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Maternal death and postpartum hemorrhage in sub-Saharan Africa – A pilot study in metropolitan Mozambique

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Abstract

Background: Maternal mortality in sub-Saharan Africa is approximately 500 to 1000 per 100 000 births (vs. approximately 5-20 in developed countries). Postpartum hemorrhage (PPH) is deemed responsible for 30% to 50% of the deaths.

Objective: To study PPH, risk factors, and mortality in metropolitan Mozambique to inform future studies and intervention strategies.

Materials/Methods: Retrospective cross-sectional data extraction from all charts available to us (n = 495) recording deliveries between January and June 2018 at Maputo Central Hospital. Data included age, maternal survival, HIV status, parity, delivery mode, complications, vital signs, laboratory values, and maternal/fetal data. PPH was determined by charted diagnosis, interventions for hemorrhaging, placental abruption, transfusion, or blood loss. Autopsy reports from all deceased patients (n = 35) were examined.

Results: Median age was 29 years with 17% HIV prevalence. Risk factors for PPH (frequency, 12%) included parity (adjusted odds ratios (AORs) for 3+ versus nulliparity, 7.20 (95% confidence interval [CI], 2.46-21.10), gestation length (AOR, 0.86; CI, 0.81-0.92 per week), and body temperature (AOR, 1.10; CI, 1.04-1.16 per 0.1°C). Maternal mortality was strongly associated with PPH (AOR, 5.22; 95% CI, 2.26-12.08) and HIV (AOR, 11.66; 95% CI, 4.72-28.78). Laboratory values (n = 241) were available from mothers experiencing complications (approximately 50%). Anemia (prevalence 54%) was a strong predictor of PPH with an inverse relationship between hemoglobin levels on admission (AOR, 0.62; 95% CI, 0.50-0.77 per g/dL higher hemoglobin) and the probability of later suffering from PPH. Mothers who died following PPH had lower median hemoglobin (6.2 g/dL) than mothers who survived (9.2 g/dL). Protocols to estimate peripartum blood loss were not used; antifibrinolytics and/or cryoprecipitate were unavailable.

Conclusion: Postpartum hemorrhage is a serious problem even in metropolitan areas of sub-Saharan Africa, and anemia influenced bleeding and death substantially. To

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address this problem, it is critical to raise awareness and region-specific prevention and intervention protocols.

Essentials

- Postpartum hemorrhage (PPH) and mortality are high in sub-Saharan Africa, but locoregional insights are limited.
- We studied PPH, maternal mortality, awareness, and practices in the largest university hospital in Mozambique.
- Postpartum hemorrhage was a serious problem and contributed substantially to mortality, especially in combination with HIV infection.
- Anemia emerged as a major risk factor for developing PPH, with low hemoglobin levels associated with the highest risk.

1 | INTRODUCTION

Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by pregnancy or its management.[1] Maternal mortality in sub-Saharan Africa is among the highest in the world.[1] Many sub-Saharan African countries, including Mozambique, have a maternal death rate of approximately 500 to 1000 per 100 000 births, compared to approximately 5 to 20 in developed countries.[1,2] According to the World Health Organization, Mozambique has one of the highest birth rates in the world, and although a substantial reduction of maternal mortality was achieved over the past 20 years, it still has one of the highest maternal mortality rates (500-999 per 100 000 live births).[1,3]

Mortality is especially high in the immediate postpartum period, during which postpartum hemorrhage (PPH) accounts for 30% to 50% of maternal deaths.[4–6] Over the past decade, substantial efforts have been made in sub-Saharan Africa to implement a variety of preventative measures and treatment protocols to reduce maternal death, resulting in a successful decline in maternal mortality of approximately 40%.[1] However, sub-Saharan Africa continues to have one of the highest maternal mortality rates, and PPH remains a major concern.[1,2] To reduce maternal mortality, it is therefore critical to study the problem of PPH on multiple levels to develop prevention and treatment strategies. A first major step in that direction was achieved with the Women Trial, demonstrating that death from PPH in developing countries can be reduced by approximately 30% if tranexamic acid is administered at the onset of bleeding.[7] This trial demonstrated that simple and relatively inexpensive interventions can impact maternal survival substantially.[8]

The prevalence of PPH, and to what extent it varies among sub-Saharan regions, is known only by rough estimation. Local data-gathering and reporting processes that feed into various repositories such as public health registries, surveillance surveys, or national statistical offices are suboptimal.[1,6,9] Medical records in sub-Saharan Africa are often incomplete, and training to assess the extent of bleeding may be lacking, especially in rural clinics.[10] Altogether, this may explain discrepancies in reporting between various agencies and also expose uncertainties

regarding the accuracy of locoregional numbers.[11] Moreover, the usual definition of PPH (blood loss ≥500 mL during vaginal delivery and ≥1000 mL during cesarean section) may not be clinically relevant in sub-Saharan Africa, where small amounts of blood loss may have detrimental outcomes in patients with preexisting severe (hemoglobin <7 g/d) or moderate anemia (hemoglobin 7-9.9 g/d). Although never formally studied, this is important to note, since the prevalence of maternal anemia approaches 80% in some countries, compared to approximately 5% in the United States.[12–15] Additionally, there is clinical evidence that anemia can increase the risk of surgical bleeding and PPH.[16–20]

