [3,4] atrial fibrillation (AF) [5], stroke [6], and other cardiovascular diseases. Globally, HF affects approximately 64 million people with more than 15 million cases reported in Europe [7]. The Framingham Heart Study showed that the majority (91%) of participants with HF had a previous diagnosis of hypertension [8] The economic burden linked with

hypertension is substantial through direct healthcare costs of treating it and its complications, productivity losses, and puts financial pressure on the healthcare systems [9].

Circulating plasma biomarkers, particularly natriuretic peptides and cardiac troponins have emerged as promising indicators for diagnosis and prognosis in cardiovascular risk assessment. Despite evidence supporting the utility of these biomarkers, their specific role in hypertension-related cardiovascular risk prediction and prognosis remains incompletely understood, especially where natriuretic peptides are increased but heart failure has been excluded.

B-type Natriuretic Peptide (BNP) and its N-terminal precursor, N-terminal pro-b-type Natriuretic peptide (NT-proBNP), in addition to cardiac troponins, are well-established markers for diagnosis of HF and acute coronary syndromes respectively [10]; they have also been incorporated into national and international clinical guidelines [11,12]. However, the utility and adoption of natriuretic peptides (NPs) and cardiac troponins in stratifying the risk of incident heart failure and cardiovascular disease in patients with hypertension where heart failure has been excluded remains underexplored.

In this retrospective study we aimed to investigate the prognostic significance of BNP/NT-proBNP) and cardiac troponins (hs-cTnT/hs-cTnI) measured by high sensitivity assay in hypertensive patients, where HF has been excluded based on electronic medical records (EMRs).

2. Materials and Methods

2.1. Study Design and Data Source

This was a retrospective cohort study conducted within TriNetX [13], a global federated health-research network providing access to electronic medical records (EMRs) from several participating healthcare organizations (HCOs) around the world. This online database provides de-identified healthcare information ranging from demographic data, diagnoses based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) [14] codes, laboratory results, and medications, which allows for accurate identification of disease cohorts. The TriNetX dataset is a Global Collaborative Network of 120+ HCOs of >250 million patients, mainly based in North America and Western Europe.

This retrospective study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [15].

2.2. Building Cohorts in TriNetX Database

TriNetX database was searched on 24 February 2024 with no time restriction to incorporate the greatest number of patients. All patients with a diagnosis of hypertension based on the International Classification of Disease (ICD-10CM: I10) were included. Patients with a known diagnosis of HF (ICD-10CM:150) were excluded as well as those who incurred a primary or secondary outcome prior to the index event.

Patients were classified as having elevated or non-elevated concentrations based on biomarker-specific thresholds, giving four cohorts for analysis.

1. BNP cohorts stratified as BNP ≥ 35 pg/mL or <35 pg/mL.
2. NT-proBNP cohorts stratified as NT-proBNP ≥ 400 pg/mL or <400 pg/mL.
3. High-sensitivity cardiac Troponin I (hs-cTnI) cohorts stratified as cTnI ≥ 18 ng/L or <18 ng/L.
4. High-sensitivity cardiac Troponin T (hs-cTnT) cohorts stratified as hs-cTnT ≥ 14 ng/L or <14 ng/L.

For each patient included in the cohort, the first biomarker measurement reported within one month of the diagnosis of hypertension was used. The biomarker-specific

thresholds used in this analysis for NT-proBNP reflect the guidelines of the National Institute of Health and Care Excellence (NICE) [16] and European Society of Cardiology (ESC) [11] for BNP. Cardiac troponin T threshold is the assay 99th percentile, while for cardiac troponin I an approximation of the 99th percentile across all clinical assay platforms was used, based on the clinical experience of one of the authors (GM) [17].

Baseline characteristics including age, sex, and common CV risk factors were collected using ICD-10CM codes. Comorbidities, including hypertensive diseases (I10-I16), ischaemic heart disease (IHD) (I20-I25), diabetes mellitus (E08-E13), as well as smoking status (F17 nicotine dependence) and common cardiovascular medications were also recorded. Renal function was assessed using laboratory results based on estimated glomerular filtration rate (eGFR using Modification of Diet in Renal Disease (MDRD) formula) and proteinuria (microalbumin mg/g), taking the first reported values within one month of diagnosis of hypertension.

2.3. Index Event

The index event was the earliest time point that each patient who met the inclusion criteria entered the analysis. The diagnosis of hypertension, with the measurement of a cardiac biomarker within 1 month of diagnosis, was used as the index event. This could have occurred at any time within 20 years preceding the data search date.

2.4. Clinical Outcomes

The primary outcome was an incident composite outcome of major adverse cardiac event (MACE) that occurred within 1 day after the index event and 5 years follow up. In this study, MACE was defined as a composite of acute myocardial infarction (AMI) (I21), HF (I50), LVEF < 40%, atrial fibrillation or flutter (I48), ischaemic stroke (I63), acute heart failure (I50: I50.21 and I50.31), and all-cause mortality (death) (Supplementary Table S1). Patients who developed a MACE prior to the index event were excluded.

Secondary clinical outcomes were the risk for each individual component of the primary outcome and patients who developed a secondary outcome before the index event were excluded.

2.5. Statistical Analysis

This study utilized the TriNetX online platform to perform all statistical analyses. Baseline characteristics were assessed through chi-squared tests for categorical variables, with results expressed as percentages of the total cohorts. Continuous variables are reported as mean standard deviation and differences tested with independent-samples *t*-test. After initial database querying and generation of cohorts, we performed 1:1 propensity score matching (PSM) [18] for characteristics likely to confound with the outcomes. The TriNetX platform uses greedy nearest-neighbor matching with a caliper of 0.1 pooled standard differences and a comparison between propensity scores ≤ 0.1 to account for potential confounding. To assess the covariate balance of cohorts, standardized mean differences (SMDs) were utilized and are presented in the supplementary results. Cohorts with SMD of <0.1 are deemed to indicate a well-matched cohort. Four cohorts were built based on biomarker-specific thresholds. Before analysis, demographics, baseline comorbidities, laboratory data (estimated glomerular filtration rate and creatinine), and medication use were included in the 1:1 PSM.

The association of cardiac biomarkers with primary and secondary outcomes at 5-year follow up was estimated using Cox proportional hazard models and reported as hazard ratio (HR) with 95% confidence intervals. Kaplan–Meier survival curves were used to show survival free from the primary outcome (MACE) and were compared with log-rank test.

