INCIDENCE, MANAGEMENT, AND OUTCOME OF REFRACTORY POSTPARTUM HEMORRHAGE AT KENYATTA NATIONAL HOSPITAL IN THE YEAR 2015 TO 2020

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DECLARATION

I hereby declare that this work has not been presented for the award of a degree at any other university and is my original work.

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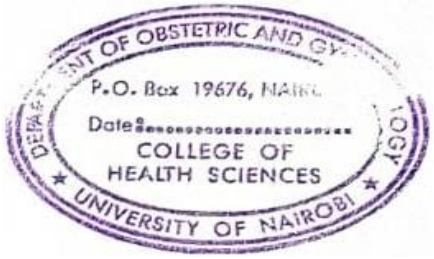

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LIST OF ABBREVIATIONS

AOR	Adjusted odds ratio
AMTSL	Active management of the third stage of labor
CI	Confidence interval
C/S	Cesarean section
IUI	Iatrogenic ureteral injury
KNH	Kenyatta National Hospital
LMIC	Lower and middle-income countries
MEOW	Modified early Obstretics warning chart
MMR	Maternal mortality ratio
PPH	Postpartum hemorrhage
rFVIIa	Recombinant activated factor VIIa
SPSS	Statistical package of social sciences
SDG	Sustainable Development Goals
SVD	Spontaneous vertex delivery
SDT	Standard deviation
UPS	Uterine preserving surgery
WHO	World Health Organization

DEFINITION OF TERMS

Active phase arrest - Arrest of cervical dilatation above 5cm and no cervical change despite rupture of membranes and either 4 hours or more of adequate contractions or, 6 hours or more of inadequate contractions despite oxytocin administration.

Augmentation of labor - The process of giving uterotonics to increase the intensity, frequency, or duration of contractions after the onset of labor.

Confidential Enquiry into Maternal Death (CEMD) -This is a systematic multidisciplinary anonymous investigation of all or a representative sample of maternal death occurring at an area, regional (state), or national level which identifies the numbers, causes, and avoidable or remediable factors associated with them. Through the lessons learned from each woman's death, and through aggregating the data, confidential inquiries provide evidence of where the main problems in overcoming maternal mortality and an analysis of what can be done in practical terms, and highlight the key areas requiring recommendations for health sector and community action as well as guidelines for improving clinical outcomes.

Delayed 2nd stage of labor - Duration longer than 3hrs in nulliparous without epidural, longer than 2 hours in multiparous with or without epidural at full dilatation of the cervix.

Direct maternal death - Direct obstetric deaths are those deaths resulting from obstetric complications of the pregnancy state (pregnancy, labor, and the puerperium), from interventions, omissions, incorrect treatment, or a chain of events resulting from any of the above.

Induction of labor – This is the stimulation of uterine contractions during pregnancy before labor begins on its own to achieve a vaginal birth. It includes the use of synthetic prostaglandins or a catheter, amniotomy, and oxytocin infusion.

Maternal death - A maternal death is the death of a woman while pregnant or within 42 days of the termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

Maternal mortality ratio(MMR) - This is defined as the number of maternal deaths during a given time per 100,000 live births during the same time. It depicts the risk of maternal death relative to the number of live births and essentially captures the risk of death in a single pregnancy or a single live birth.

A Prolonged latent phase of labor – 20 hours or more in nulliparous and 14 hours or more in multiparous women of dilatation below 5cm.

Postpartum hemorrhage - The WHO defines PPH as blood loss of more than 500mls within 24 hours following delivery and severe PPH as blood loss above 1000mls.

Refractory PPH - Bleeding that persists despite instituting first-line intervention-additional uterotonics, uterine massage, and UBT and before proceeding to more invasive procedures.

Stillbirth is the death of a baby before or during delivery.

Sustainable development goals(SDG) - These are a collection of 17 interlinked global goals designed to be a "blueprint to achieve a better and more sustainable future for all". The SDGs were set up in 2015 by the United Nations General Assembly and are intended to be achieved by the year 2030.

Uterotonics - A pharmacological agent given to induce contraction or increase tonicity of the uterus.

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ABSTRACT

Hemorrhage is among the top five direct leading causes of maternal deaths worldwide with post-partum hemorrhage accounting for two-thirds of these deaths. Refractory PPH is bleeding that persists despite instituting what is considered first-line interventions in its management. The incidence of postpartum hemorrhage is known and the existing recommendations by WHO are based on atony being the commonest cause of PPH. However, little is known about refractory PPH and there may be a different pattern of causes and risk factors associated with it. This study aims to identify its incidence in our region, the different managements instituted and their outcome and help come up with recommendations that can be implemented and help lower maternal mortality and morbidity. This will ultimately help us in reaching the SDG goal of less than 70 maternal deaths.

Objectives: To determine the incidence, management, and outcome of refractory PPH among obstetric patients in Kenyatta national hospital from the year 2015 to 2020.

Study methodology A retrospective descriptive cohort study with an analytical component looking at files of all the women who were managed for PPH at KNH from January 2015 to December 2020. We identified the files of all the patients who had primary PPH and were managed at KNH.

From these, we identified the patients who had refractory PPH, their management, and outcome as our population of interest. The maternal and clinical characteristics of those with refractory PPH were assessed as a secondary outcome.

Consecutive sampling was used to identify **540** files of those with PPH from records and from there we identified those with refractory PPH. Mean and standard deviation was computed for numerical variables while frequencies(n) and percentages were computed for categorical variables.

Data collected was entered, cleaned, and analyzed using Statistical Package for Social Sciences(SPSS)version 26.

Results: From a total of **1238** files screened,**540** patients had refractory PPH. The mean age was **29 (S.D ±5.74**). The majority of the patients were aged between **25-35 years, (66%)**., multipara **201(66%)**, married **262(86%),** unemployed **195(64%),** and had attained secondary level education at **120(39%)**

Incidence of refractory PPH was seen to be **56%** with,257(**85%**) of the patients receiving additional uterotonics. Up to **102(34%)** received tranexamic acid, 245(**81%)** of the patients received a blood transfusion and 179(5**9%)** had a EUA.

Among those that had a surgical intervention done 89(**29%**)had a uterine artery ligation done, a B lynch suture at 70(**23%**), and a hysterectomy at 68(**22%**). Only 38(**13%)** had a 3rd and 4th-degree tear repaired while the least surgical intervention used was an internal iliac artery ligation at 7(**2%).**

A UBT was done in only 55(**18%)** while a bimanual uterine compression 43(**14%)** and an abdominal aorta compression were the least done accounting for only 3**(1%).**

There was a statistically significant association between refractory PPH with maternal death occurring **(9.2%)**, renal failure, febrile **(11.8%),** Transfusion (**81%),** neurological (**10.9%)**,Urological morbidity(**2%**)and Respiratory morbidity(**7.9%).**

The only clinical factor found that can be used to predict the odds of refractory PPH occurring was the mode of the delivery being a cesarean section which had a 3 –fold increased odds of being associated with refractory PPH.

Conclusion: There was a high incidence of refractory PPH in our setting at 56%. It was associated with severe maternal outcomes. However, apart from the mode of delivery, there are no clinical and sociodemographic factors that were found to be statistically significant to be used to predict the odds of developing refractory PPH.

Recommendations: Seeing that refractory PPH has a high incidence in our setting, we need to be more vigilant in the management of any PPH case we come across. We need a more objective measurement of blood loss. Implementing the use of MEOW charts in monitoring our patients. Training and frequent drills on PPH management could be implemented to keep the health providers vigilant. Skills training on surgical interventions for the management of refractory PPH and ensuring antibiotics are used after PPH cases to reduce sepsis.

CHAPTER ONE: INTRODUCTION

1.1 Background and epidemiology of postpartum hemorrhage

Hemorrhage is among the top five direct leading causes of maternal deaths worldwide with post-partum hemorrhage accounting for two-thirds of these deaths (1).PPH occurs in 6 % of all live births(2). It is said to have occurred when we have a blood loss that is more than 500mls following a vaginal delivery or more than 1000mls following a cesarean delivery or bleeding that is severe enough to cause hemodynamic instability occurring within 24 hours post-partum (3).

Refractory PPH is bleeding that persists despite instituting what is considered first-line interventions in its management. These interventions include fluid resuscitation, medical management with uterotonics (oxytocin, misoprostol, or methyl-ergometrine), use of tranexamic acid, instituting of non-medical management(bimanual uterine compression, uterine massage, or compression of the abdominal aorta), or the suturing of cervical and vaginal lacerations, where appropriate.

According to the confidential enquiry into maternal deaths(CEMD) done in Kenya in 2017, obstetric hemorrhage was seen to be the leading cause of direct maternal deaths occurring in 40% of cases(4). It showed that for every 10 deaths that occurred due to obstetric hemorrhage, 5 of them were due to hemorrhage occurring in the postpartum period (4).

Globally, the estimated maternal mortality ratio is still high at an estimated 211 per 100000 live births with sub-Saharan Africa having the highest MMR at 542/100000 live births. This accounts for 66% of the global estimated maternal deaths (5). According to the World Bank collection of development indicators, Kenya's MMR is at 342 per 100000 in 2017 which shows a decline from the one in 2014 which was 362/100000 (5)(6). Despite there being a decline, it is slow in progress and it means we still have a long way from achieving the Sustainable Development Goal 3.1 which targets to have less than 70 maternal deaths per 100000 live births(7).

Severe maternal morbidity and death can be prevented if we institute measures to help manage refractory PPH when it occurs. However, the current existing WHO guidelines and recommendations focus majorly on the prevention and management of PPH based on atony being the commonest cause. There may be different factors coming into play in cases of refractory PPH. There is however a paucity of data on its incidence, management, outcome in our region, and the existing guidelines may not adequately address it leading to a lack of timely

intervention and consequently poor outcomes in these patients. This study will help us look into the incidence, management, and outcome of patients with PPH unresponsive to the conventional 1st line therapy and help us come up with a more focused approach to the management of these patients by prioritizing targeted interventions that will cumulatively reduce maternal morbidity and mortality and ultimately go a long way in helping accelerate reaching the SDG targets (5).

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction to refractory PPH

Post-partum Haemorrhage is a global burden that contributes significantly to maternal morbidity and mortality. The common causes of PPH are atony of the uterus which occurs in about 75% of cases, retained tissues, trauma to the cervix, vagina, or perineum, and coagulopathy. These are usually memorized with the mnemonic 4 T's (tone, tissues, tear, and thrombin)(8) (9)(10).

