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REVIEW

Disparities in death rates in women with peripartum cardiomyopathy between advanced and developing countries: A systematic review and meta-analysis

Disparité dans le taux de décès chez les femmes ayant une cardiomyopathie du péripartum selon la survenue dans un pays émergent ou développé : revue systématique et méta-analyse

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Summary There is limited information about differences in maternal deaths from peripartum cardiomyopathy (PPCM) between advanced and developing countries. To review the literature to define the global prevalence of death from PPCM, and to determine the differences in PPCM mortality rates and risk factors between advanced and developing countries. Studies in the English language reporting mortality data on patients with PPCM were included from searches of MEDLINE, Embase, CINAHL, the Cochrane Library, the Web of Science Core Collection and Scopus from 01 January 2000 to 11 May 2016. Of the 4294 articles identified, 1.07% were included.

Abbreviations: CMR, cardiovascular magnetic resonance; ESC, European Society of Cardiology; PPCM, peripartum cardiomyopathy.

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The primary outcome was death; rates of heart transplant, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, embolism and cardiac arrest were recorded. Studies were categorized as having been conducted in advanced or developing countries. Data from 46 studies, 4925 patients and 13 countries were included. There were 22 studies from advanced countries ($n = 3417$) and 24 from developing countries ($n = 1508$); mean follow-up was 2.6 (range 0—8.6) years. Overall mortality prevalence was 9% (95% confidence interval [CI] 6—11%). The mortality rate in developing countries (14%, 95% CI 10—18%) was significantly higher than that in advanced countries (4%, 95% CI 2—7%). There was no difference in the prevalence of risk factors (chronic hypertension, African descent, multiple gestation and multiparity) between advanced and developing countries. Studies with a higher prevalence of women of African descent had higher death rates (correlation coefficient 0.29, 95% CI 0.13—0.52). The risk of death in women with PPCM was higher in developing countries than in advanced countries. Women of African descent had an increased risk of death.

MOTS CLÉS
Cardiomyopathie du péripartum ;
Suivi ;
Évènement cardiovasculaire ;
Pays développés ;
Pays émergents ;
Méta-nalyse

Résumé Les données concernant les différences sur le taux de mortalité maternelle de cardiomyopathie du péripartum restent limitées pour ce qui concerne la différence entre les pays développés ou émergents. Revue de la littérature pour définir une prévalence globale du taux de décès lié à une cardiomyopathie du péripartum et déterminer les différences pour ce qui concerne les facteurs de risque entre les pays développés ou émergents. Étude de la littérature anglaise rapportant les taux de mortalité chez les patientes porteuses d'une cardiomyopathie du péripartum à partir d'une recherche sur les bases de données MEDLINE, Embase, CINAHL, Cochrane, Collection Web of Science Core et Scopus entre le 1er janvier 2000 et le 11 mai 2016. Parmi les 4294 articles identifiés, 1.07 % ont été finalement inclus. Le critère de jugement principal était le décès, le taux de transplantation cardiaque, d'infarctus du myocarde, d'insuffisance cardiaque, d'arythmie cardiaque, d'évènements cérébraux vasculaires, d'embolie et d'arrêt cardiaque avec collection systématique de ces informations. Les études ont été caractérisées comme ayant été ou non effectuées dans un pays développé ou émergent. Les données de 46, soit 4 925 patients dans 13 pays ont été inclues, ont été colligées 22 études provenant des pays développés ($n = 3417$) et 24 études provenant des pays émergents ($n = 1508$). La durée moyenne de suivi était de 2,6 ans (0—8.6). La prévalence de la mortalité globale était de 9 % (IC 95 % 6—11 %). Le taux de mortalité dans les pays émergents était de 14 % (IC 95 % 10—18 %), significativement plus élevé que celui observé dans les pays développés (taux de mortalité 4 %, IC 95 % 2—7 %). Il n'y avait pas de différence pour ce qui concerne la prévalence des facteurs de risque (HTA chronique, origine africaine, grossesses multiples, multiparité) entre les pays émergents et développés. Les études avec une prévalence plus élevée de femmes d'origine africaine rapportaient un taux plus élevé de décès avec un coefficient de corrélation à 0,29, IC 95 % 0,13—0,52. Le risque de décès chez les femmes porteuses d'une cardiomyopathie du péripartum est plus élevé dans les pays émergents comparativement aux pays développés. Les femmes d'origine africaine ont un risque accru de décès.

