Makarm *et al.*
Egyptian Rheumatology and Rehabilitation (2022) 49:33
https://doi.org/10.1186/s43166-022-00131-3

Egyptian Rheumatology and Rehabilitation

RESEARCH Open Access

Risk assessment score for adverse pregnancy outcome in systemic lupus erythematosus patients

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Abstract

Background Systemic lupus is a chronic autoimmune multisystem disease that mainly affects females of childbearing age. SLE still possesses risks during pregnancy that lead to poor maternal and fetal outcomes. The objectives of the study were to identify factors associated with unfavorable pregnancy outcomes and develop a predictive risk score for adverse pregnancy outcomes in patients with SLE.

Results The main predictive factors associated with adverse pregnancy outcomes among lupus patients in multiple linear regression were an absence of remission for at least 6 months before conception, preexisting lupus nephritis, active disease at conception, C3 hypocomplementemia, and antiphospholipid antibody syndrome. Each predictor is assigned a weighted point score, and the sum of points represents the risk score. The area under the receiver operating characteristic curve (ROC) was 0.948 (95% confidence interval, 0.908–0.988), suggesting that the score had strong discriminatory power for adverse pregnancy outcomes.

Conclusions In this study, a predictive model with a risk score classification for adverse pregnancy outcomes in SLE patients was developed. This could help rheumatologists identify high-risk pregnant patients for better disease monitoring and management, resulting in better maternal/fetal outcomes.

Keywords Pregnancy, SLE, Risk score

Key points

- There are limited long-term studies on SLE patients that entail the evaluation of maternal and fetal outcomes during pregnancy while focusing on determinant risk factors.
- We attempted to develop a prediction model and a risk score system for adverse pregnancy outcomes in lupus patients.
- This risk score may help rheumatologists identify high-risk patients during pregnancy for better disease monitoring and management.

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects predominantly females in childbearing age groups [1, 2]. The relationship between pregnancy and SLE is of great concern and is primarily related to the influence of pregnancy on SLE and the impact of SLE on pregnancy outcomes [3]. Although improvements in the management of obstetric complications and advances in neonatal care have enabled SLE women to have pregnancies with improved outcomes, lupus pregnancy continues to be associated with substantial adverse maternal and fetal morbidity [4]. It is well established that they experience an increased risk

of preeclampsia, thromboembolism, infection, fetal loss, prematurity, and intrauterine growth restriction [5].

Previous research has revealed some discrepancies; some studies indicated that women were at an increased risk of lupus flares during pregnancy, while others reported that the rate of flares remained unchanged in comparison with nonpregnant SLE patients [6]. Enhancing disease activity monitoring and managing flares promptly are essential to optimize maternal and fetal outcomes in SLE pregnancies and should thus be a top goal throughout prenatal treatment. However, making decisions and predicting pregnancy outcomes in SLE patients is a challenging task for physicians [7].

As far as we know, there are limited long-term studies on SLE patients that entail the evaluation of maternal and fetal outcomes during pregnancy while focusing on determinant risk factors. As a result, we aimed to identify factors associated with unfavorable pregnancy outcomes and develop a predictive risk score for adverse pregnancy outcomes in patients with SLE.

Methods

Study population and settings

The present study was a single-center retrospective study consisting of pregnant SLE patients receiving care at the Rheumatology, Rehabilitation, and Physical Medicine Department, Faculty of Medicine, University Hospitals.

Inclusion criteria

All pregnant SLE patients who met the criteria for SLE according to the American College of Rheumatology Classification Criteria (ACR) [8] and conceived between 2005 and 2020. If a patient had more than one pregnancy during the study period, only information about the last pregnancy was included.

Exclusion criteria

Patients with overlapping autoimmune disorders (such as rheumatoid arthritis, systemic sclerosis, polymyositis, or dermatomyositis), multiple pregnancies, or fetal losses due to other causes (such as trauma, pregnancy termination for personal reasons, thyroid disorders, or chromosomal abnormalities) were excluded. We also excluded patients with insufficient data or who had antenatal follow-ups in other hospitals.

Data collection

In this study, medical records of pregnant patients in the SLE cohort were reviewed. Demographic and clinical data were collected, including maternal age at disease onset, age at conception, comorbidities, duration of remission before conception, and pregnancy planning status for planned SLE pregnancies (who had disease control or remission for ≥ 6 months before conception).

SLE clinical features (disease duration, organ involved, presence of antiphospholipid antibody syndrome) [9], disease flare-up, current use of medications, and data collected during the most recent gestation regarding maternal/fetal outcomes, and prior adverse pregnancy outcomes, are all factors to consider.

Assessment of SLE

Lupus activity was assessed using the validated SLE disease activity index (SLEDAI-2K) [10]. Activity assessments were reviewed 6 months before conception, at the start of pregnancy, during pregnancy (first, second, and third trimesters as well as mean SLEDAI), and postpartum. Patients were categorized as having an active illness (SLEDAI-2K > 4) [11].. SLE flare (defined as a change in clinical and/or serological parameters requiring the adjustment of immunosuppressant doses) has been identified as kidney, skin, joint, or any combination of these [12].

