

## Supplemental Online Content

Koeckerling D, Reddy RK, Barker J, et al. Cardiovascular events after chimeric antigen receptor T-cell therapy for advanced hematologic malignant neoplasms: a meta-analysis. *JAMA Netw Open*. 2024;7(10):e2437222.

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**eTable 1.** Methodological Characteristics of Included Studies

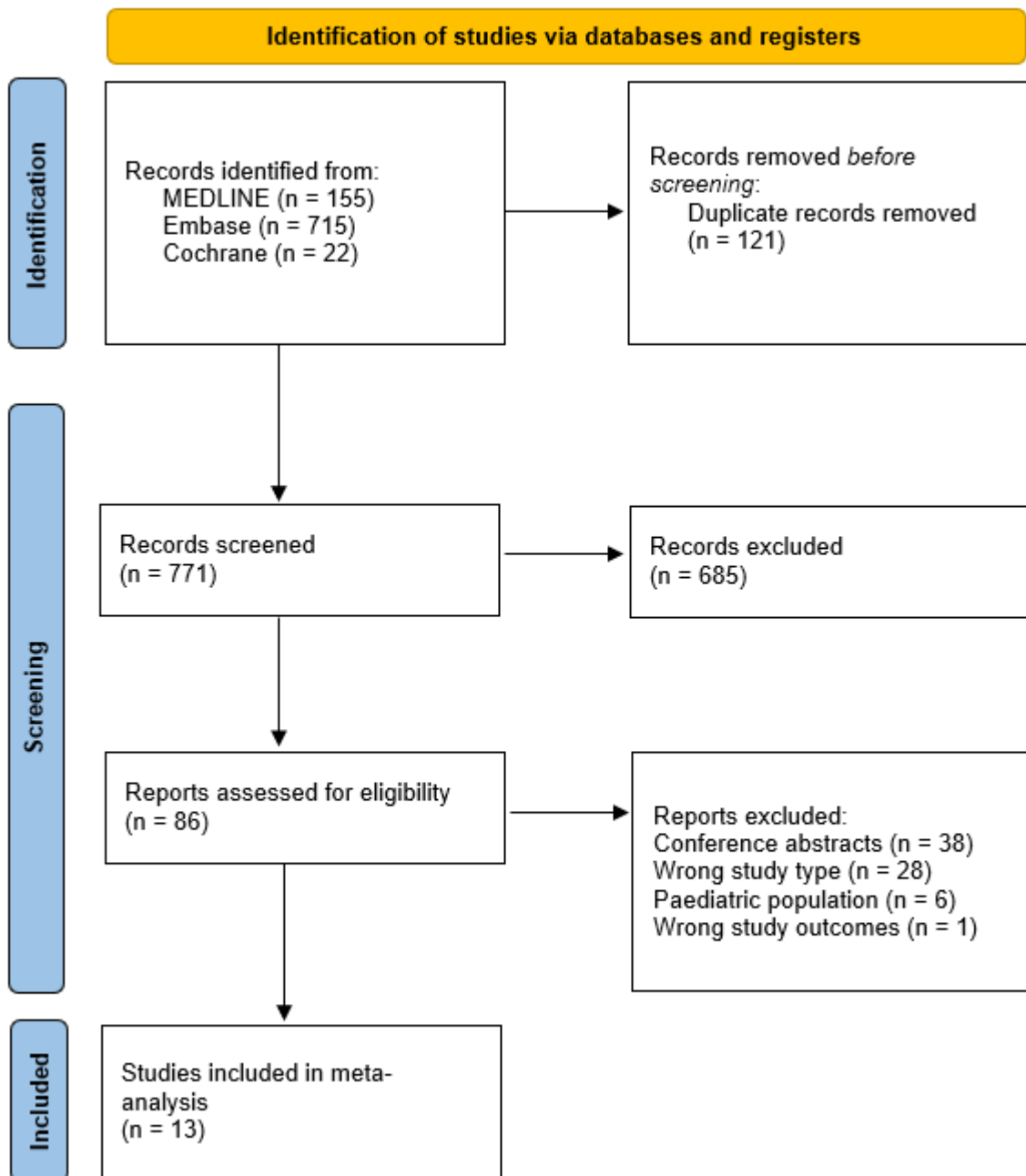
**eTable 2.** Results of Random-Effects Meta-Regression Using Patient Age and Proportion of Patients With Lymphoma as Potential Modifiers of Prevalence Estimates

**eAppendix 1.** Search Strategy

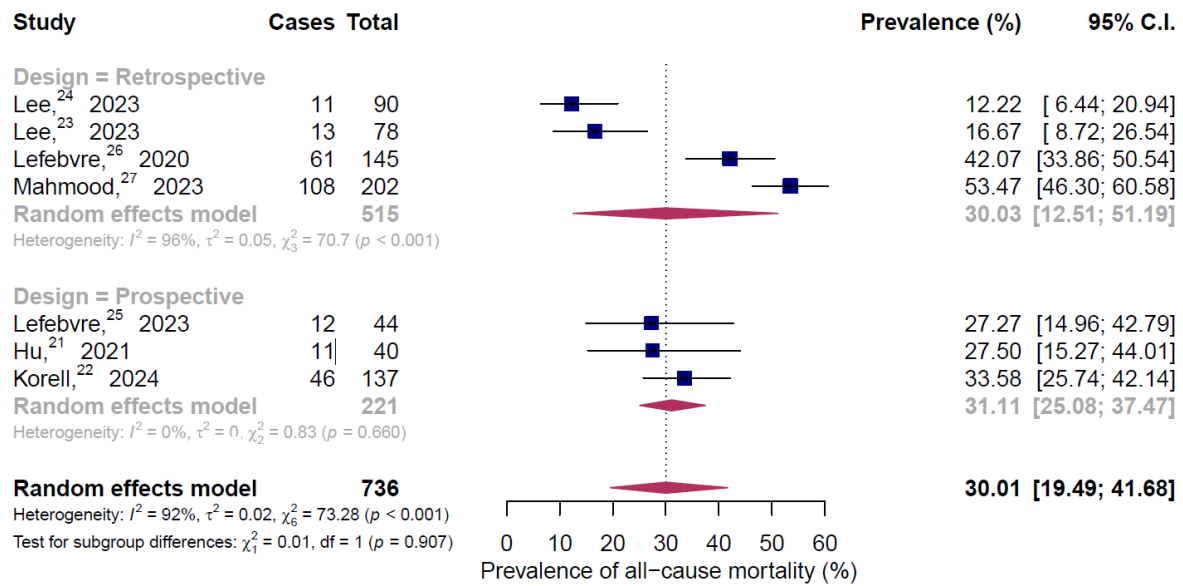
**eAppendix 2.** Quality Assessment of Included Studies Using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

This supplemental material has been provided by the authors to give readers additional information about their work.

