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Article

Epidemiological profile, survival and prognosis of mothers in intensive care unit in northeastern Brazil

Perfil epidemiológico, sobrevida e prognóstico materno em unidade de terapia intensiva no nordeste do Brasil

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ABSTRACT: *Objective.* To study the epidemiologic profile and determine maternal survival and prognosis in an Intensive Care Unit (ICU) in the Northeast of the country. *Methods.* Analytical cross-sectional design study that evaluated pregnant women, puerperae, and women in postabortion or ectopic pregnancy admitted to an obstetric ICU in Teresina between May/2016 and May/2017. *Results.* Of the 11,466 occurrences in the period, 456 women were admitted to the ICU. Among the causes of hospitalization, 80.3% patients were direct obstetric causes, 16.2% indirect and 3.5% non-obstetric. A total of 159 patients met the Near Miss criteria, with statistical significance between presentation of the criteria and mortality ($p<0.001$; $x^2=30.974$). The mortality rate was 3.5%, all of them being Near Miss cases. There was a statistically significant and direct correlation between survival and number of clinical ($p<0.001$; $rp=0.270$), laboratory ($p<0.001$; $rp=0.358$) and management ($p<0.001$; $rp=0.465$) criteria. It was identified that the higher the number of criteria, the longer the length of hospitalization and worse the prognosis ($p<0.001$). *Conclusion.* Women admitted to the ICU for indirect obstetric causes who met maternal Near Miss criteria had longer hospitalization and worse prognosis.

KEY WORDS: Intensive Care Units; Maternal Mortality; Obstetrics.

RESUMO: *Objetivo.* Estudar o perfil epidemiológico e determinar sobrevida e prognóstico materno em uma Unidade de Terapia Intensiva (UTI) no Nordeste do país. *Métodos.* Estudo de delineamento transversal analítico que avaliou gestantes, puérperas e mulheres em pós-abortamento ou gravidez ectópica internadas em UTI obstétrica em Teresina entre maio/2016 e maio/2017. *Resultados.* Das 11.466 ocorrências no período, 456 mulheres foram internadas em UTI. Dentre as causas de internação, 80.3% pacientes foram causas obstétricas diretas, 16.2% indiretas e 3.5% não obstétricas. Ao todo, 159 pacientes atendiam aos critérios do *Near Miss*, com significância estatística entre a apresentação dos critérios e a mortalidade ($p<0,001$; $x^2=30,974$). A taxa de mortalidade foi de 3.5%, sendo a totalidade, casos de *Near Miss*. Verificou-se correlação estatística significativa e direta entre sobrevida e número de critérios clínicos ($p<0,001$; $rp=0,270$), laboratoriais ($p<0,001$; $rp=0,358$) e de manejo ($p<0,001$; $rp=0,465$). Identificou-se que quanto maior o número de critérios, maior a duração da internação e pior o prognóstico ($p<0,001$). *Conclusão.* Mulheres admitidas em UTI por causas obstétricas indiretas que preencheram critérios de *Near Miss* materno tiveram internação mais duradoura e pior prognóstico.

DESCRITORES: Unidade de Terapia Intensiva; Mortalidade Materna; Obstetrícia.

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INTRODUCTION

Although only about 1% of pregnant women require intensive care unit (ICU) assistance, the likelihood of a woman during the pregnancy-puerperal cycle needing such care is significantly higher than that of a young, non-pregnant woman[1]. Over the past decade, there has been a considerable increase in obstetric emergencies due to changes in the demographics of pregnant women, as well as in obstetric practices, with a substantial rise in cesarean delivery rates[2-5].

It is therefore expected that the management of pregnant and puerperal women in intensive care units will become increasingly necessary in current obstetric practice. As such, knowledge not only of the causes of maternal mortality, which are well-documented in the global literature, but also of the causes and conditions leading to the admission of pregnant and puerperal women to intensive care units, is an indispensable tool for reducing cases of maternal mortality[6].

