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1 (65) 2023 : 001-12 • RESEARCH ARTICLE

Correlation of clinical characteristics and outcomes of patients admitted to obstetric ICU with micro-angiopathic haemolytic anaemia (MAHA): A 5-year retrospective analysis

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

Aim: The purpose of this study was to review all obstetric patients admitted to ICU in Ain Shams University Maternity Hospital over 5-years period due to thrombotic microangiopathies (SPET, HELLP, HUS, AFLP, TTP), thereby to analyze the frequency, clinical characteristics, interventions, treatment, and maternal and neonatal outcomes.

Patients and methods: We reviewed medical charts of above-mentioned patients.

Results: The patients' age was 30.22 ± 6.24 years, with parity of 3.3±1.16. Most were admitted at postpartum period, and ICU stay was 2.8 ± 1.64 days. Hypertension (24%) and DM (16%) were the most common co-morbidities. The neonatal weight was 2.35 ± 0.82, and the incidence of IUGR was 2.7%. Neonatal weight from AFLP was significantly low. Maternal death occurred in 28 (4.7%) due to HELLP (n=8), HUS (4), undiagnosed (4), AFLP (4), SPET (4), eclampsia (4). Death was due to multi-organ failure, pulmonary emboli, DIC, cerebral hemorrhage and stroke. Regarding the complications, 12 (2%) suffered with eclampsia, 28 (4.7%) with accidental hemorrhage, and 8 (1.3%) with renal failure. The incidence of antepartum Hemorrhage was higher among patients with HUS-TTP than those with PE-Eclampsia-HELLP by 33% for HUS-TTP versus 3.5% for PE-Eclampsia-HELLP. Thus, pregnant patients with TTP-HUS had a greater risk of maternal complications than those with PE-Eclampsia-HELLP.

Conclusion: Some demographic, clinical, and laboratory characteristics could correlate with specific types of MAHA. Physicians should be aware of this.

Keywords: Micro-angiopathic haemolytic anaemia; Obstetric ICU; Preeclamptic toxemia

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Word count: 3819 **Tables:** 25 **Figures:** 01 **References:** 25

Received: 05.08.2022, Manuscript No. gpmp-22-71318; **Editor assigned:** 06.08.2022, PreQC No. P-71318; **Reviewed:** 19.11.2022, QC No. Q-71318; **Revised:** 03.12.2022, Manuscript No. R-71318; **Published:** 29.03.2023

INTRODUCTION

Microangiopathic Hemolytic Anemia (MAHA) refers to anemia caused by destruction of erythrocytes due to physical shearing as a result of passage through small vessels occluded by systemic [1]. Thrombotic microangiopathies (TMA) are a group of related disorders that are characterized by thrombosis of the microvasculature and associated organ dysfunction, and encompass congenital, acquired, and infectious etiologies [1,2].

The primary diagnostic challenge is the differentiation from acute fatty liver of pregnancy (AFLP), preeclampsia or eclampsia and HELLP (hemolysis, elevated liver enzymes, low platelets). Features of PET and HELLP may be the initial presentation prior to the clinical picture evolving and subsequent diagnosis of TTP

or HUS, thus further complicating the diagnostic process. Antiphospholipid syndrome (APS), systemic lupus erythematosus and disseminated intravascular coagulation (DIC) may also present with MAHA picture in association with thrombocytopenia [3].

An important issue for the evaluation of a pregnant or postpartum woman with severe MAHA and thrombocytopenia is to appreciate the relative incidence of PE/HELLP syndrome, TTP, HUS, and AFLP. PE/HELLP syndrome is much more common than either TTP or HUS [2].

Although pregnancy-associated TTP most commonly presents in the third trimester or postpartum period, TTP remains the most likely diagnosis of a TMA presenting in the first trimester. Treatment of MAHA and TMA in pregnancy is based on maternal factors, although fetal wellbeing and viability will dictate the timing of delivery. Presentation of a TMA requires careful review of clinical features and laboratory parameters to aid in differential diagnosis. The primary decision is whether delivery will be associated with remission of the TMA (as in PET or HELLP), or whether plasma exchange (PEX) should be urgently instigated as recovery following delivery is unlikely and there is a risk of multi-organ dysfunction/death [4].

PATIENTS AND METHODS

Type of Study: Retrospective study.

Study Setting: The study was conducted at Ain Shams University Maternity Hospital, Obstetrics ICU.

Study Population: The study population comprises all women admitted to obstetric ICU at Ain Shams University Maternity Hospital, during the last 5 year, with MAHA variants including SPET, HELLP, TTP, AFLP, HUS.

Inclusion criteria:

All obstetric patients admitted to obstetric ICU due to microangiopathic anemia variants which include:

1. Severe preeclampsia (SPET).
2. HELLP syndrome.
3. Acute fatty liver of pregnancy (AFLP).
4. Thrombotic thrombocytopenic purpra(TTP).
5. Heamolytic ureamic syndrome (HUS).

Exclusion criteria:

- Patients admitted to obstetric ICU unit due to other causes

Methods:

This is a retrospective study of consecutive obstetric patients admitted to the ICU of Ain Shams maternity Hospital over a 5-year period from January 2013 to December 2017. Our ICU is a 12 bed closed unit, which admits more than 1000 patients annually.

Patients admitted within the above period was identified using the paper filed database of the Medical Records Department. The admission books of our ICU will also utilized, so as not to miss any eligible patient. The patient records will then be screened to ensure that when admitted, they were pregnant or within 42 days of termination of pregnancy.

