Current Science
CS 6 (2), 6128-6179 (2026)
Received 24 February 2026 | **Accepted 31 March** 2026 | **Online Available 03 April** 2026
https://doi.org/10.52845/CS/2026-6-2-10

Current Science

Current Science

OPEN ACCESS

ISSN (O) 2795-8639

Original Article

Global Pharmacovigilance Analysis of Epirubicin-Associated Cardiotoxicity: Real-World Insights from FAERS and EudraVigilance Databases (2004–2025)

Hong Seng An[1#], Nouth Nita[1#], Nan Luo[2*], Qionglin Huang[2*], Pengkhun Nov[2*]

[1]School of international Education, Southern Medical University

[2]Oncology Center, Zhujiang Hospital, Southern Medical University, No.253 Mid Gongye Ave, Haizhu District, Guangzhou, Guangdong Province, Postal code 510282, China

#*Contributed Equally

***Corresponding Author: Dr. Nan Luo, Dr. Qionglin Huang, Dr. Pengkhun Nov**

Abstract:

Background: Epirubicin is a cornerstone of chemotherapy, yet its dose-limiting cardiotoxicity remains a significant clinical challenge. This study aimed to characterize the real-world cardiac safety profile of epirubicin using global pharmacovigilance databases.

Methods: We performed a retrospective analysis of the FDA Adverse Event Reporting System (FAERS) (2004–2025) and validated findings using the EudraVigilance (EV) database (2003–2025). Disproportionality was assessed using ROR, PRR, IC, and EBGM algorithms. Time-to-onset (TTO) and clinical outcomes were systematically evaluated.

Results:Analysis of the FAERS and EudraVigilance databases (2004–2025) revealed a rising trend in epirubicin-associated cardiotoxicity, peaking in recent years with a marked female predominance (up to 87.56%) and high clinical severity (99.22% serious). Signal mining confirmed robust associations with heart failure (ROR=6.60) and dilated cardiomyopathy (ROR=34.97), with the highest intensities observed for heart failure with mid-range ejection fraction (ROR=406.37). Median time-to-onset was 36 days, though males experienced significantly faster onset than females (22 vs. 49 days). Age-stratified analysis identified specific vulnerabilities, notably dilated cardiomyopathy in pediatric patients and left ventricular dilatation in the elderly. External validation across both databases identifies epirubicin as a sustained, independent risk factor for diverse and severe cardiac adverse events.

Conclusion: Epirubicin-associated cardiotoxicity is characterized by early-onset, high-severity events with distinct sex and age-specific risk profiles. Intensive cardiac monitoring, particularly within the first 40 days of treatment, is critical for high-risk cohorts.

Keywords: Epirubicin;Cardiotoxicity;Pharmacovigilance;FAERS;EudraVigilance;Disproportionality analysis

Introduction

Anthracyclines, particularly epirubicin, remain indispensable in the treatment of diverse malignancies, including breast, gastric, and hematological cancers123. However, the clinical utility of epirubicin is frequently hampered by anthracycline-induced cardiotoxicity (AIC), which ranges from subclinical myocardial injury to fatal congestive heart failure45. Unlike the reversible "Type II" cardiotoxicity associated with targeted therapies, epirubicin-induced damage is predominantly "Type I," characterized by irreversible cardiomyocyte loss through

topoisomerase II β inhibition and mitochondrial oxidative stress678.

Despite decades of clinical use, our understanding of the real-world "spatiotemporal" evolution of epirubicin's cardiac risks remains incomplete. Most existing studies are limited by small sample sizes or short follow-up durations. Furthermore, as the field of cardio-oncology matures, there is an urgent need to identify specific demographic "vulnerability windows" and phenotypic variations that may not be captured in tightly controlled clinical trials.

The emergence of large-scale spontaneous reporting systems, such as the US FDA Adverse Event Reporting System (FAERS) and the European EudraVigilance (EV) database, provides a unique opportunity to conduct "big data" surveillance9. These repositories allow for the detection of rare but severe signals and the analysis of real-world reporting trends over prolonged periods.

In this study, we integrated data from both FAERS (2004–2025) and EV (2003–2025) to provide a comprehensive mapping of epirubicin-associated cardiotoxicity. By utilizing multiple disproportionality algorithms and stratified analyses, we aimed to: (1) delineate temporal reporting trends and demographic characteristics; (2) quantify the strength of associations for specific cardiac phenotypes; and (3) evaluate the impact of sex and age on the onset and severity of cardiac injury. These findings are intended to refine cardiac monitoring strategies and support personalized risk management in cancer patients receiving epirubicin.

2. Methods

2.1 Data Sources and Study Population

In this study, we conducted a global, retrospective pharmacovigilance analysis to evaluate the cardiotoxic risks associated with epirubicin. Primary data were extracted from the United States Food and Drug Administration Adverse Event Reporting System (FAERS), spanning the period from 2004 to 2025. To enhance the robustness of our findings and control for regional reporting variations, we utilized the EudraVigilance (EV) database (2003–2025) as an independent external validation cohort. The analysis was strictly restricted to spontaneous reports where epirubicin was identified as the "primary suspect" medication to ensure a focused assessment of its toxicological impact.

2.2 Case Definition and Data Cleansing

Adverse events (AEs) were standardized according to the Medical Dictionary for Regulatory Activities (MedDRA, version 27.0). Cardiotoxicity was defined using a specific cluster of Preferred Terms (PTs) within the Cardiac disorders System Organ Class (SOC), ranging from functional impairments like "Cardiac failure" and "Heart failure with reduced ejection fraction" (HFrEF) to structural pathologies such as "Left ventricular dilatation." To maintain data integrity, a comprehensive deduplication process was implemented to remove redundant reports by cross-referencing case identifiers including age, sex, event date, and reporting country.

2.3 Demographic Characterization and Time-to-Onset (TTO) Analysis

We systematically characterized the demographic landscape of epirubicin-related cardiac events, focusing on sex distribution, age cohorts (18–64 years vs. ≥65 years), and reporter qualification. Time to Onset (TTO) was calculated as the duration from the start of epirubicin administration to the manifestation of the first cardiac event. Given the typical non-normal distribution of such data, TTO was expressed as medians with interquartile ranges (IQR). The Wilcoxon rank-sum test (Mann-Whitney U test) was utilized to statistically compare the onset latency between male and female patients, with a significance threshold of $P < 0.05$.

2.4 Signal Detection and Disproportionality Analysis

To quantify the statistical association between epirubicin and cardiac adverse events, four distinct disproportionality algorithms were employed: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Information Component (IC), and Empirical Bayes Geometric Mean (EBGM).A signal was considered statistically significant only when established thresholds were met (ROR 95% CI lower bound > 1 with case count (N)≥3; PRR ≥2 with x^2≥4; IC 95% CI lower bound (IC_{025}) > 0; and EBGM 90% CI lower bound ($EBGM_{05}$) > 2)10111213.

2.5 Subgroup and Clinical Severity Analysis

Differential risk profiles were explored through stratified analyses across gender and age dimensions. We utilized ROR comparisons to identify specific cardiac phenotypes that were over-reported in certain subgroups (e.g., structural vs. functional injuries in the elderly). Furthermore, the clinical severity of each identified signal was evaluated by analyzing patient outcomes, specifically focusing on serious events such as hospitalization, life-threatening conditions, or death. Statistical differences in outcome severity were assessed using Fisher's exact test, with P-values adjusted for multiple comparisons to maintain a rigorous False Discovery Rate (FDR).

3. Results

3.1 Descriptive Characteristics and Temporal Trends (FAERS)

A longitudinal analysis of the FAERS database from 2004 to 2025 identified a fluctuating but overall upward trajectory in epirubicin-associated cardiotoxicity reports, peaking in 2020 (n=109)(Figure 1).

Demographic data revealed a significant female predominance, accounting for 79.26% (n=711) of cases, while males represented 10.14% (n=91)(Figure 2A). The age distribution was centered on the 45–64 cohort (42.14%), followed by geriatric patients (≥ 65 years, 22.52%)(Figure 2B).Reporting was largely driven by healthcare professionals, with physicians and pharmacists contributing 41.92% and 25.86% of submissions, respectively(Figure 2C). Clinical severity was exceptionally high; 99.22% (n=890) of reports were classified as serious(Figure 2D), involving hospitalization in 40.8% of cases and a mortality rate of 13.94%(Figure 3). Temporal analysis showed that 19.96% (n=179) of events occurred within the first 30 days of treatment initiation(Figure 4).

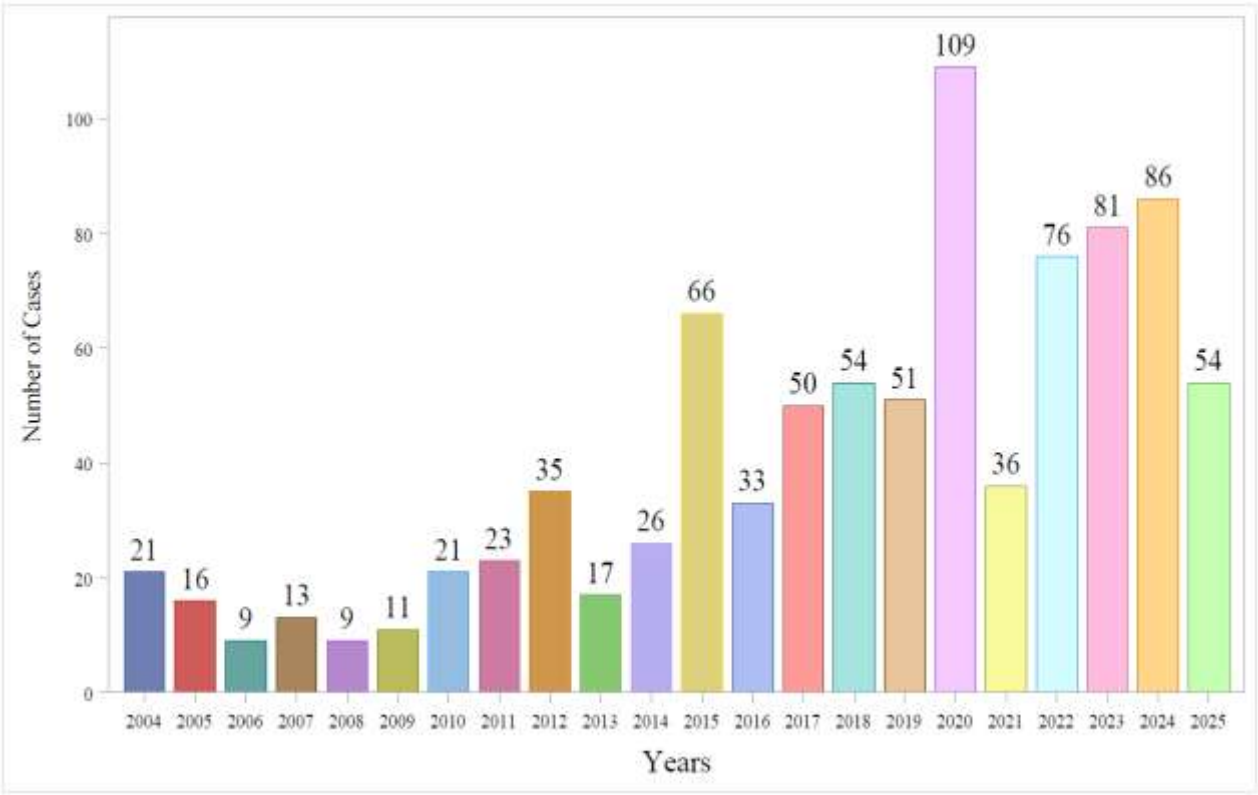
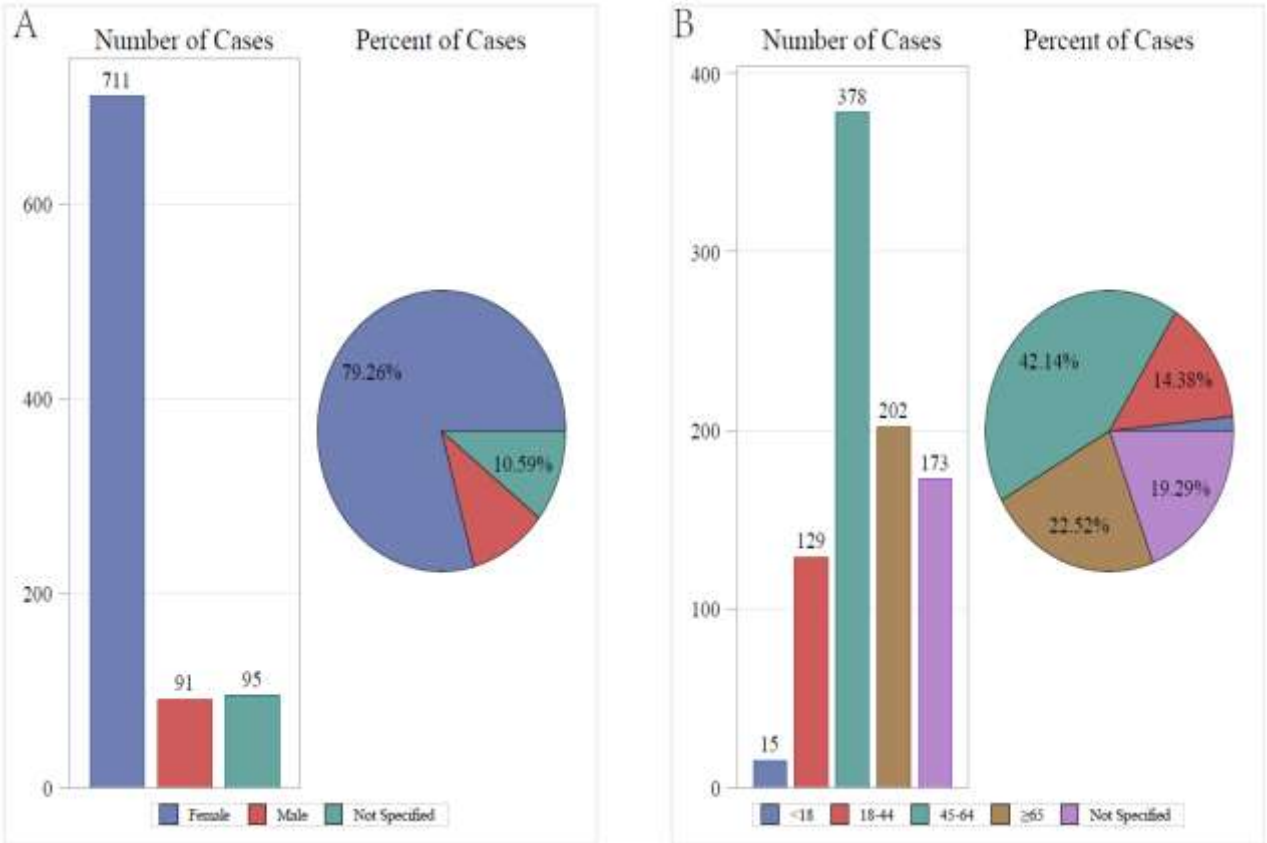


Figure 1: Annual Distribution of AE Reports



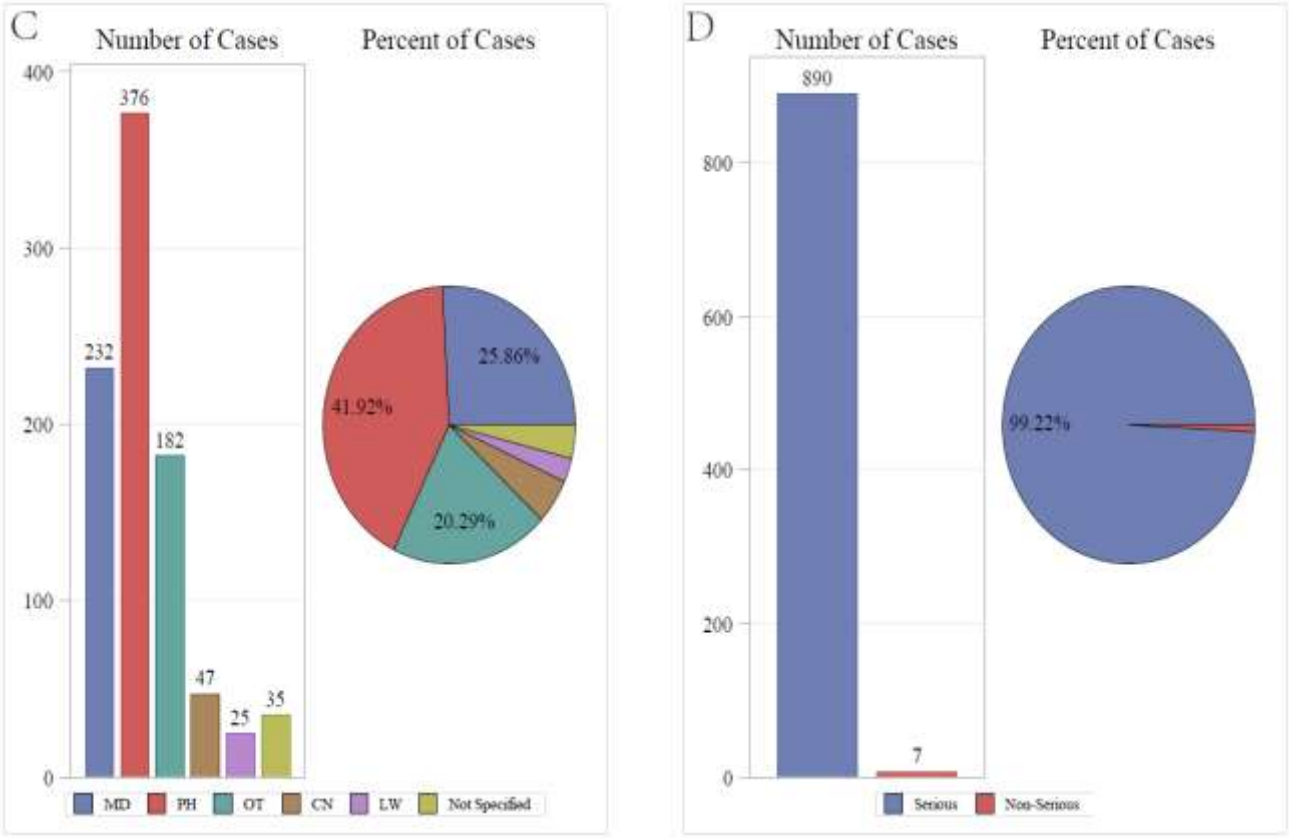


Figure 2: Distribution of AE Reports by (A) Sex, (B) Age, (C) Reporter Type, and (D) Seriousness