In an effort to target interventions to prevent and treat PPH in Mozambique, we sought to define the rate of PPH and identify risk factors that contribute to PPH and mortality in Maputo Central Hospital, the largest university hospital in Mozambique. We did so formally by extracting data retrospectively from charts of women who delivered during the 6 months from January to June 2018. Informally, this data review provided much insight regarding local awareness of PPH, PPH assessment measures, and data record keeping, as well as available treatments or a lack thereof. Such assessments are necessary to inform strategies for prospective studies and for improving management of PPH.

2 | MATERIALS AND METHODS

2.1 | Patient population and data extracted

Paper charts from pregnant patients who delivered at Maputo Central Hospital between January and June 2018 were used as data sources for retrospective review. After obtaining permission from the hospital administration, we collected all charts available to us. They came from different areas of the obstetrics/gynecology ward and hospital archive and represented approximately a quarter of all births during this period. This convenience sample was sorted into patients who had spontaneous vaginal deliveries and patients who had cesarean sections. Charts for all the deceased patients during that period, including autopsy reports, were also obtained and examined. One

Portuguese-speaking resident obstetrician (MC) and a medical student from the University of California San Diego (LL) worked together to extract information from each patient's file, supervised by the local faculty hematologist and obstetrician (PS and IB).

We extracted basic demographic information on maternal age, estimated gestational age, gravida, parity, and basic labor and delivery information such as vital signs, length of hospitalization, and mode of delivery. We also collected information on complications and comorbidities such as infection with HIV, other known infectious diseases, occurrence of PPH, and survival during hospitalization. If the chart revealed that a mother suffered from a complication during delivery, defined as any unexpected event with the potential to negatively affect maternal and/or fetal health, the delivery was recorded as "complicated." Complete blood counts and basic chemistry values were also extracted, but had been drawn only from patients experiencing complications. For subsequent analyses these patients were named "mothers in distress." Coagulation parameters (activated partial thromboplastin time, prothrombin time, fibrinogen) were not available. Fetal data were limited to infant weight, length, sex, and survival status. Since estimated blood loss was not routinely documented, we determined PPH according to a charted diagnosis of PPH, an intervention for hemorrhaging (including hysterectomy or B-Lynch sutures), a diagnosis of placental abruption, or the need for a blood transfusion.

We used internationally accepted definitions for anemia in pregnancy, thrombocytopenia, and mean cell volume.[21] More specifically, anemia was defined as hemoglobin levels <11 g/dL and divided into mild, moderate, and severe based on a hemoglobin of 10.0 to 10.9 g/dL, 7.0 to 9.9 g/dL, and <7 g/dL, respectively, according to World Health Organization guidelines for pregnant women.[22]

The study protocol was approved by the Human Research Protection Program at the University of California San Diego and the Institutional Bioethics Committee of Maputo Central Hospital (Comité Institucional de Bioética em Saúde da Faculdade de Medicina/Hospital Central de Maputo).

2.2 | Statistical methods

Patient characteristics, comorbidities, and complications were expressed as medians and interquartile ranges or as frequencies. Since continuous variables were not normally distributed, we calculated the median and interquartile range for patients who experienced PPH and those who did not. We estimated the median difference between the 2 groups by bootstrapping.[23] For categorical variables we calculated the difference in proportion between patients who bled and those who did not. We tested for trend using the Cochran-Armitage method.[24]

Many variables had missing values (Table 1). Before fitting regression models, we prepared a complete data set by the sequential multiple regression imputation method,[25] which created 20 imputed replicates. Since our main outcomes of interest—PPH and maternal death—were binary variables, we fitted logistic multiple regression models and calculated odds ratios. The logit was used to estimate the probability of each patient suffering PPH or death.[26]

3 | RESULTS

3.1 | Patient characteristics and comorbidities

Delivery charts of 495 patients were studied, and their characteristics are shown in Table 1. Median age at delivery was 29 years (range, 15-45), and 27% of women were nulliparous. Ten previous births were recorded for 1 patient, but otherwise the maximum was 5. More than half the patients came from the metropolitan area of Maputo, and median gestation length was 39 weeks (range, 10-44). Vital signs were recorded on admission for most patients. The prevalence of HIV was 17%, and malaria was detected in 4 patients. For 58% of deliveries a complication was recorded, including PPH (12%) and (pre)eclampsia (16%). Forty-six percent of the patients underwent a cesarean section.