All routine laboratory results were reviewed during pregnancy as well as antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, antiphospholipid antibodies (lupus anticoagulants, anticardiolipin IgG, and IgM antibodies, anti-β2 glycoprotein), 24-h urinary protein, anti-Ro/SSA and anti-La/SSB antibodies, and complement 3 and 4 in all patients of the lupus cohort.

Assessment of pregnancy outcomes

Adverse maternal outcomes included exacerbation of disease activity (flare) during pregnancy or postpartum periods, preeclampsia (defined as new-onset hypertension (HTN) and proteinuria after 20 weeks of gestation), eclampsia, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, thromboembolism, gestational hypertension, or diabetes, preterm delivery (defined as regular uterine contractions that result in cervix changes that begin before 37 weeks of pregnancy), or admission to the intensive care unit. Adverse fetal outcomes included the occurrence of spontaneous or therapeutic abortion before the 20th week of pregnancy, intrauterine fetal death (IUFD) (losses occurring at or after the 20th gestational week), premature birth defined as the birth of a baby before the 37th week of gestation, neonatal intensive care unit admission (NICU), and neonatal death (during the first 28 days of life). Other fetal data such as birth weight, growth, and congenital anomalies were not consistently available from medical records and were not included as a result [13–15].

Statistical analysis

All the data were recorded and analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA 2011). Continuous data were expressed as means, and standard deviations (SD) and categorical data were described using number and percentage. The Mann-Whitney or Student *t*-test was used to analyze continuous data, while the chi-square test or Fisher extract test was employed to assess categorical ones. The results were considered significant if P was ≤ 0.05. Using logistic regression, the predictive analysis was applied to assess the odds ratio (OR) and 95% confidence interval (CIs) for all potential predictors separately, and then stepwise regression was used ($P \leq 0.05$ for the forward).

The goodness-of-fit test for the regression model was assessed using the Hosmer-Lemeshow test. ROC curve analysis was done to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the curve for the risk score prediction model.

Results

A total of 229 pregnant patients with SLE were screened for the occurrence of adverse pregnancy outcomes during the last gestation. Of these, 113 patients were excluded. The study population included 116 patients who were assigned to either have adverse pregnancy outcomes ($n = 62$ [53.4%]) or patients without adverse pregnancy outcomes ($n = 54$ [46.6%]) (Fig. 1).

In Table 1, the characteristics, and medications of pregnant SLE patients, are shown. Twenty-one patients (18.1%) had preexisted HTN, and eight patients (6.89%) had prepregnancy diabetes mellitus. At the time of conception, 38 (32.76%) of 116 lupus patients had active disease status. There were 78 (67.24%) patients with