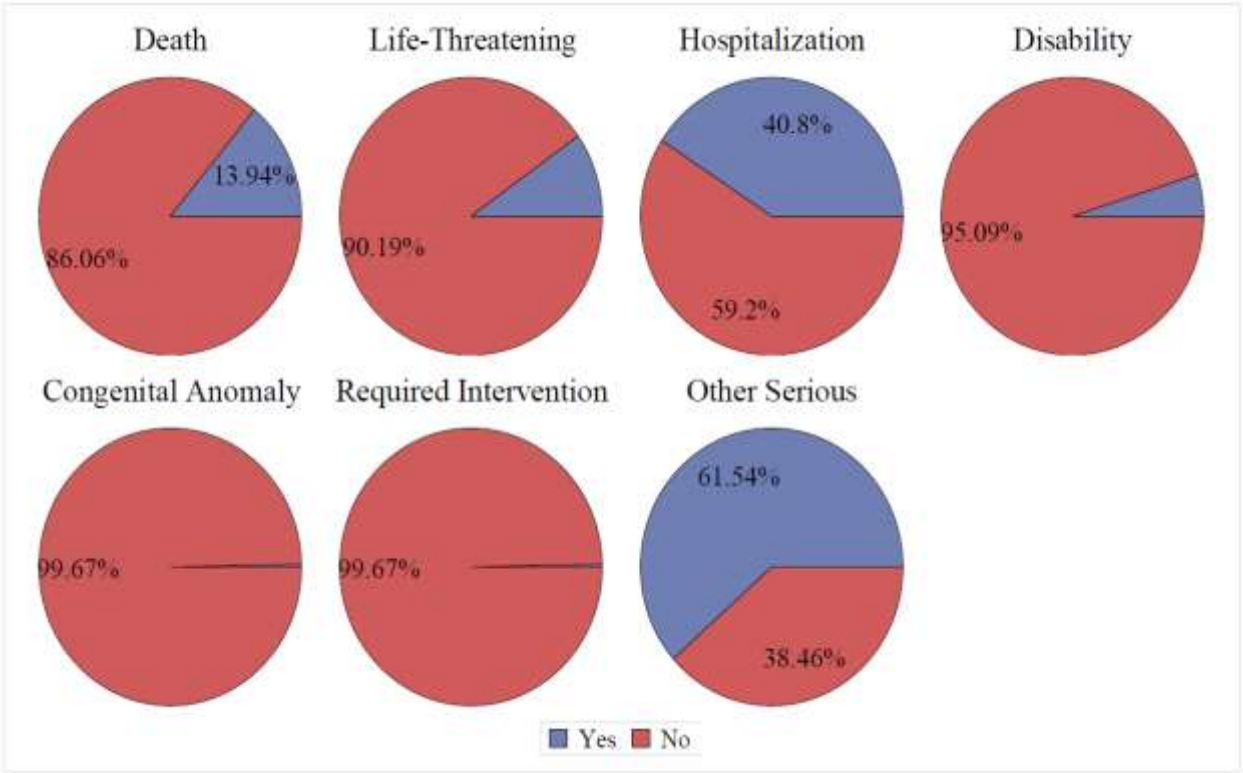


Figure 3: Distribution of Adverse Outcome Reports

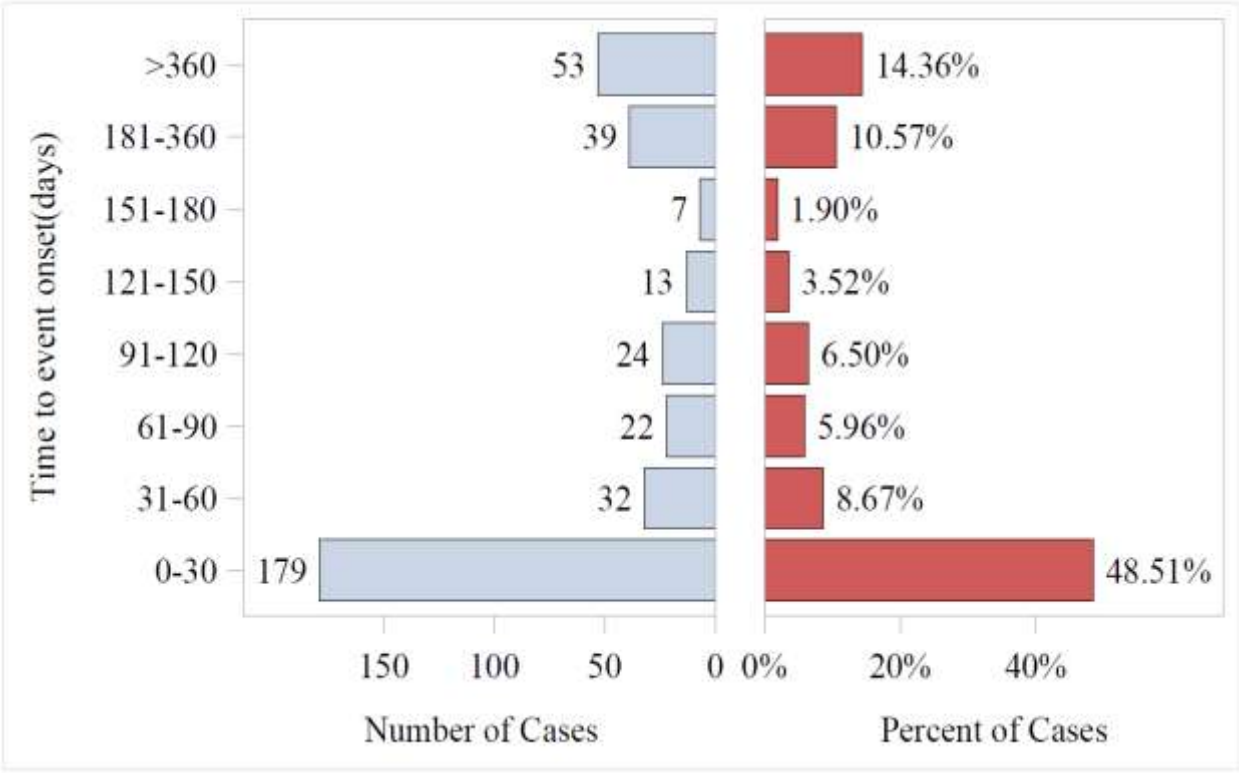


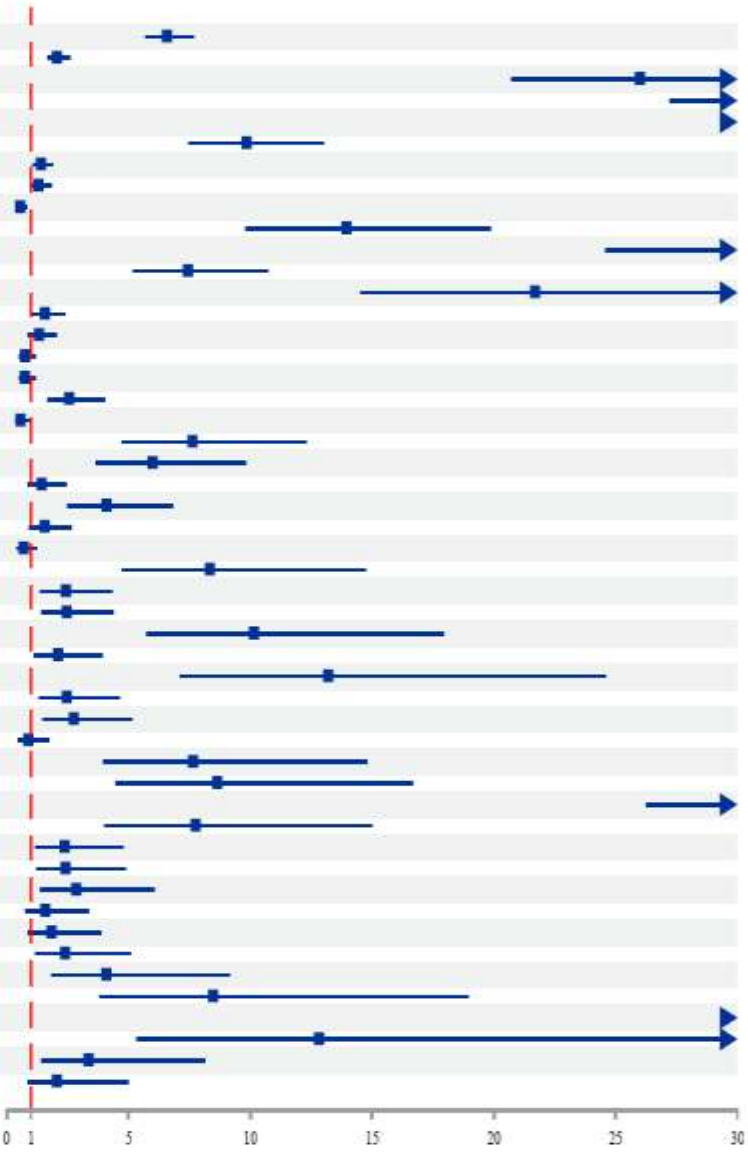
Figure 4: Distribution of Time-to-Onset for AE Reports

3.2 Signal Detection and Disproportionality Analysis (FAERS)

Signal mining established a robust statistical association between epirubicin and cardiac adverse events (AEs). Heart failure was the most frequently reported Preferred Term (PT) (N=178, ROR=6.60, 95% CI: 5.69-7.65), followed by cardiotoxicity (N=75, ROR=26.02) and dilated cardiomyopathy (N=62, ROR=34.97)(Figure 5A).The highest signal intensities were observed for specific PTs, including heart failure with mid-range ejection fraction (ROR=406.37), immune-mediated pericarditis (ROR=219.20), and endocardial fibrosis (ROR=163.32)(Figure 5A). The median time-to-onset for cardiac AEs was 36.00 days (IQR: 3.00-176.00)(Figure 5B), with male patients exhibiting a significantly shorter median onset compared to females (22.00 vs. 49.00 days; P=0.0163)(Figure 5C).

A

Preferred Term(PT)	PT Code	Case Reports	ROR (95% CI)
Cardiac failure	10007554	178	6.60(5.69,7.65)
Palpitations	10033557	82	2.08(1.67,2.58)
Cardiotoxicity	10048610	75	26.02(20.72,32.67)
Dilated cardiomyopathy	10056419	62	34.97(27.21,44.94)
Cardiac dysfunction	10007751	55	47.57(36.43,62.12)
Cardiomyopathy	10007636	50	9.87(7.47,13.03)
Atrial fibrillation	10003658	47	1.42(1.07,1.89)
Tachycardia	10043071	40	1.33(0.98,1.82)
Myocardial infarction	10028596	35	0.57(0.41,0.80)
Left ventricular dysfunction	10049694	31	13.96(9.81,19.88)
Ventricular dysfunction	10059056	30	35.26(24.59,50.56)
Mitral valve incompetence	10027727	29	7.45(5.18,10.73)
Ventricular hypokinesia	10050510	24	21.71(14.53,32.45)
Cardio-respiratory arrest	10007617	23	1.59(1.05,2.39)
Arrhythmia	10003119	22	1.35(0.89,2.05)
Cardiac arrest	10007515	22	0.78(0.51,1.18)
Cardiac failure congestive	10007559	22	0.77(0.51,1.17)
Pericardial effusion	10034474	20	2.58(1.67,4.01)
Cardiac disorder	10061024	19	0.59(0.38,0.93)
Cardiac failure acute	10007556	17	7.65(4.75,12.32)
Tricuspid valve incompetence	10044640	16	6.00(3.68,9.81)
Acute myocardial infarction	10000891	15	1.46(0.88,2.42)
Myocarditis	10028606	15	4.11(2.48,6.83)
Cardiovascular disorder	10007649	14	1.58(0.94,2.67)
Bradycardia	10006093	13	0.71(0.41,1.23)
Cardiac failure chronic	10007558	12	8.36(4.74,14.74)
Pericarditis	10034484	12	2.46(1.40,4.33)
Sinus tachycardia	10040752	12	2.48(1.41,4.36)
Supraventricular extrasystoles	10042602	12	10.17(5.77,17.94)
Cardiogenic shock	10007625	10	2.12(1.14,3.94)
Dilatation ventricular	10013012	10	13.22(7.10,24.61)
Myocardial ischaemia	10028600	10	2.49(1.34,4.62)
Ventricular extrasystoles	10047289	10	2.78(1.49,5.16)
Angina pectoris	10002383	9	0.91(0.47,1.74)
Left ventricular failure	10024119	9	7.67(3.99,14.76)
Diastolic dysfunction	10052337	9	8.66(4.50,16.66)
Right atrial dilatation	10067282	9	50.80(26.27,98.24)
Myocardial injury	10085879	9	7.78(4.04,14.97)
Sinus bradycardia	10040741	8	2.40(1.20,4.80)
Supraventricular tachycardia	10042604	8	2.44(1.22,4.87)
Arteriosclerosis coronary artery	10003211	7	2.87(1.37,6.03)
Cardiomegaly	10007632	7	1.60(0.76,3.36)
Ventricular fibrillation	10047290	7	1.85(0.88,3.89)
Acute coronary syndrome	10051592	7	2.42(1.15,5.07)
Aortic valve incompetence	10002915	6	4.11(1.84,9.15)
Coronary artery thrombosis	10011091	6	8.50(3.81,18.95)
HFWMEF	10086366	6	406.37(172.51,957.28)
Arrhythmia supraventricular	10003130	5	12.84(5.33,30.92)
Bundle branch block left	10006580	5	3.39(1.41,8.14)
Extrasystoles	10015856	5	2.07(0.86,4.98)



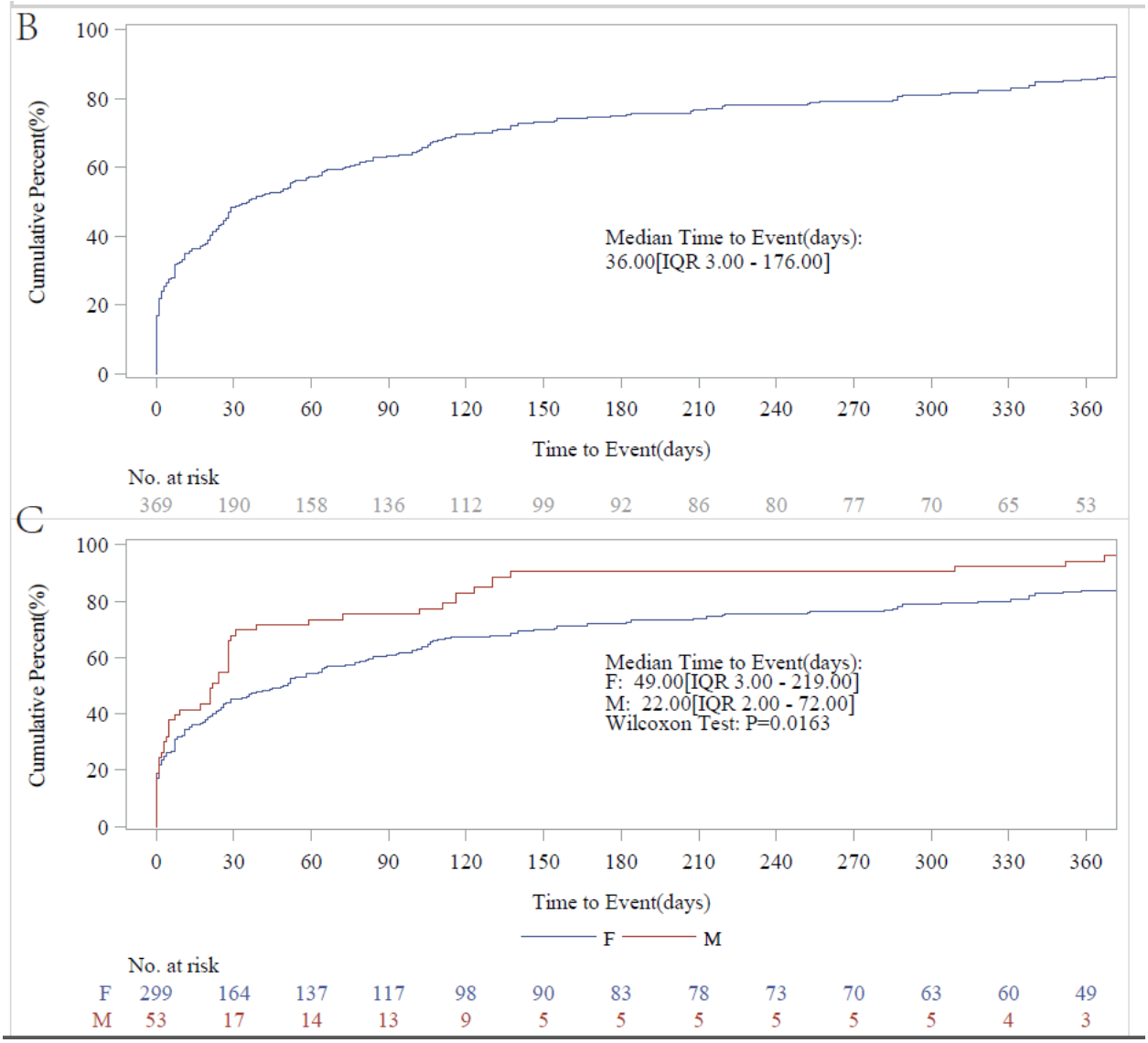


Figure 5: (A) Top 50 Frequent PTs; (B) Overall Cumulative Incidence; (C) Cumulative Incidence by Sex

3.3 Stratified Risk Profiles and Subgroup Analysis (FAERS)

Stratification revealed distinct risk patterns across age and gender. Females showed higher disproportionate reporting for cardiac failure ($P < 0.0001$, $\log_2ROR = 2.95$) and dilated cardiomyopathy ($P = 0.0029$, $\log_2ROR = 3.45$). Conversely, males were more closely associated with atrial fibrillation ($P < 0.0001$, $\log_2ROR = -2.07$) and ventricular hypokinesia ($P < 0.0001$)(Table 1).

Table 1 Gender Difference Analysis (Group 1 = Female, Group 2 = Male)

PT	P value	$\log_2ROR$
Cardiac failure	<.0001	2.954688682
Palpitations	0.0340	1.258623056
Cardiotoxicity	0.0524	1.395237859
Dilated cardiomyopathy	0.0029	3.44841221
Cardiac dysfunction	0.0134	2.315011006

Atrial fibrillation	<.0001	-2.074782583
Tachycardia	0.0633	1.822630341
Myocardial infarction	1.0000	-0.067467906
Arrhythmia	0.0621	-1.391390002
Cardiac failure congestive	0.2983	1.859918928
Pericardial effusion	1.0000	0.113334325
Cardio-respiratory arrest	0.0088	-1.807099855
Cardiac arrest	0.6670	0.78133778
Ventricular hypokinesia	<.0001	-3.268549376
Tricuspid valve incompetence	1.0000	-0.27405991
Cardiac disorder	0.5877	1.31187443
Acute myocardial infarction	0.6499	-0.804945642
Bradycardia	0.2146	-1.390487047
Cardiac failure chronic	0.8288	0.933084536
Dilatation ventricular	1.0000	-0.38951488
Supraventricular extrasystoles	0.9294	0.780988698
Sinus tachycardia	0.9294	0.780988698
Ventricular extrasystoles	0.9294	0.780988698
Pericarditis	0.9584	-0.582252692
Myocardial injury	0.9584	-0.582252692
Right atrial dilatation	0.9584	-0.582252692
Left ventricular failure	1.0000	0.418233146
Sinus bradycardia	0.8338	-0.80473784
Arteriosclerosis coronary artery	<.0001	-4.977071376
Angina pectoris	0.2479	-1.389885777
Systolic dysfunction	0.5825	-0.389399939
Arrhythmia supraventricular	0.1840	-1.805015986
Right ventricular failure	0.4079	-1.389585352

The pediatric cohort (<18 years) demonstrated a strong signal for dilated cardiomyopathy (ROR=183.64), whereas elderly patients (≥ 65 years) showed increased reporting for atrial fibrillation (P < 0.0001) and acute cardiac failure(Table 2).

Table 2 Age-Stratified Signal Detection Results Across MedDRA Hierarchical Levels

	PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
45-64	Cardiac failure	8.71(6.97,10.89)	8.64(6.93,10.79)	3.10(2.64)	8.60(6.88)	Y	Y	Y	Y
⩾65	Cardiac failure	5.29(3.99,7.01)	5.23(3.96,6.91)	2.39(1.86)	5.22(3.94)	Y	Y	Y	Y
45-64	Palpitations	2.35(1.77,3.12)	2.34(1.77,3.11)	1.23(0.77)	2.34(1.76)	Y	Y	Y	N
NS	Cardiotoxicity	47.48(33.29,67.71)	47.12(33.13,67.02)	5.55(3.75)	46.70(32.74)	Y	Y	Y	Y
45-	Cardiac	74.19(51.7	73.95(51.59,	6.14(3.	70.53(4	Y	Y	Y	Y

64	dysfunctio n	0,106.47)	105.99)	95)	9.15)				
NS	Cardiac failure	6.30(4.37,9 .08)	6.26(4.36,9. 00)	2.65(1. 88)	6.26(4. 34)	Y	Y	Y	Y
45-64	Cardiotoxi city	24.76(16.9 2,36.24)	24.69(16.89, 36.09)	4.60(3. 18)	24.31(1 6.61)	Y	Y	Y	Y
45-64	Cardiomy opathy	9.48(6.39,1 4.05)	9.45(6.38,14 .00)	3.23(2. 26)	9.40(6. 34)	Y	Y	Y	Y
45-64	Dilated cardiomyo pathy	23.73(15.9 8,35.24)	23.67(15.95, 35.11)	4.54(3. 08)	23.31(1 5.70)	Y	Y	Y	Y
⩾65	Atrial fibrillation	1.77(1.17,2 .66)	1.76(1.17,2. 65)	0.82(0. 18)	1.76(1. 17)	Y	Y	Y	N
18-44	Cardiac failure	10.89(7.09, 16.75)	10.84(7.07,1 6.62)	3.43(2. 28)	10.79(7 .02)	Y	Y	Y	Y
45-64	Mitral valve incompete nce	10.49(6.82, 16.12)	10.47(6.82,1 6.07)	3.38(2. 25)	10.40(6 .77)	Y	Y	Y	Y
18-44	Palpitatio ns	2.31(1.50,3 .55)	2.30(1.50,3. 53)	1.20(0. 50)	2.30(1. 50)	Y	Y	Y	N
45-64	Atrial fibrillation	1.52(0.95,2 .45)	1.52(0.95,2. 45)	0.61(- 0.12)	1.52(0. 95)	N	N	N	N
45-64	Tachycard ia	1.19(0.73,1 .95)	1.19(0.73,1. 94)	0.25(- 0.47)	1.19(0. 73)	N	N	N	N
18-44	Tachycard ia	1.63(0.98,2 .70)	1.62(0.98,2. 69)	0.70(- 0.08)	1.62(0. 98)	N	N	N	N
⩾65	Cardiac dysfunctio n	56.68(33.9 9,94.50)	56.46(33.93, 93.95)	5.80(2. 93)	55.55(3 3.32)	Y	Y	Y	Y
45-64	Left ventricula r dysfunctio n	12.23(7.22, 20.70)	12.21(7.22,2 0.65)	3.60(2. 05)	12.12(7 .16)	Y	Y	Y	Y
18-44	Ventricula r dysfunctio n	85.99(50.4 0,146.72)	85.67(50.31, 145.89)	6.37(2. 92)	82.68(4 8.46)	Y	Y	Y	Y
⩾65	Myocardi al infarction	0.96(0.56,1 .66)	0.96(0.56,1. 66)	-0.06(- 0.82)	0.96(0. 56)	N	N	N	N
45-64	Arrhythmi a	1.84(1.04,3 .24)	1.84(1.04,3. 24)	0.88(- 0.01)	1.84(1. 04)	Y	Y	N	N
45-64	Tricuspid valve incompete nce	10.02(5.68, 17.69)	10.01(5.68,1 7.66)	3.32(1. 75)	9.95(5. 64)	Y	Y	Y	Y
18-44	Cardiotoxi city	22.61(12.7 9,39.95)	22.54(12.77, 39.75)	4.48(2. 27)	22.33(1 2.64)	Y	Y	Y	Y
NS	Ventricula	121.50(68.	121.14(68.4	6.89(2.	118.37(	Y	Y	Y	Y

	r hypokinesia	49,215.56)	0,214.56)	75)	66.72)				
18-44	Dilated cardiomyopathy	28.02(15.84,49.54)	27.93(15.82,49.30)	4.79(2.37)	27.61(15.61)	Y	Y	Y	Y
45-64	Cardiac failure congestive	0.80(0.44,1.45)	0.80(0.44,1.45)	-0.32(-1.13)	0.80(0.44)	N	N	N	N
⩾65	Cardio-respiratory arrest	3.43(1.90,6.20)	3.42(1.90,6.18)	1.77(0.67)	3.42(1.89)	Y	Y	Y	N
NS	Cardiomyopathy	13.23(7.31,23.93)	13.20(7.31,23.83)	3.72(1.87)	13.16(7.28)	Y	Y	Y	Y
⩾65	Dilated cardiomyopathy	34.77(19.18,63.02)	34.67(19.16,62.73)	5.10(2.34)	34.33(18.94)	Y	Y	Y	Y
NS	Cardiac disorder	1.33(0.73,2.40)	1.32(0.73,2.39)	0.41(-0.47)	1.32(0.73)	N	N	N	N
⩾65	Cardiomyopathy	10.73(5.76,19.98)	10.70(5.76,19.90)	3.42(1.63)	10.67(5.73)	Y	Y	Y	Y
45-64	Ventricular dysfunction	18.26(9.79,34.08)	18.24(9.78,34.02)	4.17(1.95)	18.04(9.67)	Y	Y	Y	Y
⩾65	Cardiac arrest	1.39(0.72,2.67)	1.39(0.72,2.66)	0.47(-0.50)	1.39(0.72)	N	N	N	N
NS	Myocardial infarction	0.74(0.38,1.42)	0.74(0.38,1.41)	-0.44(-1.32)	0.74(0.38)	N	N	N	N
45-64	Myocardial infarction	0.27(0.14,0.51)	0.27(0.14,0.51)	-1.91(-2.71)	0.27(0.14)	N	N	N	N
⩾65	Palpitations	1.45(0.75,2.79)	1.45(0.75,2.78)	0.53(-0.44)	1.45(0.75)	N	N	N	N
NS	Cardiovascular disorder	2.94(1.47,5.88)	2.93(1.47,5.86)	1.55(0.31)	2.93(1.47)	Y	Y	Y	N
⩾65	Myocarditis	12.46(6.22,24.96)	12.43(6.21,24.88)	3.63(1.49)	12.39(6.19)	Y	Y	Y	Y
45-64	Pericardial effusion	2.06(1.03,4.13)	2.06(1.03,4.12)	1.04(-0.08)	2.06(1.03)	Y	Y	N	N
NS	Dilated cardiomyopathy	39.64(19.76,79.53)	39.56(19.75,79.27)	5.30(1.94)	39.27(19.57)	Y	Y	Y	Y
45-64	Myocardial injury	12.53(6.24,25.13)	12.52(6.24,25.09)	3.63(1.49)	12.42(6.19)	Y	Y	Y	Y
⩾65	Arrhythmia	1.76(0.84,3.69)	1.75(0.84,3.68)	0.81(-0.34)	1.75(0.84)	N	N	N	N
NS	Cardiac arrest	2.45(1.17,5.15)	2.45(1.17,5.14)	1.29(0.03)	2.45(1.17)	Y	Y	Y	N