In this challenging scenario for healthcare teams, understanding and establishing the needs of this population is crucial for developing public policies applicable to the realities of obstetric centers across the country. However, the limited number of studies with this objective, especially in the poorest regions that lead maternal mortality statistics, hinders the adoption of targeted measures to change this reality. Therefore, it is imperative that additional studies be conducted to better understand the situation of these patients.

With this objective, an analytical study was conducted on the profile of patients and the causes of ICU admission under the care of obstetricians in the state of Piauí, located in the northeastern region of Brazil, which has one of the lowest Human Development Indexes in the country, with an HDI of 0.646. This study aims to identify risk factors that may influence patient outcomes, identifying potential intervention points for reducing the need for critical care admissions, shortening hospital stays, and consequently reducing maternal morbidity and mortality[2,7].

MATERIALS AND METHODS

A prospective cross-sectional analytical study was conducted between May 2016 and May 2017 with women admitted to an obstetric intensive care unit (ICU) consisting of eight beds, affiliated with a reference maternity hospital in Teresina, Piauí, Brazil. The ICU had a multidisciplinary team available 24 hours a day, and case discussions, as well as patient follow-ups, were conducted jointly by obstetricians and intensivists. The study was approved by the Ethics Committee, and all participants or their guardians signed an informed consent form. Inclusion criteria were: being pregnant, postpartum, or a woman in post-abortion or ectopic pregnancy. Exclusion criteria included having a hospital stay of less than 24 hours, adopted considering that these patients exhibited less severity, mainly consisting of those under protocol observation in the unit.

A data collection form was used, specifically designed for this research, containing a checklist of epidemiological and obstetric characteristics, maternal conditions for ICU admission (cause groups and diagnoses), survival (length of stay, in days), as well as clinical, laboratory, and management criteria for Near Miss according to the World Health Organization (WHO)8. Data collection was performed through interviews with selected patients and active searches in electronic medical records. The data collected by one of the researchers using the standardized research instrument were then recorded in duplicate in an electronic database for subsequent statistical analysis.

Mortality rates and the Near Miss/maternal mortality ratio were presented as quality indicators of the care provided to patients in the obstetric ICU. The study data were processed using IBM® SPSS® software, version 23.0. Descriptive statistics were calculated (mean, standard deviation, minimum and maximum values for quantitative variables; and frequencies for qualitative variables). In inferential analysis, the Kolmogorov-Smirnov test was used to verify the normality of the data for quantitative independent variables.

Pearson's Correlation Test was used to examine the relationship between survival and the number of Near Miss criteria presented by the women, according to groups (clinical, laboratory, and management). To compare survival and the presence of clinical, laboratory, and management Near Miss criteria among women admitted to the ICU, the Mann-Whitney test was used; for cause groups of ICU admission (direct obstetric, indirect obstetric, or non-obstetric), the Kruskal-Wallis test was used.

The association between Near Miss occurrence (yes; no) and the mortality rate among the women (maternal death; discharged with recovery) was verified using Pearson's Chi-Square test. The Prevalence Ratio (PR) and its corresponding confidence interval (CI) were calculated, using the frequency of "discharged with recovery" as a reference, since no women who died did not present Near Miss criteria. The test was also used to examine relationships between mortality and maternal prognostic factors. When assumptions of this test were not met, the variables were dichotomized for the Fisher's Exact Test. The percentages in the contingency table were calculated in the columns, and the variables were interpreted (compared) in the rows. All analyses were conducted at a 5% significance level.

RESULTS

Data analysis was performed on 456 women who were admitted to the ICU. The frequency of admissions to the maternal ICU relative to the 11,466 obstetric events attended to at the maternity hospital was 3.98%. The main maternal causes for ICU admission, according to cause groups and their main diagnoses, are distributed in Table 1. Regarding the cause groups of ICU admission, 366 (80.3%) patients were admitted for direct obstetric causes, 74 (16.2%) for indirect obstetric causes, and only 16 (3.5%) for non-obstetric causes. It is observed that pregnancy-specific hypertensive disorders were the primary direct obstetric cause of ICU admission (67.8% of direct causes) and that cardiopathies were the main indirect obstetric cause (32.4% of indirect causes). Of the 16 patients admitted for non-obstetric causes, suicide attempts by exogenous poisoning accounted for 25% of the cases.