Several studies have shown the benefit of implementing active management of the third stage of labor over the expectant management of labor in preventing PPH with the use of uterotonics, uterine massage, and delayed cord clamping(11)(12). The WHO has developed recommendations for the prevention of PPH during the third stage of labor during either cesarean section or vaginal birth which include the use of uterotonics like misoprostol, carbetocin, oxytocin, ergometrine/methylergometrine, and fixed-dose ergometrine plus oxytocin in those without a hypertensive disorder. Where various options of uterotonics are available, the WHO recommends 10 I.U of oxytocin either administered using the intravenous or intramuscular route, to be used (3)(13).

In cases where AMTSL fails and PPH occurs, the treatment recommended by the WHO includes the use of 10 I.U of intravenous oxytocin but if it is unavailable, or if the bleeding does not respond to the oxytocin, then you can use either an oxytocin-ergometrine fixed-dose, intravenous ergometrine alone, or a prostaglandin drug (including sublingual misoprostol 800 µg). Doing a uterine massage together with the use of tranexamic acid is also recommended in the management of PPH in case uterotonics fail to stop the bleeding, or if it is thought that the bleeding may be partly due to trauma(3)(14). Despite all these measures bleeding may persist and now necessitate the use of additional uterotonics for treatment, additional treatment procedures that include either suturing of either cervical or a high vaginal tear, bimanual uterine compression, use of uterine balloon tamponade, exploration of the uterine cavity, uterine or hypogastric artery ligation, use of uterine compressive sutures (e.g. B-Lynch), or ultimately hysterectomy(15).

2.2 Incidence and causes of refractory PPH

Despite atony being the commonest cause of PPH, other causes may be more prevalent in refractory PPH as was seen in the secondary analysis of the WHO CHAMPION Trial by Widmer et al.The analysis had aimed to look at the maternal characteristics and causes that were associated with the occurrence of refractory PPH(15). The primary study, the CHAMPION trial, was a randomized double-blind non-inferiority trial that aimed to compare the effectiveness of the use of intramuscular prophylactic heat-stable carbetocin to prophylactic oxytocin in the prevention of PPH after vaginal birth. It involved 26 645 participants who were either assigned randomly to either the oxytocin or the heat-stable carbetocin group. The primary outcomes of the study were the proportion of women with blood loss that exceeded 500mls or who received additional uterotonics and the proportion of women with blood loss of at least 1000mls. The secondary outcome of this study was the proportion of women that had an additional surgical intervention done to control the bleeding(15).

The secondary analysis used the data collected on the women that got refractory PPH to identify the risk factors associated with it. It showed the incidence of refractory PPH to be about 16% of the PPH cases that occurred(15). It also showed that there was a difference in the pattern of maternal characteristics and PPH causes among women that had refractory PPH compared with those who responded to first-line therapy. It showed that despite atony being the sole cause of PPH in 52 % of the women with responsive PPH, it accounted for about 31.5% in the refractory group. Conversely, Placental problems were found to be the sole cause in 11 % and 5.6% of the responsive group and refractory group respectively. In addition, while tears were seen to be the sole cause in 12.8% of the responsive group, it was a cause in 28% of the refractory PPH groups. The study also showed that those that had undergone induction or augmentation of labor, got an episiotomy during delivery that required suturing and those that gave birth to infants weighing more than 3500g had increased odds of developing refractory PPH (15).

A study by Mousa et al. also showed the frequency of the causes of PPH to be different among the responders and non-responders to first-line intervention to PPH. He did a retrospective study in the United Kingdom, between 1998 to 2002 involving a total of 20,610 deliveries and looked at the risk factors and interventions that were associated with major PPH unresponsive to first-line intervention. The study defined a case of major PPH as blood loss of more than 1000mls after 24 weeks gestation or a need for a blood transfusion within 24 hours and showed that 306 women developed major PPH giving it a frequency of 14.8/1000 deliveries. Of these

that developed PPH,203 were via CS deliveries and 103 through vaginal deliveries. The study then showed that among these, 22/103(21%) went ahead to develop PPH unresponsive to first-line intervention after vaginal birth and 20/203(10%) after CS deliveries and they required further intervention like examination under anesthesia to control the bleeding.
The study showed that despite atonic uterus being the commonest cause (42%) of major PPH, it was only a major cause occurring in (52)% of responders but (36%)amongst non-responders. Genital tract trauma (21/42), occurred more commonly among the non-responders (50%)versus (30%) in responders and placental causes (10/42), which occurred in (24%) of non-responders versus 15 % of responders.

This study however did not show any differences in antepartum risk factors amongst those that responded to first-line intervention and those that had refractory PPH and thus did not bring out any known risk factor that could be used to predict those that may develop refractory PPH(16).

2.3 Management of refractory PPH

Management of refractory PPH after first-line therapy has failed includes uterine balloon tamponade which can be instituted to avoid invasive surgical procedures. It is one of the least invasive and rapid approaches that can be used in cases of refractory PPH. When done for PPH due to atony it has a success rate of 83 % to 88%(17).

A retrospective study by Mathilde et al in France comparing the rate of invasive procedures which were either surgical or vascular procedures for PPH management to UBT use was done. It looked at two networks where one was a pilot for UBT use and the other one where a UBT was not used and showed that UBT use was associated with a significant reduction in invasive procedures in women who had a vaginal delivery compared to those who had undergone a cesarean delivery after controlling for confounders(17).

A systematic review by Suarez et al looked at the efficacy, effectiveness, and safety of using a uterine balloon tamponade in the treatment of PPH. It looked at 91 studies that had 4729 women in 6 of the RCTs,1 cluster-randomized trial,15 non-randomized trials, and 69 case series and showed UBT to have an overall pooled success rate of 85.9%. The highest success rates of the UBT corresponded to those that had uterine atony at 81.7% and placenta Previa at 86.8% and the lowest rates were seen where it was used for placenta accrete spectrum at 66.7%

and retained products of conception at 76.8%. (18). Its success rate was seen to be lower when used in cesarean deliveries at 81.7% compared to after vaginal deliveries which were at a rate of 87%.

A meta-analysis done by Laas et al of 2 non-randomized before-and-after studies showed that the introduction of UBT in the management of severe postpartum hemorrhage was significantly associated with a decrease in the use of arterial embolization RR, 0.29(95% CI, 0.14-0.63)(19). Another study that was a non-randomized cluster study reported that the use of invasive procedures was significantly lower in the groups that routinely used UBT than that which did not use it (3.0/1000 vs 5.1/1000; P <0.01)(20). A retrospective study carried out in Korea by Kaya et a.also found it to be an adequate adjunct to severe PPH after a cesarean section for placenta Previa to preserve the uterus(19)(21)(22).

Surgical interventions that may be instituted for refractory PPH include uterus preserving surgeries like uterine artery ligation, internal iliac artery ligation, and hemostatic sutures like the B-lynch sutures. If all this fails, a hysterectomy can be done.

A prospective study done by Ferda et al. in Turkey looked at the effect of uterine artery ligation on ovarian reserve and blood supply to the ovaries. The study had a total of 49 participants,25 for who a uterine artery ligation was done for refractory PPH and 24 for who other measures were used including additional uterotonics, uterine massage, and bimanual compression. These patients were followed up 6 months post-surgery and a color Doppler ultrasound and ovarian reserve markers were done which included day 3 FSH, antral follicular count, and AMH levels. It showed no significant difference between the cases and controls. In addition, no significant differences were observed in the blood flow in both the ovarian and uterine arteries (23).

A study by Kayem et al looked at the characteristics, management, and outcome of women undergoing specific 2nd line therapy for PPH. It was a cohort study done in the United Kingdom between 2007-2009 and looked at 272 women who received additional interventions for the management of PPH. A total of Ninety-six percent of all women (n = 260) were managed with uterotonic therapies (oxytocin, ergometrine, carboprost, or misoprostol) to manage hemorrhage before any additional treatment for PPH. It showed that atony was the commonest cause of refractory PPH occurring in 54% of the case followed by placental causes in 19% of the cases and uterine tears at 13%. Those women who required a second-line intervention accounted for

75% after additional uterotonic use. Compression sutures were used in 199(73%)and, 36%had a pelvic vessel ligation done. 22 (8%) had an interventional radiological technique (embolization or intra-arterial balloon), and 31 (11%) received rFVIIa as the first of the specific second-line therapies used to treat PPH. However, up to 71(26%) of the women ended up getting a hysterectomy as rescue therapy(24).

Peripartum hysterectomy is a hysterectomy performed within 6 weeks postpartum due to complications of PPH. It is performed as a last resort in cases of refractory PPH and is considered a near-miss maternal event as it is performed to save the mother's life. Huque et al did a cohort study on the data collected from the WOMAN trial to look at the risk factors associated with postpartum hysterectomy in PPH cases. The primary study, the WOMAN trial, was a double-blinded placebo-controlled trial conducted in 193 hospitals in 21 countries spread across 3 continents-Africa, Asia, and Europe, that aimed to look at the effectiveness of tranexamic acid, an antifibrinolytic agent, in the management of PPH vs a placebo. The trial collected data on all women at the point of randomization and discharge from the hospital, death, or six weeks post-randomization whichever came first(25). It looked at the effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities (surgical intervention, blood transfusion, and non-fatal vascular events in women with PPH. The secondary analysis by Huque et al used completed data from both arms and showed that 1020/20017 (5%)participants had a hysterectomy.

PPH caused by placental problems like accrete and Previa carried a greater risk for a hysterectomy at 17% than surgical trauma and tears (5 %) and uterine atony at 3 %.

The adjusted odds ratio (AOR) for hysterectomy in women with placenta praevia/accreta was 3.2 (95% CI: 2.7–3.8), compared to uterine atony, and an increase in maternal age increased the risk of a hysterectomy. Cesarean section was associated with a fourfold higher odds of hysterectomy than vaginal delivery AOR 4.3, (95% CI: 3.6–5.0), and Mothers in Asia had a higher hysterectomy incidence (7%) than mothers in Africa (5%) AOR: 1.2, (95% CI: 0.9–1.7)(26).

2.4 Maternal outcomes and complications

Severe maternal outcomes associated with refractory post-partum hemorrhage include admission to an intensive care unit, acute renal failure, sepsis, near-miss, and maternal death(27)

A study done in Cameroon by Dohbit et al comparing uterine preserving surgeries vs a hysterectomy showed a hysterectomy as first-line surgical therapy to be associated with less maternal morbidity and death in low-income countries.UPS was associated with maternal deaths RR of 2.3(95% CI: 1.38–3.93.; p: 0.0015) and post-operative infection at RR of 1.96(95% CI: 1.1–3.49; p: 0.0215). However, hysterectomy did not show any statistically significant adverse outcome(28).