NS	Cardiac failure chronic	34.68(16.48,72.97)	34.62(16.47,72.75)	5.10(1.71)	34.39(16.34)	Y	Y	Y	Y
45-64	Cardio-respiratory arrest	0.95(0.45,2.00)	0.95(0.45,2.00)	-0.07(-1.08)	0.95(0.45)	N	N	N	N
45-64	Cardiogenic shock	2.96(1.41,6.21)	2.96(1.41,6.21)	1.56(0.23)	2.95(1.41)	Y	Y	Y	N
45-64	Supraventricular extrasystoles	13.64(6.48,28.72)	13.63(6.48,28.68)	3.76(1.37)	13.52(6.42)	Y	Y	Y	Y
⩾65	Tachycardia	1.48(0.70,3.10)	1.48(0.70,3.10)	0.56(-0.54)	1.48(0.70)	N	N	N	N
18-44	Left ventricular dysfunction	16.53(7.86,34.80)	16.50(7.85,34.69)	4.04(1.46)	16.40(7.79)	Y	Y	Y	Y
NS	Acute myocardial infarction	5.51(2.47,12.29)	5.51(2.47,12.26)	2.46(0.65)	5.50(2.47)	Y	Y	Y	Y
45-64	Acute myocardial infarction	0.93(0.42,2.07)	0.93(0.42,2.07)	-0.11(-1.18)	0.93(0.42)	N	N	N	N
NS	Atrial fibrillation	1.10(0.49,2.46)	1.10(0.50,2.45)	0.14(-0.97)	1.10(0.49)	N	N	N	N
⩾65	Cardiac failure congestive	0.73(0.33,1.62)	0.73(0.33,1.61)	-0.46(-1.50)	0.73(0.33)	N	N	N	N
45-64	Sinus bradycardia	3.87(1.74,8.63)	3.87(1.74,8.62)	1.95(0.36)	3.86(1.73)	Y	Y	Y	N
45-64	Ventricular extrasystoles	3.35(1.50,7.46)	3.35(1.50,7.46)	1.74(0.23)	3.34(1.50)	Y	Y	Y	N
NS	Left ventricular dysfunction	21.47(9.63,47.91)	21.44(9.62,47.78)	4.42(1.36)	21.36(9.57)	Y	Y	Y	Y
<18	Dilated cardiomyopathy	183.64(81.03,416.21)	180.36(80.73,402.96)	7.46(1.64)	175.60(77.48)	Y	Y	Y	Y
⩾65	Ventricular dysfunction	35.76(15.99,79.99)	35.71(15.98,79.76)	5.14(1.48)	35.35(15.80)	Y	Y	Y	Y

18-44	Cardiac dysfunction	52.55(23.39,118.10)	52.47(23.38,117.76)	5.68(1.54)	51.34(22.85)	Y	Y	Y	Y
45-64	Aortic valve incompetence	7.16(2.97,17.25)	7.16(2.97,17.24)	2.83(0.64)	7.13(2.96)	Y	Y	Y	Y
⩾65	Arteriosclerosis coronary artery	7.53(3.13,18.11)	7.52(3.13,18.07)	2.91(0.67)	7.50(3.12)	Y	Y	Y	Y
45-64	Cardiac arrest	0.35(0.15,0.84)	0.35(0.15,0.84)	-1.51(-2.53)	0.35(0.15)	N	N	N	N
45-64	Cardiac failure acute	5.56(2.31,13.37)	5.55(2.31,13.36)	2.47(0.48)	5.54(2.30)	Y	Y	Y	Y
⩾65	Cardiac failure acute	6.26(2.60,15.07)	6.26(2.60,15.04)	2.64(0.56)	6.25(2.60)	Y	Y	Y	Y
NS	Cardiac failure congestive	0.97(0.40,2.33)	0.97(0.40,2.33)	-0.04(-1.22)	0.97(0.40)	N	N	N	N
45-64	Cardiomegaly	2.24(0.93,5.38)	2.24(0.93,5.37)	1.16(-0.29)	2.23(0.93)	N	N	N	N
45-64	Dilatation ventricular	14.00(5.80,33.77)	13.99(5.80,33.74)	3.79(0.96)	13.87(5.75)	Y	Y	Y	Y
NS	Pericardial effusion	4.35(1.81,10.47)	4.35(1.81,10.45)	2.12(0.30)	4.35(1.81)	Y	Y	Y	N
NS	Pericarditis	6.12(2.54,14.72)	6.11(2.54,14.69)	2.61(0.54)	6.11(2.54)	Y	Y	Y	Y
45-64	Supraventricular tachycardia	3.06(1.27,7.36)	3.06(1.27,7.35)	1.61(0.01)	3.06(1.27)	Y	Y	Y	N
18-44	Ventricular hypokinesia	20.02(8.30,48.31)	20.00(8.30,48.20)	4.31(1.08)	19.84(8.22)	Y	Y	Y	Y
NS	Diastolic dysfunction	37.81(15.68,91.18)	37.76(15.68,90.98)	5.23(1.22)	37.50(15.55)	Y	Y	Y	Y
45-64	Cardiac disorder	0.44(0.18,1.06)	0.44(0.18,1.06)	-1.17(-2.21)	0.44(0.18)	N	N	N	N
45-64	Atrioventricular block complete	4.42(1.65,11.78)	4.41(1.65,11.78)	2.14(0.10)	4.40(1.65)	Y	Y	Y	N
45-64	Bradycardia	0.59(0.22,1.57)	0.59(0.22,1.57)	-0.77(-1.93)	0.59(0.22)	N	N	N	N
⩾65	Bradycard	0.68(0.26,1	0.68(0.26,1.	-0.55(-	0.68(0.	N	N	N	N

	ia	.82)	82)	1.74)	26)				
NS	Cardiac failure acute	16.60(6.22,44.32)	16.58(6.22,44.23)	4.05(0.72)	16.53(6.19)	Y	Y	Y	Y
45-64	Cardiac failure chronic	8.64(3.23,23.09)	8.64(3.23,23.07)	3.10(0.47)	8.59(3.22)	Y	Y	Y	Y
18-44	Cardiomyopathy	4.32(1.62,11.52)	4.31(1.62,11.50)	2.11(0.08)	4.31(1.61)	Y	Y	Y	N
45-64	Left ventricular failure	7.63(2.86,20.39)	7.63(2.86,20.38)	2.93(0.42)	7.60(2.84)	Y	Y	Y	Y
18-44	Myocardial infarction	0.97(0.36,2.57)	0.97(0.36,2.57)	-0.05(-1.33)	0.97(0.36)	N	N	N	N
NS	Myocardial ischaemia	7.19(2.69,19.17)	7.18(2.69,19.14)	2.84(0.39)	7.17(2.69)	Y	Y	Y	Y
45-64	Myocardial ischaemia	1.65(0.62,4.40)	1.65(0.62,4.40)	0.72(-0.75)	1.65(0.62)	N	N	N	N
NS	Palpitations	0.59(0.22,1.57)	0.59(0.22,1.57)	-0.76(-1.93)	0.59(0.22)	N	N	N	N
18-44	Pericardial effusion	3.43(1.29,9.15)	3.43(1.29,9.13)	1.78(-0.09)	3.42(1.28)	Y	Y	N	N
45-64	Pericarditis	1.88(0.70,5.01)	1.88(0.70,5.01)	0.91(-0.62)	1.88(0.70)	N	N	N	N
45-64	Sinus tachycardia	1.77(0.67,4.73)	1.77(0.67,4.73)	0.83(-0.67)	1.77(0.67)	N	N	N	N
⩾65	Sinus tachycardia	6.64(2.49,17.71)	6.63(2.49,17.68)	2.73(0.35)	6.62(2.48)	Y	Y	Y	Y
⩾65	Left ventricular dysfunction	7.92(2.97,21.15)	7.92(2.97,21.11)	2.98(0.44)	7.90(2.96)	Y	Y	Y	Y
45-64	Right atrial dilatation	67.68(24.85,184.33)	67.65(24.85,184.17)	6.02(0.91)	64.78(23.78)	Y	Y	Y	Y
18-44	Heart failure with midrange ejection fraction	521.38(176.37,1541.31)	520.81(176.34,1538.15)	8.74(0.88)	426.30(144.20)	Y	Y	Y	Y
NS	Angina pectoris	1.92(0.62,5.96)	1.92(0.62,5.95)	0.94(-0.80)	1.92(0.62)	N	N	N	N
45-64	Angina pectoris	0.55(0.18,1.70)	0.55(0.18,1.70)	-0.87(-2.14)	0.55(0.18)	N	N	N	N

⩾65	Arrhythmia supraventricular	25.28(8.12,78.74)	25.26(8.12,78.61)	4.65(0.39)	25.08(8.05)	Y	Y	Y	Y
18-44	Cardiac failure acute	9.94(3.20,30.90)	9.93(3.20,30.85)	3.31(0.17)	9.89(3.18)	Y	Y	Y	Y
NS	Cardio-respiratory arrest	2.51(0.81,7.80)	2.51(0.81,7.79)	1.33(-0.58)	2.51(0.81)	N	N	N	N
⩾65	Coronary artery thrombosis	18.18(5.84,56.58)	18.17(5.85,56.49)	4.18(0.33)	18.08(5.81)	Y	Y	Y	Y
NS	Dilatation ventricular	28.89(9.28,89.89)	28.87(9.28,89.75)	4.84(0.41)	28.71(9.23)	Y	Y	Y	Y
NS	Mitral valve incompetence	5.99(1.93,18.59)	5.98(1.93,18.56)	2.58(-0.03)	5.98(1.93)	Y	Y	N	N
18-44	Myocarditis	2.34(0.76,7.28)	2.34(0.76,7.27)	1.23(-0.63)	2.34(0.75)	N	N	N	N
45-64	Myocarditis	1.99(0.64,6.17)	1.99(0.64,6.17)	0.99(-0.77)	1.99(0.64)	N	N	N	N
⩾65	Pericardial effusion	1.69(0.54,5.24)	1.69(0.54,5.23)	0.75(-0.92)	1.69(0.54)	N	N	N	N
NS	Supraventricular extrasystoles	18.96(6.10,58.94)	18.95(6.10,58.85)	4.24(0.34)	18.88(6.07)	Y	Y	Y	Y
45-64	Torsade de pointes	2.40(0.77,7.46)	2.40(0.77,7.46)	1.26(-0.61)	2.40(0.77)	N	N	N	N
⩾65	Ventricular extrasystoles	3.41(1.10,10.58)	3.41(1.10,10.57)	1.77(-0.36)	3.41(1.10)	Y	Y	N	N
NS	Ventricular fibrillation	7.96(2.56,24.71)	7.96(2.56,24.68)	2.99(0.09)	7.94(2.56)	Y	Y	Y	Y
45-64	Ventricular fibrillation	1.50(0.48,4.65)	1.50(0.48,4.65)	0.58(-1.03)	1.50(0.48)	N	N	N	N
45-64	Ventricular tachycardia	1.07(0.35,3.32)	1.07(0.35,3.32)	0.10(-1.37)	1.07(0.35)	N	N	N	N
⩾65	Cardiotoxicity	8.29(2.67,25.75)	8.28(2.67,25.71)	3.05(0.11)	8.27(2.66)	Y	Y	Y	Y
⩾65	Ventricular	11.66(3.75,36.24)	11.65(3.75,36.18)	3.54(0.22)	11.62(3.74)	Y	Y	Y	Y

	hypokinesia								
45-64	Acute coronary syndrome	1.69(0.54,5.24)	1.69(0.54,5.24)	0.75(-0.92)	1.69(0.54)	N	N	N	N
⩾65	Right atrial dilatation	86.76(27.57,273.01)	86.70(27.58,272.56)	6.40(0.48)	84.57(26.88)	Y	Y	Y	Y
45-64	Kounis syndrome	6.28(2.02,19.53)	6.28(2.02,19.51)	2.65(-0.01)	6.26(2.01)	Y	Y	N	Y
45-64	Systolic dysfunction	17.31(5.54,54.02)	17.30(5.54,53.98)	4.10(0.31)	17.12(5.48)	Y	Y	Y	Y
45-64	Immune-mediated pericarditis	237.73(70.34,803.51)	237.65(70.34,802.97)	7.68(0.41)	205.38(60.77)	Y	Y	Y	Y
⩾65	Acute myocardial infarction	0.63(0.16,2.51)	0.63(0.16,2.51)	-0.67(-2.15)	0.63(0.16)	N	N	N	N
⩾65	Angina pectoris	0.79(0.20,3.14)	0.79(0.20,3.14)	-0.35(-1.91)	0.79(0.20)	N	N	N	N
NS	Arrhythmia	0.66(0.16,2.64)	0.66(0.16,2.64)	-0.60(-2.09)	0.66(0.16)	N	N	N	N
NS	Arrhythmia supraventricular	32.47(8.08,130.46)	32.46(8.08,130.31)	5.01(-0.18)	32.26(8.03)	N	N	N	Y
45-64	Atrioventricular block second degree	5.17(1.29,20.74)	5.17(1.29,20.73)	2.37(-0.56)	5.16(1.29)	N	N	N	N
18-44	Bradycardia	0.69(0.17,2.74)	0.69(0.17,2.74)	-0.54(-2.05)	0.69(0.17)	N	N	N	N
NS	Bradycardia	1.02(0.25,4.06)	1.02(0.25,4.06)	0.02(-1.65)	1.02(0.25)	N	N	N	N
⩾65	Bundle branch block left	3.96(0.99,15.86)	3.96(0.99,15.84)	1.98(-0.67)	3.96(0.99)	N	N	N	N
45-64	Bundle branch block left	2.69(0.67,10.76)	2.69(0.67,10.76)	1.42(-0.89)	2.68(0.67)	N	N	N	N
<18	Cardio-respiratory arrest	6.02(1.50,24.18)	5.99(1.50,23.86)	2.58(-0.51)	5.98(1.49)	N	N	N	N
NS	Cardiogenic shock	4.67(1.17,18.68)	4.66(1.17,18.66)	2.22(-0.60)	4.66(1.16)	N	N	N	N
45-64	Cardiovascular	0.67(0.17,2.68)	0.67(0.17,2.68)	-0.57(-2.07)	0.67(0.17)	N	N	N	N

	disorder								
18-44	Cardiovascular disorder	2.77(0.69,11.08)	2.77(0.69,11.07)	1.47(-0.87)	2.76(0.69)	N	N	N	N
⩾65	Cardiovascular disorder	1.65(0.41,6.59)	1.65(0.41,6.58)	0.72(-1.23)	1.65(0.41)	N	N	N	N
NS	Coronary artery thrombosis	25.91(6.46,104.02)	25.90(6.46,103.89)	4.69(-0.20)	25.78(6.42)	N	N	N	Y
<18	Dilatation ventricular	70.03(17.31,283.22)	69.61(17.36,279.23)	6.11(-0.14)	68.90(17.04)	N	N	N	Y
45-64	Endocardial fibrosis	177.11(40.91,766.73)	177.08(40.92,766.34)	7.31(-0.22)	158.54(36.62)	N	N	N	Y
NS	Extrasystoles	5.32(1.33,21.31)	5.32(1.33,21.29)	2.41(-0.54)	5.32(1.33)	N	N	N	N
45-64	Extrasystoles	1.73(0.43,6.91)	1.73(0.43,6.91)	0.79(-1.19)	1.73(0.43)	N	N	N	N
⩾65	Left ventricular failure	5.04(1.26,20.18)	5.04(1.26,20.15)	2.33(-0.57)	5.03(1.26)	N	N	N	N
18-44	Left ventricular failure	15.58(3.88,62.61)	15.57(3.88,62.53)	3.95(-0.27)	15.48(3.85)	N	N	N	Y
⩾65	Mitral valve incompetence	1.87(0.47,7.47)	1.87(0.47,7.46)	0.90(-1.13)	1.87(0.47)	N	N	N	N
18-44	Mitral valve incompetence	4.14(1.03,16.58)	4.14(1.03,16.56)	2.05(-0.65)	4.13(1.03)	N	N	N	N
⩾65	Myocardial fibrosis	50.17(12.42,202.74)	50.15(12.42,202.49)	5.63(-0.16)	49.44(12.23)	N	N	N	Y
NS	Myocardial fibrosis	52.90(13.13,213.09)	52.87(13.13,212.84)	5.71(-0.15)	52.34(12.99)	N	N	N	Y
⩾65	Nodal arrhythmia	19.01(4.73,76.32)	19.00(4.73,76.23)	4.24(-0.23)	18.90(4.71)	N	N	N	Y
⩾65	Pericarditis	4.17(1.04,16.69)	4.17(1.04,16.67)	2.06(-0.65)	4.16(1.04)	N	N	N	N
45-64	Right ventricular failure	1.59(0.40,6.35)	1.59(0.40,6.35)	0.67(-1.26)	1.59(0.40)	N	N	N	N
18-44	Sinus bradycardia	3.16(0.79,12.64)	3.16(0.79,12.63)	1.66(-0.79)	3.15(0.79)	N	N	N	N
NS	Sinus tachycardi	4.39(1.10,17.56)	4.39(1.10,17.54)	2.13(-0.63)	4.38(1.09)	N	N	N	N

	a								
18-44	Sinus tachycardia	1.04(0.26,4.16)	1.04(0.26,4.16)	0.06(-1.63)	1.04(0.26)	N	N	N	N
NS	Supraventricular tachycardia	4.24(1.06,16.96)	4.23(1.06,16.94)	2.08(-0.64)	4.23(1.06)	N	N	N	N
NS	Tachycardia	0.54(0.14,2.17)	0.54(0.14,2.17)	-0.88(-2.31)	0.54(0.14)	N	N	N	N
18-44	Tricuspid valve incompetence	5.17(1.29,20.71)	5.17(1.29,20.69)	2.37(-0.56)	5.16(1.29)	N	N	N	N
<18	Tricuspid valve incompetence	22.25(5.53,89.53)	22.12(5.54,88.28)	4.46(-0.22)	22.05(5.48)	N	N	N	Y
<18	Cardiotoxicity	25.24(6.27,101.62)	25.10(6.29,100.20)	4.64(-0.20)	25.01(6.21)	N	N	N	Y
NS	Atrial thrombosis	16.31(4.07,65.40)	16.31(4.07,65.32)	4.02(-0.25)	16.26(4.06)	N	N	N	Y
NS	Paroxysmal arrhythmia	446.17(105.16,1893.09)	445.95(105.17,1890.91)	8.68(-0.18)	410.36(96.71)	N	N	N	Y
45-64	Ventricular hypokinesia	2.92(0.73,11.71)	2.92(0.73,11.70)	1.55(-0.84)	2.92(0.73)	N	N	N	N
<18	Ventricular hypokinesia	190.08(46.42,778.34)	188.95(46.53,767.38)	7.52(-0.14)	183.73(44.87)	N	N	N	Y
NS	Acute coronary syndrome	5.91(1.48,23.66)	5.91(1.48,23.64)	2.56(-0.50)	5.90(1.47)	N	N	N	N
⩾65	Acute coronary syndrome	2.32(0.58,9.29)	2.32(0.58,9.28)	1.21(-0.98)	2.32(0.58)	N	N	N	N
NS	Left atrial enlargement	90.02(22.23,364.44)	89.97(22.24,364.02)	6.47(-0.14)	88.44(21.84)	N	N	N	Y
45-64	Diastolic dysfunction	3.46(0.86,13.85)	3.46(0.86,13.84)	1.79(-0.74)	3.45(0.86)	N	N	N	N
<18	Diastolic dysfunction	207.90(50.68,852.86)	206.67(50.79,840.86)	7.65(-0.14)	200.43(48.86)	N	N	N	Y
45-	Right	13.03(3.24,	13.03(3.24,5	3.69(-	12.93(3	N	N	N	Y