3.2 | Vitals and laboratory values on admission

Blood for complete blood count and basic chemistry on admission was drawn only from mothers in distress (n = 241; Table S1). Notably, anemia was present in 54% of cases of mothers in distress, of which 20%, 25%, and 9% had mild, moderate, and severe anemia. Red cell microcytosis (54%) and hypochromia (78%) appeared common, suggesting severe iron deficiency. The prevalence of thrombocytopenia and hypoalbuminemia was 31% and 41%, the latter suggesting a high proportion of mothers in distress, who had underlying malnutrition and/or chronic diseases.

3.3 | Parameters associated with PPH

3.3.1 | Demographic variables and comorbidities associated with PPH

The risk of PPH was lowest among mothers in their 20s and then increased with age (Figure 1A). PPH further increased steeply with parity (Figure 1B). Complicated births, cesarean sections, positive HIV status, and malaria increased the risk of PPH (Table 2). Preeclampsia and eclampsia were not associated with PPH, whereas pulse and body temperature measured on admission were higher in women who later experienced PPH. Shorter gestation and lower fetal weight were also associated with greater risk.

Multivariate analyses were run with the imputed data set. We fitted logistic multiple regression models to estimate the risk of PPH in relation to patient variables that were associated with PPH in the univariate analyses and were also recorded on admission, that is, during patient intake. These were parity, HIV status, temperature, and length of gestation. The outcome variable was PPH versus no PPH. The best model showed that increasing parity was associated with a greater risk of PPH, especially for those mothers who already had 3 or more births (adjusted odds ratio [AOR], 7.20; 95% confidence interval [CI], 2.46-21.10 compared to nulliparous mothers)

TABLE 1 Patient characteristics, vitals recorded on admission, comorbidities, and complications

Comorbidity or complication	Number of mothers (%)	Median (range); n	Missing values (%)
Age, y		29 (15-45); 492	0.6
Systolic BP, mm Hg		124 (80-206); 464	6.2
Diastolic BP, mm Hg		79 (43-151); 467	5.7
Pulse, beats/min		88 (41-150); 358	27.7
Temperature, °C		36.6 (35.0-39.8); 429	13.3
Marital status			17.6
Single	101 (20)		
Married	307 (62)		
Not recorded	87 (18)		
Place of residence			9.1
Maputo City	296 (60)		
Outside Maputo	154 (31)		
Not recorded	45 (9)		
Parity			1.4
0	132 (27)		
1	162 (33)		
2	122 (25)		
3	48 (10)		
4	14 (3)		
5	9 (2)		
10	1 (0)		
Not recorded	7 (1)		
Length of gestation, wk		39 (10-44); 357	27.9
Delivery complication			3.6
No	190 (38)		
Yes	287 (58)		
Not recorded	18 (4)		
Postpartum hemorrhage			0.0
No	436 (88)		
Yes	59 (12)		
HIV infection status			4.2
Negative	388 (78)		
Positive	86 (17)		
Not recorded	21 (4)		
Malaria			0.8
No	491 (99)		
Yes	4 (1)		
Preeclampsia			0.0
No	439 (89)		
Yes	56 (11)		

(Continues)

TABLE 1 (Continued)

Comorbidity or complication	Number of mothers (%)	Median (range); n	Missing values (%)
Eclampsia			0.0
No	470 (95)		
Yes	25 (5)		
Cesarean section			3.2
No	250 (50)		
Yes	229 (46)		
Not recorded	16 (3)		
Length of hospitalization, wk		2 (0-330) 475	4.0

Note: Metropolitan Mozambique, January to June 2018 (n = 495)

(Table 3). In addition, a shorter gestation and a high temperature on admission were associated with greater risk (Table 3). Figure 1C illustrates the estimated risk of PPH according to this model. While HIV was strongly associated with PPH in the univariate analysis (Table 2), it was no longer associated with PPH in a model where gestation length and body temperature were also predictors.

In this model (Table 3), imputation increased the sample size by 56% (495 vs. 318 without imputation), resulting in odds ratios that were a little higher and with narrower 95% CIs (except for temperature), compared to the same model run only on those with complete data.

3.3.2 | Laboratory values on admission as predictors of PPH

Blood tests on admission (available only for distressed patients) showed that albumin and total protein were both lower in patients who later suffered PPH, while creatinine was elevated (Table S2A; Figure 2). Hemoglobin, platelet count, and red blood cell count were all nearly 25% lower in patients who later experienced PPH.

