Abnormal Liver Function Tests as Predictors of Adverse Maternal Outcomes in Women With Preeclampsia

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Abstract

Objectives: To evaluate whether (1) the absolute magnitude of liver function test values, (2) the percentage change in liver function test values over time, or (3) the rate of change in liver function test values over time predicts adverse maternal outcomes in women with preeclampsia.

Methods: We used data from the PIERS (Pre-eclampsia Integrated Estimate of RiSk) study, a prospective multicentre cohort study assessing predictors of adverse maternal outcomes in women with preeclampsia. Women with at least one liver function test performed at the time of hospital admission were included. Liver functions were tested by serum concentrations of aspartate amino transferase (AST), alanine amino transferase (ALT), lactate dehydrogenase (LDH), albumin, total bilirubin, and the international normalized prothrombin time ratio. Parameters investigated were absolute levels, change within 48 hours of hospital admission, change from admission to delivery or outcome, and rate of change from admission to delivery or outcome of each liver function test. The ability of these parameters to predict adverse outcomes was assessed using logistic regression analyses and by calculating the receiver operating characteristic (ROC) area under the curve (AUC).

Results: Of the 2008 women, 1056 (53%) had at least one abnormal liver function test result. The odds of having an adverse maternal outcome were higher in women with any abnormal liver function test than in women with normal results. When test results were stratified into quartiles, women with results in the highest quartile (lowest quartile for albumin) were at higher risk of adverse outcomes than women in the lowest quartile for all parameters (highest for albumin). The absolute magnitude of AST, ALT, and LDH predicted adverse maternal outcomes (AST: ROC AUC 0.73 [95% CI 0.97 to 0.79]; ALT: ROC AUC 0.73 [95% CI 0.67 to 0.79]; LDH: ROC AUC 0.74 [95% CI 0.68 to 0.81]). Neither change of liver function test results, within 48 hours of admission or from admission to delivery or outcome, nor rate of change were predictive.

Conclusion: We found abnormal liver function test results to be associated with an increased risk for adverse maternal outcomes. Levels of AST, ALT, and LDH were found to be modestly predictive of these outcomes.

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Résumé

Objectifs : Évaluer si (1) l'ampleur absolue des valeurs d'épreuve de fonction hépatique, (2) la modification du pourcentage des valeurs d'épreuve de fonction hépatique avec le temps ou (3) le taux de modification des valeurs d'épreuve de fonction hépatique avec le temps permet de prédire les issues maternelles indésirables chez les femmes qui présentent une prééclampsie.

Méthodes : Nous avons utilisé des données issues de l'étude PIERS (*Pre-eclampsia Integrated Estimate of RiSk*), soit une étude de cohorte multicentrique prospective évaluant les facteurs prédictifs des issues maternelles indésirables chez les femmes qui présentent une prééclampsie. Les femmes ayant subi au moins une épreuve de fonction hépatique au moment de l'hospitalisation ont été admises à l'étude. Les fonctions hépatiques ont été testées au moyen des concentrations sériques d'aspartate aminotransférase (AST), d'alanine aminotransférase (ALT), de lactate-déshydrogénase (LDH), d'albumine, de bilirubine totale,

ainsi qu'au moyen du rapport international normalisé du temps de prothrombine. Parmi les paramètres étudiés, on trouvait les taux absolus, la modification dans les 48 heures de l'hospitalisation, la modification entre l'hospitalisation et l'accouchement ou l'issue et le taux de modification entre l'hospitalisation et l'accouchement ou l'issue de chacune des épreuves de fonction hépatique. La capacité de ces paramètres de prédire les issues indésirables a été évaluée au moyen d'analyses de régression logistique et en calculant la surface sous la courbe (SSC) de la fonction d'efficacité de l'observateur (FEO).

Résultats : Chez 2 008 femmes, 1 056 (53 %) avaient obtenu au moins un résultat anormal d'épreuve de fonction hépatique. La probabilité de connaître une issue maternelle indésirable était plus élevée chez les femmes ayant obtenu un ou des résultats anormaux d'épreuve de fonction hépatique que chez les femmes ayant obtenu des résultats normaux. Lorsque les résultats d'épreuve ont été stratifiés en quartiles, les femmes dont les résultats se situaient dans le quartile le plus élevé (quartile le plus faible pour ce qui est de l'albumine) étaient exposées à des risques d'issues indésirables plus élevés que ceux auxquels étaient exposées les femmes dont les résultats se situaient dans le quartile le plus faible pour tous les paramètres (le plus élevé pour ce qui est de l'albumine). L'ampleur absolue de l'AST, de l'ALT et du LDH a permis de prédire les issues maternelles indésirables (AST : SSC FEO, 0,73 [IC à 95 %, 0,97 – 0,79]; ALT : SSC FEO, 0,73 [IC à 95 %, 0,67 – 0,79]; LDH : SSC FEO, 0,74 [IC à 95 %, 0,68 – 0,81]). Ni la modification des résultats d'épreuve de fonction hépatique (dans les 48 heures de l'hospitalisation ou entre l'hospitalisation et l'accouchement ou l'issue) ni le taux de modification ne se sont avérés être des facteurs prédictifs.