Missing data were not imputed due to the restriction of the TriNetX analytical platform; however, complete case-analysis functionality excluded cases with missing data or those lost to follow-up. Patients were censored at the date of their last event in their electronic medical record. In instances where the patient experienced multiple events, analysis focused on first time-event analysis. Statistical analysis was performed using the 'Analytics' functionality on TriNetX, which used the R Survival package v3.2-3. The level of statistical significance was set at $p < 0.05$.

2.6. Exploratory Analyses and Rationale

In order to assess the robustness of the observed study findings, we further investigated the prognostic association of NPs and cardiac troponins on incident MACE based on inclusion of ICD10CM-defined signs and symptoms of HF. These signs included R06.02—shortness of breath; R06.00—dyspnoea, unspecified; R06.09—other forms of dyspnoea; R53.83—other fatigue; R60.0—localized oedema (Supplementary Table S1).

We conducted 3 additional exploratory analyses following a 1:1 PSM, as in the main analysis, to understand:

1. The prognostic significance of NTproBNP and cTnI biomarkers based on inclusion of clinical signs and symptoms of HF.
2. The prognostic value of cardiac biomarkers stratified by female-only cohorts.
3. The prognostic value of a combined biomarker approach.

2.7. Ethical Approval and Data Access

This analysis was conducted on TriNetX platform. Data access can be requested from TriNetX (https://live.trinetx.com/, accessed on 24 February 2024), subject to application costs and a data sharing agreement [13]. Studies utilizing TriNetX do not require ethical approval because no patient-identifiable data are shared.

3. Results

3.1. Cohort Demographics

The initial query on TriNetX platform encompassed data from 114 HCOs across 16 countries (Figure 1). Prior to PSM, there were 184,015 patients with BNP ≥ 35 pg/mL from 64 healthcare organization (HCOs), and 89,743 patients from 61 HCOs with a BNP < 35 pg/mL. Additionally, 58,140 patients from 61 HCOs had NTproBNP ≥ 400 pg/mL and 86,918 patients from 60 HCOs had NTproBNP < 400 pg/mL. There were 198,493 patients from 71 HCOs who had cardiac troponin I ≥ 18 ng/L and 235,375 patients with cardiac troponin I < 18 ng/L. Finally, 50,628 patients from 35 HCOs had cardiac Troponin T ≥ 14 ng/L and 13,141 patients from 30 HCOs with cardiac troponin < 14 ng/L.

3.2. Socio-Demographics and Comorbidities

Table 1 shows the patient demographics and CV risk profile for all the four biomarker cohorts post PSM matching. The initial (pre PSM) cohorts for NTproBNP ≥ 400 pg/mL consisted of 63,359 patients who were older (mean age 71.3 SD 13.9; 52.1% females) with majority 63.5% from a white ethnicity background. Prior to PSM, patients in the NTproBNP ≥ 400 pg/mL had a higher prevalence of hypertensive diseases (73.1%), diabetes mellitus (27.8%), and chronic IHD (24%).

Under specific biomarker cohorts, patients were well matched for age, sex, and ethnicity. The study comprised of 46,164 patients (mean age 68.4 SD 14.1; 51.6% female) for NTproBNP cohorts as shown below while BNP, cardiac troponin I, and T had 80,740, 183,346,

and 13,785 patients respectively. Diabetes mellitus was the most common comorbidity in all the four cohorts.

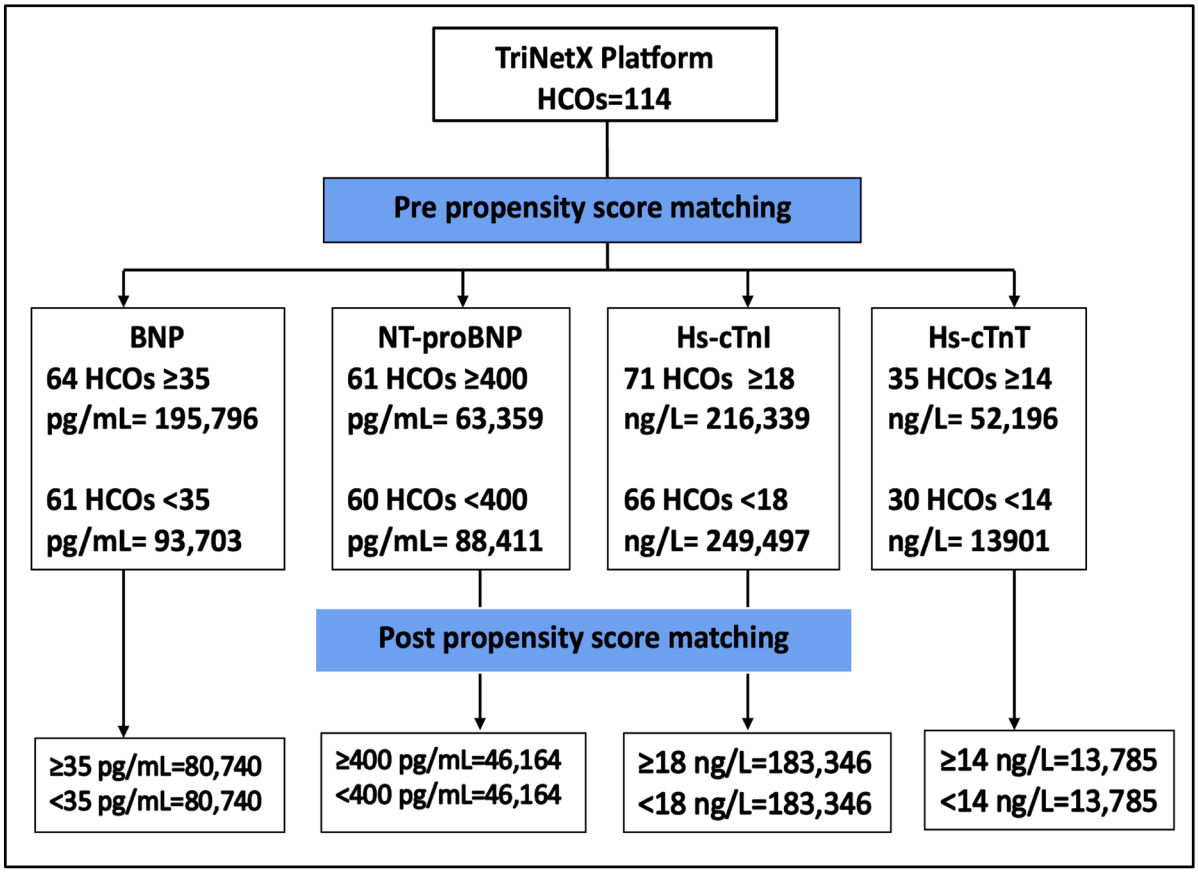


Figure 1. Shows the patient flow and number of patients pre and post PSM in each cohort.