A study by Mir et al looked at Pregnancy-related Acute Kidney Injury in India between 2013-2015. It aimed to identify the rate of postpartum AKI and showed that of 713 patients with AKI admitted, 61 had PR-AKI with an incidence of 4.27%. Out of the 61 patients, 28 had PP-AKI with an incidence of 1.96 and out of the 61 patients,7(25%) developed postpartum AKI due to PPH while sepsis accounted for 11(39.28%) of the cases(29).

A secondary analysis by Sotunsa et al in Nigeria on the near-miss and maternal death survey was done among women with severe PPH. It showed that a total of 0.3%(354/2087) of women had an SMO with PPH. It also showed PPH caused maternal death in 103(10.3%)and it had a high Mortality index of(29.1%), and a case fatality rate of(4.9%). Maternal death was more likely to occur in 83% of those who went to ICU and had either a neurological (80%), renal(73.5%), or (58.7%) respiratory dysfunction(30).

A study by Kolin et al looking at risk factors associated with blood transfusion between traumatic(CRASH-2 trial) vs PPH(WOMAN trial)and showed that in the CRASH-2 trial, out of the 20,207 traumatic hemorrhage patients,10,232(51%)received blood components while in the WOMAN trial out of the 20,060 women who got PPH,55% received blood components. It showed that PPH had an increased likelihood of transfusion if they gave birth outside the hospital ARR1.33CI 1.09-1.39), gave birth more than 3 hours before hospitalization (ARR1.09 CI 1.01-1.17), had a cesarean section(ARR1.16, CI1.08-1.25) and if they had any identifiable causes of hemorrhage other than atony. (31)

Krishna et al looking at admissions to ICU secondary to PPH over 1 year in a hospital in India showed that out of 21 patients admitted to ICU,12 (57%)of them had features suggestive of disseminated intravascular coagulation,2(9.5%) had renal failure and required dialysis. There were 2 (9.5%)mortalities despite them receiving blood component transfusion and were seen

to have multiple organ dysfunction syndromes (MODS). The study also showed the development of MODS and DIC as poor prognostic factors for those that got PPH(32).

However, a study by Krawczyk et al that looked at the pregnancy and postpartum-related admissions to ICU in a tertiary facility in Poland showed that 266 women were admitted to ICU, making up (21.08%). The mean age was 30.2 ± 5.6 years, mean gestational age was 30.8 ± 7.6 weeks. Two hundred forty patients (90.23%) were primiparous, and 17 (6.4%) were twin pregnancies. Main reasons of admission included hypertensive disorders of pregnancy n = 99 (37.22%; 4.68 per 1000 deliveries), hemorrhage n = 46 (17.29%; 2.17 per 1000 deliveries) and sepsis/infection n = 46 (17.29%; 2.17 per 1000 deliveries)(33).

A retrospective descriptive study by Tijani et al done between 2000-2010 looked at the incidence, management, and outcome of iatrogenic ureteric injury in obstetric and gynecology patients in a Nigerian teaching hospital and showed that total abdominal hysterectomy was responsible for 75%of the IUI, while cesarean sections were responsible for 10%.In cases that required emergency hysterectomy during surgery, complicated myomectomy accounted for 3 (20%), the uterine rupture was responsible for 2(13.3%), cesarean section1(6.7%), and uncontrolled PPH was responsible for1(6.7%) of the causes(34).

A prospective descriptive cross-sectional study done at KNH in 2008 by Owiti et al showed that hemorrhage was the leading cause of near-miss morbidity at 36.8% (35). A systematic review done on English published articles between 1995 and 2014 looking at the prevalence of maternal near-miss found the median near-miss ratio for PPH to be at 3 per 1000 live births. It showed the mortality index of PPH to be at 6.6% with it being higher in low-income countries(LIC) and lower in middle-income countries (LMIC). Those in LMIC were likely to die of severe PPH and PPH-related consequences compared to those in high-income countries(36).

2.5 Conceptual framework

2.5.1 Narrative

Post-partum hemorrhage despite being a preventable cause of death accounts for 6% of maternal morbidity worldwide. Studies done show the incidence of refractory PPH to be about 14-16% among the PPH cases but there exists a paucity of data on its incidence management, outcome, and associated risk factors within our region. A few studies have shown the risk factors associated with refractory PPH to include but are not limited to previous PPH, multiple gestation, episiotomy during delivery, augmentation of labor, induction of labor, and birth weight of a baby of >3500g.

This study aims to look at the independent variables associated with refractory PPH and will also look at the sociodemographic and clinical factors associated with those that have refractory PPH.

We shall also look at the different management instituted for the patient with refractory PPH and their outcome.

2.5.2 Schematic conceptual framework

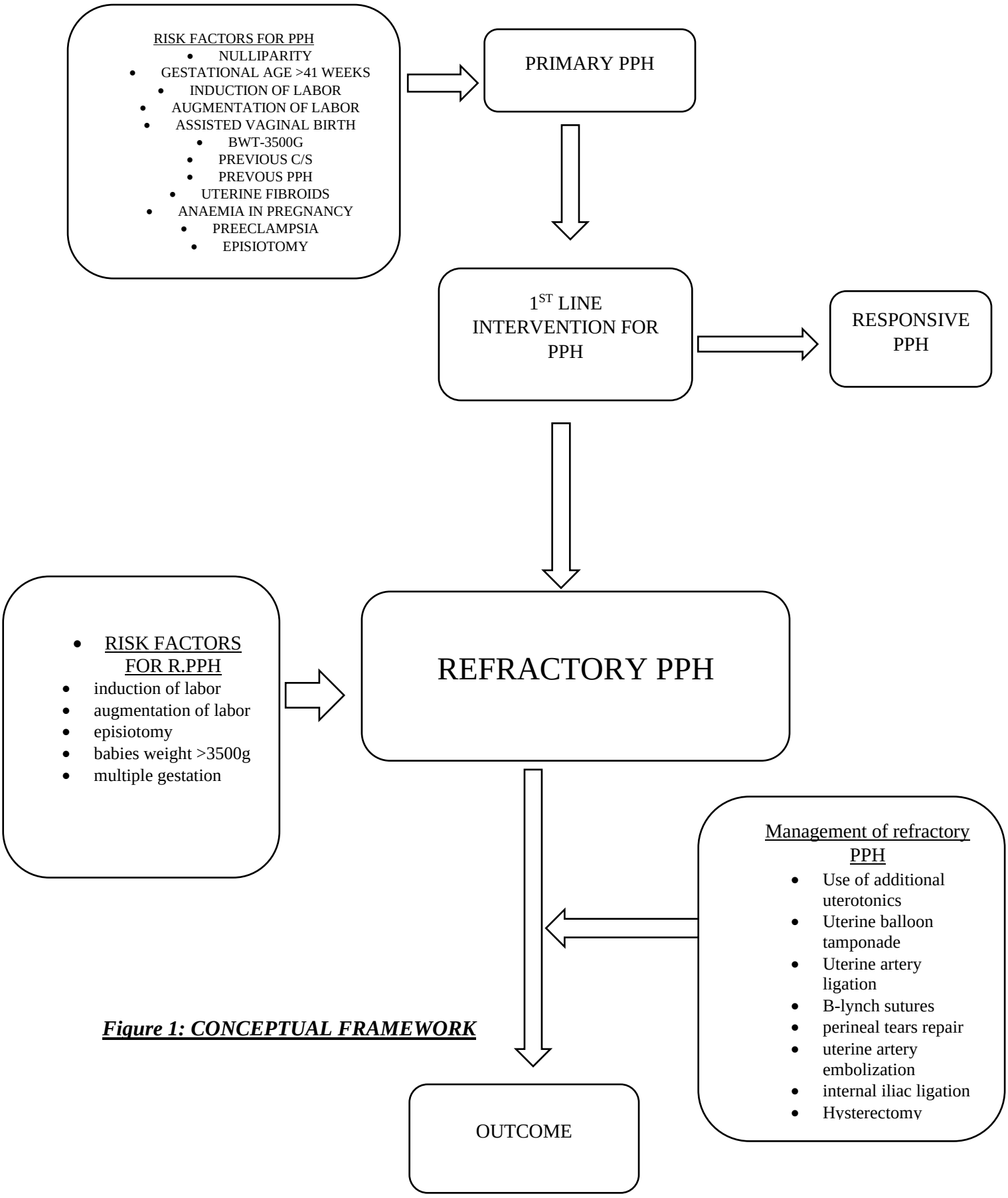

Figure 1: CONCEPTUAL FRAMEWORK

2.6 Study justification

Post-partum hemorrhage is among the top five commonest direct causes of maternal deaths occurring in about 6 % of live births. It is a leading cause of maternal death in LMIC.

Refractory PPH which is bleeding that persists despite instituting 1st line interventions, is a major contributor to maternal mortality and morbidity among those with PPH. We however do not have any local or regional studies beyond the CHAMPION trial that looks into it.

The current existing WHO recommendations and guidelines on the prevention and management of PPH which we adapt our local practice from are based on atony being a major cause of PPH.

This study will help further evaluate refractory PPH as a cause of maternal morbidity and death and the quality of obstetrics care given at KNH, the biggest referral hospital in our region, leading to an improved understanding of the determinants of maternal mortality and identifying areas of intervention. This will take us a step forward in achieving the SDG 3.1 of MMR of less than 70 maternal deaths.

2.7 Research question

What are the incidence, management, and outcome of refractory PPH among women with postpartum hemorrhage at Kenyatta national hospital between the years 2015 to 2020?

2.8 Objectives of the study

2.8.1 Broad objectives

To determine the incidence, management, and outcome of refractory PPH among women with postpartum hemorrhage in Kenyatta national hospital from the year 2015 to 2020.

2.8.2 Specific objectives

Among women with postpartum hemorrhage at KNH in the year, 2015 to 2020 to

1. Determine the incidence of patients that had refractory PPH.
2. Describe the interventions used in the management of patients who had refractory PPH.
3. Determine the adverse maternal outcome associated with refractory PPH.

2.8.3 Secondary objective

Among women with postpartum hemorrhage (PPH)at KNH from the year 2015 to 2020, to

1. Compare the sociodemographic and clinical factors between those with responsive PPH and refractory PPH.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This study was a retrospective descriptive cohort study with an analytical component looking at medical records of all the women who had PPH at KNH from January 2015 December 2020. From these, we identified those that had refractory PPH and looked at their incidence, management, and outcome. The maternity files and records were checked for completeness before data collection.