Background

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy, defined as the development of cardiac failure in the last month of pregnancy or within 5 months of delivery, with an ejection fraction of < 45%, in the absence of an alternative aetiology or previous heart disease [1,2]. PPCM is a global disease, with an estimated prevalence of about 1 in 1000 pregnancies, with a possible trend towards an increase in prevalence in certain regions of the world, including the USA [3—5]. The reported mortality from PPCM varies widely from < 1% to > 30%, depending on patient population studied, type of study, follow-up time, definition of PPCM and availability and access to adequate treatment and resources [5,6]. There is limited information regarding possible differences in maternal death rates among women with PPCM in advanced countries compared with developing countries. While previous studies have pointed to factors associated with the development of PPCM, such as age > 30 years, black race, pre-eclampsia, hypertension and multiple gestations [7], it is unknown whether there are differences in the prevalences of these risk factors between developing and

advanced countries, and if there is any impact on death rates. Additionally, previous studies have pointed to worse outcomes in women of African descent [8], but it is not clear if African descent is a risk factor for death in PPCM.

In this study, we sought to review the contemporary global PPCM literature in order to define the global prevalence of death, to compare the prevalence of death in advanced and developing countries, and to define the prevalence of risk factors for the development of PPCM in advanced and developing countries, and their impact on death rates.

Methods

Literature search

The methods and inclusion criteria were specified in advance and documented in a protocol. We followed the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [9]. Six bibliographic databases were used: MEDLINE (PubMed; National Library of Medicine, NIH, Bethesda, MD, USA); Embase (Elsevier, Amsterdam, Netherlands); CINAHL (EBSCOhost; EBSCO Information Services, Ipswich, MA, USA); the Cochrane Library (John Wiley & Sons, Hoboken, NJ, USA); the Web of Science Core Collection (Clarivate Analytics, Philadelphia, PA, USA); and Scopus (Elsevier). Searches were limited to English language articles published between 01 January 2000 and 11 May 2016, regardless of geographical origin. If the publication type was a case report, letter, commentary or editorial, the article was excluded. The following PubMed (MEDLINE) search strategy was used, and then adapted appropriately for the other databases: ''(((cardiomyopathies[mh] OR cardiomyopath*[tw]) AND (Pregnancy[mh] OR pregnan*[tw] OR gestation[tw] OR peripartum[tw])) OR ''peripartum cardiomyopathy''[tw] OR ''peripartum-associated cardiomyopathy''[tw] OR ''peripartum-associated cardiomyopathy''[tw]) AND English[la] AND 2000:2016[dp] NOT (Case Reports[pt] OR ''case study''[tw] OR ''case report''[tw] OR ''case reports''[tw] OR ''case studies''[tw] OR ''case series''[tw] OR letter[pt] OR comment[pt] OR editorial[pt] OR news[pt])''. Bibliographic database searching was supplemented by citation tracking (checking selected article cited reference lists) and consulting with experts in the field.

Study selection

Once the literature search was completed, articles were imported into EndNote software (Clarivate Analytics) and duplicate citations were removed. The article set was then imported into Covidence (www.covidence.org; Covidence, Melbourne, Australia), an online organizational tool for systematic reviews. The titles and abstracts of the studies were independently screened by two authors (K. K. and F. V. L.; Fig. 1), and exclusions were based on the following predefined criteria:

- not written in the English language;
- not a primary research article (e.g. a case report or a review) or;
- did not mention PPCM in the title or abstract.

