Systematic Review

Maternal mortality due to cardiac disease in low- and middle-income countries

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Abstract

OBJECTIVES 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.

CONCLUSIONS 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.

keywords cardiac disease, maternal mortality, low- and middle-income countries

Sustainable Development Goals (SDGs): SDG 3 (good health and well-being), SDG 17 (partnerships for the goals)

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 under-reported 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, Ecmare, 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 S1). 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), 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 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 S2.

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.

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**Table 1** Quality assessment of mortality reports

| 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                     | Panel with O&G specialist | 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.
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 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 [23,26-27,31,33-34,37-38,40-41,43,46-50,54-55,57,59-60]. 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 S2) [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...
Table 2 Overview of 47 included maternal mortality reports

| Country                          | LIC/MIC/other MIC | MMR | Period          | Cardiac MD/total MD | Proportion cardiac MD (%) | cMMR | OFD included | Review at facility level | Review central level | Case review by |
|---------------------------------|-------------------|-----|-----------------|---------------------|---------------------------|------|--------------|--------------------------|---------------------|-------------------|
| Bangladesh                      | LIC               | 479†| 1996–1997       | 291/7086            | 4.1%                      | 19.7 | Yes          | Research team            | None                | Recent medical graduates |
| Ethiopia                        | LIC               | 523†| 2008           | 14/633              | 2.2%                      | 11.6 | Yes          | MD notification form     | None                | Staff at facility     |
| Ghana, Upper West reg.          | LIC               | 325†| 2009         | 0/47                | 0.0%                      | 0.0  | if reported  | Audit of complete file | Panel, expertise unclear |
| Ghana, Accra reg.*              | LIC               | 467†| 2002         | 3/178               | 1.7%                      | 7.9  | Yes          | Audit of complete file  | Panel with O&G specialist |
| Malawi                          | LIC               | 629†| 2008–2012     | */1433              | N/A                       | N/A  | No           | Facility audit           | Panel with O&G specialist |
| Malawi, Central reg.*           | LIC               | 648†| 2007         | 1/43                | 2.3%                      | 15.1 | No           | Facility audit           | Staff at facility |
| Nepal, 8 reg.                   | LIC               | 229†| 2008–2009     | 11/160              | 6.9%                      | 15.7 | Yes          | Facility audit           | Staff at facility |
| Rwanda                          | LIC               | 381†| 2009–2013     | 23/987              | 2.3%                      | 8.9  | No           | Audit of complete file  | Staff at facility |
| Tanzania, Arusha reg.*          | LIC               | 961†| 1995–1996     | */45                 | N/A                       | N/A  | Yes          | Audit of complete file  | Panel with O&G specialist |
| Zimbabwe                        | LIC               | 725†| 2006         | 16/364              | 4.4%                      | 31.9 | Yes          | Review of MD notification forms | Staff at facility |
| Egypt, Dakahlia reg.            | l-MIC             | 71† | 2004–2005     | 15/171              | 8.8%                      | 6.3  | Yes          | Audit of complete file  | Panel, expertise unclear |
| Egypt*                          | l-MIC             | 84† | 2000         | 45/580              | 7.8%                      | 6.5  | Yes          | Audit of complete file  | Panel with O&G and non-O&G specialists |
| El Salvador                     | l-MIC             | 50† | 2011         | 4/64                | 6.3%                      | 3.2  | Yes          | Audit of complete file  | Panel, expertise unclear |
| Guatemala, ‘dep. of Guatemala’  | l-MIC             | 156†| 1993–1996     | 2/435               | 0.5%                      | 0.7  | Yes          | Audit of complete file  | Data clerk |
| India, Kerala reg.              | l-MIC             | 29† | 2004–2009     | 32/501              | 6.4%                      | 1.9  | No           | MD notification form     | Panel with O&G and non-O&G specialists |
| Jamaica*                        | l-MIC             | 95† | 1998–2003     | 12/232              | 5.2%                      | 4.9  | Yes          | Audit of complete file  | Panel, expertise unclear |
| Jamaica                         | l-MIC             | 96† | 1993–1995     | 3/141               | 2.1%                      | 2.1  | Yes          | Audit of complete file  | Panel, expertise unclear |
| Country                     | LIC/l-MIC/a-MIC | MMR | Period         | Cardiac MD/total MD | Proportion cardiac MD (%) | cMRR | OFD included | Review at facility level | Review central level | Case review by                                |
|----------------------------|-----------------|-----|----------------|---------------------|---------------------------|------|--------------|--------------------------|---------------------|---------------------------------------------|
| Jordan                     | l-MIC           | 19† | 2007–2008      | 8/76                | 10.5%                     | 2.0  | Yes          | None                     | Audit of complete file | Panel, expertise unclear                      |
| Moldova*                   | l-MIC           | 34† | 2009–2013      | 2/49                | 4.1%                      | 1.4  | No           | MD notification form     | CEMD, audit of complete file | Panel with O&G and non-O&G specialists         |