3.2 The Study site and setting

The study was done at the Kenyatta National Hospital(KNH), a teaching and referral hospital located in Nairobi, Kenya. It offers both preventative and curative services for various illnesses, to patients countrywide. It has a total bed capacity of 1800. It has an obstetrics and gynecology department which has a labor ward unit with 35 beds and 3 postnatal wards (GFA, GFB,1A) with a capacity of 150 beds, a dedicated critical care unit with 4 beds, and two labor ward theatres adjacent to labor ward which operate 24 hours a day. KNH sees an average of 13,212 deliveries which is an average of all deliveries from the year beginning of 2014 to December 2020 with an average of 5730 of these deliveries being via cesarean section.

The unit is run by consultant obstetricians and gynecologists, registrars, medical officers, nurse/midwives, and clinical officers. The patients are usually assigned to the midwives as their primary caregivers upon admission where one nurse may be assigned 5-7 patients per shift. Upon reaching 2nd stage of labor, patients have AMTSL following recommendations given by the WHO which are on how to prevent and treat PPH. These include the use of uterotonics, delayed cord clamping of 1-3 minutes, controlled cord traction, and uterine massage to assess for contraction.

When PPH occurs, we have protocols that give systemic and stepwise management which are achieved with the use of the mnemonic '**HAEMOSTASIS**' and are followed in rapid succession. The mnemonic is divided into two parts-medical and surgical. It includes; **H** - CALL FOR HELP; **A** - Assess(vital parameters-airway, breathing, circulation, blood loss) and resuscitate-provide oxygen, obtain wide bore intravenous line, catheterize and monitor output, assess the need for blood, order laboratory tests(blood count, coagulation screen, blood group, and match)

Establish the etiology of PPH by looking out for the 4Ts associated with causing PPH(TONE, TISSUE, TRAUMA, THROMBIN); followed by **M**-massaging of the uterus.

O – use of an Oxytocin infusion, prostaglandins use with either (rectal, intramuscular intravenous,intramyometrial)route of administration. This is given together with tranexamic acid.

When these fail to control the bleeding, refractory PPH is diagnosed and a bimanual compression or antishock garment use is recommended as we **S**hift to the operating theatre; **T**-Trauma and Tissue are then excluded as a cause before proceeding to uterine balloon tamponade which can either be done before going to the theatre or while there. In the theatre, we **A**-Apply compression B-lynch or modified B-lynch suture then proceed with **S**-Stepwise devascularization of either the internal iliac, uterine, or ovarian; **I**-Interventional Radiology can also be done where available which entails uterine artery embolization and If all these fail, then a **S**ubtotal hysterectomy is done.

When delivery is through a C/S, refractory PPH is diagnosed after delivery of the placenta and before repair of the incision, active bleeding from the placental bed is noted despite administration of uterotonics, or, after repair of the uterus incision site and inspection of bleeding, we either have an atonic uterus despite giving 2 or more uterotonics and uterine massage or after the operation during vulvovaginal toilet it is noted that the patient still has active bleeding from the vaginal opening despite the use of uterotonics.

This was a retrospective study, looking at the labor ward delivery records and maternity theatre records from the year 2015 through to 2020 over a six-year period to identify all mothers that were managed for PPH until the sample size was achieved. From these, we identified those that had refractory PPH which was our study population of interest.

3.3 Study population

3.3.1 Population characteristics and definition of cohort

We identified the medical records of all the patients who were attended to at KNH and had primary PPH. We then looked at the incidence of the patient that had refractory PPH among them, their management, and outcome as our population of interest. The maternal and clinical characteristics of those with refractory PPH were assessed as a secondary outcome.

3.3.2 Inclusion criteria

For a patient's record to be eligible for inclusion it had to meet the following criteria

1. Managed for PPH and at Kenyatta National Hospital within the first 24 hours post-delivery,
2. All referrals to KNH with a diagnosis of PPH,
3. Deliveries that occurred at 28weeks and above
4. All near misses and maternal deaths that were directly associated with PPH

3.3.3. Exclusion criteria

1. Women who received a blood transfusion for other causes other than PPH,
2. Those with the onset of PPH more than 24 hours post-delivery,
3. Incomplete records for key variables which were the management instituted at our facility and the referring facility for PPH,

3.3 Sample size determination

Fischer's formula (Daniel,1999) was used to calculate the sample size

$$\boldsymbol{n = \frac{Z^2 p(1-p)}{d^2}}$$

Where,

n = Desired sample size

$\boldsymbol{Z}$ = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

$\boldsymbol{p}$ = the expected proportion in the population ***(based on the study by Mousa et al,2008, which showed the incidence of refractory PPH to be at approx. 14%amongst those with PPH)***

$\boldsymbol{d}$ = absolute error or precision

$$\boldsymbol{\frac{1.96^2 \times 0.14 \times (1-0.14)}{0.03^2} = 514}$$

CONCLUSION

Our final sample size was 540 after allocating a 5%margin of error in the records

3.4 Sampling procedure

A consecutive sampling method was used to achieve the study sample.

A complete sampling frame was used containing inpatient numbers of all patients who were admitted and managed for postpartum Hemorrhage during the retrospective study period. These files were retrieved for data collection. All files that fit the inclusion criteria were considered starting from 31st December 2020 backward to January 2015.

3.5 Sources and method of recruitment

Patient files to be included in the study were identified from the labor ward delivery register and theatre register as this is where all women who have PPH within 24 hours of delivery or came as referral cases for PPH were attended to. These were looked at to identify the women who had refractory PPH to be included in the study. Inpatient numbers of all that met the criteria were recorded and submitted to the records department for retrieval of the files after getting ethical approval and health record approval to access patient files. The files were checked for eligibility for the study.

3.6 Data variables

	Exposure variables	**Outcome variables**	**Source of Data**
Objective 1 Incidence of refractory PPH	1. 3 or more uterotonics 2. Need for secondary intervention	1. Refractory PPH 2. Non-refractory PPH	Patient Records/clinical files
Objective 2 Management for patients with refractory PPH		1. Use of additional uterotonics 2. Uterine balloon tamponade 3. Uterine artery ligation 4. B-lynch sutures 5. uterine artery embolization 6. internal iliac ligation 7. Hysterectomy 8. 3rd and 4th-degree perineal tear repair	Patient Records/clinical files
Objective 3 The outcome of patients with PPH		1. **Maternal mortality** 2. **Renal failure** 3. **Cardiac arrest** 4. **febrile morbidity**-wound infection,pneumonia,UTI,haematoma septic thrombophlebitis,sepsis 5. **Respiratory**-atelectasis, ARDS, chest tube placement pulmonary edema, 6. **Urological**-bladder injury, fistula,ureteral injury, 7. **Neurological**-seizure,coma,stroke 8. **Hematologica**l-DIC, transfusion reaction 9. **Thromboembolic**-DVT, pulmonary embolism, stroke	Patient Records/clinical files
Secondary objective	**Sociodemographic characteristics** 1. Maternal age 2. Parity 3. Marital status		Patient Records/files

	4. Occupation 5. Education level 6. Blood group a. A b. B c. AB d. O 7. Rhesus status **Clinical characteristics** 1. Duration of labor 2. 1st stage 3. 2nd stage 4. 3rd stage 5. prolonged latent phase of labor 6. Active phase arrest 7. Mode of delivery ● C/S ● SVD ● assisted vaginal delivery 8. Pregnancy-induced hypertension 9. preeclampsia 10. gestational diabetes 11. previous c/s 12. previous PPH 13. APH		

	14. Hydromnious 15. Multiple gestations 16. induction of labor 17. augmentation of labor 18. episiotomy **Risk factors** 1. Atony of the uterus 2. Lacerations to the vagina 3. Lacerations to the cervix 4. 3rd and 4th-degree perineal tears 5. Retained placenta 6. Coagulopathy/DIC		

Table 2:Data variable

3.7 Data collection instruments (appendix-data collection tools)

3.7.1 Data collection

Following approval from the Ethics and Review committee and acceptance from the head of the health information department for retrieval of patients' records, the principal investigator together with 2 trained research assistants proceeded to collect data. Data on all exposure variables and outcomes of interest were extracted from the patient's records; patients' case notes-maternal case notes, nursing cardex, and treatment sheets.

3.7.2 Study procedure

The principal researcher worked together with the research assistants to collect data. The assistant was a qualified clinical officer and medical officer who had rotated in the obstetrics and gynecology department. Following their recruitment, the principal investigator trained the assistants on the study protocol and procedures before the commencement of data collection and entry.

The research assistants were provided with face masks and sanitizer after their training on the MoH's recommendations and guidelines on the prevention of COVID-19 infection. This included social distancing, wearing a mask, hand washing, and use of sanitizer.

3.7.3 Data collection instruments

Data was collected using an abstraction form for every patient's case note retrieved. The principal investigator and research assistants filled in data based on information obtained from the patient's records. All data abstraction tools were checked for completeness and accuracy before being uploaded to a Google form by the principal investigator.

3.8 Data management and data analysis methods (appendix dummy tables)

3.8.1 Data management and quality assurance

Quality assurance was ensured by the principal researcher by training the research assistants on the study protocols and any procedures before the commencement of data collection and entry. This was done a week before the commencement of data collection and continued during the data collection time till the principal investigator was confident about their competence in data collection and entry.

3.8.2 Data validation and reliability

Information collected from the data abstraction forms was double-checked for completeness daily before being entered using a password-protected Google form. A spreadsheet was then generated and cleaned using the hard copy forms and analyzed using SPSS version 26. The electronic file was backed up and stored safely.

3.9 Research ethics

This study was carried out upon approval from the Department of Obstetrics and Gynaecology (UON), and KNH/UON/-ERC – p827/10/2021. All recommendations made

were implemented. The collected data was kept in a computer with a password lock and the data was only reachable to the principal investigator and research assistants.

The participant's details were de-identified by use of an assigned unique identifier, only applicable to the study. The uploaded data was password-protected to maintain confidentiality and backup data was kept in a password-encrypted external hard drive, only known to the principal investigator.

