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A model to predict risk of postpartum infection after Caesarean delivery*

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ABSTRACT

Purpose: The purpose of this study is to build and validate a statistical model to predict infection after caesarean delivery (CD).

Methods: Patient and surgical variables within 30 d of CD were collected on 2419 women. Postpartum infection included surgical site infection, urinary tract infection, endomyometritis and pneumonia. The data were split into model development and internal validation (1 January–31 August; $N=1641$) and temporal validation subsets (1 September–31 December; $N=778$). Logistic regression models were fit to the data with concordance index and calibration curves used to assess accuracy. Internal validation was performed with bootstrapping correcting for bias.

Results: Postoperative infection occurred in 8% (95% CI 7.3–9.9), with 5% meeting CDC criteria for surgical site infections (SSI) (95% CI 4.1–5.8). Eight variables were predictive for infection: increasing BMI, higher number of prior Caesarean deliveries, emergent Caesarean delivery, Caesarean for failure to progress, skin closure using stainless steel staples, chorioamnionitis, maternal asthma and lower gestational age. The model discriminated between women with and without infection on internal validation (concordance index = 0.71 95% CI 0.67–0.76) and temporal validation (concordance index = 0.70, 95% CI 0.62, 0.78).

Conclusions: Our model accurately predicts risk of infection after CD. Identification of patients at risk for postoperative infection allows for individualized patient care and counseling.

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Introduction

Over 1 million Caesarean deliveries (CD) were performed in the USA in 2014 accounting for 32% of all births [1]. Recent estimates of postoperative infection after CD range between 3% and 20% [2–4]. In high-risk groups, such as those who are morbidly obese, rates may be as high as 30% [5,6]. Postoperative infections significantly increase health care costs due to hospital readmissions, reoperations and home health-care needs [7,8].

Evidence-based strategies for prevention of infection after CD are recommended by the Centers for Disease Control and Prevention (CDC) and endorsed by the American College of Obstetricians & gynecologists (ACOG) [9,10]. In recent years, recommendations for prophylactic antibiotics to be given within 30–60 min of incision and preoperative skin preparation with antiseptic solutions have been universally adopted as standard surgical practice within the USA [10]. While these preventive measures have decreased

the rate of infections, they remain a common and significant problem [2–7].

Increasing data support that multidisciplinary initiatives involving various preoperative, perioperative and postoperative measures can lead to reductions in surgical site infection and other infections that occur in the postoperative period [11–13]. Riley et al. demonstrated a significant decline in surgical site infections (SSI) rates by 63.5% after implementing various evidence-based infection control interventions aimed at risk reduction [12]. Although the total infection rate after CD is low, certain populations of patients appear to be at significantly higher risk of postpartum infectious complications. Therefore, identification of at-risk groups for implementation of quality improvement measures and infection control interventions is likely to have the most benefit. Improved accuracy in identifying patients increased risk for infection may allow clinicians to implement additional preventive measures during, or immediately following delivery. The objectives of this study were to build, and validate a



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Table 1. Comparison of maternal characteristics between women who did or not develop an infection after Caesarean delivery.

Characteristics	Post-Caesarean infection (n = 201)	No infection (n = 2218)	p Value
Age (years)	30.4 (6.1)	31.0 (5.4)	.22
Gestational age (days)	270 (16.8)	267 (22.6)	.47
Parity			.47
0	93 (46.3)	914 (41.2)	
1	62 (30.8)	793 (35.7)	
2	23 (11.4)	370 (16.7)	
3	16 (8.0)	87 (4.0)	
4	4 (2.0)	32 (1.4)	
>5	3 (1.5)	22 (1.0)	
GBS colonization	47 (23.4)	509 (22.9)	.85
BMI	37.0 (9.5)	33.2 (7.0)	<.001
Smoking	24 (11.9)	164 (7.4)	.02
Comorbidities			
Pregestational DM	10 (5.0)	61 (2.8)	.07
Asthma	30 (15.0)	139 (6.3)	<.001
Preeclampsia	19	152	.17
IUGR	13	126	.64
Oligohydramnios	10	77	.27
Gestational HTN	8	62	0.34

Number (N) or mean rates and their % or standard deviation. Bold values represent the significance $p > .05$.

statistical model that can predict an individual's risk of infection after Caesarean delivery.