Each patient record was reviewed in detail. The data that was retrieved for analysis include demographics (age, smoking and drinking status), comorbidities, obstetric features (parity, detailed antepartum history about current and previous pregnancies as number of abortions, ectopic, living children, still birth, history of accidental hge, gestational HTN or DM, weeks of gestation, antenatal abnormalities as IUGR, macrosomia, oligohydramnios, polyhydraminos, mode of delivery, vital signs including pulse, blood pressure, temperature, oxygen saturation, urine output, and Glasgow Coma Scale score on admission, lowest score during admission and discharge score).

Lab investigations and radiological investigations done to the patients at the time of admission and during the admission including, urinalysis, FBC and blood film, reticulocytes, schistocytes, clotting screen, urea and electrolytes, liver function tests, lactate dehydrogenase, FDPs, fibrinogen level, D-dimer, assessment of fetal wellbeing (age, weight, APGAR score at 1 and 5 minutes from delivery, and fetal outcome.

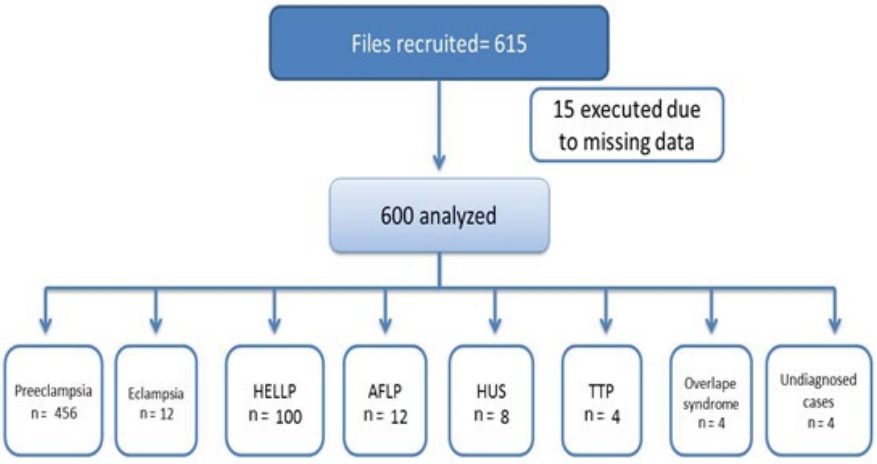
RESULTS

Our obstetric ICU admit more than 1000 patients annually. This study was a retrospective record based study that included 615 files from the year 2013 to the year 2017. Fifteen files were excluded due to missing data and lack of registration sufficiency. The data collection process is shown in **fig. 1.**

Descriptive analysis:

Demographic data of the population of the studied files are represented in **Tab. 1. Tab. 2.** shows the obstetric history represented by number of parity and abortions in the studied population. Fifty nine percent of the women of the included files were multiparous (para 1-5), while 40.6% were nulliparous. **Tab. 3.** shows prevalence of relevant medical diseases in the study population. Twenty four percent of the patients were hypertensive, 16% diabetic, 12% had autoimmune disease mostly was systemic lupus erythematous. **Tab. 4.** shows obstetric complications of the study population. Gestational hypertension was more common than gestational diabetes, antepartum haemorrhage occurred in about 4.7% of the study population. **Tab. 5.** shows mode of delivery of the study population. Regarding operative complications and mode of delivery 92.7% of the patients of the studied files were delivered by caesarean section, 24% delivered by normal vaginal delivery. **Tab. 6. & 7.** Shows ICU data and different lab investigations collected from the files of the studied population. Mean systolic B/P at the time of

Fig. 1. Data collection flow chart.



Tab. 1. Demographic data.

Variables		No.=600
Age	Mean ± SD	30.27 ± 6.25
	Range	20–40
Special habit	No	584 (97.3%)
	Smoker	16 (2.7%)

Tab. 2. Obstetric history.

Variables		No.=600
Parity	PO(previous miscarriage)	80 (13.3%)
	PG	164 (27.3%)
	P(1-3)	288 (48.0%)
	P(4-5)	68 (11.3%)
Abortion	Median(IQR)	3.00 (2-4)
	Range	1.00–10.00

Tab. 3. Prevalence of relevant medical diseases in the whole study population.

Variables		No.=600
Hypertension.	No	456 (76.0%)
	Yes	144 (24.0%)
Diabetes mellitus.	No	504 (84.0%)
	Yes	96 (16.0%)
Auto immune disease	No	588 (98.0%)
	SLE	12 (2.0%)
Gestational Age	Mean ± SD	33.42 ± 3.98
	Range	22.2–40

Tab. 4. Obstetric complications.

Variables		No.	%
Gestational diabetes	No	572	95.3%
	Yes	28	4.7%
Gestational hypertension	No	564	94.0%
	Yes	36	6.0%
Ante partum haemorrhage	No	568	95.3%
	Yes	28	4.7%

Tab. 5. Mode of delivery.

Variables		No.	%
Mode OF Delivery	LSCS	556	92.7%
	NVD	24	4.0%
	Suction evacuation	8	1.3%
	CS Hysterectomy	4	0.7%
	D & C	4	0.7%
	Hystrotomy	4	0.7%

Tab. 6. ICU data.

Variables		No.=600
Highest ICU PULSE	Mean ± SD	97.05 ± 9.05
	Range	80–120
Highest ICU Systolic Blood pressure.	Mean ± SD	176.00 ± 21.71
	Range	110–220
Highest ICU Diastolic Blood pressure	Mean ± SD	105.60 ± 13.75
	Range	70–160
Highest ICU Temperature.	Mean ± SD	37.00 ± 0.36
	Range	36.5–39
Lowest ICU Urine output/hour	Mean ± SD	59.70 ± 15.84
	Range	40–110
ICU Glasgow base	Mean ± SD	11.37 ± 1.87
	Range	3–14
Glasgow lowest	Mean ± SD	11.11 ± 1.54
	Range	3–14
Glasgow discharge*	Mean ± SD	13.40 ± 2.36
	Range	3–15
Duration of ICU stay (day)	Median (IQR)	2 (1-2)
	Range	0–17
*Discharge refers to improvement or death.		