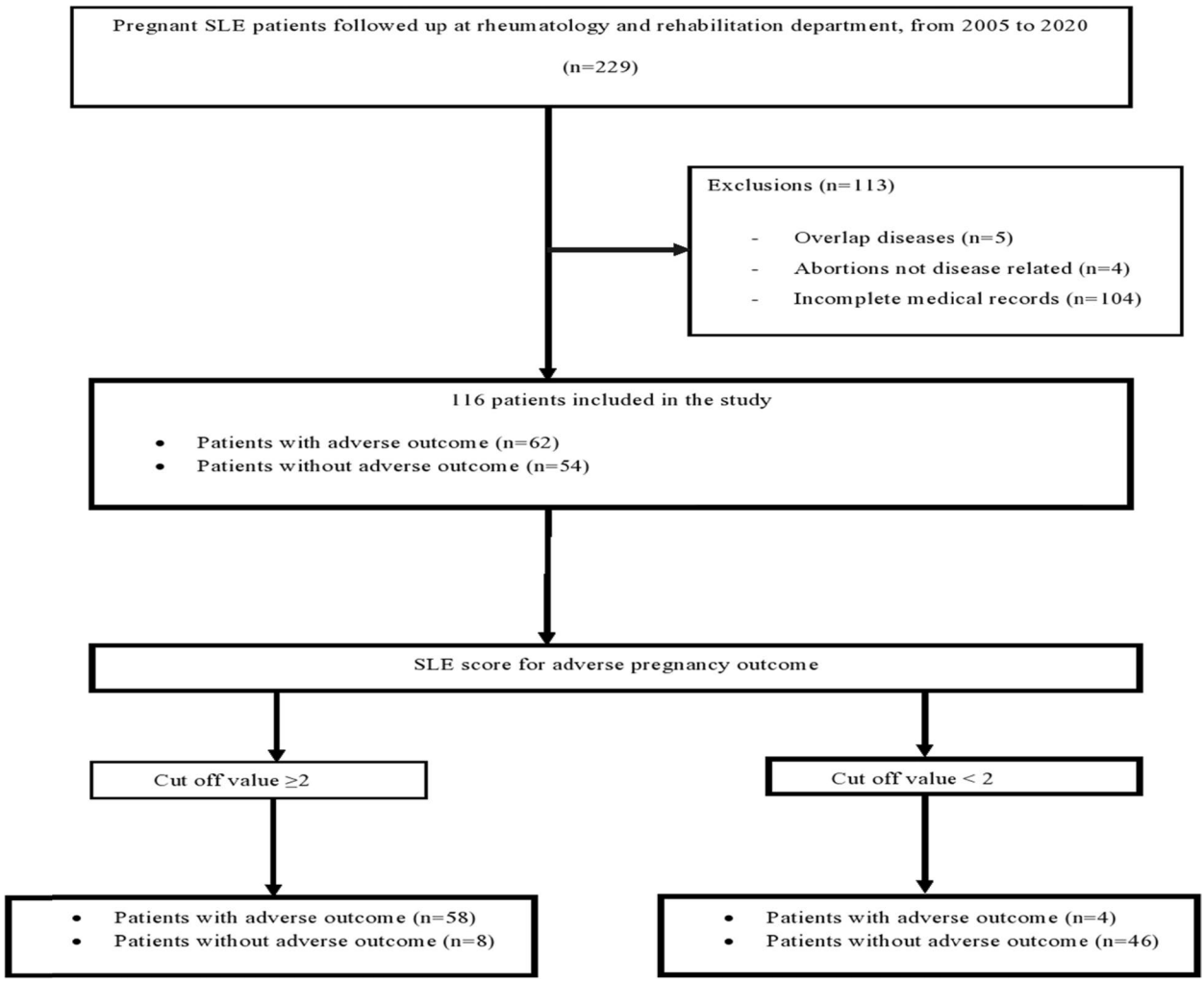

Fig. 1 Flowchart displaying the cutoff values for the risk score model predicts adverse outcomes in pregnant lupus patients

Table 1 Patients' characteristics at conception according to the occurrence of adverse outcomes

Characteristics	All SLE patients (*n* = 116)		With adverse outcomes *n* = 62 (53.4%)		Without adverse outcomes *n* = 54 (46.6%)		Test *P*	
	no.	%	no.	%	no.	%		
Age at onset	23.35 ± 3.45		23.14 ± 2.97		23.59 ± 3.91		*t* = 0.703	0.483a
Age at conception	26.7 ± 3.54		26.4 ± 3.52		26.81 ± 3.67		*t* = 0.613	0.54a
Disease duration	3 (0–16)		3 (0–16)		2 (1–13)		*U* = 1.604	0.46b
Gestational age at delivery	38.09 ± 1.3		37.77 ± 1.56		38.46 ± 0.79		*t* = 3.05	**0.003*a**
Comorbidities								
Preexisted hypertension	21	18.1	15	24.2	6	11.1	5.1	**0.02*c**
Pulmonary hypertension	5	4.3	4	6.45	1	1.9	f	0.37d
Diabetes mellitus	8	6.89	5	8.1	3	5.6	f	0.72c
Dyslipidemia	24	20.7	16	25.8	8	14.8	2.125	0.145c
Prior complications								
Maternal	3	2.6	3	4.84	0	0	f	0.24d
Fetal	23	19.8	18	29.03	5	9.3	7.1	**0.007*c**
Preexisted lupus nephritis	46	39.7	41	64.5	5	9.3	39.1	**0.000*c**
Absence of remission for at least 6 months at conception	55	47.41	40	64.51	15	27.77	15.01	**0.0001*c**
Active disease at conception	38	32.8	36	58.1	2	3.7	f	**0.000*d**
Clinical data of SLE patients								
Rash	51	43.96	31	50.0	20	37.03	1.96	0.16c
Photosensitivity	21	18.1	14	22.58	7	12.96	1.8	0.17c
Arthritis	29	25	18	29.03	11	20.37	1.15	0.28c
Oral ulcer	19	16.37	13	20.97	6	11.1	2.04	0.15c
Hair falling	18	15.52	12	19.4	6	11.1	1.496	0.221c
Raynaud's phenomenon	20	17.24	8	12.9	12	46.3	1.75	0.185c
Seizer	4	3.4	3	4.8	1	1.9	f	0.62d
Psychosis	8	6.89	5	8.1	3	5.6	f	0.722d
Fever	6	5.17	4	6.45	2	3.7	f	0.68d
Vasculitis	7	6.03	5	8.1	2	3.7	f	0.44d
Pericarditis	5	4.3	4	6.45	1	1.9	f	0.37d
Pleuritis	4	3.4	2	3.2	2	3.7	f	0.99d
Prior thrombotic events	5	4.3	5	8.1	0	0	f	0.06d
Antiphospholipid antibody syndrome	40	34.48	33	53.23	7	12.96	20.7	**0.0001*c**
SLEDAI-2K at conception	2 (0–44)		5.5 (0–44)		1 (0–14)		*U* = 5.35	**0.000*b**
SLEDAI-2K during pregnancy	3.8 (0–16.6)		4.8 (0–15.6)		3 (0–16.6)		*U* = 2.21	**0.0026*b**
SLEDAI-2k postpartum	5 (0–24)		8 (0–24)		3 (0–22)		*U* = 4.41	**0.000*b**
Treatment								
Prednisone	68	58.6	39	62.9	29	53.7	1.01	0.32c
Prednisone ≥ 20	22	18.96	16	25.8	6	11.1	4.1	**0.04*c**
Prednisone < 20	46	39.6	26	41.9	30	55.5	2.7	0.09c
Azathioprine	32	27.6	13	20.96	19	35.2	2.9	0. 08c
Hydroxychloroquine	41	35.3	17	27.4	24	44.4	3.7	**0.06*c**
Low-molecular-weight heparin	17	14.7	5	8.1	12	22.2	4.6	**0.03*c**
Low dose aspirin	19	16.4	9	14.51	10	18.51	0.337	0.56c
Anti-hypertension	10	8.6	4	6.4	6	11.1	f	0.51d