Patient demographic characteristics before and after PSM are shown in the Supplementary Table S2.

3.3. Medications and Laboratory Variables

Table 2 displays the included patients' CV medications and laboratory data. In all the cohorts, beta adrenergic antagonists were the most common medication prescribed followed by ACE inhibitors and aspirin. Baseline kidney function, proteinuria, and BMI were measured across the cohorts. Overall, all cohorts were well balanced. Initial and post-PSM medication and laboratory data is provided in Supplementary Table S2.

3.4. Clinical Outcomes

Figure 2 shows Kaplan–Meier survival curves for the primary composite outcome, stratified by biomarker levels among hypertensive patients with heart failure excluded. The curves illustrate the increased risk of incident MACE and its individual components among the cohorts. Primary and secondary clinical outcomes are summarized in Supplementary Table S3.

Table 1. Patient demographics and cardiovascular risk profile post-propensity score matching for BNP, NT proBNP, and Troponin T and I biomarkers.

	BNP			NT-proBNP			Cardiac Troponin T			Cardiac Troponin I		
Demographics												
Demographics	**≥35 pg/mL**	**<35pg/mL**	**SMD**	**≥400 pg/mL**	**<400pg/mL**	**SMD**	**≥14 ng/L**	**<14 ng/L**	**SMD**	**≥18 ng/L**	**<18 ng/L**	**SMD**
Sample Size	**80,740**	**80,740**		**46,164**	**46,164**		**13,785**	**13,785**		**183,346**	**183,346**	
Age at index mean ± SD	60.5 ± 13.4	60.5 ± 12.5	0.004	68.4 ± 14.1	68.2 ± 12.8	0.018	68.5 ± 14.1	68.1 ± 13.9	0.029	65.5 ± 14.1	65.5 ± 14.1	0.009
Female N (%)	40,740 (50.4%)	40,847 (50.6%)	0.003	23,802 (51.6%)	23,976 (51.9%)	0.008	6359 (46.1%)	6362 (46.2%)	<0.001	86,627 (47.2%)	85,367 (46.6%)	0.014
Black or African American N (%)	19,303 (23.9%)	19,606 (24.3%)	0.009	6307 (13.7%)	6452 (14.0%)	0.009	1074 (7.8%)	1133 (8.2%)	0.016	33,291 (18.2%)	32,184 (17.6%)	0.016
Male N (%)	38,943 (48.2%)	38,798 (48.1%)	0.004	22,242 (48.2%)	22,066 (47.8%)	0.008	7143 (51.8%)	7111 (51.6%)	0.005	94,162 (51.4%)	95,405 (52.0%)	0.014
White N (%)	47,049 (58.3%)	46,793 (58.0%)	0.006	27,796 (60.2%)	27,486 (59.5%)	0.014	6811 (49.4%)	7033 (51.0%)	0.032	108,066 (58.9%)	109,325 (59.6%)	0.014
American Indian or Alaska Native N (%)	207 (0.3%)	180 (0.2%)	0.007	176 (0.4%)	180 (0.4%)	0.001	11 (0.1%)	10 (0.1%)	0.003	648(0.4%)	647 (0.4%)	0.001
Unknown race N (%)	6795 (8.4%)	6776 (8.4%)	0.001	8885 (19.2%)	9149 (19.8%)	0.014	4075 (29.6%)	3776 (27.4%)	0.048	21,811 (11.9%)	21,760 (11.9%)	0.001
Native Hawaiian or Other Pacific Islander	793 (1.0%)	763 (0.9%)	0.004	354 (0.8%)	380 (0.8%)	0.006	92 (0.7%)	96 (0.7%)	0.004	2060 (1.1%)	2028 (1.1%)	0.002
Unknown ethnicity N (%)	10,566 (13.1%)	10,413 (12.9%)	0.006	12,460 (27.0%)	12,672 (68.8%)	0.010	5972 (43.3%)	5590 (40.6)	0.056	36,451 (19.9%)	36,922 (20.1%)	0.006
Not Hispanic or Latino N (%)	62,166 (77.0%)	62,038 (76.8%)	0.004	31,964 (69.2%)	31,771 (68.8%)	0.009	7497 (54.4%)	7867 (57.1%)	0.054	136,611 (74.5%)	136,150 (74.3%)	0.006
Hispanic or Latino N (%)	8008 (9.9%)	8289 (10.3%)	0.012	1740 (33.8%)	1721 (3.7%)	0.002	316 (2.3%)	328 (2.4%)	0.006	10,284 (5.6%)	10,274 (5.6%)	0.001
Other race N (%)	2820 (3.5%)	2857 (3.5%)	0.002	1044 (2.3%)	1025 (2.2%)	0.003	145 (1.1%)	171 (1.1%)	0.018	6929 (3.8%)	6765 (3.7%)	0.005
Asian N (%)	3773 (4.7%)	3765 (4.7%)	<0.001	1602 (3.5%)	1492 (3.2%)	0.013	1577 (11.4%)	1568 (11.4%)	0.002	10,541 (5.7%)	10,637 (5.8%)	0.002