Tab. 7. Lab investigations.

Variables		No.=600
Lowest Hb	Mean ± SD	9.08 ± 0.97
	Range	6.5–11
Hb at discharge	Mean ± SD	9.97 ± 0.96
	Range	6–11.9
TLC	Mean ± SD	11.43 ± 4.02
	Range	5.8–22.5
Lowest PLT	Mean ± SD	173.79 ± 72.87
	Range	47–401
PLT at discharge	Mean ± SD	197.37 ± 55.97
	Range	23–389
Albumin in urine at admission	ALB nil	16 (2.7%)
	ALB +	64 (10.7%)
	ALB ++	268 (45.0%)
	ALB +++	232 (38.9%)
	ALB trace	16 (2.7%)
Highest Clotting INR	Mean ± SD	1.01 ± 0.15
	Range	0.7–2.24
Highest Urea	Median (IQR)	40 (32-50)
	Range	14–300
Highest Serum Creatnine	Median (IQR)	0.9 (0.8–10.3)
	Range	0.5–10.3
Serum Creatnine at discharge	Median (IQR)	0.9 (0.9–1)
	Range	0.6–8
Highest ALT	Median (IQR)	44 (22-90)
	Range	9–340
ALT at discharge	Median (IQR)	26 (20–34)
	Range	11–410
Highest AST	Median (IQR)	29 (17-89)
	Range	7–410
AST at discharge	Median (IQR)	26.5 (22–33)
	Range	7–433
Highest LDH	Median (IQR)	507 (275.5-667)
	Range	180–5268

admission was 176.00 ± 21.71 systolic and diastolic B/P 105.60 ± 13.75. Mean of the lowest Glasgow coma score was 11.11 ± 1.54 and at discharge which refers to either improvement of the patient or death was 13.40 ± 2.36. The average length of ICU stay was 2 days. Range from 1 day to 17 days.

Lab investigations:

Mean of Hb at the time of admission was 9.08 ± 0.97, at time of discharge 9.97 ± 0.96. Mean of PLT at time of admission 173.79 ± 72.87 at time of discharge 197.37 ± 55.97. Mean of highest serum creatnine was 0.9 (0.8 – 10.3) and at discharge was 0.9 (0.9 – 1). The final diagnosis and maternal outcome of the women of the studied files are represented in table 8. Unfortunately there were 28 deaths among study population. The most common diagnosis was SPET (76%) followed by HELLP syndrome (16.7), while the lowest were TTP, overlap syndrome & undiagnosed MAHA was reported in 0.7% of files. The neonatal outcome of the studied files is represented in **Tab. 8.** Percentage of live birth was 92.4 among them 4.8% were twins. The mean of neonatal weight was 2.35 ± 0.82, with 8% of them was IUFD 2.7% was IUGR as shown (**Tab. 9.). Tab. 10.** Shows that the total number of neonatal deaths is 48 case, 44 cases of them were born to mothers with PE-Eclampsia-HEELP and 4 of them with AFLP. Their gestational ages ranges from 22week to 39week and mean 29 week with neonatal weight ranges from 0.7 kg to 3.2 kg and Mean 2.11 kg.

Comparative analysis

Comparison between study cases regarding demographic data shown in **Tab. 11.** The previous table shows that there was statistically significant difference found between 4 groups of diseases in present study regarding age, AFLP presents more frequent in older age females while TTP/ HUS were more in younger age females. Regarding smoking there was no statistically significant difference found between 4 groups of diseases in present study which means smoking was not risk factor for any of the diseases included in the study. Comparison between study cases regarding parity and number of abortions shown in **Tab. 12**. This table shows that there was statistically significant difference found between 4 groups of diseases in present study regarding number of parity and abortion, AFLP has higher incidence among primigravidas more than multiparas woman, while overlape syndrome and undiagnosed MAHA was higher among multiparus women, also TTP/ HUS was higher among primigravidas than multiparus. Comparison between study cases regarding different medical conditions found among study population shown in **Tab. 13**. The previous table shows that there was statistically significant

Tab. 8. Final diagnosis and maternal outcome.

Variables		No.	%
Outcome	Death	28	4.7%
	Recovery	572	95.3%
Final diagnosis	SPET	456	76.0%
	HELLP	100	16.7%
	AFLP	12	2.0%
	ECLAMPSIA	12	2.0%
	HUS	8	1.3%
	TTP	4	0.7%
	Overlap syndrome	4	0.7%
	Undiagnosed MAHA	4	0.7%

Tab. 9. Neonatal outcome.

Variables		No.=600	
Neo Weight (Kg)	Mean ± SD	2.35 ± 0.82	
	Range	0.5–4	
APGAR score 1 min	Median (IQR)	7 (6-8)	
	Range	4–8	
APGAR score 5min	Median (IQR)	9 (8-9)	
	Range	7–9	
FETAL ANOMALY	No	520	86.7%
	IUFD	48	8.0%
	IUGR	16	2.7%
	Invietable abortion	4	0.7%
	Lost diastolic flow	8	1.3%
	Twin to twin transfusion syndrome	4	0.7%
Number of live birth	No	48	8.4%
	One	504	86.8%
	Two	28	4.8%

Tab. 10. IUFD cases.