Table 1 - Main maternal reasons for admission to the obstetric ICU according to cause groups and their main diagnoses (n=456). Teresina, PI, Brazil, 2018

Obstetric Cause	Cause group	n	%
Direct n = 366 (80.3%)	*Hypertensive*	*248*	67.8
	Severe preeclampsia	125	50.4
	Eclampsia	63	25.4
	HELLP syndrome	60	24.2
	Hemorrhagic	*83*	22.7
	Uterine atony	22	26.5
	PPD	20	24.1
	Other causes	41	49.4
	puerperal infection	*19*	5.2
	Other causes	*11*	3.0
	Other infections	*05*	1.4
Indirect n = 74 (16.2%)	*Other causes*	*54*	*73.0*
	Heart disease	24	44.4
	Epilepsy	09	16.7
	Other causes	21	38.9
	Infections	*15*	*20.3*
	Pneumonia	11	73.3
	Other causes	04	26.7
	Hypertensive	*05*	*6.8*
Non-obstetric	*Other causes*	*15*	*93.8*
	Exogenous intoxication	04	26.7
	Polytraumatism	02	13.3
	Other causes	09	60.0
n = 16 (3.5%)	*Infections*	*01*	*6.3*

HELLP: hemolytic anemia, elevated liver enzymes and low platelet count; PPD: placental abruption
Source: Own preparation

The epidemiological and obstetric characteristics are listed in Table 2. The average age of the women was 26.7 (±7.2) years, with a minimum age of 13.0 and a maximum of 49.0 years. Regarding the patients' place of origin, out of the 456 admitted patients, 368 women (80.7%) were referred from healthcare services outside the city where the ICU is located. Only 21.5% of the total admitted patients had more than 11 years of education.

Regarding the number of pregnancies, the average was 2.3 ± 1.7 pregnancies. Concerning the number of prenatal visits, the average was 5.6 (± 2.2) visits, and 367 patients (80.5%) admitted to the ICU were receiving low-risk prenatal care. The primary mode of delivery was cesarean section in 71.5% of cases. The gestational age at delivery for those who had a vaginal birth was, on average, 34.6 (± 6.7) weeks, ranging from 20.0 to 41.0 weeks; for those who had a cesarean section, the average gestational age was 35.1 (± 3.7) weeks, ranging from 22.0 to 41.0 weeks.

Eighty-six (18.9%) women had a history of chronic systemic disease prior to pregnancy, with hypertension being the most prevalent in 23 (5.0%) cases, followed by epilepsy in 11 (2.4%), heart disease in 11 (2.4%), and diabetes in 9 (2.0%). There were 16 deaths among the 456 women admitted to the ICU, resulting in a mortality rate of 3.5%. Of the total deaths, 10 cases (62%) were due to direct obstetric causes, 5 cases (31.2%) were due to indirect obstetric causes, and only 1 case (6.8%) was due to a non-obstetric cause. Among the 10 deaths from direct obstetric causes, 5 women died from infections, 3 from hemorrhagic syndromes, and 2 from acute fatty liver of pregnancy. Regarding the 5 deaths from indirect obstetric causes, 2 patients died from pneumonia, 1 from complications of systemic lupus erythematosus, and 1 from a cerebrovascular accident in a patient with thrombophilia. The single death from a non-obstetric cause was due to complications from colon cancer.