Table 1. *Cont.*

	BNP			NT-proBNP			Cardiac Troponin T			Cardiac Troponin I		
Co-morbidities												
Diabetes mellitus N (%)	20,626 (25.5%)	20,367 (25.2%)	0.007	11,967 (25.9%)	11,924 (25.8%)	0.002	3772 (27.4%)	3774 (27.4%)	<0.001	36,385 (19.8%)	36,010 (19.6%)	0.005
Nicotine dependence N (%)	12,301 (15.2%)	12,039 (14.9%)	0.009	5356 (11.6%)	5304 (11.5%)	0.004	1588 (11.5%)	1593 (11.6%)	0.001	17,777 (9.7%)	17,326 (9.4%)	0.008
Hypertensive diseases (deprecated 2018) N (%)	53,860 (66.7%)	53,618 (66.4%)	0.006	31,796 (68.9%)	31,603 (68.5%)	0.009	9814 (71.2%)	9957 (72.2%)	0.023	103,285 (56.4%)	102,489 (55.9%)	0.010
Atrial fibrillation and flutter N (%)	2439 (3.0%)	2729 (3.4%)	0.020	4288 (9.3%)	4449 (9.6%)	0.012	1726 (12.5%)	1708 (12.4%)	0.004	12,179 (6.6%)	11,890 (6.5%)	0.006
Chronic ischemic heart disease N (%)	11,504 (14.2%)	11,648 (14.4%)	0.005	9360 (20.3%)	9302 (20.1%)	0.003	3301 (23.9%)	3332 (24.1%)	0.005	25,715 (14.0%)	25,218 (13.8%)	0.008
Acute myocardial infarction N (%)	2577 (3.2%)	2617 (3.2%)	0.003	2006 (4.3%)	1970 (4.3%)	0.004	765 (5.5%)	719 (5.2%)	0.015	3896 (2.1%)	3311 (1.8%)	0.023
Angina pectoris N (%)	3783 (4.7%)	3851 (4.8%)	0.004	2169 (4.7%)	2141 (4.6%)	0.003	1137(8.2%)	1137 (8.2%)	0.001	5716 (3.1%)	5546 (3.0%)	0.005
Other chronic obstructive pulmonary diseases N (%)	7671 (9.5%)	7493 (9.3%)	0.008	5283 (11.4%)	5232 (11.3%)	0.003	1490 (10.8%)	1454 (10.5%)	0.008	11,627 (6.3%)	11,508 (6.3%)	0.003

Table shows the demographics and cardiovascular risk factors for all four biomarker cohorts after PSM on age, sex, ethnicity, and comorbidities. SMD, Standardized mean difference.

Table 2. Patients' cardiovascular risk profile post-propensity score matching for BNP, NT-proBNP, and Troponin T and I biomarkers.

	BNP			NT-proBNP			Cardiac Troponin T			Cardiac Troponin I		
Medications												
Demographics	**≥35 pg/mL**	**<35 pg/mL**	**SMD**	**≥400 pg/mL**	**<400 pg/mL**	**SMD**	**≥14 ng/L**	**<14 ng/L**	**SMD**	**≥18 ng/L**	**<18 ng/L**	**SMD**
Beta-adrenergic receptor antagonists N (%)	24,086 (29.8%)	24,196 (30.0%)	0.003	18,003 (39.0%)	17,821 (38.6%)	0.008	5593 (40.6%)	5653 (41.0%)	0.009	51,518 (28.1%))	51,051 (27.8%)	0.006
Calcium channel blockers N (%)	18,854 (23.4%)	18,898 (23.4%)	0.001	13,227 (28.7%)	12,894 (27.9%)	0.016	4666 (33.8%)	4691 (34.0%)	0.004	36,262 (19.8%)	36,065 (19.7%)	0.003
ACE Inhibitors N (%)	21,515 (26.6%)	21,625 (26.8%)	0.003	12,513 (27.1%)	12,205 (26.4%)	0.015	3978 (28.9%)	3925 (28.5%)	0.009	38,893 (21.2%)	38,488 (21.0%)	0.005

Table 2. *Cont.*

	BNP			NT-proBNP			Cardiac Troponin T			Cardiac Troponin I		
Other Antihypertensive N (%)	11,162 (13.8%)	11,197 (14.1%)	0.005	7986 (17.3%)	8047 (17.4%)	0.003	2133 (15.5%)	2154 (15.6%)	0.004	23,136 (12.6%)	23,021 (12.6%)	0.002
Angiotensin II inhibitors N (%)	11,162 (13.8%)	11,197 (13.9%)	0.001	7548 (16.4%)	7340 (15.9%)	0.012	2647 (19.2%)	2646 (19.2%)	0.001	21,022 (11.5%)	20,834 (11.4%)	0.003
Alpha blockers N (%)	5653 (7.0%)	5707 (7.1%)	0.003	4290 (9.3%)	4153 (9.0%)	0.010	1718 (12.5%)	1719 (12.5%)	0.001	11,882 (6.5%)	11,814 (6.4%)	0.002
Clopidogrel N (%)	4601 (5.7%)	4670 (5.8%)	0.004	3851 (8.3%)	3697 (8.0%)	0.012	1438 (10.4%)	1455 (10.6%)	0.004	9352 (5.1%)	9204 (5.0%)	0.004
Aspirin N (%)	20,528 (25.4%)	20,751 (25.7%)	0.006	14,465 (31.2%)	14,164 (30.7%)	0.014	5077 (36.8%)	5000 (36.3%)	0.012	38,576 (21.0%)	38,223 (20.8%)	0.005
Antilipemic agents N (%)	25,500 (31.6%)	25,431 (31.5%)	0.002	16,996 (36.8%)	16,475 (35.7%)	0.023	5456 (39.6%)	5461 (39.6%)	0.001	48,633 (26.5%)	48,203 (26.3%)	0.005
Laboratory												
Glomerular Filtration Rate N (%)	53,027 (65.7%)	52,602 (65.1%)	0.038	28,942 (62.7%)	28,685 (62.1%)	0.050	9488 (68.8%)	9454 (68.6%)	0.041	98,904 (53.9%)	98,245 (53.6%)	0.066
15–29 mL/min/1.73 m^2	2303 (2.9%)	2363 (2.9%)	0.004	2542 (5.5%)	2451 (5.3%)	0.009	986 (7.2%)	967 (7.0%)	0.005	6928 (3.8%)	6502 (3.5%)	0.012
30–59 mL/min/1.73 m^2	18,911 (23.4%)	18,766 (23.2%)	0.004	14,785 (32.0%)	14,849 (32.2%)	0.003	4887 (35.5%)	4785 (34.7%)	0.016	41,342 (22.5%)	41,006 (22.4%)	0.004
60–89 mL/min/1.73 m^2	40,984 (50.8%)	40,667 (50.4%)	0.008	22,290 (48.3%)	21,922 (47.5%)	0.016	7256 (52.6%)	7372 (53.5%)	0.017	71,225 (38.9%)	70,873 (38.7%)	0.005
90–0 mL/min/1.73 m^2	29,924 (37.1%)	29,992 (37.1%)	0.002	14,177 (30.7%)	13,798 (29.9%)	0.018	4842 (35.1%)	4926 (35.7%)	0.013	46,320 (25.3%)	15,599 (24.9%)	0.009
0–15 mL/min/1.73 m^2	4437 (5.5%)	4449 (5.5%)	0.001	1246 (2.7%)	1156 (2.5%)	0.012	331 (2.4%)	342 (2.5%)	0.005	9717 (5.3%)	9173 (5.0%)	0.013
BMI	4855 (6.0%)	4835 (6.0%)	0.165	10,079 (21.8%)	11,146 (24.1%)	0.238	3593 (26.1%)	3888 (28.2%)	0.095	51,701 (28.2%)	48,347 (26.4%)	0.045
0–18.5 kg/m^2	1467 (1.8%)	1125 (1.4%)	0.034	775 (1.7%)	555 (1.2%)	0.040	346 (2.5%)	424 (3.1%)	0.034	2985 (1.6%)	2054 (1.1%)	0.044

