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Maternal health in Namibia: Lessons learned from obstetric surveillance

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Part II.

The impact of cardiac disease and acute Hepatitis E on maternal outcome

Chapter 5.

Maternal mortality due to cardiac disease in low- and middle-income countries: a systematic review

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Abstract

Objective

To assess the frequency of maternal death (MD) due to cardiac disease in low- and middle-income countries (LMIC).

Methods

Systematic review searching Medline, EMBASE, Web of Science, Cochrane Library, Emcare, LILACS, African Index Medicus, IMEMR, IndMED, WPRIM, IMSEAR up to 01/Nov/2017. Maternal mortality reports from LMIC reviewing all MD in a given geographical area were included. Hospital-based reports or those solely based on verbal autopsies were excluded. Numbers of MD and cardiac-related deaths were extracted. We calculated cardiac disease MMR (cMMR, cardiac-related MD/100 000 live births) and proportion of cardiac-related MDs among all MDs. Frequency of cardiac MD was compared with the MMR of the country.

Results

Forty-seven reports were included, which reported on 38,486 maternal deaths in LMIC. Reported cMMR ranged from 0/100 000 live births (Moldova, Ghana) to 31.9/100 000 (Zimbabwe). The proportion of cardiac-related MD ranged from 0% (Moldova, Ghana) to 24.8% (Sri Lanka). In countries with a higher MMR, cMMR was also higher. However, the proportion of cardiac-related MD was higher in countries with a lower MMR.

Conclusion

The burden of cardiac-related mortality is difficult to assess due limited availability of mortality reports. The proportion of cardiac deaths among all MD appeared to be higher in countries with a lower MMR. This is in line with what has been called 'obstetric transition': pre-existing medical diseases including cardiac disease are becoming relatively more important where the MMR falls.

Introduction

It is generally assumed that cardiac disease is rare in women of reproductive age. However, in high-income countries such as the United Kingdom, the United States of America or the Nordic countries, cardiac disease has become the commonest cause of maternal deaths (MD).¹⁻³ Data regarding the number of maternal deaths due to cardiac disease in low- and middle-income countries (LMIC) are scarce. Attention to cardiac disease as a cause of maternal mortality is rare compared with conditions such as hypertensive disorders, postpartum haemorrhage and HIV/AIDS, which are regarded as more important causes.^{4,5} However, the prevalence of cardiac disease is most likely underreported in LMIC due to inadequate diagnostic means and poor registration.⁶⁻⁸

Global progress reports on maternal mortality have emphasised the increased importance of indirect maternal deaths due to pre-existing medical conditions in LMICs that have managed to reduce their maternal mortality ratio (MMR).^{5,9} It is likely that the role of cardiac disease in maternal deaths could become increasingly important where other causes, primarily direct obstetric causes, become less prevalent.

This is the first systematic review to assess the frequency of maternal deaths due to cardiac disease based on national and regional maternal mortality reports from LMIC and to compare these findings with the MMR of that country.

Methods

Search strategy and selection criteria

Maternal mortality reports from LMIC were identified by a systematic review of literature. Medline (using Pubmed), EMBASE, Web of Science, Cochrane Library, Emcare, LILACS, African Index Medicus, IMEMR, IndMED, WPRIM and IMSEAR databases were searched from January 1 2000 to November 1 2017 with the assistance of a qualified librarian at the Leiden University Medical Centre (Appendix 1). We screened the website of the Maternal Death Surveillance and Response (MDSR) Action Network and references from the maternal mortality country profiles of the WHO for eligible publications.^{10,11} If a publication mentioned a different or more recent report, this reference was searched, or, if it could not be retrieved, the first author of the referring publication was contacted to obtain the report. The systematic review was conducted following the PRISMA guidelines.¹²

Regional and national maternal death reviews (MDR) performed in a low- or middle-

income country were eligible if the aim of the study was to review all maternal deaths (MD) in a given geographical area, preferably including out-of-facility deaths. However, a facility-based approach, exclusively reviewing facility-based MDs, is commonly used in regions with high institutional birth rates and in several mortality reports of high quality such as the confidential enquiries into maternal deaths of South Africa, Moldova and Kerala region, India.¹³⁻¹⁹ Therefore, we considered reports documenting MDs from all health facilities of all levels within the study area, including health posts and health centres. Reports from single or non-population-based groups of hospitals were excluded as the data were unlikely to be representative of the study area. The World Bank rating of 2017 was used to assess whether a country was considered an LMIC.²⁰

Reports were included if maternal deaths met the WHO definition of ‘deaths of women while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes’, and if the total number of MD and the number of deaths specified per cause were provided.²¹ To identify MD due to cardiac disease, one of the following identifiers had to be used: cardiac disease, heart disease or the specific cardiac condition such as rheumatic heart disease (RHD), any type of cardiomyopathy or congenital heart disease. Authors of reports using less specific definitions such as ‘cardiovascular disorders’ or ‘cardiac failure’ were contacted to provide the exact number of MD due to cardiac disease. If these data could not be retrieved, the report was excluded.