| Moldova                    | l-MIC           | 39† | 2006–2008      | 0/29                | 0.0%                      | 0.0  | No           | MD notification form     | CEMD, audit of complete file | Panel with O&G and non-O&G specialists         |
| Morocco, 6 priority reg.   | l-MIC           | 121†| 2015           | 7/152               | 4.6%                      | 5.6  | Yes          | MD notification form     | CEMD, audit of complete file | Panel with O&G and non-O&G specialists         |
| Morocco*                   | l-MIC           | 153†| 2009           | 16/303              | 5.3%                      | 8.1  | If reported  | MD notification form     | CEMD, audit of complete file | Panel with O&G and non-O&G specialists         |
| Pakistan, Sindh reg.       | l-MIC           | 279†| 2006–2008      | 3/72                | 4.2%                      | 11.6 | Yes          | MD notification form     | None                     | Staff at facility                           |
| Russia, St. Petersburg     | l-MIC           | 43 †| 1992–2003      | 12/179              | 6.7%                      | 2.9  | Yes          | Facility audit           | None                     | Research team with O&G specialist            |
| Sri Lanka*                 | l-MIC           | 34† | 2015           | 28/113              | 24.8%                     | 8.4  | Yes          | District audit           | Audit of complete file | Panel with O&G and non-O&G specialists         |
| Sri Lanka                  | l-MIC           | 32† | 2014           | 16/112              | 14.3%                     | 4.6  | Yes          | District audit           | Audit of complete file | Panel with O&G and non-O&G specialists         |
| Sudan                      | l-MIC           | 349†| **898          | N/A                 | N/A                       | If reported | MD notification form     | Review of MD notification forms | None                     | Panel, expertise unclear                      |
| Swaziland                  | l-MIC           | 586†| 2000–2001      | 2/43                | 4.7%                      | 27.3 | No           | None                     | Audit of complete file | Panel, expertise unclear                      |
| Botswana                   | u-MIC           | 12† | 2005–2007      | 2/73                | 2.7%                      | 3.5  | Unknown      | Unclear MD notification form | National statistics | Unknown                                    |
| Botswana*                  | u-MIC           | 169†| 2015           | 7/55                | 12.7%                     | 21.5 | Yes          | MD notification form     | Audit of complete file | Panel, expertise unclear                      |
| China, Wuhan reg.          | u-MIC           | 14,5†| 2001–2012      | 8/91                | 8.8%                      | 1.3  | Yes          | MD notification form     | Audit of complete file | Panel, expertise unclear                      |
| China, Henan reg.          | u-MIC           | 45,5†| 1996–2009      | 90/1129             | 8.0%                      | 3.6  | Yes          | MD notification form     | Audit of complete file | Panel with O&G specialist                      |
| Country                      | LIC/MIC/u-MIC | MMR | Period  | Cardiac MDR/total MD (%) | cMRR | OFD included | Review at facility level | Review central level | Case review by                          |
|------------------------------|---------------|-----|---------|--------------------------|------|--------------|--------------------------|----------------------|----------------------------------------|
| China, Shanghai reg.         | u-MIC 20,5‡   | 2000–2009 | 24/262  | 9.2%                     | 1.9  | Yes          | MD notification form     | Audit of complete file | Panel with O&G specialist              |
| China, Zhejiang reg.         | u-MIC 58‡     | 1995–2008 | 95/901  | 10.5%                    | 6.1  | Yes          | MD notification form     | Audit of complete file | Panel, expertise unclear              |
| China combined§              | u-MIC 35§     | 1995–2012 | 217/2383| 9.1%                     | 3.2  |              | None                     | Staff at facility        |                                        |
| Fiji                         | u-MIC 34†     | 2008–2012 | 5/37    | 13.5%                    | 4.6  | If reported  | MD notification form     | Audit of complete file | Panel with O&G specialist              |
| Irak                         | u-MIC 27‡     | 2010–2012 | 79/1039 | 7.6%                     | 2.1  | Yes          | MD notification form     | Audit of complete file | Panel with O&G specialist              |
| Iran, Yazd reg.              | u-MIC 34†     | 2002–2011 | 8/40    | 20.0%                    | 6.8  | Unknown      | MD notification form     | Unclear               | Unclear                              |
| Malaysia*                    | u-MIC 28,7‡   | 2009–2011 | 65/430  | 15.1%                    | 4.3  | Yes          | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
| Malaysia                     | u-MIC 27‡     | 2006–2008 | 49/396  | 12.4%                    | 3.4  | Yes          | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
| South Africa*                | u-MIC 138†    | 2014    | 49/1238 | 4.0%                     | 5.5  | No           | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
| South Africa                 | u-MIC 154†    | 2011–2013| 169/4333| 3.9%                     | 6.0  | No           | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
| South Africa                 | u-MIC 154†    | 2008–2010| 157/4867| 3.2%                     | 5.0  | No           | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
| South Africa                 | u-MIC 112†    | 2005–2007| 97/3959 | 2.5%                     | 2.7  | No           | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
| South Africa                 | u-MIC 112†    | 2002–2004| 85/3296 | 2.6%                     | 2.9  | No           | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
| South Africa                 | u-MIC 85†     | 1999    | 23/584  | 3.9%                     | 3.3  | No           | Facility audit           | CEMD, audit of complete file | Panel with O&G and non-O&G specialists |
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).