Table 2. *Cont.*

	BNP			NT-proBNP			Cardiac Troponin T			Cardiac Troponin I		
18.5–24.9 kg/m^2	7654 (9.5%)	6572 (8.1%)	0.047	3658 (7.9%)	3099 (6.7%)	0.047	1304 (9.5%)	1309 (9.5%)	0.001	17,801 (9.7%)	15,234 (8.3%)	0.049
25-29.9 kg/m^2	10,969 (13.6%)	11,777 (14.6%)	0.029	4893 (10.6%)	5466 (11.8%)	0.039	1845 (13.4%)	2044 (14.8%)	0.041	23,624 (12.9%)	22,683 (12.4%)	0.015
30–0 kg/m^2	14,041 (17.4%)	16,802 (20.8%)	0.087	5129 (11.1%)	6633 (14.4%)	0.098	1838 (13.3%)	2173 (15.8%)	0.069	25,081 (13.7%)	23,921 (13.0%)	0.019

Table 2 shows cardiovascular risk factors for all four biomarker cohorts following PSM on CV medications, kidney function, and body-mass index (BMI). SMD, Standardized mean difference.

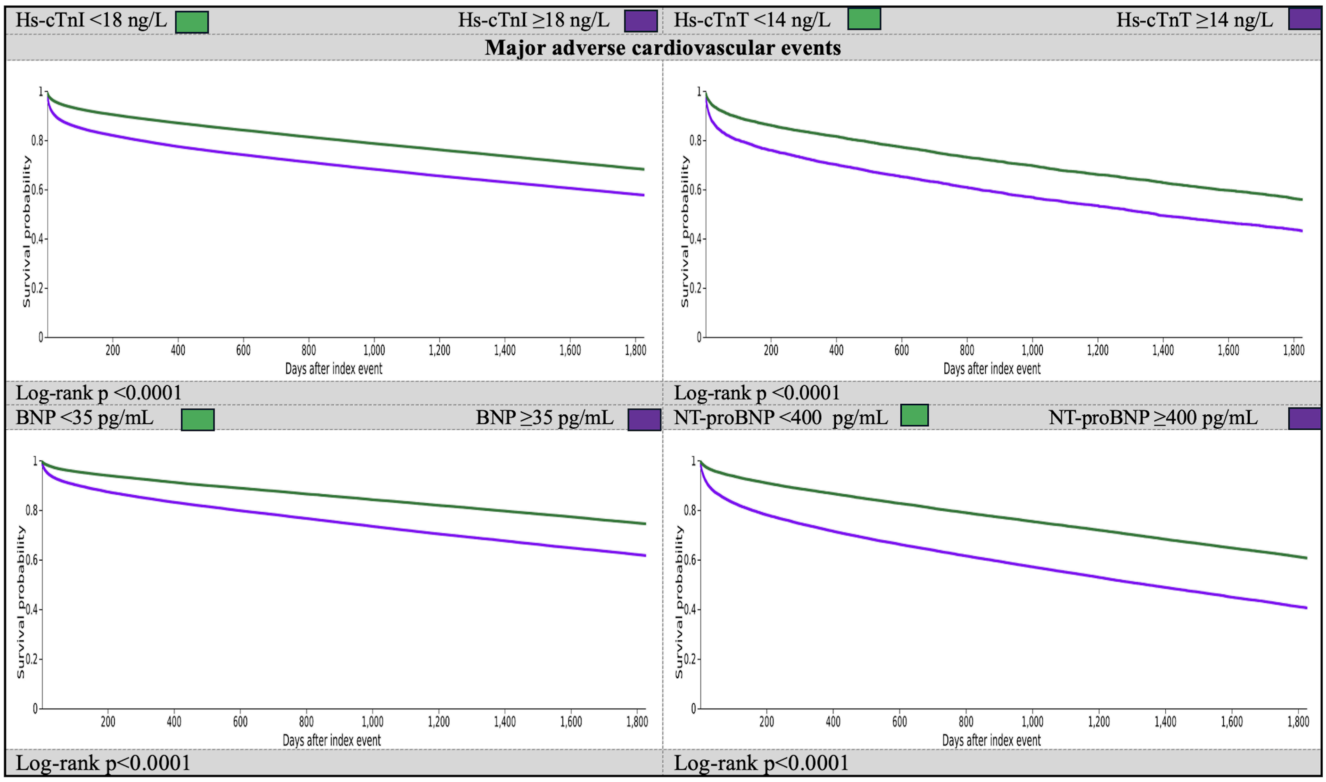


Figure 2. Shows Kaplan–Meier survival analysis for the primary outcome (MACE) by each biomarker.

3.5. NT-proBNP/BNP

Of the patients with NTproBNP ≥ 400 pg/mL, 14,284 developed the primary outcome of incident MACE with (HR of 1.9, 95% CI 1.86, 1.96 $p < 0.001$). For secondary outcomes, NTproBNP biomarker was associated with an increased risk of all-cause mortality (HR 2.13 95% CI 2.07, 2.18 $p < 0.001$), CVA (1.14 95% CI 1.07, 1.22 $p < 0.028$), HF (1.57 95% CI 1.49, 1.65 $p < 0.001$), AF (HR 1.72 95% CI 1.64, 1.80 $p < 0.001$), AHF (HR 2.25 95% CI 2.02, 2.50 $p < 0.001$), and LVEF < 40% (HR 2.52 95% CI 2.11, 3.01 $p < 0.007$). AMI (HR 1.52 95% CI 1.42, 1.62 $p < 0.058$) was not statistically significant in this analysis.