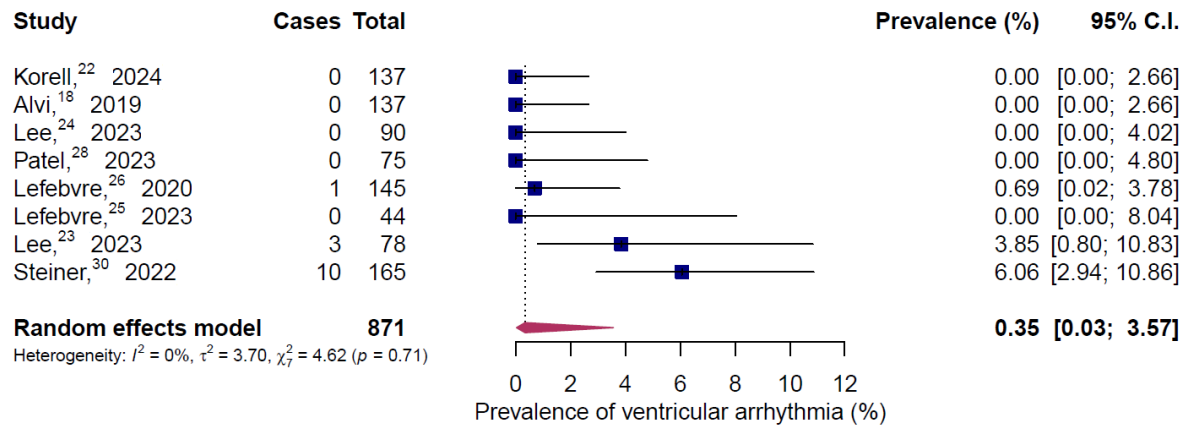
eFigure 1: PRISMA flowchart displaying the study selection process



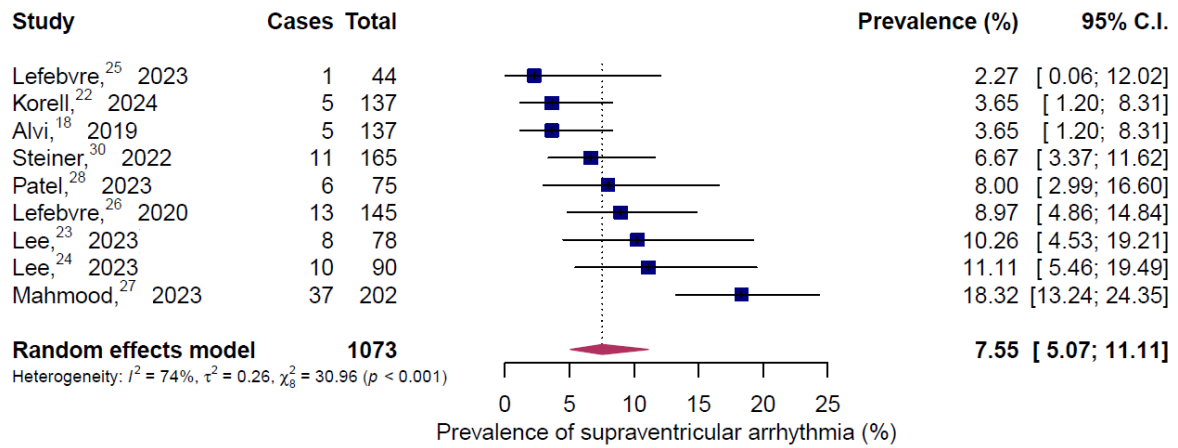
eFigure 2: Forest plot displaying the pooled prevalence of all-cause death using inverse-variance random effect models with Freeman-Tukey double arcsine transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.



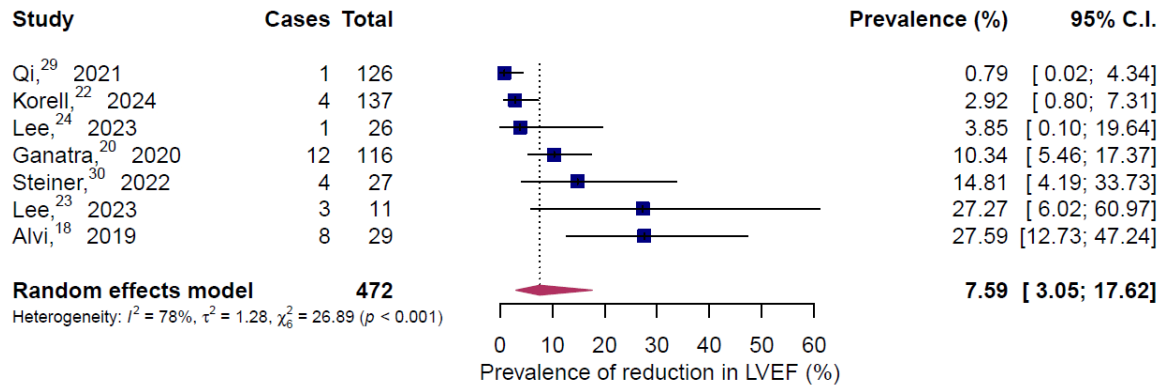
eFigure 3: Forest plot displaying the pooled prevalence of ventricular arrhythmia using a generalized linear mixed model with logit transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.



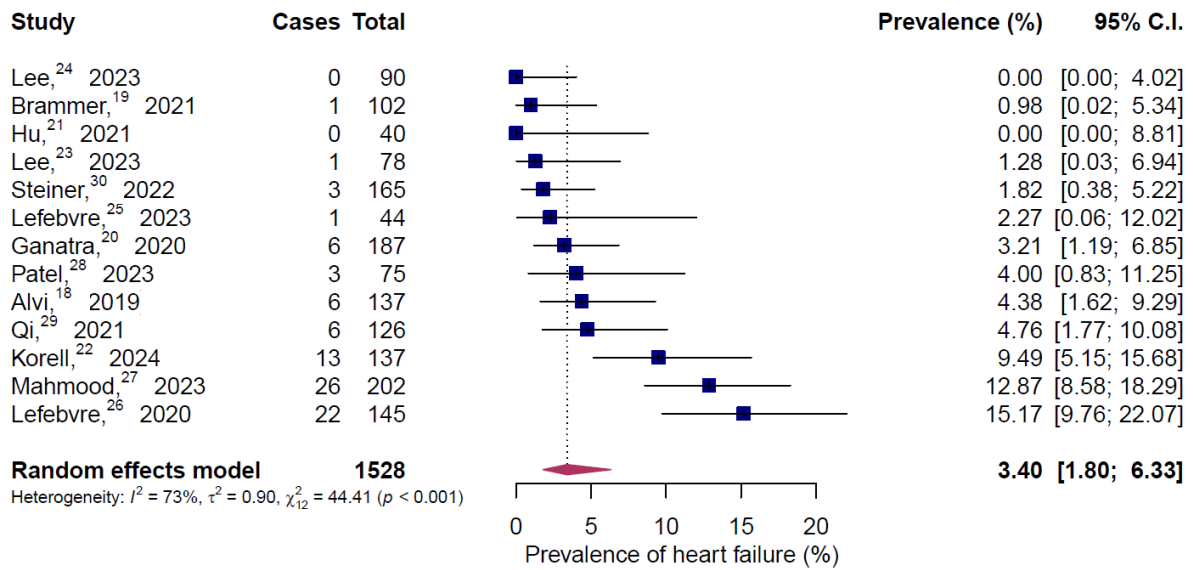
eFigure 4: Forest plot displaying the pooled prevalence of supraventricular arrhythmia using a generalized linear mixed model with logit transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.



eFigure 5: Forest plot displaying the pooled prevalence of reduction in LVEF using a generalized linear mixed model with logit transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.