Because anemia appears to influence postpartum bleeding tendency[17–20] and was found to be profound in many women even prior to developing PPH, we studied the association between PPH and anemia in more detail. We fitted logistic multiple regression models with PPH as the outcome and hemoglobin as the predictor of interest. The objective was to identify the best predictive model for PPH that included hemoglobin as a measure for anemia. We examined age, HIV status, parity, body temperature on admission, and length of gestation as covariates. The best model had just 2 predictors: hemoglobin concentration in grams per deciliter (AOR, 0.62; 95% CI, 0.50-0.77) and gestation length in weeks (AOR, 0.92; 95% CI, 0.85-0.99) (Table S2B). The probability of PPH in relation to hemoglobin illustrates how the risk of PPH increased steeply when hemoglobin fell below about 9 g/dL (Figure 3). In other words, moderate and severe anemia were associated with considerably greater risk of
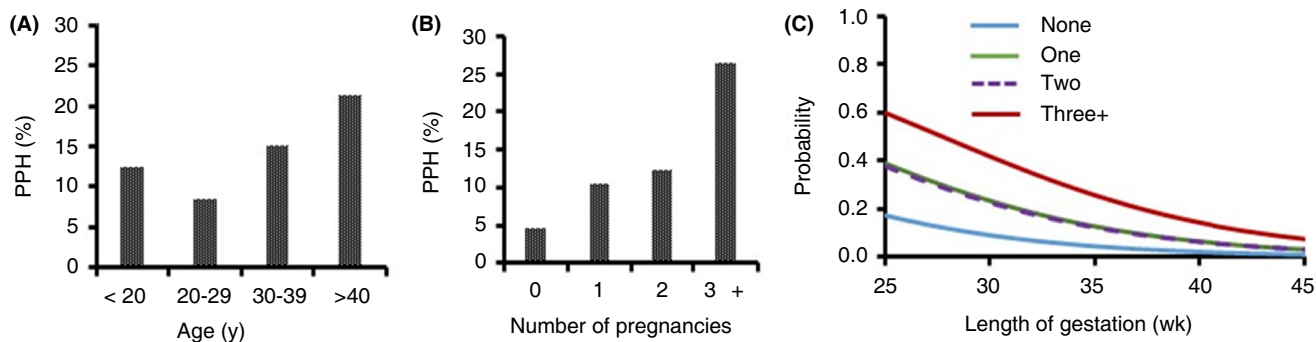
FIGURE 1 Associations between postpartum hemorrhage and age, parity, and length of gestation. A, Frequency of PPH differed between age classes (Fisher's exact test: *P* = .09), B, Frequency of PPH increased with the number of pregnancies (Cochran-Armitage test for trend: *P* = <.01), C, Probability of PPH in relation to length of gestation and parity, adjusted for body temperature. PPH, postpartum hemorrhage

PPH than mild anemia. However, the 95% CIs for the predictions increased in width with higher estimated probability of PPH (Figure 3).

3.3.3 | HIV infection and relationship to anemia

The proportion of HIV infection in mothers arriving in distress was more than double that in nondistressed mothers (25% vs. 11%, respectively; percent difference, 14; 95% CI, 7-21). In the distressed mothers, anemia was present in 62% of HIV-infected mothers, compared to 51% in mothers without HIV (percent difference, 12; 95% CI, −3 to 26). The distressed mothers who were positive for HIV had 10.1 g/dL hemoglobin compared to 10.9 g/dL for HIV negative (median difference, −0.95; 95% CI, −2.0 to 0.1).

3.3.4 | Transfusion management

Altogether, 18 mothers received blood products. Red cells, plasma, and platelets were administered in 17, 16, and 2 instances, respectively. Red cell, plasma, and platelet transfusions comprised 61 units (range per patient, 2-7), 89 units (range per patient, 1-18) and 5 units (range per patient, 2-3), respectively. Therefore, only 18 of the 59 mothers (32%) determined to have suffered from PPH received blood component support.

3.4 | Association of PPH with mortality

Thirty-five patients died during hospitalization. The following potential predictors were tested for association with mortality: age, parity, PPH, and infection with malaria or HIV. The frequency of mortality in relation to age was U-shaped, peaking in the <20 years and >40 years age groups (Figure 4A). There was no association with parity. PPH and HIV were strongly associated with maternal mortality (Table 4). Patients with PPH were nearly 5 times more likely to die than those who showed no signs of PPH, and the risk of death was 10 times greater for HIV-positive patients. Also, 3 of the 4 patients

with malaria died. Among the distressed patients from whom blood was drawn on admission, patients who later died showed elevated creatinine and lower albumin, hemoglobin/red cell counts, and platelet counts (Table S3). While these laboratory abnormalities are reminiscent of HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), HELLP syndrome was not a diagnosis mentioned in the autopsy reports. Eclampsia, which may be associated with HELLP syndrome, was present in only 6 deceased mothers. Therefore, the laboratory values appear not specific but rather indicative of generalized severe sickness and organ failure.