In the BNP ≥ 35 pg/mL cohort, 19,542 (31.4%) developed the primary outcome MACE with HR of 1.70, 95% CI 1.67, 1.74 $p < 0.0001$). For secondary outcomes, BNP was associated with a statistically significant increase in all-cause mortality (HR 1.97 95% CI 1.92, 2.02 $p < 0.001$), CVA (HR 1.24 95% CI 1.18, 1.30 $p < 0.008$), HF (HR 1.71 95% CI 1.63, 1.78 $p < 0.001$), AMI (HR 1.36 95% CI 1.29, 1.42 $p < 0.0001$), and AF (HR 1.78 95% CI 1.71, 1.86 $p < 0.001$) The secondary outcomes of AHF (HR 2.33 95% CI 2.07, 2.62 $p = 0.17$) and LVEF < 40% (HR 1.88 95% CI 1.68, 2.12 $p = 0.70$) did not reach statistical significance.

3.6. Cardiac Troponins T and I

Patients with cTnT ≥ 14 ng/L, 3217 (47%) developed the primary outcome MACE with (HR of 1.53 95% CI 1.46, 1.61 $p < 0.001$). For secondary outcomes, cTnT was associated with a statistically significant increased risk of all-cause mortality (HR 1.40 95% CI 1.34, 1.47 $p < 0.001$), AMI (HR 1.47 95% CI 1.33, 1.63 $p < 0.001$), CVA (HR 1.06 95% CI 0.95, 1.17 $p < 0.026$), and LVEF < 40% (HR 1.71 95% CI 1.34, 2.18 $p < 0.001$). HF (HR 1.08 95% CI 0.99, 1.18 $p = 0.50$), AF (HR 1.06 95% CI 0.97, 1.16 $p = 0.11$), and AHF (HR 0.94 95% CI 0.75, 1.18 $p = 0.30$) were not statistically significant. Similarly, of the patients with cTnI ≥ 18 ng/L, 39,124 (35%) developed the primary outcome of MACE with HR 1.52 95% CI 1.50, 1.54 $p < 0.0001$). cTnI was associated with a statistically significant increased risk of other secondary outcomes apart from CVA (HR 1.01 95% CI 0.98, 1.04 $p = 0.09$).

3.7. Exploratory Analysis: Signs and Symptoms of HF

In this analysis, we explored the risk of CV outcomes based on the inclusion of signs and symptoms of HF, but where heart failure has been excluded. Patient demographics and cardiovascular risk profile pre and post PSM are shown in Supplementary Table S4. In the BNP ≥ 35 pg/mL cohort, the primary outcome MACE had an HR of 1.71, (95% CI 1.67, 1.74 $p < 0.001$). Both NT-proBNP ≥ 400 pg/mL and cTnT ≥ 14 ng/L were associated with the primary outcome MACE (HR 2.06, 95% CI 1.99, 2.14 and HR 1.42, 95% CI 1.34, 1.51; $p < 0.001$), while cTnI was excluded due to insufficient sample size. Secondary outcomes are summarized in Figure 3.

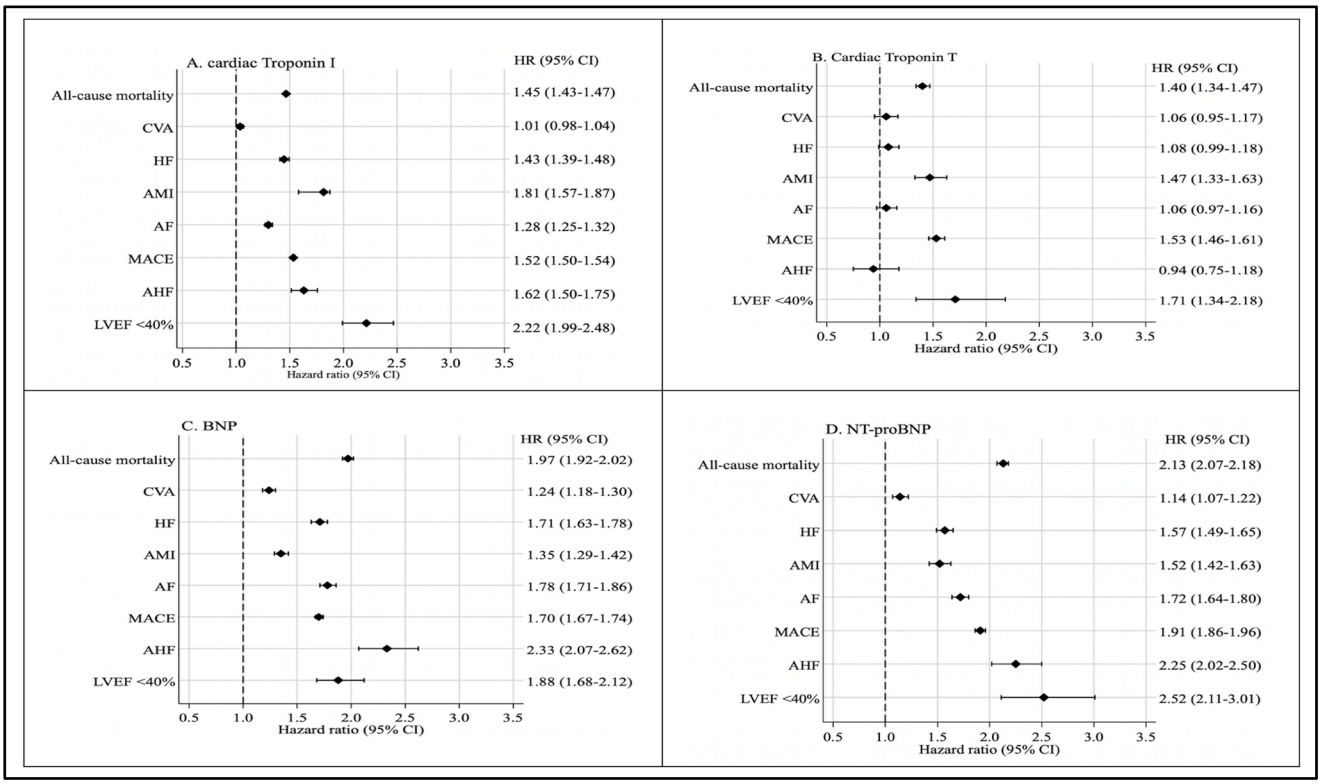


Figure 3. Hazard ratios (95% CI) for all-cause mortality, MACE, and individual cardiovascular outcomes: (**A**) cardiac troponin I, (**B**) cardiac troponin T, (**C**) BNP, (**D**) NT-proBNP.

