

BACKGROUND AND HYPOTHESIS

Standardised birth characteristics are collected and reported annually by the Office of National Statistics for births in England and Wales¹. However, there still isn't an agreed international classification system for outcomes in the obstetrics populations². Given that there are over 200 options for coding Congenital and Adult cardiac disease in the 11th revision of the International Classification of Diseases³, this has led to inconsistencies in reported maternal and foetal outcomes for pregnancies in women with cardiac disease⁴.

Survival from childhood congenital heart disease (CHD) has increased a dramatic 31% since the end of the 20th century⁵. Due to a combination of improved survival into adulthood and increasingly older maternal populations, cardiac disease is now the leading cause of maternal mortality in the UK⁶ and the USA⁷.

There is a “therapeutic alliance” between clinicians and patients with chronic disease, with more patients taking an active part in decision making⁸. This has led to a concept of “P4 medicine” in shared decision making (SDM) that is personalised, preventative, predictive and participatory⁹. This also means that both should have access to data that is “accurate, relevant and evidence based”⁹.

However, rates of maternal cardiac morbidity and mortality can vary dramatically depending on the underlying cardiac lesion, pregnancy characteristics and development of obstetric complications (which may be increased in certain cardiac disease types¹⁰). More than 20% of women with dilated cardiomyopathy died from pregnancy in a cohort of 38¹¹, whereas there were no reported adverse complication or deaths in a group of 20 pregnant women with known long QT syndrome¹².

Informed consent formalises a patient's involvement in SDM and should reflect the fact that they understand their diagnosis and associated risks¹³. Due to the evolving prognosis of congenital and acquired cardiac lesions, there is a strong agenda to report outcomes using contemporaneous data of pregnant women with heart disease¹⁴ which reflects recent developments and changes in survival in this at-risk cohort.

The main objective of this review will be to report what are the pooled outcomes of pregnancy in women with heart disease, that have been reported in recent literature.

Contemporaneous reported clinical outcomes of pregnancy in maternal cardiac patients: a systematic review

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Methods

A summary protocol for a systematic review of the maternal cardiac outcomes literature to inform a wider research piece on risk prediction modelling, was registered on the Open Science Framework on 16th March 2023¹⁵.

Study Selection

Soft searches were initially conducted on the USA based National Institute of Health, National Library of Medicine database website Pubmed® in August 2021 to explore variation of search terms. Formal searches were then conducted between January 2022- March 2022 using the online database websites for Pubmed®, Web of Science ®, and the PLOS journals®. Selected articles were reviewed between July 2022 – February 2023 and the reference lists manually scanned by the Principal Investigator. Titles of potential interest were included in the study review and selection process.

Eligibility criteria

Reports concerning pregnant adult women with cardiac disease were published in the preceding 10 years (2012-2022) were included. This is to reflect contemporaneous outcomes of women encountered in today’s medical environment. The exclusion criteria for this review are presented as appendix 1 of the supplementary material.

Search Strategy

The search strategy used in all three website databases are presented in appendix 2 of the supplementary material, including details of filters and limits used.

Selection Process

After removal of duplications, study titles were reviewed independently by Reviewer 1 (also Principal Investigator) and Reviewer 2 (an Obstetric Anaesthetic Consultant) using Microsoft Excel®, with a view to identifying studies meeting either the inclusion or exclusion criteria. Discrepancies were reviewed by Reviewer 3 (a maternal cardiac Consultant expert) who had the authority to identify titles that should be included in the review. Abstracts of selected study titles were reviewed by Reviewer 1 using AbstrackR® and filtered for inclusion. Full text studies were then subject to comprehensive analysis and data extraction. Full text studies that were found to be ineligible at this stage were then also excluded.