Materials and methods

Study design and data collection

Data were collected by retrospective chart review for all women who underwent Caesarean delivery from 1 January 2013 through 31 December 2013 at a multi-center tertiary care academic health care institution. Institutional Review Board approval for the study was obtained. Potential subjects were identified by their *Current Procedural Terminology* code for Caesarean section (59,510, 59,514, 59,515, 59,618, 59,620 and 59,622). All patients who underwent Caesarean delivery during the time period were included. There were no exclusionary criteria. All data were collected by one reviewer and entered into a secure REDCap database [14]. Data were collected after reviewing all available prenatal visits, prenatal laboratory testing, and documentation provided during labor and delivery, including the Caesarean section operative reports. Documentation after delivery and postoperative visits for 6 weeks after delivery was also reviewed.

A list of all collected candidate predictors is provided in Table 1. Type of Caesarean delivery was categorized as emergent, scheduled or unscheduled as designated in Table 2. The designation of emergent Caesarean section was defined as occurring at least 30 min from decision to incision time, using the quality metric promoted by ACOG and the American Society of Anesthesiologists [15]. Unscheduled Caesarean sections

Table 2. Comparison of surgical characteristics between women who did or not develop an infection after Caesarean delivery.

Characteristics	Post-Caesarean infection (n = 201)	No infection (n = 2218)	p Value
Surgical indication			
Prior Caesarean	65 (32.3)	924 (41.7)	.01
Fetal Presentation	19 (9.5)	376 (17.0)	.006
Arrest of Labor	76 (37.8)	457 (20.6)	<.001
Fetal Intolerance	54 (26.9)	389 (17.5)	.001
Macrosomia	9 (4.5)	76 (3.4)	.44
Timing of Delivery			<.001
Emergent	28 (13.9)	113 (5.1)	
Scheduled	62 (30.8)	1040 (46.9)	
Unscheduled	111 (55.2)	1065 (48.0)	
Preoperative Hgb	12.0 (1.3)	12.1 (1.2)	.08
Chorioamnionitis diagnosis	24 (11.9)	111 (5.0)	<.001
Blood transfusion	15 (7.5)	50 (2.3)	<.001
Estimated blood loss (mL)	819 (551)	732 (310)	.07
Length of surgery (min)	58.3 (27.7)	53.7 (20.1)	.06
Skin closure			<.001
Staples	51 (25.4)	359 (16.2)	
Suture	150 (74.6)	1857 (83.7)	
Resident participation	27 (13.4)	174 (7.8)	.83

Number (N) or mean rates and their % or standard deviation.

Bold values represent the significance $p > .05$.

BMI: body mass index; DM: diabetes mellitus; IUGR: intrauterine growth restriction; GBS: Group Beta Streptococcus; HTN: hypertension.

were classified as those not planned in advance, but not performed emergently within a 30 min timeframe from delivery to incision time. Scheduled Caesarean sections were defined as Caesarean deliveries planned in advance in the medical record, prior to the patient's arrival on the labor and delivery unit. All indwelling bladder catheters are routinely removed by 8AM on the morning of postoperative day 1 at our institution. Exceptions to this include patients in whom accurate assessment of urine output is important such as those receiving magnesium sulfate therapy and intraoperative cystostomy. Postoperative drains were not used in the study population.

Postpartum infection model outcomes

The outcome of the model was defined as a patient diagnosed with any infection within 30 d after delivery attributable to the surgical procedure defined as surgical site infections, urinary tract infection, endomyometritis, pneumonia, *Clostridium difficile* infection and bloodstream infection. All postpartum infections were grouped into one infectious outcome to determine a single estimate of risk for providers and patients to easily understand and to help guide management of postpartum infection which consists of administering goal-directed therapy with broad-spectrum antibiotics while awaiting results of cultures to guide directed treatment. Specifically, SSI were defined using the CDC criteria and categorized as superficial incisional primary SSI, deep incisional SSI and organ/space SSI [16].