3.8. Exploratory Analysis in Females Only

We explored the risk of CV outcomes among a female-only cohort based on the exclusion of HF. Patient demographic characteristics prior and after PSM are shown in Supplementary Table S5. Within the BNP ≥ 35 pg/mL and NT-proBNP ≥ 400 pg/mL cohorts, both were associated with the primary outcome MACE (HR 1.65, 95% CI 1.60, 1.71; and HR 1.97, 95% CI 1.90, 2.04; $p < 0.001$) respectively. Similarly, cTnT ≥ 14 ng/L and cTnI ≥ 18 ng/L were associated with MACE (HR 1.57, 95% CI 1.46, 1.68 and HR 1.54, 95% CI 1.50, 1.57; $p < 0.001$). Further clinical outcomes are summarized in Figure 4.

3.9. Exploratory Analysis: Combined Biomarkers

Further analysis evaluated the risk of CV outcomes associated with combined BNP and Troponin 1 levels, with both biomarkers greater than their respective thresholds. For the primary composite outcome, elevations in both biomarkers was associated with an HR 2.74, 95% CI 2.17, 3.46, $p < 0.0001$. In addition, combining NTproBNP and Troponin T resulted in an HR of 2.32, 95% CI 2.02, 2.66, $p < 0.0001$ for the primary composite outcome.

A similar association among secondary outcomes was observed. Further details may be found in Supplementary Table S6.

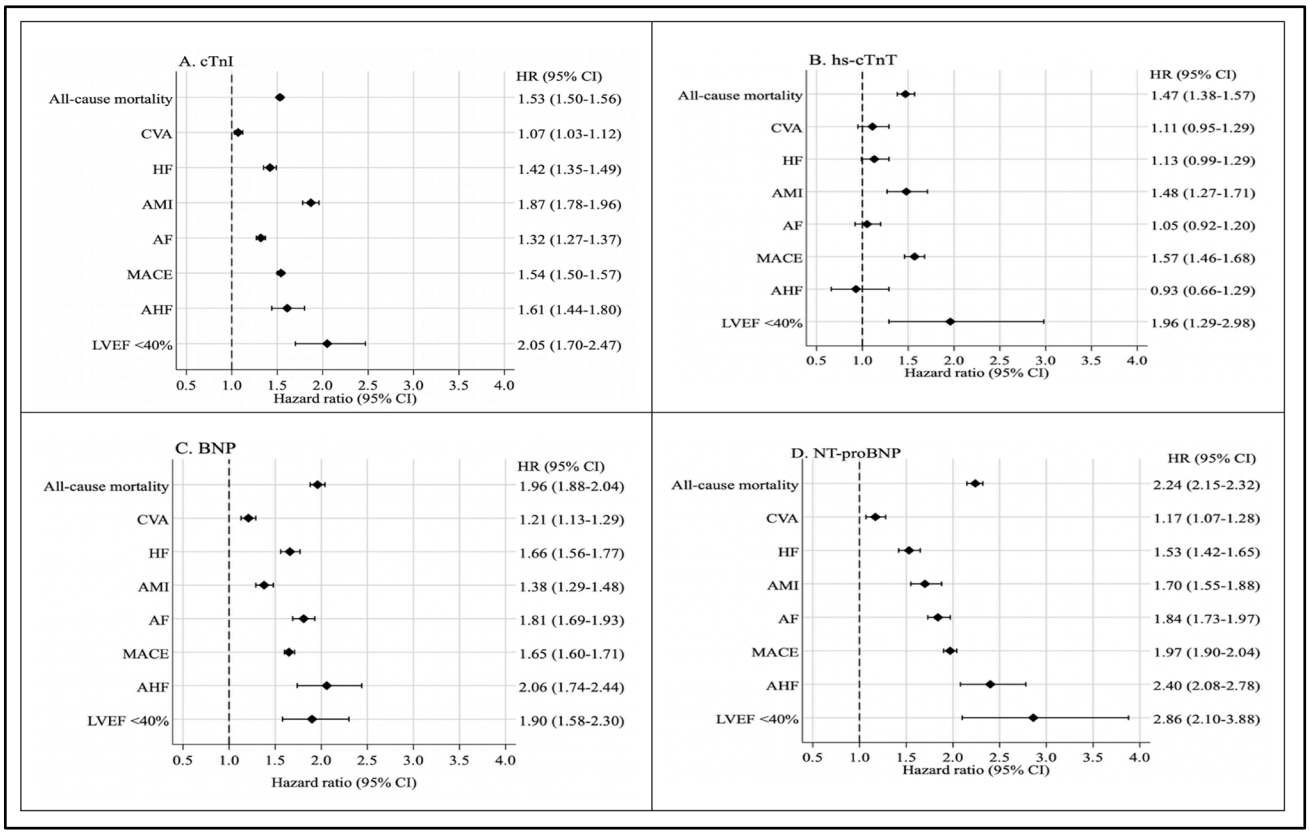


Figure 4. Hazard ratios (95% CI) for all-cause mortality, MACE, and individual cardiovascular outcomes over 5-year follow up stratified among female-only cohort: (**A**) cardiac troponin I, (**B**) cardiac troponin T, (**C**) BNP, (**D**) NT-proBNP.

4. Discussion

The results from this global multicenter, retrospective cohort study indicates that elevated natriuretic peptides and cardiac troponin in hypertensive patients, without HF, were associated with an increased risk of MACE and its individual components. Our analysis highlights that routine clinical laboratory cardiac biomarkers (BNP/NTproBNP and cardiac troponin T and I), frequently utilized in clinical practice, can predict incident MACE in patients with hypertension including after excluding HF. Prior studies [19–21] have evaluated the prognostic role of NPs and cardiac troponins in HF and acute coronary syndromes. However, their predictive role to identify incident MACE in patients with hypertension without HF (based on available data) has not been comprehensively addressed, particularly in a large patient cohort.