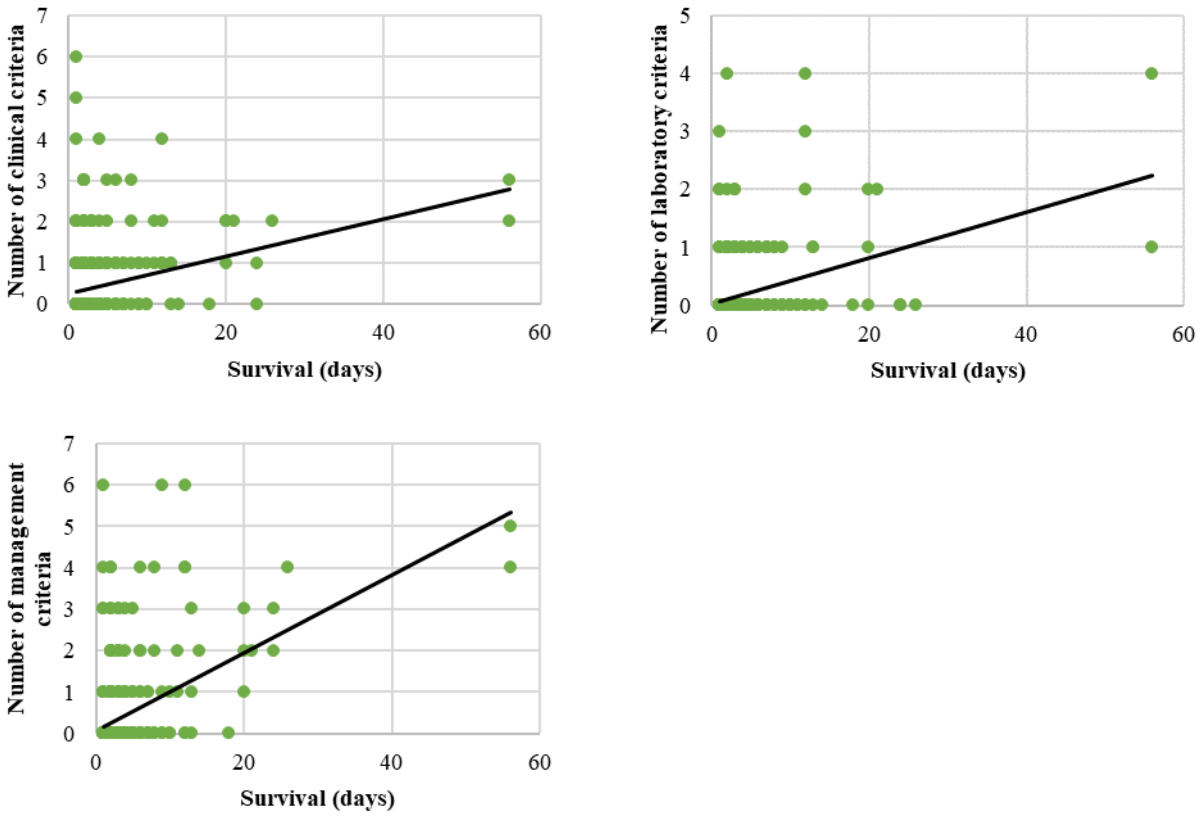
Statistically significant and direct correlations were found between survival and the number of clinical ($p<0.001$; $rp=0.270$), laboratory ($p<0.001$; $rp=0.358$), and management ($p<0.001$; $rp=0.465$) Near Miss criteria, ranging from low to moderate relationships. It was identified that the greater the number of Near Miss criteria, the longer the duration of the women's stay in the intensive care unit (Figure 1).

Table 2 - Epidemiological and obstetric characteristics of women admitted to the ICU (n = 456). Teresina, Piauí, Brazil, 2018