Multivariate analyses were run with the imputed data set to estimate the risk of death in relation to PPH, HIV, and age. The outcome variable was "died" vs. "survived." A fourth-order polynomial of age ($Cage + Cage^2 + Cage^3 + Cage^4$ where $Cage$ was the centered form of age [28]) described the association between mortality and age. The imputed data set increased the sample from 471 to 495 and resulted in smaller standard errors. The best multiple logistic regression model showed that a greater risk of death was strongly associated with both HIV (AOR, 11.66; 95% CI, 4.72-28.78) and PPH (AOR, 5.22; 95% CI, 2.26-12.08) (Table S4). Note the very high odds ratio for HIV: The risk of dying was an order of magnitude higher for HIV-positive patients after adjusting for PPH. This is illustrated by Figure 4B: The risk of death increased with PPH, with HIV, and especially with a combination of HIV and PPH. Moreover, among the mothers who died, those who had experienced PPH had the lowest hemoglobin concentrations on admission (median, 6.2 g/dL; interquartile range, 4.3-8.3; n = 12). Their median hemoglobin levels were much lower than in mothers who died but did not bleed (10.0 g/dL; median difference, −3.5, 95% CI, −6.1 to −0.85), and lower than in those who survived PPH (9.2 g/dL; median difference, −3.0; 95% CI, −5.8 to −0.35) (Figure S1).

4 | DISCUSSION

We sought to shed light on the prevalence and predictors of PPH as well as associated mortality in Mozambique, one of the world's poorest countries with a known high maternal mortality rate.[1,3] While PPH has been described as a major contributor to maternal mortality

TABLE 2 Mothers with post-partum hemorrhage (PPH) compared to those who did not suffer post-partum hemorrhage

	Frequency or Median (IQR) n		Difference in percentage or median (95% CI)
	No PPH	PPH	
Residence			1 (−5 to 8)
Maputo city	263	33	
Outside city	135	19	
Marital Status			6 (0, 11)
Not married	96	5	
Married	275	32	
Caesarian Section			14 (8, 19)
No	237	13	
Yes	186	43	
Delivery complication			18 (13, 23)
No	188	2	
Yes	233	54	
Human Immunodeficiency Virus Infection Status			11 (2, 19)
Negative	352	36	
Positive	69	17	
Malaria			38 (−11 to 9)
Negative	434	57	
Positive	2	2	
Systolic BP (mm Hg)	124 (115, 137) 427	120 (106, 130) 37	−5 (−14 to 5)
Pulse (beats/min)	87 (80, 95) 327	92 (80, 104) 31	5 (−2 to 9.5)
Temperature (degrees C)	36.6 (36.4, 36.8) 395	36.7 (36.5, 37.0) 34	0.1 (0, 0.25)
Birth weight (gm)	3200 (2900, 3510) 417	2800 (2100, 3550) 41	−400 (−840 to 0)
Length of gestation (wk)	39 (38, 40) 321	36 (30.5, 38) 36	−3 (−6.5 to −1.5)

Note: Metropolitan Mozambique, January to June 2018.

TABLE 3 Odds ratios of PPH in relation to parity, gestation length, and body temperature on admission

Predictor	Adjusted odds ratio	95% CI	P value
Parity			
0	1.00		
1	3.08	1.06-8.95	0.04
2	2.96	1.01-8.67	0.05
≥3	7.20	2.46-21.10	<0.01
Length of gestation, wk	0.86	0.81-0.92	<0.01
Temperature, per 0.1 °C	1.10	1.04-1.16	<0.01

Note: Metropolitan Mozambique, January to June 2018. Hosmer-Lemeshow test for goodness of fit: chi-square = 5.59, *df* = 8, *P* = 0.69.

increased approximately 5-fold if a woman suffered from PPH. The prevalence of 12% is likely an underestimate based on the absence of established guidelines dedicated to recognition, recording, assessment, and management of PPH at the time. Indeed, PPH and/or volumetric estimates of blood loss were most often not recorded when interventions occurred that are usually associated with hemorrhaging (such as placental abruption) or when transfusions were triggered. These findings suggest that awareness among health care providers regarding the importance and detrimental effects of PPH may have been relatively low. Undiagnosed abnormal postpartum blood loss has been found to be frequent (approximately 11%-16%) even in developed countries, as identified by change in parameters after delivery such as hemoglobin (drop of ≥2 gm/d), development of anemia or drop in hematocrit of ≥5%.[30] Numbers may be even higher in developing countries where a standard approach to recognition, recording, and management of PPH is lacking.