Studies exclusively based on verbal autopsy, sisterhood methods or household survey were excluded since these were considered insufficient to robustly identify MD due to cardiac disease. Studies with a sample size below twenty were excluded. Reports were screened for duplication. If one of the duplicate reports contained data from a larger study area or longer study period, this report was included. Full text had to be available in English, French, German, Spanish or Portuguese.

Study selection was done by two independent researchers (SH and AP). The opinion of a third researcher (TA) was sought if consensus was not reached. Data extraction was performed by one author (SH) and reviewed by a second (AP).

Data analysis

To assess the quality of the included reports, we evaluated the methods used for identification of MD in the study area, and those for establishing cause of death, as well as the level of expertise available for case review. For each item, the best available method is listed at the top in Table 1. First, we evaluated robustness of MD

identification in the study area and whether out-of-facility deaths were included. We considered MD identification of the highest quality if there was a system in place to trace maternal deaths in an enhanced manner, including identifying out-of-facility deaths, for example through a Reproductive Age Mortality Survey (RAMOS),

Identification of MD	Review at facility level	Review at central level	Cause of death established by
OFD included, systematically traced	Facility-based audit	Audit of complete file	Panel with O&G and non-O&G specialists
OFD included, but not systematically traced	MD notification form	Review of MD notification form	Panel with O&G specialist
Excluded women who died outside a facility		None	Staff at facility
			Other

Presented are the different methods used to identify maternal deaths in the study area, to review cases at facility and central level and which level of expertise was available to establish cause of death. The best available method is listed at the top of each section.

MD, maternal death; OFD, out-of-facility death; O&G, obstetrics and gynaecology.

involvement of communities and/or analysis of information from mortuaries. Secondly, the method used to establish the cause of maternal deaths was assessed. At facility level, establishment of the cause of death could range from a MD notification form, filled in by the attending healthcare worker, up to a facility-based audit. At central level, for example regional or national level, review of the cause of death could range from analysing information of the MD notification forms up to a complete review of medical records. Finally, level of expertise for case review was based on the presence of an obstetrician and additional medical specialists such as anaesthetists, physicians, pathologists or paediatricians.

We did not produce a summary quality measure since we considered the robustness of MD identification of equal importance to the methods and level of expertise used to establish cause of death. For some reports, a high level of expertise was available at central level to review all cases, but identification of MD and quality of data collection at facility level was poor. On the contrary, some reports used a well-functioning MD notification system but had limited expertise available for case review. The total number of MD, deaths from cardiac disease and the study period were extracted from each report. The proportion of cardiac MDs among all MDs (%cMD) was calculated by dividing the number of reported cardiac MD by the total number of MD and is presented as a percentage. The MMR was calculated as the number of reported MD per 100 000 live births and cardiac disease MMR (cMMR) as the number of reported cardiac-related MD per 100 000 live births. For population-based studies, the MMR was extracted from the report. Reports were defined as population-based when the aim of the study was to review all MD that occurred during the study period in the study area, including women who died outside a health facility. For facility-based reports or if the report did not provide data to calculate an MMR, the national MMR estimated by the WHO for the closest corresponding year of the study period was

extracted from the ‘Maternal mortality country profiles’.¹¹ Reports mentioning zero cardiac deaths were assessed for possible missed cardiac deaths. If the report included deaths due to unknown causes or unclear diagnoses, for example death due to anaemia, sudden death or out-of-facility death and no autopsy was performed, this meant that MDs due to cardiac disease were possibly missed. In such cases, the number of cardiac deaths was reported as ‘missing’, and the report excluded from data analysis. The level of income of a country was categorised as either upper MIC, lower MIC or LIC based on the World Bank rating at the time of data collection of each country.²⁰

For all reports, the relation of the frequency of cardiac-related MD with the MMR of its country was assessed using plots. For countries with multiple reports of different study periods, but reporting data of the same geographical area, progress over time was explored using detailed plots. Data regarding the total number of cardiac MD were plotted in a world map. When multiple reports were available for one country, the most recent report, covering the largest geographical area and/or of highest quality, was used for comparison. Selection process is detailed further in Appendix 2.