Data Extraction and Synthesis

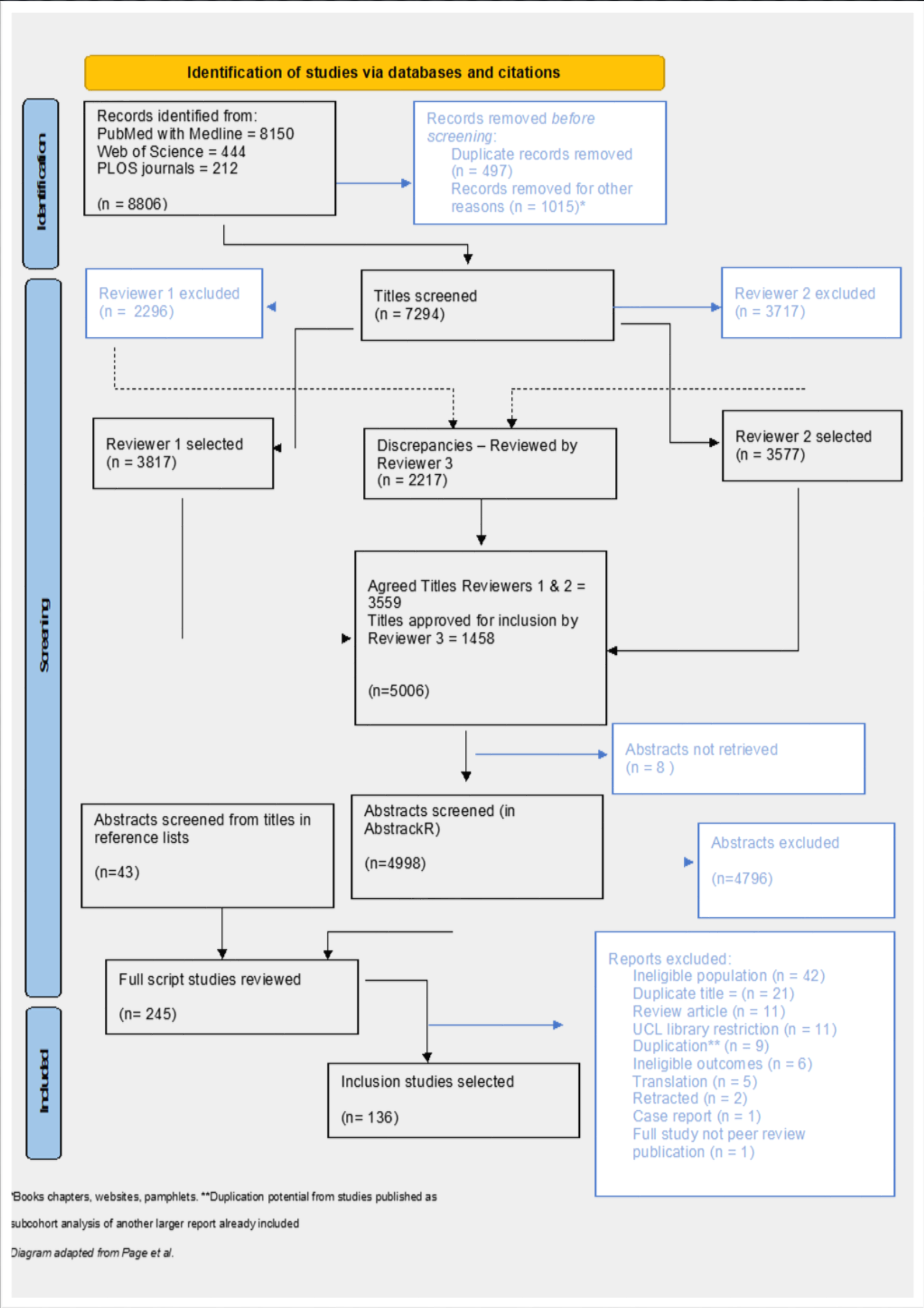
Initially, ten random studies for inclusion were used to ascertain a baseline structure and categorisation across what appeared to be patterns of reporting outcomes of pregnancy in women with cardiac disease. It was noted that studies regarding outcomes of pregnancy in maternal cardiac patients, reported across four general areas; one descriptive and three outcomes based. Studies described cardiac disease characteristics of the maternal population studied at baseline then would describe outcomes across three general areas: maternal/cardiac, obstetric and foetal outcomes. A further forty articles for inclusion were then used to specify details for collection in each category of outcomes (maternal, obstetric and foetal) in the data collection sheets. Manual data entry sheets were designed in Microsoft Excel® to collect information.