Characteristic	M	SD	n	%
Age (in complete years)	26.7	7.2	-	-
Maternal age				
Pregnant teenager (13 to 19 years old)	-	-	94	20.6
Adult pregnant woman (20 to 35 years old)	-	-	302	66.2
Elderly pregnant woman (>35 years old)	-	-	60	13.2
Birthplace	-	-		
Teresina	-	-	150	32.9
Other municipalities in Piauí	-	-	216	47.4
Other states	-	-	90	19.7
Place of origin of the patient (origin of hospitalization)				
Own service	-	-	88	19.3
External to the service (metropolitan area of Teresina)	-	-	103	22.6
External to the service (outside Teresina)	-	-	265	58.1
Education				
0 to 3	-	-	6	1.3
4 to 7	-	-	142	31.1
8 to 10	-	-	206	45.2
11 or more	-	-	98	21.5
Not informed	-	-	4	0.9
Marital status				
Single	-	-	159	34.9
Married	-	-	118	25.9
Stable union	-	-	154	33.8
Separated/divorced	-	-	24	5.3
Not informed	-	-	1	0.2
Color/race				
White	-	-	118	25.9
Black	-	-	68	14.9
Brown	-	-	202	44.3
Not informed	-	-	68	14.9
Profession/occupation				
Employee	-	-	64	14.0
Autonomous	-	-	66	14.5
Student	-	-	71	15.6
Unemployed	-	-	183	40.1
Not informed	-	-	72	15.8
Number of pregnancies	2.3	1.7	-	-
Number of births	1.5	1.5	-	-
Number of abortions	0.3	0.6	-	-
Mode of delivery* and gestational age (in weeks)				
Vaginal	34.6	5.7	47	10.3
Cesarean section	35.1	3.7	326	71.5
Prenatal				
Low risk (usual risk)	-	-	367	80.5
High risk	-	-	63	13.8
Did not perform PN	-	26	5.7	-
Number of prenatal consultations in the current pregnancy	5.6	2.2	-	-
History of chronic systemic disease prior to pregnancy				
Yes	86	18.9	-	-
No	370	81.1	-	-

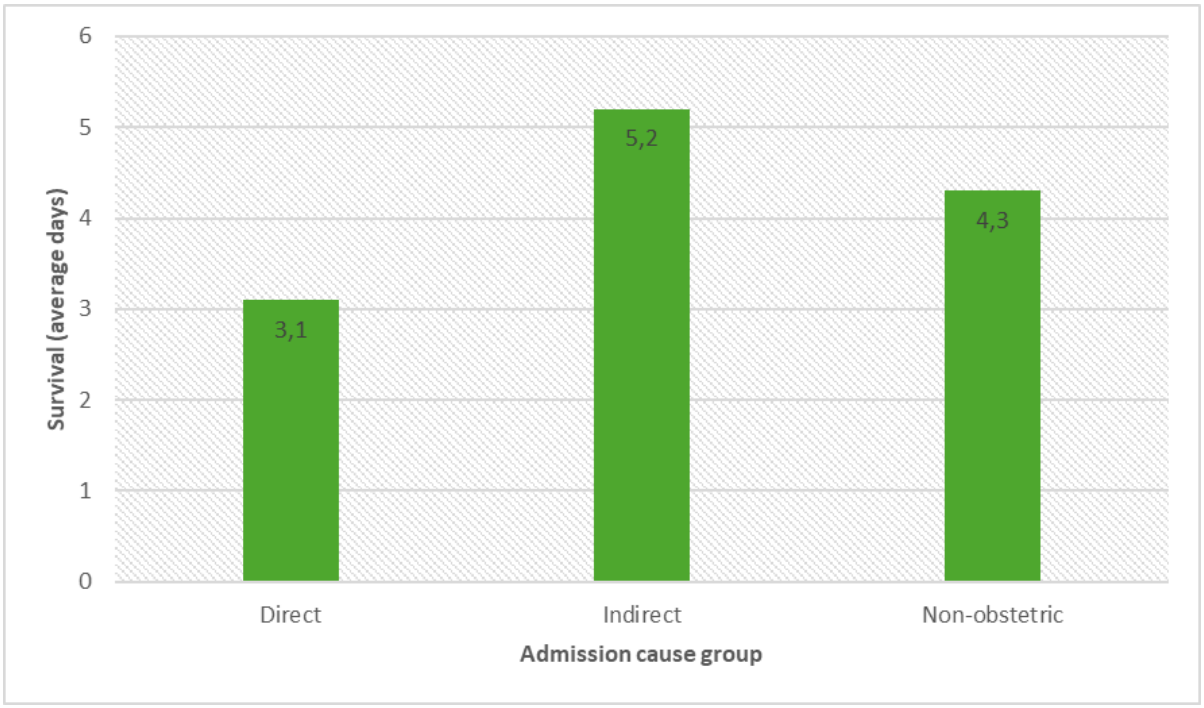
M: medium; SD: standard deviation; *: attended in the postpartum period (81.8%)
Source: Own preparation

Regarding the admission cause group, a statistically significant difference was observed between the distributions of the women's average length of stay (p=0.010; Kruskal-Wallis Test), with the greatest difference found for indirect causes, showing an average that was 2.1 days longer compared to direct causes and 0.9 days longer compared to non-obstetric causes in this sample (Figure 2).