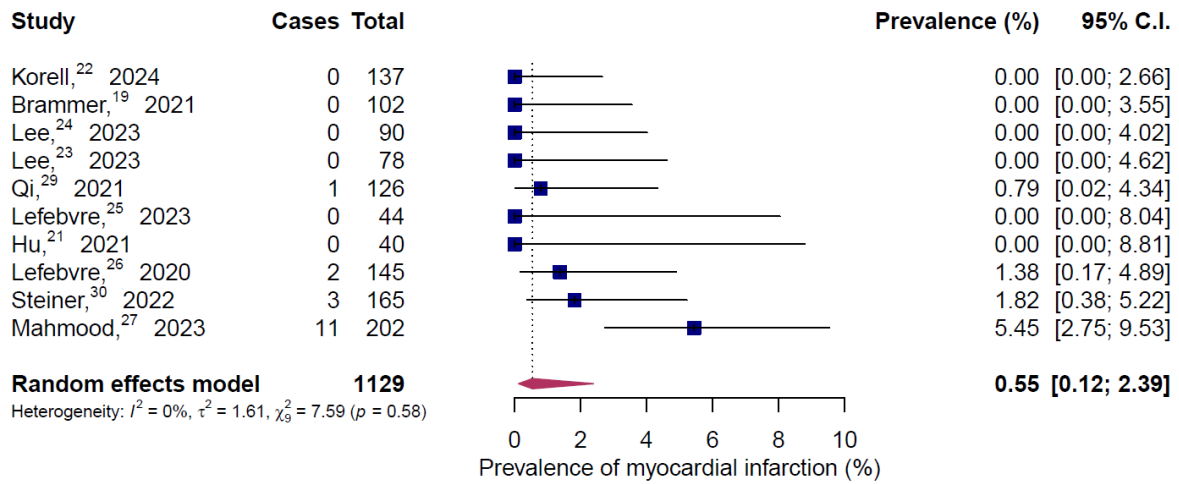


eFigure 6: Forest plot displaying the pooled prevalence of heart failure events using a generalized linear mixed model with logit transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.

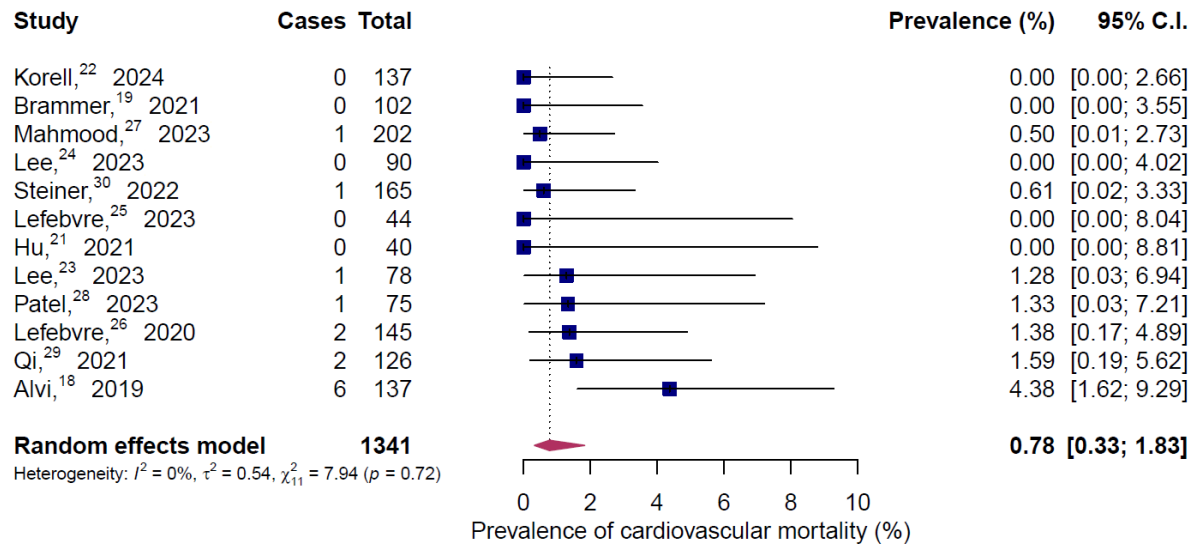




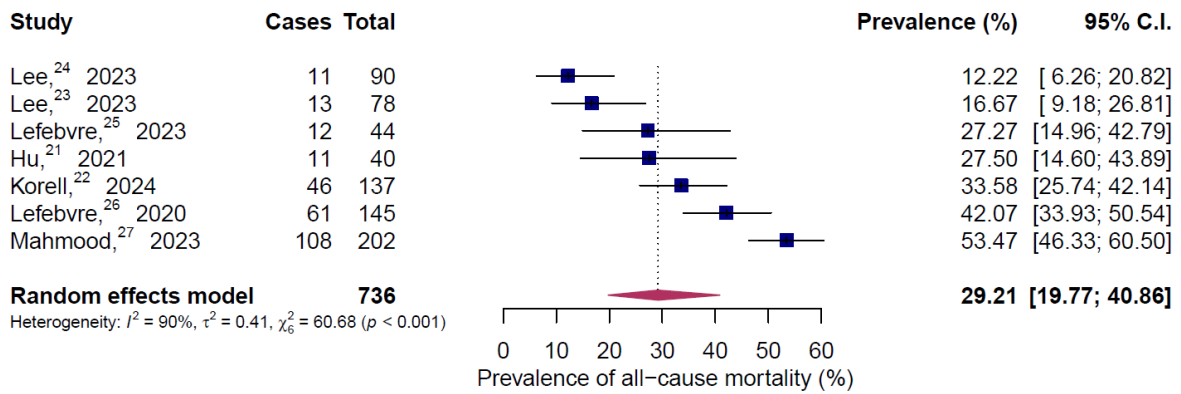
eFigure 7: Forest plot displaying the pooled prevalence of myocardial infarction using a generalized linear mixed model with logit transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.