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Considering the low number and heterogeneity of the included reports, frequency of cardiac MD in relation to the MMR or time was not compared statistically. Data were analysed using SPSS version 22 (IBM Corp., Armonk, NY). Plots were drafted with Prism version 8.1 (GraphPad Software). The review was registered with PROSPERO (CRD42018089452). All results are presented in the tables and figures and therefore not published in a separate online database.

Results

Forty-seven maternal mortality reports were included, reporting on a total of 38,486 maternal deaths in LMIC.^{13-19,22-61} Study selection is summarised in Figure 1. Titles and abstracts of 2064 identified records were screened, which resulted in 132 eligible records. Full-text articles of these records were evaluated and 85 reports excluded. In 11 of 132 reports, it was unclear whether the definition used comprised maternal deaths due to cardiac disease alone. In four reports, the quality of the methods section was insufficient to assess the methods used to identify MD and establish the cause of death. Three hospital-based reports reviewed MD for one or multiple hospitals only but were not population-based. Two regional reports from South Africa were excluded as national reports were available for the same study period.

The 47 included reports included maternal mortality data from 29 countries. Characteristics of these reports are presented in Table 2. The included reports presented data from eight LIC, thirteen lower MIC and eight upper MIC. Twenty

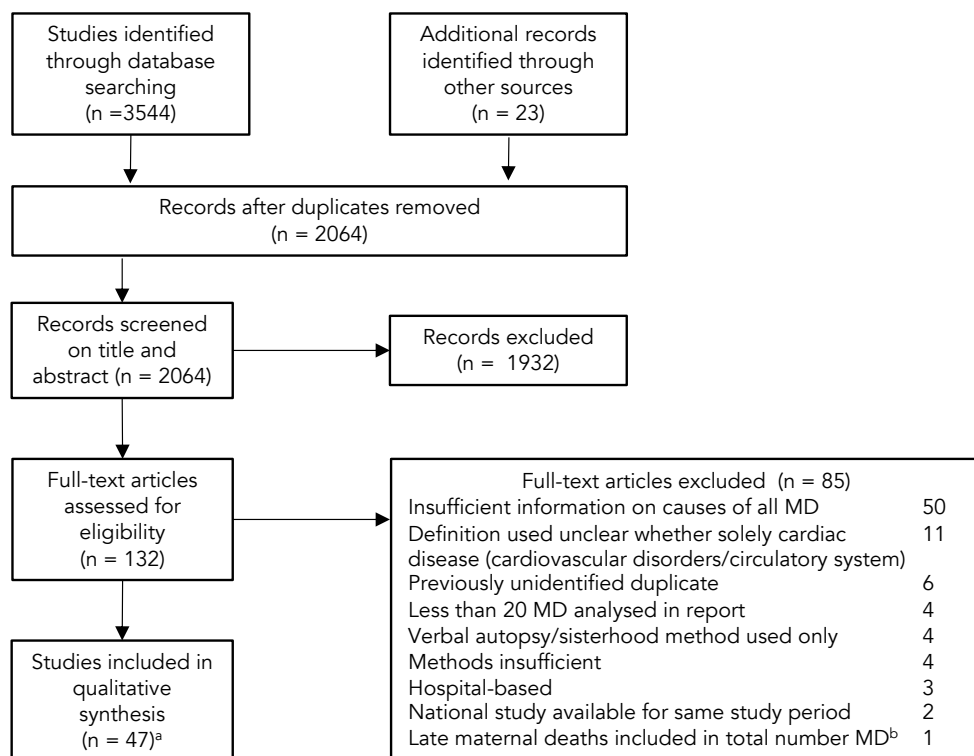


Figure 1. Flowchart showing selection of studies included in review.

MD, Maternal death

^aThe corresponding author of a report from Rwanda confirmed that MDs described as 'due to cardiac failure' were all MD due to cardiac disease. The report from Moldova for 2006–2008 only mentioned the total number of indirect deaths. The author of this report confirmed none of these deaths were caused by cardiac disease. The same author provided us with the mortality data of the review of 2009–2013, of which the report in English is not yet available.