Source: Own preparation

Figure 1 - Correlations between the length of stay and the number of *Near Miss* criteria in women admitted to the intensive care unit (n=456). Teresina, PI, Brazil, 2018



Source: Own preparation

Figure 2 - Medium duration of hospitalization according to the cause of maternal ICU admission (n=456). Teresina, Piauí, Brazil, 2018

In Table 3, prognostic factors related to the pregnant woman, the pregnancy, and complications during the ICU stay are listed. Regarding the analysis of the prognostic factors evaluated in the study, it is noted that patients who did not meet Near Miss criteria had a better prognosis ($p< 0.001$).

Table 3 - Relationship between mortality and individual characteristics of women admitted to an intensive care unit (n=456). Teresina, PI, Brazil, 2018

Individual characteristics	Outcome						*p*
	Death		High		Total		
	n	%	n	%	n	%	
Maternal age							0.796q
Pregnant teenager (14 to 19 years old)	3	18.8	91	20.7	94	20.6	
Adult pregnant woman (20 to 35 years old)	10	62.5	292	66.4	302	66.2	
Elderly pregnant woman (> 35 years old)	3	18.8	57	13.0	60	13.2	
Birthplace							0.345q
Teresina	6	37.5	144	32.7	150	32.9	
Other municipalities in Piauí	5	31.3	211	48.0	216	47.4	
Other states	5	31.3	85	19.3	90	19.7	
Origin of hospitalization							0.212q
Own service	1	6.3	87	19.8	88	19.3	
External to the service (metropolitan area)	6	37.5	97	22.0	103	22.6	
External to the service (outside the city)	9	56.3	256	58.2	265	58.1	
Admission Cause Group							0.191q
Direct obstetric	10	62.5	356	80.9	366	80.3	
Indirect obstetrics	5	31.3	69	15.7	74	16.2	
Non-obstetric	1	6.3	15	3.4	16	3.5	
Prenatal							0.173q
Low risk	10	62.5	357	81.1	367	80.5	
High risk	4	25.0	59	13.4	63	13.8	
Didn't do it	2	12.5	24	5.5	26	5.7	
History of previous systemic disease							0.094f
Yes	6	37.5	80	18.2	86	18.9	
No	10	62.5	360	81.8	370	81.1	
Group of primary causes							-
Hypertensive	-	-	253	57.5	253	55.5	
Hemorrhages	3	18.8	80	18.2	83	18.2	
Infections	7	43.8	33	7.5	40	8.8	
Other causes	6	37.5	74	16.8	80	17.5	
Delivery route							0.067f
Vaginal	3	37.5	44	12.1	47	10.3	
Cesarean section	5	62.5	321	87.9	326	71.5	
Time of admission							0.032q
During pregnancy	9	56.3	208	47.3	217	47.6	
Postpartum	4	25.0	209	47.5	213	46.7	
Post-abortion/ectopic pregnancy	3	18.8	23	5.2	26	5.7	
Near Miss clinical criteria							< 0.001q
Yes	15	93.8	113	25.7	128	28.1	
No	1	6.3	327	74.3	328	71.9	
Near Miss laboratory criteria							< 0.001q
Yes	16	100.0	40	9.1	56	12.3	
No	-	-	400	90.9	400	87.7	
Near Miss management criteria							< 0.001q
Yes	16	100.0	72	16.4	88	19.3	
No	-	-	368	83.6	368	80.7	

p: significance of the association; *q*: Pearson's Chi -Square Test; *f*: Fisher's Exact Test; -: did not meet test assumptions

