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Risk factors, early and late postpartum complications of retained placenta: A case control study

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ABSTRACT

Objectives: To identify risk factors and complications associated with 3rd stage of labor removal of placental fragments (3rd SRPF) by manual uterine revision under a strict protocol.

Study design: Ten years retrospective register-based cohort study of vaginal deliveries. Women with 3rd SRPF n = 3297 (exposed) and those without n = 97,888 (non exposed) were compared.

Main outcomes measures: (1) risk factors for 3rd SRPF aOR (95%CI) (2) early (2a) and late (2b) maternal complications.

Results: (1) Risk factors for 3rd SRPF procedure were assisted reproductive technologies 2.20 (1.73–2.34), preterm delivery 2.53 (2.21–2.88), preeclampsia 1.66 (1.25–2.21) Multiple previous early pregnancy loss (>3) 1.40(1.19–1.66), VBAC 1.26(1.13–1.47) and epidural analgesia 1.56 (1.46–1.69). (2a) Early complications: puerperal fever 1.1% vs 0.3%, blood transfusion 9.0% vs. 0.5%, prolonged maternal hospitalization 21.0% vs. 11.4%, all P < 0.0001. Puerperal readmission was 0.819% in the 3rd SRPF vs. 0.315% the control group, P < 0.0001. (2b) Late complications: retained placenta and hysteroscopy / D&C rates were significantly higher among the 3rd SRPF vs. controls: 40.7% vs. 7.1%, 14.8% vs. 3.6% and 48.1% vs. 18.2%, respectively, all P < 0.0001.

Conclusion: Uterine revision for 3rd SRPF is associated with significant early and late maternal morbidity; should be considered discriminative of a population at risk and postpartum health care planning, beyond being a therapeutic intervention.

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Introduction

Retained placenta, which is diagnosed in 0.1–3.3% of vaginal deliveries [1], is associated with significant maternal morbidity and mortality in up to 10% of cases without intervention [2].

The approach to diagnosis and treatment of retained placenta or suspected retained placental fragments is manual revision of the uterine cavity under appropriate analgesia/anesthesia. Due to the intrusive nature of this action, the risk of uterine infection and bleeding is increased, together with late sequelae such as readmission for additional procedures, hysteroscopy and subsequent secondary infertility [3]. Although studies have directly

addressed abnormalities of the 3rd stage of labor, there is currently no accepted protocol for its management, including the manual revision of the uterus [4].

We aimed to identify risk factors for the procedure of manual revision of the uterine cavity due to retained placenta or suspected retained placental fragments, performed under a strict protocol; as well as early and late maternal complications of this procedure.

Materials and methods

This is a retrospective register-based cohort study of women who had vaginal delivery at the Shaare Zedek Medical Center between 1/7/2005 and 30/04/2014. For the purpose of the study we defined 3rd stage retained placental fragments (3rd SRPF) as manual removal of placenta or placental fragments performed in the 3rd stage of labor. The study group included all women that had 3rd SRPF, exposed. Those who had a vaginal birth with a normal 3rd stage of labor were included as reference, group non-exposed.

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The departmental protocol for diagnosis and management of the 3rd stage of labor includes administration of 10 IU prophylactic oxytocin (IM) after delivery of the fetal shoulder. In case of suspected retained fragments of the placenta or the placenta has not been spontaneously expelled within 40 min from neonate delivery, and decision to perform a manual revision is taken by the senior obstetrician present [5,6]. "Free hand" manual revision of the uterine cavity is performed and prophylactic IV 2nd generation cephalosporin antibiotic therapy is administered. The procedure is performed by a trained obstetrician in a sterile field under appropriate analgesia. Hospital discharge is not preceded by a routine sonographic examination of the uterine cavity.

Study data was pulled from the real-time electronic medical records and cross linked with hospital blood bank records and readmissions. Relevant data from the two digital records for individual patients was matched. The data extraction was performed by two independent authors (RF and SGG) and reevaluated before statistical analyses by another two authors (MBL and IZ). Discrepancies were extracted and reevaluated separately and in the data reported in accordance to the STROBE guidelines [7].

The study protocol was approved by the local Institutional Review Board with a waiver of informed consent due to retrospective observational nature of study.