IUFD cases		No.=48
Gestational age	Mean ± SD	29.42 ± 4.60
	Range	22.2–39.3
Neonatal weight (Kg)	Mean ± SD	2.11 ± 0.91
	Range	0.7–3.2

Tab. 11. Comparison between study cases regarding demographic data.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
Age	Mean ± SD	30.22 ± 6.24	25.67 ± 4.70	38.50 ± 0.54	32.50 ± 2.67	7.383•	0.000	HS
	Range	20–40	22–32	38–39	30–35			
special habit	No	552 (97.2%)	12 (100.0%)	12 (100.0%)	8 (100.0%)	0.805*	0.848	NS
	Smoker	16 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: One Way ANOVA test; ‡: Kruskal Wallis test

difference found between 4 groups of diseases in present study regarding different medical conditions found in the study population, chronic HTN was found in patients with PE-Eclampsia-HELLP more frequent than patients with AFLP – HUS –TTP, also DM is a risk factor for developing PE-Eclampsia-HELLP but not a risk factor for HUS-TTP among study population. Comparison between study cases regarding different obstetric problems shown in **Tab. 14**. The previous table shows that there was no statistically significant difference found between 4 groups of diseases in present study regarding gestational DM and gestational HTN, However there was statistically significant difference found between 4 groups of diseases in present study regarding the incidence of antepartum Hge, antepartum Hge was higher among patients with HUS-TTP & AFLP than patients with PE-ECLAMPSIA-HELLP. Comparison between study cases regarding mode of delivery shown in **Tab. 15**.

The previous table shows that there was high statistically significant difference found between 4 groups of diseases in present study regarding mode of delivery, patients with AFLP,HUS and TTP all delivered by emergency CS, CS hysterectomy was done in 4 cases diagnosed with overlap syndrome, NVD only found in 24 cases all of them preeclampsia, eclampsia and HELLP syndrome. Comparison between study cases regarding neonatal outcome shown in **Tab. 16**.

The previous table shows that there was high statistically significant difference found between 4 groups of diseases in present study regarding neonatal outcome, IUFD was more in cases with AFLP and Preeclampsia-eclampsia-

Tab. 12. Comparison between study cases regarding parity and number of abortions.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No. =568	No. =8	No. =12	No. =8			
Parity	PO(previous miscarriage)	72 (12.6%)	0 (0.0%)	4 (33.3%)	0 (0.0%)	38.661*	0.000	HS
	PG	152 (26.6%)	8 (66.7%)	8 (66.7%)	0 (0.0%)			
	P(1-3)	280 (49.0%)	4 (33.3%)	0 (0.0%)	4 (50.0%)			
	P(4-5)	64 (11.2%)	0 (0.0%)	0 (0.0%)	4 (50.0%)			
Abortion	Median(IQR)	3.00 (2-4)	-	3.00 (3-3)	1.00 (1-1)	-2.809‡	0.005	HS
	Range	1.00–10.00	-	3.00–3.00	1.00–1.00			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: Chi-square test; ‡: Kruskal Wallis test

Tab. 13. Comparison between study cases regarding different medical conditions found among study population.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
Hypertension	No	428 (75.3%)	12 (100.0%)	12 (100.0%)	4 (50.0%)	9.352*	0.025	S
	Yes	140 (24.5%)	0 (0.0%)	0 (0.0%)	4 (50.0%)			
Diabetes mellitus	No	480 (84.5%)	12 (100.0%)	8 (66.6%)	4 (50.0%)	16.209*	0.001	HS
	Yes	88 (15.4%)	0 (0.0%)	4 (33.3%)	4 (50.0%)			
Auto immune disease	No	556 (97.8%)	12 (100.0%)	12 (100.0%)	8 (100.0%)	0.599*	0.897	NS
	SLE	12 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *:Chi-square test; ‡: Kruskal Wallis test

HELLP syndrome, APGAR score was lowest in AFLP, neonatal weight was significantly low among patients with AFLP. There was also high statistically significant difference found between 4 groups of diseases in present study regarding APGAR score but this difference of no clinical significance. Regarding gestational age there was high statistically significant difference between four groups of diseases in our study, AFLP and overlap syndrome were more frequent at earlier gestational age than preeclampsia and HUS/TTP group. Comparison between study cases as regards ICU data shown in **Tab. 17**.

This table show that that there was statistically significant difference found between 4 groups of diseases in present study regarding ICU data, elevated systolic and diastolic blood pressure was mostly prominent in PE-ECLAMPSIA-HELLP group more than other groups. GALASCOW coma scale base and at discharge was significant low in patients with AFLP than other groups. Urine output was lowest in patients with HUS and TTP.

Comparison between study cases as regard haemoglobin level & INR shown in **Tab. 18**. This table show that there was high statistically significant difference found between 4 groups of diseases in present study regarding haemoglobin level at time of admission and discharge, Hb was lowest in patient with TTP&HUS, also INR was highest in patients with overlap syndrome then AFLP. Comparison between HELLP, HUS and TTP regarding PLT level lowest and at discharge **(Tab. 19.)**. This table shows that there was high statistically significant increase in the lowest PLT level in cases with HUS and TTP than those cases with HELLP and at discharge PLT level was lowest in HUS then in TTP highest in HELLP. with p-value=0.00. **Tab. 20.** shows that there was high statistically significant difference found between 4 groups of diseases in present study regarding kidney function tests, serum creatnine level was highest in patients with overlap syndrome and HUS at admission to ICU and also at discharge. The median of ALT at time of admission was statically highly significant higher in AFLP patients (p0.000) compared to HUS/TTP and Preeclampsia, eclampsia and HELLP group (**Tab. 21.**). **Tab. 22.** Shows that the median of ALT at time of admission was statically highly significant in cases with AFLP than those cases with SPET and even also at discharge, with p-value=0.00. **Tab. 23**. Shows that there was statistically significant difference found between 4 groups of diseases in present study regarding duration of ICU stay, it was more in patients with AFLP than other groups, also there was statistically significant difference regarding maternal outcome between 4 groups. The maternal death rate was highest in patients with HUS/TTP than other groups by 66% versus 2.1%, 33.3% and 50% for PE-Eclampsia – HELLP, AFLP and Overlap syndrome respectively. Highest recovery was in patients with PE-ECLAMPSIA-HELLP.

