Thieme

The Role of Hypertension for Maternal Outcomes of Women with HELLP Syndrome – a Retrospective Study from a Tertiary Obstetric Center

Die Rolle der Hypertonie für das mütterliche Outcome von Frauen mit HELLP-Syndrom – eine retrospektive Untersuchung aus einem geburtshilflichen Zentrum der Maximalversorgung

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Keywords
HELLP syndrome, arterial hypertension, hypertensive crisis, cardiovascular risk, hypertension in pregnancy

Schlüsselwörter
HELLP-Syndrom, arterielle Hypertonie, hypertensive Krise, kardiovaskuläres Risiko, Hypertonie in der Schwangerschaft

received 18.1.2024
accepted after revision 17.4.2024

Bibliography
Geburtsh Frauenheilk
DOI 10.1055/a-2308-9698
ISSN 0016-5751

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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Supplementary Material is available at https://doi.org/10.1055/a-2308-9698.

ABSTRACT

Introduction
HELLP syndrome is a serious disorder that can occur in pregnancy; it has many possible complications and is associated with adverse maternal outcome. Due to the lack of predictive parameters for HELLP syndrome, finding the right time for delivery is challenging. In contrast to preeclampsia, hypertension is not an essential part of the diagnosis; nevertheless, many women with HELLP syndrome are hypertensive. The role and possible implications of hypertension in HELLP syndrome are not fully understood.

Material and Methods
In this retrospective cohort study, we analyzed the maternal outcomes of 59 patients diagnosed with HELLP syndrome. The patients were divided into three groups according to their blood pressure levels during their stay in hospital. These three groups were compared in terms of patient characteristics and maternal outcomes. A combined endpoint for adverse maternal outcome was defined which included blood pressure and antihypertensive medication at discharge from hospital, severe postpartum anemia, and eclampsia.

Results
Women with hypertensive crises had an unfavorable outcome compared to women with lower blood pressure levels. Patients with higher blood pressure during pregnancy were more likely to be hypertensive at discharge and needed a combination of antihypertensive agents significantly more often. The risk of an adverse maternal outcome increased with the severity of hypertension. An increase in systolic blood pressure by 10 mmHg raised the risk of an adverse outcome by 74 % (95 % CI: 1.22–2.66).

Conclusion
Hypertension not only plays an important role in preeclampsia but also affects the outcomes of patients with HELLP syndrome. These patients need to be identified quickly and treated accordingly as they are at risk of cardiovascular impairment. Patients should be followed up closely after delivery to reduce cardiovascular morbidity.

ZUSAMMENFASSUNG

Einleitung
Das HELLP-Syndrom stellt eine ernsthafte Schwangerschaftserkrankung dar; es ist mit vielen potenziellen Komplikationen behaftet und geht mit ungünstigen mütterlichen Outcomes einher. Da es an prädiktiven Parametern für das HELLP-Syndrom fehlt, ist es schwierig, den richtigen Zeitpunkt für die Entbindung zu ermitteln. Im Gegensatz zur Präeklampsie stellt das Auftreten einer Hypertonie keinen Bestandteil der Diagnose HELLP-Syndrom dar, dennoch haben viele Frauen mit HELLP-Syndrom Bluthochdruck. Die Rolle und die möglichen Implikationen einer Hypertonie beim HELLP-Syndrom sind noch nicht vollständig erforscht.

Material und Methoden
In dieser retrospektiven Kohortenstudie haben wir die mütterlichen Outcomes von 59 Patientinnen mit HELLP-Syndrom analysiert. Die Patientinnen wurden in 3 Gruppen unterteilt entsprechend ihrem jeweiligen Blutdruckniveau während ihres Aufenthalts im Krankenhaus. Die 3 Gruppen wurden bezüglich ihrer Patientencharakteristika und mütterlichen Outcomes verglichen. Es wurde ein kombinierter Endpunkt für ungünstiges mütterliches Outcome definiert, welcher den Blutdruck der Patientin und die Einnahme blutdrucksenkender Medikamente bei der Entlassung aus dem Krankenhaus, starke Anämie postpartal sowie das Auftreten einer Eklampsie einschloss.

Ergebnisse
Frauen mit hypertensiven Krisen hatten ein ungünstigeres mütterliches Outcome verglichen mit Frauen mit niedrigerem Blutdruck. Patientinnen mit Bluthochdruck während der Schwangerschaft hatten eher Bluthochdruck und benötigten signifikant häufiger eine Kombination blutdrucksenkender Mittel bei der Entlassung aus dem Krankenhaus. Das Risiko eines ungünstigen mütterlichen Outcomes nahm mit dem Schweregrad der Hypertonie zu. Eine Erhöhung des systolischen Blutdrucks um 10 mmHg erhöhte das Risiko eines ungünstigen Ergebnisses um 74 % (95 %-KI [1.22–2.66]).

Schlussfolgerung
Die Hypertonie spielt nicht nur bei der Präeklampsie eine wichtige Rolle, sie beeinflusst auch das Outcome von Patientinnen mit HELLP-Syndrom. Diese Patientinnen müssen schnell identifiziert und entsprechend behandelt werden, da sie ein höheres Risiko für kardiovaskuläre Schäden haben. Ein engmaschiges Programm zur Überwachung dieser Patientinnen nach der Entbindung sollte eingeführt werden, um die kardiovaskuläre Morbidität zu senken.