Incomplete charting posed a challenge for this study but, importantly, exposed current practices, probably representative for many regions in sub-Saharan Africa. The recognition of local limitations is critical to create opportunities to increase the quality of record keeping and health care provider awareness algorithms and protocols to assess and treat PPH. Wide regional variations in PPH prevalence have been noted in African countries, described in a large meta-analysis by Calvert et al,[31] ranging between approximately 14% to 40% and approximately 0.5% to 15% for blood loss ≥500 and ≥1000 mL, respectively. In contrast, there was little regional variation when comparing several North American studies, where the prevalence for PPH was approximately 10% to 12% and approximately 4% for blood loss ≥500 mL and ≥1000 mL, respectively.[31] The wide variation of PPH recordings in African countries was ascribed to heterogeneity in method and/or timing of blood loss measurement (if any) and locally divergent management practices of delivery. In fact, hemorrhage was defined adequately in only 71 of the 887 studies analyzed,[31] underscoring our local observations at Maputo Central Hospital. Altogether, these observations stress the need to interpret collected percentages carefully (not only from this study but in general), with the goal to design prospective studies prudently, bearing in mind the degree of local PPH awareness and practices of blood loss assessment, if performed at all.
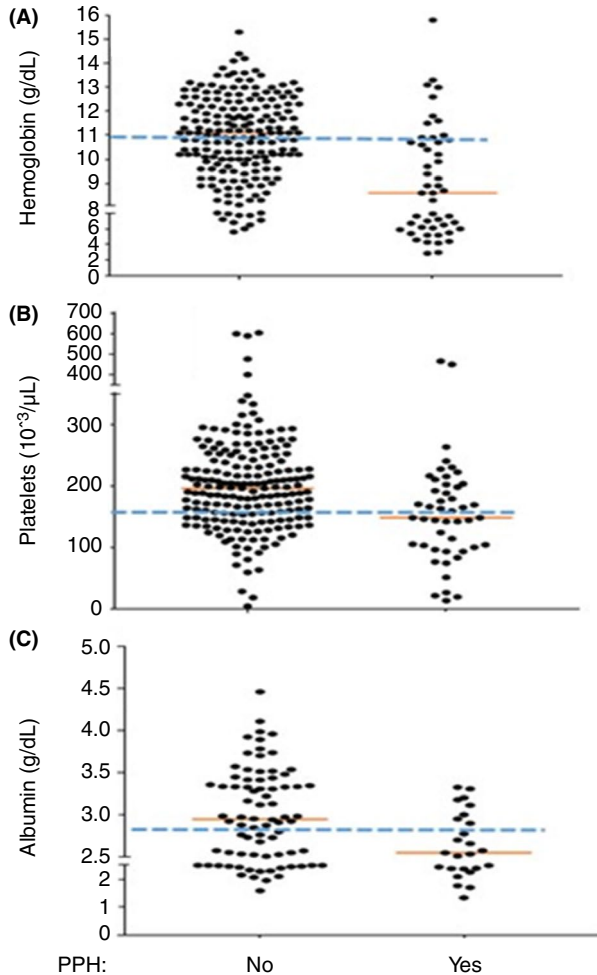
in Mozambique,[29] no precise contemporary local data other than rough regional estimates[1,6,11] are available to determine the true magnitude of the problem. It was the intent to create a baseline assessment to subsequently increase awareness and inform the design of interventional studies to reduce PPH. Data collection was focused on deliveries in the Central Hospital Maputo, the largest university hospital in the country, with a broad metropolitan catchment. In addition, it receives difficult cases referred from nearby rural health care centers and clinics.

We found that PPH in this hospital was recorded in 12% of deliveries and was strongly associated with mortality; mortality

FIGURE 2 Comparison of the distributions of hemoglobin, platelets, and albumin concentrations between patients with and without PPH. Among 495 women at delivery, 241 women were in distress and received laboratory evaluations on admission. A, Hemoglobin (g/dL); B, platelet count (10^3/μL) and serum albumin (g/dL) were determined. The solid orange lines represent the median values. The broken blue lines represent the threshold for anemia (A), thrombocytopenia (B), or hypoalbuminemia (C), adjusted for pregnancy.[21] PPH, postpartum hemorrhage

FIGURE 3 Probability of PPH in relation to hemoglobin for patients with the median length of gestation. Among 495 women at delivery, 241 women were in distress and received laboratory evaluations on admission. The graph depicts an inverse relationship between the probability of suffering from PPH and hemoglobin levels on admission. Probability is shown by the solid line, and its 95% confidence limits by the broken lines. The normal range of hemoglobin in pregnancy is ≥11 g/dL. PPH, postpartum hemorrhage

Extensive staff training pertaining to record completeness will be critical on many levels to make an impactful difference for studying PPH and change in medical practice.