Conclusion : Nous avons constaté que les résultats anormaux d'épreuve de fonction hépatique étaient associés à un risque accru d'issues maternelles indésirables. Nous avons également constaté que les taux d'AST, d'ALT et de LDH constituaient de modestes facteurs prédictifs quant à ces issues.

INTRODUCTION

Preeclampsia is a multisystem disease that has substantial adverse effects for pregnant women and their fetuses, and it is a major cause of maternal morbidity and mortality worldwide.[1] Obstetrical organizations have produced guidelines to assist in its diagnosis and management.[2–5] As the clinical presentation of preeclampsia is variable, we cannot currently identify the women who will go on to develop severe disease and those who will have only mild effects. Therefore, the management of preeclampsia is initially similar for all women and can be individualized only as their disease progresses. Being able to determine which women and fetuses are most at risk early in the course of the illness would enable clinicians to tailor individual management more effectively. Identifying women at risk for adverse outcomes would allow intensive monitoring or intervention and effective use of resources; conversely, identifying women at low risk for these outcomes could decrease iatrogenic adverse maternal and neonatal outcomes by reducing unnecessary intervention and monitoring.

Routine clinical management of women with preeclampsia often includes quantifying analytes of hepatic function and integrity; these include aspartate amino transferase, alanine amino transferase, lactate dehydrogenase, bilirubin, albumin, and international normalized prothrombin time ratio. Previous studies have shown varying results for the ability of liver function tests to predict adverse maternal outcomes. While some studies have found strong associations between levels of AST, ALT, LDH, bilirubin, and adverse outcomes, others have found only weak associations or none at all. No consensus on reproducible predictive parameters has been reached.[6–13] Some authors suggest that analytes such as LDH, bilirubin, and possibly AST may prove to be more predictive because they reflect multiple organ dysfunction.[9–12] The LDH level reflects hemolytic cell damage and hepatic dysfunction, the bilirubin level reflects both hemolysis and hepatic dysfunction, and the AST level reflects tissue damage and hepatic dysfunction. The value of changes to these liver function tests over time in predicting adverse maternal outcomes has yet to be assessed in women with preeclampsia.

In this study, we assessed the extent to which liver function tests can be used to predict adverse maternal outcomes in a large cohort of women with preeclampsia. We also investigated whether the percentage change over time and the rate of change of each liver function test were predictive of adverse maternal outcomes in this same well-described cohort of women with preeclampsia.

ABBREVIATIONS

ALT	alanine amino transferase
AST	aspartate amino transferase
AUC	area under the curve
BP	blood pressure
HELLP	hemolysis elevated liver enzymes and low platelets
INR	international normalized prothrombin time ratio
LDH	lactate dehydrogenase
PIERS	Pre-eclampsia Integrated Estimate of RiSK
ROC	receiver operating characteristic

MATERIALS AND METHODS

The data used in this study were obtained from the PIERS. The PIERS study is a multicentre prospective cohort study examining predictors of adverse maternal outcomes in women with preeclampsia. The PIERS cohort methodologies and multivariable results have been published elsewhere.[5] Data from eligible women admitted to tertiary care centres were collected between September 2003 and January 2010. The centres that participated were seven in Canada (British Columbia's Women's

Hospital, Vancouver, BC; Kingston General Hospital, Kingston, ON; Ottawa Hospital, Ottawa, ON; and Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC), one in New Zealand (Christchurch Women's Hospital in Christchurch), one in Australia (King Edward Memorial Hospital, Subiaco, Western Australia), and two in the United Kingdom (St. James Hospital, Leeds, Yorkshire and Nottingham University Hospital, Nottingham). In four of these sites, women were required to give informed consent to participate in the study. At the remaining sites, PIERS was conducted as a continuous quality improvement project that entailed the introduction of predetermined guidelines for the initial assessment and ongoing surveillance of women admitted to hospital with a suspected or confirmed preeclampsia. The details of these guidelines have been published elsewhere.[14,15]