Background

HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome is an important clinical challenge due to the limited therapeutic options and high mortality rates of both mother and child [1, 2, 3, 4]. HELLP syndrome occurs in 0.2–0.8 % of all pregnancies and 70–80 % are associated with preeclampsia [5]. With regards to its etiopathogenesis, there are similarities between hypertensive pregnancy disorders such as preeclampsia and gestational hypertension and HELLP syndrome. Some authors classify HELLP syndrome as a complication of preeclampsia. But although hypertension is mandatory for the definition of preeclampsia, HELLP syndrome can be normotensive [6]. Poor placentation is believed to be responsible for the development of HELLP syndrome as it can lead to systemic inflammatory disorder initiated by the complement system [7]. However, the pathogenesis of HELLP syndrome is still not fully understood, and the only therapy is delivery of the child. Delivery is regularly initiated from 34 weeks of gestational age; between 24 and 34 weeks, the timing of delivery is based on an evaluation of possible neonatal versus maternal morbidity and mortality.

The maternal outcome is often unpredictable, particularly as relapses are common and the course may be progressive [8, 9]. HELLP syndrome mostly occurs between weeks 27 and 37 of gestation. However, up to one third of cases develop postpartum within the first 48 hours after delivery [9]. The clinical symptoms vary and include right-sided epigastric pain, nausea, and hypertension, and neurological symptoms such as visual disturbances and headaches. Possible maternal complications are liver hematoma, rarely leading to hepatic capsular rupture, acute kidney failure, eclampsia, disseminated intravascular coagulation (DIC), intracere-

bral hemorrhage, and hypertensive crises [6]. Complications affecting the course of pregnancy are placental abruption and intrauterine fetal death [2, 3].

Despite its fulminant course and potential for complications, there still is no parameter which can predict the outcome of women with HELLP syndrome. Existing classification systems such as the Tennessee/Mississippi classification are not used in routine clinical care, as there is no reliable correlation between laboratory results and the outcome of women with HELLP syndrome [9, 10, 11]. Therefore, timing the delivery correctly, especially in women with early-onset HELLP syndrome, remains challenging. Decisions are not only based on clinical evidence but on subjective considerations of maternal risk and the child's risk of preterm birth. Thus, clinical markers and an algorithm for decision-making are needed to estimate the severity of the individual course of disease and decide whether prolongation of the pregnancy is justified or delivery should be initiated.

A previous study focusing on preeclampsia pointed out that the likelihood of an adverse maternal outcome is elevated when maternal blood pressure is high [12]. Based on this study, we hypothesized that patients with HELLP syndrome and hypertension have a higher risk of adverse outcomes compared to normotensive patients. This study aims to evaluate the severity of hypertension as a potential marker of maternal outcome in women with HELLP syndrome. Due to the close relationship between HELLP syndrome and preeclampsia, we sought to identify the effect of maternal blood pressure as well as additional associated parameters on the outcome of HELLP patients to optimize individual risk stratification.

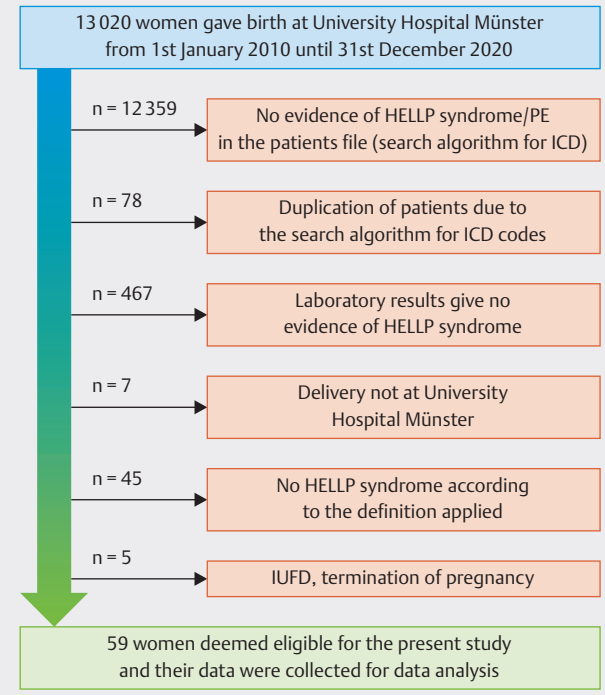
Material and Methods

Patients included in the study and data collection

In this retrospective cohort study carried out at the University Hospital Münster, a tertiary care obstetric center, we reviewed all births between 1 January 2010 and 31 December 2020. This study was designed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the local medical council and the University of Münster (trial no. 2023–074-f-S).

To identify all patients with HELLP syndrome in the hospital's database, we searched the documentation system using the ICD-10 codes O10–O16. These codes include chronic hypertension with complications in pregnancy, hypertensive pregnancy disorders, preeclampsia, eclampsia and HELLP syndrome. We then proceeded as shown in ▶ **Fig. 1** and excluded all duplicates, all patients who did not meet the criteria for a diagnosis of HELLP syndrome, and all patients for whom data was incomplete.

A total of 59 women who met the following diagnostic criteria for HELLP syndrome were included in the study. The criteria for HELLP syndrome listed below are based on the definition of HELLP syndrome of the American College of Obstetricians and Gynecologists (ACOG) and the Tennessee Classification [9, 13]:



▶ **Fig. 1** Flow chart of patients screened and included in the study. Abbreviations: PE = preeclampsia, IUFD = intrauterine fetal death.

- **Low Platelet count**: platelet count < 100 000 cells/µl
- **Hemolysis**: lactate dehydrogenase (LDH) ≥ twice the upper limit for normal values and/or haptoglobin below normal values
- **Elevated liver enzymes**: alanine aminotransferase (GPT) and/or aspartate aminotransferase (GOT) elevated to more than twice the upper limit for normal values.

We excluded three cases of intrauterine fetal death (IUFD) and two terminations of pregnancy (due to maternal conditions) because of incomplete data. These patients were either transferred to our hospital after a diagnosis of IUFD and/or were primarily treated in another department and complete data collection for this study was therefore not possible.