Maternal death occurred in 28 cases (4.7%), 8 (7.2%) of them were HELLP syndrome, 4 cases (0.6%) were HUS, 4 cases (0.6%) were undiagnosed cases, 4 cases (0.6%) were AFLP, 4 cases were SPET, 4 cases were Eclampsia. The main causes of death were multi-organ dysfunction, pulmonary emboli, DIC, Cerebral haemorrhage and stroke. Regarding the case fatality rate it was 8% for HELLP, 50% for HUS, 100% for undiagnosed cases & 33% for AFLP.

Poor outcome represented in death, renal failure and the occurrence of fits. **Tab. 24.** shows that there was statistically significant difference in blood pressure regarding the 3 groups with increase in systolic and diastolic blood pressure in cases with eclamptic fits than renal failure cases and maternal deathes with p-value 0.002 and < 0.01 in systolic and diastolic groups respectively.

Also there was statistically significant difference between three poor outcomes regarding Glasgow coma scale at time of discharge, ICU Glasgow scale at admission was high in cases with eclamptic fits than renal failure patients or

Tab. 14. Comparison between study cases regarding different obstetric problems.

Variables		PE-Eclampsia-HELLP		HUS/TTP		AFLP		Overlap syndrome		Test value	P-value	Sig.
		No.	%	No.	%	No.	%	No.	%			
G DM	No	540	95%	12	100.0%	12	100.0%	8	100.0%	1.438	0.697	NS
	Yes	28	4.9%	0	0.0%	0	0.0%	0	0.0%			
GHTN	No	532	93.6%	12	100.0%	12	100.0%	8	100.0%	1.875	0.599	NS
	Yes	36	6.3%	0	0.0%	0	0.0%	0	0.0%			
Ante partum He	No	548	96.5%	8	66.7%	12	100.0%	4	50.0%	60.799	0.000	HS
	Yes	20	3.5%	4	33.3%	0	0.0%	4	50.0%			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test

Tab. 15. Comparison between study cases regarding mode of delivery.

Variables		PE-Eclampsia-HELLP		HUS/TTP		AFLP		Overlap syndrome		Test value	P-value	Sig.
		No.	%	No.	%	No.	%	No.	%			
M OF DELIVERY	LSCS	528	92.9%	12	100.0%	12	100.0%	4	50.0%	299.653	0.000	HS
	NVD	24	4.2%	0	0.0%	0	0.0%	0	0.0%			
	Suction evacuation	8	1.4%	0	0.0%	0	0.0%	0	0.0%			
	CS Hysterectomy	0	0.0%	0	0.0%	0	0.0%	4	50.0%			
	D & C	4	0.7%	0	0.0%	0	0.0%	0	0.0%			
	Hystrotomy	4	0.7%	0	0.0%	0	0.0%	0	0.0%			

Tab. 16. Comparison between study cases regarding neonatal outcome.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
NEO WT (Kg)	Mean ± SD	2.36 ± 0.81	2.73 ± 0.94	1.00 ± 0.11	3.00 ± 0.00	9.287•	0.000	HS
	Range	0.5–4	2–4	0.9–1.1	3–3			
APGAR score 1 min	Median (IQR)	7 (6-8)	7 (7-8)	6 (6-6)	8 (8-8)	15.368‡	0.002	HS
	Range	4–8	7–8	6–6	8–8			
APGAR score 5min	Median (IQR)	9 (8-9)	9 (8-9)	7 (7-7)	9 (9-9)	15.837‡	0.001	HS
	Range	7–9	8–9	7–7	9–9			
FETAL ANOMALY	No	492 (86.6%)	12 (100.0%)	8 (66.6%)	8 (100.0%)	22.526	0.095	NS
	IUFD	44 (7.7%)	0 (0.0%)	4 (33.3%)	0 (0.0%)			
	IUGR	16 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
	Inevitable abortion	4 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
	Lost diastolic flow	8 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
	Twin to twin transfusion syndrome	4 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Number of live birth	No	40 (7.2%)	0 (0.0%)	4 (50.0%)	0 (0.0%)	3.080	0.001	HS
	One	488 (87.8%)	12 (100.0%)	4 (50.0%)	4 (100.0%)			
	Two	28 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Gestational Age	Mean ± SD	33.49 ± 3.91	34.40 ± 4.36	29.30 ± 0.11	30.7 ± 6.84	4.486	0.004	HS
	Range	22.2–40	30–40	29.2–29.4	24.3–37.1			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: One Way ANOVA test; ‡: Kruskal Wallis test

whose died with p-value 0.020 while the lowest Glasgow scale level was greater in maternal death than renal failure and eclamptic fits mothers with p-value 0.168, while the highest glascow coma scale at discharge was in renal failure patients than the other groups with p-value <0.01.

High blood pressure is indicator to developing eclampsia and low galscow coma scale at admission indicate poor prognosis and death. There was statistically significant difference between three poor outcomes regarding creatinine, ALT&AST at discharge, creatinine was highest in patients with renal failure, ALT & AST were highest in patients died. Low Hb level, elevated liver enzymes and elevated serum creatnine indicate poor prognosis and death (**Tab. 25.**).

DISCUSSION

Microangiopathic hemolytic anemia (MAHA) is used to designate any hemolytic anemia related to RBC fragmentation, occurring in association with small vessel disease. The term "thrombotic microangiopathy (TMA)" is also used to describe syndromes characterized by MAHA, thrombocytopenia, and thrombotic lesions in small blood vessels [5].