The outcomes were: 1. Risk factors for 3rd SRPF procedure 2(a) early and (b) late postpartum maternal morbidity related to 3rd SRPF procedure. Thus, we set our dependent variables as early and late postpartum maternal morbidity.

Early postpartum maternal morbidity was defined as: 1. postpartum hemorrhage (PPH), including a decrease in hemoglobin $\geq 3\%$ between admission and the lowest measured level or a cumulative blood loss greater or equal to estimated 1000 ml or signs or symptoms of hypovolemia that were treated by RBC units transfusion. 2. Puerperal febrile morbidity within 72 h after delivery without evidence of source other than endometritis or which presented with fever proceeding labor or intrapartum 3. Prolonged hospital stay: more than 72 h after delivery; postpartum hysterectomies and admission to intensive care unit (ICU) due to hypovolemic instability.

Late postpartum maternal morbidity was defined as readmission to within six weeks after delivery due to suspicion of genital tract related complications: bleeding (a decrease in hemoglobin $\geq 3\%$ between readmission and the lowest measured level), fever or surgical intervention.

The independent variables were maternal age, education, ethnicity, parity, previous cesarean section, preterm labor, neonatal birth weight, gestational complication (gestational hypertension, gestational diabetes mellitus (GDM), assisted reproductive technology (ART), and multiple previous early pregnancy loss (>3).

Maternal and labor characteristics were depicted as percentages, means \pm SD, and/or medians with interquartile ranges. Comparisons included Chi-square test or Fisher exact test for categorical variables and *t*-test or Mann-Whitney test for continuous variables. Multivariate backward, stepwise logistic regression analysis models were fitted to identify risk factors and complications associated with 3rd SRPF. The criteria for inclusion in the model were a univariate probability value ≤ 0.05 . Goodness-of-fit was checked by Hosmer-Lemeshow test. Odds ratios (OR) and 95% confidence intervals (95% CI) were reported. All *p* values presented are 2-sided and *p* values < 0.05 were considered as statistically significant. Analyses were carried out with the IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY

Ethics approval: The study protocol was approved by the local Institutional Review Board and a waiver of informed consent was endorsed due to retrospective observational nature of study.

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Results

Overall, 101,185 women who had a vaginal delivery at our Medical Center during the study period. A total of 3297 (3.3%) women underwent manual revision of the uterine cavity for retained placental fragments during the 3rd stage of delivery, exposed and 97,888 (96.7%) women were included in the non-exposed group.

Risk factors for retained placenta and manual uterine revision

The univariate analysis of the maternal characteristics of the exposed and non-exposed groups showed that mean age of women in the control group was slightly higher, although not clinically significant; a higher proportion of women were aged >35 years in the exposed group. Ethnicity and level of education were similar in the two groups. The exposed group was characterized also by significantly higher proportions of women had ART, multiple early pregnancy losses and were diagnosed with preeclampsia. The delivery of this group had a significantly higher rate of vaginal birth after Cesarean (VBAC), induction of labor, instrumental delivery, and epidural anesthesia ($P < 0.0001$). The neonatal characteristics examined were significantly different in the 3rd SRPF group compared to the control group; higher rates of preterm delivery, small for gestational age (SGA) neonates, and female gender ($P < 0.01$) (Table 1).

After adjusting for co-variables, the significant clinical history related risk factors for 3rd SRPF were ART 2.20, [1.73–2.34], $P < 0.0001$, preterm delivery 2.53, [2.21–2.88], $P < 0.0001$, preeclampsia 1.66, [1.25–2.21] $p < 0.0001$, and multiple previous pregnancy losses 1.40, [1.19–1.66], $P < 0.0001$. Notably, delivery related risk factors were identified: VBAC 1.26, [1.13–1.47], induction of labor 1.21, [1.08–1.35], instrumental delivery 1.69, [1.49–1.93], and epidural anesthesia 1.56, [1.46–1.69], (Table 1).

(a). Early maternal morbidity

Complications were significantly more common in the exposed, 3rd SRPF group compared to the non exposed group. Significantly, we found a higher rate of postpartum hysterectomy and admission to intensive care unit (ICU). Maternal complications risks in this group were also significantly higher: early puerperal fever 3.47 [2.43–4.94], hemoglobin drop of 3 g% or more 8.18 [7.45–8.97], blood product transfusion 17.66 [15.14–20.63] and prolonged maternal hospital stay 1.73 [1.58–1.89] (Table 2).