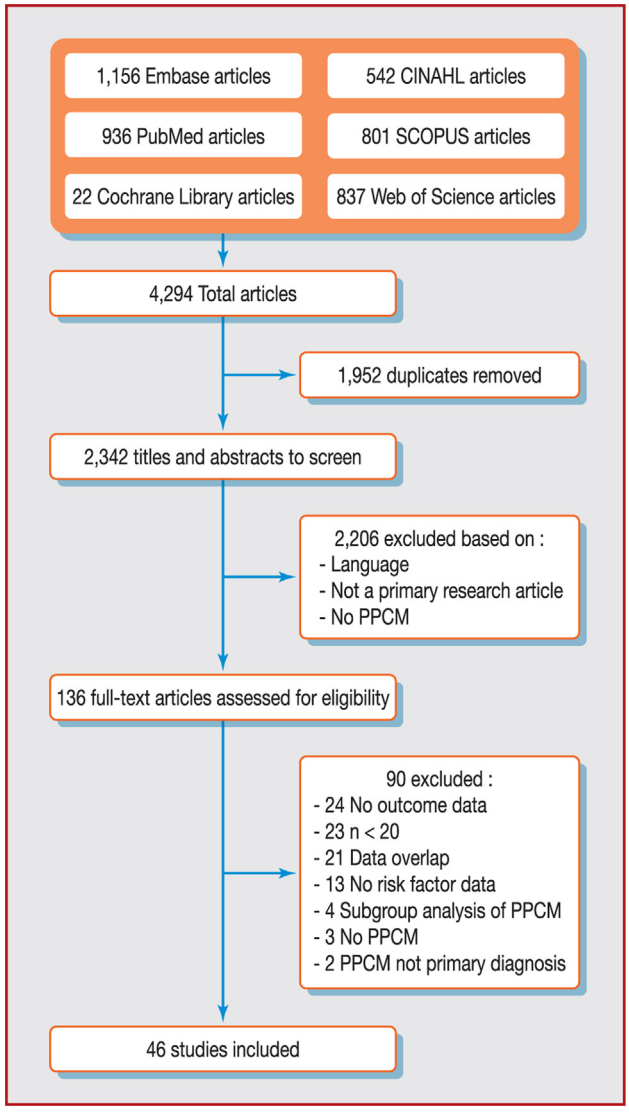

Figure 1. Flow diagram depicting the process of study selection for inclusion in the systematic review and meta-analysis, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses. PPCM: peripartum cardiomyopathy.

Once both authors agreed upon each inclusion/exclusion decision, both authors then independently assessed the full-text articles for eligibility. The following predefined exclusion criteria were applied:

- death was not reported;
- sample size was < 20;
- data overlap between studies;
- no risk factor data reported (i.e. hypertension, African descent, multiparity, multiple gestation);
- PPCM sample was a subgroup and not the primary study population and;
- PPCM was not the primary diagnosis.

For exclusion criterion (3), if there was data overlap between studies, the study with the largest sample size was included. Once the final set of studies was chosen, data were extracted independently for the predefined categories by

two authors (K. K., P. K.-S.), and then cross-checked and corrected.

Data extraction

Definition of diagnosis of PPCM

The definitions and criteria that each study used to establish the diagnosis of PPCM in their patient population were recorded.

Risk factors for PPCM

The rates of different risk factors for PPCM, including age, chronic hypertension, pre-eclampsia/eclampsia, gestational hypertension, African descent, multiparity and multiple gestations, were recorded. Data on hypertension were collected from the studies, and subclassified by type as specified by the author (chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia). All other hypertensive syndromes were classified as ''hypertension not otherwise specified''. Heart transplant refers to those listed or those who received a transplant.

Outcome measures

Outcomes of interest recorded were death, heart transplant, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, embolism and cardiac arrest.

Country group

Studies were divided into representative subgroups of advanced or developing countries according to the International Monetary Fund classification, as previously described [10–12]. ''USA'', ''Germany'', ''Japan'' and ''Israel'' were classified as advanced; ''Turkey'', ''Africa'', ''Haiti'', ''South Africa'', ''Pakistan'', ''China'', ''Nigeria'', ''India'' and ''Argentina'' were classified as developing.

Statistical analysis

Meta-analyses and forest plots were completed for each variable for overall prevalence as well as subgroup prevalence in developing countries and advanced countries. Cochran's Q test was used to test heterogeneity among studies. If the equal variance hypothesis was rejected, a random-effect model was used to estimate the pooled prevalence; otherwise a fixed-effect model was used. Freeman-Tukey (double arcsine) transformation for proportions was used in the estimation [13]. No pooled prevalence of a variable was estimated if there were fewer than five studies reporting that variable's prevalence. Sensitivity analysis was done by estimating the pooled prevalence after excluding one specific study at a time to ensure that no single study was unduly influencing the results. 95% confidence intervals (CIs) based on the Z-test were reported for all estimated prevalence. Permutation tests were used to compare prevalences of pre-eclampsia, hypertension, African descent, multiple gestation and multiparity between advanced and developing countries. Weighted correlation coefficient was used to examine the linear relationship between pre-eclampsia/African descent prevalence and death rate. Here, the weighted correlation coefficient (between variables x and y) was calculated, using the formula:

$$\left(\sum[\text{weightx}][\text{weighty}][x-\text{meanx}][y-\text{weightedmeany}]\right)/$$

$$\sqrt{\left([\sum(\text{weightx})^2(x-\text{weightedmeanx})^2]\right.}$$

$$\left.[\sum(\text{weighty})^2(y-\text{weightedy})]\right)$$

where weighted mean:

$$x = \left(\sum[x][\text{weightx}]/\left(\sum[\text{weightx}]\right)\right.$$

and weight is the reciprocal of the CI length for the prevalence within a specific study. 95% bootstrapped CIs were reported for weighted correlation coefficients. Statistical analysis was performed using the R package ''metafor'' (The R Foundation, Vienna, Austria), and the significance level was set at 0.05.