We collected the following data from the clinical records of all patients with HELLP syndrome: demographic data, medical history, blood pressure recordings, laboratory results, clinical symptoms, and obstetric outcomes. The clinical symptoms we focused on were epigastric pain, headaches, hyperreflexia, visual disturbances, and other neurological symptoms (e.g., vomiting, nausea).

Hypertension groups

According to previous studies on maternal outcomes with pre-eclampsia and based on the current international guidelines on arterial hypertension, we divided the patients into three groups according to their maximum prepartum blood pressure [12, 13, 14]:

- Group 1 included all patients with mild to moderate or no hypertension (blood pressure below 160/110 mmHg).
- Group 2 consisted of patients with severe hypertension (systolic blood pressure between 160 and 179 mmHg and/or diastolic pressure between 110 and 119 mmHg)
- Group 3 included patients with hypertensive crisis (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 120 mmHg).

The Results section presents patient characteristics such as mean age, BMI, pre-existing medical conditions, laboratory results, and HELLP-specific symptoms and compares the characteristics of the three hypertension groups. Other presented data include birth and perinatal outcome, including gestational age at delivery, mode of delivery, birth weight, and APGAR score. Maternal outcomes are presented, and blood pressure and antihypertensive medication at discharge from hospital are shown for the different groups, as well as postpartum anemia and eclampsia. Lastly, an individual risk stratification based on maternal outcome and severity of hypertension is discussed.

Endpoint for adverse maternal outcome

A combined endpoint was used to analyze adverse maternal outcomes. The endpoint included the following criteria: blood pressure above 140/90 mmHg at discharge, necessity of anti-hypertensive medication at discharge, postpartum hemoglobin levels below 8 g/dl, or onset of eclampsia as a complication of HELLP syndrome. To confirm our hypothesis, we tested the probability of adverse maternal outcomes in the hypertension groups. Investigations also included analyzing the correlation between systolic and diastolic blood pressure and each outcome parameter individually as well as for the combined endpoint.

Statistical analysis

All statistical calculations were performed using SPSS Statistics, version 28 (IBM, Armonk, NY, USA). Mean values and standard deviation were used for descriptive analysis of continuous variables. Categorical data were expressed as frequencies/percentages. Inferential analyses of differences between the three groups were performed using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis test for non-normally distributed ordinal or continuous variables, and Fisher's exact test for categorical variables. In addition, the datasets for the hypertension groups were preselected to carry out a pairwise Fisher's exact test to compare significant variables between the groups. Using closed testing procedures, all non-significant variables were not tested pairwise [15]. Univariable binary logistic regression was done to evaluate the statistical relationship between blood pressure and adverse maternal outcome. The Box–Tidwell test was performed to verify linearity as an assumption for logistic regression. A p value ≤ 0.05 was considered statistically significant for all statistical tests. The results should be considered as exploratory as no adjustment for multiple testing was done.

The program R (The R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/) was used to plot the odds ratios in forest plots.

Results

Patient characteristics

The prevalence of HELLP syndrome in all women who gave birth in University Hospital Münster between 2010 and 2020 was 0.45 %.

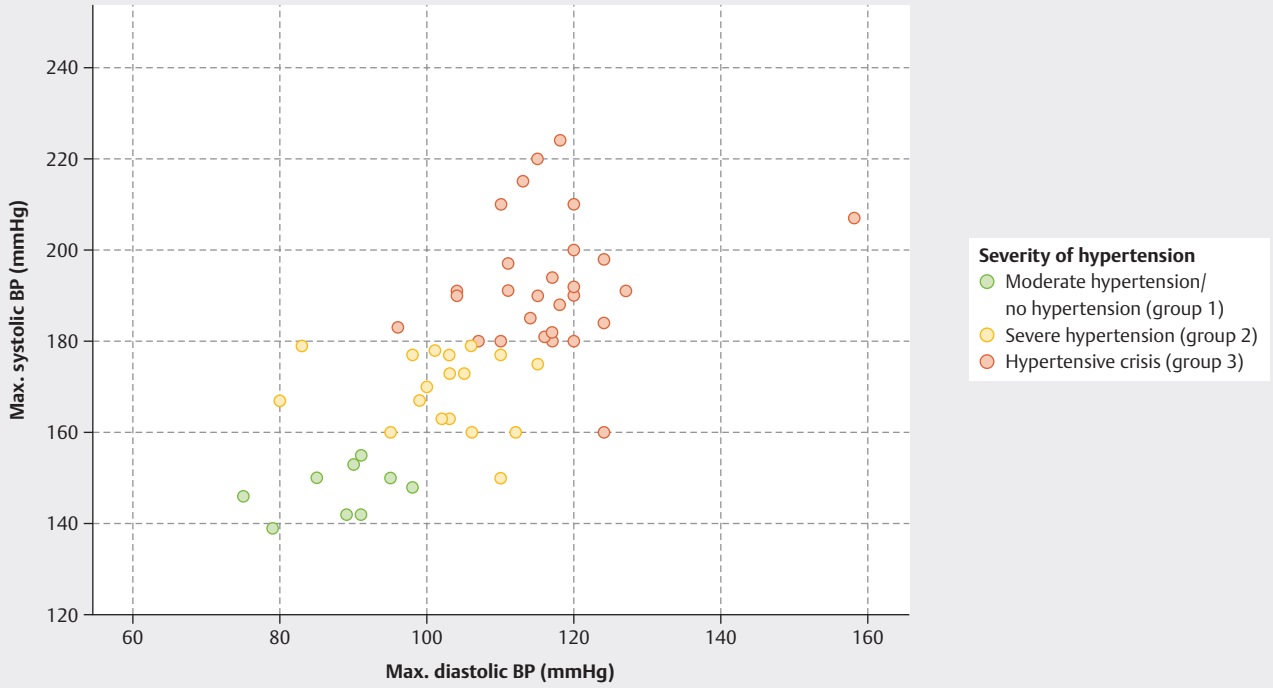
The mean maternal age of the study population of 59 patients with HELLP syndrome was 31.27 ± 4.54 years. The mean BMI was 26.80 ± 5.42 kg/m^2; 22 % of patients had a preconception BMI of more than 30 kg/m^2. Most women were primiparous (66.1 %) and had no pre-existing medical conditions (66.1 %). Five of seven women (11.9 %) with a history of pre-existing hypertension were on long-term antihypertensive medication prepartum. 10.2 % of patients had a coagulation disorder and three women had suffered from thrombosis in the past. While none of the patients had pre-existing diabetes, three developed gestational diabetes in pregnancy. One out of five pregnancies in our cohort was conceived by assisted reproductive technology. There were nine twin pregnancies (15.3 %) and 14 cases with fetal growth restriction (23.7 %). Fifteen patients (25.4 %) developed HELLP syndrome peri- or postpartum.