CHAPTER FOUR: RESULTS

4.1 Data collection flow chart

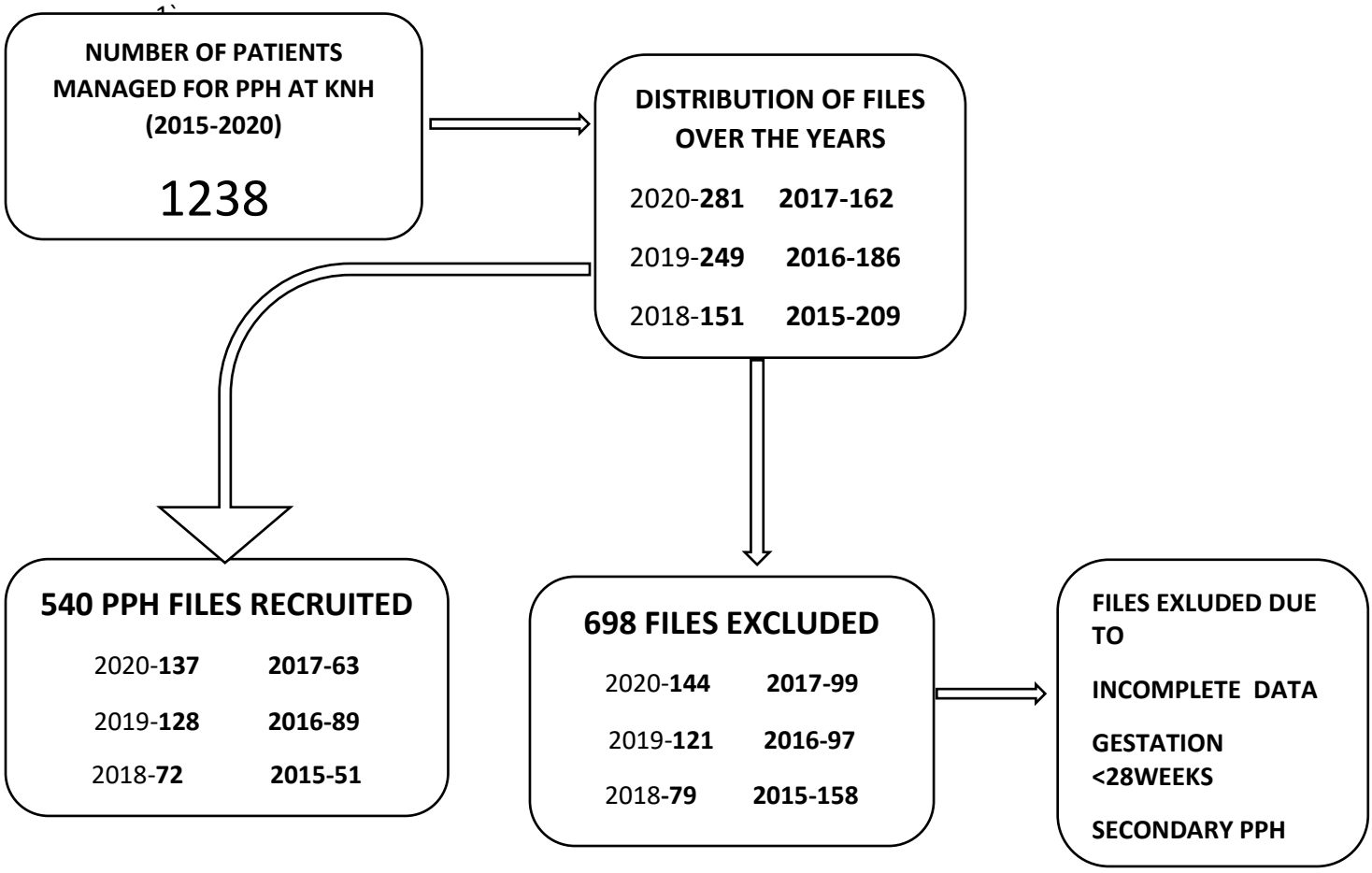

Figure 2:Study flow chart

Out of the 1238 files screened, the Total files excluded over the 6 years was 698 (56%)while those included in the study amounted to 540(44%). Those excluded were due to either incomplete data, gestation below 28 weeks, or had secondary PPH

The incidence of refractory PPH was determined from the sample of patients identified from the records. Summary tables with frequencies and percentages were developed to describe the various management techniques applied to the refractory PPH patients.

The outcomes recorded and extracted were summarized into frequency tables as per their various categories. The comparison of the sociodemographic, and clinical characteristics was analyzed using chi-square and Fisher's exact for categorical variables while the t-test was used

for continuous variables. Odds ratios and 95% CI were calculated where applicable. All statistical tests were considered significant where $p<0.05$.

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4.2 Sociodemographic characteristics of patients managed for refractory PPH at KNH in the year, 2015 to 2020.

Table 2. Sociodemographic characteristics of patients managed for refractory PPH at KNH in the year, 2015 T0 2020.

Sociodemographic characteristics		Refractory PPH N=304
Age (Mean ± SD)		29 ±5.74
Age	<25	67(22%)
	25-35	200(66%)
	>35	37(12%)
Parity	Primipara	85(28%)
	Multipara	201(66%)
	Grand Multipara	18(6%)
Marital Status	Single	42(14%)
	Married	262(86%)
Occupation	Unemployed	195(64%)
	Employed	109(36%)
Education	None	4(1%)
	Primary	96(32%)
	Secondary	120(39%)
	Tertiary	84(28%)

Findings: In patients managed for refractory PPH at KNH, the mean age of patients was 29 (S.D ±5.74). The majority of the patients were aged between 25-35 years, accounting for 200(66%). The least group were aged >35 which accounted for 37(12%).

The majority of the patients were multipara 201(66%) followed by the primipara (28%)with the least number being the grand multipara at18(6%.) The table also showed that the majority of the women were married accounting for 262(86%).

The unemployed made up 195(64%) of the patients and the majority of the patients had acquired a secondary level education at 120(39%) which was followed by primary education at 96(32%) and only 4(1%) lacked any formal education.

4.3 Incidence of refractory PPH among patients with postpartum hemorrhage at KNH in the year, 2015 to 2020.

Table 3:Incidence of refractory PPH among patients with postpartum hemorrhage at KNH in the year, 2015 to 2020.

		Frequency	Percent
Refractory PPH	Yes	304	**56%**
	No	236	44%

Findings: All the women who had PPH had primary interventions instituted. Those that continued to bleed despite these interventions accounted for (304/540) giving an incidence of 56% for refractory PPH.

4.4 Interventions used in the management of patients who had refractory PPH at KNH in the year, 2015 to 2020

Table 4:Interventions used in the management of patients who had refractory PPH at KNH in the year, 2015 to 2020.

	Frequency	**Percentage**
Additional uterotonics	257	85%
Blood transfusion	245	81%
Examination under anesthesia	179	59%
Tranexamic acid	102	34%
Uterine artery ligation	89	29%
B-lynch suture	70	23%
Hysterectomy	68	22%
Uterine balloon tamponade	55	18%
Bimanual uterine compression	43	14%
3rd and 4th-degree perineal tear repair	38	13%
Internal iliac artery ligation	7	2%
Abdominal aorta compression	3	1%
Uterine artery embolization	0	0%

Findings: In the table above, among those managed for refractory PPH,257(85%) of the patients received additional uterotonics while 102(34%) received tranexamic acid. Up to 245 of the patients received a blood transfusion during their management accounting for (81%). A total of 179(59%) of the patients went for examination under anesthesia.

Among those that had a surgical intervention done 89(29%)had a uterine artery ligation done being the commonest intervention followed by B lynch suture at 70(23%). This was then followed closely by a hysterectomy which was done for

68(22%) of the patients. Only 38(13%) had a 3rd and 4th-degree tear repaired while the least surgical intervention used was an internal iliac artery ligation at 7(2%). Non-surgical interventions were not frequently used with A UBT done in only 55(18%) while a bimanual uterine compression was done in 43(14%) and an abdominal aorta compression was the least done accounting for only 3(1%).

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4.4. Adverse maternal outcomes associated with refractory PPH at KNH in the year, 2015 to 2020.

Table 5(a): Adverse maternal outcomes associated with refractory PPH at KNH in the year 2015 to 2020.

		PPH					
		Non-refractory PPH N=236	**Refractory PPH N=304**	**OR (95%CI)**	**P-value**	**AOR (95%CI)**	**P-value**
Maternal mortality	Yes	1(0.4%)	28(9.2%)	23.84(3.22-176.55)	**0.002**	17.53(2.12-144.78)	**0.008**
	No	235(99.6%)	276(90.8%)				
Cardiac arrest	Yes	1(0.4%)	35(11.5%)	30.58(4.16-224.91)	**0.001**	27.71(3.29-233.61)	**0.002**
	No	235(99.6%)	269(88.5%)				
Renal failure	Yes	4(1.7%)	39(12.8%)	8.54(3.01,24.25)	**<0.001**	8.41(2.33,30.34)	**0.001**
	No	232(98.3%)	265(87.2%)				
Febrile morbidity	Yes	6(2.5%)	36(11.8%)	5.15(2.13,12.44)	**<0.001**	3.32(1.22,9.02)	**0.019**
	No	230(97.5%)	268(88.2%)				
Sepsis	Yes	5(2.1%)	23(7.6%)	3.78(1.42,10.10)	**0.008**	2.76(0.89,8.56)	0.079
	No	231(98.7%)	281(92.4%)	Ref		Ref	
Wound infection	Yes	0(0.0%)	15(4.9%)	-		-	
	No	236(100.9%)	289(95.1%)				
Infected Haematoma	Yes	1(0.4%)	8(2.6%)	6.35(0.79,51.14)	0.082	2.34(0.24,22.82)	0.464
	No	235(100.4%)	296(97.4%)	Ref		Ref	
Respiratory morbidity	Yes	0(0.0%)	27(8.9%)	-		-	
	No	236(100.0%)	277(91.1%)				
ARDS	Yes	0(0.0%)	24(7.9%)	-		-	
	No	236(100.9%)	280(92.1%)				
Pulmonary edema	Yes	0(0.0%)	6(2.0%)	-		-	
	No	236(100.9%)	298(98.0%)				
Chest tube placement	Yes	0(0.0%)	1(0.3%)	-	1	-	
	No	236(100.9%)	303(99.7%)				
Atelectasis	Yes	0(0.0%)	1(0.3%)	-	1	-	
	No	236(100.9%)	303(99.7%)				
Urological morbidity	Yes	1(0.4%)	16(5.3%)	13.06(1.72,99.17)	**0.013**	7.94(0.84,75.28)	0.071

	No	235(99.6%)	288(94.7%)				
Fistula	Yes	1(0.4%)	2(0.7%)	1.56(0.14,17.27)	0.719		
	No	235(100.4%)	302(99.3%)	Ref		Ref	
Ureteral injury	Yes	0(0.0%)	6(2.0%)	-	**0.038**	-	-
	No	236(100.9%)	298(98.0%)				
Bladder injury	Yes	0(0.0%)	8(2.6%)	-	**0.024**	-	-
	No	236(100.9%)	296(97.4%)				

Findings: in the table above, there was a statistically significant association between refractory PPH with maternal mortality AOR 17.53(CI,2.12-144.75), cardiac arrest, AOR 27.71(CI,3.29-233), renal failure AOR 8.41 (CI, 2.33-30.34), febrile morbidity AOR 3.32(1.22-9.02).