Diagnosis of urinary tract infection was made in two ways and the method of diagnosis was recorded. Primarily, the guidelines of the Infectious Disease Society of America (IDSA) for patients with recent catheter use were followed requiring documentation of a positive urine culture with greater than 10^3 colony forming units (CFU) of bacteria per mL along with patient reported symptoms [17]. Additionally, symptomatic urinary tract infections (patient reported dysuria, fever or urgency) along with urine sample indicative of potential infection without a documented urine culture that resulted in treatment with antibiotic therapy at the discretion of the treating provider were included.

Diagnosis of endomyometritis was made if patient developed a fever of $\geq 38.0^\circ\text{C}$ greater than 24 h from delivery with clinical signs of endomyometritis, including fundal tenderness, foul-smelling lochia, maternal tachycardia and/or maternal leukocytosis (WBC $>15,000$) documented within the medical record within 30 d of surgery in the absence of another infection. Diagnosis of pneumonia was made based upon clinical symptoms and radiographic findings suggestive of pneumonia. *Clostridium difficile* infection was defined by positive stool PCR test after testing was performed for new onset diarrhea symptoms that began during hospitalization. Bloodstream infection was defined as postpartum fever of ≥ 38.0 degrees Celsius with positive blood culture of a non-contaminant bacteria.

Model building

The original 12 months dataset was split into two parts: (1) a model development and internal validation subset consisting of all patients who delivered between 1 January through 31 August and (2) a temporal validation subset consisting of all patients that delivered between 1 September and 31 December. Temporal validation is considered a method of validation in between internal and external validation and is preferred over randomly splitting data into a training and testing subset [18]. This subset was held out of the model development and internal validation analysis.

A multivariable logistic regression model was fit onto the model development subset. Prior to reducing the variables in this full model, each variable was checked for issues of collinearity using the variable inflation factor. If collinearity was present, then that variable was removed from the full model. The model was further reduced to find the best parsimonious model. Variable reduction was performed using

Harrell's "Stepdown" approximation method, which reduces the variables by ranking each variable's reduction in the model's R^2 from the smallest change in R^2 to the largest change [19]. At each removal, the discrimination of the model was calculated and stopped when the change in discrimination was less than 0.001.

Model accuracy

Model accuracy was measured using two methods: discrimination and calibration. Discrimination was determined using the concordance index or c-statistic. The concordance index reflects the probability that for any randomly selected pair of individuals, one with and one without the outcome, the model assigns a higher probability to the individual with the outcome [20]. The concordance index ranges from 0 to 1, where 1 indicates perfect discrimination (model discriminates 100% of the time) and 0.5 indicates the model performs no better than chance (model discriminates 50% of the time). The model's accuracy was also visualized using a calibration plot, which plots the model's predicted risk versus actual risk along a range of predicted probabilities. This plot displays the direction and magnitude of model miscalibration across the probability range and a straight 45° line indicates perfect relationship. Finally, a measure of overall performance was assessed using the Brier score [21]. During internal validation, bias-corrected estimates of discrimination and calibration were measured using 1000 bootstrap resampling to reduce overfitting bias in the reported measurement or plot. Once the model was built and internally validated, the model's performance was tested on the remaining temporal validation subset. A nomogram was created for easier visualization of the risk factors and outcome and an online calculator was built to facilitate clinical use of the model.

Finally, a decision curve was plotted to inform clinicians about the range of threshold probabilities for which the prediction model would be of clinical value [22]. Decision curve analysis offers insight into clinical consequences of using the model by determining the relationship between a chosen predicted probability threshold and the relative value of false-positive and false-negative results to obtain a value of net benefit of using the model at that threshold [23–26]. All analyses were performed using R version 3.2.3 (SPSS Inc., Chicago, IL) and methods of Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) were followed [18].