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 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 S2). 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

| Country          | LIC/L-MIC/u-MIC | MMR | Period | Cardiac MD/total | Proportion cardiac MD (%) | cMMR | OFD | Review at facility level | Review at central level | Case review by Panel with O&G and non-O&G specialists | Panel with complete file | Review by non-O&G specialists | Review of O&G certification forms and medical records | MD | OFD | Review by non-O&G specialists | Review by non-O&G specialists | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records |
|------------------|------------------|-----|--------|-----------------|--------------------------|------|-----|-------------------------|------------------------|---------------------------------------------------|-------------------------|---------------------------------|---------------------------------|------|-----|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| South Africa     | u-MIC            | 5.0%| 2010-2014 | 1/45 | 4.2 | No | Facility audit CEMD, audit of complete file | MD | OFD | Review by non-O&G specialists | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records | MD | OFD | Review by non-O&G specialists | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records |
| Surinam          | u-MIC            | 3.1%| 2014 | 2/65 | 3.1% | Yes | Audit of complete file | MD | OFD | Review by non-O&G specialists | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records | MD | OFD | Review by non-O&G specialists | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records | Review of O&G certification forms and medical records |

CEMD, Confidential enquiry into maternal deaths; LIC, low-income country; L-MIC, lower middle-income country; u-MIC, upper middle-income country; MD, maternal death; cMMR, cardiac-related maternal mortality ratio/100 000 live births; MD, maternal death; OFD, out-of-facility death; O&G, obstetrics and gynaecology.

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

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

MMR from report, population-based study.

MMR from report, population-based study.

MMR based on average of 4 reports from China.

MMR based on average of 4 reports from China.

MMR based on average of 4 reports from China.
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 be 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

![Figure 2](image-url)
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 pre-
conception counselling and during pregnancy, birth, and the
postpartum period has been shown to improve mater-
nal outcome, but remains unattainable in most LMIC
[16,19,54,72,73].

In LMIC, women of reproductive age with cardiac dis-
ease are facing challenges far different from those that
women in high-income countries (HIC) face. Most man-
gagement 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 differ-
ent approach than RHD, which is the most common car-
diac 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 cover-
age of contraceptive use of 3%

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 cover-
age of contraceptive use of 3-6%.

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 con-
sider becoming pregnant in the future. With the need for
lifelong anticoagulation therapy, the risks of maternal
morbidity and mortality and foetal complications are
high, based on findings mainly from HIC [77,78]. As pre-
viously 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 problem-
atic to provide adequate risk assessment and treatment
for a young woman with a cardiac condition, who is con-
sidering 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 addi-
tional 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 fre-
cuency 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 dis-
ease. 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 under-
reporting. Our findings are in line with the obstetric transi-
tion 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 mater-
nal mortality, more attention is needed for pre-existing
medical disease like cardiac disease as a cause of maternal
mortality. Prospective studies on prevalence, pregnancy out-
come and interventions are needed to assess the real burden
or cardiac-related maternal mortality in LMIC and establish
feasible and relevant guidelines.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Database search strategy.

Appendix S2. Quality assessment for reports mentioning zero cardiac deaths and when multiple reports per country were available.

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