Data reporting: Population outcome data and effect measure

Studies included may report their denominator population as either number of women, number of pregnancies, or both. For the purposes of this analysis, the number of pregnancies will be used where provided and otherwise, the number of women. Where the population size of a particular outcome is unclear, that study will be excluded from weighted summary analysis of that outcome. Where studies report basic descriptive continuous data such as age, gestational week or weight for each case separately or subcategorised into groups in comparative subpopulations, an aggregated weighted summary statistic is computed and included here. Collected outcome data will be cleaned and standardised in Microsoft Excel®. Data stratification, analysis and visualisation will be conducted using R Statistical Software (v4.3.1; R Core Team 2021). Where studies report a two-population effect comparison (rates in cardiac pregnant women versus pregnant women without cardiac disease), a random effects model meta-analysis with associated DerSimonian and Laird test of heterogeneity will be conducted for a pooled estimate of adverse maternal outcomes of morbidity and mortality. For single armed studies, a pooled effect size of proportions suffering MACE and/or mortality will be reported. Pooled weighted estimates for the most commonly reported obstetric and foetal outcomes will be shared. R scripts are available to view on the principle investigator’s Github repository¹⁶.

Study heterogeneity and Bias assessment

A widely cited review article by Ma et al recommends the Newcastle Ottawa Scale ¹⁷ risk of bias tools¹⁸ for separate assessments of observational and case control studies¹⁹. The same reviewer (Reviewer 1) scored the relevant NOS assessment for all included studies.