In the present study, hypertensive patients, with HF excluded, and elevated NT-proBNP levels had a 1.9-fold increased risk of MACE and 2.1-fold increased risk of all-cause mortality over a 5-year period. The second highest risk was observed in patients with BNP $\geq$ 35 pg/mL with corresponding 1.7-fold and 1.97-fold increases in the risk of MACE and all-cause mortality respectively. Although cardiac troponin T and I were significant predictors of MACE and all-cause mortality, their predictive value was lower compared for NT proBNP and BNP. Increased predictive value of NPs over cardiac troponins in hypertension is likely related to ventricular wall stress and volume overload, unlike cardiac troponins, which primarily indicate myocardial injury, although there seems to be added benefit to a combined biomarker approach. Similar findings were observed in a meta-analysis on

BNP/NT-proBNP prognosis in patients with and without HF involving 66 studies with overall 83 846 patients which revealed that an increase in NPs by one SD was associated with a 1.7-fold higher MACE rate (HR 1.74 CI 1.58–1.91, $p < 0.01$) [22] revealing that this relationship remains robust despite differences in cohort populations. Furthermore, most MACE began to occur within the first 200 days of follow-up across the four cardiac biomarkers, although the excess risk persisted beyond this period (Figure 2). This pattern is consistent with the high short-term risk associated with elevated cardiac biomarkers. A similar pattern is apparent in the Kaplan–Meier curves of patients with glomerulonephritis, in whom troponin I ≥ 18 ng/L and NT-proBNP ≥ 400 pg/mL were associated with MACE over 5 years (HR 1.79, 95% CI 1.70–1.88, and HR 1.99, 95% CI 1.86–2.14, respectively) [23].

When considering biomarkers for CV risk assessment, NPs and cardiac troponin predictive value can be affected by multiple factors including age, sex, ethnicity genetic variations, and cardiac/non-cardiac disorders [21]. In our exploratory analysis of the female-only cohort, we observed strong associations in both primary and secondary outcomes. Previous studies have shown sex differences in CV biomarker in general populations [24–26]. However, a similar finding in this cohort not only highlights the need for sex-specific thresholds to provide equivalent CV risk prediction, but also for approaches that target women who may be missed by conventional risk assessment. Cardiac troponin T and I are established biomarkers for myocardial infarction (AMI), acute coronary syndromes (ACS), and non-ACS myocardial injury [27]. Cardiac Troponin elevation suggests myocardial injury due to chronic hypertension and left ventricular hypertrophy. Their elevation with NPs are a sign of multifactorial underlying diseases that is linked to poorer patient outcomes [28]. Therefore, if raised in hypertensive patients without HF above the thresholds further diagnostic evaluation and preventive treatments should be made early to improve prognosis. However, biomarker validated cutoff levels in non-HF remain uncertain [28].

Elevated cardiac troponin levels have also been reported in healthy individuals who do not have CVD risk factors [29–31] with NPs showing that they can be utilized in early stages of hypertension diagnosis to detect hypertension-mediated organ damage [32]. Our study confirms, in a large study population reflective of real-world clinical use, that cardiac troponins and NPs readily available laboratory tests, provide valuable results that can complement further cardiovascular risk prediction in patients with hypertension. Furthermore, beyond risk prediction of MACE and mortality as observed in our PSM analysis, this prognostic information could be used to stage hypertensive heart disease. A concept recently examined in the prospective REMODEL study [33], in which NT-proBNP and hs-cTnT identified individuals with essential hypertension who had more advanced cardiac remodeling and a higher risk of cardiovascular events, with the greatest risk when both biomarkers were elevated. Our findings show that these prognostic associations also hold in a large, real-world population with hypertension, supporting further evaluation of biomarker-based staging in routine clinical practice.

Strengths and Limitations

This propensity score-matched analysis of a large retrospective cohort examined the prognostic significance of four cardiac biomarkers routinely measured in clinical practice. It used real world electronic medical records (EHR) from over 114 participating healthcare organizations across the globe. Despite these strengths, several limitations should be considered when interpreting the results.

The major limitation of this study is its retrospective design that relies on EMRs from HCOs, which can have data gaps and entry errors.

Furthermore in TriNetX, biomarker type and values are standardized through Logical Observation Identifiers Names and Codes (LOINCs); however, the specific assay platforms

and institutional reference ranges are not provided. In our analysis, cardiac troponin assays included were all categorized as high-sensitivity assays, although it is not possible to ascertain the manufacturer. While this variability in assay methods may introduce heterogeneity in biomarker measurements, it is unlikely to influence the observed effect in the outcomes. In addition, clinical laboratory assays (for natriuretic peptides and high-sensitivity cardiac troponin) are all traceable to international standards and clinical laboratories are required to participate in internal and external quality control schemes to provide re-assurance of the reproducibility and consistency of results between providers.

As with any observational study, residual confounding cannot be excluded despite 1:1 PSM. TriNetX database does not record indications for testing, and we cannot exclude that some patients were tested because of symptoms or clinical suspicion of cardiac disease. Other unmeasured factors including social determinants of health (SDoH), lifestyle factors, and other clinical characteristics may have contributed. Finally, the lack of linked echocardiographic data restricted our analysis to biomarker-based risk assessment.

5. Conclusions

Elevated NPs and cardiac troponins in hypertensive patients, where HF has been excluded, demonstrate a significant risk of MACE and its individual components. Further prospective validation is warranted to evaluate the prognostic significance of these biomarkers in this specific population.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/labmed3040026/s1. Table S1: ICD 10 CM codes used; Table S2: Patient demographics and cardiovascular risk factor profile pre and post propensity score matching; Table S3: Survival analysis among biomarker cohorts; results for troponin I and T, BNP and NT proBNP; Table S4: Patient demographics and cardiovascular risk factor profile pre and post PSM based on signs and symptoms of HF; Table S5; Patient demographics and cardiovascular risk factor profile pre and post PSM-Females only cohort; Table S6: Exploratory Survival Analysis amongst combined biomarker cohort.

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