Women were included in this study if they met any of the following criteria: (1) hypertension (BP ≥ 140/90 mmHg recorded on two occasions at least four hours apart, after 20+0 weeks' gestation, by any method in the hospital) and *either* proteinuria (urine protein ≥ 2+ by dipstick, ≥ 0.3 g/day by 24-hour urine collection, or > 30 mg/mmol by spot urinary protein:creatinine ratio) *or* hyperuricemia (value greater than local upper limit of normal for non-pregnant individuals); (2) HELLP syndrome with or without hypertension; or (3) superimposed preeclampsia (pre-existing hypertension with any of clinician-determined accelerated hypertension, systolic blood pressure ≥ 170 mmHg, diastolic blood pressure ≥ 120 mmHg, new or accelerated proteinuria, or new hyperuricemia). Women were excluded from the study if they were admitted to hospital in active labour or if any element of the combined adverse maternal outcome occurred prior to collection of predictor variables or prior to their meeting the eligibility criteria. This inclusive definition was chosen to reflect the variable and multisystem nature of preeclampsia seen in clinical practice.[16–18]

The PIERS database collected a wide range of data pertaining to liver function (INR, serum albumin, unconjugated bilirubin) and cellular integrity (serum AST, ALT, LDH, total bilirubin) from all women who met eligibility criteria for the study. This information was collected on admission to hospital and at various times over the period of hospital admission. All women who had baseline liver function tests performed after meeting eligibility criteria and at least one subsequent liver function test were included. The independent variables included for analysis in this study were levels of AST, ALT, LDH, albumin, total bilirubin, and INR. The normal reference ranges at BC Women's Hospital are AST: 10 to 40 U/L, ALT: 10 to 55 U/L, LDH: 300 to 600 U/L, albumin: 37 to 56 g/L, total bilirubin: 2 to 8 μM/L, and INR: 0.87 to 1.06. The normal reference ranges for all tests were similar between the institutions with the exception of LDH, which differed between institutions depending on the particular laboratory test used by each site. To account for the discrepancy between the two LDH assays, results were corrected to the midpoint of the relevant laboratory's normal range.[5]

The list of adverse maternal outcomes for the PIERS study was developed by iterative Delphi consensus (members of the consensus are listed in the Acknowledgements).[19,20] The combined maternal adverse outcome included maternal mortality and any of the following maternal morbidities: hepatic dysfunction, hematoma, or rupture; one or more seizures of eclampsia; Glasgow coma score < 13; stroke; reversible ischemic neurological deficit; transient ischemic attack; posterior reversible encephalopathy; cortical blindness or retinal detachment; need for positive inotrope support; infusion of a third parenteral antihypertensive; myocardial ischemia or infarction; acute renal insufficiency; acute renal failure; dialysis; pulmonary edema; SpO_2 < 90%; requirement of ≥ 50% FiO_2 for more than one hour; intubation (other than solely for Caesarean section); transfusion of any blood product; severe thrombocytopenia ($< 50 \times 10^{12}$/L) in the absence of blood transfusion; and placental abruption. The combined perinatal adverse outcome comprised perinatal or infant mortality; bronchopulmonary dysplasia; necrotizing enterocolitis; grade III/IV intraventricular hemorrhage; cystic periventricular leukomalacia; and stages 3 to 5 retinopathy of prematurity.

Lead-time bias was addressed by standardizing eligibility from hospitalization with preeclampsia, and not necessarily from disease onset. Incompetence bias (missing values and misclassification) was reduced by abstractor training, development and validation of the Microsoft Access database (Microsoft Corp., Redmond WA), feasibility and development studies using that database, and random re-abstraction of the charts. Misclassification errors were further minimized by database surveillance and 5% re-abstraction. The study was pragmatic and, consistent with clinical care, test reproducibility was not examined; we relied on in-house training and review for ensuring test reproducibility. Customized case report forms and a Microsoft Access database were created for data entry and were used at all participating sites. Data were collected from the women's medical records and included past obstetrical and family history, information regarding current pregnancy surveillance and outcomes, antenatal ultrasound findings, laboratory testing, and delivery and neonatal outcomes.

Table 1. Maternal and perinatal characteristics of women in the PIERS cohort with abnormal and normal liver function tests results