Urological morbidity 13.06(1.72-99.17)and Respiratory morbidity were only significantly associated in the bivariate analysis but significance was lost after multivariate analysis.

Table 5(b): Adverse maternal outcomes associated with refractory PPH at KNH in the year, 2015 to 2020.

		PPH					
		Non-refractory PPH N=236	**Refractory PPH N=304**	**OR (95%CI)**	**P-value**	**AOR (95%CI)**	**P-value**
Neurological morbidity	Yes	4(1.7%)	40(13.2%)	8.79(3.10,24.93)	**<0.001**	5.76(1.85,17.97)	**0.003**
	No	232(98.3%)	264(86.8%)				
coma	Yes	4(1.7%)	33(10.9%)	7.06(2.47,20.23)	**<0.001**	4.37(1.39,13.76)	**0.012**
	No	232(99.1%)	271(89.1%)	Ref			
Stroke	Yes	0(0.0%)	1(0.3%)	-		-	-
	No	236(100.9%)	303(99.7%)				
seizure	Yes	0(0.0%)	6(2.0%)	-		-	-
	No	236(100.9%)	298(98.0%)				
Hematological complication	Yes	102(43.2%)	253(83.2%)	6.52(4.39,9.68)	**<0.001**	4.81(2.96,7.83)	**<0.001**
Transfusion	No	134(56.8%)	51(16.8%)				
	Yes	102(43.6%)	251(82.6%)	6.22(4.20,9.21)	**<0.001**	4.49(2.77,7.29)	**<0.001**
	No	134(57.3%)	53(17.4%)	Ref		Ref	
Anemia	Yes	42(17.9%)	128(42.1%)	3.36(2.24,5.03)	**<0.001**	2.43(1.53,3.86)	**<0.001**
	No	194(82.9%)	176(57.9%)	Ref		Ref	
Transfusion reaction	Yes	1(0.4%)	7(2.3%)	5.54(0.68,45.33)	0.111	3.79(0.35,40.88)	0.273
	No	235(100.4%)	297(97.7%)	Ref		Ref	
DIC	Yes	8(3.4%)	45(14.8%)	4.95(2.29,10.73)	**<0.001**	3.71(1.53,9.02)	**0.004**
	No	228(97.4%)	259(85.2%)	Ref			
Thromboembolic event	Yes	1(0.4%)	4(1.3%)	3.13(0.35,28.22)	0.308	71.97(0.01,458071.87)	0.339
	No	235(99.6%)	300(98.7%)				
Pulmonary embolism	Yes	0(0.0%)	2(0.7%)	-			
	No	236(100.9%)	302(99.3%)				

DVT	Yes	1(0.4%)	2(0.7%)	1.56(0.14,17.27)	0.719	-	-
	No	235(100.4%)	302(99.3%)	Ref			

Findings: hematological morbidity AOR4.81CI,(2.96-7.83) and neurological morbidity AOR3.76(CI185-17.97)were statistically significantly associated with refractory PPH while Thromboembolic events did not have any statistically significant association with refractory PPH

4.5 Comparison of the sociodemographic and clinical factors among those with responsive PPH and refractory PPH in patients managed for postpartum hemorrhage (PPH)at KNH from the year 2015 to 2020.

Table 6(a): Comparison of the sociodemographic factors among those with responsive PPH and refractory PPH in patients managed for PPH at KNH from the year 2015 to 2020.

		PPH					
		Non-refractory PPH N=236	**Refractory PPH N=304**	**OR (95%CI)**	**P-value**	**AOR (95% CI)**	**P- value**
Age (Mean ± SD)		27 ±5.91	29 ±5.74		**0.002**		
Age	<25	86(36%)	67(22%)	Ref		Ref	
	25-35	125(53%)	200(66%)	2.05(1.39,3.03)	**<0.001**	1.75(1.13,2.71)	**0.012**
	>35	25(11%)	37(12%)	1.90(1.04,3.46)	**0.036**	1.68(0.85,3.33)	0.139
Parity	Primipara(1)	91(39%)	85(28%)	Ref		Ref	
	Multipara(2-4)	139(59%)	201(66%)	1.55(1.07,2.23)	**0.019**	1.11(0.68,1.83)	0.679
	Grand Multipara(>5)	6(3%)	18(6%)	3.21(1.22,8.47)	**0.018**	2.11(0.67,6.60)	0.199
Marital Status	Single	34(14%)	42(14%)	Ref			
	Married	202(86%)	262(86%)	1.05(0.65,1.71)	0.845		
Occupation	Unemployed	151(64%)	195(64%)	Ref			
	Employed	85(36%)	109(36%)	0.99(0.70,1.42)	0.969		
Education	None	3(1%)	4(1%)	Ref			
	Primary	56(24%)	96(32%)	1.29(0.28,5.95)	0.748		
	Secondary	99(42%)	120(39%)	0.91(0.20,4.16)	0.902		
	Tertiary	78(33%)	84(28%)	0.81(0.18,3.72)	0.784		
C.REFFERAL	Yes	60(25%)	76(25%)	0.98(0.66,1.45)	0.91		
	No	176(75%)	228(75%)	Ref			

Findings: the mean age among the refractory and non-refractory groups was comparable at 27 ±5.91 vs 29 ±5.74.

The age group of 25-35 years was significantly associated with the occurrence of refractory PPH with an AOR of 1.75(CI,1.13-2.71)

Multipara and grand multipara women were significantly associated with the occurrence of refractory PPH on bivariate analysis with a p value of <0.05 but the significance was lost on multivariate analysis.

Marital status, level of education occupation, and a patient being a referral were not statistically significant.

Table 6(b) Comparison of clinical factors among those with responsive PPH and refractory PPH in patients managed for postpartum hemorrhage (PPH)at KNH from the year 2015 to 2020

		Refractory PPH					
		No N=236	**Yes N=304**	**OR (95%CI)**	**P-value**	**AOR (95% CI)**	**P-value**
presence of anemia	Yes	48(20%)	58(19%)	0.92(0.60,1.42)	0.715		
	No	188(80%)	246(81%)	Ref			
Blood group	A	55(23%)	79(26%)	Ref			
	B	49(21%)	72(24%)	1.02(0.62,1.69)	0.929		
	AB	8(3%)	10(3%)	0.87(0.32,2.35)	0.784		
	O	124(53%)	143(47%)	0.80(0.53,1.22)	0.305		
Rhesus status	Negative	14(6%)	10(3%)	Ref		Ref	
	Positive	222(94%)	294(97%)	1.85(0.81,4.25)	0.145	2.36(0.95,5.85)	0.064
History of previous cs	Yes	31(13%)	85(28%)	2.57(1.63,4.04)	**<0.001**	0.84(0.44,1.61)	0.604
	No	205(87%)	219(72%)	Ref		Ref	
history of previous PPH	Yes	3(1%)	9(3%)	2.37(0.63,8.85)	0.2		
	No	233(99%)	295(97%)	Ref			
APH in current pregnancy	Yes	16(7%)	38(13%)	1.96(1.07,3.62)	**0.03**	1.28(0.64,2.55)	0.487
	No	220(93%)	266(88%)	Ref		Ref	
Polyhydramnios in current pregnancy	Yes	1(0%)	3(1%)	2.34(0.24,22.66)	0.462		
	No	235(100%)	301(99%)	Ref			
multiple gestation	Yes	11(5%)	14(5%)	0.99(0.44,2.22)	0.976		
	No	225(95%)	290(95%)	Ref			
pregnancy-induced hypertension in the current pregnancy	Yes	8(3%)	9(3%)	0.87(0.33,2.29)	0.777		
	No	228(97%)	295(97%)	Ref			
preeclampsia in the current pregnancy	Yes	25(11%)	52(17%)	1.74(1.05,2.90)	**0.033**	1.63(0.92,2.89)	0.095
	No	211(89%)	252(83%)	Ref		Ref	
gestational diabetes in the current pregnancy	Yes	0(0%)	6(2%)	-			
	No	236(100%)	298(98%)				
chronic illness	Yes	15(6%)	18(6%)	0.93(0.46,1.88)	0.834		
	No	221(94%)	286(94%)	Ref			

Findings; in this study, the presence of anemia, patient's blood group, rhesus factor, previous PPH, polyhydramnios, multiple gestations,pregnancy-induced hypertension, gestational diabetes, and presence of chronic illness were not significantly associated with the occurrence of refractory PPH.

However, the presence of APH in the current pregnancy, OR 1.96(CI,1.07-3.62), previous c/s OR2.57(CI,1.63-4.04), and having preeclampsia in the current pregnancy OR 1.74(CI,1.05-2.90) were seen to be significantly associated with the occurrence of refractory PPH.the significance was however lost in all after another analysis.

Table 6(c): Comparison of clinical factors among those with responsive PPH and refractory PPH in patients managed for postpartum hemorrhage (PPH)at KNH from the year 2015 to 2020.