Source: Own preparation

DISCUSSION

In the present study, it was observed that 3.98% of the total obstetric cases treated in the service corresponded to admissions to a maternal ICU. However, when considering only patients admitted from within the service, this frequency drops to 0.2%. In another study conducted in northeastern Brazil, the frequency was 16%, while in Australia/New Zealand, it was 1.3%. Generally, the average admission rate in developed countries is between 0.9% and 1.0%, while in developing countries, it is 2.4%. Several factors could explain the disparity between the figures from Brazilian and Dutch studies, such as the quality of prenatal care, childbirth, and postpartum care, as well as the criteria used for ICU admission. In Brazilian ICUs, one of the admission criteria is eclampsia prophylaxis with magnesium sulfate, with hypertensive conditions, particularly severe preeclampsia, being the primary reason for admission. This discrepancy in numbers between Brazilian and European studies could be justified by this factor. The frequency of ICU admissions relative to the number of deliveries was 49.6 per 1,000 deliveries, a number significantly higher than those in developed countries. It is worth noting that as this is the only maternal ICU in the state and region, most cases admitted to the unit are referred to the service. To accurately calculate this ratio,

information on the number of deliveries from the originating hospitals would be necessary.

Approximately 67% of the admitted patients come from the interior of Piauí or other states, and 80.7% of the women are admitted from outside the service, either from the metropolitan area or outside the city of Teresina, indicating that most patients originate from outside the studied center. Regarding prenatal care, 80.5% of the patients admitted to the ICU were being followed in low-risk prenatal care, highlighting an inadequate risk classification for these pregnant women and demonstrating that many of these women required specialized prenatal care and adequate hospital support.

During the study period, 456 patients were admitted to the ICU. Regarding the groups of causes of admission, 366 (80.3%) patients were admitted for direct obstetric causes, 74 (16.2%) for indirect obstetric causes, and only 16 (3.5%) for non-obstetric causes.

Regarding the main conditions for admission by cause groups, of the 366 patients with direct obstetric causes, 248 (67.8%) were due to hypertensive disorders, 83 (22.7%) due to hemorrhagic syndromes, and 24 (6.6%) due to infection. In the group of indirect obstetric causes, of the 74 admitted patients, 24 (32.4%) had heart disease. In the group of non-obstetric causes, of the 16 patients, 4 (25%) were admitted due to exogenous intoxication from suicide attempts.

Analyzing the 456 women admitted regarding the main diagnoses by cause group, we found that in the group of direct obstetric causes, comprising 366 patients, 248 were hypertensive (67.8%), with 125 patients (34.1%) having severe preeclampsia, 63 (17.2%) eclampsia, and 60 (16.4%) HELLP syndrome. Regarding the 83 patients with hemorrhagic syndromes, the main causes were uterine atony (22 patients - 6%) and placental abruption (20 patients - 5.5%). Regarding infectious conditions, among the 24 admitted women, 19 patients (5.2%) had puerperal infection, and 5 patients (1.4%) had infections from other sites. In the group of indirect obstetric causes, among the 74 patients, 24 (32.4%) were due to heart disease, 11 (14.9%) due to pneumonia, and 9 (12.2%) were admitted due to epilepsy. In the group of non-obstetric causes, among the 16 patients, about 25% were admitted for suicide attempts with exogenous intoxication. The numbers found are consistent with Brazilian and global literature, where the main causes of admission are hypertensive disorders, followed by hemorrhages, infections, and heart disease. The data regarding non-obstetric causes, with suicide attempts being the main cause, reveal the desperation of these women facing an unwanted pregnancy.

Regarding maternal mortality, of the 456 admitted patients, 16 women died, with a mortality rate of 3.5%. Of the total deaths, 10 cases (62.5%) were due to direct obstetric causes, 4 cases (25%) due to indirect obstetric causes, and 1 case (6.3%) due to a non-obstetric cause. The main cause was infection, with 7 deaths (43.8%). Although hypertensive disorders represented the leading cause of admission to the Intensive Care Unit, in our study, no patient died from hypertension[2,10,12,13]. When comparing our numbers with the literature, we observed a mortality rate consistent with that found in a study conducted in southeastern Brazil (4.7%) and lower than that in Indian (33.66%) and African (54.3%) studies[14-16].