	Abnormal liver function test(s) (N = 1056 women) (N = 1168 fetuses)	Normal liver function tests (N = 952 women) (N = 1035 fetuses)	*P**
Characteristic			
Maternal age, years	31 (28 to 36)	31 (26 to 36)	0.03
Gestational age at eligibility, weeks	36.0 (32.6 to 38.3)	36.0 (33.2 to 38.1)	0.8
Gestational age at eligibility < 34 weeks	30.7 (28.1 to 32.6)	31.3 (28.7 to 32.9)	0.03
Multiple pregnancy	108 (10.2)	82 (8.6)	0.2
Parity ≥ 1	284 (26.6)	296 (31.1)	0.04
Smoking in current pregnancy	98 (9.9) n = 988	152 (16.6) n = 917	< 0.001
Preeclampsia description			< 0.001
Hypertension and proteinuria	172 (16.3)	146 (15.3)	
Hypertension and hyperuricaemia	696 (65.9)	635 (66.7)	
HELLP without hypertension or proteinuria	52 (4.9)	0 (0)	
Superimposed preeclampsia	135 (12.8)	171 (16.2)	
Clinical			
Peak blood pressure (mmHg)			
Mean arterial pressure	123.3 (115.0 to 130.3)	120 (113.3 to 126.7)	< 0.001
Systolic BP	166 (153 to 180)	160 (150 to 170)	< 0.001
Diastolic BP	103 (98 to 110)	100 (96 to 108)	< 0.001
Worst dipstick proteinuria	2 (1 to 3)	2 (0.5 to 3)	< 0.001
Lowest platelet concentration × 10^{12}/L	172 (132 to 222)	214 (172 to 261)	< 0.001
Interventions			
Corticosteroid administered	400 (37.9)	407 (42.8)	0.02
Antihypertensive medications administered	277 (26.2)	260 (27.3)	0.6
$MgSO_4$ administered	458 (43.4)	227 (23.8)	< 0.001
Pregnancy outcomes			
Admission-to-delivery interval in days	1 (1 to 3)	3 (1 to 11)	< 0.001
Gestational age at delivery in weeks	36.43 (33.29 to 38.57)	37.00 (35.00 to 38.57)	< 0.001
Birth weight in grams	2523 (1653 to 3178)	2685 (2000 to 3335)	< 0.001
Intrauterine fetal death	15 (1.3)	5 (0.5)	0.07
Neonatal death	11 (0.9)	9 (0.9)	> 0.99
Infant death	15 (1.3)	11 (1.1)	0.7

$MgSO_4$: magnesium sulphate
Data are expressed as medians with interquartile ranges or percentages
*Fisher exact test (categorical variables) or Mann-Whitney *U* test (continuous)

Women who had abnormal liver function test results were compared with women who had normal results. Descriptive data are expressed as median and interquartile range for non-normally distributed data. Fisher exact test was used for categorical variables, and Mann-Whitney *U* test was used for continuous variables. For each liver function test, we calculated the absolute test magnitude, percentage change of test result within 48 hours of hospital admission, percentage change of the test results from study eligibility to delivery or outcome, and rate of change from eligibility to delivery or outcome. Test results were grouped into quartiles, and the relationship between quartiles of liver function test results and adverse maternal outcome was examined using logistic regression analysis. The lowest quartile of liver function test results was used as the reference group for all tests except albumin (highest quartile was the reference group for albumin). Receiver operating characteristic curves were constructed for each liver function test to evaluate any potential value for predicting an adverse maternal outcome. Area under the curve of ROC values > 0.7 were considered to be adequately predictive. *P* values < 0.05 were considered to be

Table 2. Adverse maternal outcomes within 48 hours of study eligibility in women with or without any abnormal liver function tests results.

Test	AST n = 1937		ALT n = 2002		LDH n = 1616		Albumin n = 1741		Total bilirubin n = 1903		INR n = 1748	
Test result	Ab	N	Ab	N	Ab	N	Ab	N	Ab	N	Ab	N
n	490	1447	228	1714	895	721	48	1693	56	1847	53	1695
%	25.3	74.7	14.4	85.6	55.4	44.6	2.8	97.2	2.9	97.1	3.0	97.0
All maternal outcomes												
n	59	41	49	54	67	17	3	90	20	87	16	82
%	12.0	2.8	17.0	3.2	7.5	2.4	6.3	5.3	35.7	4.4	30.2	4.8
P	< 0.001		< 0.001		< 0.001		0.7		< 0.001		< 0.001	
Hepato-specific maternal outcomes												
n	4	3	5	5	5	2	0	9	4	6	3	6
%	0.8	0.2	1.7	0.2	0.6	0.3	0	0.5	7.1	0.3	5.7	0.4
P	0.07		0.006		0.5		> 0.99		< 0.001		0.002	

Ab: abnormal; N: normal

statistically significant. Statistical analyses were performed using SPSS 18.0 (IBM Corp., Armonk NY).

Research Ethics Board approval was obtained at all sites.

RESULTS

Of the 2023 women entered into the PIERS database, 2008 had at least one liver function test performed at the time of hospital admission and at least one subsequent liver function test. Of these 2008 women, 1065 (53%) had at least one abnormal liver function test result. Demographic and clinical characteristics of the women, and the pregnancy outcomes of women with normal and abnormal test results, are shown in Table 1. There were no clinically significant differences between the groups in maternal age, gestational age at eligibility, multiple pregnancy rates, or parity, despite some statistically significant differences. Women with abnormal liver function test results had higher maximum systolic and diastolic blood pressures and a trend towards more proteinuria and lower platelet concentrations. Women with abnormal test results were more likely than others to use magnesium sulphate and corticosteroids. Women with abnormal liver function tests also had significantly shorter admission to delivery intervals, lower gestational age at delivery, and infants with lower birth weights. Stillbirth was also more common in these women.