Results

Of the 2419 women, 8.3% ($n=201$; 95% CI 7.3–9.9) developed a postoperative infection. Postoperative infections are displayed in Table 3. On further analysis, 5.8% ($n=140$; 95% CI 4.6–6.5) developed a CDC defined surgical site infection including: 4.9% ($n=131$; 95% CI 4.1–5.8) superficial incisional SSI, 0.6% ($n=15$; 95% CI 0.4–1.0), deep incisional infection, and 0.3% ($n=7$; 95% CI 0.1–0.6) with organ/space infection. 1.5 percent ($n=36$; 95% CI 1.1–2.1) experienced a UTI, 1.6% ($n=38$; 95% CI 1.1–2.2) endometritis, 0.2% ($n=4$; 95% CI 0.1–0.5) pneumonia, 0.1% ($n=2$; 95% CI 0–0.3) *C. difficile* colitis and 0.1% ($n=3$; 95% CI 0–0.4) with bacteremia.

Table 1 illustrates the comparison of baseline maternal characteristics in women who underwent Caesarean delivery and had an infection compared to those who did not have an infection. Table 4 demonstrates the surgical characteristics of women who underwent Caesarean delivery who did and who did not develop an infection.

The model development and internal validation subset included 1641 patients and the temporal

Table 3. Postoperative infections after Caesarean delivery.

Infection	<i>N</i> = 201	%
Surgical site infection	140	5.8
Superficial SSI	131	4.9
Deep incisional SSI	15	0.6
Organ/space SSI	7	0.3
Endomyometritis	38	1.6
Urinary tract infection	36	1.5
Pneumonia	4	0.2
<i>C. difficile</i> colitis	2	0.1
Bacteremia	3	0.1

Data displayed as number (*N*) and percentage (%).

validation subset included 778 patients. Forty-six candidate risk factors were considered during creation of the model. The variable elimination process resulted in eight factors in the final best parsimonious model that predicted risk of infection including: increasing BMI, increased number of prior Caesarean deliveries, emergent timing of Caesarean delivery, Caesarean for failure to progress, closing skin using staples, chorioamnionitis, maternal asthma and lower gestational age. Table 4 illustrates each variable in the final model and the interquartile-range odds ratios for continuous predictors and simple odds ratios for categorical predictors. Since there was an interaction allowed in the model between Caesarean type and BMI, each odds ratio in the table depends on the setting of at least one other factor. Increasing BMI, emergent Caesarean, and previous number of Caesarean deliveries were the strongest predictors for infection in the final model. The nomogram illustrated in Figure 1 allows one to visualize the relationship of the predictors to one another to manually calculate predictions and is available as an online tool at Temporary link for peer review.

On internal validation, the final model was able to accurately discriminate between women with and without infection 71.2% of the time (concordance index = 0.712, 95% CI 0.672–0.755, Brier = 0.068). When the final model was tested on the temporal validation subset, the model was able to discriminate 69.6% of the time (concordance index = 0.696 (95% CI 0.621, 0.776), Brier score = 0.076). Figure 2 demonstrates accuracy of the model using the calibration curve during temporal validation. The curve demonstrates that the model is most accurate when predicted

Table 4. Interquartile-range odds ratios for continuous predictors and simple odds ratios for categorical predictors for a final model predicting risk of infection after Caesarean delivery.

Risk factor	Low	High	Diff	Effect	SE.	Lower 0.95	Upper 0.95
Body mass index (kg/m ²)	28.15	36.79	8.64	0.361	0.134	0.099	0.623
Odds ratio	28.15	36.79	8.64	1.435		1.104	1.865
Number of prior CDs	1	5	4	2.412	0.647	1.143	3.680
Odds ratio	1	5	4	11.154		3.137	39.662
Emergent: unscheduled	3	1		0.791	0.367	0.0722	1.510
Odds ratio	3	1		2.205		1.075	4.525
Scheduled: unscheduled	3	2		−0.268	0.289	−0.834	0.299
Odds ratio	3	2		0.765		0.434	1.348
CD for failure to progress	2	1		1.040	0.283	0.486	1.595
Odds ratio	2	1		2.830		1.625	4.927
Skin closure – staples: suture	2	1		0.294	0.223	−0.144	0.732
Odds ratio	2	1		1.342		0.866	2.078
Chorioamnionitis	1	2		0.569	0.312	−0.043	1.181
Odds ratio	1	2		1.767		0.958	3.257
Asthma	2	1		0.579	0.296	−0.0003	1.158
Odds ratio	2	1		1.784		1.000	3.184
Gestational age (days)	266	277	11	−0.146	0.057	−0.257	−0.035
Odds ratio	266	277	11	0.864		0.773	0.966