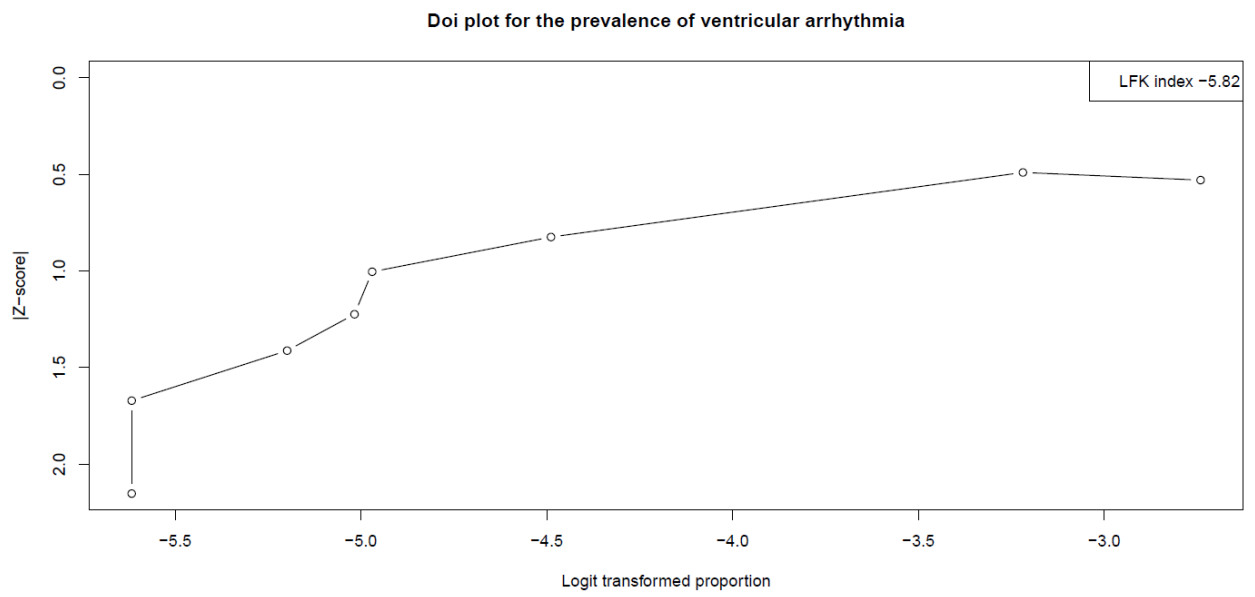
eFigure 8: Forest plot displaying the pooled prevalence of cardiovascular death using a generalized linear mixed model with logit transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.



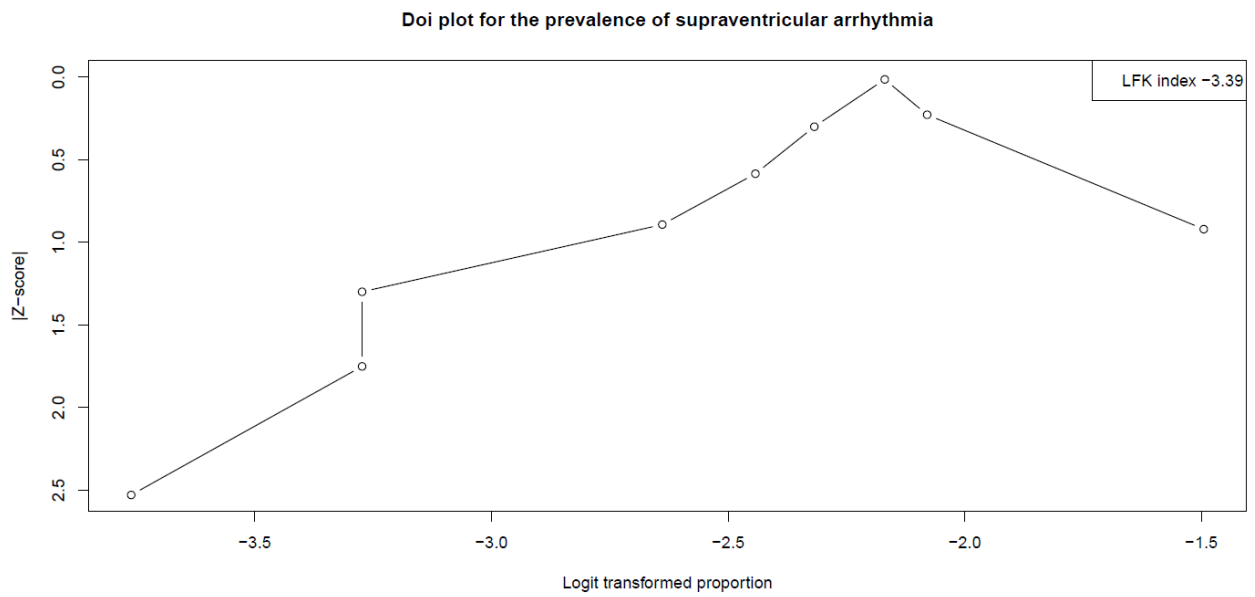
eFigure 9: Forest plot displaying the pooled prevalence of all-cause death using a generalized linear mixed model with logit transformation. Error bars represent 95% CIs. Diamonds indicate pooled estimate.



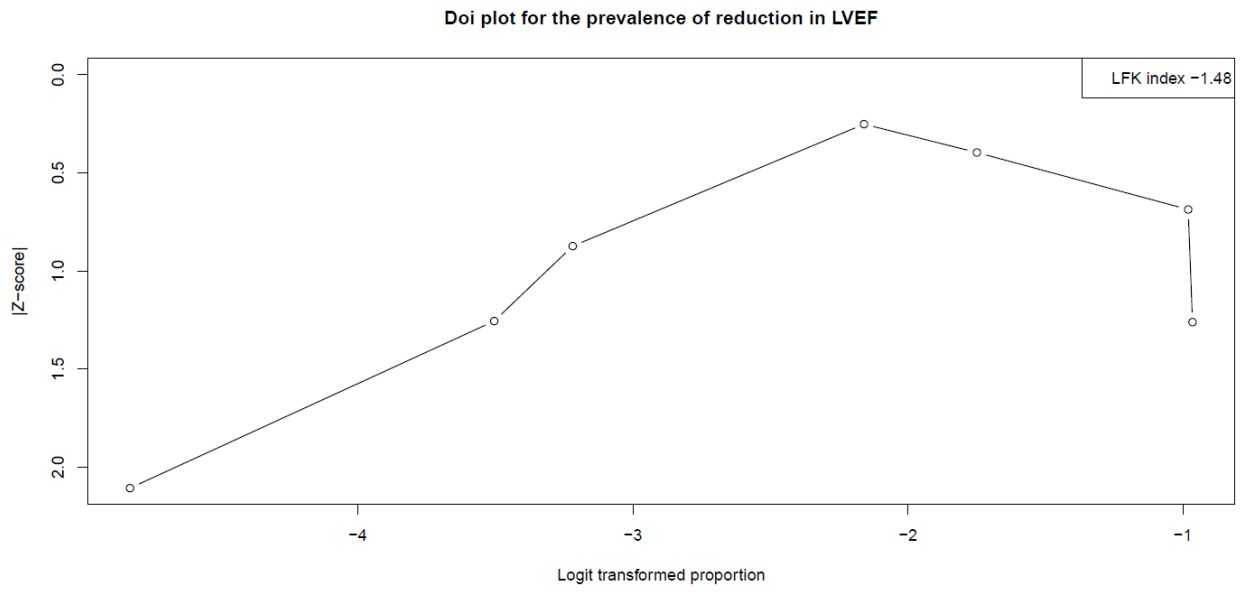
eFigure 10: Doi plot and its associated Luis Furuya-Kanamori index for the prevalence ventricular arrhythmia



eFigure 11: Doi plot and its associated Luis Furuya-Kanamori index for the prevalence of supraventricular arrhythmia