		Refractory PPH					
		No N=236	**Yes N=304**	**OR (95%CI)**	**P-value**	**AOR (95% CI)**	**P-value**
Bloodloss	<1000	113(48%)	41(13%)	Ref		Ref	
	>=1000	123(52%)	263(87%)	5.89(3.89,8.94)	**<0.001**	3.58(2.28,5.64)	**<0.001**
Mode of delivery	SVD	199(84%)	153(50%)	Ref		Ref	
	AVD	4(2%)	4(1%)	1.30(0.32,5.28)	0.713	1.23(0.28,5.40)	0.783
	Elective CS	6(3%)	24(8%)	5.20(2.08,13.04)	**<0.001**	3.44(1.17,10.16)	**0.025**
	Emergency CS	27(11%)	123(40%)	5.93(3.72,9.45)	**<0.001**	3.60(2.01,6.44)	**<0.001**
Gestation_Age	<37	39(17%)	63(21%)	1.80(0.67,4.81)	0.245		
	37-41	187(79%)	232(76%)	1.38(0.55,3.46)	0.495		
	>=42	10(4%)	9(3%)	Ref			
Macrosomia>4kg	Yes	19(8.1%)	29(9.5%)	1.20(0.66,2.21)	0.547		
	No	217(91.9%)	275(90.5%)				
delayed 2nd stage	Yes	12(5%)	23(8%)	1.53(0.74,3.14)	0.248		
	No	224(95%)	281(92%)	Ref			
induction of labor	Yes	29(12%)	43(14%)	1.18(0.71,1.95)	0.529		
	No	207(88%)	261(86%)	Ref			
augmentation of labor	Yes	59(25%)	78(26%)	1.04(0.70,1.53)	0.862		
	No	177(75%)	226(74%)	Ref			
episiotomy	Yes	52(22%)	39(13%)	0.52(0.33,0.82)	**0.005**	1.16(0.68,1.99)	0.586
	No	184(78%)	265(87%)	Ref		Ref	

Findings; in the table above, it was seen that a blood loss of 1000mls AOR 5.8(CI,2.28-5.64), having an emergency cesarean section as a mode of delivery AOR 3.60(CI,2.01-6.44), and an elective cesarean section AOR 3.44(1.77-10.1) were significantly associated with the occurrence of refractory PPH.

Factors not significantly associated with the occurrence of refractory PPH include gestational age, vaginal delivery, macrosomia, delayed second stage, augmentation of labor, and an episiotomy.

4.6 Comparison of the underlying etiology in responsive PPH and refractory PPH in patients managed for postpartum hemorrhage (PPH)at KNH from the year 2015 to 2020.

Table 7: Comparison of the underlying etiology in responsive PPH and refractory PPH in patients managed for postpartum hemorrhage (PPH)at KNH from the year 2015 to 2020.

		Refractory PPH			
		No N=236	**Yes N=304**	**OR (95%CI)**	**P-value**
atony of the uterus	Yes	148(63%)	243(80%)	2.37(1.61,3.48)	**<0.001**
	No	88(37%)	61(20%)	Ref	
lacerations of the vagina	Yes	79(33%)	67(22%)	0.56(0.38,0.82)	**0.003**
	No	157(67%)	237(78%)	Ref	
lacerations of the cervix	Yes	95(40%)	97(32%)	0.70(0.49,0.99)	**0.045**
	No	141(60%)	207(68%)	Ref	
any perineal tears	Yes	66(28%)	60(20%)	0.63(0.42,0.95)	**0.026**
	No	170(72%)	244(80%)	Ref	
retained placenta	Yes	40(17%)	43(14%)	0.81(0.51,1.29)	0.371
	No	196(83%)	261(86%)	Ref	
coagulopathy Disseminated intravascular coagulopathy	Yes	6(3%)	26(9%)	3.59(1.45,8.86)	**0.006**
	No	230(97%)	278(91%)	Ref	

Findings; in this study, it was seen that the commonest cause of refractory PPH was seen to be atony of the uterus occurring in 243(80%)of the patients which were statistically significant with an OR2.37(CI,1.61-3.48).it was followed by lacerations of the cervix 97(32%)with an OR of 0.70(CI,0.49-0.99). Vaginal lacerations occurred in 67(22%) of the cases with refractory PPH with an OR of 0.56(CI,0.38-0.82).

Perineal tears 60(20%)and coagulopathy26(9%) were also significantly associated with refractory PPHwith an OR of 0.63(CI,0.42,0.95) and 3.59(1.45,8.86)respectively.

However, having a retained placenta was not seen to be statistically significant as a cause of refractory PPH.

CHAPTER FIVE: DISCUSSION

In this study, the mean age of refractory PPH was 29 ±5.74. This was comparable to a study by Mousa et.al which showed the mean age of women who get refractory PPH to be between 29 ±7 in those who delivered vaginally and 32±5 after cesarean delivery (16).

5.1 Incidence of refractory PPH

The incidence of refractory PPH was found to be at 56% among patients with PPH. This defers from the studies by Mousa et al and Widmer et al as they both had an incidence of 14.8% and 16% respectively(15)(16). This difference could be because the study by Widmer looked at a smaller sample size of 29,539 deliveries and was a secondary analysis of a trial that only collected data on refractory PPH in women following vaginal birth while this study looked at a total of 87,616 deliveries over 6 years. The study by Mousa et al also looked at a smaller population of 26,010 despite being done over 4 years and the difference in incidence could also be attributed to the difference in geographical regions and our high patient load since our facility is the national referral hospital(15)(16).

5.2 Interventions used in the management of refractory PPH

Among those managed for refractory PPH,257(85%) of the patients received additional uterotonics. This was not comparable with the study by Widmer et al. where only 73% received additional uterotonics. This however could be due to the study by Widmer only looking at vaginal deliveries. (15)

For those that had a second-line treatment done, a UBT was used in 55/304 (18%) of the women with refractory PPH. This was comparable to its use in the study by Widmer et al where it was used in 22 (15.4%).

Suturing of a high vaginal and cervical tear under EUA was done in (n=179,)59% of the patients. This was comparable to the study by Widmer where suturing of these tears occurred in (n = 59) 41.3%. This could also be explained by a high annual birth rate in our facility hence more cases of PPH.this was also good seeing that it meant that we were diagnosing patients with tears more effectively and managing them appropriately.

A bimanual uterine compression was done in (43) 14% of the patients with refractory PPH. This was not comparable with any of the studies. This could be due to a lower threshold among the personnel managing PPH and easy access to more operating theatres allowing utilization of more surgical interventions.

Pelvic artery ligation(uterine and internal iliac artery ligation) was performed in 96(31%)of the refractory case. This was comparable to findings in the study by Kayem et al that showed

it was used successfully in 36% of PPH cases. Increased utilization of these modalities could be due to the majority of the patient falling in the age group where fertility preservation would be desired(24). However, the use of Internal iliac artery ligation on its own was only done in 7(2%) of the women with refractory PPH. This is comparable with the findings in Mousa's study which was done only on 1 patient (0.3%). The low use of this procedure could be due to its complexity in performing, time-consuming, or the perception of the surgeon on the procedure's efficacy.

B lynch suture was done for only 70(23%)of the patients. Its utilization was also seen to be low despite atony being the commonest cause of refractory PPH in our study. This could be possible because of a lack of skill in performing it. This intervention could be useful in our setup as seen in a study by Kayem et al where it had a 73%success rate in control of refractory PPH(24).

A hysterectomy was done for 68(22%) of the patients. This was done when all modalities failed. It was seen to be comparable with a study by Kayem et al where up to 71(26%) of the women ended up getting a hysterectomy as rescue therapy in the management of refractory PPH.(24)In comparison, only 5(3.5%) of the patients in the Widmer et al study received a hysterectomy. whereas in Mousa et al's study,(7/13, 54%)had a hysterectomy done among the c/s group. Our lower rate compared to this study could be due to the utilization of other uterus preserving surgeries like uterine and internal iliac artery ligation,b-lynch, and UBT.

5.3 The adverse maternal outcome for those managed for refractory PPH

Maternal death was seen to have occurred in 28(9.2%)of the patients with refractory PPH AOR 17.53(CI,2.12-144.75).this was a high compared to the case fatality rate seen in the study by Sotunsa et al which showed a CFR of 4.9%(30). This could be explained by our high patient numbers and our facility being the regional referral center.

Acute renal failure occurred in 39(12.8%) AOR 8.41 (CI, 2.33-30.34). This was however not comparable to the rate of postpartum acute renal failure (25%)seen in the study by Mir et al.This could be due to either our high rate of blood replacement during and after PPH has occurred as our transfusion rate was as high as of 81 %of women with refractory PPH allowing for adequate volume replacement in patients with PPH.(29)

Febrile morbidity, majorly sepsis, and wound infection occurred in 36(11.8%) of the cases with an AOR of 3.32(1.22-9.02). This was statistically significant and comparable to the finding in Mousa et als study where it was seen in 10% of the cases. This highlights the need for prophylactic antibiotics in patients managed for PPH.(16)

Hematological morbidity was also observed with transfusion occurring in 83 % of the case. This was higher than was seen in the WOMAN trial where up to 55%of those who had PPH needed transfusion with blood components. This could be due to a functioning blood transfusion unit that works well with the maternity unit and the fact that all women who go for a cesarean section at our facility have a sample taken for crossmatching preoperatively. This makes getting blood easier in case of a need(31).

Neurological morbidity like being in a coma occurred in 33(10.9%) and was statistically significantly associated with refractory PPH. This was comparable to the frequency seen in Krishna et al study(19%) and Krawcyzk et al (17%).this could be due to the good resuscitative measures in our facility and the existence of a PPH care bundle.

Urological morbidity like bladder injury and ureteral injuries occurred in2%of the patients.This was lower than what was seen n a study by Tijani et al that was 6.7%following uncontrollable PPH.this could be due to the involvement of a senior consultant anytime an emergency hysterectomy is done(34).

Thromboembolic events did not have any statistically significant association with refractory PPH which was comparable with the study by Mousa et al where only one case occurred after repositioning an inverted uterus(16)

5.4 Sociodemographic, clinical, and risk factors associated with refractory PPH

This study's findings showed that there are no sociodemographic characteristics that could be used to predict the patients with PPH that would progress to develop refractory PPH as none was found to be statistically significant. This agrees with the study by Mousa et al which also did not show any association of the sociodemographic factors.

The only clinical factor in our study that was shown to be associated with a patient developing refractory PPH was the mode of delivery where either an elective or emergency cesarean section was shown to have a 3-fold increased odds of compared to vaginal delivery. this was not comparable to any of the other studies as in Mousa's study risk of refractory PPH was higher in vaginal deliveries than in cesarean section while the study by Widmer only

looked at vaginal deliveries(15)(16)This could be due to attributed to the fact that we are a referral facility with a large flow of patients.

Other clinical factors in this study like the presence of anemia, patient's blood group, rhesus factor, previous PPH, polyhydramnios, multiple gestations,pregnancy-induced hypertension, gestational diabetes, and presence of chronic illness were not significantly associated with the occurrence of refractory PPH. This was in agreement with Mousa's study. (16)

Other intrapartum factors were also not significantly associated with the occurrence of refractory PPH and these included gestational age, vaginal delivery, macrosomia, APH in the current pregnancy, previous c/s, and having preeclampsia in the current pregnancy delayed second stage, augmentation of labor, and an episiotomy. These findings were however inconsistent with study findings by Widmer et al which showed that induction and augmentation of labor and an episiotomy were associated with the development of refractory PPH(15).