Interquartile-range odds ratios for continuous predictors and simple odds ratios for categorical predictors.

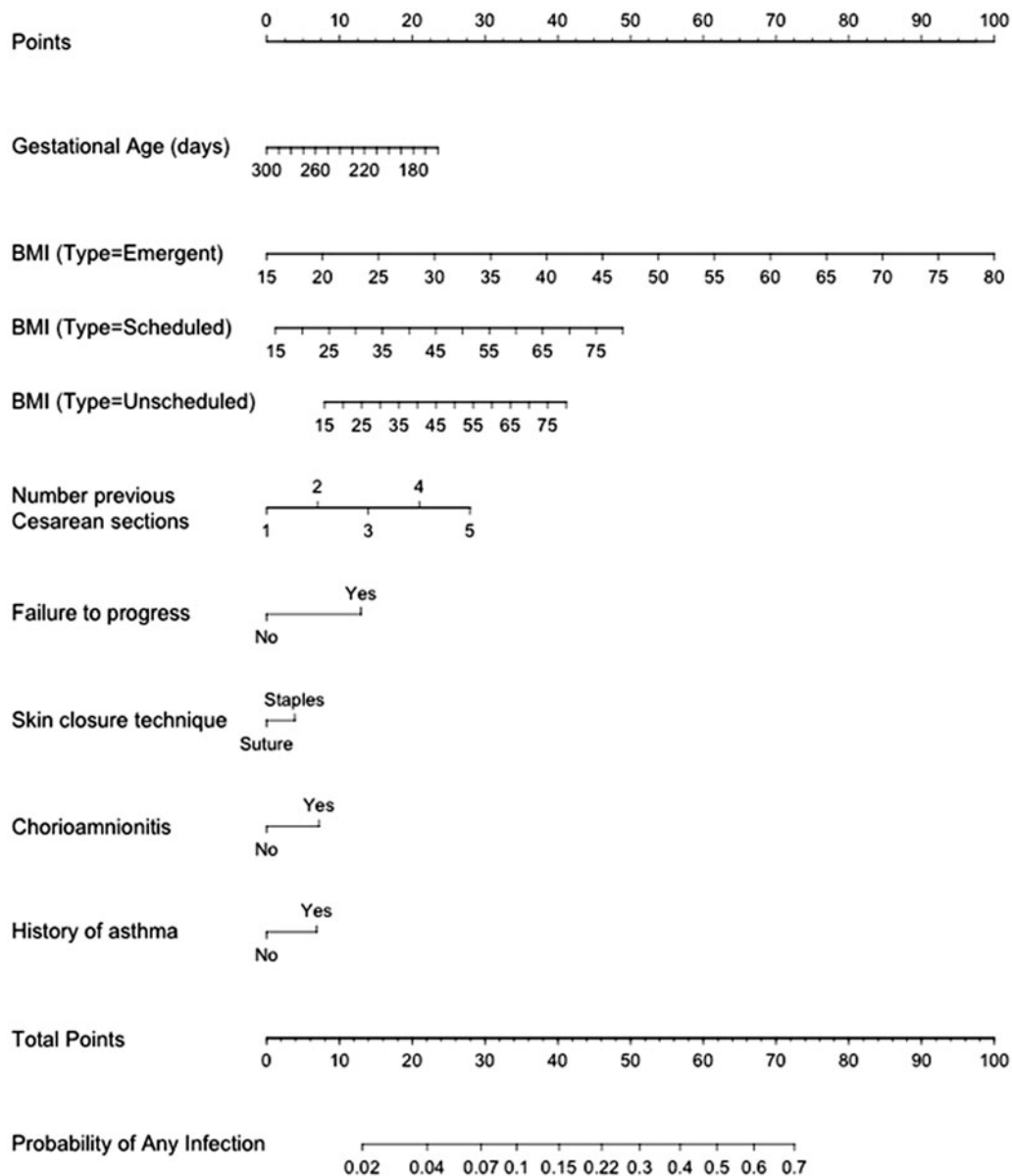


Figure 1. Nomogram for predicting the probability of postoperative infection after Caesarean section. The first row (points) is the point that is assigned to each variable from rows 2 to 10, which are the variables that are included in the predictive model. The assigned points for all variables are then added to determine the total points. A vertical line can be drawn from the total points to the predicted probability of postoperative infection line.

probabilities range from 0 to 45% and the model begins to predict slightly higher than actual probabilities when predictions exceed 50–60%.

The decision curve analysis in [Figure 3](#) displays the net benefit curves for the model predicting risk of developing a postoperative infection after Caesarean section. For example, if a clinician's threshold of 10% is used to designate an