Maternal outcomes experienced by women with normal and abnormal test results are shown in Table 2. Women were grouped according to individual liver function test for analysis. Adverse maternal outcomes were more common in women with abnormal AST, ALT, LDH, total bilirubin, and INR results ($P < 0.05$). The specific maternal outcomes of hepatic dysfunction or failure, hepatic rupture, and hepatic hematoma were more common in women who had abnormal ALT, total bilirubin, and INR results ($P < 0.05$).

Women with abnormal results were at higher risk than women with normal liver function tests results for adverse maternal outcomes (OR for AST 4.7 [95% CI 3.1 to 7.1]; for ALT 6.3 [95% CI 4.2 to 9.5]; for LDH 3.4 [95% CI 1.9 to 5.8]; for albumin 1.2 [95% CI 0.4 to 3.9]; for total bilirubin 12.1 [95% CI 6.7 to 21.9]; and for INR 8.5 [95% CI 4.5 to 15.9]). The association between quartiles of liver function test results and risk of adverse maternal outcomes is shown in Table 3. For all liver function tests, women in the highest quartile (lowest quartile for albumin) were at higher risk of adverse maternal outcomes than women with laboratory results in the lowest quartile (highest quartile for albumin). Women in the second and third quartiles were not at significantly increased risk of adverse outcome, suggesting that the relationship between liver function test values and risk of adverse outcome has a threshold effect rather than following a linear dose–response pattern. The odds ratios for percentage change within 48 hours were comparable to those for absolute test values. There were no significant differences in the odds of having an adverse outcome according to quartiles of percentage change prior to adverse outcome or delivery and rate of change.

Results of the ROC AUC analysis for liver function tests predicting adverse maternal outcomes in women with preeclampsia are shown in Table 4. The worst laboratory result within 48 hours of study eligibility was considered predictive of adverse maternal outcome for AST

Table 3. Risk of adverse maternal events according to quartile stratification of liver function test results by absolute magnitude of test result, percentage change of test result within 48 hours of hospital admission, percentage change of test result from admission to delivery/outcome, and rate of change of test result from admission to delivery/outcome