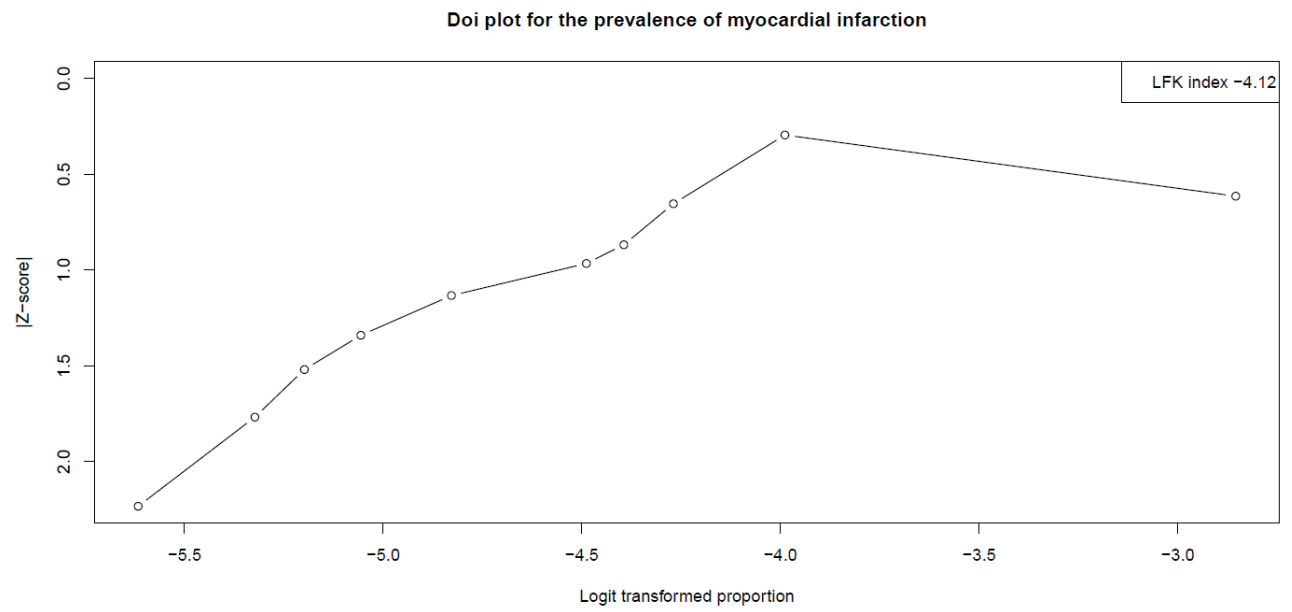
eFigure 12: Doi plot and its associated Luis Furuya-Kanamori index for the prevalence of reduction in LVEF



eFigure 13: Doi plot and its associated Luis Furuya-Kanamori index for the prevalence of heart-failure events

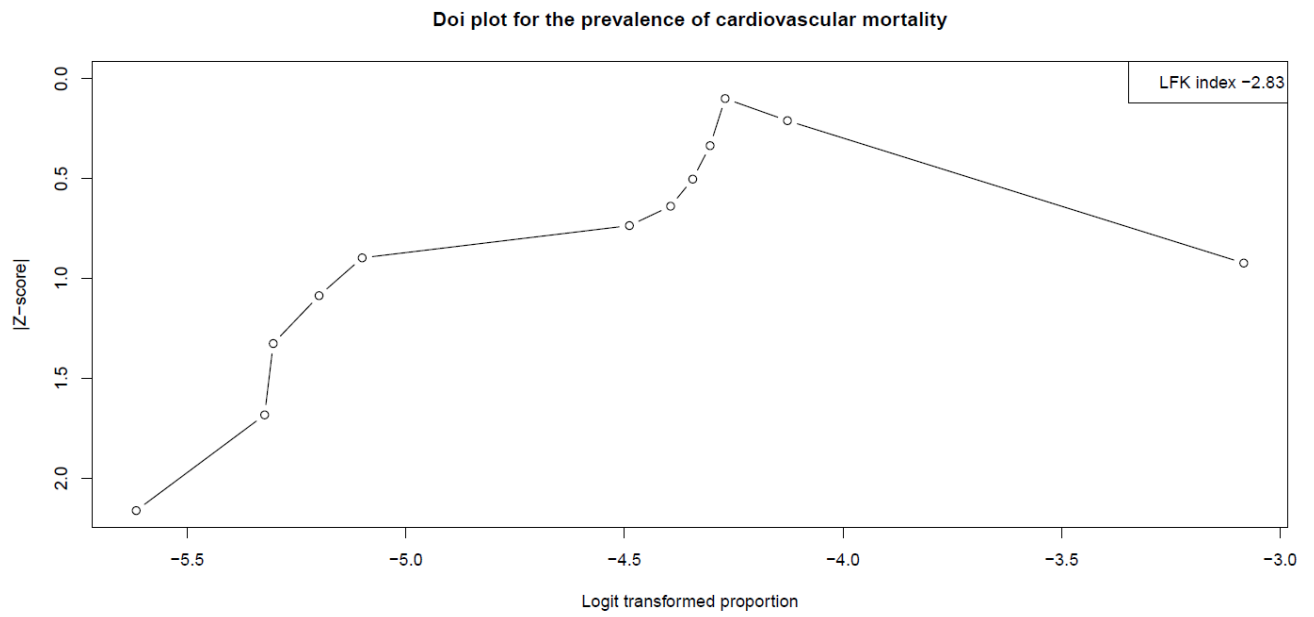


eFigure 14: Doi plot and its associated Luis Furuya-Kanamori index for the prevalence of myocardial infarction