^bLate maternal death is a death of a woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.

reports presented regional maternal mortality data, and twenty-seven reported national data. The study period was clearly defined in all studies and ranged from 1992 until 2015. Twenty-seven studies were population-based.^{23,26-28,31,33-34,37-38,40-41,43-44,46,55,57,59-61} Fourteen reports were facility-based.^{13,19,22,32,35,42,45,56,58} The proportion of reviewed deaths outside facilities ranged from 1.8% (Botswana, 2010) to nearly half of the reviewed deaths in Zimbabwe (49.3%), Pakistan (50.0%), Bangladesh (51.6%) and Nepal (53.8%).^{48,50,53,57} In 21 out of 27 population-based reports, an MMR was extracted directly from the report.^{23,26-27,31,33-34,37-38,40-41,43,46-50,54,55,57,59,60} Five reports stated zero cardiac deaths of which data were reported as missing of the reports from Tanzania, Malawi and Sudan as possible deaths due to cardiac disease were missed (Appendix 2).^{14,25,36,45,51} In these reports, cause of death was not known (330/1433 deaths in the report from Malawi), or unclear (75/898 deaths due to anaemia in the report from Sudan, 213/1433 deaths due to anaemia in the report from Malawi, 1/45 death due to anaemia and one sudden death in the report from Tanzania and in all three reports no autopsies were performed).

Table 2. Overview of 47 included maternal mortality reports							
Country	LIC/I-MIC/u-Mic	MMR	Period	Cardiac MD/ total MD	Proportion cardiac MD (%)	cMMR	
Bangladesh	LIC	479 ^b	1996-1997	291/7086	4.1%	19.7	
Ethiopia	LIC	523 ^b	2008	14/633	2.2%	11.6	
Ghana, Upper West reg.	LIC	325 ^b	2009	0/47	0.0%	0.0	
Ghana, Accra reg. ^a	LIC	467 ^b	2002	3/178	1.7%	7.9	
Malawi	LIC	629 ^b	2008-2012	XX ⁱ /1433	N/A	N/A	
Malawi, Central reg. ^a	LIC	648 ^b	2007	1/43	2.3%	15.1	
Nepal, 8 reg.	LIC	229 ^c	2008-2009	11/160	6.9%	15.7	
Rwanda	LIC	381 ^b	2009-2013	23/987	2.3%	8.9	
Tanzania, Arusha reg.	LIC	961 ^b	1995-1996	XX ⁱ /45	N/A	N/A	
Zimbabwe	LIC	725 ^c	2006	16/364	4.4%	31.9	
Egypt, Dakahlia reg.	I-MIC	71 ^c	2004-2005	15/171	8.8%	6.3	
Egypt ^a	I-MIC	84 ^c	2000	45/580	7.8%	6.5	
El Salvador	I-MIC	50 ^c	2011	4/64	6.3%	3.2	
Guatemala, "dep. of Guatemala"	I-MIC	156 ^c	1993-1996	2/435	0.5%	0.7	
India, Kerala reg.	I-MIC	29 ^a	2004-2009	32/501	6.4%	1.9	
Jamaica ^a	I-MIC	95 ^c	1998-2003	12/232	5.2%	4.9	
Jamaica	I-MIC	96 ^c	1993-1995	3/141	2.1%	2.1	
Jordan	I-MIC	19 ^c	2007-2008	8/76	10.5%	2.0	
Moldova ^a	I-MIC	34 ^b	2009-2013	2/49	4.1%	1.4	
Moldova	I-MIC	39 ^b	2006-2008	0/29	0.0%	0.0	
Morocco, 6 priority reg.	I-MIC	121 ^c	2015	7/152	4.6%	5.6	
Morocco ^a	I-MIC	153 ^b	2009	16/303	5.3%	8.1	
Pakistan, Sindh reg.	I-MIC	279 ^c	2006-2008	3/72	4.2%	11.6	
Russia, St. Petersburg	I-MIC	43 ^c	1992-2003	12/179	6.7%	2.9	
Sri Lanka a	I-MIC	34 ^c	2015	28/113	24.8%	8.4	
Sri Lanka	I-MIC	32 ^c	2014	16/112	14.3%	4.6	
Sudan	I-MIC	349 ^b	2010	XX ⁱ /898	N/A	N/A	
Swaziland	I-MIC	586 ^b	2000-2001	2/43	4.7%	27.3	
Botswana	u-MIC	129 ^b	2015	2/73	2.7%	3.5	
Botswana ^a	u-MIC	169 ^b	2010	7/55	12.7%	21.5	
China, Wuhan reg.	u-MIC	15 ^c	2001-2012	8/91	8.8%	1.3	
China, Henan reg.	u-MIC	45 ^c	1996-2009	90/1129	8.0%	3.6	
China, Shanghai reg.	u-MIC	21 ^c	2000-2009	24/262	9.2%	1.9	
China, Zhejiang reg.	u-MIC	58 ^b	1995-2008	95/901	10.5%	6.1	
China combined ^d	u-MIC	35 ^d	1995-2012	217/2383	9.1%	3.2	
Fiji	u-MIC	34 ^b	2008-2012	5/37	13.5%	4.6	
Irak	u-MIC	27 ^c	2010-2012	79/1039	7.6%	2.1	
Iran, Yazd reg.	u-MIC	34 ^b	2002-2011	8/40	20.0%	6.8	
Malaysia ^a	u-MIC	29 ^c	2009-2011	65/430	15.1%	4.3	
Malaysia	u-MIC	27 ^c	2006-2008	49/396	12.4%	3.4	
South Africa ^a	u-MIC	138 ^b	2014	49/1238	4.0%	5.5	
South Africa	u-MIC	154 ^b	2011-2013	169/4333	3.9%	6.0	
South Africa	u-MIC	154 ^b	2008-2010	157/4867	3.2%	5.0	
South Africa	u-MIC	112 ^b	2005-2007	97/3959	2.5%	2.7	
South Africa	u-MIC	112 ^b	2002-2004	85/3296	2.6%	2.9	
South Africa	u-MIC	85 ^b	1999	23/584	3.9%	3.3	
South Africa	u-MIC	85 ^b	1998	28/565	5.0%	4.2	
Surinam	u-MIC	130 ^c	2010-2014	2/65	3.1%	4.0	