SLE systemic lupus erythematosus. All values are presented as mean ± SD or median (range) or number (%). a Independent *t*-test, b Mann-Whitney *U*-test, c chi-square test, d Fisher test, *SLEDAI* systemic lupus erythematosus disease activity index. Insignificant, $P > 0.05$; significant, $*P \leq 0.05$

stable lupus disease at conception; of those, 61 (52.59%) patients had been in remission for at least 6 months before conception, and 39 (72.2%) had favorable pregnancy outcomes with statistical significance, $P < 0.0001$, compared to those who had not been in remission (not tabulated).

The most common SLE clinical manifestations in these patients were cutaneous lesions, which occurred in 43.96% of cases.

There were statistically significant differences in the incidence of preexisted hypertension and previous fetal complications in lupus patients with adverse pregnancy outcomes compared to those without adverse outcomes ($P \leq 0.05$).

The median SLEDAI at conception, during pregnancy, and postpartum periods was significantly higher in lupus patients with adverse pregnancy outcomes compared to those without adverse outcomes, ($P \leq 0.05$). Moreover, there were statistically significant differences in the frequency of absence of remission for at least 6 months at conception, preexisted lupus nephritis, and active disease at conception in patients with adverse pregnancy outcomes compared to those without adverse outcomes ($P < 0.0001$).

There were no statistically significant differences in the incidence of adverse pregnancy outcomes, between the two groups regarding demographics or medications, except for prednisone intake ≤ 20 mg per day, HCQ, and LMWH heparin. Adverse pregnancy outcomes were signifcantly increased in lupus patients receiving prednisone ≥ 20 mg per day ($P \leq 0.05$). However, there was a statistically signifcant reduction in adverse outcomes among patients receiving HCQ and low-molecularweight heparin during pregnancy ($P \leq 0.05$).

As shown in Table 1, there was no statistically significant difference in adverse outcomes among pregnant patients who received azathioprine or aspirin compared to those without. However, those who received either of them tended to have a lower proportion of adverse outcomes, but this did not reach statistical significance ($P > 0.05$).

As regards laboratory variables at conception, there were statistically significant differences in the frequency of hypocomplementemia C3 and C4 and positive anti-ds DNA in lupus patients with adverse pregnancy outcomes compared to those without adverse outcomes ($P \leq 0.05$). In all SLE populations, 25 (21.06%) patients were positive for lupus anticoagulant antibody. In addition, 16 (13.79%) were positive for IgG anticardiolipin antibody, 14 (12.1%) patients were positive for IgM anticardiolipin antibody and 6 (5.17%) for anti-β2 glycoprotein antibody with statistically significant differences regarding lupus anticoagulant and IgG anticardiolipin antibody in lupus patients with adverse pregnancy outcomes compared to those without adverse outcomes ($P \leq 0.05$).

The values of serum albumin were significantly lower in lupus patients with adverse pregnancy outcomes compared to those without adverse outcomes ($P = 0.002$). The median 24-h urinary protein level was significantly higher in lupus patients with adverse pregnancy outcomes compared to those without adverse outcomes ($P < 0.0001$). Besides, there were significant differences in the incidence of proteinuria > 500 mg in lupus patients with adverse pregnancy outcomes (46.8%) compared to those without (9.3%), ($P < 0.0001$). Moreover, there was no difference regarding the other tested laboratory parameters, as shown in Table 2.

A total of 116 pregnant lupus patients were included in this study. There were 38 (32.76%) patients with active lupus disease and 78 (67.24%) with stable lupus disease at conception. The rates of adverse maternal and or fetal outcomes in the active SLE group (94.7%) were significantly higher than those in the inactive group (33.3%) ($P = 0.0001$). Of those active 38 (32.76%) patients, 7 (21.1%) eventually developed preeclampsia, and one patient developed eclampsia. There were significant statistical differences in the incidence of preeclampsia in the active lupus group compared with the non-active lupus group ($P = 0.001$).

A total of 16 patients (13.8%) had a disease flare during pregnancy, while 12 (10.34%) had a disease flare during the postpartum period. The rates of either disease flare during pregnancy or the postpartum period were higher in the active lupus group compared with the non-active lupus group ($P \leq 0.05$). Furthermore, the incidence of preterm labor in the active SLE group was 7/38 (18.4%), which is significantly higher than that in the inactive group (2/78, 3.84%) ($P = 0.013$).

The mean gestational age at delivery was significantly lower in the active lupus group compared with the non-active group. Moreover, the rates of adverse fetal outcomes in the active SLE group were significantly higher than those in the inactive group; there were significant statistical differences in the rates of abortion and preterm birth in the active lupus group compared with the non-active lupus group ($P \leq 0.05$), as shown in Table 3.