Results

Overall, data from 46 studies ($n = 4925$, range 20–1337) and 13 countries were included in this analysis (Table 1); there were 22 studies from advanced countries ($n = 3417$) and 24 from developing countries ($n = 1508$). The mean duration of follow-up was 2.6 (range 0–8.6) years. Most studies (70%) used the National Heart, Lung and Blood Institute and Office of Rare Diseases Workshop definition of PPCM, or a modified version of it [1]; however, there were differences in the absolute cut-off for left ventricular ejection fraction. The mean age was 29.7 (range 21–34) years.

The overall pooled prevalence rate of pre-eclampsia/eclampsia was 16% (95% CI 12–21%; Table 2), of gestational hypertension was 21% (95% CI 15–28%), of chronic hypertension was 24% (95% CI 15–34%), of African descent was 48% (95% CI 32–64%), of multiple gestations was 66% (95% CI 56–74%) and of multiparity was 11% (95% CI 8–14%). There were no significant differences in the prevalence of risk factors for PPCM in developing compared with advanced countries, with the exception of hypertension not otherwise specified.

In Table 2, the overall prevalence of death was 9% (95% CI 6–11%; range 0–33%) and of heart transplant was 4% (95% CI 1–7%; range 0–34%). Our analysis revealed that there was a significant difference in the death rate between advanced countries (4%, 95% CI 2–7%) and developing countries (14%, 95% CI 10–18%; Fig. 2).

Pre-eclampsia prevalence was not significantly correlated to death rates in this analysis (weighted correlation coefficient 0.15, 95% CI 0.70–0.87). African descent prevalence and death rates were positively correlated (weighted correlation coefficient 0.29, 95% CI 0.13–0.52).

Discussion

To the best of our knowledge, the present study is the largest global contemporary systematic review and meta-analysis performed to date of PPCM studies describing the overall

Table 1 Characteristics of studies included in the meta-analysis.

References	Country; advanced or developing	Number of patients	Age (years)[a]	Follow-up (years)	Criteria for diagnosis of PPCM
Afana et al. 2016 [25]	USA; advanced	1337	NC	0	ICD code[c]
Akil et al. 2016 [26]	Turkey; developing	58	31.5 ± 6	2.7	NHLBI/ORD Workshop definition[e]
Amos et al. 2006 [27]	USA; advanced	55	29.0 ± 6	3.6	NHLBI/ORD Workshop definition[d]
Bernstein et al. 2001 [28]	USA; advanced	23	30.9 ± 4	1	NHLBI/ORD Workshop definition[e]
Biteker et al. 2012 [29]	Turkey; developing	42	27.0 ± 5	3.7	NHLBI/ORD Workshop definition[e]
Blauwet et al. 2013 [30]	South Africa; developing	176	30.7 ± 7	0.5	NHLBI/ORD Workshop definition[d]
Brar et al. 2007 [31]	USA; advanced	60	33.0 ± 7	4.7	NHLBI/ORD Workshop definition[e]
Chapa et al. 2005 [32]	USA; advanced	32	27.0 ± 6	3.8	Other[i]
Cooper et al. 2012 [33]	USA; advanced	39	30 ± 7	2.1	Other[i]
Elkayam et al. 2001 [34]	USA; advanced	44	29.0 ± 6	7	Other[i]
Elkayam et al. 2005 [35]	USA; advanced	100	30.7 ± 6	1.9	NHLBI/ORD Workshop definition[d]
Felker et al. 2000 [36]	USA; advanced	42	29.0 ± 6	8.6	NHLBI/ORD Workshop definition[e]
Fett et al. 2005 [37]	Haiti; developing	98	32.2 (range 16—50)	2.2	NHLBI/ORD Workshop definition[d]
Forster et al. 2008 [38]	South Africa; developing	43	30[b]	0.5	NHLBI/ORD Workshop definition[e]
Goland et al. 2009 [17]	USA; advanced	182	29.0 ± 7	1.6	NHLBI/ORD Workshop definition[d]
Gunderson et al. 2011 [39]	USA; advanced	110	NC	3	NHLBI/ORD Workshop definition[d]
Habli et al. 2008 [40]	USA; advanced	70	NC	3.4	NHLBI/ORD Workshop definition[e]
Haghikia et al. 2013 [41]	Germany; advanced	115	34.0 ± 6	0.5	ESC Working Group on PPCM[f]
Harper et al. 2012 [42]	USA; advanced	85	NC	7	NHLBI/ORD Workshop definition[d]
Hasan et al. 2010 [43]	Pakistan; developing	32	32.0 ± 3	0.5	Other[i]
Huang et al. 2012 [44]	China; developing	52	29.1 ± 6	0.1	NHLBI/ORD Workshop definition[e]
Isezuo et al. 2007 [45]	Nigeria; developing	65	28.2 ± 8	0.8	NHLBI/ORD Workshop definition[e]
Kamiya et al. 2011 [46]	Japan; advanced	102	32.7 (range 22—43)	0.8	NHLBI/ORD Workshop definition[e]
Kao et al. 2013 [47]	USA; advanced	535	NC	0	ICD code[c]
Karaye et al. 2015 [48]	Nigeria; developing	39	25.9 ± 6	0.5	ESC Working Group on PPCM[g]
Karaye et al. 2016 [49]	Nigeria; developing	45	26.6 ± 7	1	NHLBI/ORD Workshop definition[e]
Li et al. 2016 [50]	China; developing	71	28.0 ± 6	3.6	NHLBI/ORD Workshop definition[d]
Libhaber et al., 2015 [51]	South Africa; developing	206	30.6 ± 6	0.5	NHLBI/ORD Workshop definition[d]
Liu et al. 2014 [52]	China; developing	37	29.0 ± 6	1	NHLBI/ORD Workshop definition[d]
Loyaga-Rendon et al. 2014 [53]	USA; advanced	99	32.9 ± 9	3	INTERMACS protocol[h]
Mandal et al. 2011 [54]	India; developing	36	NC	NR	NHLBI/ORD Workshop definition[d]