Most females complete their pregnancy with no

Tab. 17. Comparison between study cases as regards ICU data.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
Highest ICU PULSE	Mean ± SD	96.82 ± 8.83	103.33 ± 4.92	97.50 ± 13.36	104.00 ± 17.10	3.685	0.012	S
	Range	80–120	100–110	85–110	88–120			
Highest ICU SBP	Mean ± SD	177.83 ± 19.63	126.67 ± 4.92	140.00 ± 10.69	155.00 ± 48.11	37.679	0.000	HS
	Range	110–220	120–130	130–150	110–200			
Highest ICU DBP	Mean ± SD	106.57 ± 12.97	80.00 ± 8.53	90.00 ± 10.69	90.00 ± 21.38	24.222	0.000	HS
	Range	70–160	70–90	80–100	70–110			
Highest ICU TEMP	Mean ± SD	36.99 ± 0.33	37.53 ± 1.08	36.90 ± 0.11	36.90 ± 0.11	9.528	0.000	HS
	Range	36.5–39	36.8–39	36.8–37	36.8–37			
Lowest ICU UOP/hour	Mean ± SD	60.28 ± 15.91	45.00 ± 7.39	50.00 ± 10.69	50.00 ± 0.00	5.841	0.001	HS
	Range	40–110	40–55	40–60	50–50			
ICU Glasgow base	Mean ± SD	11.60 ± 1.47	5.33 ± 3.45	8.00 ± 1.07	7.00 ± 1.07	101.861	0.000	HS
	Range	3–14	3–10	7–9	6–8			
Glasgow Lowest	Mean ± SD	11.22 ± 1.37	9.00 ± 0.00	7.50 ± 4.81	10.00 ± 1.07	27.816	0.000	HS
	Range	7–14	9–9	3–12	9–11			
Glasgow Discharge	Mean ± SD	13.68 ± 1.65	6.67 ± 5.42	8.50 ± 5.88	8.50 ± 5.88	82.025	0.000	HS
	Range	3–15	3–14	3–14	3–14			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: One Way ANOVA test

Tab. 18. Comparison between study cases as regard haemoglobin level & INR.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
Lowest Hb	Mean ± SD	9.10 ± 0.91	7.63 ± 1.03	11.00 ± 0.00	8.10 ± 1.18	24.867	0.000	HS
	Range	6.5–11	6.5–8.9	11–11	7–9.2			
Hb at discharge	Mean±SD	10.06 ± 0.80	7.33 ± 1.89	9.75 ± 1.06	7.90 ± 2.69	14.081	0.000	HS
	Range	6–11.9	6–9.5	9–10.5	6–9.8			
Clotting INR	Mean ± SD	0.99 ± 0.11	1.07 ± 0.10	1.25 ± 0.05	2.24 ± 0.00	205.907	0.000	HS
	Range	0.7–1.4	1–1.2	1.2–1.3	2.24–2.24			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *:Chi-square test; •: One Way ANOVA test; ‡: Kruskal Wallis test

Tab. 19. Comparison between HELLP, HUS and TTP regarding PLT level lowest and at discharge.

Variables		HELLP	HUS	TTP	Test value	P-value	Sig.
		No.=100	No.=8	No.=4			
PLT	Mean ± SD	99.88 ± 34.80	147.00 ± 93.01	90.00 ± 0.00	5.176	0.007	HS
	Range	47–210	60–234	90–90			
PLT at discharge	Mean ± SD	165.52 ± 29.13	92.50 ± 40.09	180.00 ± 0.00	23.463	0.000	HS
	Range	55–230	55–130	180–180			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *:Chi-square test; ‡: Kruskal Wallis test

Tab. 20. Shows comparison between study cases as regard kidney function tests.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
Urinary albumin	ALB nil	8 (1.4%)	0 (0.0%)	8 (66.6%)	4 (50.0%)	150.232	0.000	HS
	ALB +	64 (11.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
	ALB ++	256 (45.1%)	4 (33.3%)	4 (33.3%)	4 (50.0%)			
	ALB +++	224 (39.4%)	8 (66.7%)	0 (0.0%)	0 (0.0%)			
	ALB trace	16 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Urea	Median (IQR)	40 (31-50)	135 (130-300)	41.5 (33-50)	50 (50-50)	37.858	0.000	HS
	Range	14–300	130–300	33–50	50–50			
Serum creatnine	Median (IQR)	0.9 (0.8-1)	2 (1.5-2.3	1.8 (1.3-2.3)	2.35 (0.8 -3.9)	50.817	0.000	HS
	Range	0.5–103	1.5–2.3	1.3–2.3	0.8–3.9			
Serum creatnine at discharge **	Median (IQR)	0.9 (0.9–1)	5 (4.2–5.5)	2.25 (1–3.5)	5.15 (4.8–5.5)	73.460	0.000	HS
	Range	0.6–8	4.2–5.5	1–3.5	4.8–5.5			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; •: One Way ANOVA test; ‡: Kruskal Wallis test
** discharge refers to improvement or death or renal failure.

Tab. 21. Comparison between study cases as regard liver function tests.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
ALT	Median (IQR)	40 (22-81)	60 (50-340)	154.5 (119-190)	87.5 (58-117)	20.731	0.000	HS
	Range	9–340	50–340	119–190	58–117			
ALT at discharge	Median (IQR)	25 (20–34)	400 (30–410)	116 (32–200)	126.5 (40–213)	12.384	0.006	HS
	Range	11–323	30–410	32–200	40–213			
AST	Median (IQR)	27 (16-80)	65 (44-400)	200 (175-225)	207.5 (31-384)	24.541	0.000	HS
	Range	7–410	44–400	175–225	31–384			
AST at discharge	Median (IQR)	26 (19–33)	420 (25–433)	126.5 (36–217)	194.5 (33–356)	11.434	0.010	S
	Range	7–354	25–433	36–217	33-356			
LDH	Median (IQR)	350 (211-600)	2951 (634-5268)	621 (542-700)	600 (600-600)	19.743	0.000	HS
	Range	180–943	634–5268	542–700	600–600			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; •: One Way ANOVA test; ‡: Kruskal Wallis test

Tab. 22. Comparison between SPET and AFLP regarding liver enzymes.