In the univariate analysis, preexisted hypertension, the absence of remission for at least 6 months preconception, active disease at conception, lupus nephritis, hypocomplementemia C3, hypocomplementemia C4, anti-dsDNA, antiphospholipid antibody syndrome, hypoalbuminemia, 24-h urinary protein > 500 mg, and lupus anticoagulant were significantly associated with adverse pregnancy outcomes among lupus patients. However, HCQ treatment and LMWH were associated with a lower risk of adverse pregnancy outcomes, as shown in Table 4.

Table 2 Laboratory characteristics of SLE patients at conception according to the occurrence of adverse outcomes

Variable	All SLE patients ($n = 116$)		With adverse outcomes $n = 62$ (53.4%)		Without adverse outcomes $n = 54$ (46.6%)		Test	*P*
	no.	%	no.	%	no.	%		
Anemia	73	62.9	43	69.4	30	55.6	2.356	0.125_c
Leucopenia	19	16.37	11	17.74	8	14.81	0.18	0.67c
Thrombocytopenia	10	8.62	6	9.67	4	7.4	f	0.74d
Antinuclear antibody	113	97.41	61	98.38	52	96.29	f	0.59 d
Hypocomplementemia C3	47	40.51	42	67.74	5	9.3	54.03	**.000c***
Hypocomplementemia C4	41	35.34	28	45.2	13	24.1	5.6	**0.017c***
Anti-ds DNA antibody	30	25.9	23	37.1	7	12.96	8.767	**.003c***
Lupus anticoagulant	25	21.6	21	33.9	4	7.4	f	**.0006d***
Anticardiolipin IgG antibody	16	13.79	13	20.96	3	5.6	f	**.028d***
Anticardiolipin IgM antibody	14	12.1	10	16.13	4	7.4	f	0.16d
Anti-β2 glycoprotein antibody	6	5.17	4	6.45	2	3.7	f	0.68d
Anti-Ro antibody	3	2.6	3	4.83	0	0	f	0.24d
Anti-La antibody	2	1.72	2	3.23	0	0	f	0.49d
Erythrocyte sedimentation rate	33 (6–130)		36 (6–99)		25 (10–130)		$u = 2.023$	0.30b
C-reactive protein	3.2 (0.2–39)		3.3 (0.3–39)		3.2 (0.2–20.9)		$U = 0.969$	0.332b
Serum albumin	3.66 ± 0.59		3.52 ± 0.57		3.83 ± 0.49		$t = 3.13$	**.002a***
Alanine aminotransferase	18 (6.7–46)		19.2 (7.4–42)		17 (6.7–46)		$U = 2.079$	0.41b
Aspartate aminotransferase	22 (9.1–48)		21.5 (9.1–45)		22 (12.3–48)		U = 2.742	0.32b
Blood urea nitrogen	2 2 (7–59)		22 (7–59)		23 (9–43)		$U = 2.66$	0.99b
Creatinine	0.5 (0.2–1.8)		0.4 (0.3–1.8)		0.5 (0.2–1.5)		$U = 2.57$	0.48b
24-h urinary protein	145.5 (70–6500)		569 (78–6500)		119.5 (70–932)		$U = 6.128$	**.000b***
24-h urinary proteinuria > 500 mg, *n* (%)	34 (29.3%)		29 (46.8%)		5 (9.3%)		40.9	**0.000c***
Creatinine clearance	94.2 (37–140)		96 (3–140)		91.2 (49.6–125)		$U = 1.96$	0.94b

SLE systemic lupus erythematosus; SLE, all values are presented as mean ± SD or median (range) or number (%). a, Independent *t*-test; b, Mann-Whitney *U*-test; c, chi-square test; d, Fisher test; insignificant, $P > 0.05$; significant, $*P \leq 0.05$

Table 5 shows the B regression coefficient estimate in the multivariable analysis model for the prediction of adverse pregnancy outcomes. We found that the absence of remission for at least 6 months at conception, preexisted lupus nephritis, active SLE disease at conception, C3 hypocomplementemia, and antiphospholipid antibody syndrome was significantly associated with the risk of adverse pregnancy outcomes in SLE patients.

The result of the Hosmer-Lemeshow test was $P = 0.129$, which indicated that the logistic regression model had a good fit. The AUC was 0.948 (Fig. 2), with a confidence interval of lower value = 0.908 and upper value = 0.988. In $P = 0.0001$, this suggests that the SLE score was excellent for discriminating against adverse pregnancy outcomes.

The risk score is based on five predictors identified from the multivariable logistic regression model (absence of remission for at least 6 months preconception, preexisted lupus nephritis, active SLE disease at conception, C3 hypocomplementemia, and antiphospholipid antibody syndrome). Each predictor is assigned a weighted point score. The sum of points represents the risk score, as shown in Table 6.

Table 7 coordinates potential development set cutoffs for the risk scoring system; a score of 2 was the best cutoff value (sensitivity of 93.55%, specificity of 85.19%, accuracy of 89.66%, PPV 87.88%, and NPV 92.00%). The rates of adverse pregnancy outcomes among pregnant SLE patients based on their cumulative risk score were risked score 0 (0%), risk score 1 (18.2%), risk score 2 (68.4%), risk score 3 (95.2%), risk score 4 (95.5%), and risk score 5 (100%). Trends toward increased risk of adverse outcomes with higher scores were observed).