	OFD included	Review at facility level	Review central level	Case review by
	Yes	Research team	None	Recent medical graduates
	Yes	MD notification form	None	Staff at facility
	if reported	MD notification form	Audit of complete file	Panel, expertise unclear
	Yes	None	Audit of complete file	Panel with O&G specialist
	No	Facility audit	CEMD, audit of complete file	Panel with O&G specialist
	No	Facility audit	None	Staff at facility
	Yes	Facility audit	None	Staff at facility
	No	Facility audit	None	Staff at facility
	Yes	None	Audit of complete file	Panel with O&G specialist
	Yes	MD notification form	Review of MD notification forms	Staff at facility
	Yes	MD notification form	Audit of complete file	Panel, expertise unclear
	Yes	None	Audit of complete file	Panel with O&G and non O&G specialists
	Yes	MD notification form	Audit of complete file	Panel, expertise unclear
	Yes	None	Audit of complete file	Data clerk
	No	MD notification form	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	Yes	None	Audit of complete file	Panel, expertise unclear
	Yes	None	Audit of complete file	Panel, expertise unclear
	Yes	None	Audit of complete file	Panel, expertise unclear
	No	MD notification form	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	MD notification form	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	Yes	MD notification form	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	If reported	MD notification form	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	Yes	MD notification form	None	Staff at facility
	Yes	Facility audit	None	Research team with O&G specialist
	Yes	District audit	Audit of complete file	Panel with O&G and non O&G specialists
	Yes	District audit	Audit of complete file	Panel with O&G and non O&G specialists
	If reported	MD notification form	Review of MD notification forms	Panel, expertise unclear
	No	None	Audit of complete file	Panel, expertise unclear
	Unknown	Unclear	National statistics	Unknown
	Yes	MD notification form	Audit of complete file	Panel, expertise unclear
	Yes	MD notification form	Audit of complete file	Panel, expertise unclear
	Yes	MD notification form	Audit of complete file	Panel with O&G specialist
	Yes	MD notification form	Audit of complete file	Panel with O&G specialist
	Yes	MD notification form	Audit of complete file	Panel, expertise unclear
	If reported	MD notification form	None	Staff at facility
	Yes	MD notification form	Audit of complete file	Panel with O&G specialist
	Unknown	MD notification form	Unclear	Unclear
	Yes	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	Yes	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	No	Facility audit	CEMD, audit of complete file	Panel with O&G and non O&G specialists
	Yes	MD notification form	Audit of complete file	Panel with O&G and non O&G specialists

Table 2. Overview of 47 included maternal mortality reports. (Table shown on previous page)

LIC, low-income country; L-MIC, lower middle-income country; u-MIC, upper middle-income countries; MMR, maternal mortality ratio/100,000 live births; MD, maternal death; cMMR, cardiac related maternal mortality ratio/100,000 live births; N/A, not available; OFD, out of facility deaths; CEMD, Confidential enquiry into maternal deaths; O&G, obstetrics and gynaecology.

^a Data report used for figure 3, as most representative data for country.

^b MMR estimation of WHO, population-based study but no MMR available in report or not population-based study.

^c MMR from report, population-based study.

^d MMR based on average of 4 reports from China.