Variables		SPET	AFLP	Test value	P-value	Sig.
		No.=456	No.=12			
ALT	Median (IQR)	30 (19–60)	190 (119–190)	-5.056	0.000	HS
	Range	9–340	119–190			
AST	Median (IQR)	21 (15–63)	175 (175–225)	-5.126	0.000	HS
	Range	7–410	175–225			
ALT at discharge	Median (IQR)	25 (19–32)	41 (32–200)	-4.814	0.000	HS
	Range	11–154	32–200			
AST at discharge	Median (IQR)	25 (19–32)	36 (32–217)	-4.557	0.000	HS
	Range	7–123	32–217			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; ‡: Kruskal Wallis test

Tab. 23. Shows comparison between study cases regarding duration of ICU stay and maternal outcome.

Variables		PE-Eclampsia-HELLP	HUS/TTP	AFLP	Overlap syndrome	Test value	P-value	Sig.
		No.=568	No.=12	No.=12	No.=8			
Duration of ICU (day)	Median(IQR)	2 (1-2)	3 (2-9)	9 (1-17)	2 (1-3)	14.048‡	0.003	HS
	Range	0–17	2–9	1–17	1–3			
Outcome	Death	12 (2.1%)	8 (66.6%)	4 (33.3%)	4 (50.0%)	186.078*	0.000	HS
	Recovery	556 (97.8%)	4 (33.3%)	8 (66.6%)	4 (50.0%)			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; ‡: Kruskal Wallis test

Tab. 24. Shows correlation between clinical data and poor outcome.

Variables		Outcome			Test value•	P-value	Sig.
		Death	Renal failure	Fits			
		No.=24	No.=8	No.=12			
ICU systolic blood pressure	Mean ± SD	150.00 ± 36.83	115.00 ± 5.35	163.33 ± 9.85	7.328	0.002	HS
	Range	110–200	110–120	150–170			
ICU diastolic Blood pressure	Mean ± SD	90.00 ± 15.60	70.00 ± 0.00	106.67 ± 4.92	22.702	0.000	HS
	Range	70–110	70–70	100–110			
ICU Glasgow BASE	Mean ± SD	6.00 ± 2.36	8.00 ± 2.14	7.67 ± 0.98	4.310	0.020	S
	Range	3–9	6–10	7–9			
Glasgow LOWEST	Mean ± SD	8.17 ± 2.53	10.00 ± 1.07	8.67 ± 2.46	1.864	0.168	NS
	Range	3–11	9–11	7–12			
Glasgow discharge	Mean ± SD	4.83 ± 4.19	14.00 ± 0.00	9.67 ± 4.92	17.151	0.000	HS
	Range	3–5	14–14	3–13			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: One Way ANOVA test

complications, yet a few of them develop unexpected events due to pregnancy and require ICU care [6]. There are several studies discussing indications for admission, interventions and outcome of critically ill obstetric patients admitted in the intensive care unit, but there are few studies discuss criteria of patients admitted to obstetric ICU for MAHA variants.

Tab. 25. Showing correlation between laboratory finding and poor outcome.

Variables		Outcome			Test value	P-value	Sig.
		Death	Renal failure	Fits			
		No.=24	No.=8	No.=12			
Hb	Mean ± SD	8.53 ± 1.68	9.05 ± 0.16	10.00 ± 0.74	4.962•	0.012	S
	Range	6.5–11	8.9–9.2	9.5–11			
PLT	Mean ± SD	151.00 ± 92.15	185.50 ± 102.09	123.33 ± 4.92	1.423•	0.253	NS
	Range	55–281	90–281	120–130			
Creat at discharge	Median(IQR)	3.85(3.2-5)	5.15(4.8-5.5)	1(0.9-2.5)	29.125‡	0.000	HS
	Range	2.9–5.5	4.8–5.5	0.9–2.5			
ALT at discharge	Median(IQR)	268(200-400)	35(30-40)	43(37-250)	23.976‡	0.000	HS
	Range	154–410	30–40	37–250			
AST at discharge	Median(IQR)	355(217-420)	29(25-33)	35(26-234)	26.777‡	0.000	HS
	Range	123–433	25–33	26–234			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: One Way ANOVA test; ‡: Kruskal Wallis test

In present study; the most common reasons for ICU admission were preeclampsia and HELLP (92.7%), followed by Eclampsia (2%) and AFLP (2%), then HUS (1.3%), TTP (0.7%), whereas overlap syndrome &cases which we could not reach a final diagnosis represented (1.4)%.

The mean maternal age for patients admitted with HELLP syndrome in the study was 30.22 ± 6.24 years at the time of presentation which was in agreement with what Cappell reported in his study [7]. The mean age of our patients with TTP at time of presentation was 25.67 ± 4.70 years and that was in contrast to the same author who reported a mean age of 40 years at time of presentation. AFLP presents more frequent in older age females while TTP/HUS were more in younger age females. The mean distribution of age in the patients of the current study was 30.22 ± 6.24 years, while in the study conducted by Ashraf N, et al. [8] this was 26.34 ± 5.34years, and in that of Lin this was 31 years [9]. This variation might be due to differences in cultures that effect age of marriage.