64	ventricular dysfunction	52.44)	2.41)	0.30)	.21)				
⩾65	Cardiac disorder	0.28(0.07,1.14)	0.29(0.07,1.14)	-1.81(-3.08)	0.29(0.07)	N	N	N	N
NS	Myocardial oedema	81.44(20.14,329.36)	81.40(20.14,328.97)	6.32(-0.14)	80.15(19.82)	N	N	N	Y
<18	Right atrial dilatation	251.06(60.93,1034.43)	249.56(61.06,1019.89)	7.91(-0.14)	240.52(58.37)	N	N	N	Y
⩾65	Heart failure with reduced ejection fraction	51.69(12.79,208.95)	51.67(12.79,208.69)	5.67(-0.16)	50.91(12.60)	N	N	N	Y
NS	Cardiac dysfunction	8.11(2.02,32.46)	8.10(2.02,32.42)	3.02(-0.40)	8.09(2.02)	N	N	N	Y
45-64	Cardiac perfusion defect	334.55(72.27,1548.63)	334.48(72.28,1547.87)	8.10(-0.29)	273.84(59.16)	N	N	N	Y
45-64	Toxic cardiomyopathy	44.28(10.85,180.70)	44.27(10.85,180.60)	5.43(-0.18)	43.03(10.54)	N	N	N	Y
⩾65	Heart failure with midrange ejection fraction	1364.73(264.69,7036.54)	1364.01(264.71,7028.49)	9.93(-0.37)	974.58(189.02)	N	N	N	Y
18-44	Acute myocardial infarction	1.02(0.14,7.26)	1.02(0.14,7.25)	0.03(-2.03)	1.02(0.14)	N	N	N	N
18-44	Angina pectoris	0.96(0.13,6.78)	0.96(0.13,6.78)	-0.07(-2.08)	0.96(0.13)	N	N	N	N
45-64	Angina unstable	0.55(0.08,3.91)	0.55(0.08,3.91)	-0.86(-2.54)	0.55(0.08)	N	N	N	N
⩾65	Aortic valve incompetence	2.45(0.34,17.40)	2.45(0.34,17.39)	1.29(-1.54)	2.45(0.34)	N	N	N	N
18-44	Arrhythmia	0.46(0.07,3.28)	0.46(0.07,3.28)	-1.11(-2.70)	0.46(0.07)	N	N	N	N
45-64	Arteriosclerosis coronary artery	0.64(0.09,4.53)	0.64(0.09,4.53)	-0.65(-2.40)	0.64(0.09)	N	N	N	N
NS	Arterioscl	3.35(0.47,2	3.35(0.47,23	1.74(-	3.35(0.	N	N	N	N

	erosis coronary artery	3.81)	.79)	1.42)	47)				
45-64	Arteriospasm coronary	1.00(0.14,7.10)	1.00(0.14,7.09)	0.00(-2.04)	1.00(0.14)	N	N	N	N
18-44	Atrial fibrillation	0.94(0.13,6.69)	0.94(0.13,6.69)	-0.09(-2.09)	0.94(0.13)	N	N	N	N
⩾65	Atrial tachycardia	4.55(0.64,32.34)	4.55(0.64,32.31)	2.18(-1.33)	4.54(0.64)	N	N	N	N
18-44	Atrioventricular block	4.12(0.58,29.31)	4.12(0.58,29.28)	2.04(-1.36)	4.11(0.58)	N	N	N	N
⩾65	Atrioventricular block	1.06(0.15,7.55)	1.06(0.15,7.54)	0.09(-2.00)	1.06(0.15)	N	N	N	N
NS	Atrioventricular block	2.57(0.36,18.24)	2.57(0.36,18.23)	1.36(-1.52)	2.57(0.36)	N	N	N	N
⩾65	Atrioventricular block first degree	2.01(0.28,14.27)	2.01(0.28,14.26)	1.01(-1.63)	2.01(0.28)	N	N	N	N
18-44	Atrioventricular block first degree	3.74(0.53,26.59)	3.74(0.53,26.57)	1.90(-1.39)	3.73(0.52)	N	N	N	N
45-64	Atrioventricular block first degree	1.53(0.22,10.87)	1.53(0.22,10.87)	0.61(-1.77)	1.53(0.22)	N	N	N	N
<18	Bradycardia	1.92(0.27,13.64)	1.91(0.27,13.54)	0.94(-1.66)	1.91(0.27)	N	N	N	N
<18	Bradycardia foetal	60.30(8.39,433.17)	60.12(8.42,429.37)	5.90(-1.09)	59.59(8.29)	N	N	N	Y
NS	Bundle branch block left	6.27(0.88,44.58)	6.27(0.88,44.55)	2.65(-1.26)	6.26(0.88)	N	N	N	N
⩾65	Bundle branch block right	2.20(0.31,15.65)	2.20(0.31,15.64)	1.14(-1.58)	2.20(0.31)	N	N	N	N
45-64	Bundle branch block right	1.54(0.22,10.92)	1.54(0.22,10.91)	0.62(-1.77)	1.54(0.22)	N	N	N	N
18-44	Cardiac arrest	0.14(0.02,1.02)	0.14(0.02,1.02)	-2.80(-4.03)	0.14(0.02)	N	N	N	N
⩾65	Cardiac asthma	52.48(7.28,378.27)	52.46(7.28,377.98)	5.69(-1.10)	51.68(7.17)	N	N	N	Y

<18	Cardiac failure	4.18(0.59,29.81)	4.18(0.59,29.57)	2.06(-1.36)	4.17(0.59)	N	N	N	N
18-44	Cardiac failure chronic	12.88(1.80,91.96)	12.88(1.80,91.89)	3.68(-1.16)	12.81(1.79)	N	N	N	N
45-64	Cardiac sarcoidosis	20.34(2.83,146.35)	20.34(2.83,146.30)	4.33(-1.14)	20.08(2.79)	N	N	N	Y
NS	Cardiac tamponade	5.48(0.77,38.96)	5.48(0.77,38.93)	2.45(-1.29)	5.47(0.77)	N	N	N	N
⩾65	Cardiogenic shock	0.83(0.12,5.86)	0.83(0.12,5.86)	-0.28(-2.19)	0.83(0.12)	N	N	N	N
⩾65	Cardiomegaly	0.99(0.14,7.00)	0.99(0.14,6.99)	-0.02(-2.05)	0.99(0.14)	N	N	N	N
NS	Cardiomegaly	1.57(0.22,11.18)	1.57(0.22,11.17)	0.65(-1.75)	1.57(0.22)	N	N	N	N
NS	Chordae tendinae rupture	394.59(51.61,3017.18)	394.50(51.62,3015.03)	8.52(-1.18)	366.39(47.92)	N	N	N	Y
⩾65	Coronary artery disease	0.36(0.05,2.57)	0.36(0.05,2.57)	-1.46(-2.95)	0.36(0.05)	N	N	N	N
NS	Coronary artery disease	0.69(0.10,4.87)	0.69(0.10,4.86)	-0.55(-2.34)	0.69(0.10)	N	N	N	N
⩾65	Coronary artery occlusion	0.81(0.11,5.75)	0.81(0.11,5.75)	-0.30(-2.20)	0.81(0.11)	N	N	N	N
45-64	Coronary artery thrombosis	2.18(0.31,15.47)	2.18(0.31,15.46)	1.12(-1.59)	2.17(0.31)	N	N	N	N
NS	Endocardial fibrosis	854.95(102.90,7103.30)	854.74(102.92,7098.35)	9.52(-1.28)	732.78(88.20)	N	N	N	Y
18-44	Extrasystoles	2.60(0.37,18.47)	2.60(0.37,18.46)	1.38(-1.51)	2.60(0.37)	N	N	N	N
NS	Left ventricular failure	6.98(0.98,49.62)	6.98(0.98,49.59)	2.80(-1.24)	6.97(0.98)	N	N	N	N
<18	Mitral valve incompetence	15.21(2.13,108.55)	15.17(2.14,107.61)	3.92(-1.14)	15.14(2.12)	N	N	N	Y
18-44	Myocardial fibrosis	10.95(1.54,78.15)	10.95(1.54,78.08)	3.45(-1.18)	10.91(1.53)	N	N	N	N
⩾65	Myocardial ischaemia	0.96(0.14,6.83)	0.96(0.14,6.83)	-0.06(-2.07)	0.96(0.14)	N	N	N	N
18-	Myocardi	2.42(0.34,1	2.42(0.34,17	1.27(-	2.42(0.	N	N	N	N

44	al ischaemia	7.21)	.20)	1.54)	34)				
NS	Myocarditis	2.31(0.33,16.44)	2.31(0.33,16.43)	1.21(-1.56)	2.31(0.33)	N	N	N	N
⩾65	Nodal rhythm	5.84(0.82,41.54)	5.84(0.82,41.51)	2.54(-1.27)	5.83(0.82)	N	N	N	N
18-44	Pericarditis	0.55(0.08,3.91)	0.55(0.08,3.91)	-0.86(-2.53)	0.55(0.08)	N	N	N	N
⩾65	Pericarditis constrictive	35.53(4.95,254.89)	35.52(4.95,254.69)	5.14(-1.10)	35.17(4.90)	N	N	N	Y
⩾65	Prinzmetal angina	11.68(1.64,83.23)	11.68(1.64,83.16)	3.54(-1.17)	11.64(1.63)	N	N	N	N
<18	Right ventricular failure	32.04(4.48,229.22)	31.95(4.49,227.22)	4.99(-1.10)	31.80(4.45)	N	N	N	Y
45-64	Sinus arrhythmia	6.87(0.96,49.02)	6.87(0.96,49.01)	2.78(-1.25)	6.85(0.96)	N	N	N	N
18-44	Supraventricular extrasystoles	6.74(0.95,47.97)	6.73(0.95,47.93)	2.75(-1.25)	6.72(0.94)	N	N	N	N
⩾65	Supraventricular extrasystoles	2.80(0.39,19.93)	2.80(0.39,19.92)	1.49(-1.48)	2.80(0.39)	N	N	N	N
⩾65	Supraventricular tachycardia	1.44(0.20,10.23)	1.44(0.20,10.22)	0.53(-1.80)	1.44(0.20)	N	N	N	N
18-44	Ventricular extrasystoles	1.54(0.22,10.96)	1.54(0.22,10.96)	0.63(-1.76)	1.54(0.22)	N	N	N	N
⩾65	Ventricular fibrillation	1.12(0.16,7.95)	1.12(0.16,7.94)	0.16(-1.96)	1.12(0.16)	N	N	N	N
⩾65	Ventricular hypertrophy	4.56(0.64,32.42)	4.56(0.64,32.40)	2.19(-1.33)	4.55(0.64)	N	N	N	N
18-44	Ventricular tachycardia	0.84(0.12,5.94)	0.84(0.12,5.94)	-0.26(-2.18)	0.84(0.12)	N	N	N	N
45-64	Tachyarrhythmia	2.96(0.42,21.04)	2.96(0.42,21.03)	1.56(-1.47)	2.95(0.42)	N	N	N	N
NS	Left ventricula	39.46(5.52,282.32)	39.45(5.52,282.11)	5.29(-1.09)	39.16(5.47)	N	N	N	Y

	r dilatation								
⩾65	Left ventricular dilatation	35.16(4.90, 252.23)	35.15(4.90,252.04)	5.12(-1.10)	34.81(4.85)	N	N	N	Y
18-44	Right ventricular enlargement	53.28(7.34, 386.82)	53.26(7.34,386.51)	5.70(-1.11)	52.10(7.18)	N	N	N	Y
NS	Cardiopulmonary failure	5.91(0.83,42.01)	5.91(0.83,41.98)	2.56(-1.27)	5.90(0.83)	N	N	N	N
⩾65	Left atrial enlargement	20.55(2.88, 146.77)	20.54(2.88,146.66)	4.35(-1.12)	20.43(2.86)	N	N	N	Y
NS	Cardiac ventricular thrombosis	4.14(0.58,29.42)	4.14(0.58,29.40)	2.05(-1.36)	4.14(0.58)	N	N	N	N
45-64	Cardiac ventricular thrombosis	1.38(0.19,9.84)	1.38(0.19,9.84)	0.47(-1.83)	1.38(0.19)	N	N	N	N
⩾65	Cardiac ventricular thrombosis	3.20(0.45,22.72)	3.20(0.45,22.70)	1.68(-1.44)	3.19(0.45)	N	N	N	N
45-64	Cardiac discomfort	3.05(0.43,21.72)	3.05(0.43,21.72)	1.61(-1.45)	3.05(0.43)	N	N	N	N
<18	Bradycardia neonatal	11.15(1.56, 79.49)	11.11(1.57,78.81)	3.47(-1.17)	11.10(1.56)	N	N	N	N
45-64	Left atrial hypertrophy	68.42(9.22, 507.69)	68.42(9.22,507.53)	6.03(-1.15)	65.48(8.83)	N	N	N	Y
NS	Right ventricular dysfunction	18.86(2.65, 134.40)	18.85(2.65,134.31)	4.23(-1.12)	18.79(2.64)	N	N	N	Y
NS	Ventricular failure	86.94(12.04,627.69)	86.92(12.05, 627.24)	6.42(-1.09)	85.49(11.84)	N	N	N	Y
18-44	Cardiac disorder	0.50(0.07,3.57)	0.50(0.07,3.57)	-0.99(-2.62)	0.50(0.07)	N	N	N	N
NS	Pericardia	61.80(8.60,	61.79(8.60,4	5.93(-	61.06(8	N	N	N	Y

	l disease	444.07)	43.74)	1.09)	.50)				
⩾65	Pericardial disease	57.81(8.01, 417.38)	57.80(8.01,417.06)	5.83(-1.10)	56.85(7.87)	N	N	N	Y
45-64	Tricuspid valve disease	15.52(2.16, 111.30)	15.52(2.16,111.26)	3.94(-1.15)	15.37(2.14)	N	N	N	Y
45-64	Myocardial oedema	22.14(3.07, 159.45)	22.13(3.07,159.40)	4.45(-1.13)	21.83(3.03)	N	N	N	Y
45-64	Ventricular tachyarrhythmia	26.41(3.66, 190.74)	26.41(3.66,190.68)	4.70(-1.13)	25.97(3.60)	N	N	N	Y
NS	Left atrial dilatation	14.70(2.06, 104.67)	14.69(2.06,104.59)	3.87(-1.14)	14.66(2.06)	N	N	N	Y
18-44	Left atrial dilatation	22.98(3.21, 164.78)	22.98(3.21,164.65)	4.51(-1.12)	22.76(3.18)	N	N	N	Y
45-64	Heart valve incompetence	2.69(0.38,19.12)	2.69(0.38,19.11)	1.42(-1.50)	2.68(0.38)	N	N	N	N
18-44	Systolic dysfunction	12.47(1.75, 89.01)	12.47(1.75,88.94)	3.63(-1.16)	12.41(1.74)	N	N	N	N
⩾65	Systolic dysfunction	14.33(2.01, 102.19)	14.33(2.01,102.11)	3.84(-1.15)	14.27(2.00)	N	N	N	Y
45-64	Microvascular coronary artery disease	23.52(3.26, 169.56)	23.52(3.26,169.51)	4.53(-1.13)	23.17(3.21)	N	N	N	Y
45-64	Sinus node dysfunction	3.08(0.43,21.94)	3.08(0.43,21.94)	1.62(-1.45)	3.08(0.43)	N	N	N	N
<18	Cardiac dysfunction	45.12(6.29, 323.41)	44.99(6.31,320.58)	5.48(-1.09)	44.69(6.24)	N	N	N	Y
45-64	Immune-mediated myocarditis	5.45(0.77,38.86)	5.45(0.77,38.85)	2.44(-1.29)	5.44(0.76)	N	N	N	N
18-44	Cardiac perfusion defect	468.86(54.76,4014.28)	468.73(54.77,4011.23)	8.61(-1.32)	390.77(45.64)	N	N	N	Y
NS	Toxic cardiomyopathy	94.99(13.14,686.86)	94.97(13.14, 686.36)	6.54(-1.09)	93.26(12.90)	N	N	N	Y
18-44	Myocardial injury	5.89(0.83,41.93)	5.89(0.83,41.90)	2.55(-1.27)	5.88(0.83)	N	N	N	N

Analysis of fatal outcomes identified cardiac arrest ($P < 0.0001$, $log_2ROR = 2.96$), cardiovascular disorder ($P < 0.0001$, $log_2ROR = 4.40$), and coronary artery arteriosclerosis ($P = 0.0002$) as significant risk factors associated with death(Table 3).

Table 3 Age Difference Analysis (Group 1 < 65, Group 2 ≥ 65)

PT	P value	log_2ROR
Cardiac failure	0.0021	-0.768445132
Palpitations	0.0208	1.152891804
Dilated cardiomyopathy	0.7160	0.177495365
Cardiac dysfunction	0.3049	-0.45037646
Cardiotoxicity	0.0129	1.986075787
Atrial fibrillation	<.0001	-2.150306213
Cardiomyopathy	0.6306	-0.254446126
Tachycardia	0.5529	0.357704696
Ventricular dysfunction	0.7492	0.210473233
Myocardial infarction	0.0007	-1.793402515
Mitral valve incompetence	0.0714	1.796956762
Left ventricular dysfunction	0.4404	0.603221247
Cardio-respiratory arrest	0.0013	-2.08258679
Arrhythmia	0.2801	-0.898032562
Cardiac failure congestive	0.3265	-0.916487639
Pericardial effusion	1.0000	0.210294113
Cardiac arrest	0.0015	-2.377610701
Myocarditis	0.0052	-2.207304991
Cardiac failure acute	0.2921	-1.112834241
Ventricular hypokinesia	1.0000	-0.205073207
Bradycardia	0.4554	-0.983280832
Sinus tachycardia	0.3406	-1.205783161
Ventricular extrasystoles	0.8456	-0.567863126
Acute myocardial infarction	1.0000	0.017479481
Right atrial dilatation	0.7006	-0.790365455
Supraventricular extrasystoles	0.6783	1.210614481
Cardiogenic shock	0.8028	1.017859488
Left ventricular failure	1.0000	-0.205022847
Cardiac disorder	1.0000	-0.205022847
Pericarditis	1.0000	-0.468167152
Heart failure with midrange ejection fraction	0.8801	-0.790205137
Arteriosclerosis coronary artery	0.0020	-4.113603473
Myocardial ischaemia	1.0000	0.532212855
Angina pectoris	0.8801	-0.790205137
Cardiomegaly	1.0000	0.532212855
Supraventricular tachycardia	1.0000	0.532212855
Aortic valve incompetence	1.0000	0.532212855
Cardiovascular disorder	0.8801	-0.790205137
Acute coronary syndrome	0.6849	-1.205352518
Systolic dysfunction	1.0000	0.21017487
Coronary artery thrombosis	0.0375	-3.375877365
Ventricular fibrillation	1.0000	-0.204972511
Bundle branch block left	0.2192	-1.790424892

Myocardial fibrosis	0.1284	-2.790534758
Atrioventricular block first degree	0.5333	-0.790044886
Atrioventricular block	0.3983	-1.790154751
Bundle branch block right	0.3983	-1.790154751
Cardiac ventricular thrombosis	0.3983	-1.790154751

Table 4 Fatal Outcome Difference Analysis (Group 1 = Fatal, Group 2 = Non-Fatal)

PT	P value	$\log_2$ROR
Cardiac failure	0.3118	0.327044812
Palpitations	0.0057	-3.268873088
Cardiotoxicity	<.0001	1.910700851
Dilated cardiomyopathy	0.0079	1.166994189
Cardiac dysfunction	0.0342	-2.681825042
Cardiomyopathy	0.7470	0.202616513
Atrial fibrillation	0.8195	-0.350403465
Tachycardia	0.5168	0.575356538
Myocardial infarction	0.0372	1.324811663
Mitral valve incompetence	1.0000	-0.038955424
Ventricular hypokinesia	0.4887	-1.448108693
Cardio-respiratory arrest	<.0001	2.957280146
Cardiac failure congestive	0.9070	0.414096178
Cardiac arrest	<.0001	2.819124262
Arrhythmia	1.0000	-0.245593958
Pericardial effusion	0.7821	0.574714926
Cardiac disorder	0.7168	0.6622548
Cardiac failure acute	0.8121	-0.924007426
Tricuspid valve incompetence	0.5134	0.962046153
Acute myocardial infarction	<.0001	3.273884926
Myocarditis	1.0000	0.376433643
Cardiovascular disorder	<.0001	4.40470274
Bradycardia	1.0000	-0.50866184
Pericarditis	1.0000	-0.383053946
Sinus tachycardia	0.8304	0.755176301
Cardiogenic shock	0.6510	1.077258398
Dilatation ventricular	0.6510	1.077258398
Left ventricular failure	0.2459	1.269980471
Diastolic dysfunction	0.2459	1.269980471
Myocardial injury	0.2459	1.269980471
Right atrial dilatation	0.2459	1.269980471
Arteriosclerosis coronary artery	0.0002	4.401599308
Cardiomegaly	0.5436	0.491800167
Bundle branch block left	0.4289	1.076916638
Right ventricular failure	0.2854	2.077070591
Toxic cardiomyopathy	0.2854	2.077070591
Myocardial oedema	0.0313	4.077797278
Atrioventricular block	0.2854	2.077070591
Left ventricular dilatation	0.2007	3.077147561
Left atrial dilatation	0.2007	3.077147561

3.4 External Validation via the EudraVigilance (EV) Database

The findings from the FAERS analysis were corroborated by data from the EV database (2003–2025), which similarly demonstrated an upward reporting trend peaking in 2024 (n=117)(Figure S1). The demographic profile remained consistent, with females representing 87.56% (n=1197) of reports(Figure S2). Robust signals were confirmed for Cardiac failure (n=349, ROR=4.22) and Heart failure with mid-range ejection fraction (ROR=114.25)(Figure S3). Sensitivity analysis excluding concomitant medications sustained these associations for PTs such as cardiotoxicity (ROR=63.09) and cardiac failure (ROR=5.08), validating epirubicin as an independent risk factor(Figure S4). Furthermore, the EV data reinforced age-specific vulnerabilities, with the elderly cohort (≥ 65) showing heightened signal strength for structural impairments like left ventricular dilatation (ROR=38.58, 95% CI: 19.08-78.02)(Table S1).