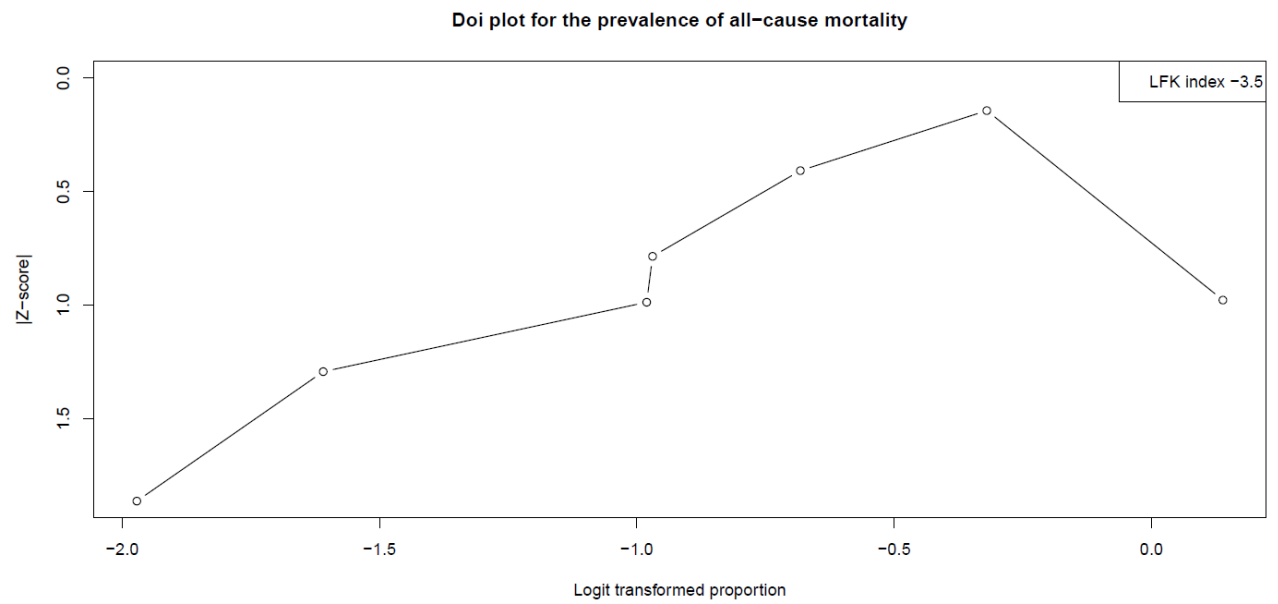




eFigure 15: Doi plot and its associated Luis Furuya-Kanamori index for the prevalence of cardiovascular mortality



eFigure 16: Doi plot and its associated Luis Furuya-Kanamori index for the prevalence of all-cause mortality



eTable 1: Methodological characteristics of included studies

<b>Author, year</b>	<b>Study size</b>	<b>Study design</b>	<b>Centers</b>	<b>Inclusion criteria</b>	<b>CAR T-cell products</b>	<b>Assessment of cardiac events</b>	<b>FU duration</b>
Alvi, <sup>18</sup> 2019	137	Retrospective	2	All patients receiving CAR T-cell therapy at the 2 study centers between Jan 2016 and Nov 2018	Axicabtagene ciloleucel; Tisagenlecleucel; investigational CAR-T	Cardiac testing was not prespecified and performed at the discretion of the treating physicians. Outcomes were assessed and adjudicated by review of electronic health records by the study team blinded to other variables.	294 ± 205 days
Brammer, <sup>19</sup> 2021	102	Retrospective	1	Consecutive adult patients receiving CAR T-cell therapy for relapsed/refractory diffuse large B-cell Lymphoma, follicular lymphoma or mantle-cell lymphoma from Jan 2016 to Dec 2019	Axicabtagene ciloleucel; Tisagenlecleucel; Brexucabtagene autoleucel	Cardiac testing was not prespecified and performed at the discretion of the treating physicians. All patient charts were manually searched for adverse events including CRS, neurotoxicity and cardiotoxicity, as well as cardiovascular and all-cause death.	530 ± 499 days
Ganatra, <sup>20</sup> 2020	187	Retrospective	2	All patients receiving CAR T-cell therapy for refractory or relapsed non-Hodgkin lymphoma at the study centers from Feb 2016 to Apr 2019	Axicabtagene ciloleucel; Tisagenlecleucel	All patients underwent baseline echocardiography. As per institutional protocols follow-up echocardiograms were performed in patients with high-grade CRS (≥grade 2); other patients had follow-up echocardiograms at the discretion of the treating physicians. In-hospital cardiac complications were	168 ± 78 days

						assessed through review of the electronic health records.	
Hu, <sup>21</sup> 2021	40	Prosp.	1	All adult patients receiving CAR T-cell therapy for relapsed/refractory B-cell lymphoma, leukemia or multiple myeloma from Feb 2016 to Oct 2020	Axicabtagene-ciloleucel; Brexucabtagene autoleucel; Tisagenlecleucel	High-sensitivity troponin T and NTproBNP were assessed at baseline, day 1, day 7 and day 21 after CAR T-cell infusion; other cardiac testing was not pre-specified and performed at the discretion of treating physicians. Cardiovascular outcomes were assessed and adjudicated by two physicians through review of electronic health records.	614 ± 304 days
Korell, <sup>22</sup> 2024	137	Prosp.	1	Consecutive patients receiving CAR T-cell therapy at the study center from Oct 2018 to Sep 2022	Axicabtagene ciloleucel; Tisagenlecleucel; Brexucabtagene autoleucel; Idecabtagene vicleucel	Echocardiography was performed at baseline, day 7, and between day 28 and day 180; 12-lead ECGs were performed at baseline, day 7, day 14, day 28, day 56, day 90, day 180. High-sensitivity troponin T and NTproBNP were assessed at baseline, day 1, day 3, day 5, day 7, day 14, day 28, day 56, day 90, day 180.	276 ± 262 days
Lee, <sup>24</sup> 2023	90	Retrosp.	1	Patients with diffuse large B cell lymphoma, mantle cell lymphoma, follicular lymphoma, B-cell acute lymphoblastic leukemia treated with CAR T-cell therapy	Axicabtagene ciloleucel; Tisagenlecleucel; Brexucabtagene autoleucel; Lisocabtagene maraleucel	All patients underwent baseline ECG, transthoracic echocardiogram and troponin I and BNP measurement. Follow-up ECGs, troponin I and BNP levels were performed on day 5 post CAR T-cell infusion and in the event of CRS Grade ≥2. Cardio-oncologists	NA

				from Oct 2020 to Oct 2021		reviewed all electrocardiograms and transthoracic echocardiograms. In case of abnormal baseline ECG or troponin/BNP, repeat echocardiogram and cardiac MRI were performed at the discretion of the cardio-oncology team. Two cardiology fellows reviewed patients' clinical progress $\geq 3$ times a week; in case of cardiac events, these events were adjudicated and managed by the cardio-oncology attending. After index hospitalisation, patients were seen in cardio-oncology outpatient clinic 2 times per week until day 30, then at 3,6, and 12 months.	
Lee, <sup>23</sup> 2023	78	Retrospective	1	All consecutive patients with relapsed and refractory multiple myeloma undergoing CAR T-cell therapy with Idecabtagene vicleucel from May 2021 to Oct 2022.	Idecabtagene vicleucel	All patients received baseline cardiac workup including ECG, transthoracic echocardiogram, troponin I and BNP measurements. Repeat echocardiograms were performed at the discretion of treating physicians. All cardiac outcomes were assessed and adjudicated by cardio-oncologists through review of electronic medical records.	NA
Lefebvre, <sup>25</sup> 2023	44	Prospective	1	All consecutive adult patients with CD19 malignancies treated with commercial CAR	NA	All patients underwent an echocardiogram and cardiac biomarker measurement at baseline, at 2 days, 1 week, 1 month and 6 months post CAR	487 $\pm$ 264 days