(b) Late maternal complications: late readmission and procedures

During the study period, 335 (0.33%) women were readmitted due to birth or pelvic-related complications. Compared to women with no registered readmission, these women were older, had a higher rate of multiple previous pregnancy losses, had undergone ART, preterm deliveries, and significant PPH as reflected by a decline in the HB level at the index delivery (Table 3). The significant independent predictors of readmission were: multiple previous early pregnancy losses 1.93 [1.11–2.71], use of ART 1.73 [1.19–3.11] and peripartum hemorrhage associated with hemoglobin drop 2.73 [1.94–3.86]. Markedly, 3rd SRPF lost significance as a risk factor for late readmission in multivariate analysis. Nevertheless, 27/335 (0.08%) women who were readmitted had manual uterine revision compared to the 308/97,871 (0.003%) women with no record of readmission, $P < 0.0001$ (Table 3).

The evaluation of the diagnosis at readmission showed that persistent residual placenta was a much more common recorded diagnosis for those with a previous 3rd SRPF, 40.7% vs. 7.1%, $p < 0.001$. Hysteroscopy and D&C were performed significantly

Table 1
Demographic, maternal, pregnancy, delivery and neonatal characteristics of the study groups: univariate and multivariate analysis.

	Non exposed No 3 rd SRPF [*] (N=97,888)	Exposed 3 rd SRPF [*] (N=3,297)	P value	aOR ^{**}	95%CI ^{**}
Maternal Characteristics					
Age (years) (mean ± SD)	29.0 ± 5.7	28.3 ± 5.6	<0.0001		
Age >35 (years)	12,280 (12.5%)	514 (15.6%)	<0.0001	1.19	1.07–1.32
Education ≥12y	90,575 (98.1%)	3,083 (98.3%)	0.492	2.20	1.73–2.34
ART [†]	2,668 (2.7%)	208 (6.3%)	<0.0001	2.20	1.73–2.34
Pregnancy Complications					
Multiple previous early pregnancy loss (>3)	3,364 (3.4%)	173 (5.2%)	<0.0001	1.40	1.19–1.66
Preterm delivery (GA [‡] <37 weeks)	3,348 (3.4%)	276 (8.4%)	<0.0001	2.53	2.21–2.88
GDM [§]	2,110 (2.2%)	78 (2.4%)	0.414	NS	
PET	784 (0.8%)	57 (1.7%)	<0.0001	1.66	1.25–2.21
Delivery Characteristics					
Nulliparous	23,594 (24.1%)	792 (24.0%)	0.915	0.8	0.73–0.88
VBAC [#]	7,206.3 (7.3%)	335 (10.2%)	<0.0001	1.28	1.13–1.47
Epidural analgesia	51,168 (52.3%)	2,129 (64.6%)	<0.0001	1.56	1.46–1.69
Induction of labor	7,950 (8.1%)	402 (12.2%)	<0.0001	1.21	1.08–1.35
Instrumental delivery	5,400 (5.5%)	313 (9.5%)	<0.0001	1.69	1.49–1.93
Home delivery ^{**}	901 (0.9%)	29 (0.9%)	0.809	NS	
Neonatal Characteristics					
GA at delivery	40 (39–40)	40 (38–40)	<0.0001		
Birth weight	3299 ± 464	3211 ± 601	<0.0001		
SGA ^{††}	6,580 (6.7%)	272 (8.2%)	0.001	1.23	1.07–1.40
Female gender	47,583 (48.6%)	1,789 (54.3%)	<0.0001	1.28	1.19–1.38

* 3rd SRPF - 3rd stage uterine cavity revision procedures performed due to suspected retained placental fragments; † ART - assisted reproductive technology; ‡ GA - gestational age; § GDM - gestational diabetes mellitus; || PET - pre-eclampsia; # VBAC - vaginal birth after caesarian after one or two previous documented low segment caesarean section; ** Home delivery - delivery at home or on the way to the hospital; †† SGA - small for gestational age.