individual at high risk of developing an infection and if patients met this threshold they would receive additional therapy, the net benefit of the model is that the model identifies 35 more cases per

1000 without increasing the number treated unnecessarily when compared with treating all patients with prophylactic antibiotics plus additional therapy (e.g. more antibiotics). There seems to be no net benefit in using the 60% threshold for the model for identifying women who are at an increased risk of developing infection. Making decisions based on the model provides superior net benefit to the patient compared with the curve for "treat all" (i.e. additional antibiotic dosing above the recommended prophylactic therapy to everyone) for thresholds between 5 and 55%.

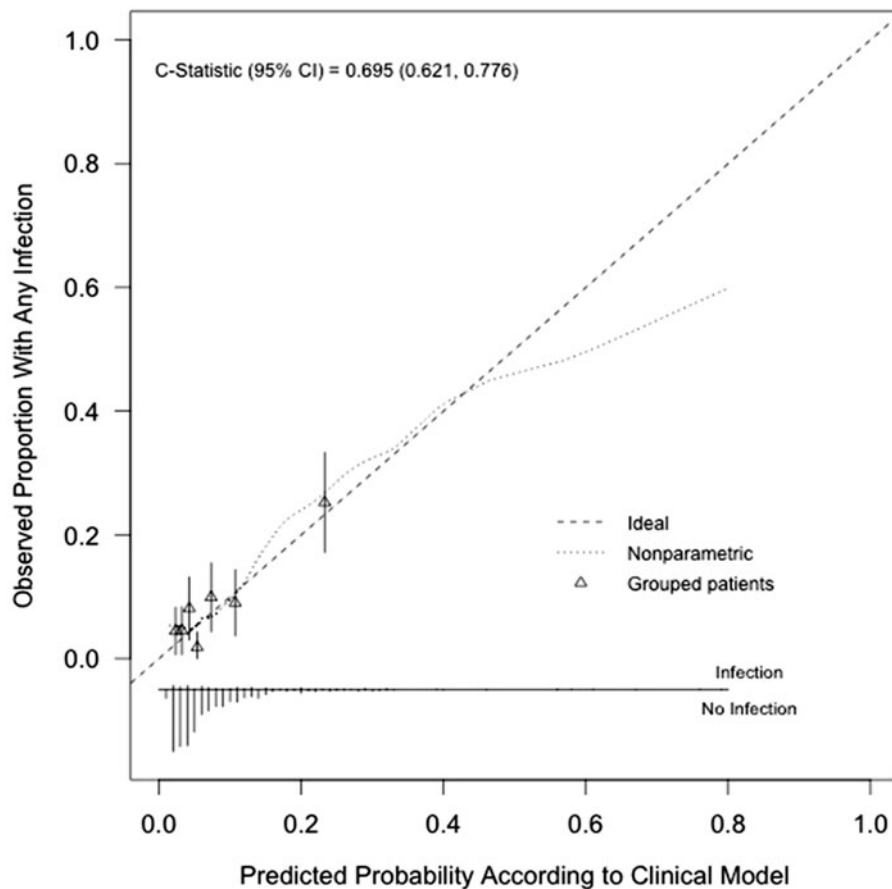


Figure 2. Calibration curve demonstrating the model's performance predicting risk of developing a postoperative infection after Caesarean section on the temporal validation dataset.