Liver function test	Parameter		Quartile 1	Quartile 2	Quartile 3	Quartile 4
AST	Absolute magnitude, U/L	Range	12 to 21	22 to 28	29 to 41	42 to 2475
		n/N	13/515	9/468	19/484	59/470
		OR (95% CI)	Reference	0.8 (0.3 to 1.8)	1.3 (0.8 to 3.2)	5.5 (3.0 to 10.2)
	Change within 48 hr of admission, %	Range	−57 to 8	9 to19	20 to 41	45 to 5400
		n/N	6/275	12/263	13/264	28/255
		OR (95% CI)	Reference	2.1 (0.8 to 5.8)	2.3 (0.9 to 6.2)	5.5 (2.3 to 13.6)
	Change from admission to outcome/delivery, %	Range	−81 to −10	−9 to 3	4 to 20	21 to 5400
		n/N	41/357	36/343	40/349	57/331
		OR (95% CI)	Reference	0.9 (0.6 to 1.5)	1.0 (0.6 to 1.6)	1.6 (1.0 to 2.5)
	Rate of change admission to outcome/delivery, unit/hr	Range	−19 to −0.04	−0.03 to 0	0.01 to 0.10	0.11 to 100
		n/N	44/355	35/352	39/319	55/332
		OR (95% CI)	Reference	0.8 (0.5 to 1.2)	1.0 (0.6 to 1.6)	1.4 (0.9 to 2.2)
ALT	Absolute magnitude, U/L	Range	2 to 13	14 to 19	20 to 32	33 to 2020
		n/N	13/569	10/434	19/510	61/489
		OR (95% CI)	Reference	1.0 (0.4 to 2.3)	1.7 (0.8 to 3.4)	6.1 (3.3 to 11.2)
	Change within 48 hr of admission, %	Range	−98 to 9	10 to 22	23 to 56	57 to 10 355
		n/N	14/274	12/266	9/271	29/267
		OR (95% CI)	Reference	0.9 (0.4 to 1.9)	0.8 (0.4 to 1.8)	2.3 (1.2 to 4.4)
	Change from admission to outcome/delivery, %	Range	−99 to −15	−14 to 1	2 to 31	32 to 10 355
		n/N	33/365	43/361	46/358	61/361
		OR (95% CI)	Reference	1.3 (0.8 to 2.1)	1.5 (0.9 to 2.4)	2.0 (1.3 to 3.2)
	Rate of change admission to outcome/delivery, unit/hr	Range	−256 to −0.04	−0.03 to 0	0.01 to 0.11	0.12 to 539
		n/N	37/363	38/378	47/337	58/346
		OR (95% CI)	Reference	1.1 (0.7 to 1.7)	1.4 (0.9 to 2.3)	1.8 (1.1 to 2.8)
LDH	Absolute magnitude, U/L	Range	0.38 to 1.13	1.14 to 1.35	1.36 to 1.70	1.71 to 19.90
		n/N	7/406	11/403	15/403	51/404
		OR (95% CI)	Reference	1.6 (0.6 to 4.2)	2.2 (0.9 to 5.4)	8.2 (3.7 to 18.4)
	Change within 48 hr of admission, %	Range	−39 to 8	9 to 22	23 to 49	50 to 1386
		n/N	8/253	11/242	8/229	27/241
		OR (95% CI)	Reference	1.5 (0.6 to 3.7)	1.1 (0.4 to 3.0)	3.9 (1.7 to 8.7)
	Change from admission to outcome/delivery, %	Range	−83 to −11	−10 to 2	3 to 20	21 to 1248
		n/N	34/276	25/264	26/275	48/264
		OR (95% CI)	Reference	0.7 (0.4 to 1.3)	0.7 (0.4 to 1.3)	1.6 (1.0 to 2.5)
	Rate of change admission to outcome/delivery, unit/hr	Range	−109 to −0.67	−0.66 to 0.07	0.08 to 1.58	1.59 to 600
		n/N	46/299	25/306	33/293	45/298
		OR (95% CI)	Reference	0.5 (0.3 to 0.8)	0.7 (0.4 to 1.1)	1.0 (0.6 to 1.5)
Albumin	Absolute magnitude, g/L	Range	11 to 26	27 to 29	30 to 32	33 to 40
		n/N	45/500	16/387	17/456	15/398
		OR (95% CI)	2.5 (1.4 to 4.6)	1.1 (0.5 to 2.3)	1.0 (0.5 to 2.0)	Reference
	Change within 48 hr of admission, %	Range	−57 to −18	−17 to −10	−9 to −6	−5 to 23
		n/N	28/248	9/263	7/248	9/219
		OR (95% CI)	3.0 (1.4 to 6.4)	0.8 (0.3 to 2.1)	0.7 (0.2 to 1.9)	Reference
	Change from admission to outcome/delivery, %	Range	−36 to −10	−9 to −4	−3 to 0	1 to 45
		n/N	43/255	32/251	34/284	29/285
		OR (95% CI)	1.8 (1.1 to 1.3)	1.3 (0.8 to 2.2)	1.2 (0.7 to 2.0)	Reference
	Rate of change admission to outcome/delivery, unit/hr	Range	−6.0 to −0.05	−0.04 to −0.09	−0.08 to 0.003	0.004 to 6.0
		n/N	38/262	39/276	36/272	27/256
		OR (95% CI)	1.4 (0.9 to 2.4)	1.4 (0.9 to 2.4)	1.3 (0.8 to 2.2)	Reference

continued

Table 3. *continued*

Liver function test	Parameter		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Bilirubin	Absolute magnitude, μM	Range	1 to 3	4 to 6	7 to 9	10 to 45
		n/N	8/240	24/813	22/483	47/367
		OR (95% CI)	Reference	0.9 (0.4 to 2.0)	1.4 (0.6 to 3.2)	4.3 (2.0 to 9.2)
	Change within 48 hr of admission, %	Range	−83 to 20	21 to 33	34 to 61	62 to 900
		n/N	11/240	11/219	5/186	24/215
		OR (95% CI)	Reference	1.1 (0.5 to 2.6)	0.6 (0.2 to 1.7)	2.6 (1.2 to 5.5)
	Change from admission to outcome/delivery (%)	Range	−83 to −1	0 to 14	15 to 50	51 to 3550
		n/N	34/288	42/307	34/317	47/353
		OR (95% CI)	Reference	0.7 (0.5 to 1.2)	0.7 (0.4 to 1.1)	0.9 (0.5 to 1.4)
	Rate of change admission to outcome/delivery, unit/hr	Range	−6 to 0	0.001 to 0.004	0.005 to 0.05	0.06 to 6.0
		n/N	79/536	12/87	37/288	33/303
		OR (95% CI)	Reference	0.9 (0.6 to 1.4)	0.8 (0.5 to 1.3)	0.7 (0.4 to 1.1)
INR	Absolute magnitude	Range	0.70 to 0.90	0.91 to 0.92	0.93 to 0.94	0.95 to 1.31
		n/N	21/574	14/356	17/385	43/433
		OR (95% CI)	Reference	1.1 (0.5 to 2.1)	1.2 (0.6 to 2.3)	2.9 (1.7 to 5.0)
	Change within 48h of admission, %	Range	−11 to 1	2 to 3	4 to 10	11 to 43
		n/N	9/255	8/104	15/115	19/136
		OR (95% CI)	Reference	2.2 (0.8 to 5.9)	4.1 (1.7 to 9.7)	4.4 (1.9 to 10.1)
	Change from admission to outcome/delivery, %	Range	−25 to −1	−0.9 to 0	0.01 to 3.2	3.3 to 33
		n/N	23/292	43/518	10/145	25/149
		OR (95% CI)	Reference	1.0 (0.6 to 1.7)	0.8 (0.4 to 1.8)	2.4 (1.3 to 4.3)
	Rate of change admission to outcome/delivery, unit/hr	Range	−0.15 to −0.00002	−0.00001 to 0	0 to 0.00003	0.00004 to 0.1
		n/N	35/269	25/288	31/273	50/265
		OR (95% CI)	Reference	0.7 (0.4 to 1.2)	0.8 (0.5 to 1.3)	1.5 (0.9 to 2.4)