** Multivariate logistic model for 3rd stage labor, adjusted for: advanced maternal age, history of 3 or more miscarriages, ART, preterm delivery, PET, Nulliparous, VBAC, Induction of labor, epidural analgesia, mode of delivery, neonatal gender and small for gestational age. Hosmer and Lemeshow Test = 0.479.

more often among the exposed women as compared to non exposed, 14.8% vs. 3.6%, $p < 0.01$ and 48.1% vs. 18.2%, $p < 0.001$, respectively. Although hemoglobin levels measured during readmission were significantly lower in the 3rd SRPF group, $P < 0.0001$; the rates of blood product transfusion, antibiotic therapy, and hysterectomy were similar (Table 4).

Discussion

Retained placenta after vaginal delivery is a potentially life-threatening complication because of its strong association with PPH [3–5]. Previous studies offered limited definitions of risk factors for retained placenta, lacked report of the complications related to the procedure of uterine manual revision or late puerperal complications. The diagnostic criteria and management protocols also varied [1,8–,9,10,11,12,13].

We present here a comprehensive assessment of risk factors for retained placenta, early and late complications, in a large

population throughout a decade, treated by a constant and strict peripartum protocol. In concordance with others, we showed that a cluster of significant risk factors for retained placenta and manual uterine cavity revision: late maternal age, previous caesarean section, nulliparity, induction of labor, instrumental delivery, and preterm labor [9,12–16]. Additionally, we found that significant clinical history risk factors the use of ART, multiple miscarriages, as well as pregnancy-related complications such as preterm birth and preeclampsia are risk factors for this abnormal 3rd stage of labor and related interventions.

Notably we have also explored into the early significantly higher risk of blood loss and puerperal fever as well as higher readmission rate and interventions associated with the manual uterine revision [22]. The mean duration of the 3rd stage is 5.46 min (SD ± 5.4), while The 90th, 95th, and 99th percentiles were defined by 9, 13, and 28 min, respectively. Women with a 3rd stage longer than the 90th centile, compatible with our protocol (≤ 40 min), might inherently have a higher risk of PPH [23]. Our

Table 2
Independent associations between 3rd SRPF and early maternal complications; (3rd SRPF as compared to reference normal 3rd stage labor): multivariate analysis.

	Non exposed No 3 rd SRPF [*] (N=97,888)	Exposed 3 rd SRPF [*] (N=3297)	aOR	95% CI	P value
Hb decline [†]	4364 (4.5%)	834 (25.3%)	8.18	7.45–8.97	<0.0001 [*]
Blood products transfusion	507 (0.5%)	298 (9.0%)	17.66	15.14–20.63	<0.0001 [*]
Early puerperal fever [‡]	253 (0.3%)	37 (1.1%)	3.47	2.43–4.94	<0.0001 ^{**}
Prolonged maternal LOS	11,102 (11.4%)	690 (21.0%)	1.73	1.58–1.89	<0.0001 ^{**}
Postpartum hysterectomy	0 (0.000%)	11 (0.334%)			<0.0001 ^{**}
ICU Admission [§]	2 (0.002%)	8 (0.243%)			<0.0001 ^{**}

* 3rd SRPF - 3rd stage uterine cavity revision procedures performed due to suspected retained placental fragments; † Hb decline - hemoglobin decline of 3 g% or more from admission to lowest value; ‡ Early puerperal fever (fever within 72 h from delivery); § ICU - intensive care unit; || Prolonged maternal LOS - length of stay - 3 or more days after delivery * Hosmer and Lemeshow Test <0.05.

** Hosmer and Lemeshow Test NS.

*** due to small number of events multivariate analysis were not performed.

Table 3

Late readmission and complications: univariate and multivariate analysis.