Mean systolic blood pressure was 178.53 mmHg ± 20.42 and mean diastolic blood pressure was 107.69 mmHg ± 14.13. The most common symptom was right upper quadrant abdominal pain or epigastric pain (72.9 %), and 59.3 % of all women suffered from headaches. Visual impairment (15.3 %), hyperreflexia (18.6 %), and other neurological symptoms (15.3 %) were less common. In total, 7 cases (11.9 %) had none of the above-listed symptoms.

With regards to HELLP-specific laboratory results, all patients showed distinct deviations from the norm, as this was part of the inclusion criteria. The mean value of the lowest platelet level measured during the hospital stay was 55.5 × 10^3/µl ± 20.43. The mean value of the highest measured GPT levels was 484.78 U/l ± 887.39 and the mean value of the highest LDH levels was 1266.03 U/l ± 1596.80. In addition, 23.7 % of women had elevated creatinine levels above the upper limit of normal.

IUFD/termination of pregnancy due to HELLP syndrome

Due to incomplete data, patients with IUFD or termination of pregnancy were not included in the statistical analysis. The mean age of these patients (n = 5) was 32.4 ± 5.13 years, and their mean BMI was 24.5 ± 3.87 kg/m^2. All patients were primiparous. The mean gestational age was 21 + 4 weeks. One patient had a pre-existing chronic kidney disease and the fetus of one patient had a congenital malformation. In the hypertension groups, one patient had mild to moderate hypertension, one had severe hypertension and three patients experienced hypertensive crises.



▶ **Fig. 2** Scatterplot of systolic and diastolic blood pressure levels for each group according to the severity of hypertension. Each marker represents one patient. Abbreviation: BP = blood pressure.

Patient characteristics in the hypertension groups

Patients were divided into three groups, according to the highest blood pressure measured before delivery: eight patients (15.25 %) had mild to moderate hypertension and one patient was normotensive (Group 1). Nineteen patients (32.20 %) had severe hypertension (Group 2), and 31 patients (52.54 %) experienced at least one hypertensive crisis during pregnancy (Group 3). ▶ **Fig. 2** shows the systolic and diastolic blood pressure of every patient in each hypertension group.

The demographic data of the different blood pressure groups are displayed in ▶ **Table 1**. Most parameters did not differ significantly between groups. When analyzing clinical symptoms, women with a hypertensive crisis were more likely to develop headaches (p = 0.039).

Birth and perinatal outcome

The mean gestational age at delivery was 33 weeks + 6 days. In total, 72.88 % of births were preterm deliveries and 49.15 % of all births were delivered early due to HELLP syndrome. In 76.27 % of cases, delivery was by cesarean section. The mode of delivery in the different hypertension groups is shown in ▶ **Table 2**. The mean time between the diagnosis of HELLP syndrome and delivery was 2.78 ± 5.75 days. As regards the perinatal outcome, 44 newborns (74.58 %) were admitted to the neonatal care unit. The mean birth weight was 2020.03 ± 961.52 g and the mean birth weight percentile was 28.72 ± 21.43. Mean umbilical cord arterial pH was 7.25 ± 0.11, but 27.11 % of all newborns had pH levels of less than 7.2. Fourteen newborns (23.73 %) had an APGAR score of less than 8 after 5 or 10 minutes. When the groups were compared, no significant differences were found between groups (see ▶ **Table 2** for details and p values).

Adverse maternal outcome

78 % of patients had an adverse maternal outcome as defined by the criteria given above. Five women developed eclampsia (8.5 %; two patients from Group 1 and three patients from Group 3). 81.4 % of patients received intravenous magnesium as prophylaxis against eclampsia. If magnesium was indicated, it was administered for at least 24 hours postpartum. Severe postpartum anemia (hemoglobin < 8 g/dl) was found in 28.8 % of women. ▶ **Table 3** shows the number of patients in each hypertension group who received intravenous magnesium as well as the number of patients with severe anemia. Online Supplement **Fig. S1** shows how many poor outcome parameters were reached in each hypertension group. Six patients only met one criterion for adverse maternal outcome when they presented with severe postpartum anemia.

Women with hypertensive crises were more likely to have an adverse outcome than women in the other two blood pressure groups. The difference between Group 1 and Group 3 was statistically significant (p = 0.049), see ▶ **Fig. 3** for details.

▶**Table 1** Patient characteristics in the three blood pressure groups.