In our study, the maternal prevalence of HIV infection was high (17%), similar to a previously reported study performed in metropolitan Maputo.[32] Not unexpectedly, HIV infection was associated with high maternal mortality, also reported by others for this region.[29,33,34] Remarkably, though, HIV-related mortality was exacerbated by PPH. The probability of maternal mortality from PPH when the mother was infected with HIV was well over 50%. Younger mothers (aged <20), and older mothers (aged >40) were at highest risk. Interestingly, HIV status was a risk factor for PPH in univariate analysis but not in multivariate analysis, where body temperature, parity, length of gestation, or the degree of anemia were much stronge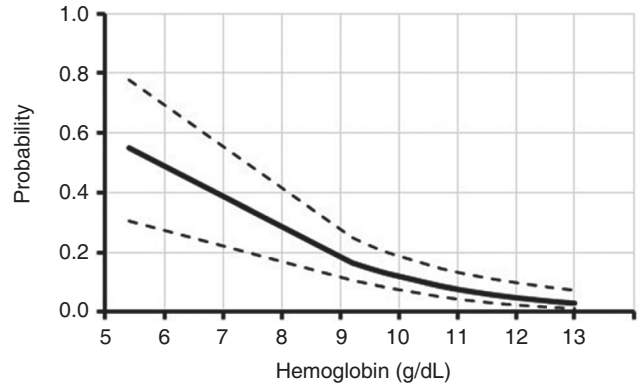r predictors of PPH. In part, this may be explained by the fact that parameters such as HIV and body temperature are not independent of each other. Since it is well established that HIV increases the risk of antepartum and intrapartum infection, it is plausible that body temperature was a marker of intrapartum infection, such as chorioamnionitis, which has been shown to facilitate uterine atony and PPH.[35] There is some evidence that body temperature in extreme situations may influence coagulation.[36,37] However, higher body temperature may also affect uterine contractility, in turn amplifying uterine atony, known to be a major risk factor for PPH.[38] We speculate that the combination of febrile infection in the setting of HIV, paired with higher severity of anemia (compared to HIV-negative patients) may exacerbate PPH, thereby resulting in a high mortality rate. However, a clear understanding of causation will require further investigation in future studies.

Very importantly, anemia on admission to this hospital portended a high risk of subsequent PPH for mothers in distress, a finding that has been observed by others.[17-20] Here, we demonstrated that the risk of PPH increased inversely with hemoglobin levels for mothers in distress and that, for these subjects, anemia was associated with maternal death. Mothers with PPH who died had much lower hemoglobin concentrations on admission compared to mothers with PPH who survived, indicating a poor tolerance of blood loss when the anemia is severe. While the prevalence of anemia was similar in mothers with and without HIV infection, hemoglobin levels were lower in HIV-infected mothers. These findings suggest that HIV infection may have contributed at least indirectly to bleeding risk through a greater degree of anemia.

In contrast to other studies originating from higher-developed parts of the world,[39-42] shorter gestation and lower fetal weight were also associated with a greater risk of PPH. It is possible that
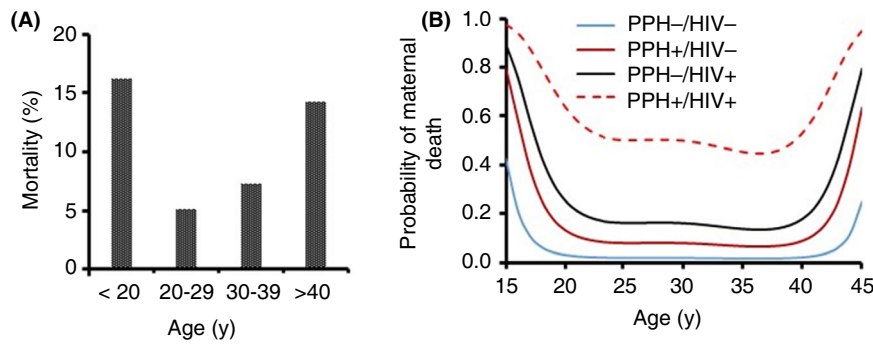
FIGURE 4   Association between maternal mortality, age, and HIV. Depictions of A, the percentage of patients who died in each age group, yielding a U-shaped distribution (Fisher's exact test: P = .06) with peaks in the youngest and oldest age classes; and B, the interaction of age, PPH, and HIV as predictors in a logistic multiple regression model after imputing the missing data, illustrating how these 3 variables act together to influence the risk of maternal mortality. PPH, post-partum hemorrhage

TABLE 4   Comparison of mothers who died with those who survived

Categorical predictors	Number who survived	Number who died	% patients who died	Difference in percentage (95% CI)
Residence				7 (1-12)
Maputo city	285	11	4	
Outside city	138	16	10	
Postpartum hemorrhage				19 (8-30)
No	415	21	5	
Yes	45	14	24	
HIV infection status				21 (12-30)
Negative	379	9	2	
Positive	66	20	23	
Malaria				69
Negative	459	32	7	
Positive	1	3	75	

Note: Metropolitan Mozambique, January to June 2018.

premature delivery and/or small infants were a surrogate for poor fetal/maternal health, rendering mothers more vulnerable to PPH. Further investigations to elucidate this aspect are warranted.