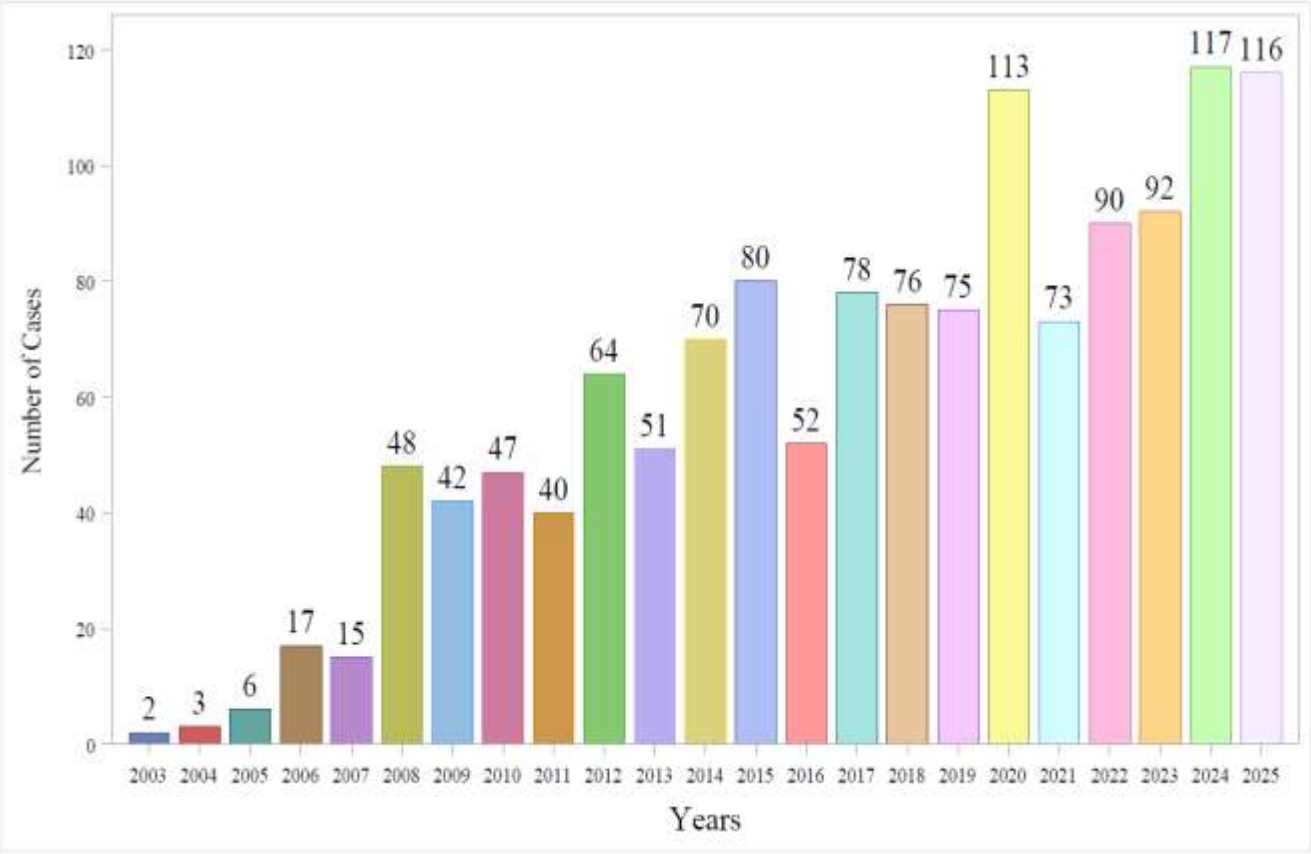


Figure S1: Annual Distribution of AE Reports(EV)

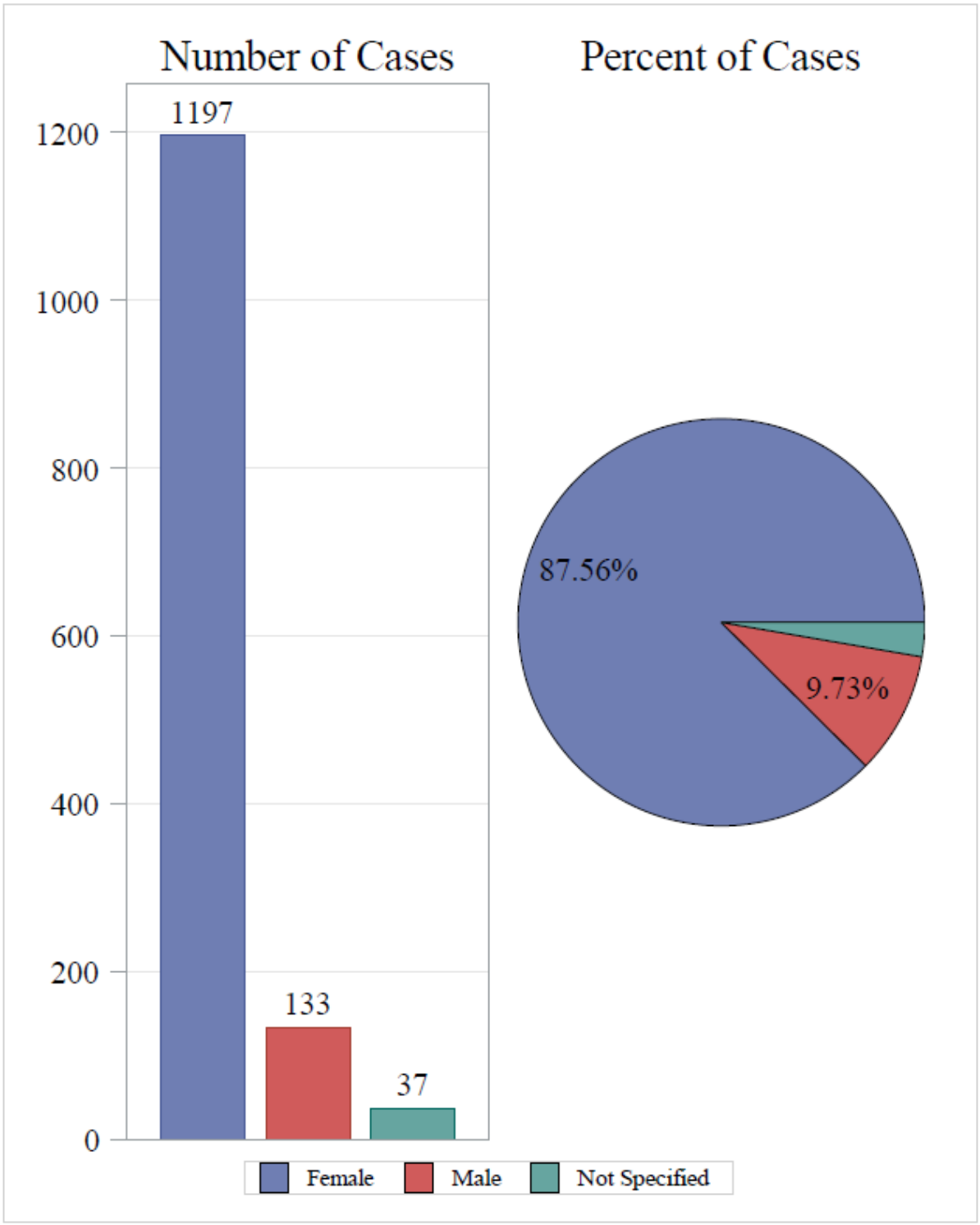


Figure S2: Sex Distribution of AE Reports(EV)

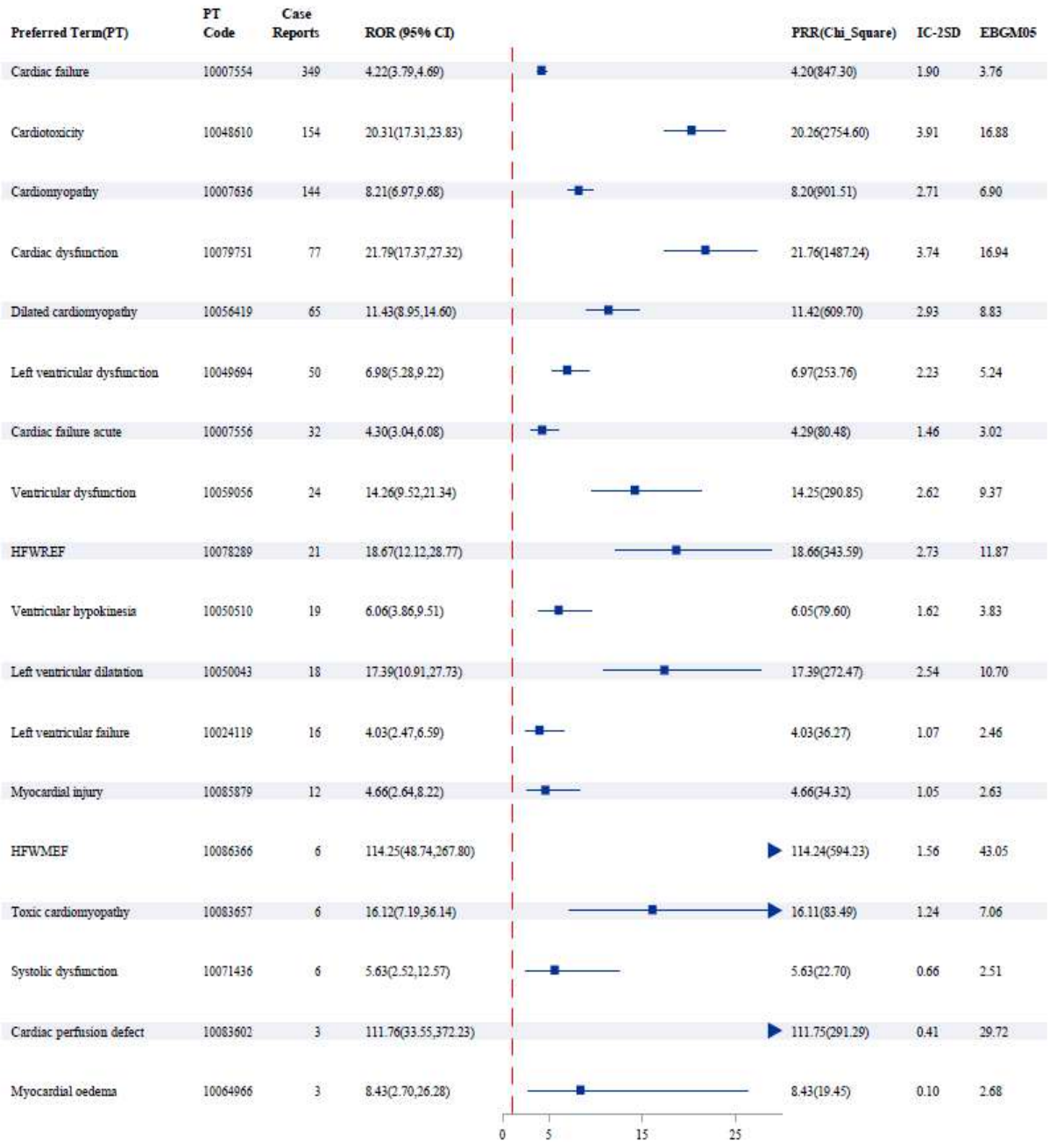


Figure S3: Signal Strength Analysis at the PT Level (Ranked by Reports)

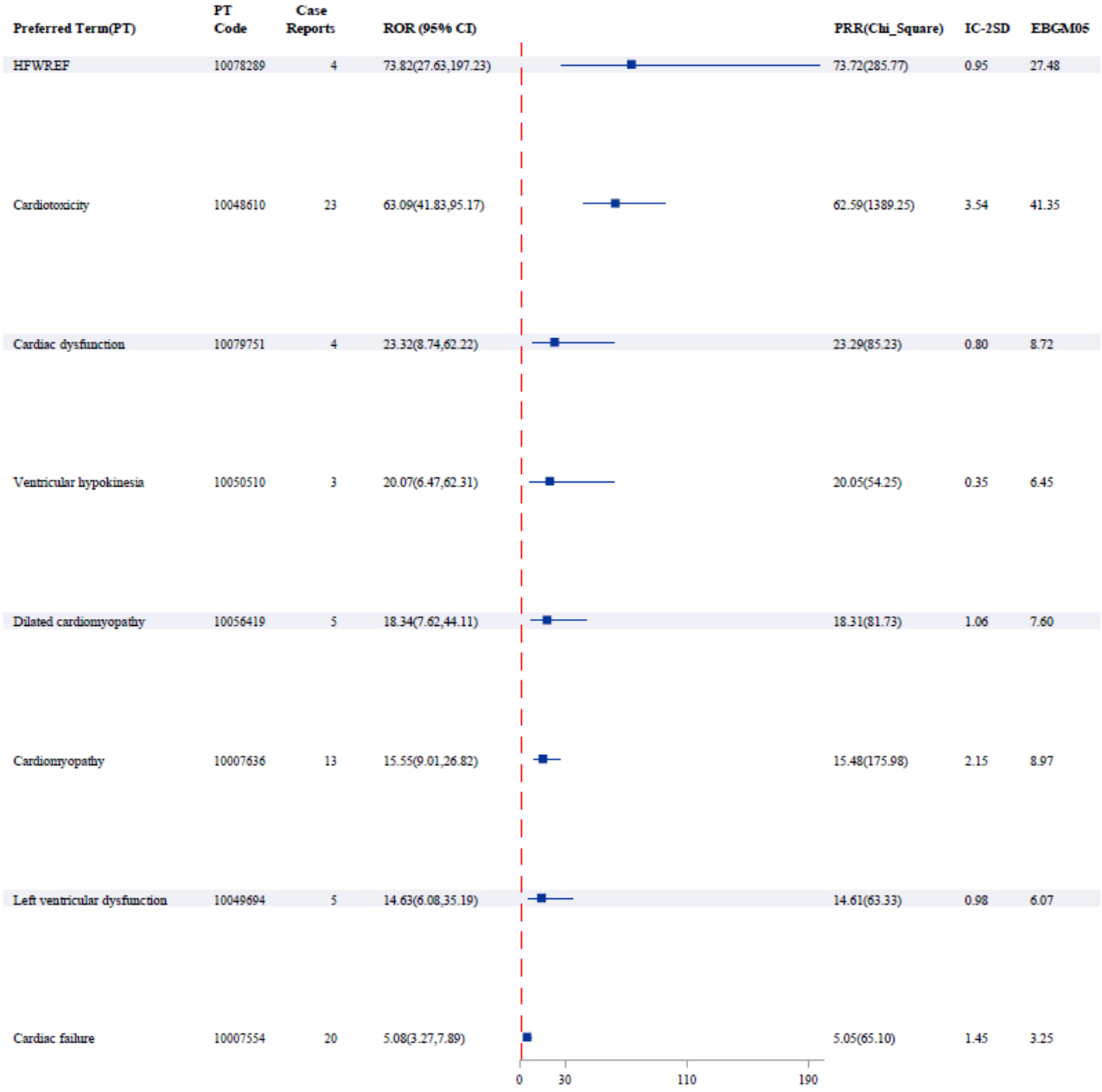


Figure S4: Sensitivity Analysis for PT-Level Signals (Ranked by ROR; Excluding Concomitant Medications)

Table S1 Age-Stratified Signal Detection Results Across MedDRA Hierarchical Levels

age	PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
<18	Cardiac failure	10.93(4.53,26.35)	10.87(4.53,26.09)	3.44(0.85)	10.84(4.50)	Y	Y	Y	Y
⩾65	Cardiac failure	3.07(2.48,3.79)	3.05(2.47,3.76)	1.61(1.26)	3.04(2.46)	Y	Y	Y	Y
18-64	Cardiac failure	5.94(5.20,6.78)	5.91(5.18,6.75)	2.55(2.33)	5.86(5.14)	Y	Y	Y	Y

ALL	Cardiac failure	4.22(3.79,4.69)	4.20(3.78,4.66)	2.06(1.90)	4.18(3.76)	Y	Y	Y	Y
NS	Cardiac failure	8.05(5.77,11.24)	7.97(5.73,11.09)	2.99(2.25)	7.96(5.70)	Y	Y	Y	Y
<18	Cardiotoxicity	16.87(6.30,45.14)	16.80(6.31,44.77)	4.06(0.71)	16.73(6.25)	Y	Y	Y	Y
⩾65	Cardiotoxicity	25.89(17.12,39.14)	25.83(17.10,39.02)	4.66(3.06)	25.31(16.74)	Y	Y	Y	Y
18-64	Cardiotoxicity	17.39(14.13,21.41)	17.36(14.11,21.36)	4.08(3.54)	16.87(13.70)	Y	Y	Y	Y
ALL	Cardiotoxicity	20.31(17.31,23.83)	20.26(17.27,23.76)	4.31(3.91)	19.81(16.88)	Y	Y	Y	Y
NS	Cardiotoxicity	73.31(52.35,102.68)	72.48(51.95,101.12)	6.15(4.10)	70.93(50.64)	Y	Y	Y	Y
<18	Cardiomyopathy	14.31(4.60,44.55)	14.27(4.60,44.25)	3.83(0.27)	14.22(4.57)	Y	Y	Y	Y
⩾65	Cardiomyopathy	14.39(10.57,19.60)	14.34(10.55,19.50)	3.83(2.98)	14.18(10.42)	Y	Y	Y	Y
18-64	Cardiomyopathy	6.40(5.19,7.90)	6.39(5.18,7.88)	2.66(2.27)	6.33(5.13)	Y	Y	Y	Y
ALL	Cardiomyopathy	8.21(6.97,9.68)	8.20(6.96,9.66)	3.02(2.71)	8.13(6.90)	Y	Y	Y	Y
NS	Cardiomyopathy	12.58(7.13,22.20)	12.53(7.12,22.07)	3.64(1.92)	12.49(7.08)	Y	Y	Y	Y
⩾65	Palpitations	0.72(0.44,1.18)	0.73(0.44,1.18)	-0.46(-1.14)	0.73(0.44)	N	N	N	N
18-64	Palpitations	0.60(0.49,0.73)	0.60(0.49,0.73)	-0.74(-1.04)	0.60(0.49)	N	N	N	N
ALL	Palpitations	0.71(0.59,0.85)	0.71(0.59,0.85)	-0.49(-0.76)	0.71(0.59)	N	N	N	N
NS	Palpitations	0.68(0.26,1.82)	0.68(0.26,1.82)	-0.55(-1.75)	0.68(0.26)	N	N	N	N
<18	Cardiac dysfunction	26.33(3.68,188.39)	26.30(3.68,187.79)	4.71(-1.11)	26.13(3.65)	N	N	N	Y
⩾65	Cardiac dysfunction	25.44(16.82,38.46)	25.38(16.80,38.34)	4.64(3.04)	24.88(16.46)	Y	Y	Y	Y
18-64	Cardiac dysfunction	21.13(15.52,28.76)	21.11(15.52,28.73)	4.35(3.36)	20.38(14.97)	Y	Y	Y	Y
ALL	Cardiac dysfunction	21.79(17.37,27.32	21.76(17.36,27.28)	4.41(3.74)	21.24(16.94)	Y	Y	Y	Y

		)							
NS	Cardiac dysfunction	52.79(29.07,95.88)	52.61(29.03,95.34)	5.69(2.46)	51.79(28.52)	Y	Y	Y	Y
<18	Cardiac failure congestive	7.57(1.06,53.93)	7.57(1.06,53.77)	2.92(-1.23)	7.55(1.06)	N	N	N	N
⩾65	Cardiac failure congestive	1.17(0.75,1.81)	1.17(0.75,1.81)	0.23(-0.42)	1.17(0.75)	N	N	N	N
18-64	Cardiac failure congestive	1.40(1.02,1.91)	1.40(1.02,1.91)	0.48(0.01)	1.40(1.02)	Y	Y	Y	N
ALL	Cardiac failure congestive	1.17(0.93,1.48)	1.17(0.93,1.48)	0.23(-0.12)	1.17(0.93)	N	N	N	N
NS	Cardiac failure congestive	2.28(1.22,4.23)	2.27(1.22,4.22)	1.18(0.15)	2.27(1.22)	Y	Y	Y	N
<18	Dilated cardiomyopathy	35.10(11.24,109.60)	34.99(11.25,108.85)	5.12(0.43)	34.68(11.11)	Y	Y	Y	Y
⩾65	Dilated cardiomyopathy	18.15(11.07,29.74)	18.12(11.06,29.67)	4.16(2.46)	17.87(10.90)	Y	Y	Y	Y
18-64	Dilated cardiomyopathy	8.76(6.50,11.80)	8.75(6.50,11.78)	3.11(2.45)	8.63(6.41)	Y	Y	Y	Y
ALL	Dilated cardiomyopathy	11.43(8.95,14.60)	11.42(8.94,14.58)	3.50(2.93)	11.28(8.83)	Y	Y	Y	Y
NS	Dilated cardiomyopathy	9.54(2.38,38.25)	9.54(2.38,38.19)	3.25(-0.36)	9.51(2.37)	N	N	N	Y
⩾65	Tachycardia	0.42(0.21,0.83)	0.42(0.21,0.83)	-1.26(-2.13)	0.42(0.21)	N	N	N	N
18-64	Tachycardia	0.27(0.20,0.37)	0.27(0.20,0.37)	-1.88(-2.29)	0.27(0.20)	N	N	N	N
ALL	Tachycardia	0.33(0.25,0.43)	0.33(0.25,0.43)	-1.60(-1.97)	0.33(0.25)	N	N	N	N
NS	Tachycardia	0.44(0.11,1.76)	0.44(0.11,1.76)	-1.19(-2.56)	0.44(0.11)	N	N	N	N
⩾65	Left ventricular dysfunction	5.55(2.77,11.13)	5.55(2.77,11.12)	2.47(0.91)	5.53(2.76)	Y	Y	Y	Y
18-64	Left ventricular dysfunction	6.23(4.51,8.62)	6.23(4.50,8.61)	2.62(1.97)	6.17(4.46)	Y	Y	Y	Y
ALL	Left ventricular dysfunction	6.98(5.28,9.22)	6.97(5.28,9.21)	2.79(2.23)	6.92(5.24)	Y	Y	Y	Y