(0.73 [95% CI 0.67 to 0.79]), ALT (0.73 [95% CI 0.67 to 0.79]), and LDH (0.74 [95% CI 0.68 to 0.81]). All other liver function tests had ROC AUC results < 0.7. Test result change within 48 hours of study eligibility, change from study eligibility to delivery or outcome, and rate of change from eligibility to delivery or outcome of the test results were not predictive of adverse maternal outcome for any liver function test. All ROC AUC results were < 0.7. A quadratic term to assess for a non-linear relationship between the liver function tests and adverse maternal outcomes was also included in the data analysis. This, however, did not improve the AUC of the model.

DISCUSSION

This study used a large cohort to assess the value of liver function tests to predict adverse maternal outcomes in women with preeclampsia. Abnormal liver function test results were found to be associated with a higher risk of adverse outcomes than normal results. We also found that within the range of test results, women with results in the highest quartile (or lowest for albumin) had higher risk of adverse outcomes than women with test results in the lowest quartile (or highest for albumin). Our results show that the levels of ALT, AST, and LDH are all predictive of adverse maternal outcomes in hospitalized women with preeclampsia. All three tests had an ROC AUC > 0.70. Change over time (from eligibility to delivery) and rate of change for each test all had ROC AUC < 0.7 and thus were not considered predictive of adverse outcomes.

Strengths of this study include the relatively large sample size of women from multiple centres in several countries, ensuring that our cohort was heterogeneous in nature. Women with and without abnormal liver function test values were demographically similar, although there was more use of magnesium sulphate and corticosteroids in women with abnormal test results than in women with normal results. This difference likely reflects the fact that abnormal laboratory testing, including elevated levels of AST, ALT or LDH, is considered to be an adverse condition that is used to categorize preeclampsia as severe.[2–4] Women with these results are therefore more likely to undergo interventions such as administration of magnesium sulphate or corticosteroids or to have iatrogenic preterm delivery.

Table 4. Predictive value of liver function tests to predict adverse maternal outcomes in women with preeclampsia

Parameter	Liver function test	ROC AUC (95%CI)
Worst result in 48 hours of study eligibility	AST	0.73 (0.67 to 0.79)
	ALT	0.73 (0.67 to 0.79)
	LDH	0.74 (0.68 to 0.81)
	Albumin	0.63 (0.57 to 0.69)
	Total bilirubin	0.68 (0.61 to 0.74)
	INR	0.65 (0.58 to 0.71)
Test change within the first 48 hours of study eligibility	AST	0.66 (0.59 to 0.74)
	ALT	0.62 (0.54 to 0.70)
	LDH	0.65 (0.57 to 0.74)
	Albumin	0.66 (0.57 to 0.75)
	Total bilirubin	0.62 (0.53 to 0.71)
	INR	0.67 (0.59 to 0.75)
Test change from eligibility to outcome/delivery	AST	0.55 (0.50 to 0.61)
	ALT	0.58 (0.53 to 0.62)
	LDH	0.56 (0.50 to 0.61)
	Albumin	0.56 (0.50 to 0.61)
	Total bilirubin	0.50 (0.44 to 0.56)
	INR	0.58 (0.51 to 0.65)
Rate of change from eligibility to outcome or delivery (unit/hour)	AST	0.55 (0.50 to 0.59)
	ALT	0.56 (0.52 to 0.61)
	LDH	0.52 (0.47 to 0.58)
	Albumin	0.54 (0.49 to 0.59)
	Total bilirubin	0.47 (0.42 to 0.51)
	INR	0.55 (0.49 to 0.60)