	Mild to moderate/ no hypertension (Group 1), n = 9	Severe hypertension (Group 2), n = 19	Hypertensive crisis (Group 3), n = 31	p value
Baseline characteristics				
Mean age ± SD	31.22 ± 1.64	31.32 ± 4.92	31.26 ± 4.95	n.s. (p = 0.998)
Mean BMI ± SD	24.80 ± 2.43	27.32 ± 4.60	26.83 ± 6.42	n.s. (p = 0.425)
Pre-existing hypertension	1 (11.1%)	3 (15.8%)	3 (9.7%)	n.s. (p = 0.858)
Antihypertensive medication prepartum	0	1 (5.26%)	4 (12.9%)	n.s. (p = 0.550)
Multiple pregnancies	2 (22.2%)	5 (26.3%)	2 (6.5%)	n.s. (p = 0.110)
Assisted reproduction	0	3 (15.8%)	9 (29.0%)	n.s. (p = 0.160)
Nulliparous	8 (88.9%)	14 (73.7%)	17 (54.8%)	n.s. (p = 0.099)
Symptoms				
No symptoms	1 (11.1%)	4 (21.1%)	2 (6.5%)	n.s. (p = 0.288)
Right upper quadrant abdominal/epigastric pain	6 (66.7%)	12 (63.2%)	25 (80.6%)	n.s. (p = 0.345)
Headache	3 (33.3%)	9 (47.4%)	23 (74.2%)	p = 0.037 p = 0.687 (1 vs. 2) p = 0.044 (1 vs. 3) p = 0.073 (2 vs. 3)
Laboratory findings				
Potassium (mmol/l) ± SD	4.76 ± 0.45	4.86 ± 0.46	4.92 ± 0.40	n.s. (p = 0.491)
Creatinine (mg/dl) ± SD	1.67 ± 1.43	1.02 ± 0.42	1.29 ± 1.36	n.s. (p = 0.604)
Uric acid (mg/dl) ± SD	7.70 ± 2.23	7.50 ± 1.79	7.60 ± 1.46	n.s. (p = 0.953)
GPT (U/l) ± SD	781.11 ± 1683.56	371.16 ± 476.35	468.40 ± 771.79	n.s. (p = 0.989)
LDH (U/l) ± SD	1302.44 ± 1733.34	951.37 ± 890.62	1448.32 ± 1885.47	n.s. (p = 0.243)
Hemoglobin prepartum (g/dl) ± SD	10.64 ± 1.76	10.79 ± 0.92	11.18 ± 1.69	n.s. (p = 0.282)
Hemoglobin postpartum (g/dl) ± SD	8.26 ± 1.47	9.07 ± 1.67	8.92 ± 1.63	n.s. (p = 0.338)
Platelet count (10^3/µl) ± SD	55.30 ± 16.29	53.84 ± 19.90	56.74 ± 22.26	n.s. (p = 0.681)

Abbreviations: GPT = alanine aminotransferase; LDH = lactate dehydrogenase; n.s. = not significant; SD = standard deviation

Blood pressure and antihypertensive medication at discharge from hospital

At discharge, 24 women (40.7%) were hypertensive with blood pressure levels > 140/90 mmHg and 29 women (49.2%) needed antihypertensive medication. When the blood pressure groups were analyzed, patients with higher blood pressure levels during pregnancy were more likely to have persistent hypertension at discharge than patients with lower blood pressure levels during pregnancy (see ▶ **Fig. 4a**). Statistical analysis showed that Group 3 patients were more likely to need a combination of antihypertensive agents at discharge from hospital than women in Group 1 or 2. The difference between blood pressure groups with regards to the number of prescribed antihypertensive agents at the time of discharge was significant (p = 0.013), as shown in ▶ **Fig. 4b**.

Risk stratification

Statistical evaluation showed that the risk of an adverse maternal outcome increased with the severity of hypertension. Women in Group 3 were more likely to meet the criteria for the defined endpoint "adverse maternal outcome". Univariable logistic regression for the endpoint "adverse maternal outcome" showed that an increase in systolic blood pressure of 1 mmHg increased the chances of meeting the criteria for the endpoint by 5.7%. An increase of 10 mmHg raised the risk of an adverse outcome by 74%. The forest plot in ▶ **Fig. 5a** shows an odds ratio of 1.74 (95% CI: 1.22–2.66) as well as the odds ratios for each outcome parameter in relation to a stepwise increase in systolic blood pressure by 10 mmHg. An increase in diastolic blood pressure of 10 mmHg raised the risk of an adverse maternal outcome by 55% (odds ratio = 1.55; 95% CI: 0.99–1.58). The odds ratios for all outcome parameters and for the combined endpoint in relation to diastolic blood pressure are displayed in ▶ **Fig. 5b**.

▶**Table 2** Pregnancy and birth-related characteristics for the three blood pressure groups.

	Mild to moderate/ no hypertension (Group 1), n = 9	Severe hypertension (Group 2), n = 19	Hypertensive crisis (Group 3), n = 31	p value
Pregnancy and birth characteristics				
Gestational age at delivery (weeks) ± SD (days)	36 ± 3.11	33 ± 1.82	33 ± 2.36	n.s. (p = 0.119)
Number of preterm deliveries (%)	5 (55.6%)	14 (73.7%)	24 (77.4%)	n.s. (p = 0.481)
Birth weight ± SD (grams)	2705.00 ± 553.46	1848.79 ± 1066.46	2200.00 ± 650.538	n.s. (p = 0.063)
Umbilical cord arterial pH-value ± SD	7.25 ± 0.12	7.24 ± 0.97	7.25 ± 0.111	n.s. (p = 0.832)
APGAR (5 min) ± SD	8.78 ± 2.05	8.00 ± 1.83	8.23 ± 1.5	n.s. (p = 0.185)
APGAR (10 min) ± SD	9.56 ± 1.01	9.11 ± 0.94	9.13 ± 0.89	n.s. (p = 0.249)
Time between diagnosis and delivery ± SD (days)	1.22 ± 1.986	2.53 ± 3.24	3.39 ± 7.451	n.s. (p = 0.605)
Delivery indicated because of HELLP syndrome (%)	6 (66.7%)	7 (36.8%)	16 (51.6%)	n.s. (p = 0.308)
Mode of delivery				
Cesarean section (%)	5 (55.6%)	15 (79.0%)	25 (80.7%)	n.s. (p = 0.390)
Spontaneous vaginal delivery (%)	2 (22.2%)	1 (5.3%)	5 (16.1%)	
Operative vaginal delivery (%)	2 (22.2%)	3 (15.8%)	1 (3.2%)	

Abbreviations: n.s. = not significant; SD = standard deviation

▶**Table 3** Outcome parameters in the three blood pressure groups.