	No record of readmission (N = 100,850)	Readmission within 6 weeks from delivery (N = 335)	P value	aOR**	95%CI**
Maternal Characteristics					
Age (years)>35	12,760 (12.7%)	34 (10.1%)	0.168	0.77	0.53-1.12
Pregnancy Complications					
ART [†]	2,854 (2.8%)	22 (6.6%)	<0.0001	1.73	1.11-2.71
Multiple previous early pregnancy loss (>3)	3,518 (3.5%)	19 (5.7%)	0.030	1.93	1.19-3.11
Preterm delivery (GA [‡] <37 weeks)	3,604 (3.6%)	20 (6.0%)	0.018	1.45	0.92-2.31
GDM [§]	2,175 (2.2%)	13 (3.9%)	0.030	1.83	1.04-3.22
Prior CS	7,429 (7.4%)	21 (6.3%)	0.442	NS	
Delivery Characteristics					
Nulliparous	24,271 (24.1%)	115 (34.3%)	<0.0001	1.31	1.01-1.69
Induction of labor	8,317 (8.2%)	35 (10.4%)	0.144	NS	
Oxytocin during labor	19,922 (19.8%)	82 (24.5%)	0.030	0.98	0.74-1.29
Epidural analgesia	53,100 (52.7%)	197 (58.8%)	0.024	1.13	0.89-1.4
Early Complications					
Hb decline [#]	5,138 (5.1%)	60 (17.9%)	<0.0001	2.73	1.94-3.86
Blood products transfusion	790 (0.8%)	15 (4.5%)	<0.0001	1.54	0.83-2.85
PPH ^{**}	2,219 (2.2%)	26 (7.8%)	<0.0001	1.72	1.06-2.80
3 rd SRPF ^{††}	308 (0.03%)	27 (0.8%)	<0.0001	1.44	0.91-2.26

[†] ART - assisted reproductive technology; [‡]GA- gestational age; [§]PET- pre-eclampsia toxemia; [§]GDM- gestational diabetes mellitus; ^{||}CS- caesarean section; [¶]SGA - small for gestational age; [#]Hb decline - decline of 3 g% or more from admission to lowest value; ^{**}PPH - postpartum hemorrhage as coded in diagnosis records; ^{††}3rd SRPF - 3rd stage uterine cavity revision procedures performed due to suspected retained placental fragments.

^{**} Multivariate analysis adjusted for: maternal age, nulliparous, preterm delivery, epidural analgesia, GDM, ART, HB decline, blood products transfusion, PPH, history of miscarriage oxytocin during labor and 3rd SRPF. Hosmer and Lemeshow Test = 0.304.

Table 4

Readmission characteristics of the study groups: Univariate analysis.

	Readmission without 3 rd SRPF and uterine revision procedure (N=308)	Readmission after 3 rd SRPF and uterine revision procedure (N=27)	P value
Readmission Diagnosis			
Late PPH [†]	70 (22.7%)	8 (29.6%)	0.416
Fever (pelvic infection)	144 (46.8%)	10 (37.0%)	0.331
Residual placenta fragments	22 (7.1%)	11 (40.7%)	<0.0001
Other complication [*]	70 (22.7%)	2 (7.4%)	0.063
Management			
Blood products transfusion	22 (7.1%)	4 (14.8%)	0.153
Antibiotics (IV or PO)	222 (72.1%)	21 (77.8%)	0.525
Hysteroscopy	11 (3.6%)	4 (14.8%)	0.007
Curettage	56 (18.2%)	13 (48.1%)	<0.0001
Emergency hysterectomy	1 (0.3%)	0 (0.0%)	0.767
Lowest Hb, g% (Median[IQR]) [‡]	11.4 [10.0-12.5]	9.0[8.1-10.2]	<0.0001

^{*} Other complication: more than one database diagnosis and combined complications ; [†]PPH - postpartum hemorrhage; [‡]Lowest Hb - lowest hemoglobin level during readmission, IQR - interquartile range.

service is a busy maternity center, originally served by limited operation room time and anesthesia personnel. The 40 min limit was originally intended to avoid using surgical resources unless occurrence of 3rd stage bleeding.

Albeit strict sterile field preparation and prophylactic antibiotics the puerperal fever risk remained significant for the women that underwent a manual revision of the uterus ; some studies report no difference if antibiotics used [24] and the second generation cephalosporins, appropriate for lower genital tract originated infections eliminate the explanation of the antibiotic incompatibility.