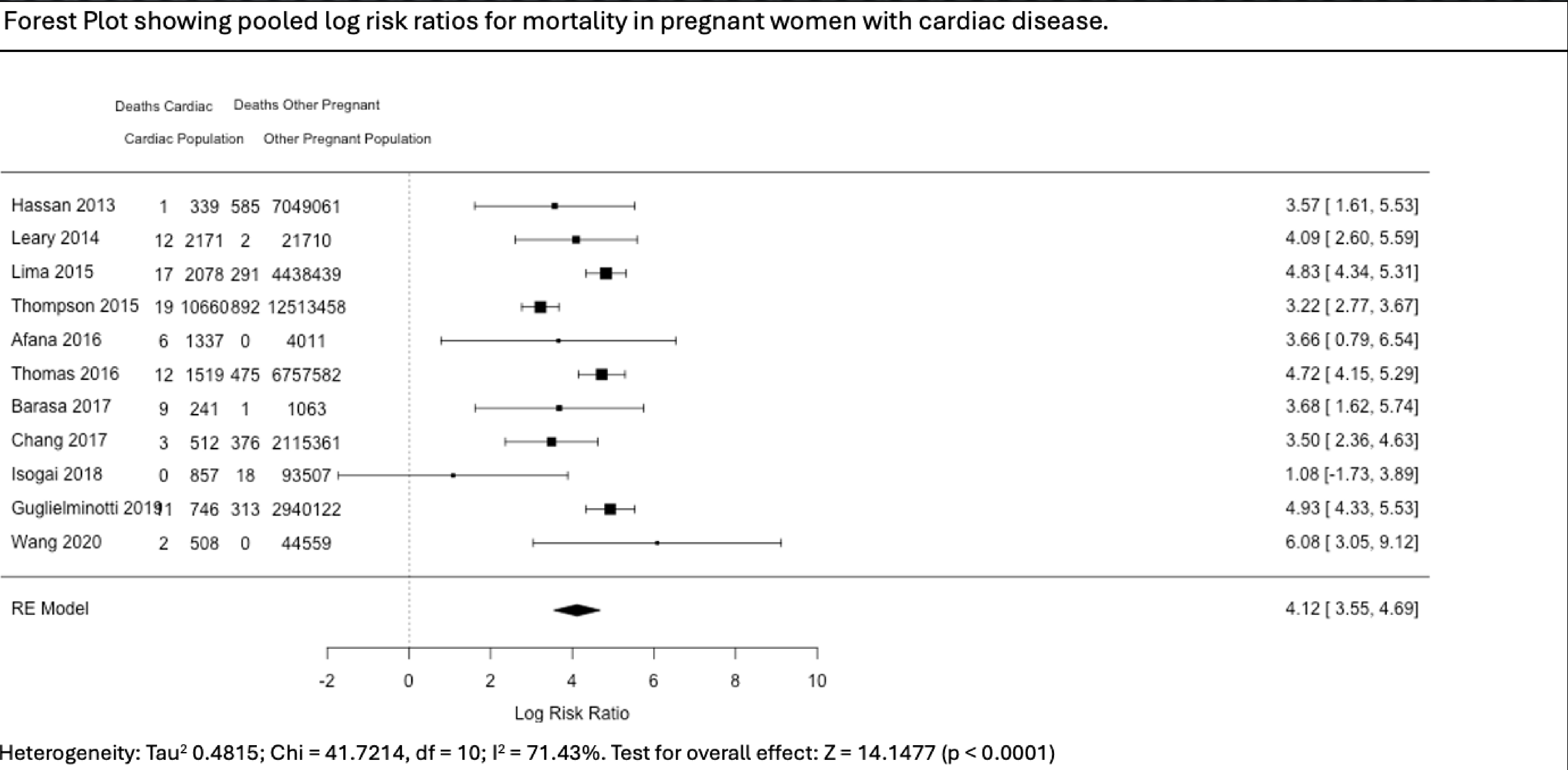
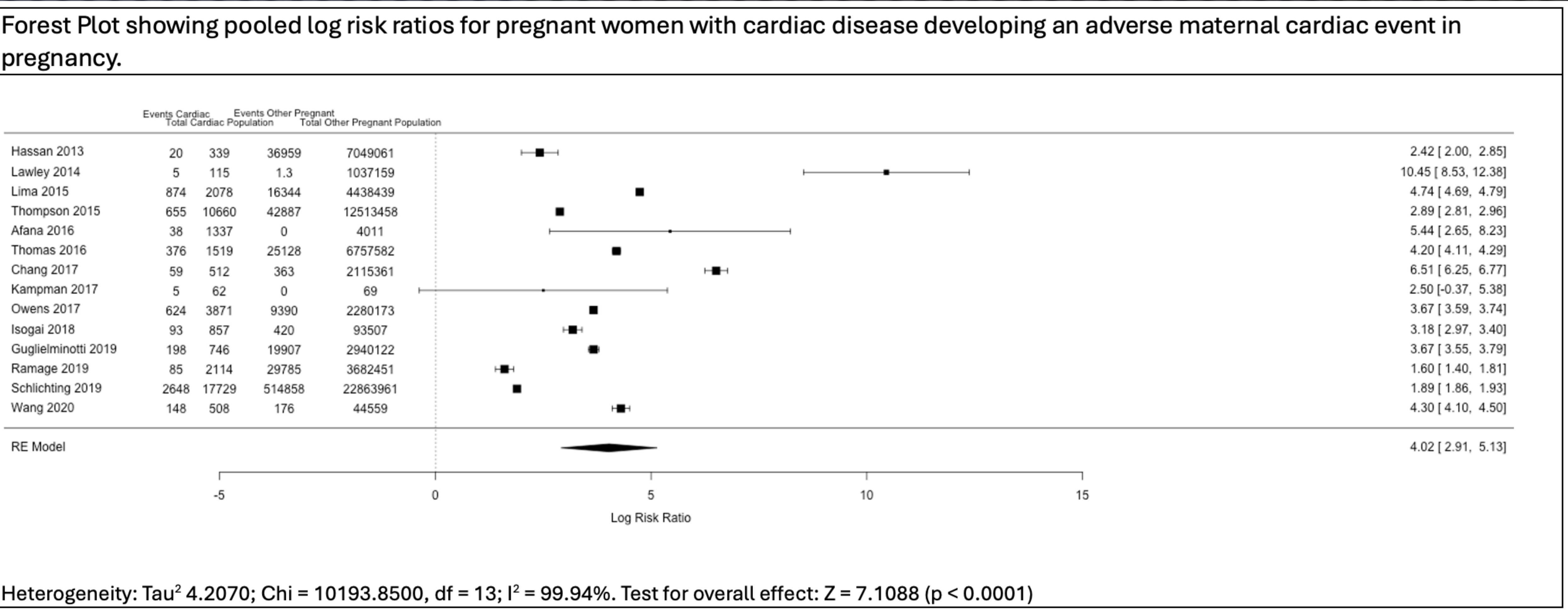
RESULTS