As shown in Table 8 and Fig. 3, the rates of adverse pregnancy outcomes in low-risk groups (< 2 points) were 4 (8 %) and 58 (87.8%) in high-risk groups (≥ 2 points).

Discussion

Despite advances in the care of pregnant lupus patients, pregnancy is still associated with an increased risk of poor outcomes in SLE patients [16]. This work aims to identify factors associated with unfavorable pregnancy

Table 3 Maternal and fetal outcomes in SLE patients according to disease activity

Variable	All SLE patients ($n = 116$)		Active SLE ($n = 38$)		Inactive SLE ($n = 78$)		Test	*P*
	no.	%	no.	%	no.	%		
Adverse pregnancy outcome maternal and or fetal	62	53.4	36	94.7	26	33.3	38.72	**0.000c***
Gestational age at delivery, mean ± SD, weeks	38.09 ± 1.3		37.6 ± 1.4		38.36 ± 1.08		$t = 3.21$	**.0017a**
Maternal complications	no.	%	no.	%	no.	%	**Test**	*P*
Gestational diabetes	2	1.7	1	2.6	1	1.3	f	0.55 d
Pregnancy-induced hypertension	6	5.2	4	10.6	2	2.6	f	0.08d
Thromboembolism	2	1.72	2	5.3	0	0.0	f	0.11d
Preeclampsia	8	6.9	7	21.1	1	1.3	f	**.001 d***
Eclampsia	1	0.9	1	2.6	0	0.0	f	0.32d
Disease flare during pregnancy	16	13.8	11	28.94	5	6.41	10.9	**0.000c***
Disease flare postpartum	12	10.34	9	23.7	3	3.84	f	**0.002d***
Preterm delivery	10	8.62	7	18.42	3	3.84	f	0.**013d***
Intensive care admission	1	0.9	0	.0	16	1.3	f	0.99d
Fetal complications	no.	%	no.	%	no.	%	**Test**	***P***
Abortion	28	24.13	19	50	9	20.6	18.3	**0.000c***
Intrauterine fetal death	6	5.2	4	10.6	2	2.6	f	0.08d
Preterm birth	10	8.62	7	18.42	3	3.84	f	0.**013d***
Neonatal lupus	2	1.7	2	5.3	0	0	f	0.11d
Neonatal intensive care admission	1	0.9	1	2.6	0	0	f	0.32d

SLE systemic lupus erythematosus. All values are presented as mean ± SD or median (range) or number (%). a Independent *t*-test, c chi-square test, d Fisher test. Insignificant, $P > 0.05$; significant, $^*P \leq 0.05$

Table 4 Univariate analysis for predicting adverse pregnancy outcomes in lupus patients

Variable	Sig.	Odds ratio	95% CI for EXP(B)	
			Lower	Upper
Age at disease onset	0.54	0.666	0.176	2.513
Age conception	0.79	0.869	0.308	2.45
Preexisted hypertension	**0.04***	2.78	1.0017	7.7300
Absence of remission for at least 6 months	**0.000***	4.668	2.089	10.431
Active SLE disease at conception	**0.000***	36.000	8.035	161.290
Malar rash	0.16	1.7	0.808	3.58
Arthritis	0.28	1.6	0.676	3.778
Preexisted lupus nephritis	**0.000***	19.133	6.6296	55.2194
Antiphospholipid antibody syndrome	**0.000***	7.64	2.9912	19.5157
Hydroxychloroquine	**0.029***	0.385	0.163	0.909
Low-dose aspirin	0.56	0.747	0.279	2.001
Low-molecular-weight heparin	**0.0382***	0.307	0.101	0.938
Anti-hypertension	0.17	0.471	0.159	1.397
Hypoalbuminemia	**0.003***	0.333	0.159	0.694
Serum blood urea nitrogen	0.92	0.86	0.053	14.23
Serum creatinine	0.51	1.79	0.315	10.19
24-h urinary protein > 500 mg	**0.000***	8.533	3.19	22.82
Creatinine clearance	0.85	1.08	0.473	2.464
Hypocomplementemia C3	**0.000***	20.580	7.108	59.587
Hypocomplementemia C4	**0.01***	2.59	1.1675	5.7782
Anti-double-stranded DNA	**0.004***	3.960	1.53	10.204
Lupus anticoagulant (LA) antibody	**0.002***	6.4	2.035	20.14

SLE systemic lupus erythematosus, *CI* confidence interval, *OR* odds ratio; insignificant, $P > 0.05$; significant, $^*P \leq 0.05$

Table 5 Multivariate analysis for the prediction of adverse pregnancy outcomes in lupus patients

Variables	B	S.E.	Sig.	Exp. (B)	95% CI for EXP(B)	
					Lower	Upper
Absence of remission for at least 6 months at conception	1.651	.698	**.018***	5.213	1.326	20.490
Preexisted lupus nephritis	1.904	.876	**.030***	6.714	1.206	37.370
Hypocomplementemia C3	1.920	.692	**005***	6.824	1.759	26.469
Active SLE disease at conception	2.769	.881	**.002***	15.942	2.838	89.552
Antiphospholipid antibody syndrome	2.225	.703	**0.006***	9.257	2.335	36.706