In our study, it was shown that atony was the commonest cause of refractory PPH occurring in 243/304(80%)of the patients which were statistically significant with an OR 2.37(CI,1.61-3.48). Lacerations of the cervix occurred in 97(32%)with an OR of 0.70(CI,0.49-0.99)while vaginal lacerations occurred in 67(22%) of the cases with refractory PPH with an OR of 0.56(CI,0.38-0.82). Perineal tears 60(20%)and coagulopathy26(9%) were also the least prevalent but significantly associated with refractory PPH with an OR of 0.63(CI,0.42-0.95) and OR of 3.59(1.45-8.86)respectively. This was inconsistent with the study by Mousa and Widmer which showed that despite atony being the commonest cause of overall PPH I, genital tract trauma(21/42) 50% and placental causes (10/42)24% took precedence in refractory PPH(37).

5.5 Conclusion

There was a high incidence of refractory PPH in our setting at 56%. There is wide use of additional uterotonics, and blood transfusion in cases of refractory PPH and despite there being a wide range of adverse outcomes, we had good utilization of blood transfusion services and this helped lower the frequency of occurrence of neurological and morbidity and acute kidney injury due to our timely intervention. We however had a low utilization of tranexamic acid and uterine balloon tamponade despite recommendations on their usage by WHO being made. However, there were no clinical and sociodemographic factors that were identified that could be used to predict the odds of developing refractory PPH.

5.6 Recommendations

1 Seeing that refractory PPH has a high incidence in our setting, we need to be more vigilant in the management of any PPH case we come across
2 Training and frequent drills on PPH management could be implemented to keep the health providers vigilant
3 Government subsidizing the price of acquiring heat-stable drugs like carbetocin making it more available
4 Skills training on proven ways of PPH management like UBT,B lynch and artery ligation could also promote fertility preservation in our commonest group to get PPH
5 Ensure antibiotics are used after PPH cases to reduce sepsis
6 Train and encourage more UBT use in PPH management
7 Objective measurement of blood loss

5.7 Study strength

1 The study had a large sample size in a national teaching and referral center that can promptly diagnose and manage PPH
2 The first study in this region could form the basis of more studies into key variables surrounding refractory PPH
3 The study has generated baseline data from which future studies could be conducted

5.8 Study limitations

1. It is a retrospective study, so there is a probability of missing data or inaccurate information-however, any missing file was replaced with a file that had complete data.

2. The use of visual estimation of blood loss may have underestimated the actual blood loss.
3. The poor filing system especially for death files in the facility made tracing key files difficult and time-consuming.
4. Selection bias it being a study done in a single facility.

5.9 Study timelines

PROJECT	**jan2-022**	**feb2021-july2021**	**July-aug 2021**	**oct 2021**	**nov2021-feb 2022**	**March-may 2022**	**May-june 2022**	**june 2022**	**july 2022**	**August 2022**
Concept note presentation										
Proposal development										
Proposal marking by 2 internal examiners										
Powerpoint presentation to the department										
Ethical approval										
Data collection										
Data analysis										
Results presentation to the department										
Manuscript writing										
Submission of a manuscript to a peer-reviewed journal										

Table 8:STUDY TIMELINES

5.10 Budget

		UNITS	UNIT COST	TOTAL
Proposal development	Photocopying	10	540	5400
	Printing charges	300	10	3000
	Binding charges	3	300	900
Data collection	Photocopying	1000		3000
	Stationary i.e. pens,	30	10	300
	Printing	300	10	3000
	Internet		15000	15000
	Research assistance levy	2	5000	50000
Data analysis	Statistician's fees	1	30000	30000
Thesis write up	Stationary	80	10	800
Miscellaneous	Transport, communication, and logistics		20000	20000
TOTAL				87000

Table 9:BUDGET

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APPENDIX

2.2 APPENDIX 1: Questionnaire

A.PATIENTS HOSPITAL IDENTIFICATION NUMBER……

B. FILE NUMBER……

C. MATERNAL SOCIODEMOGRAPHIC DETAILS

1. What is the patients' Age…….
2. What is the patient's Parity (_)+(_)
3. What is the patient's Marital status(*tick where applicable*)
    a) Single (_)
    b) married (_)
    c) separated (_)
4. what is the patient's Occupation……
5. what is the patient's Educational level(*tick where applicable*)
    a) none (_)
    b) primary (_)
    c) secondary (_)
    d) tertiary (_)
6. what is the patient's blood group(*tick where applicable*)
    a) A
    b) B
    c) AB
    d) O
    e) OTHER
7. What is the patient's Rhesus status(*tick where applicable*)
    a) positive (_)
    b) negative (_)
    c) OTHER(indicate)…….

B.MATERNAL CLINICAL CHARACTERISTICS

I. ANTENATAL FACTORS

1. Is there the presence of anemia YES (_) NO (_)
   if yes indicate the Haemoglobin level…….
2. Any history of a previous cesarean section YES (_) NO (_)
3. *if yes, how many……*

4. Any history of PPH in a previous pregnancy? YES (_) NO (_)
5. Any history of Antepartum hemorrhage? YES (_) NO (_)
6. Is there a history of Polyhdromnious in current pregnancy? YES (_)NO (_)
7. Was this current pregnancy a multiple gestation? YES (_) NO (_)
8. Did the patient have pregnancy-induced hypertension in the current pregnancy? YES (_) NO(_)
9. Did the patient have preeclampsia in the current pregnancy? YES (_) NO (_)
10. Did the patient have gestational diabetes in the current pregnancy? YES (_) NO (_)

II. INTRAPARTUM FACTORS

11. What is the estimated blood loss?…….
12. What was the Gestation at delivery? ……..
13. What was the mode of delivery? (*tick where applicable*)

a. spontaneous vaginal delivery (_)
b. cesarean section (_)
c. assisted vaginal delivery (_)

14. what was the duration of labor? (in hours)

a. was there a prolonged latent phase? YES (_) NO (_)
   i. 1st stage duration ……
   ii. 2nd stage duration ……..
   iii. 3rd stage duration……..

15. Was there active phase arrest? YES (_) NO (_)
16. Was there a delayed 2nd stage? YES (_) NO (_)
17. Was induction of labor done? YES (_) NO (_)
18. Was there augmentation of labor? YES (_) NO (_)
19. Was the patient given an episiotomy? YES (_) NO (_)

C. CAUSES OF REFRACTORY PPH IN CURRENT PREGNANCY

1. Was there atony of the uterus? YES (_) NO (_)
2. Were there lacerations of the vagina? YES (_) NO (_)
3. Were there lacerations of the cervix? YES (_) NO (_)

4. Were there any perineal tears? YES (_) NO (_)
5. Was there a retained placenta? YES (_) NO (_)
6. Was there a coagulopathy/Disseminated intravascular coagulopathy? YES (_) NO (_)

D. MANAGEMENT OF PRIMARY PPH DONE

1. Were uterotonics used?(*tick where applicable*)
    a) Oxytocin YES ( ) NO ( )
    b) Ergometrine YES ( ) NO ( )
    c) Ergometrine and oxytocin fixed combination YES ( ) NO( )
2. Were Prostaglandins used ? YES( ) NO ( )
3. Was there use of tranexamic acid? YES( ) NO()
4. Was a uterine massage done? YES() NO()

E.MANAGEMENT OF REFRACTORY PPH

1. Were additional uterotonics used? YES ( ) NO ( )
   if yes which ones?.....
2. Was additional tranexamic acid administered YES ( ) NO ( )
3. Was a bimanual uterine compression done YES ( ) NO ( )
4. Was an abdominal aorta compression done YES ( ) NO ( )
5. Was the patient taken for examination under anesthesia? YES( ) NO( )
6. Was a Uterine balloon tamponade used? YES ( ) NO ( )
7. Was a uterine artery ligation done? YES ( ) NO ( )
8. Was an Internal iliac artery ligation done? YES ( ) NO ( )
9. Was uterine artery embolization done? YES ( ) NO ( )
10. Did the patient receive a blood transfusion? YES ( ) NO ( )
11. Was a b-lynch suture done? YES ( ) NO ( )
12. Was a hysterectomy done? YES ( ) NO ( )
13. Were a 3rd and 4th-degree perineal tear repair done? YES ( ) NO ( )

F. PRESENCE OR ABSENCE OF THE FOLLOWING OUTCOMES

1. Was there a Maternal mortality YES (_) NO (_)
2. Did the patient get Cardiac arrest YES (_) NO (_)
3. Did the patient go into renal failure, YES (_) NO (_)
4. Did the patient suffer from any febrile morbidity- YES (_) NO (_)

if yes,(indicate which one where applicable)…….

(*wound infection,pneumonia,UTI,haematoma septic thrombophlebitis,sepsis*)

5. Did the patient suffer any Respiratory morbidity YES (_) NO (_)
   if yes,(indicate which one where applicable)…….

(*ARDS, pulmonary edema, atelectasis, chest tube placement*)

6. Did the patient suffer any Urological morbidity (YES (_) NO (_) *if yes,(indicate which one where applicable)*……..

(*bladder injury, ureteral injury, fistula*)

7. Did the patient suffer any Neurological morbidity YES (_) NO (_) if *yes,(indicate which one where applicable)*……
   (*coma seizure, stroke)*
8. Did the patient suffer any Hematological complication YES (_) NO (_)
   if yes,(indicate which one where applicable)…….
   (*DIC, transfusion reaction)*
9. Did the patient suffer any Thromboembolic event YES (_) NO (_) if *yes,(indicate which one where applicable*)…….

(*DVT, pulmonary embolism, stroke)*

G. OUTCOME OF BABY

1. What was the baby's APGAR score …….
2. What was the baby's birth weight……
3. Did the baby get a Newborn unit (NBU) admission YES (_) NO (_)

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24th February, 2022

Dr. Hadija Waithera Juma
Reg. No. H58/11440/2018
Dept. of Obstetrics and Gynecology
Faculty of Health Sciences
University of Nairobi

Dear Dr. Juma,

RESEARCH PROPOSAL: INCIDENCE MANAGEMENT AND OUTCOME OF REFRACTORY POSTPARTUM HEMORRHAGE AT KENYATTA NATIONAL HOSPITAL IN THE YEAR 2016 TO 2020 (P827/10/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P827/10/2021.** The approval period is 24th February 2022 – 23rd February 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
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