136 studies, of which 25 were case control designs, were included. 51,290 women across 36 geographical regions were represented. Women with cardiac disease had more than a 50x (RR 55.96 (95% CI: 18.45-169.74)) increased risk of a cardiac complication and more than 60x (RR 61.37 (95% CI: 34.69 – 108.55)) increased risk of death in the peripartum period (Figure 1). A pooled estimated 16.83% (95% CI: 14.3-19.53%) of women with cardiac disease suffered a cardiac complication, and a pooled estimated 2.93% (95% CI: 2.13-3.84%) did not survive beyond the puerperium.

Pooled rate of Caesarean section delivery was 48.01% (95% CI: 42.33 – 53.75%). Obstetric and Foetal adverse outcomes were also raised compared to nationally reported UK outcomes from the general obstetric population. A pooled estimated 9.8% (95% CI: 6.96-13.52%) of women suffered a PPH event. Rate of premature birth were 21.83% (95% CI: 18.38 – 25.72%). 20.16% (95% CI:14.89-26.72%) of fetuses delivered were small for gestational age and 1.26% (95% CI: 0.76-2.09%) did not survive past the first 30 days of life.

Table 1 Pooled estimates of the top three most commonly reported obstetric outcomes in the maternal cardiac population.			
Caesarean section deliveries	Model	Proportion of deliveries	95% CI
	Common effects model	0.4183	(0.4140; 0.4226)
	Random effects model	0.4801	(0.4233; 0.5375)
	tau^2 = 0.8840; tau = 0.9402; I^2 = 97.4% (97.1%; 97.7%); H = 6.26 (5.90; 6.63)		
Postpartum haemorrhage	Model	Proportion experiencing postpartum haemorrhage	95% CI
	Common effects model	0.047	(0.0448-0.0502)
	Random effects model	0.098	(0.0696-0.1352)
	Quantifying heterogeneity: tau^2 = 1.1125; tau = 1.0547; I^2 = 95.8% (94.9%; 96.5%); H = 4.88 (4.45; 5.37)		
78 studies			
41 studies			

Table 2: Pooled estimates of premature birth rates, small for gestational age and neonatal mortality					
Outcome	Pooled proportion, %	95% CI, %	Number of included studies	Number of events/ observations	Tests of heterogeneity
Premature birth	21.83	(18.38-25.72)	70	5451/28631	T 0.8384 I^2 92.3% (90.9-93.4%)
Neonatal mortality	1.26	(0.76-2.09)	34	114/8770	T 1.0459 I^2 79.4% (71.8-85%)
SGA	20.16	(14.89-26.72)	29	1758/6352	T 0.9027 I^2 97.1 (96.4-97.6%