NS	Left ventricular dysfunction	20.85(8.65,50.26)	20.81(8.64,50.11)	4.37(1.09)	20.69(8.58)	Y	Y	Y	Y
⩾65	Atrial fibrillation	0.70(0.47,1.05)	0.70(0.47,1.05)	-0.51(-1.07)	0.70(0.47)	N	N	N	N
18-64	Atrial fibrillation	0.60(0.38,0.92)	0.60(0.38,0.92)	-0.75(-1.35)	0.60(0.38)	N	N	N	N
ALL	Atrial fibrillation	0.55(0.41,0.73)	0.55(0.41,0.73)	-0.87(-1.27)	0.55(0.41)	N	N	N	N
NS	Atrial fibrillation	0.88(0.33,2.35)	0.88(0.33,2.35)	-0.18(-1.44)	0.88(0.33)	N	N	N	N
⩾65	Sinus tachycardia	1.81(0.58,5.63)	1.81(0.58,5.63)	0.86(-0.85)	1.81(0.58)	N	N	N	N
18-64	Sinus tachycardia	1.64(1.14,2.37)	1.64(1.14,2.37)	0.72(0.16)	1.64(1.14)	Y	Y	Y	N
ALL	Sinus tachycardia	2.04(1.46,2.86)	2.04(1.46,2.86)	1.03(0.50)	2.04(1.46)	Y	Y	Y	N
NS	Sinus tachycardia	6.65(1.66,26.63)	6.64(1.66,26.59)	2.73(-0.46)	6.63(1.66)	N	N	N	N
⩾65	Cardiac failure acute	4.30(2.38,7.77)	4.29(2.38,7.76)	2.10(0.91)	4.28(2.37)	Y	Y	Y	Y
18-64	Cardiac failure acute	4.59(2.96,7.13)	4.59(2.96,7.13)	2.19(1.33)	4.56(2.94)	Y	Y	Y	Y
ALL	Cardiac failure acute	4.30(3.04,6.08)	4.29(3.03,6.08)	2.10(1.46)	4.28(3.02)	Y	Y	Y	Y
NS	Cardiac failure acute	5.09(0.72,36.19)	5.09(0.72,36.16)	2.34(-1.30)	5.08(0.71)	N	N	N	N
⩾65	Cardiac disorder	0.43(0.19,0.96)	0.43(0.19,0.96)	-1.22(-2.18)	0.43(0.19)	N	N	N	N
18-64	Cardiac disorder	0.71(0.46,1.09)	0.71(0.46,1.09)	-0.49(-1.09)	0.71(0.46)	N	N	N	N
ALL	Cardiac disorder	0.52(0.37,0.74)	0.52(0.37,0.74)	-0.93(-1.41)	0.52(0.37)	N	N	N	N
NS	Cardiac disorder	0.90(0.37,2.17)	0.90(0.38,2.16)	-0.15(-1.31)	0.90(0.37)	N	N	N	N
⩾65	Myocardial infarction	0.35(0.19,0.65)	0.35(0.19,0.66)	-1.50(-2.29)	0.35(0.19)	N	N	N	N
18-64	Myocardial infarction	0.21(0.13,0.34)	0.21(0.13,0.34)	-2.26(-2.89)	0.21(0.13)	N	N	N	N
ALL	Myocardial infarction	0.25(0.17,0.35)	0.25(0.17,0.35)	-2.02(-2.49)	0.25(0.17)	N	N	N	N
NS	Myocardial infarction	0.54(0.22,1.30)	0.54(0.22,1.30)	-0.89(-1.95)	0.54(0.22)	N	N	N	N
<18	Arrhythmia	2.04(0.29,14.53)	2.04(0.29,14.49)	1.03(-1.62)	2.04(0.29)	N	N	N	N
⩾65	Arrhythmia	0.35(0.15,0.85)	0.35(0.15,0.85)	-1.50(-2.52)	0.35(0.15)	N	N	N	N
18-64	Arrhythmia	0.37(0.23,0.58)	0.37(0.23,0.58)	-1.45(-2.06)	0.37(0.23)	N	N	N	N
AL	Arrhythmia	0.45(0.3	0.45(0.31,0.64)	-1.16(-	0.45(0.	N	N	N	N

L		1,0.64)		1.65)	31)				
NS	Arrhythmia	1.76(0.79,3.93)	1.76(0.79,3.92)	0.82(-0.42)	1.76(0.79)	N	N	N	N
⩾65	Ventricular dysfunction	26.31(12.44,55.65)	26.29(12.44,55.58)	4.69(1.62)	25.76(12.18)	Y	Y	Y	Y
18-64	Ventricular dysfunction	11.31(7.00,18.28)	11.30(6.99,18.27)	3.47(2.14)	11.10(6.87)	Y	Y	Y	Y
ALL	Ventricular dysfunction	14.26(9.52,21.34)	14.25(9.52,21.33)	3.81(2.62)	14.03(9.37)	Y	Y	Y	Y
⩾65	Pericardial effusion	0.66(0.21,2.04)	0.66(0.21,2.04)	-0.60(-1.92)	0.66(0.21)	N	N	N	N
18-64	Pericardial effusion	0.92(0.55,1.52)	0.92(0.55,1.52)	-0.12(-0.84)	0.92(0.55)	N	N	N	N
ALL	Pericardial effusion	1.03(0.69,1.55)	1.03(0.69,1.55)	0.05(-0.55)	1.03(0.69)	N	N	N	N
NS	Pericardial effusion	4.84(2.01,11.64)	4.83(2.01,11.61)	2.27(0.38)	4.83(2.01)	Y	Y	Y	Y
<18	Mitral valve incompetence	10.32(1.45,73.52)	10.31(1.45,73.29)	3.36(-1.18)	10.28(1.44)	N	N	N	N
⩾65	Mitral valve incompetence	1.17(0.38,3.62)	1.17(0.38,3.62)	0.22(-1.28)	1.17(0.38)	N	N	N	N
18-64	Mitral valve incompetence	2.33(1.44,3.74)	2.32(1.44,3.74)	1.21(0.43)	2.32(1.44)	Y	Y	Y	N
ALL	Mitral valve incompetence	2.19(1.46,3.30)	2.19(1.46,3.30)	1.13(0.47)	2.19(1.45)	Y	Y	Y	N
NS	Mitral valve incompetence	4.53(1.13,18.14)	4.53(1.13,18.11)	2.18(-0.61)	4.52(1.13)	N	N	N	N
⩾65	Heart failure with reduced ejection fraction	23.00(11.42,46.31)	22.98(11.42,46.25)	4.50(1.76)	22.57(11.21)	Y	Y	Y	Y
18-64	Heart failure with reduced ejection fraction	17.72(10.20,30.78)	17.71(10.20,30.77)	4.10(2.21)	17.20(9.90)	Y	Y	Y	Y
ALL	Heart failure with reduced ejection fraction	18.67(12.12,28.77)	18.66(12.11,28.76)	4.19(2.73)	18.29(11.87)	Y	Y	Y	Y
⩾65	Acute myocardial infarction	0.71(0.32,1.57)	0.71(0.32,1.57)	-0.50(-1.53)	0.71(0.32)	N	N	N	N
18-	Acute	0.55(0.3	0.55(0.30,0.99)	-0.87(-	0.55(0.	N	N	N	N

64	myocardial infarction	0,0.99)		1.64)	30)				
ALL	Acute myocardial infarction	0.69(0.44,1.07)	0.69(0.44,1.07)	-0.54(-1.15)	0.69(0.44)	N	N	N	N
NS	Acute myocardial infarction	2.88(0.93,8.95)	2.88(0.93,8.93)	1.53(-0.47)	2.88(0.93)	N	N	N	N
<18	Bradycardia	0.66(0.09,4.66)	0.66(0.09,4.66)	-0.61(-2.38)	0.66(0.09)	N	N	N	N
⩾65	Bradycardia	0.33(0.16,0.66)	0.33(0.16,0.66)	-1.61(-2.46)	0.33(0.16)	N	N	N	N
18-64	Bradycardia	0.23(0.13,0.43)	0.23(0.13,0.44)	-2.09(-2.86)	0.23(0.13)	N	N	N	N
ALL	Bradycardia	0.26(0.17,0.40)	0.26(0.17,0.40)	-1.96(-2.54)	0.26(0.17)	N	N	N	N
NS	Bradycardia	0.42(0.06,2.98)	0.42(0.06,2.98)	-1.25(-2.80)	0.42(0.06)	N	N	N	N
<18	Ventricular hypokinesia	117.13(37.06,370.16)	116.75(37.08,367.60)	6.82(0.49)	113.31(35.86)	Y	Y	Y	Y
⩾65	Ventricular hypokinesia	9.54(4.53,20.08)	9.53(4.53,20.05)	3.24(1.18)	9.47(4.50)	Y	Y	Y	Y
18-64	Ventricular hypokinesia	2.61(1.24,5.49)	2.61(1.24,5.48)	1.38(0.09)	2.60(1.24)	Y	Y	Y	N
ALL	Ventricular hypokinesia	6.06(3.86,9.51)	6.05(3.86,9.51)	2.59(1.62)	6.02(3.83)	Y	Y	Y	Y
NS	Ventricular hypokinesia	30.92(7.68,124.52)	30.90(7.68,124.33)	4.94(-0.19)	30.63(7.61)	N	N	N	Y
⩾65	Cardiomegaly	1.23(0.40,3.82)	1.23(0.40,3.82)	0.30(-1.22)	1.23(0.40)	N	N	N	N
18-64	Cardiomegaly	1.71(1.03,2.84)	1.71(1.03,2.84)	0.77(-0.01)	1.71(1.03)	Y	Y	N	N
ALL	Cardiomegaly	1.57(1.00,2.47)	1.57(1.00,2.47)	0.65(-0.04)	1.57(1.00)	Y	Y	N	N
NS	Cardiomegaly	1.63(0.23,11.58)	1.63(0.23,11.57)	0.70(-1.73)	1.63(0.23)	N	N	N	N
<18	Cardiac arrest	0.89(0.13,6.35)	0.89(0.13,6.33)	-0.16(-2.13)	0.89(0.13)	N	N	N	N
⩾65	Cardiac arrest	0.35(0.16,0.78)	0.35(0.16,0.78)	-1.51(-2.46)	0.35(0.16)	N	N	N	N
18-64	Cardiac arrest	0.15(0.08,0.28)	0.15(0.08,0.28)	-2.73(-3.49)	0.15(0.08)	N	N	N	N
ALL	Cardiac arrest	0.23(0.15,0.36)	0.23(0.15,0.36)	-2.11(-2.70)	0.23(0.15)	N	N	N	N
NS	Cardiac arrest	0.76(0.19,3.04)	0.76(0.19,3.04)	-0.40(-1.94)	0.76(0.19)	N	N	N	N
⩾65	Left ventricular	38.58(19.08,78.02	38.55(19.07,77.91)	5.22(1.91)	37.39(18.49)	Y	Y	Y	Y

	dilatation	)							
18-64	Left ventricular dilatation	8.41(3.98,17.73)	8.40(3.98,17.73)	3.05(1.09)	8.29(3.93)	Y	Y	Y	Y
ALL	Left ventricular dilatation	17.39(10.91,27.73)	17.39(10.90,27.72)	4.09(2.54)	17.06(10.70)	Y	Y	Y	Y
NS	Left ventricular dilatation	75.09(23.90,235.99)	75.02(23.90,235.50)	6.20(0.48)	73.36(23.34)	Y	Y	Y	Y
⩾65	Left ventricular failure	2.50(0.80,7.75)	2.50(0.80,7.75)	1.32(-0.59)	2.49(0.80)	N	N	N	N
18-64	Left ventricular failure	4.03(2.16,7.51)	4.03(2.16,7.50)	2.00(0.78)	4.01(2.15)	Y	Y	Y	Y
ALL	Left ventricular failure	4.03(2.47,6.59)	4.03(2.47,6.58)	2.01(1.07)	4.02(2.46)	Y	Y	Y	Y
NS	Left ventricular failure	20.16(6.47,62.75)	20.14(6.48,62.62)	4.32(0.35)	20.02(6.43)	Y	Y	Y	Y
⩾65	Myocarditis	1.23(0.46,3.27)	1.23(0.46,3.27)	0.29(-1.06)	1.23(0.46)	N	N	N	N
18-64	Myocarditis	0.36(0.19,0.67)	0.36(0.19,0.67)	-1.47(-2.25)	0.36(0.19)	N	N	N	N
ALL	Myocarditis	0.51(0.31,0.85)	0.51(0.31,0.85)	-0.96(-1.64)	0.51(0.31)	N	N	N	N
NS	Myocarditis	1.04(0.15,7.38)	1.04(0.15,7.38)	0.06(-2.01)	1.04(0.15)	N	N	N	N
⩾65	Cardiogenic shock	0.70(0.23,2.17)	0.70(0.23,2.17)	-0.52(-1.85)	0.70(0.23)	N	N	N	N
18-64	Cardiogenic shock	0.90(0.47,1.73)	0.90(0.47,1.73)	-0.16(-1.05)	0.90(0.47)	N	N	N	N
ALL	Cardiogenic shock	0.98(0.58,1.65)	0.98(0.58,1.65)	-0.04(-0.78)	0.98(0.58)	N	N	N	N
NS	Cardiogenic shock	6.62(1.65,26.53)	6.62(1.65,26.49)	2.72(-0.47)	6.61(1.65)	N	N	N	N
⩾65	Ventricular extrasystoles	1.20(0.39,3.74)	1.20(0.39,3.73)	0.27(-1.25)	1.20(0.39)	N	N	N	N
18-64	Ventricular extrasystoles	1.23(0.68,2.22)	1.23(0.68,2.22)	0.30(-0.56)	1.23(0.68)	N	N	N	N
ALL	Ventricular extrasystoles	1.25(0.74,2.11)	1.25(0.74,2.11)	0.32(-0.45)	1.25(0.74)	N	N	N	N
<18	Cardio-respiratory arrest	1.44(0.20,10.26)	1.44(0.20,10.23)	0.53(-1.80)	1.44(0.20)	N	N	N	N
⩾65	Cardio-respiratory arrest	0.50(0.19,1.32)	0.50(0.19,1.32)	-1.01(-2.15)	0.50(0.19)	N	N	N	N
18-	Cardio-	0.19(0.0	0.19(0.09,0.37)	-2.42(-	0.19(0.	N	N	N	N

64	respiratory arrest	9,0.37)		3.25)	09)				
ALL	Cardio-respiratory arrest	0.28(0.16,0.49)	0.28(0.16,0.49)	-1.83(-2.52)	0.28(0.16)	N	N	N	N
⩾65	Cardiac failure chronic	0.52(0.07,3.72)	0.52(0.07,3.72)	-0.93(-2.58)	0.52(0.07)	N	N	N	N
18-64	Cardiac failure chronic	5.43(3.00,9.84)	5.43(3.00,9.83)	2.43(1.14)	5.39(2.98)	Y	Y	Y	Y
ALL	Cardiac failure chronic	2.41(1.37,4.25)	2.41(1.37,4.25)	1.27(0.32)	2.41(1.37)	Y	Y	Y	N
18-64	Myocardial injury	6.28(3.55,11.09)	6.28(3.55,11.09)	2.64(1.34)	6.22(3.52)	Y	Y	Y	Y
ALL	Myocardial injury	4.66(2.64,8.22)	4.66(2.64,8.22)	2.21(1.05)	4.64(2.63)	Y	Y	Y	Y
<18	Tricuspid valve incompetence	8.94(1.26,63.68)	8.93(1.26,63.49)	3.16(-1.20)	8.91(1.25)	N	N	N	N
⩾65	Tricuspid valve incompetence	0.78(0.11,5.55)	0.78(0.11,5.55)	-0.36(-2.23)	0.78(0.11)	N	N	N	N
18-64	Tricuspid valve incompetence	2.19(1.14,4.22)	2.19(1.14,4.22)	1.13(0.05)	2.19(1.14)	Y	Y	Y	N
ALL	Tricuspid valve incompetence	1.93(1.10,3.40)	1.93(1.10,3.40)	0.95(0.05)	1.93(1.09)	Y	Y	Y	N
NS	Tricuspid valve incompetence	3.07(0.43,21.83)	3.07(0.43,21.81)	1.62(-1.45)	3.07(0.43)	N	N	N	N
⩾65	Myocardial ischaemia	1.18(0.38,3.66)	1.18(0.38,3.66)	0.24(-1.27)	1.18(0.38)	N	N	N	N
18-64	Myocardial ischaemia	1.13(0.56,2.25)	1.13(0.56,2.25)	0.17(-0.81)	1.12(0.56)	N	N	N	N
ALL	Myocardial ischaemia	1.07(0.59,1.93)	1.07(0.59,1.93)	0.10(-0.74)	1.07(0.59)	N	N	N	N
⩾65	Immune-mediated myocarditis	0.79(0.11,5.61)	0.79(0.11,5.61)	-0.34(-2.22)	0.79(0.11)	N	N	N	N
18-64	Immune-mediated myocarditis	5.47(2.84,10.55)	5.47(2.84,10.54)	2.44(0.99)	5.42(2.81)	Y	Y	Y	Y
AL	Immune-	3.53(1.9	3.53(1.95,6.39)	1.82(0.	3.52(1.	Y	Y	Y	N

L	mediated myocarditis	5,6.39)		71)	95)				
NS	Immune-mediated myocarditis	15.03(2.11,107.23)	15.03(2.11,107.13)	3.90(-1.14)	14.96(2.10)	N	N	N	Y
⩾65	Supraventricular tachycardia	1.61(0.52,4.99)	1.61(0.52,4.99)	0.68(-0.96)	1.61(0.52)	N	N	N	N
18-64	Supraventricular tachycardia	0.97(0.46,2.04)	0.97(0.46,2.04)	-0.04(-1.06)	0.97(0.46)	N	N	N	N
ALL	Supraventricular tachycardia	1.12(0.62,2.03)	1.12(0.62,2.03)	0.17(-0.68)	1.12(0.62)	N	N	N	N
NS	Supraventricular tachycardia	2.47(0.35,17.52)	2.46(0.35,17.51)	1.30(-1.53)	2.46(0.35)	N	N	N	N
⩾65	Ventricular tachycardia	0.44(0.11,1.75)	0.44(0.11,1.75)	-1.19(-2.56)	0.44(0.11)	N	N	N	N
18-64	Ventricular tachycardia	0.46(0.21,1.02)	0.46(0.21,1.02)	-1.13(-2.10)	0.46(0.21)	N	N	N	N
ALL	Ventricular tachycardia	0.62(0.34,1.12)	0.62(0.34,1.12)	-0.69(-1.48)	0.62(0.34)	N	N	N	N
NS	Ventricular tachycardia	6.31(2.03,19.59)	6.30(2.03,19.56)	2.65(-0.01)	6.29(2.03)	Y	Y	N	Y
⩾65	Sinus bradycardia	0.29(0.04,2.06)	0.29(0.04,2.06)	-1.78(-3.19)	0.29(0.04)	N	N	N	N
18-64	Sinus bradycardia	1.06(0.53,2.12)	1.06(0.53,2.12)	0.08(-0.89)	1.06(0.53)	N	N	N	N
ALL	Sinus bradycardia	0.89(0.48,1.66)	0.89(0.48,1.66)	-0.16(-1.02)	0.89(0.48)	N	N	N	N
NS	Sinus bradycardia	5.18(0.73,36.82)	5.18(0.73,36.79)	2.37(-1.30)	5.17(0.73)	N	N	N	N
⩾65	Right ventricular failure	1.35(0.34,5.40)	1.35(0.34,5.40)	0.43(-1.40)	1.35(0.34)	N	N	N	N
18-64	Right ventricular failure	1.21(0.54,2.70)	1.21(0.54,2.70)	0.28(-0.86)	1.21(0.54)	N	N	N	N
ALL	Right ventricular failure	1.34(0.70,2.57)	1.34(0.70,2.57)	0.42(-0.54)	1.34(0.70)	N	N	N	N
NS	Right ventricular failure	3.23(0.45,22.93)	3.22(0.45,22.91)	1.69(-1.43)	3.22(0.45)	N	N	N	N
⩾65	Acute coronary syndrome	0.43(0.06,3.04)	0.43(0.06,3.04)	-1.22(-2.78)	0.43(0.06)	N	N	N	N
18-64	Acute coronary syndrome	1.26(0.60,2.65)	1.26(0.60,2.65)	0.33(-0.74)	1.26(0.60)	N	N	N	N