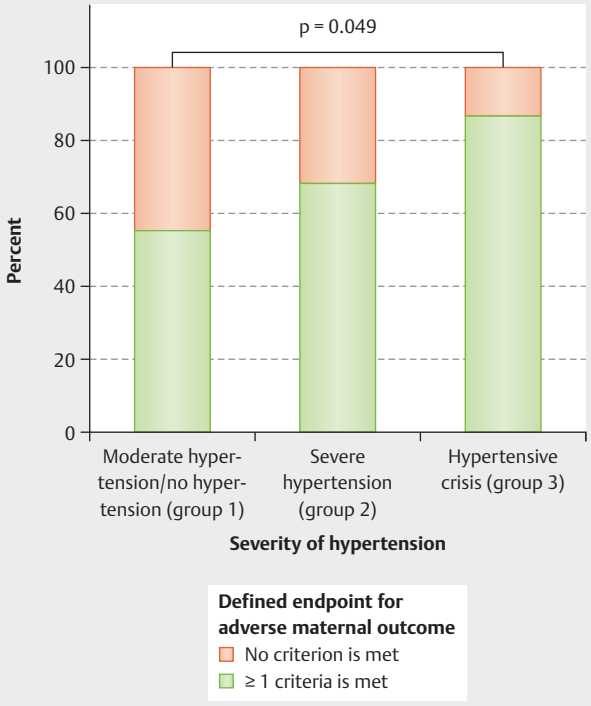
	Mild to moderate/ no hypertension (Group 1), n = 9	Severe hypertension (Group 2), n = 19	Hypertensive crisis (Group 3), n = 31	p value
Intravenous magnesium (%)	6 (66.7%)	15 (79.0%)	27 (87.1%)	n.s. (p = 0.351)
Number of patients with eclampsia (%)	2 (22.2%)	0	3 (9.7%)	n.s. (p = 0.094)
Number of patients with severe anemia (%)	3 (33.3%)	6 (31.6%)	8 (25.8%)	n.s. (p = 0.791)
Diagnosis of HELLP syndrome postpartum (%)	2 (22.2%)	5 (26.3%)	8 (25.8%)	n.s. (p = 0.308)
Number of outcome criteria of the combined endpoint found in each group				
1	4 (44.4%)	6 (31.6%)	14 (45.2%)	n.s. (p = 0.125)
2	0	6 (31.6%)	11 (35.5%)	
3	0	1 (5.3%)	2 (6.3%)	
4	1 (11.1%)	0	1 (3.2%)	

Abbreviation: n.s. = not significant

Discussion

This study shows that hypertension does not only play an important role in preeclampsia but also in HELLP syndrome and affects patient outcomes. We found that when hypertension increased, women were more likely to have an adverse outcome, were more likely to be hypertensive at discharge and to need antihypertensive medication. According to our analysis, even a small increase in systolic blood pressure significantly increases the chance of an adverse maternal outcome. An increase in diastolic blood pressure did not show this correlation. We suggest that maternal blood pressure could serve as a predictive parameter for adverse outcomes in patients with HELLP syndrome and that this could influence the therapeutic strategy.

To date, the role of elevated blood pressure in women with HELLP syndrome has not been fully understood. HELLP syndrome is considered a subtype or complication of preeclampsia, even