Discussion

In current obstetric practice, providers have few strategies to counsel a woman regarding her risk of developing an infection in the postpartum period. At this time, the most accurate method uses current literature to describe the reported rates of infection within entire populations or certain cohorts of women having Caesarean delivery. While evidence based, the accuracy of this approach is unknown and it does not attempt to personalize prediction for women who have significantly different risk factors. This study has demonstrated the amount of accuracy in making clinical predictions using a model which we believe is more useful than an unknown degree of accuracy in routine clinical practice. Although we did not compare the model's predictions to clinical guess, most models outperform individual and groups of expert predictions [27].

In this study, we have developed and validated a statistical model that can predict a woman's individual probability of developing a postoperative infection after Caesarean delivery. The model provides a predicted probability of an individual's risk of infection

while accounting for multiple risk factors and is accurate in discriminating patients approximately 70% of the time.

Multivariate logistic regression techniques were used in this study since they result in interpretable and accurate prediction models and they have been used to develop other common prediction tools with similar accuracy such as a vaginal birth after Caesarean delivery model (external validation area under the curve = 0.70), the National Cancer Institute model for predicting breast cancer (concordance index of 0.58), and the Framingham cardiovascular risk model (concordance index of 0.72) [28–31]. As with the above prediction models that are widely used in clinical practice, our model provides obstetric providers and patients with an accurate, personalized and tangible assessment of their individualized risk of developing an infection within the first 30 d after CD. This nomogram, which incorporates eight variables determined immediately postpartum, allows for a patient-specific risk assessment of postpartum infection in women undergoing CD. This individualized nomogram acknowledges the many surgical and patient risk factors that have been associated with postpartum

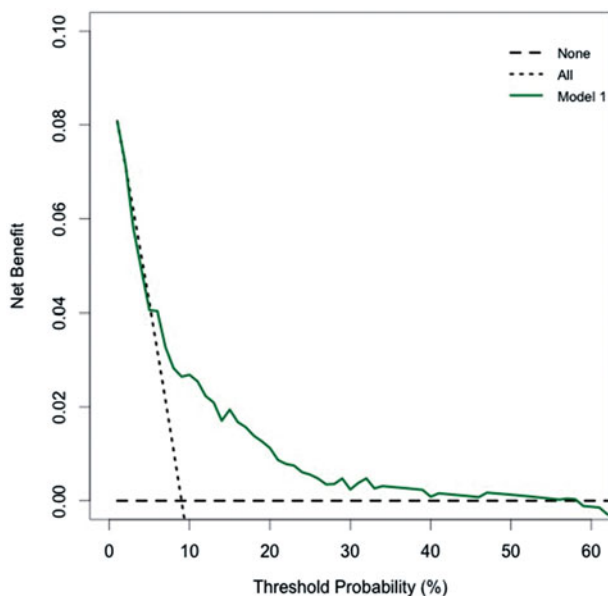


Figure 3. Decision curve analysis of the model. The figure displays the net benefit curves for the model predicting risk of developing a postoperative infection after Caesarean section. For example, if a clinician's threshold of 10% is used to designate an individual at high risk of developing an infection and if patients met this threshold they would receive additional therapy, the net benefit of the model is that the model identifies 35 more cases per 1000 without increasing the number treated unnecessarily when compared with treating all patients with prophylactic antibiotics plus additional therapy (e.g. more antibiotics). There seems to be no net benefit in using the 60% threshold for the model for identifying women who are at an increased risk of developing infection.

infection over time and allows for improved provider to patient counseling regarding infectious outcomes.