ALL	Acute coronary syndrome	1.11(0.58,2.13)	1.11(0.58,2.13)	0.15(-0.78)	1.11(0.58)	N	N	N	N
NS	Acute coronary syndrome	3.18(0.45,22.57)	3.17(0.45,22.55)	1.67(-1.44)	3.17(0.45)	N	N	N	N
⩾65	Supraventricular extrasystoles	0.96(0.14,6.84)	0.96(0.14,6.84)	-0.05(-2.07)	0.96(0.14)	N	N	N	N
18-64	Supraventricular extrasystoles	3.08(1.54,6.16)	3.08(1.54,6.16)	1.62(0.35)	3.06(1.53)	Y	Y	Y	N
ALL	Supraventricular extrasystoles	2.30(1.19,4.42)	2.30(1.19,4.42)	1.20(0.11)	2.29(1.19)	Y	Y	Y	N
⩾65	Cardiac ventricular thrombosis	1.36(0.19,9.67)	1.36(0.19,9.67)	0.44(-1.84)	1.36(0.19)	N	N	N	N
18-64	Cardiac ventricular thrombosis	2.89(1.44,5.79)	2.89(1.44,5.79)	1.53(0.29)	2.88(1.44)	Y	Y	Y	N
ALL	Cardiac ventricular thrombosis	2.24(1.17,4.32)	2.24(1.17,4.32)	1.16(0.08)	2.24(1.17)	Y	Y	Y	N
18-64	Pericarditis	0.11(0.05,0.27)	0.11(0.05,0.27)	-3.14(-4.08)	0.11(0.05)	N	N	N	N
ALL	Pericarditis	0.16(0.08,0.33)	0.16(0.08,0.34)	-2.64(-3.51)	0.16(0.08)	N	N	N	N
NS	Pericarditis	0.74(0.19,2.98)	0.74(0.19,2.97)	-0.43(-1.97)	0.74(0.19)	N	N	N	N
⩾65	Ventricular fibrillation	0.31(0.04,2.21)	0.31(0.04,2.21)	-1.68(-3.12)	0.31(0.04)	N	N	N	N
18-64	Ventricular fibrillation	0.55(0.25,1.23)	0.55(0.25,1.23)	-0.85(-1.85)	0.55(0.25)	N	N	N	N
ALL	Ventricular fibrillation	0.52(0.25,1.10)	0.52(0.25,1.10)	-0.93(-1.87)	0.52(0.25)	N	N	N	N
⩾65	Cardiovascular disorder	0.83(0.27,2.58)	0.83(0.27,2.58)	-0.26(-1.65)	0.83(0.27)	N	N	N	N
18-64	Cardiovascular disorder	0.12(0.03,0.48)	0.12(0.03,0.48)	-3.05(-4.22)	0.12(0.03)	N	N	N	N
ALL	Cardiovascular disorder	0.28(0.13,0.59)	0.28(0.13,0.59)	-1.83(-2.71)	0.28(0.13)	N	N	N	N
NS	Cardiovascular disorder	0.93(0.23,3.71)	0.93(0.23,3.71)	-0.11(-1.74)	0.93(0.23)	N	N	N	N
⩾65	Heart failure with midrange ejection fraction	201.62(45.12,901.00)	201.59(45.12,900.60)	7.43(-0.26)	172.93(38.70)	N	N	N	Y
18-64	Heart failure with	71.74(25.32,203.2	71.73(25.32,203.21)	5.99(0.85)	63.65(22.47)	Y	Y	Y	Y

	midrange ejection fraction	4)							
ALL	Heart failure with midrange ejection fraction	114.25(48.74,267.80)	114.24(48.74,267.75)	6.66(1.56)	100.91 (43.05)	Y	Y	Y	Y
18-64	Toxic cardiomyopathy	16.12(7.16,36.29)	16.11(7.16,36.28)	3.97(1.23)	15.69(6.97)	Y	Y	Y	Y
ALL	Toxic cardiomyopathy	16.12(7.19,36.14)	16.11(7.19,36.14)	3.99(1.24)	15.84(7.06)	Y	Y	Y	Y
⩾65	Systolic dysfunction	5.28(0.74,37.66)	5.28(0.74,37.65)	2.40(-1.30)	5.26(0.74)	N	N	N	N
18-64	Systolic dysfunction	4.54(1.70,12.14)	4.54(1.70,12.14)	2.17(0.11)	4.51(1.69)	Y	Y	Y	N
ALL	Systolic dysfunction	5.63(2.52,12.57)	5.63(2.52,12.57)	2.49(0.66)	5.60(2.51)	Y	Y	Y	Y
NS	Systolic dysfunction	23.58(3.30,168.60)	23.57(3.30,168.44)	4.55(-1.12)	23.41(3.27)	N	N	N	Y
⩾65	Bundle branch block left	1.56(0.39,6.26)	1.56(0.39,6.26)	0.64(-1.27)	1.56(0.39)	N	N	N	N
18-64	Bundle branch block left	1.05(0.34,3.25)	1.05(0.34,3.25)	0.07(-1.40)	1.05(0.34)	N	N	N	N
ALL	Bundle branch block left	1.40(0.63,3.11)	1.40(0.63,3.11)	0.48(-0.69)	1.39(0.63)	N	N	N	N
NS	Bundle branch block left	6.62(0.93,47.10)	6.62(0.93,47.06)	2.72(-1.25)	6.61(0.93)	N	N	N	N
⩾65	Arteriosclerosis coronary artery	1.55(0.50,4.81)	1.55(0.50,4.81)	0.63(-1.00)	1.55(0.50)	N	N	N	N
18-64	Arteriosclerosis coronary artery	0.17(0.02,1.24)	0.17(0.02,1.24)	-2.52(-3.79)	0.17(0.02)	N	N	N	N
ALL	Arteriosclerosis coronary artery	0.64(0.27,1.54)	0.64(0.27,1.54)	-0.64(-1.73)	0.64(0.27)	N	N	N	N
NS	Arteriosclerosis coronary artery	2.84(0.40,20.20)	2.84(0.40,20.18)	1.51(-1.48)	2.84(0.40)	N	N	N	N
⩾65	Angina pectoris	0.25(0.06,1.00)	0.25(0.06,1.00)	-2.00(-3.25)	0.25(0.06)	N	N	N	N
18-64	Angina pectoris	0.11(0.04,0.35)	0.11(0.04,0.35)	-3.15(-4.24)	0.11(0.04)	N	N	N	N

ALL	Angina pectoris	0.14(0.06,0.34)	0.14(0.06,0.34)	-2.82(-3.77)	0.14(0.06)	N	N	N	N
⩾65	Extrasystoles	0.52(0.07,3.66)	0.52(0.07,3.66)	-0.96(-2.60)	0.52(0.07)	N	N	N	N
18-64	Extrasystoles	0.47(0.18,1.26)	0.47(0.18,1.26)	-1.08(-2.21)	0.47(0.18)	N	N	N	N
ALL	Extrasystoles	0.49(0.20,1.18)	0.49(0.20,1.18)	-1.02(-2.08)	0.49(0.20)	N	N	N	N
⩾65	Bundle branch block right	0.85(0.12,6.07)	0.85(0.12,6.07)	-0.23(-2.16)	0.85(0.12)	N	N	N	N
18-64	Bundle branch block right	1.21(0.45,3.23)	1.21(0.45,3.23)	0.28(-1.08)	1.21(0.45)	N	N	N	N
ALL	Bundle branch block right	1.07(0.44,2.56)	1.07(0.44,2.56)	0.09(-1.10)	1.07(0.44)	N	N	N	N
18-64	Diastolic dysfunction	1.59(0.51,4.93)	1.59(0.51,4.93)	0.67(-0.98)	1.59(0.51)	N	N	N	N
ALL	Diastolic dysfunction	1.39(0.52,3.71)	1.39(0.52,3.71)	0.48(-0.92)	1.39(0.52)	N	N	N	N
NS	Diastolic dysfunction	6.73(0.95,47.88)	6.73(0.95,47.84)	2.75(-1.25)	6.71(0.94)	N	N	N	N
⩾65	Myocardial fibrosis	12.60(1.76,90.38)	12.60(1.76,90.35)	3.64(-1.17)	12.48(1.74)	N	N	N	N
18-64	Myocardial fibrosis	2.30(0.57,9.21)	2.30(0.57,9.21)	1.20(-0.99)	2.29(0.57)	N	N	N	N
ALL	Myocardial fibrosis	4.63(1.73,12.37)	4.63(1.73,12.37)	2.21(0.13)	4.61(1.73)	Y	Y	Y	N
NS	Myocardial fibrosis	29.26(4.08,209.60)	29.25(4.09,209.40)	4.86(-1.11)	29.00(4.05)	N	N	N	Y
18-64	Right ventricular dysfunction	5.31(1.98,14.21)	5.31(1.98,14.21)	2.40(0.21)	5.27(1.97)	Y	Y	Y	N
ALL	Right ventricular dysfunction	3.86(1.45,10.31)	3.86(1.45,10.31)	1.94(0.00)	3.85(1.44)	Y	Y	N	N
⩾65	Left atrial dilatation	3.89(0.55,27.70)	3.89(0.55,27.69)	1.96(-1.38)	3.88(0.54)	N	N	N	N
18-64	Left atrial dilatation	5.98(1.48,24.08)	5.98(1.48,24.08)	2.57(-0.52)	5.92(1.47)	N	N	N	N
ALL	Left atrial dilatation	4.96(1.86,13.25)	4.96(1.86,13.25)	2.30(0.17)	4.94(1.85)	Y	Y	Y	N
NS	Left atrial dilatation	17.16(2.40,122.47)	17.15(2.40,122.35)	4.09(-1.13)	17.07(2.39)	N	N	N	Y
⩾65	Atrioventricular block	0.32(0.05,2.27)	0.32(0.05,2.27)	-1.64(-3.09)	0.32(0.05)	N	N	N	N
18-	Atrioventricu	0.49(0.1	0.49(0.12,1.96)	-1.03(-	0.49(0.	N	N	N	N

64	lar block	2,1.96)		2.43)	12)				
ALL	Atrioventricular block	0.45(0.17,1.21)	0.45(0.17,1.21)	-1.14(-2.26)	0.45(0.17)	N	N	N	N
NS	Atrioventricular block	2.69(0.38,19.15)	2.69(0.38,19.13)	1.43(-1.50)	2.69(0.38)	N	N	N	N
⩾65	Atrioventricular block complete	0.29(0.04,2.04)	0.29(0.04,2.04)	-1.80(-3.20)	0.29(0.04)	N	N	N	N
18-64	Atrioventricular block complete	0.54(0.13,2.15)	0.54(0.13,2.15)	-0.90(-2.32)	0.54(0.13)	N	N	N	N
ALL	Atrioventricular block complete	0.47(0.18,1.26)	0.47(0.18,1.26)	-1.08(-2.21)	0.47(0.18)	N	N	N	N
NS	Atrioventricular block complete	4.31(0.61,30.62)	4.30(0.61,30.59)	2.10(-1.35)	4.30(0.60)	N	N	N	N
18-64	Atrial thrombosis	2.86(0.92,8.88)	2.86(0.92,8.88)	1.51(-0.49)	2.85(0.92)	N	N	N	N
ALL	Atrial thrombosis	1.79(0.67,4.78)	1.79(0.67,4.78)	0.84(-0.66)	1.79(0.67)	N	N	N	N
NS	Atrial thrombosis	6.35(0.89,45.18)	6.35(0.89,45.14)	2.66(-1.26)	6.34(0.89)	N	N	N	N
18-64	Cardiac perfusion defect	151.63(42.30,543.53)	151.62(42.30,543.46)	6.90(0.34)	119.34 (33.29)	Y	Y	Y	Y
ALL	Cardiac perfusion defect	111.76(33.55,372.23)	111.75(33.55,372.19)	6.63(0.41)	98.97(29.72)	Y	Y	Y	Y
18-64	Myocardial oedema	11.27(3.59,35.35)	11.27(3.59,35.34)	3.47(0.19)	11.06(3.53)	Y	Y	Y	Y
ALL	Myocardial oedema	8.43(2.70,26.28)	8.43(2.70,26.27)	3.06(0.10)	8.35(2.68)	Y	Y	Y	Y
⩾65	Tachyarrhythmia	1.29(0.18,9.17)	1.29(0.18,9.17)	0.37(-1.87)	1.29(0.18)	N	N	N	N
18-64	Tachyarrhythmia	1.00(0.25,3.99)	1.00(0.25,3.99)	-0.01(-1.67)	1.00(0.25)	N	N	N	N
ALL	Tachyarrhythmia	1.05(0.34,3.26)	1.05(0.34,3.26)	0.07(-1.39)	1.05(0.34)	N	N	N	N
⩾65	Atrioventricular block first degree	0.65(0.09,4.63)	0.65(0.09,4.63)	-0.62(-2.38)	0.65(0.09)	N	N	N	N
18-64	Atrioventricular block first degree	0.71(0.18,2.83)	0.71(0.18,2.83)	-0.50(-2.02)	0.71(0.18)	N	N	N	N
ALL	Atrioventricular block first degree	0.62(0.20,1.94)	0.62(0.20,1.94)	-0.68(-1.98)	0.62(0.20)	N	N	N	N
18-64	Heart valve incompetenc	2.59(0.83,8.05)	2.59(0.83,8.05)	1.37(-0.56)	2.58(0.83)	N	N	N	N

	e								
ALL	Heart valve incompetence	1.47(0.47,4.56)	1.47(0.47,4.56)	0.55(-1.05)	1.47(0.47)	N	N	N	N
18-64	Aortic valve incompetence	0.69(0.17,2.75)	0.69(0.17,2.75)	-0.54(-2.05)	0.69(0.17)	N	N	N	N
ALL	Aortic valve incompetence	0.70(0.22,2.16)	0.70(0.22,2.16)	-0.52(-1.85)	0.70(0.22)	N	N	N	N
NS	Aortic valve incompetence	4.82(0.68,34.27)	4.82(0.68,34.24)	2.27(-1.32)	4.81(0.68)	N	N	N	N
18-64	Low cardiac output syndrome	9.84(2.43,39.83)	9.84(2.43,39.83)	3.28(-0.38)	9.69(2.39)	N	N	N	Y
ALL	Low cardiac output syndrome	4.57(1.14,18.34)	4.57(1.14,18.34)	2.19(-0.61)	4.55(1.13)	N	N	N	N
18-64	Kounis syndrome	1.47(0.37,5.90)	1.47(0.37,5.90)	0.56(-1.32)	1.47(0.37)	N	N	N	N
ALL	Kounis syndrome	1.37(0.34,5.49)	1.37(0.34,5.49)	0.45(-1.38)	1.37(0.34)	N	N	N	N
⩾65	Cardiac tamponade	1.46(0.36,5.83)	1.46(0.36,5.82)	0.54(-1.33)	1.45(0.36)	N	N	N	N
ALL	Cardiac tamponade	0.42(0.11,1.70)	0.42(0.11,1.70)	-1.24(-2.60)	0.42(0.11)	N	N	N	N
18-64	Chronic myocarditis	74.13(16.95,324.16)	74.12(16.95,324.13)	6.03(-0.26)	65.52(14.98)	N	N	N	Y
ALL	Chronic myocarditis	71.40(16.87,302.12)	71.40(16.87,302.10)	6.04(-0.22)	65.98(15.59)	N	N	N	Y
18-64	Ventricular hypertrophy	2.36(0.59,9.45)	2.36(0.59,9.45)	1.23(-0.98)	2.35(0.59)	N	N	N	N
ALL	Ventricular hypertrophy	1.56(0.39,6.24)	1.56(0.39,6.24)	0.64(-1.28)	1.56(0.39)	N	N	N	N
<18	Right ventricular enlargement	73.42(10.14,531.68)	73.34(10.15,529.97)	6.17(-1.10)	71.98(9.94)	N	N	N	Y
18-64	Right ventricular enlargement	2.06(0.29,14.67)	2.06(0.29,14.67)	1.04(-1.62)	2.06(0.29)	N	N	N	N
ALL	Right ventricular enlargement	3.16(0.79,12.65)	3.16(0.79,12.65)	1.65(-0.80)	3.15(0.79)	N	N	N	N
⩾65	Right atrial dilatation	15.31(2.13,110.07)	15.31(2.13,110.03)	3.92(-1.16)	15.13(2.10)	N	N	N	Y
18-64	Right atrial dilatation	7.51(1.04,54.04)	7.51(1.04,54.04)	2.89(-1.25)	7.43(1.03)	N	N	N	N

ALL	Right atrial dilatation	6.25(1.56,25.13)	6.25(1.56,25.13)	2.64(-0.49)	6.22(1.55)	N	N	N	N
18-64	Left atrial hypertrophy	28.51(6.88,118.08)	28.51(6.88,118.06)	4.76(-0.24)	27.17(6.56)	N	N	N	Y
ALL	Left atrial hypertrophy	28.09(6.87,114.89)	28.09(6.87,114.88)	4.77(-0.22)	27.23(6.66)	N	N	N	Y
⩾65	Left atrial enlargement	3.29(0.46,23.40)	3.29(0.46,23.39)	1.71(-1.43)	3.28(0.46)	N	N	N	N
ALL	Left atrial enlargement	1.50(0.38,6.01)	1.50(0.38,6.01)	0.59(-1.31)	1.50(0.37)	N	N	N	N
NS	Left atrial enlargement	14.31(2.01,102.06)	14.31(2.01,101.96)	3.83(-1.15)	14.25(2.00)	N	N	N	N
⩾65	Arrhythmia supraventricular	2.82(0.40,20.06)	2.82(0.40,20.06)	1.49(-1.48)	2.82(0.40)	N	N	N	N
ALL	Arrhythmia supraventricular	1.55(0.39,6.19)	1.55(0.39,6.19)	0.63(-1.28)	1.55(0.39)	N	N	N	N
NS	Arrhythmia supraventricular	20.74(2.90,148.20)	20.73(2.90,148.06)	4.37(-1.12)	20.61(2.88)	N	N	N	Y
18-64	Sinus arrhythmia	2.08(0.52,8.33)	2.08(0.52,8.33)	1.05(-1.06)	2.07(0.52)	N	N	N	N
ALL	Sinus arrhythmia	1.55(0.39,6.20)	1.55(0.39,6.20)	0.63(-1.28)	1.55(0.39)	N	N	N	N
18-64	Torsade de pointes	0.27(0.07,1.07)	0.27(0.07,1.07)	-1.90(-3.16)	0.27(0.07)	N	N	N	N
ALL	Torsade de pointes	0.20(0.05,0.79)	0.20(0.05,0.79)	-2.33(-3.55)	0.20(0.05)	N	N	N	N
18-64	Ventricular arrhythmia	0.38(0.05,2.72)	0.38(0.05,2.72)	-1.38(-2.89)	0.38(0.05)	N	N	N	N
ALL	Ventricular arrhythmia	0.57(0.14,2.29)	0.57(0.14,2.29)	-0.80(-2.25)	0.57(0.14)	N	N	N	N
NS	Ventricular arrhythmia	8.36(1.17,59.51)	8.36(1.17,59.46)	3.06(-1.21)	8.34(1.17)	N	N	N	N
⩾65	Tachycardia paroxysmal	7.12(1.00,50.81)	7.11(1.00,50.80)	2.82(-1.24)	7.08(0.99)	N	N	N	N
18-64	Tachycardia paroxysmal	1.80(0.25,12.86)	1.80(0.25,12.85)	0.85(-1.69)	1.80(0.25)	N	N	N	N
ALL	Tachycardia paroxysmal	3.03(0.76,12.14)	3.03(0.76,12.13)	1.59(-0.82)	3.02(0.75)	N	N	N	N
18-64	Endocardial fibrosis	34.75(8.33,145.00)	34.75(8.33,144.98)	5.03(-0.24)	32.76(7.85)	N	N	N	Y
ALL	Endocardial fibrosis	29.04(7.10,118.87)	29.04(7.10,118.86)	4.81(-0.22)	28.12(6.87)	N	N	N	Y
<18	Cardiopulmo	11.00(1.	10.99(1.55,78.16)	3.45(-	10.96(	N	N	N	N

	nary failure	54,78.41)		1.17)	1.54)				
ALL	Cardiopulmonary failure	0.27(0.04,1.95)	0.27(0.04,1.95)	-1.86(-3.26)	0.27(0.04)	N	N	N	N
18-64	Ventricular failure	4.28(0.60,30.59)	4.28(0.60,30.59)	2.09(-1.36)	4.25(0.59)	N	N	N	N
ALL	Ventricular failure	3.68(0.52,26.22)	3.68(0.52,26.21)	1.87(-1.40)	3.67(0.51)	N	N	N	N
18-64	Heart failure with preserved ejection fraction	1.12(0.16,7.97)	1.12(0.16,7.97)	0.16(-1.97)	1.12(0.16)	N	N	N	N
ALL	Heart failure with preserved ejection fraction	0.99(0.14,7.01)	0.99(0.14,7.01)	-0.02(-2.05)	0.99(0.14)	N	N	N	N
18-64	Hepatojugular reflux	6.95(0.97,49.94)	6.95(0.97,49.94)	2.78(-1.26)	6.88(0.96)	N	N	N	N
ALL	Hepatojugular reflux	7.72(1.08,55.28)	7.72(1.08,55.28)	2.94(-1.24)	7.66(1.07)	N	N	N	N
ALL	Coronary artery disease	0.03(0.00,0.24)	0.03(0.00,0.24)	-4.86(-5.95)	0.03(0.00)	N	N	N	N
NS	Coronary artery disease	0.54(0.08,3.80)	0.54(0.08,3.80)	-0.90(-2.56)	0.54(0.08)	N	N	N	N
⩾65	Coronary artery thrombosis	2.06(0.29,14.68)	2.06(0.29,14.68)	1.04(-1.62)	2.06(0.29)	N	N	N	N
ALL	Coronary artery thrombosis	0.45(0.06,3.20)	0.45(0.06,3.20)	-1.15(-2.73)	0.45(0.06)	N	N	N	N
⩾65	Prinzmetal angina	2.77(0.39,19.74)	2.77(0.39,19.74)	1.47(-1.49)	2.77(0.39)	N	N	N	N
ALL	Prinzmetal angina	0.77(0.11,5.47)	0.77(0.11,5.47)	-0.38(-2.24)	0.77(0.11)	N	N	N	N
18-64	Arteriospasm coronary	0.28(0.04,2.00)	0.28(0.04,2.00)	-1.83(-3.23)	0.28(0.04)	N	N	N	N
ALL	Arteriospasm coronary	0.27(0.04,1.89)	0.27(0.04,1.89)	-1.91(-3.29)	0.27(0.04)	N	N	N	N
18-64	Microvascular coronary artery disease	6.70(0.93,48.12)	6.70(0.93,48.11)	2.73(-1.27)	6.63(0.92)	N	N	N	N
ALL	Microvascular coronary artery disease	5.42(0.76,38.74)	5.42(0.76,38.74)	2.43(-1.30)	5.39(0.76)	N	N	N	N
18-	Immune-	14.25(1.	14.25(1.96,103.75)	3.80(-	13.92(	N	N	N	N