Maternal Outcomes

Across all the included studies in this review, 96% reported at least one adverse maternal outcome in their study population. Basude et al²⁴ reported the highest adverse maternal outcomes (66%), in women with significant mitral valve disease and/or replacement (correlating to a mWHO class 4¹³⁹). Pooled rates of MACE are clinically significant affecting 15.39% (95% CI: 12.03-19.49%) in population studies. The increased relative risk (applying the inverse to the reported log RRs) of cardiac complications in pregnancy for women with cardiac disease compared to a healthy obstetric population is 18.44 (95% CI: 2.53-169.74). The wide range of RR here probably reflects the diversity and pathophysiological impact of the included cardiac conditions. A consistent finding is also noted with the risk of death. Population mortality was 3.6% (95% CI: 2.4-5.38%), but the risk of death was 61.37 (95%CI: 34.69 -108.55) times more for pregnant women with cardiac disease.

Obstetric Outcomes

Both fixed and random effects assumptions estimate Caesarean section (LSCS) rates in this population as approximately 40%. Hayward⁵², Thompson⁹¹ and Hrycyk¹¹⁸ demonstrated significantly increased rates of Caesarean section in women with CHD compared to a healthy obstetric population, as well as increased rates of LSCS associated with increasing severity of disease¹¹⁸. Increased severity of pulmonary arterial hypertension (PAH) was also associated with increased rates of LSCS^{76,87}. An increased proportion of second pregnancies in women with PAH necessitated emergency general anaesthesia for LSCS compared to first pregnancies¹⁰⁹, suggesting that sequential late-stage pregnancies may be less poorly tolerated. Estimated rates of PPH more than double depending on fixed effects estimate of 4.7% (95% CI: 4.48-5.02%) and random effects assumption at 9.8% (95% CI: 6.96 – 13.52%). As the I² estimates that 95% of the result heterogeneity is due to between study variations, it is likely that the random effects model is more accurate as it would attempt to take into account the heterogeneity of reported study diseases that were pooled for this review. Patients with PPCM⁴¹, Marfan’s syndrome⁴⁴ and mechanical valve disease⁶⁷ were specifically noted to be at increased risk of PPH. Lameijer et al⁶⁷ and Cauldwell et al³⁷ both identified treatment dose anticoagulation as contributory to increased rates of post-delivery bleeding. Caesarean section compared to vaginal delivery was also identified as an independent risk factor for PPH^{43,140}.

Foetal outcomes

Rates of neonatal death were 1.26% (95% CI: 0.76-2.09%), which is more than four times higher than the latest ONS figures of 2.9 deaths per 1,000 live births in England and Wales in 2022¹⁴¹. Yaghoubi et al found that foetal mortality was statistically more significant in pregnancies where the mother has CHD compared to other cardiac conditions (p = 0.031)⁹⁵, with pulmonary artery pressures above 40mmHg and/or left ventricular ejection fraction <25% being particularly important aggravating factors. Afshar et al also reported significantly higher mortality in patients with heart failure (p < 0.001), a diagnosis of lower systemic ventricular output state.

Estimated rates of premature birth and SGA were both approximately 20% (Table 2), both with I² values above 90% suggesting that between study variation was responsible for most of the heterogeneity in the model.

Although being part of a mixed heart disease cohort increased the risk of premature delivery, when compared to the general obstetric population^{79,81}, certain conditions were specifically identified as potential predictors. Higher rates of premature delivery were seen in patients with pulmonary hypertension^{90,116}, Marfan’s syndrome¹¹⁷, Heart Failure⁵⁰ and Cardiomyopathy¹²². Obstetric predictors for premature delivery were pregnancy induced hypertension (OR 3.15, 1.37-7.24)¹²² and Pre-eclampsia⁷³ which predicts earlier delivery of the foetus (at 32.1 vs 38.6 weeks)⁷³.

Conclusion

Although the risks of suffering a cardiac complication during pregnancy are still relatively small for women with cardiac disease, their risks are dramatically higher than the baseline population. Risks of obstetric and foetal complications are also raised.

Future work should be aimed at standardising reported outcomes in this complicated and vulnerable group of patients. This would lay the foundation for more precise disease specific outcomes.

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