^e MMR from report used even though facility based report. The region is known for a consistently lower MMR than the national MMR due better health indicators, more details available in appendix 2.

^f Missing data.

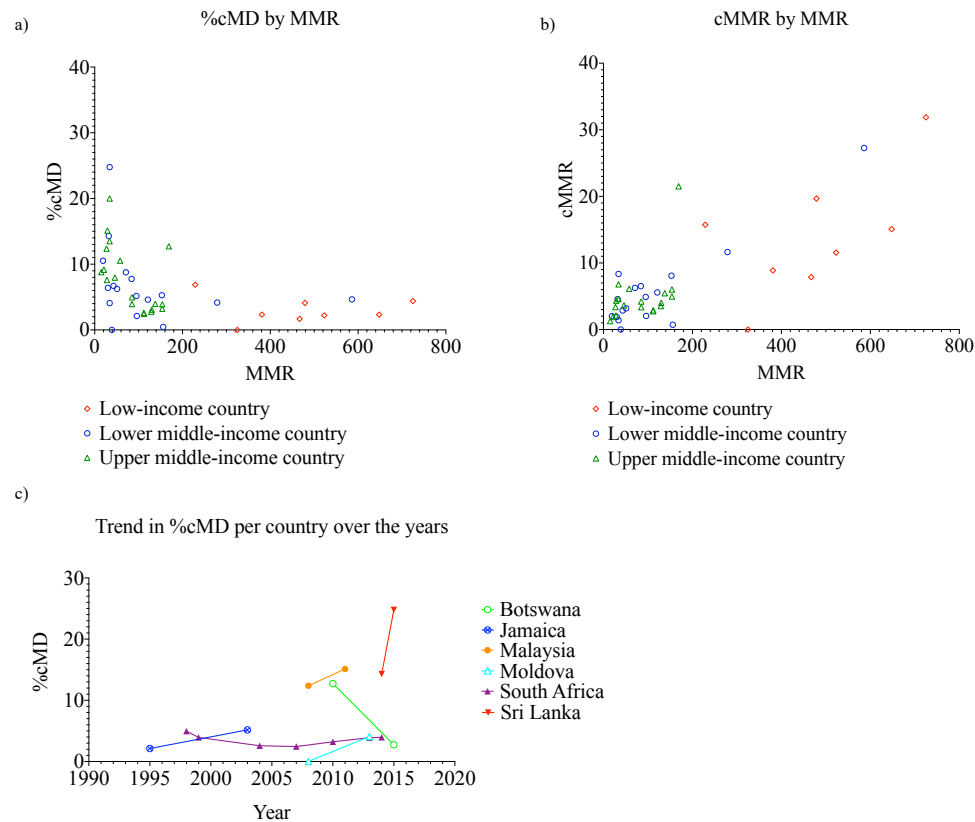


Figure 2. Three plots showing the trends of maternal deaths due to cardiac disease in relation to the MMR of it's country and over time.

a) The relation of the proportion of cardiac related maternal deaths with the MMR of it's country. All included studies are plotted.

b) The relation of cMMR with the MMR of it's country. All included studies are plotted.

c) For the available studies with multiple reports the proportion of cardiac related maternal deaths over time are plotted. cMD, cardiac related maternal death.

MMR, maternal mortality ratio/100,000 live births; cMMR, cardiac related maternal mortality ratio/100,000 live births

Reported cMMR ranged from 0/100 000 live births in reports from Ghana and Moldova to 31.9/100 000 live births in Zimbabwe.^{4,36,48} The proportion of reported cardiac-related MD among all MD ranged from 0% in reports from Ghana and Moldova to 24.8% in Sri Lanka.^{14,36,38} Figure 2 shows the relation of the frequency of cardiac MD with the MMR of its country. Level of economy of the countries is indicated by colour. Reports from countries with a lower MMR appear to have a higher proportion of cardiac MD (Figure 2a), but the cardiac MMR is higher in countries with a higher MMR (Figure 2b). In reports from LIC, the proportion of cardiac MDs appeared to be lower compared with MIC; however, the cMMR is higher in LIC. For six countries, multiple reports of the same study area were available, and trends over time were plotted in Figure 2c. For five countries, the same methods were used to collect data over time, whereas two different methods were used for the two reports from Botswana.