Hosmer and Lemeshow test ($P = 0.129$)

CI confidence interval, *SLE* systemic lupus erythematosus

* $P \leq 0.05$

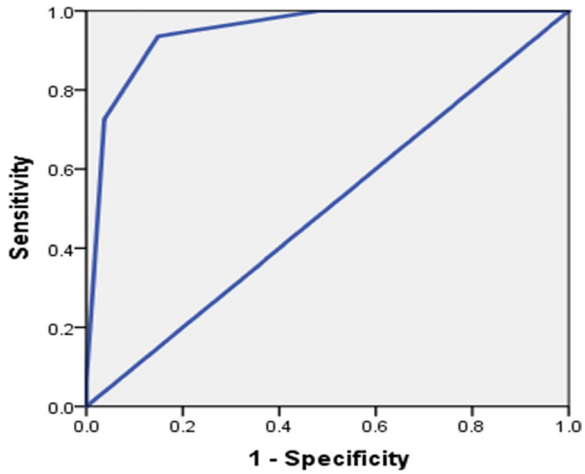

Fig. 2 Showing the ROC curve of the SLE score to discriminate against adverse pregnancy outcomes

Table 6 The B coefficient from the multivariable logistic regression model and corresponding risk score for predicting adverse pregnancy outcomes in lupus patients

Variables	B coefficient from multivariable	Score
Absence of remission for at least 6 months at conception	1.651	1
Preexisted lupus nephritis	1.904	1
Hypocomplementemia C3	1.920	1
Active SLE disease at conception	2.769	1
Antiphospholipid antibody syndrome	2.225	1
Total score	**Minimum (0)-maximum (5)**	

SLE systemic lupus erythematosus

outcomes and develop a predictive risk score for adverse pregnancy outcomes in patients with SLE.

Identifying risk factors for adverse outcomes is crucial in the counseling and care of SLE patients during pregnancy. Management should be planned accordingly to provide optimum care and support for the mother and her baby [17].

This work has demonstrated that 62 (53.4%) pregnant lupus women experienced adverse outcomes. Of these, 28 (24.3%) patients had abortions, 16 patients (13.8%) had disease flare during pregnancy, and 12 (10.34%) had disease flare postpartum. Ten (8.62%) patients had preterm labor, eight (6.9%) women had preeclampsia, six (5.2%)

Table 7 Prediction of adverse pregnancy outcomes in lupus patients using a risk score

Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
≥ 2	93.55%	85.19%	87.88%	92.00%	89.66%

PPV positive predictive value, *NPV* negative predictive value

Table 8 The adverse pregnancy outcome of lupus patients based on their cumulative risk score

Cumulative risk score (*n*)		Pregnancy outcome *N* (%)	
		Normal outcome (*n* = 54)	Adverse outcome (*n* = 62)
Risk score 0	(28)	28	0
	%	100.0%	0.0%
Risk score 1.00	(22)	18	4
	%	81.8%	18.2%
Risk score 2.00	(19)	6	13
	%	31.6%	68.4%
Risk score 3.00	(21)	1	20
	%	4.8%	95.2%
Risk score 4.00	(22)	1	21
	%	4.5%	95.5%
Risk score 5.00	(4)	0	4
	%	0.0%	100.0%

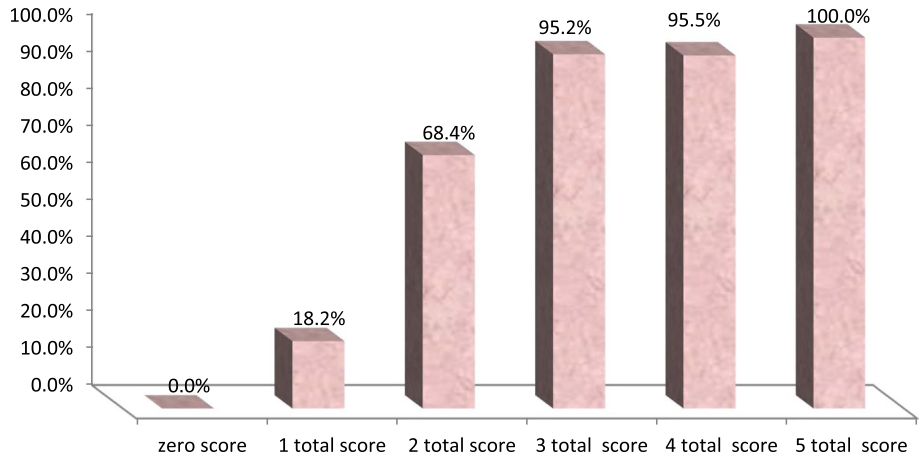

Fig. 3 The percent of adverse pregnancy outcomes and the risk score value.

had pregnancy-induced hypertension, and six (5.2%) patients had intrauterine fetal death, while thromboembolism, neonatal lupus, gestational diabetes, and eclampsia were found in 1.7%, 1.7%, 1.7%, and 0.9%, respectively. Previous cohorts have reported an increased risk of preterm labor, fetal losses, and hypertensive disorders including preeclampsia and eclampsia in SLE patients [18, 19].