				T-cell products from Jul 2019 to Feb 2022		T-cell infusion. In the event of CRS, a repeat echocardiogram was performed within 72h. Electronic health records of all patients were reviewed at 1 year post CAR T-cell infusion for further cardiac events. All cardiac events were adjudicated by 2 cardiologists blinded to all other clinical and echocardiographic information.	
Lefebvre, <sup>26</sup> 2020	145	Retrospective	1	All consecutive adult patients with CD19 malignancy treated with CAR T-cell products from Aug 2010 and Jan 2019	NA	Cardiac events were assessed and adjudicated through review of electronic health records by two independent cardiologists blinded to all other clinical and echocardiographic parameters.	599 ± 813 days
Mahmood, <sup>27</sup> 2023	202	Retrospective	4	Consecutive adult patients receiving CAR T-cell products for CD19 malignancies at the study centers from Feb 2010 to Feb 2021	Axicabtagene ciloleucel; Tisagenlecleucel; Lisocabtagene maraleucel	Cardiac biomarkers were collected before and after CAR T-cell infusion based on the institutional protocols. Cardiac testing was not pre-specified and performed at the discretion of treating physicians. Cardiac events were assessed and adjudicated through manual review of electronic health records	349 ± 405 days
Patel, <sup>28</sup> 2023	75	Retrospective	1	Patients with an available baseline echocardiogram within 6 months prior to	NA	Cardiac testing was not prespecified and performed at the discretion of the treating physicians. Cardiac events were assessed and adjudicated through	NA

				receiving CAR T-cell therapy at the study center from 2016 to 2020		manual review of electronic health records.	
Qi, <sup>29</sup> 2021	126	Retrospect.	1	Patients receiving CAR T-cell products at the study center from Jan 2019 to Nov 2020	NA	Cardiac biomarkers including high sensitivity troponin T and NTproBNP were collected at baseline, day 1-3, day 4-6, day 7-10, day 11-13, day 14-16, day 17-20, day 21-24, day 25-30, day 31-40, day 41-50. Conduction of echocardiography and electrocardiograms was not pre-specified and left to the discretion of treating physicians. Cardiac events were assessed and adjudicated through manual review of electronic health records.	NA
Steiner, <sup>30</sup> 2022	165	Retrospect.	1	Consecutive adult patients with relapsed or refractory aggressive large B-cell lymphoma treated with CAR T-cell products from Jan 2018 to Apr 2020.	Axicabtagene ciloleucel; Tisagenlecleucel	Cardiac testing was not prespecified and performed at the discretion of the treating physicians. Cardiac events were assessed and adjudicated through manual review of electronic health records. All ECGs and echocardiograms were reviewed by a cardiologist.	493 ± 24 days

CRS – cytokine release syndrome; ECG – electrocardiogram; NTproBNP – N-terminal pro brain natriuretic peptide;

eTable 2: Results of random-effects meta-regression using patient age and proportion of patients with lymphoma as potential modifiers of prevalence estimates

<b>Outcome</b>	<b>Modifier</b>	<b>P-value</b>
Heart-failure events	Age	0.01
	Proportion of lymphoma	0.29
Myocardial infarction	Age	0.10
	Proportion of lymphoma	0.92
Cardiovascular mortality	Age	0.82
	Proportion of lymphoma	0.22



eAppendix 1: Search Strategy

Database	Provider	No. of results
MEDLINE	Ovid	155
Embase	Ovid	715
Cochrane CENTRAL	Wiley	22

All databases searched from their inception to the date shown (searches performed on Monday 26<sup>th</sup> February 2024), no language or date limits applied.

Ovid MEDLINE(R) ALL <1946 to February 23, 2024>

1 (t-cell\* adj1 therap\*).mp. or (tcell\* adj1 therap\*).tw. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 8837

2 ((chimeric\* adj3 antigen receptor\*) or (chimeric\* adj3 immunoreceptor\*) or (chimeric\* adj3 T cell receptor\*) or (chimeric\* adj3 Tcell receptor\*)).tw,kf. 11013

3 Receptors, Chimeric Antigen/4875

4 ((artificial\* adj3 T cell receptor\*) or (artificial\* adj3 Tcell receptor\*)).tw,kf. 12

5 axicabtagene\*.tw,kf. 441

6 (yescarta\* or axi-cel\* or KTE-C19 or "CTL 019").tw,kf. 286

7 tisagenlecleucel\*.tw,kf. 518

8 (kymriah\* or CART-19 or CART19).tw,kf. 213

9 Lisocabtagene\*.tw,kf. 107

10 (liso-cel\* or JCAR017\*).tw,kf. 53

11 Brexucabtagene\*.tw,kf. 81

12 Idecabtagene vicleucel.tw,kf. 105

13 Abecma.tw,kf. 6

14 or/1-13 15223

15 Cardiotoxicity/ 4757

16 cardiotoxic\*.tw,kf. 19197

17 exp heart/ or heart.tw,kf. or cardiac.tw,kf. 1672885

18 (ae or co or mo or po or to).fs. 4994874

19 17 and 18 449502

20 exp Cardiovascular Diseases/ci [Chemically Induced] 89368

21 Arrhythmias, Cardiac/68172

22 arrhythm\*.tw,kf. 121095

23 exp Cardiomyopathies/ 114772

24 cardiomyopath\*.tw,kf. 92156

25 exp Heart Failure/ 151997

26 ((cardiac or heart) adj2 fail\*).tw,kf. 241303

27 ejection fraction.tw,kf. 85218  
 28 Ventricular Dysfunction, Left/ 31389  
 29 exp Acute Coronary Syndrome/ 20724  
 30 acute coronary syndrome.tw,kf. 31297  
 31 LVEF.mp. or left ventricular ejection fraction.tw,kf. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 41006  
 32 myocardial infarction/ or myocardial infarction.tw,kf. 280540  
 33 exp Myocardial Ischemia/ 477715  
 34 myocardial isch?emi\*.tw,kf. 38742  
 35 exp Troponin/ 20958  
 36 troponin.tw,kf.33496  
 37 myocarditis.tw,kf. 21825  
 38 (cardiovascular adj2 (death or mortality)).tw,kf. 37000  
 39 exp Myocarditis/ 17551  
 40 15 or 16 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 1313418  
 41 14 and 40 155