We show here that the increased risk of early puerperal complications for those who underwent a 3rd stage manual revision of the uterus translated into two fold higher rates of prolonged hospital stay and a three times higher hospital readmission rate. Several other studies reported of postpartum readmission following high-risk deliveries, ranging from 0.33 to 0.83%, few reporting the association with the uterine revision procedure [25–29]. Notably, we did not find the manual revision to be a significant risk factor for readmission, while pregnancy complication associated with abnormal placentation, i.e.

late maternal age, a history of the use of ART, multiple miscarriages, preterm birth, and early PPH remained significant risks. [25–28,30,31]. Remarkably, a diagnosis of persistent retained placenta fragments was five to six times more frequent among those who had manual uterine revision compared to women who were readmitted but did not have such a procedure. Our protocol that requires manual revision to be performed by trained obstetricians lessens the option of an inadequate technique at the basis of this difference. This underscores the concept that risk factors for an *a priori* abnormal trophoblast invasion are also similar for the continuum of infertility, pregnancy complications, retained placenta, uterine revision and readmission; thus, it may be that the failure of the uterine revision procedure is inherent to the initiation event of an abnormal placentation, rather than in the procedure itself [9,16–21].

The hysteroscopy or curettage procedure was the only significant different intervention modality at readmission for women who has a previous postpartum manual revision of the uterine cavity. The lack of use of sonographic evaluation of the uterine cavity during or after the procedure of the uterine revision may be associated with this difference; however perinatal ultrasonic imaging of retained

placenta, has a limited sensitivity. future studies are required to determine the impact of routine ultrasound use on maternal morbidity [32–35].

This study as limitations: [1] The large sample size can cause insignificant details to become statistically significant. An analysis of absolute risk reduction or calculation of NNT for the manual revision after delivery might be appropriate; however this type of analysis is theoretical, since the management is not optional; i.e. it is mandatory to perform manual revision of the uterus in the setup of an abnormal 3rd stage. Thus, we addressed this by choosing well defined variables, aimed to reduce the chance of taking in consideration clinically insignificant variables and the calculation of sensitivity and specificity predictive values, discriminatory for each risk factor/characteristic included in the study [2]. The number of re- admissions is relatively small and there is little power to generalize the findings, as compared to the original cohorts [3]. Additional variables that can influence the results were not included in our study, such as antenatal sonographic characteristics of the placenta, maternal blood type [36], undiagnosed coagulation disorders such as Von Willebrand disease [36], maternal weight [37], and presence or absence of maternal anemia at presentation [4]. There are inherent database limitations and coding [5]. Single center population; thus, the ability to extrapolate our findings to other settings may be limited [6]. Lack of histopathological reports of the suspected retained placental fragments removed at the uterine revision or later readmission procedures; however this was beyond the aim of the present study, not aimed to determine the accuracy of the retained placenta diagnosis [8]. Longer-term sequelae of manual uterine cavity revision and readmission curettage, such as Asherman's syndrome and secondary infertility were not evaluated, which may lead to an underestimation of the late complications [9]. some patients may have chosen to refer to other hospitals with post-delivery complications, hence lost to follow-up is a possible bias.

The study's strengths: [1] The large sample size which allowed sensitivity and specificity calculation for the individual risk factors [2]. The diagnoses and interventions are performed according to a strict and constant protocol, by trained obstetricians only, which reduces practice related confounders [3]. The population characteristics; the center is the largest tertiary maternity in the region, so we may assume that the readmission rate represents the vast majority of readmitted cases [4]. The health system underlying this study; uniform health costs coverage; covered by National Health Insurance [5]. The study period; this study reports a time period of almost a decade, compensating for changes that may have occurred in population characteristics.

Conclusions

The 3rd stage of labor uterine revision procedure under a strict diagnosis and intervention protocol is yet associated with significant maternal morbidity. Postpartum manual uterine cavity revision due to a diagnosis of retained placenta does not reduce the risk of early maternal morbidity as well as the readmission and long-term morbidity, but rather demarcates a population at risk and assist in health care programs for postpartum care

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Author's roles

Each author has participated sufficiently in the work to take responsibility for its content and is willing to provide relevant data upon request. The authors have made the following contributions:

Sorina Grisar Granovsky: research concept, research performance and author of manuscript

Itay Zmora: research performance, first draft of manuscript

Maayan Bas Lando: research performance, first draft of manuscript

Shunit Armon : critical review of the manuscript, performance of readmission interventions

Rivka Frakash : statistical analyses

Alex Ioschovitch : anesthesia review and critical review of the manuscript

Arnon Samueloff: critical review of the manuscript

Ethics approval

The study protocol was approved by the local Institutional Review Board with a waiver of informed consent due to retrospective observational nature of study.

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Conflict of interest

The authors report no conflict of interest and no financial disclosure.

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