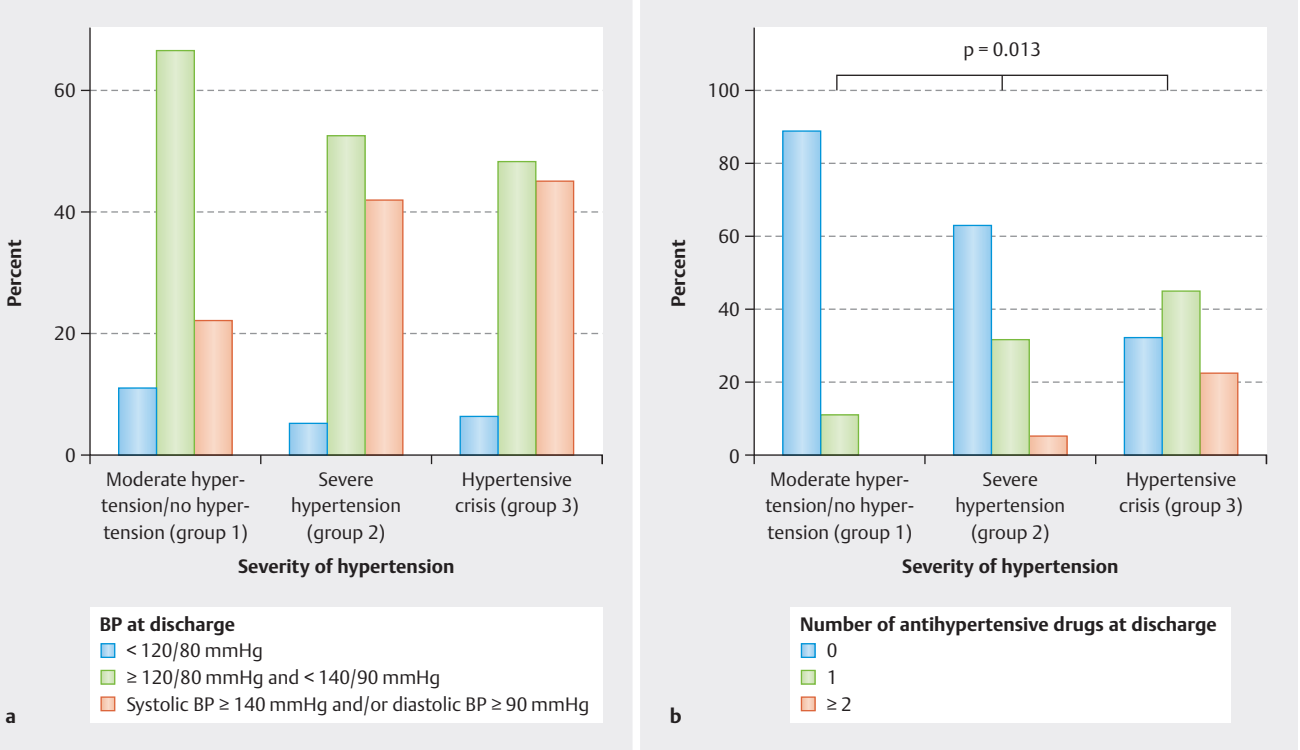
▶ **Fig. 3** Percentage of patients who met the criteria for the combined endpoint "adverse maternal outcome" in each hypertension group. The difference between Group 1 and Group 3 is significant (p = 0.049).

though patients with HELLP syndrome may be normotensive. In our study, almost all patients were hypertensive, and the extent of hypertension seemed to play an important part in maternal outcome. Whether systolic or diastolic blood pressure or a combination of both has the greatest impact cannot be clearly answered based on the data from our study.

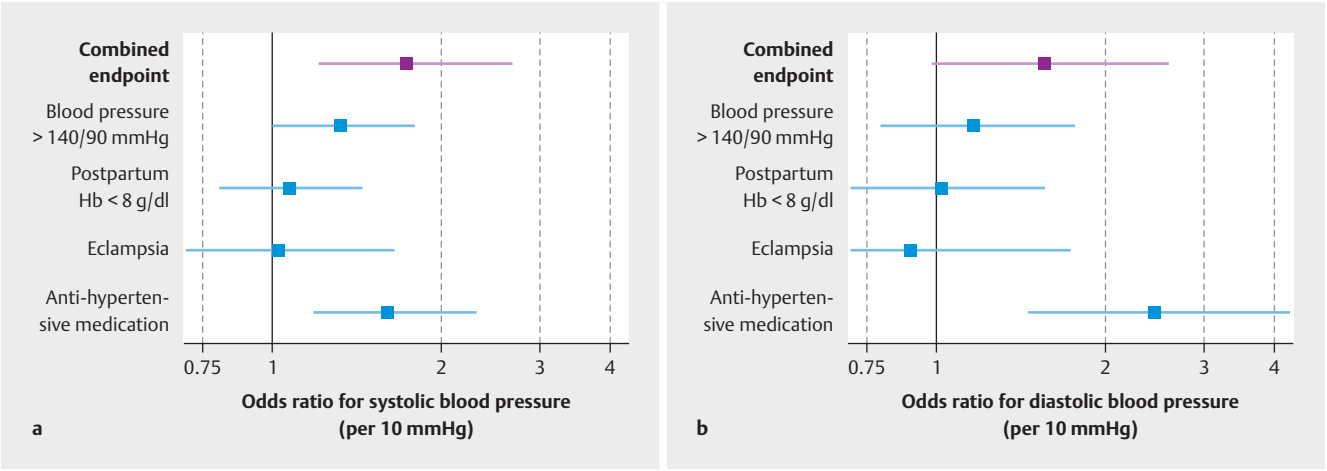
Tita et al. showed that patients with chronic hypertension benefit from antihypertensive therapy during pregnancy, even if hypertension is mild [16]. In the past, most of these patients did not receive antihypertensive medication during pregnancy. It is not clear whether an improvement in maternal outcomes of patients with gestational hypertension and preeclampsia could be achieved by adjusting the indication for antihypertensive treatment. It is also not clear whether close monitoring and strict control of blood pressure could improve maternal outcomes of patients with HELLP syndrome.

In a previous study, we showed that patients with preeclampsia and very high blood pressure during pregnancy developed HELLP syndrome significantly more often than patients with lower blood pressure levels [12]. Therefore, strict blood pressure control might be a possible preventative option to delay or even avoid the severe complications of preeclampsia and related disorders such as HELLP syndrome. Patients' blood pressure levels should be recorded frequently and need to be considered when scheduling delivery.

So far, little attention has been paid to blood pressure as a possible predictive parameter for maternal outcome in HELLP syndrome. Attention has focused on laboratory parameters and clinical symptoms. Aziz et al. noted that laboratory results and clinical



▶ **Fig. 4** Blood pressure levels (**a**) and number of antihypertensive agents prescribed (**b**) at hospital discharge for each blood pressure group. The difference in the number of prescribed antihypertensive agents between the three groups was significant (p = 0.013). Abbreviation: BP = blood pressure.