Embase <1974 to 2024 February 23>

1 (t-cell\* adj1 therap\*).mp. or (tcell\* adj1 therap\*).tw. 17333  
 2 ((chimeric\* adj3 antigen receptor\*) or (chimeric\* adj3 immunoreceptor\*) or (chimeric\* adj3 T cell receptor\*) or (chimeric\* adj3 Tcell receptor\*)).tw,kf. 20166  
 3 chimeric antigen receptor t-cell immunotherapy/ 11633  
 4 chimeric antigen receptor T-cell/ 12071  
 5 ((artificial\* adj3 T cell receptor\*) or (artificial\* adj3 Tcell receptor\*)).tw,kf. 46  
 6 axicabtagene\*.tw,kf. 1496  
 7 (yescarta\* or axi-cel\* or KTE-C19 or "CTL 019").tw,kf. 1566  
 8 axicabtagene ciloleucel/ 2515  
 9 tisagenlecleucel T/ 2835  
 10 tisagenlecleucel\*.tw,kf. 1492  
 11 (kymriah\* or CART-19 or CART19).tw,kf. 1005  
 12 lisocabtagene maraleucel/ 776  
 13 Lisocabtagene\*.tw,kf. 381  
 14 (liso-cel\* or JCAR017\*).tw,kf. 308  
 15 brexucabtagene autoleucel/ 609  
 16 Brexucabtagene\*.tw,kf. 228  
 17 idecabtagene vicleucel/ 681  
 18 Abecma.tw,kf.94  
 19 or/1-1834023  
 20 cardiotoxicity/ 54047

21 cardiotoxic\*.tw,kf. 28091  
 22 exp heart/ or heart.tw,kf. or cardiac.tw,kf. 2339152  
 23 (ae or si or to).fs. 1950930  
 24 22 and 23 114341  
 25 chemically induced disorder/ 79411  
 26 exp cardiovascular disease/ 5137785  
 27 25 and 26 12515  
 28 arrhythm\*.tw,kf. 184756  
 29 heart arrhythmia/ 144842  
 30 cardiomyopath\*.tw,kf. 150343  
 31 cardiomyopathy/ 70887  
 32 exp heart failure/ 660728  
 33 ((cardiac or heart) adj2 fail\*).tw,kf. 397159  
 34 exp heart ejection fraction/ 200346  
 35 heart left ventricle failure/ 32504  
 36 exp acute coronary syndrome/ 77509  
 37 acute coronary syndrome.tw,kf. 57616  
 38 LVEF.mp. or left ventricular ejection fraction.tw,kf. 90221  
 39 heart infarction/ 317256  
 40 myocardial infarction.tw,kf. 326609  
 41 exp heart muscle ischemia/ 102858  
 42 myocardial isch?emi\*.tw,kf. 54363  
 43 exp troponin/ 89649  
 44 troponin.tw,kf.59218  
 45 exp myocarditis/ 41076  
 46 myocarditis.tw,kf. 30732  
 47 (cardiovascular adj2 (death or mortality)).tw,kf. 58752  
 48 cardiovascular mortality/ 64351  
 49 20 or 21 or 24 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38  
 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 1661216  
 50 19 and 49 715

Search Name: CAR-T cell therapy

Date Run: 27/02/2024 01:48:54

Comment: 26.2.24

ID Search Hits

#1 (t-cell\* near/1 therap\*) or (tcell\* near/1 therap\*) 330  
 #2 ((chimeric\* near/3 antigen receptor\*) or (chimeric\* near/3 immunoreceptor\*) or  
 (chimeric\* near/3 T cell receptor\*) or (chimeric\* near/3 Tcell receptor\*)) 340  
 #3 [mh "Receptors, Chimeric Antigen"] 24  
 #4 (artificial\* near/3 (T NEXT cell NEXT receptor\*)) or (artificial\* near/3 (Tcell NEXT  
 receptor\*)) 2  
 #5 axicabtagene\* 67

#6 yescarta\* or axi-cel\* or KTE-C19 or "CTL 019" 69

#7 tisagenlecleucel\* 32

#8 (kymriah\* or CART-19 or CART19) 17

#9 Lisocabtagene\* 21

#10 (liso-cel\* or JCAR017\*) 24

#11 Brexucabtagene\* 1

#12 Idecabtagene vicleucel 16

#13 Abecma 0

#14 5-#13 538

#15 [mh Cardiotoxicity] 203

#16 cardiotoxic\* 2285

#17 [mh heart] or heart or cardiac 223733

#18 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE, complications - CO, mortality - MO, poisoning - PO, toxicity - TO] 268839

#19 #17 and #18 44513

#20 MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [chemically induced - CI] 4448

#21 MeSH descriptor: [Arrhythmias, Cardiac] explode all trees 13560

#22 arrhythm\* 15922

#23 [mh Cardiomyopathies] 2684

#24 cardiomyopath\* 5673

#25 [mh "Heart Failure"] 14344

#26 (cardiac or heart) near/2 fail\* 39190

#27 ejection fraction 18674

#28 [mh "Ventricular Dysfunction, Left"] 2588

#29 [mh "Acute Coronary Syndrome"] 3078

#30 acute coronary syndrome 8639

#31 LVEF or left ventricular ejection fraction 14088

#32 [mh "myocardial infarction"] 15580

#33 myocardial infarction 37736

#34 [mh "Myocardial Ischemia"] 38574

#35 myocardial isch?emi\* 17553

#36 [mh Troponin] or troponin 5343

#37 myocarditis 1387

#38 [mh myocarditis] 139

#39 cardiovascular near/2 (death or mortality) 10310

#40 22-#16, #19-#39 139611

#41 #14 and #40 22

eAppendix 2: Quality assessment of included studies using the JBI critical appraisal checklist for studies reporting prevalence data

Author	Sample frame appropriate?	Study participants sampled appropriately?	Sample size adequate?	Study subjects and setting described in detail?	Data analysis conducted with sufficient coverage of identified sample?	Valid methods for identification of the condition?	Condition measured in a standard way?	Appropriate statistical analysis?	Response rate adequate?	Overall Score
Lefebvre 2023	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	8/9
Hu 2021	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	7/9
Korell 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9
Patel 2023	No	No	Yes	No	Yes	No	No	Yes	Yes	5/9
Alvi 2019	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	7/9
Lefebvre 2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8/9
Lee 2023	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8/9
Ganatra 2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8/9
Brammer 2021	Yes	Yes	Yes	Yes	No	No	No	No	Yes	5/9
Mahmood 2023	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7/9
Steiner 2022	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	7/9
Lee 2023	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7/9
Qi 2021	Yes	Yes	Yes	No	Yes	No	No	No	No	4/9

# Quality assessment using the JBI critical appraisal checklist for prevalence data