Table 1 (*Continued*)

References	Country; advanced or developing	Number of patients	Age (years)[a]	Follow-up (years)	Criteria for diagnosis of PPCM
McNamara et al. 2015 [18]	USA; advanced	100	30 ± 6	1	NHLBI/ORD Workshop definition[e]
Mishra et al. 2006 [55]	India; developing	56	31.0 ± 5	6.1	NHLBI/ORD Workshop definition[e]
Modi et al. 2009 [56]	USA; advanced	44	25.2 ± 6	2	NHLBI/ORD Workshop definition[d]
Ntusi et al. 2015 [57]	South Africa; developing	30	31.5 ± 7	3.5	NHLBI/ORD Workshop definition[d]
Peradejordi et al. 2013 [58]	Argentina; developing	23	28.7 ± 8	7.3	ESC Working Group on PPCM[f]
Pillarisetti et al. 2011 [59]	USA; advanced	100	30 ± 6	2.9	ICD code[c]
Saltzberg et al. 2012 [60]	USA; advanced	107	31.2 ± 6	3.0	ICD code[c]
Sarojini et al. 2013 [61]	India; developing	46	21.0 ± 14	0.5	NHLBI/ORD Workshop definition[e]
Shah et al. 2012 [62]	Pakistan; developing	61	30.9 ± 6	1	NHLBI/ORD Workshop definition[d]
Shani et al. 2015 [63]	Israel; advanced	36	33.5 ± 6	NR	NHLBI/ORD Workshop definition[e]
Sharieff et al. 2002 [64]	Pakistan; developing	35	30.8 ± 6	0.5	NHLBI/ORD Workshop definition[e]
Sliwa et al. 2002 [65]	South Africa; developing	59	NC[b]	0.5	Other[i]
Sliwa et al. 2006 [66]	South Africa; developing	100	31.6 ± 6	0.5	NHLBI/ORD Workshop definition[e]
Sliwa et al. 2010 [67]	South Africa; developing	20	26.0	0.5	Other[i]
Tibazarwa et al. 2012 [68]	South Africa; developing	78	29.0 ± 6	0.5	NHLBI/ORD Workshop definition[d]
Year range 2000—2016	Total of 46 studies: 22 from advanced countries; 24 from developing countries	Total 4925; range 20—1337	Mean 29.7; range 21—34	Mean 2.6; range 0—8.6	

EF: ejection fraction; ESC: European Society of Cardiology; HF: heart failure; ICD: International Classification of Diseases; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LV: left ventricle/ventricular; NHLBI/ORD: National Heart, Lung and Blood Institute and Office of Rare Diseases; NC: not calculable (indicates that the study did include some form of the data in the said category, but it was not able to be translated into a clear per cent statistic for the purposes of our table); NR: not reported; PPCM: peripartum cardiomyopathy.

[a] Data are expressed as mean ± standard deviation or mean (range).

[b] Median age, not mean age.

[c] An ICD code was used for PPCM.

[d] NHLBI/ORD Workshop definition of PPCM, which included: (1) development of HF in the last month of pregnancy or within 5 months after delivery; (2) absence of another identifiable cause of the HF; (3) absence of recognizable heart disease before the last month of pregnancy; (4) LV systolic dysfunction demonstrated by classic echocardiographic criteria, such as depressed EF <45% or depressed fractional shortening <30% [1].

[e] NHLBI/ORD Workshop definition of PPCM with modification, which included the above definition with modification of the EF cut-off (some studies used EF <50% or EF <40%) or modification of the timing of the diagnosis.