▶ **Fig. 5** Forest plot showing the increased probability of meeting the criteria for the combined endpoint "adverse maternal outcome" in relation to an increase in blood pressure by 10 mmHg for **a** systolic and **b** diastolic blood pressure. The individual parameters of the combined endpoint are shown in both diagrams. An increase in systolic blood pressure of 10 mmHg raised the risk of an adverse outcome by 74 % (OR = 1.74; 95 % CI: 1.22–2.66), and an increase of diastolic blood pressure by 10 mmHg increased the risk by 55 % (OR = 1.55; 95 % CI: 0.99–1.58).

symptoms were unable to predict maternal outcome but suggested placental factors and underlying medical conditions could play a role in adverse maternal outcomes [17]. Due to the rather small study population of 74 women and the subjectivity of clinical symptoms, the power of their study is limited. In contrast, Miranda et al. were able to show a correlation between the severity of symptoms and the rate of maternal complications. Postpartum onset of symptoms seemed to be particularly associated with a more adverse outcome [18]. Lind Malte et al. evaluated a combination of sFlt-1, CT-pro-ET-1, and blood pressure to predict the course of severe preeclampsia and HELLP syndrome. The authors suggested that a combination of these parameters could be used to identify patients at risk for progression [19]. Placental factors such as sFlt-1, PlGF, and sFlt-1/PlGF ratio are already used and being discussed as predictors for maternal outcome in patients with preeclampsia [20].

The high number of patients in our cohort with eclampsia (n = 5) emphasizes the need for improved risk stratification. According to our hypothesis, stricter blood pressure control could lead to more favorable outcomes for patients with HELLP syndrome, especially if blood pressures are very high. An alternative explanation for the high number of adverse outcomes could be the narrow definition of HELLP syndrome we chose for our study, which may have led to a selection bias with a greater inclusion of more severely affected women. Comparable studies include patients who only meet one or two of the diagnostic criteria for HELLP syndrome, also known as partial HELLP syndrome (e.g., the study by Huang et al. [21]).

In addition to the importance of improving the perinatal outcomes of mother and child, long-term follow-up is necessary, as women with a history of preeclampsia face higher cardiovascular risks in later life [12, 13, 22]. Results from previous studies have shown that patients who previously suffered from HELLP syndrome had a higher risk of obstetric complications and a higher risk of recurrence of hypertensive disorders during pregnancy of up to 20.7 % [23, 24, 25]. According to Sibai et al., the risk of hypertension is related to pre-existing hypertension rather than to HELLP syndrome itself. There is also a higher prevalence of cardiovascular impairment such as cardiovascular remodeling including hypertrophy of the left ventricle [26]. Sciatti et al. showed that HELLP syndrome was associated with myocardial dysfunction and impairment of end-systolic elastance due to a larger aorta following HELLP syndrome [27, 28]. They proposed initiating a form of cardiovascular risk management for women with a history of HELLP syndrome. In our study, nearly half of the cohort needed antihypertensive medication at discharge, which demonstrates the importance of cardiovascular follow-up to prevent long-term cardiovascular morbidity in patients with preeclampsia and HELLP syndrome [29]. According to Riemer et al., postpartum lifestyle interventions including aerobic endurance exercise can lower cardiovascular morbidity by having a positive effect on arterial stiffness [30].

One limitation of this study is the small population size. This could be a general problem due to the low prevalence of HELLP syndrome, and the patient populations in comparable studies by Huang et al. and Li et al. were no bigger [21, 31]. In addition, maternal outcome was based on a retrospective analysis and a constructed endpoint with chosen parameters; this cannot portray the full complexity of adverse maternal outcomes. Long-term follow-up is needed to understand more about obstetric complications and the risk of recurrence of HELLP syndrome in subsequent pregnancies as well as the increased risk of cardiovascular disease in general. The indication for antihypertensive treatment in pregnancy is currently changing and the trend is to treat women with mild hypertension as well. The study of Tita et al. showed no increased risk of small-for-gestational-age fetuses when women with mild chronic hypertension were treated with antihypertensive agents [16]. Since our study investigated patients with HELLP syndrome over a longer period (10 years), there was a trend to control blood pressure more strictly in the last years of the study.

But German guidelines on the indications for treatment with antihypertensive agents did not change during this period and neither did the in-house guidelines, therefore we assume that the impact was low [8, 13].

One of the strengths of this study is the clear definition of HELLP syndrome and the focus only on patients with HELLP syndrome. Other studies often did not differentiate between severe preeclampsia and HELLP syndrome. Huang et al. compared patients with preeclampsia complicated by HELLP syndrome with patients with only preeclampsia. He found significant differences in gestational age at onset and in laboratory results, indicating that are independent risk factors for HELLP syndrome [21]. This suggests that HELLP syndrome and preeclampsia cohorts should be evaluated separately. Another problem is that there is no universal consensus regarding the cut-off values of laboratory results or the classification of HELLP syndrome, which makes it difficult to compare different studies on HELLP syndrome. Compared to other studies such as the study by Huang et al. [21], the inclusion criteria in our study were strict (no patients with partial HELLP syndrome). This may have led to a selection bias towards more severely affected women but it will also have increased the specificity of the diagnosis and lowered the risk of including patients with a false diagnosis. So far, little attention has been paid to the role of hypertension in HELLP syndrome. The correlation between preeclampsia and HELLP syndrome with regards to pathogenesis suggests that hypertension might play an important role in HELLP syndrome and its risk stratification.

In conclusion, more HELLP syndrome-specific research is necessary to fully understand its pathophysiology, discover possible new parameters for the prediction of maternal outcomes and develop better therapeutic approaches. Our hypothesis that the severity of hypertension could function as a predictive marker for adverse maternal outcome needs to be tested in different and larger study populations. A prospective study is needed to investigate whether good blood pressure management can reduce the rate of complications in women with HELLP syndrome.

Supplementary Material

Fig. S1 Number of outcome parameters of the combined endpoint for adverse maternal outcome identified in the three hypertension groups.

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