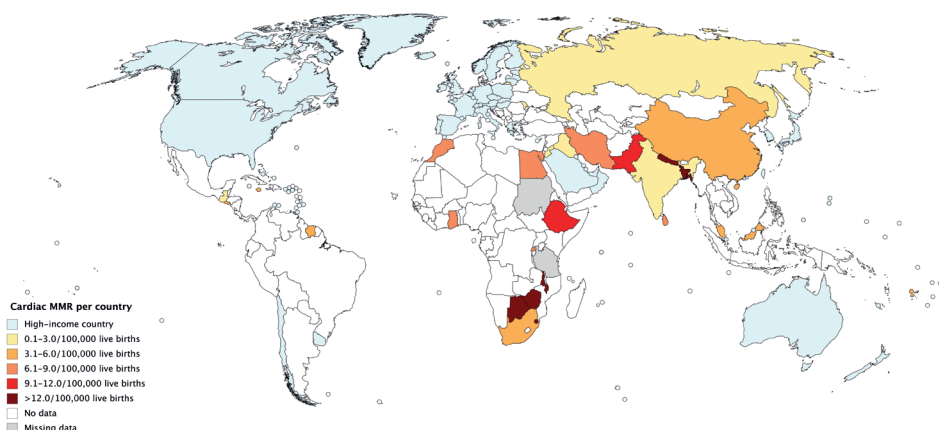


Figure 3. World map showing incidence of maternal deaths due to cardiac disease per country. MMR, maternal mortality ratio.

Figure 3 shows the cardiac MMR for each country. For this figure, the national or most recent study was selected if multiple reports were available for these countries, Table 2. For Botswana, Ghana and Malawi, a regional or less recent report was considered to have more representative data and selected for country comparison (Appendix 2). For China, four regional reports with similar methods were available. The findings of these four reports were combined for country comparison in Figure 3.

The included reports used different methods to establish the cause of maternal deaths. In six reports, information regarding the cause of death was only based on maternal death notification forms, filled in at facility level (Table 2).^{25,28,30,39,48,50} The report from Botswana in 2015 was a national statistics mortality report. In this report, it was unclear whether the cause of death was based on information from

death certificates, maternal death notification forms or audits.²⁹ Four reports were based on information from audits at facility level only.^{34,42,56,57} For the 36 remaining reports, review of medical records was performed at regional or national level. Table 2 indicates the level of expertise available to establish cause of death. In the reports from Guatemala and Botswana (2015), the actual number of deaths due to cardiac disease may have been higher, but the definitions applied were unclear, thus we have reported the minimum number. In both reports, two maternal deaths due to cardiomyopathy were presented. In the report from Botswana, another eight MD due to 'diseases of the circulatory system' were documented and for Guatemala four maternal deaths due to 'cardiovascular problems'. We were unable to contact the authors, so we report the number of cardiac MD as two for both reports.^{29,40}

Discussion

This review shows a substantial incidence of maternal deaths due to cardiac disease in LMIC. In the included reports, cardiac-related MMR was highest in countries with a high MMR, but the proportion of cardiac deaths among all maternal deaths appeared to be higher in countries with a lower MMR. Probably, we identified only 'the tip of the iceberg', and the number of MD due to cardiac disease is likely to be even higher.

Health facilities are insufficiently equipped to identify cardiac deaths and cardiac MD might have been missed. In many LMIC, women do not have access to health facilities equipped with the diagnostic means or clinicians to diagnose cardiac disorders and it is not uncommon that a cardiac disorder is only identified during pregnancy when a woman presents in extremis with heart failure.⁶⁻⁸ This might explain the finding of a lower proportion of cardiac deaths in countries with a lower level of income. A study undertaken in Eritrea identified rheumatic heart disease (RHD) in 2.3% of asymptomatic pregnant women during antenatal visits.⁶² The Sudanese report included in our review suggested that there were no cardiac deaths although the country has a high prevalence of RHD among young women.^{7,63,64} Underdiagnosis of cardiac disease in LMIC may explain the wide range of maternal mortality from 0 to 34% that has been reported among pregnant women with cardiac disease.^{6,8,65-69} It is likely that only the most severe cases are identified in settings with limited access to facilities where cardiac disease can be diagnosed. Lastly, many maternal deaths due to medical conditions including cardiac disease happen between six weeks and one year after the end of pregnancy and are therefore not included in the WHO definition of MD.^{4,66}

Quality of the included reports varied and might have influenced the incidence

figures as well. For three reports, we had to report missing data due to the high likelihood of missed cardiac MD. The national report from Malawi noted a high level of missing data and although MD is notifiable by law, zero MDs were reported at central level.⁴⁵ The report from Ethiopia had information on only 6% of the expected number of MD.²⁸ No medical doctor was involved to confirm the cause of death for two reports.^{40,53} Some reports used unclear definitions like cardiovascular disorder, which includes for example stroke. These were excluded since we could not establish the number of deaths due to cardiac disease. In four reports, half of the cases were out-of-facility deaths and no autopsies were performed.^{48,50,53,57} Possible cardiac MDs were missed in these reports. Autopsy can assist in establishing the underlying cause of the MD, and several cardiac-related MDs were identified by autopsy in LMIC.^{70,71}