Although absolute levels of liver function test results were found to be associated with increased odds of adverse maternal outcomes, their usefulness in a clinical setting may be limited. Serial monitoring is required to determine when test results reach a certain level. Women cannot be reassured that they are at low risk if their levels are below a certain threshold because the possibility for an increase in risk exists as long as the pregnancy continues. However, normal liver function test results do provide some justification for expectant management, especially remote from term in women whose levels are (with the exception of albumin) below the highest quartile values. Second, for the purposes of our analysis no distinction was made between the various hypertensive disorders of pregnancy. This may, however, be of minimal significance. A useful predictor of the severity of disease should be applicable to all such disorders, because it is often only in retrospect that we can determine precisely which disorder a woman was affected by. Last, although some of the analyses in our study appear to be predictive, a proportion of women who may go on to have severe disease will not be identified. A more robust model that takes into account the various end organ systems that can be affected by preeclampsia will likely yield a more clinically useful means for predicting disease severity. These findings are consistent with those of Martin et al. in a retrospective study of 970 patients with severe preeclampsia or HELLP.[13] These authors found significant differences in values on admission for ALT, AST, and LDH in women who experienced maternal morbidity versus women who did not. Both their study and ours examined women with severe preeclampsia with or without HELLP syndrome. Martin et al. proposed a protocol for early risk assessment of severe preeclampsia that assessed symptoms and levels of AST, ALT, LDH, uric acid, proteinuria, and creatinine, measured once shortly after meeting study admission criteria. They proposed that their findings could be used as an adjunct to the Mississippi triple class system for categorizing and comparing patients with severe preeclampsia/HELLP.[21] They suggested that regardless of a woman's initial or eventual HELLP

classification, measurement of LDH, ALT, and AST could be used to assess whether patients were at low, moderate, or high risk of experiencing significant maternal morbidity.

Peralta et al. described their findings in 400 pregnant patients, of whom 63 had mild preeclampsia, 153 had severe preeclampsia, and the remainder were healthy control subjects.[22] In contrast to our findings, these authors found no difference in levels of AST, ALT, and total bilirubin between women with preeclampsia and normal control subjects. They did find LDH levels to be significantly different between the groups, and they concluded that LDH levels were useful in the diagnosis and classification of severity of preeclampsia, consistent with our findings. The difference in results between the study of Peralta et al.[22] and our own may be due to differences in sample size and study patient populations. They compared women with preeclampsia with normotensive pregnant control subjects, whereas in our study only women who met criteria for having a hypertensive disorder of pregnancy were included.

Von Dadelszen et al. retrospectively reviewed data from 54 women with preeclampsia and found that AST levels were significantly greater in women who had an adverse outcome than in those who did not.[11] This study was much smaller than the current study, which may explain why only AST levels were identified as significant.

Our results pertaining to the magnitude of liver function test values may reflect differences in end organ dysfunction at or near the time of presentation. Preeclampsia is a systemic process characterized by increased systemic vascular resistance, increased platelet aggregation, abnormal coagulation, and endothelial dysfunction.[23,24] The increased odds of adverse maternal outcomes occurring in women in the highest quartiles (lowest for albumin) may be because they experience more severe effects of the underlying disease process. Alternatively, women with more severely abnormal liver function tests could experience more adverse events as a result of the physiologic derangements conferred by the systemic changes. For example, increased INR leads to increased risk of hemorrhage, while low serum albumin will increase the risk of pulmonary edema.

To our knowledge, no previous studies have assessed changes in liver function test values over time in relation to maternal outcomes. It is therefore unknown why the relationships seen in the first 48 hours do not remain when a longer time period is analyzed, nor why rate of change is non-contributory. It may be that we were unable to account for rapid changes that occurred over short periods of time. We compared only the initial and end point results of each woman's tests and the changes seen in test values may have accrued over only a portion of the overall time period used to calculate the data. Thus our analysis would have missed these changes by averaging them over a longer time period. Future research that more meticulously examines the relationship of change in liver values will be necessary to determine whether this is true. In assessing women with preeclampsia, liver function tests are only one set of variables, and, although they do provide some insight into a woman's disease status, a more robust multivariate model that takes into account the other organ systems affected by preeclampsia is needed. The recently published full PIERS model is such a multivariate model.[5]

CONCLUSION

This study has shown that a higher absolute magnitude of liver function test results (or a lower serum albumin) is associated with increased occurrence of adverse maternal outcomes. As well, percentage change in liver function test results within 48 hours appears to be associated with an increased occurrence of adverse maternal outcomes. A clinically useful means for predicting disease severity based on change or rate of change was not achieved by this study. However, as our knowledge of the underlying pathophysiology of the hypertensive disorders of pregnancy increases and further research in the area is undertaken, it is likely that the relationship between change or rate of change in test results and maternal outcomes will be clarified.

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