In this study, the rate of fetal and maternal complications was significantly reduced in lupus patients who were planning to become pregnant, as we observed that a total of 61 pregnant patients (52.59%) had been in remission for at least 6 months before conception, with 39 (72.2%) having a favorable pregnancy outcome. These results were in line with earlier studies [20–23]. Planned pregnancy has been demonstrated to improve fetal and maternal outcomes, including a lesser risk of fetal loss, better preterm infant outcomes, and less severe disease flares throughout pregnancy [24, 25].

Additionally, SLE patients with adverse pregnancy outcomes had higher frequencies of active disease at conception, antiphospholipid antibody syndrome, preexisting hypertension, prior fetal complications, preexisted lupus nephritis, hypocomplementemia C3 and C4, and positive anti-ds DNA.

Similarly, a retrospective cohort study comparing adverse pregnancy outcomes between normal pregnancies and pregnancies with SLE concluded that SLE pregnancies, even in uncomplicated cases with remission, increase the risk of poor pregnancy outcomes, and the presence of lupus nephritis, chronic hypertension, antiphospholipid syndrome, active disease at the onset of pregnancy, and proteinuria was significantly associated with such outcomes [25]. This is consistent with prior findings as it was concluded that renal involvement, anti-dsDNA positivity, and antiphospholipid syndrome increased the risk of pregnancy complications [26–28].

In this study, there was a statistically significant reduction in adverse outcomes among pregnant patients taking HCQ and LMWH, which is consistent with previous studies showing that HCQ [29] and LMWH [30] intake decreased the incidence of adverse pregnancy outcomes in lupus patients.

Hence, after multivariate regression analysis, we observed the absence of remission for at least 6 months at conception, preexisted lupus nephritis, active SLE disease at conception, C3 hypocomplementemia, and antiphospholipid antibody syndrome were independent risk factors for poor pregnancy outcome. So, in terms of the performance of the risk score in predicting unfavorable pregnancy outcomes, we found that it had a sensitivity and specificity of 93.55% and 85.19%, with a PPV and NPV of 87.88% and 92.00%, respectively. Consequently, this simple scoring system might be useful to predict adverse outcomes in pregnant lupus women and, subsequently, optimum management in women with SLE who are planning for pregnancy.

So far, only a few studies have attempted to establish a prediction model and a risk score system for adverse pregnancy outcomes in lupus patients [31, 32]. As a result, the cumulative risk score, which suggests that a score of 2 is the best cutoff value, and the rates of adverse pregnancy outcomes were 4 (8%) in low-risk groups (< 2 points), and 58 (87.8%) in high-risk groups (≥ 2 points), is the key new findings in this study.

Overall, our data showed that well-controlled disease activity before and throughout pregnancy, management of antiphospholipid syndrome, and blood pressure adjustments during pregnancy are all necessary for pregnant SLE patients to have a favorable pregnancy outcome. As a result, comprehensive preconception

prenatal clinical screening is critical in risk-stratifying pregnant women with SLE.

In the absence of external validation of this prediction model's score, fundamental large-multicenter prospective studies are essential to reassess and verify the findings for generalization and clinical implications.

Limitations

The study had its limitations as a retrospective and single-center-based design and a relatively small study number, resulting in an underestimation of disease variables. Furthermore, fetal parameters such as intrauterine growth restriction and anomalies could not be accessed due to a lack of medical data. Large-scale prospective studies are warranted to verify the influence of various predicting factors on maternal and fetal prognosis.

Conclusions

A predictive model with a risk score classification for adverse pregnancy outcomes in SLE patients was developed in this study. This could help rheumatologists identify high-risk pregnant patients for better disease monitoring and management, resulting in better maternal/fetal outcomes.

Abbreviations

ACR	American College of Rheumatology Classification Criteria
Anti-dsDNA	Anti-double-stranded DNA antibodies
ANA	Antinuclear antibodies
AUC	Area under the receiver operating characteristic curve
HTN	Hypertension
HCQ	Hydroxychloroquine
IUFD	Intrauterine fetal death
HELLP	Hemolysis, elevated liver enzymes, and low platelet count
LMWH	Low-molecular-weight heparin
NICU	Neonatal intensive care unit
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating characteristics
SLE	Systemic lupus erythematosus
SLEDAI	SLE disease activity index

Acknowledgements

Declared none.

Authors' contributions

All authors have contributed to designing the study, collecting and analyzing, interpretation of data, and preparing and revising the manuscript. Design of the study: WM, RZ, and LK. Recruitment of patients: WM, RZ, and LK. Data collection: WM, RZ, and LK. Manuscript preparation and revision: WM, RZ, and LK. All co-authors have approved the final version of the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Availability of data and materials

The data will be available upon request.

Declarations

Ethics approval and consent to participate

An approval was obtained from the ethics committee of the Faculty of Medicine, Zagazig University, and the approval number was ZU-IRB#6437. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Informed written consents were obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 15 December 2021 Accepted: 7 May 2022
Published online: 03 June 2022

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