Cardiac-related MMR was highest in countries with a high MMR, but the proportion of cardiac deaths among all maternal deaths appeared to be larger in countries with a lower MMR. This is an important finding since this is in line with what has been titled the 'obstetric transition model', a common pathway that has been identified among countries that were able to reduce their maternal mortality.⁵ As the MMR falls, MDs from direct causes are of relative decreasing importance, while the opposite is true for maternal deaths due to pre-existing medical diseases. Since most LMIC are achieving progress in reducing maternal mortality, focus needs to shift from the prevention of deaths from the traditional 'big killers' such as hypertensive disorders, postpartum haemorrhage and HIV/AIDS to pre-existing medical diseases in these countries. Deaths from direct causes can be prevented by improving obstetric care. Different interventions will be needed to prevent deaths from cardiac disease. A multidisciplinary approach available for preconception counselling and during pregnancy, birth, and the postpartum period has been shown to improve maternal outcome, but remains unattainable in most LMIC.^{16,19,54,72,73}

In LMIC, women of reproductive age with cardiac disease are facing challenges far different from those that women in high-income countries (HIC) face. Most management guidelines are based on research performed in HIC and not applicable or implementable in LMIC. Besides the differences in availability of resources, the most prevalent cardiac disorder among pregnant women in HIC is congenital heart disease, which needs a different approach than RHD, which is the most common cardiac condition among pregnant women in LMIC.^{8,74} A global study on RHD, a cardiac condition preventable with timely administration of antibiotics, found that RHD patients were predominately young women of reproductive age. These women have limited access to family planning as is shown by the alarmingly low coverage of contraceptive use of 36%.⁶⁴ Surgical intervention for RHD patients with placement of mechanical valves is increasingly available for young girls and women in LMIC

and has increased survival in this group.^{63-64,75,76} At the same time, these women might consider becoming pregnant in the future. With the need for lifelong anticoagulation therapy, the risks of maternal morbidity and mortality and fetal complications are high, based on findings mainly from HIC.^{77,78} As previously mentioned, the limited available data from LMIC show a wide range of maternal mortality among cardiac patients. There is an adapted WHO risk classification available that classifies risk of maternal complications based on various cardiac conditions.⁷⁹ However, a global study showed that this risk classification does not perform as well in LMICs as compared with HICs.⁷⁴ Given all these limitations in LMIC, it is highly problematic to provide adequate risk assessment and treatment for a young woman with a cardiac condition, who is considering a pregnancy.

Despite the extensive search in several databases, we could only identify reports from 29 LMIC countries. It is possible that mortality reports from other countries have been missed. MDRs may not have been published in our searched databases or in any other online database. We attempted to overcome this by searching the publications of the MDSR Action Network website and references of the maternal mortality country profiles of the WHO, since both of these organisations are well-informed regarding the presence of MDRs globally.^{9,10} An additional 23 reports were identified for possible inclusion using this strategy. Nevertheless, only for six countries multiple reports were available to assess the progress over time, for which one even used different methods for data collection. Even though Figure 2c indicates that for most of these countries, the impact of cardiac MD appears to increase over time, more data are needed to adequately assess this development.

Conclusion

To our knowledge, this is the first review assessing the frequency of maternal deaths due to cardiac disease in LMIC. Due to the limited availability of mortality reports from LMIC and the varying quality of the reports, it is hard to assess the real burden of maternal death due to cardiac disease. However, in the available reports a high incidence of cardiac-related maternal deaths was identified, which may in reality be even higher due to the likely presence of underreporting. Our findings are in line with the obstetric transition model: indirect deaths including cardiac deaths are becoming relatively more important in several countries as obstetric care improves and obstetric deaths are reduced. Since most LMIC are achieving progress in reducing maternal mortality, more attention is needed for pre-existing medical disease like cardiac disease as a cause of maternal mortality. Prospective studies on prevalence, pregnancy outcome and interventions are needed to assess the real burden of cardiac-related maternal mortality in LMIC and establish feasible and relevant guidelines.

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Appendix 1. Search strategy

Available at <https://onlinelibrary.wiley.com/doi/10.1111/tmi.13386>

Appendix 2. Quality assessment for reports mentioning zero cardiac deaths and when multiple reports per country were available

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