64	mediated pericarditis	96,103.76)		1.19)	1.91)				
ALL	Immune-mediated pericarditis	12.60(1.75,90.74)	12.60(1.75,90.74)	3.64(-1.18)	12.43(1.73)	N	N	N	N
18-64	Ischaemic cardiomyopathy	0.50(0.07,3.58)	0.50(0.07,3.58)	-0.99(-2.62)	0.50(0.07)	N	N	N	N
ALL	Ischaemic cardiomyopathy	0.31(0.04,2.17)	0.31(0.04,2.17)	-1.71(-3.13)	0.31(0.04)	N	N	N	N
<18	Restrictive cardiomyopathy	136.36(18.53,1003.26)	136.21(18.55,1000.06)	7.04(-1.12)	131.54(17.88)	N	N	N	Y
ALL	Restrictive cardiomyopathy	4.20(0.59,29.96)	4.20(0.59,29.96)	2.06(-1.36)	4.18(0.59)	N	N	N	N
⩾65	Cardiac amyloidosis	1.88(0.26,13.38)	1.88(0.26,13.37)	0.91(-1.66)	1.88(0.26)	N	N	N	N
ALL	Cardiac amyloidosis	0.87(0.12,6.20)	0.87(0.12,6.20)	-0.20(-2.14)	0.87(0.12)	N	N	N	N
18-64	Stress cardiomyopathy	0.28(0.04,2.01)	0.28(0.04,2.01)	-1.82(-3.22)	0.28(0.04)	N	N	N	N
ALL	Stress cardiomyopathy	0.21(0.03,1.47)	0.21(0.03,1.47)	-2.27(-3.58)	0.21(0.03)	N	N	N	N
18-64	Cardiac sarcoidosis	4.56(0.64,32.61)	4.56(0.64,32.61)	2.18(-1.35)	4.53(0.63)	N	N	N	N
ALL	Cardiac sarcoidosis	4.22(0.59,30.11)	4.22(0.59,30.11)	2.07(-1.36)	4.20(0.59)	N	N	N	N
<18	Right atrial enlargement	152.72(20.67,1128.30)	152.55(20.69,1124.69)	7.20(-1.13)	146.72(19.86)	N	N	N	Y
ALL	Right atrial enlargement	2.44(0.34,17.38)	2.44(0.34,17.38)	1.29(-1.54)	2.44(0.34)	N	N	N	N
18-64	Right ventricular dilatation	2.70(0.38,19.25)	2.70(0.38,19.25)	1.43(-1.51)	2.69(0.38)	N	N	N	N
ALL	Right ventricular dilatation	1.44(0.20,10.24)	1.44(0.20,10.24)	0.53(-1.81)	1.44(0.20)	N	N	N	N
18-64	Left ventricular enlargement	2.18(0.31,15.54)	2.18(0.31,15.54)	1.12(-1.60)	2.18(0.31)	N	N	N	N
ALL	Left ventricular enlargement	1.74(0.24,12.36)	1.74(0.24,12.36)	0.80(-1.70)	1.74(0.24)	N	N	N	N
⩾65	Left ventricular hypertrophy	0.99(0.14,7.00)	0.99(0.14,7.00)	-0.02(-2.05)	0.99(0.14)	N	N	N	N

ALL	Left ventricular hypertrophy	0.20(0.03,1.44)	0.20(0.03,1.44)	-2.30(-3.61)	0.20(0.03)	N	N	N	N
18-64	Atrial tachycardia	0.64(0.09,4.54)	0.64(0.09,4.54)	-0.65(-2.40)	0.64(0.09)	N	N	N	N
ALL	Atrial tachycardia	0.38(0.05,2.73)	0.38(0.05,2.73)	-1.38(-2.89)	0.38(0.05)	N	N	N	N
⩾65	Nodal rhythm	1.93(0.27,13.70)	1.93(0.27,13.69)	0.94(-1.65)	1.92(0.27)	N	N	N	N
ALL	Nodal rhythm	0.66(0.09,4.71)	0.66(0.09,4.71)	-0.59(-2.37)	0.66(0.09)	N	N	N	N
18-64	Sinus node dysfunction	0.71(0.10,5.05)	0.71(0.10,5.05)	-0.49(-2.31)	0.71(0.10)	N	N	N	N
ALL	Sinus node dysfunction	0.28(0.04,1.99)	0.28(0.04,1.99)	-1.84(-3.23)	0.28(0.04)	N	N	N	N
18-64	Accelerated idioventricular rhythm	10.11(1.40,73.05)	10.11(1.40,73.04)	3.31(-1.22)	9.95(1.38)	N	N	N	N
ALL	Accelerated idioventricular rhythm	8.32(1.16,59.62)	8.32(1.16,59.62)	3.04(-1.23)	8.25(1.15)	N	N	N	N
18-64	Rhythm idioventricular	5.15(0.72,36.88)	5.15(0.72,36.88)	2.35(-1.32)	5.11(0.71)	N	N	N	N
ALL	Rhythm idioventricular	3.14(0.44,22.36)	3.14(0.44,22.36)	1.65(-1.45)	3.13(0.44)	N	N	N	N
<18	Bradycardia foetal	13.63(1.91,97.24)	13.62(1.91,96.93)	3.76(-1.15)	13.58(1.90)	N	N	N	N
ALL	Bradycardia foetal	0.53(0.07,3.74)	0.53(0.07,3.74)	-0.93(-2.58)	0.53(0.07)	N	N	N	N
ALL	Foetal heart rate disorder	2.93(0.41,20.90)	2.93(0.41,20.90)	1.55(-1.47)	2.93(0.41)	N	N	N	N
NS	Foetal heart rate disorder	22.29(3.12,159.37)	22.28(3.12,159.21)	4.47(-1.12)	22.14(3.10)	N	N	N	Y
ALL	Paroxysmal arrhythmia	7.26(1.01,51.98)	7.26(1.01,51.97)	2.85(-1.25)	7.21(1.01)	N	N	N	N
NS	Paroxysmal arrhythmia	131.08(17.75,967.71)	131.04(17.76,966.78)	6.98(-1.13)	126.03 (17.07)	N	N	N	Y
18-64	Conduction disorder	0.73(0.10,5.21)	0.73(0.10,5.21)	-0.45(-2.28)	0.73(0.10)	N	N	N	N
ALL	Conduction disorder	0.55(0.08,3.89)	0.55(0.08,3.89)	-0.87(-2.54)	0.55(0.08)	N	N	N	N
18-64	Atrioventricular block second degree	0.41(0.06,2.91)	0.41(0.06,2.91)	-1.29(-2.83)	0.41(0.06)	N	N	N	N
AL	Atrioventricu	0.26(0.0	0.26(0.04,1.82)	-1.96(-	0.26(0.	N	N	N	N

L	lar block second degree	4,1.82)		3.33)	04)				
18-64	Bundle branch block	1.46(0.20,10.36)	1.46(0.20,10.36)	0.54(-1.80)	1.45(0.20)	N	N	N	N
ALL	Bundle branch block	0.98(0.14,6.97)	0.98(0.14,6.97)	-0.03(-2.06)	0.98(0.14)	N	N	N	N
⩾65	Paroxysmal atrioventricular block	40.32(5.50,295.71)	40.32(5.50,295.62)	5.29(-1.14)	39.05(5.32)	N	N	N	Y
ALL	Paroxysmal atrioventricular block	17.49(2.41,126.63)	17.48(2.41,126.62)	4.10(-1.16)	17.16(2.37)	N	N	N	Y
18-64	Mitral valve prolapse	0.81(0.11,5.78)	0.81(0.11,5.78)	-0.30(-2.20)	0.81(0.11)	N	N	N	N
ALL	Mitral valve prolapse	0.65(0.09,4.63)	0.65(0.09,4.63)	-0.62(-2.38)	0.65(0.09)	N	N	N	N
ALL	Pulmonary valve stenosis	1.23(0.17,8.78)	1.23(0.17,8.78)	0.30(-1.90)	1.23(0.17)	N	N	N	N
NS	Pulmonary valve stenosis	7.52(1.06,53.49)	7.51(1.06,53.44)	2.91(-1.23)	7.50(1.05)	N	N	N	N
18-64	Tricuspid valve disease	3.63(0.51,25.96)	3.63(0.51,25.96)	1.85(-1.41)	3.62(0.51)	N	N	N	N
ALL	Tricuspid valve disease	2.99(0.42,21.27)	2.99(0.42,21.27)	1.57(-1.47)	2.98(0.42)	N	N	N	N
18-64	Pericardial cyst	16.85(2.30,123.18)	16.85(2.30,123.17)	4.03(-1.19)	16.38(2.24)	N	N	N	Y
ALL	Pericardial cyst	14.28(1.98,103.04)	14.28(1.98,103.03)	3.81(-1.17)	14.06(1.95)	N	N	N	N
18-64	Cardiac ventricular disorder	4.56(0.64,32.61)	4.56(0.64,32.61)	2.18(-1.35)	4.53(0.63)	N	N	N	N
ALL	Cardiac ventricular disorder	3.05(0.43,21.72)	3.05(0.43,21.72)	1.60(-1.46)	3.04(0.43)	N	N	N	N
18-64	Cardiac discomfort	0.21(0.03,1.49)	0.21(0.03,1.49)	-2.25(-3.57)	0.21(0.03)	N	N	N	N
ALL	Cardiac discomfort	0.20(0.03,1.39)	0.20(0.03,1.39)	-2.35(-3.65)	0.20(0.03)	N	N	N	N

4. Discussion

This study provides a comprehensive longitudinal mapping of epirubicin-associated cardiotoxicity, synthesizing data from both the FAERS and EudraVigilance (EV) databases over two decades. Our findings reveal a persistent upward trajectory in reporting, with peaks observed in 2020 and 2024. While this trend likely reflects the expanded clinical utility of epirubicin in breast and gastrointestinal oncology, it also highlights an evolving "pharmacovigilance consciousness." The high proportion of reports submitted by healthcare

professionals (over 67% in FAERS) lends significant weight to these signals, suggesting that the observed cardiotoxicity is not merely a statistical artifact but a recognized clinical challenge that has intensified with the maturation of the cardio-oncology field14.

A striking feature of our analysis is the "sex paradox" regarding cardiotoxicity risk. While females comprised the vast majority of cases (nearly 80% in FAERS and 87% in EV)—largely due to epirubicin's role in breast cancer—male patients exhibited a significantly more aggressive clinical timeline. The median time-to-onset for cardiac adverse events (AEs) was nearly halved in men compared to women (22 vs. 49 days). This suggests that while women are more frequently exposed, men may possess a higher intrinsic sensitivity to the acute oxidative stress and myocardial injury triggered by anthracyclines. This disparity may be biological, potentially involving the lack of estrogen's cardioprotective effects or sex-specific differences in topoisomerase IIβ expression1516.

The age-stratified data further delineate distinct "vulnerability profiles." The pediatric cohort (<18 years) demonstrated an exceptionally high signal for dilated cardiomyopathy (ROR=183.64), confirming that the young heart is particularly susceptible to the permanent structural remodeling induced by anthracyclines1718. Conversely, the geriatric population (≥65 years) showed a predisposition toward atrial fibrillation and acute cardiac failure, likely exacerbated by a diminished cardiac reserve and pre-existing cardiovascular comorbidities. These findings align with the 2022 ESC guidelines, which emphasize that age is not just a number but a critical determinant of the "Type I" irreversible cardiac damage characteristic of epirubicin 19.

The signal intensity for specific Preferred Terms (PTs), such as "heart failure with mid-range ejection fraction" (HFmrEF, ROR=406.37) and "immune-mediated pericarditis," provides a nuanced view of epirubicin's toxicological footprint. The robust association with HFmrEF and HFrEF underscores the drug's direct impact on myocardial contractility through mitochondrial dysfunction and the inhibition of topoisomerase IIβ in cardiomyocytes20. Interestingly, the emergence of signals like "immune-mediated pericarditis" suggests that epirubicin may also modulate inflammatory pathways, a factor that warrants further mechanistic investigation in the context of contemporary combination therapies.

From a clinical management perspective, the observed median time-to-onset of 36 days is transformative. It challenges the traditional "late-onset" dogma of anthracycline toxicity, which often focuses on cumulative doses over months or years. Instead, our data identifies a "critical window" within the first 30 days where nearly 20% of events occur. This early vulnerability necessitates a shift from reactive monitoring to proactive surveillance. The high mortality rate (13.94%) and the frequency of hospitalization (40.8%) underscore that when epirubicin-induced injury occurs, it is rarely trivial.

5.Conclusion

This dual-database pharmacovigilance analysis establishes a comprehensive real-world profile of epirubicin-induced cardiotoxicity, validating signals from FAERS with independent data from EudraVigilance. Our findings challenge the conventional understanding of anthracycline toxicity by identifying a distinct "sex-onset paradox," where male patients, though less frequently reported, exhibit a significantly accelerated trajectory to cardiac events compared to females. Furthermore, the stratification of risk reveals divergent toxicological phenotypes: a

predisposition toward structural remodeling (dilated cardiomyopathy) in pediatric populations versus functional decompensation (atrial fibrillation, acute failure) in the elderly. Critically, the identification of a median time-to-onset of just 36 days—with a substantial burden of cases occurring within the first month—dismantles the reliance on cumulative-dose monitoring alone. Consequently, clinical protocols must pivot toward "precision cardio-oncology," necessitating baseline risk stratification and hyper-vigilant surveillance during the initial 30 days of therapy to mitigate the high severity and mortality associated with these adverse events.

6. Limitations

This study is constrained by the inherent nature of spontaneous reporting systems, which are prone to under-reporting, incomplete clinical data, and the lack of a total patient denominator to calculate absolute incidence. Information such as cumulative dosage, baseline LVEF, and specific comorbidities was frequently missing, limiting the depth of multivariate risk assessments. Additionally, while disproportionality signals are robust, they represent statistical associations rather than definitive causality. The potential for confounding by polypharmacy exists, although sensitivity analyses were performed to mitigate the influence of other cardiotoxic agents. These findings serve as a signal for clinicians but require further validation through prospective longitudinal registries.

Acknowledgements: None

Funding: None

Availability of Data and Materials: All the data for the present article can be found on the US FDA Adverse Event Reporting System (FAERS) database and the EudraVigilance (EV) database.

Authors' Contributions: Hong Seng An and Nouth Nita collected, analyzed, and interpreted the data, wrote the manuscript. Nan Luo, Pengkhun Nov and Qionglin Huang designed, revised, and supervised the study. All authors had reviewed and approved the final manuscript.

Ethics Approval and Consent to Participate: Not applicable.

Patient Consent for Publication: Not applicable.

Competing Interests: The authors declare that they have no competing interests.

Clinical Trial Number: Not applicable.

References

1. Moodley T, Singh M. Sterically Stabilised Polymeric Mesoporous Silica Nanoparticles Improve Doxorubicin Efficiency: Tailored Cancer Therapy. Molecules. 2020 Feb 8;25 (3):742. doi:10.3390/molecules25030742. PM ID:32046364; PMCID: PMC7037074.
2. Zhang J, Cui X, Yan Y, Li M, Yang Y, Wang J, Zhang J. Research progress of cardioprotective agents for prevention of anthracycline cardiotoxicity. Am J Transl Res. 2016 Jul 15;8(7):2862-75. PMID: 27508008; PMCID: PMC4969424.
3. Zhang M, Yang H, Xu C, Jin F, Zheng A. Risk Factors for Anthracycline-Induced Cardiotoxicity in Breast Cancer Treatment: A Meta-Analysis. Front Oncol. 2022 Jun 17;12 :899782. doi: 10.3389/fonc.2022.899782. PMID: 35785172; PMCID: PMC9248259.
4. Li W, Zhang Y, Wei Y, Ling G, Zhang Y, Li Y, Guo S, Tan N, Ma L, Li W, Sun Q, Wang W, Wang Y. New insights into mitochondrial quality control in anthracycline-induced cardiotoxicity: molecular mechanisms, therapeutic targets, and natural products. Int J Biol Sci. 2025 Jan 1;21(2):507-523. doi: 10. 7150/ijbs.103810. PMID: 39781459; PMCID: PMC11705644.
5. Li W, Zhang Y, Wei Y, Ling G, Zhang Y, Li Y, Guo S, Tan N, Ma L, Li W, Sun Q, Wang W, Wang Y. New insights into mitochondrial quality control in anthracycline-induced cardiotoxicity: molecular mechanisms, therapeutic targets, and natural products. Int J Biol Sci. 2025 Jan 1;21(2):507-523. doi: 10. 7150/ijbs.103810. PMID: 39781459; PMCID: PMC11705644.
6. Zhou Z, Liu H, Wang X, Sang X, Zhang Y,

Liu Y, Zhang X. Effect of different intraoperative blood pressure regulation levels on postoperative myocardial injury in patients undergoing radical mastectomy for breast cancer after receiving neoadjuvant chemotherapy: a study protocol for a randomised controlled trial. BMJ Open. 2025 Jan 6;15(1):e088559. doi: 10.1136/bmjopen-2024-088559. PMID: 39762100; PMCID: PMC11748768.

7. Dhir AA, Sawant SP. Cardiac morbidity & mortality in patients with breast cancer: A review. Indian J Med Res. 2021 Aug;154(2): 199-209. doi: 10.4103/ijmr.IJMR_879_20. PMID: 35295010; PMCID: PMC9131763.
8. D'Amario D, Camilli M, Migliaro S, Canonico F, Galli M, Arcudi A, Montone RA, Borovac JA, Crea F, Savarese G. Sex-Related Differences in Dilated Cardiomyopathy with a Focus on Cardiac Dysfunction in Oncology. Curr Cardiol Rep. 2020 Aug 8;22(10):102. doi: 10.1007/s11886-020-01377-z. PMID: 32770480; PMCID: PMC7413835.
9. Khan Z, Karatas Y, Akici A, Martins MAP, Ahmad N. Editorial: Pharmacoepidemiology and pharmacovigilance post-marketing drug safety studies. Front Pharmacol. 2024 Aug 20;15:1473052. doi: 10.3389/fphar.2024.1473052. PMID: 39228524; PMCID: PMC11368867.
10. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002 Jan-Feb;11(1):3-10. doi: 10.1002/pds.668. PMID: 11998548.
11. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001 Oct-Nov;10(6):483-6. doi: 10.1002/pds.677. PMID: 11828828.
12. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998 Jun;54(4):315-21. doi: 10.1007/s002280050466. PMID: 9696956.
13. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf. 2002;25(6):381-92. doi: 10.2165/00002018-200225060-00001. PMID: 12071774.
14. Erratum to: 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J. 2023 May 7;44(18):1621. doi: 10.1093/eurheartj/ehad196. Erratum for: Eur Heart J. 2022 Nov 1;43 (41):4229-4361. doi:10.1093/eurheartj/ehac244. PMID: 36952225.
15. Vejpongsa P, Yeh ET. Topoisomerase 2β: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. Clin Pharmacol Ther. 2014 Jan; 95(1):45-52. doi: 10.1038/clpt.2013.201. Epub 2013 Oct 3. PMID: 24091715.
16. Gianni L, Herman EH, Lipshultz SE, Minotti G, Sarvazyan N, Sawyer DB. Anthracycline cardiotoxicity: from bench to bedside. J Clin Oncol. 2008 Aug 1;26(22):3777-84. doi: 10.1200/JCO.2007.14.9401. PMID: 18669466; PMCID: PMC3018290.
17. Giantris A, Abdurrahman L, Hinkle A, Asselin B, Lipshultz SE. Anthracycline-induced cardiotoxicity in children and young adults. Crit Rev Oncol Hematol. 1998 Jan; 27(1):53-68. doi:10.1016/s1040-8428 (97)10007-5. PMID: 9548017.

18. Simbre VC, Duffy SA, Dadlani GH, Miller TL, Lipshultz SE. Cardiotoxicity of cancer chemotherapy: implications for children. Paediatr Drugs. 2005;7(3):187-202. doi: 10.2165/00148581-200507030-00005. PMID: 15977964.
19. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016 Sep 21;37(36):2768-2801. doi: 10.1093/eurheartj/ehw211. Epub 2016 Aug 26 . Erratum in: Eur Heart J. 2018 Mar 7;39 (10): 839. doi:10.1093/eurheartj/ehw562. PMID:27567406.
20. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, Yeh ET. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med. 2012 Nov;18(11): 1639-42. doi: 10.1038/nm.2919. Epub 2012 Oct 28. PMID: 23104132.