Increasing BMI was a strong predictor for postoperative infection, particularly in patients undergoing emergent surgery in this study. Stamilio et al. demonstrated that wound separation, incisional seroma, wound hematoma, wound infection, endometritis and hospital readmission were also significantly higher in obese patients (BMI > 30), and rates were 2–4 times higher in those with extreme obesity (BMI > 45) [6]. Therefore, it is not surprising that the combination of increasing BMI with emergent surgery had significant prognostic impact in our model. At this time, however, there is conflicting evidence whether giving higher antibiotic dosages above a certain weight impacts infectious outcomes [32,33]. This model may be useful in this situation. Using the model, providers can obtain a more specific individual risk while accounting for multiple risk factors rather than just BMI alone. If elevated above a threshold, clinicians might consider additional therapy or closer surveillance during the postoperative period. If a clinician's threshold for using additional therapy or increased surveillance is for

patients with risks anywhere between 5 and 55% then our decision analysis demonstrates there is net benefit to using the model compared to treating or monitoring all high risk (e.g. obese) patients without increasing false positives. The model supports the informed consent process by providing a better estimation of risks to the patient, which may heighten the patient's awareness of signs and symptoms of infection in the postoperative period.

Several additional risk factors were also predictive of postoperative infection. Increasing number of prior CDs was identified as a significant predictor which is consistent with previous large observational studies have shown that patients undergoing multiple repeat CDs have higher maternal morbidity and the associated risks of blood transfusion, cystotomy and hysterectomy are increased with each subsequent surgery [34–37]. Similar to the model, previous studies have demonstrated failure to progress as a risk factor for postoperative infection [2,38]. Several well-documented factors have been implicated for labor dystocia including older maternal age, increasing obesity, uterine abnormalities, short maternal stature (<150 cm), late term pregnancy, suspected cephalopelvic disproportion, nulliparity and fetal macrosomia [38,39]. Skin closure with stainless steel staples versus suture was also a predictor in the model and consistent with prior studies that have shown overall reduced wound complication rates with suture closure compared to staple closure [4]. Our model supports previous research that wound closure with suture material has improved outcomes compared to staples.

A strength of the model is that it combines these risk factors into a single prognostic probability that is easily interpretable to the patient and clinician and predicts risk of any infection within the postpartum period that would be attributed to their surgery. We deliberately grouped all infections into a single outcome for three reasons. Primarily, to provide a single estimate of risk for patients to easily understand and because the number of events were too few to build an accurate model for each subtype of infection. While many unique risk factors do contribute to each individual infection, the purpose of the model is to be able to provide a simple risk assessment that is helpful for patient counseling and treatment planning based upon patient, surgical and obstetric variables. Additionally, while there may be different risk factors associated with each infection type, current clinical decision-making focuses on treatment of all causes of postpartum febrile morbidity in a similar way around the time of delivery. That is, preventive treatment management consists of administering broad-spectrum

antibiotics initially and awaiting results of cultures to guide directed treatment. Since some antibiotics typically used for surgical site infections also affect some pathogens that contribute to endometritis and urinary tract infections, it makes sense to have those infections in a prediction model.

The data used for our model were collected from a standardized obstetric electronic medical record from three different hospitals in a single multicenter academic institution with approximately 10,000 deliveries per year. While the patient population seen at this institution is geographically and demographically diverse, the model should be further tested in additional geographical areas. The retrospective nature of our study introduces the potential for documentation bias. Despite these limitations, we feel that the model is ready for clinical use given the model's performance during temporal validation and since the model improves upon the alternative which includes highly variable clinician estimates. In the future, our model could also be useful for researchers to determine inclusion criteria for trials evaluating impact of certain interventions on infectious outcomes after CD, especially when attempting to enroll patients at high risk of infection after delivery.

This predictive nomogram, which incorporates eight variables determined immediately postpartum, allows for the determination of a patient-specific risk of postpartum infection in women undergoing CD. Identification of patients at risk for postoperative infection allows for individualized patient risk assessment, implementation of multidisciplinary strategies for infection reduction and patient-specific counseling.

Disclosure statement

No financial benefit or interest has arisen from direct applications of this research for all authors.

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