[f] ESC Working Group definition of PPCM, which included: (1) development of HF towards the end of pregnancy or in the months following delivery; (2) absence of another identifiable cause of the HF; (3) LV systolic dysfunction, with EF nearly always <45%. The LV may or may not be dilated [2].

[g] ESC Working Group definition of PPCM with modification, which included the above definition with modification of the EF cut-off (one study used EF < 50%).

[h] Diagnosis of PPCM performed at the implanting site of the mechanical circulatory support [69,70].

[i] Studies that used variable definitions for PPCM, including only echocardiographic criteria or only symptoms or different timing cut-offs for diagnosis, not categorized as above.

Table 2 Estimated prevalence of risk factors and major adverse cardiac events in developing and advanced countries in women with peripartum cardiomyopathy.

Variable	Overall		Developing countries		Advanced countries		P^a
	Number of studies	Prevalence (95% CI)	Number of studies	Prevalence (95% CI)	Number of studies	Prevalence (95% CI)	
Risk factors for PPCM							
Pre-eclampsia	11	0.16 (0.12—0.21)	2	—	9	0.14 (0.11—0.16)[b]	—
Gestational hypertension	18	0.21 (0.15—0.28)	7	0.22 (0.11—0.35)	11	0.21 (0.13—0.3)	0.92
Chronic hypertension	13	0.24 (0.15—0.34)	5	0.24 (0.11—0.41)	8	0.24 (0.12—0.37)	0.93
Hypertension NOS	27	0.38 (0.32—0.45)	10	0.29 (0.19—0.4)	17	0.44 (0.38—0.5)	0.0258
African descent	40	0.48 (0.32—0.64)	19	0.59 (0.29—0.86)	21	0.38 (0.27—0.49)	0.16
Twins or multiples	24	0.66 (0.56—0.74)	14	0.73 (0.59—0.85)	10	0.56 (0.5—0.61)	0.07
Multiparous	23	0.11 (0.08—0.14)	9	0.07 (0.03—0.14)	14	0.13 (0.1—0.15)	0.21
MACE in women with PPCM							
Death	46	0.09 (0.06—0.11)	24	0.14 (0.1—0.18)	22	0.04 (0.02—0.07)	<0.0001
Heart transplant	19	0.04 (0.01—0.07)	4	—	15	0.04 (0.01—0.08)	—
Heart failure	44	1 (1—1)[b]	24	1 (1—1)[b]	20	1 (1—1)[b]	—
Myocardial infarction	1		0	—	1	—	—
Arrhythmia	15	0.08 (0.04—0.15)	9	0.11 (0.04—0.21)	6	0.05 (0.01—0.14)	0.32
Embolism	12	0.05 (0.03—0.08)	7	0.07 (0.03—0.13)	5	0.03 (0.01—0.05)[b]	0.38
Cerebrovascular accident	8	0.01 (0—0.04)	5	0.03 (0—0.09)	3	—	—
Cardiac arrest	6	0.04 (0.02—0.06)	2	—	4	—	—

MACE: major adverse cardiac events; NOS: not otherwise specified; PPCM: peripartum cardiomyopathy.
[a] *P*-value was based on permutation test.
[b] Based on fixed-effect model; otherwise random-effect model.