Regarding the past obstetric history of present study population, the mean parity was 3.3 ± 1.16. In our cases, AFLP has higher incidence among primigravidas more than multiparas woman, 60% were primigravida, while overlap syndrome and undiagnosed MAHA was higher among multiparous women all 8 cases with overlap syndrome and undiagnosed MAHA were multiparas. Also, TTP HUS was higher among primigravidas than multiparous (8 cases were primigravidas, while 4 cases were multiparous).

Most of the patients in present study were admitted at post-partum period. However, in the study of Ashraf N, et al. [8]; the majority of their patients were admitted during the antepartum period. On the other hand, most of the authors reported a higher incidence of postpartum admission [8,9]. This might be related to hemodynamic changes in the postpartum period, including plasma oncotic pressure changes, increase in cardiac output and acute blood loss during delivery that might precipitate MAHA complications [10,11].

The average length of ICU stays in our cases was 2.8 ± 1.64 days which was comparable to other studies such as [12,13]. Patients with AFLP had the highest duration of stay in the ICU among all other variants of MAHA (median was 9 days – range from one day to 17 days), while preeclampsia- eclampsia and HELLP syndrome have the lowest duration of ICU stay (median 2 days).

This reported incidence of IUGR in present study is lower than that reported by other studies, who reported incidence of IUGR was 27.5% among patients with preeclampsia –eclampsia and HELLP syndrome and Chandil N, et al. [14]. In present study we also found that 28 cases (33.7%) were complicated by pre-term labor. this was lower than that reported by Haram K, et al. [15] who reported that incidence of preterm labour was 65% for HELLP syndrome patients, with a mean gestation at delivery of 33.5 weeks. Also, Egerman RS, et al. [16] reported an incidence of pre-term labor 62.5% for TTP patients.

Present study showed that maternal death occurred in 28 cases (4.7%), 8 (1.3%) of them were HELLP syndrome, 4 cases (0.6%) were HUS, 4 cases (0.6%) were undiagnosed cases, 4 cases (0.6%) were AFLP. However, when the case fatality rates were calculated it was 8% for HELLP, 50% for HUS, 100% for undiagnosed cases & 33% for AFLP. This was comparable to Vigil-de Gracia P, et al. [17] who reported that mortality rate in AFLP was 11.4% and was in agreement with that reported by Noris M and Remuzzi G [18] who reported maternal mortality related to HUS was 50-60%.

In another retrospective cohort study comprising 442 pregnancies complicated by the HELLP syndrome, the overall maternal mortality was 1.1% [19]. However, higher maternal mortality (up to 25%) has been reported by Aslan H, et al. [20]. The main causes of death were multi-organ dysfunction, pulmonary emboli, DIC and cerebral hemorrhage

Regarding risk factors among study population smoking was found not to be a risk factor for any of the diseases included in the study. This was in agreement with Mostello D, et al. [21] who reported that Smoking was protective from devolving preeclampsia.

In present study renal failure occurred in 8 cases 4 of them was HUS patients. In a case series of 442 women with HELLP syndrome, Sibai BM, et al. [19] reported

that 33 (7%) had acute renal failure, defined by creatinine clearance <20 ml/min. However, an earlier report from these authors described acute renal failure in only three of 303 (1%) patients; all three were associated with abruptio placentae and DIC; all recovered normal renal function [19].

Regarding thrombocytopenia and microangiopathic hemolytic anemia, in present study thrombocytopenia was more in TTP, HELLP then in HUS. In another study [22] in which half of women with preeclampsia were thrombocytopenic, half of the thrombocytopenic women had platelet counts <100,000 μL.

Regarding the management of those cases, we found that termination of pregnancy after trial of correction of maternal general condition was done, 556 cases (92.7%) ended by caesarian section and the remaining 24 cases (4.0%) ended by successful vaginal delivery. CS hysterectomy was done in 0.7% of the cases, D&C and suction evacuation were done in 2% of the cases.

This was comparable to Murphy DJ and Stirrat GM [23] who reported incidence of ceaseran section in patients with preeclampsia eclampsia and help syndrome was 80%. Also Zhang Y, et al. [24] who reported incidence of ceaseran section in patients with preeclampsia, eclampsia and HELLP syndrome was 88.258%. In another retrospective study for acute fatty liver in pregnancy Dwivedi S and Runmei M [25] reported 109 (86.5%) pregnancies were terminated by cesarean section and of those cases 14 patients died. Seventeen (13.4%) patients delivered vaginally resulting in 6 deaths. The mortality rate of the mothers who underwent cesarean section (12.8%) was lower than those who delivered vaginally (35.2%).

STRENGTHS AND WEAKNESS OF STUDY

Strengths: The study highlights a clinically challenging, yet rare, situation of a thrombotic microangiopathy in pregnancy. The large number of files recruited (600 files), and the long duration covered (5 years) are points of strength in this study. Additionally the study examined a wide spectrum of different demographic, clinical and laboratory parameters against the development of each type of MAHA and also their correlation to maternal and neonatal morbidity and mortality.

Weakness: Given the retrospective nature of our study, we were unable to trace the long term outcomes of different diseases in the study. Besides, correlations between the risk factors and negative fetal/infant outcomes could not be sufficiently explained. Insufficient data and poor registration were found in some files. Finally the data recruited represent only the magnitude of the problem in our hospital (A tertiary referral centre) which cannot be generalized to the magnitude of the problem in the general obstetric population.

CONCLUSION

Present study concluded that these are acute conditions with significant morbidity and mortality. Certain demographic, clinical and laboratory characteristics could correlate to specific types of MAHA. Additionally, such factors can be used as predictors of prognosis in different MAHA variants. Early diagnosis and termination of pregnancy can result in marked reduction of maternal mortality in such cases.

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