The mean age of 26 years ± 7.2 years found in our study was similar to that in several studies in the literature, corresponding to the reproductive age of women, including two Brazilian studies: one conducted in northeastern Brazil, where the mean age was 25 years, and the other in the southeastern region, where the mean age was 27 years[1,13]. Regarding the number of pregnancies, the average was 2.3 ± 1.7 pregnancies. This finding is consistent with the national panorama but differs from other findings in the global literature, where most of the ICU-admitted patients were primigravidae[1,14,16].

Regarding the mode of delivery, 71.5% were cesarean sections. This high number of upper route deliveries aligns with most studies and is related to the need for early pregnancy termination due to severe maternal complications associated with fetal vitality changes in pregnant women, often with an unfavorable cervix for induction[1,5].

Regarding the timing of admission, 52.4% of the patients were admitted during the puerperium. Our numbers are consistent with the literature, where most patients are admitted postpartum. In a center in Minas Gerais, 72.5% of admissions were during the puerperium, and in a study conducted in Recife, 87% were postpartum. Possibly, the blood loss that occurs in the immediate postpartum period, leading to hemodynamic decompensation and the need for pregnancy termination due to complications, may explain these findings[1,17].

Regarding the analysis of prognostic factors related to survival, a statistically significant difference was found between the distributions of the average length of hospital stay for women (p=0.010; Kruskal-Wallis Test), with the most significant difference observed for indirect causes, with an average of 2.1 days longer compared to direct causes and 0.9 days longer than non-obstetric causes in this sample. Thus, patients admitted due to indirect obstetric causes, who are women with pre-existing or pregnancy-developed diseases that worsened due to the physiological changes imposed by pregnancy, had longer hospital stays and worse prognoses. Additionally, statistically significant and direct correlations were found between survival and the number of clinical, laboratory, and management criteria of *Near Miss* as recommended by the WHO[8], such that the higher the number of criteria, the longer the duration of these women's ICU stays. Patients who were admitted and met clinical, laboratory, or management criteria for *Near Miss* had a worse prognosis. Furthermore, it was observed that all maternal death cases met maternal *Near Miss* criteria, highlighting the importance of identifying and managing this condition to reduce maternal mortality.

In this sense, analyzing the health situation of the population served by this intensive care service helps identify patients at higher risk for critical maternal illness. This knowledge allows for the establishment of early and targeted measures for the leading causes of morbidity and mortality, aiding in decision-making and formulating more specific policies for this population.

CONCLUSIONS

The results of this study indicate that direct obstetric

causes, represented by hypertensive disorders of pregnancy, followed by hemorrhagic complications during pregnancy and the postpartum period, and puerperal infections, are the primary indications for admission to obstetric ICUs. Maternal heart disease was identified as the leading indirect obstetric cause of ICU admission. Although admissions due to direct obstetric causes account for most ICU admissions, they are associated with lower morbidity and mortality compared to indirect obstetric and non-obstetric causes, which typically require longer ICU stays due to the need for more interventions. Patients who met the diagnostic criteria for Near Miss events had a worse prognosis compared to those who did not meet such criteria. The mortality rate of patients treated by obstetricians trained in Intensive Care is consistent with the global average described in the literature, suggesting that this model of care could be a viable alternative in regions where there is a shortage of specialists in the care of critically ill patients.

Ethical Considerations: There are no potential conflicts of interest (professional, financial, or direct/indirect benefits) that could have influenced the research results or content. This project was approved by the Research Ethics Committee of the Faculty of Medicine of the University of São Paulo (FMUSP); report number: 1.560.856 (CAAE 56265616.5.0000.0065).

Author Contributions: José Arimatéa dos Santos Júnior: research conception and design, data acquisition and interpretation, critical revision of the manuscript. Rossana Pulcineli Vieira Francisco: data interpretation and critical revision of the manuscript. Bruna Benigna Sales Armstrong: literature review, data acquisition and interpretation, manuscript writing. Vinícius Araújo do Vale: literature review, manuscript writing, and translation.

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