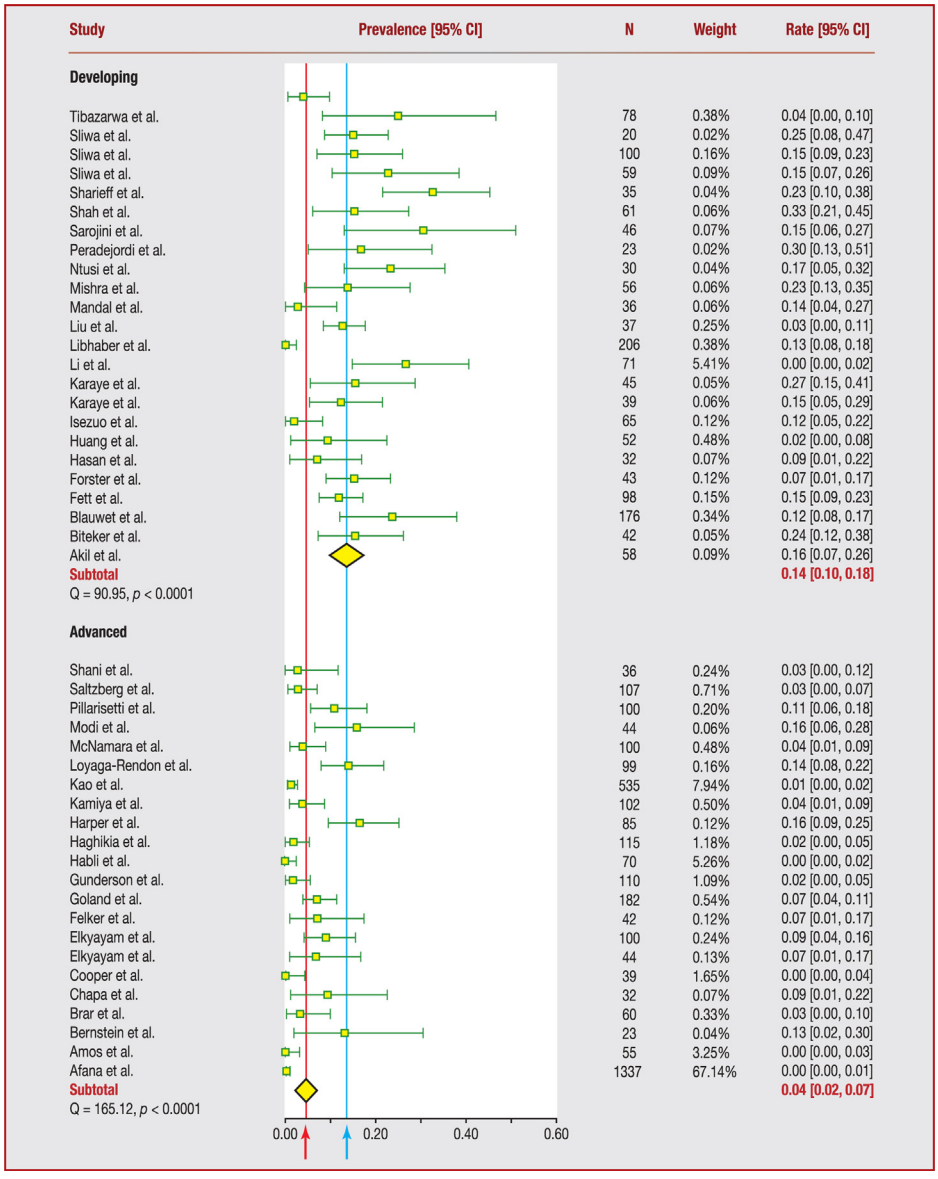

Figure 2. Forest plot showing prevalence estimates for death in women with PPCM in developing and advanced countries. The red arrow and dotted line represent the prevalence of death in advanced countries; the blue arrow and dotted line represent the prevalence of death in developing countries.

prevalence of death. PPCM is a global disease with similar risk factors in advanced and developing countries. A large proportion of women of African descent (48%) were represented in the present analysis. Death was prevalent in 9% of patients studied, while the risk of death was notably higher in women with PPCM from developing countries compared with advanced countries. While pre-eclampsia was not associated with an increased risk of death in this study population, studies that had a higher percentage of women of African descent tended to report an increased risk of death in this global study population.

A significant difference in death between advanced and developing countries was present, and is not surprising. The overall death rate was 4% in advanced countries and 14% in developing countries. Potential explanations contributing to the poorer outcomes seen in developing countries could include socioeconomic disparities in lack of access to care and education, and access to less optimal medical therapy [14]. Differences in the death rates are not fully explained by differences in the prevalence of risk factors for the development of PPCM in the studies included here. While differences in mortality at 1 month follow-up were not noted in a large registry of patients with PPCM between European Society of Cardiology (ESC) and non-ESC countries, the lack of mortality difference may be related to registry patients from advanced-care hospitals receiving state-of-the-art care, in addition to limited follow-up time [6]. Moreover, non-ESC countries were not necessarily developing countries (i.e. countries from North America, among others). Notably, in a recent single-centre study from within the USA, questions about socioeconomic variables and access to care on disease progression were raised in women with PPCM [8]. In

the present study, while we were unable to record socioeconomic variables other than country of origin, we recorded data available on heart transplants; however, several of the studies from developing countries noted that heart transplant was not an available treatment option. This could be a surrogate of availability of advanced treatment options, and may corroborate the concept that treatment modalities in developing compared with advanced countries may differ. Future studies should address the influence of socioeconomic variables on the outcomes in PPCM.

The follow-up time of each individual study is one of the major complicating factors in assessing an accurate death rate in this population. Some authors reported on inpatient mortality alone, while others reported prolonged follow-up periods in the order of years, which may account for the wide variability in the death rate. Recent studies have reported low inpatient mortality rates, which are reassuring [6,15]; however, these rates may not reflect the true mortality or natural history of this disease. Certainly, there is room for improvement in this area, as the long-term prognosis of this disease has not been defined clearly. Moreover, there are patients that fail to reach medical attention before they are properly diagnosed, because of lack of education, lack of access to care or subtlety of the symptom complex, and unfortunately may experience cardiac events or die. These patients would not be reflected in any of the studies recorded, and may be missed by most analyses. Focusing on early diagnosis, education and treatment may be key elements in having a positive impact on disease severity and survival.