Irrespective of etiology, the notion of anemia and its influence on the risk of bleeding drew our attention and appears interesting on several levels. First, there may be a contribution of altered red cell physiology facilitating bleeding. Preliminary basic scientific studies demonstrate that lower-than-normal red cells in circulation may alter shearing forces, thereby diminishing contact of platelets with the vessel wall and their ability to seal vascular defects.[43–45] It is conceivable that anemia may render the uterus and/or placenta particularly vulnerable to bleeding since they are highly vascular organs. Second, there is some evidence that the chronic hypoxic environment caused by anemia can upregulate or dysregulate placental vascularity,[46–50] which may increase the vulnerability of the placenta and uterus to vascular fragility and PPH. Third, anemia has been associated in some studies,[51,5253] with uterine atony (implicated in PPH[54,55]), perhaps related to tissue iron deficiency. Fourth, postpartum blood loss of <500 mL (not meeting the standard definitions of PPH), which is the volume of a blood donation and therefore considered inconsequential for nonanemic individuals, may be poorly tolerated in patients with low hemoglobin levels. Our observations suggest the need to lower the current PPH definition for anemic mothers, perhaps in graded fashion according to anemia severity, to better meet the sub-Saharan situation. Acute blood loss during delivery also affects subsequent well-being. Postpartum hemorrhage increases the risk of anemia, which may persist for many months or even years after delivery.[56] Blood loss in the setting of preexisting anemia will undoubtedly worsen underlying iron deficiency, which is a major contributor to anemia in the region,[57] as also shown in our cohort by the high prevalence of microcytosis and hypochromia. Since iron deficiency will be difficult to correct given the prevailing nutritional challenges in sub-Saharan Africa,[58,59] detrimental effects on physical function may not only be perpetuated, but also aggravated. Therefore, taken together, blood loss below the conventional PPH definition may be disproportionally detrimental in anemic mothers on many levels, stipulating the need for new definitions and thresholds to inform management and anemia prevention programs.

This study revealed that only approximately one-third of mothers with PPH received blood component support with red cells, plasma, and/or platelets. Cryoprecipitate (major source of fibrinogen) and/or tranexamic acid were unavailable. The scarcity of transfusions was probably a result of limited availability of blood components, as frequently experienced in sub-Saharan Africa,[60] as well as a lack of PPH awareness and of massive transfusion protocols. To alert staff and deploy blood products most sparingly and efficiently, it will be important to train staff to implement a model that predicts the risk of PPH when the mother is first admitted to the hospital.

This study has several limitations. First, it was concentrated on a single hospital that is not representative of other hospitals in the country and does not reflect health care in remote rural areas. Second, of the approximately 2000 deliveries during the

retrospective observation period, only about a quarter of medical charts were available for review (n = 495). The remainder of the charts could not be located or tracked easily, which emphasizes again the regional challenges for data collection. While the availability of charts was not strictly random, it had a random element, since charts were not filed systematically nor were they made available according to specific criteria. We confirmed with the obstetricians that the sample is representative of the overall regional situation, and recorded the main features of the maternal population delivering at Central Maputo Hospital well. This is evidenced by several elements, such as (1) congruency of HIV prevalence with the overall reported regional prevalence, (2) oral confirmation from the local obstetricians at Maputo Central Hospital that approximately 50% of all deliveries are indeed cesarean sections, and (3) confirmation of already established associations such as rising risk of PPH with parity. That said, this study clearly brought to light the challenges of data collection in sub-Saharan Africa, emphasizing that prospective studies capturing each delivery are urgently needed to critically elucidate the intricacies and circumstances of PPH. Third, laboratory data on admission were available for only approximately half of the study population, namely, mothers in distress. Results in relation to laboratory data may therefore not apply to mothers whose births were uncomplicated. Fourth, mothers who died after leaving the hospital were not recorded due to a general lack of follow-up. Therefore, maternal mortality may have been underestimated.

In conclusion, PPH was found to be a notable yet not well recognized or recorded complication with high mortality in the largest metropolitan university hospital in Mozambique. Among several other factors, anemia emerged not only as an important predictor of PPH but also as a risk factor for maternal mortality. Innovative interventions are needed to develop regional practices and guidelines and should encompass close collaborations between local teams representing hematology, blood banking, and obstetrics. They should address record keeping, measurement of blood loss, and the timely prevention and treatment of PPH. Prospective studies should also examine in depth the role of anemia in bleed propagation.

AUTHOR CONTRIBUTIONS
LL and MC collected data. RFWB performed all statistical analysis. AvD and LL contributed to data analysis and data interpretation. EL, IB, and PS contributed to study concept and data interpretation, and facilitated and oversaw the local data collection process. AvD and PS designed the study and assumed responsibilities for study oversight, coordination, data analysis, and manuscript writing. AvD, LL, and RFWB wrote the manuscript, with critical input from EL, IB, and PS.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.