African-American women have significantly higher odds of having PPCM compared with their non-African-American counterparts [16,17]; they often have worse outcomes and more frequent transplants [16,17]. In our study, we found that studies that had a higher percentage of women of African descent tended to report an increased risk of death. In the Investigations of Pregnancy-Associated Cardiomyopathy study, a multicentre study of PPCM outcomes in North America, black women had more left ventricular dysfunction initially and at 12-month follow-up [18]. Additionally, in a recent single-centre retrospective cohort study, African-American women with PPCM had a different disease profile to non-African-American women; African-American women were more likely to present later in the postpartum period, and were more likely to present with an ejection fraction < 30% and to fail to recover [8].

We estimated prevalence rates for various risk factors in women with PPCM, and found few differences in the major risk factors for PPCM. There was a significant difference for hypertension not otherwise specified, but not for pre-eclampsia or for chronic or gestational hypertension. Surprisingly, studies that had higher rates of pre-eclampsia were not associated with death. Another meta-analysis on PPCM, performed by Bello et al. [19], found an association with a higher prevalence of hypertensive disorders in patients with PPCM than in the general population, supporting the concept of hypertensive disorders in the pathogenesis of PPCM. Our study and that of Bello et al. [19] noted similar overall rates of pre-eclampsia/eclampsia. Interestingly, we were not able to find any statistical differences in most risk factor rates between developing and advanced countries. The classification of hypertensive disorders of pregnancy can be complicated in clinical practice. The reporting of these disorders is not standardized, and may be difficult to discern accurately from retrospective cohort studies. Moreover, hypertensive syndromes of pregnancy exist on a spectrum of less severe to more severe, and can be acute or chronic as well as new or pre-existing, further complicating classification. Notably, in a study of PPCM hospitalizations from the National Inpatient Sample, pre-eclampsia, severe pre-eclampsia, valvular heart disease, multiple gestation and caesarean delivery were independently associated with an increased risk of major adverse cardiac events [15]. Moreover, in a recent single-centre retrospective cohort study, PPCM with concomitant pre-eclampsia was associated with increased morbidity and mortality compared with PPCM not complicated by pre-eclampsia [20].

The vast majority of studies evaluating the degree of cardiac disease in PPCM have focused on left ventricular dysfunction informed by echocardiography [1]. However, the advent and increasing usage of cardiovascular magnetic resonance (CMR) in recent years has led it to become the imaging modality of choice in the diagnosis of cardiomyopathies, especially non-ischaemic heart disease. Moreover, multiparametric CMR allows for better evaluation of right ventricular structure and function than traditional echocardiography, and thus new insights into the phenotypic profile of PPCM can be gained [21]. In the last decade, CMR has started to be applied to evaluate cardiac dysfunction, particularly right ventricular dysfunction, in patients with PPCM [22,23]; Right ventricular dysfunction and dilatation are observed in about one third of patients with PPCM at time of diagnosis, and portend worse outcomes [21].

PPCM has traditionally been managed with standard medical therapy for heart failure. With new insights into the pathophysiology of PPCM and the damaging role of cleaved prolactin fragments (16 kDa N-terminal fragment of prolactin), studies are increasingly recognizing bromocriptine as a potential disease-specific therapy for PPCM. Hilfiker-Kleiner et al. recently demonstrated in a multicentre trial the significant benefit of even a week of therapy with bromocriptine. Furthermore, bromocriptine was well-tolerated in that study, with no patient mortality or need for heart transplant or left ventricular assist device [24].

Study limitations

These data should be interpreted within the context of certain limitations. This is a meta-analysis of the pooled results reported from each individual study because individual patient-level data were not available. As a meta-analysis, this study is intrinsically limited to the strengths and weaknesses of the included studies, as well as the search criteria and the inclusion and exclusion criteria set. The data were extracted mainly from retrospective studies, which can have their own biases and limitations. Patients studied in registries, retrospective analyses or administrative datasets may not be representative of patients seen in actual clinical practice. Data on PPCM from developing countries is probably underestimated in the published literature; therefore, the true prevalence of outcomes and risk factors may be under-represented. In addition, the International Monetary Fund classification may be a gross oversimplification of

a country's status, although it is the best available classification.

Conclusions

To date, this study is the largest global contemporary systematic review and meta-analysis of PPCM studies to examine the prevalence of death from and risk factors for PPCM. The risk of death in women with PPCM was higher in developing countries compared with advanced countries. Women with PPCM of African descent had an increased risk of death. Future studies should target early diagnosis and treatment as well as public health measures aimed towards these vulnerable patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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