

Original Research

Complete blood count parameters, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in hydatidiform mole versus missed abortion

Ala Aiob^{1,2,*}, Karina Naskovica¹, Inna Amdur Zilberfarb¹, Avishalom Sharon^{1,2},
Jacob Bornstein², Lior Lowenstein^{1,2}¹Department of Obstetrics and Gynecology, Galilee Medical Center, 22100 Nahariya, Israel²Azrieli Faculty of Medicine, Bar Ilan University, 52000 Safed, Israel*Correspondence: ala.aiob@gmail.com (Ala Aiob)

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Abstract

Objective: Molar pregnancy is the most common type of gestational trophoblastic disease. Gestational trophoblastic disease is characterized by lower absolute and relative lymphocyte levels and a lower white blood cell (WBC) count relative to normal pregnancy. However, no studies have examined the WBC count relative to missed abortion. The aim of this study was to investigate whether blood parameters, such as neutrophil and lymphocyte counts, the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), WBC count and platelets can distinguish gestational trophoblastic disease from missed abortion. **Methods:** This retrospective study included 104 women diagnosed with molar pregnancy and 110 women with missed abortions during 2010–2020 at one institution. Sixty-nine women had partial moles (PM) and 35 had complete moles (CM). We extracted and compared maternal and pregnancy characteristics, and laboratory parameters of all the women with molar pregnancy, and separately for those with PM and CM, compared to women with missed abortion. **Results:** The mean neutrophil level was higher in the molar pregnancy than the missed abortion group (5.67 ± 1.92 vs. 5.02 ± 1.65 , $p = 0.013$); the patients with PM largely drove this difference. In multivariable linear models, women with molar pregnancy were more likely to have higher neutrophil values than women with missed abortion ($p = 0.023$). Platelet, WBC, NLR and PLR values did not differ significantly between women with gestational trophoblastic disease and women with missed abortion. **Conclusions:** A higher neutrophil level was observed among women with molar pregnancies than among women with missed abortion. This suggests that molar pregnancies may cause a higher inflammatory response due to continued trophoblastic growth. However, the magnitude of the difference was small and not useful for establishing a diagnosis.

Keywords: gestational trophoblastic disease; neutrophils; lymphocytes; inflammatory measures; diagnosis

1. Introduction

Gestational trophoblastic disease (GTD) originates in the placenta and can result in local invasion and metastasis. The pathogenesis of GTD is peculiar as the maternal tumor arises from gestational rather than maternal tissue [1]. Hydatidiform mole (HM) is a non-malignant form of GTD, which can be represented as a partial mole (PM) or complete mole (CM). PM and CM differ in chromosomal pattern, microscopic and gross histopathology, clinical representation and outcomes [2–4]. PM occurs in approximately 1 in 700 pregnancies; CM occurs in 1 in 2000 [5].

The risk for molar pregnancy and its relation to maternal age is much greater in CM than in PM [6]. Nonetheless, HM occurs most often in women under age 35 years because of the higher rate of pregnancies in this age group [6]. Risks for both CM and PM were shown to increase in women with a history of prior spontaneous abortion and infertility [7–9].

The presentation of HM usually involves first or second-trimester vaginal bleeding. Women with early dis-

ease may be diagnosed before they develop symptoms. The diagnosis is based on an unusually high serum human chorionic gonadotropin (HCG) level or on ultrasound findings by routine ultrasound scanning of early pregnancy, which consistently demonstrate non-viable conception [10]. After diagnosis, molar tissue is evacuated by surgical curettage, and the patient is followed by serial serum or urine HCG [11].

Many women with HM, particularly with PM, are presumed to have a spontaneous abortion. A molar pregnancy is detected only after pathological evaluation of a uterine curettage sample. In a series of 81 women with PM, clinical diagnosis prior to uterine evacuation was deemed incomplete or as a missed abortion in 74 (91%) and molar pregnancy in only five (6%) [12]. In a recent cohort study of 24 women with a molar pregnancy in our institute, molar pregnancy was suspected prior to evacuation in only 40% [13].

If the products of conception are not examined histologically, the diagnosis of HM may be missed. HCG monitoring to detect persistent disease is generally omitted in



these women, and early diagnosis of gestational trophoblastic neoplasia is delayed. This indicates low sensitivity of ultrasound and beta HCG in the diagnosis of molar pregnancy [14].

GTD is characterized by lower absolute and relative lymphocyte levels and a lower white blood cell (WBC) count relative to normal pregnancy. This may be related to an inadequate inflammatory response in GTD to enhanced trophoblastic invasion [15,16].

The neutrophil-to-lymphocyte ratio (NLR) was found to be a possible predictor of invasive moles for women with HM; the pretreatment NLR can be used as a biomarker of invasion in GTD [17]. The NLR was shown to be higher in women who developed invasive moles than in women who did not [17]. The NLR is a simple and easily calculated marker obtained from the differential WBC count, and has been reported as predictive of outcomes of endometrial precancerous and cancerous lesions in women with abnormal uterine bleeding, in ovarian and cervical cancer, trophoblastic diseases and uterine sarcoma [18–22]. Furthermore, NLR may be a useful prognostic factor in patients with advanced cancer treated with PD-1/PD-L1 inhibitors [23]. According to previous studies [15,16], we expected a decrease in inflammatory measures in GTD.

To the best of our knowledge, no published study evaluated the predictive role of the NLR, the platelet-to-lymphocyte ratio (PLR) and WBC components in molar pregnancy. Therefore, we conducted this retrospective analysis to determine if pretreatment (surgical evacuation) NLR, PLR and WBC count; and neutrophil, lymphocyte and platelet (PLT) levels differ between molar pregnancy and missed abortion. The aim was to improve the diagnostic sensitivity of PM and CM; and to seek parameters that may help explain the pathophysiologic mechanisms of molar pregnancy, and differentiate it from missed abortion.

2. Materials and methods

2.1 Study design and population

This retrospective study was approved by the Institutional Review Board (Helsinki Committee) of Galilee Medical Center (authorization number 0158-20-NHT on October 2020).

The study population consisted of women diagnosed with a CM or PM in the Department of Obstetrics and Gynecology at the Galilee Medical Center, Israel, between January 2010 and December 2020. For all the patients, the diagnosis was made following evaluation of the evacuated uterine contents by a pathologist at our institution, based on histopathologic features and P57 immunostaining.

We identified all the women with a final diagnosis of CM or PM recorded from 2010 to 2020. In addition, we arbitrarily selected women of similar gestational ages who had undergone surgical uterine evacuation due to missed abortion of singleton pregnancy during the same period. These women had a final histological diagnosis of normal

villi, according to evaluation of the evacuated uterine contents by a pathologist at our institution.

A study inclusion criterion for both groups was elective surgical evacuation of the uterus due to a suspected mole or a missed abortion, for which the final histology was CM, PM or normal villi. We excluded women with diabetes mellitus, Body Mass Index (BMI) >30 kg/m², hypertension, endometriosis and autoimmune diseases; and women who had undergone a surgical evacuation due to incomplete abortion, septic abortion, failed medical treatment (miso-prostol) or retained portion of the placenta.

2.2 Data collection

Data retrieved from the medical records of all the women included: age, gravidity, parity, BMI, the indication for surgical management, and gestational age by the last menstrual period or first crown-rump length. Blood samples collected from women before the surgical evacuation of the uterus provided the following data: WBC, absolute neutrophils, absolute lymphocytes and PLT analysis. In addition, the mean values of NLR and PLR were calculated for each study group, and all the data were compared between the groups (mole pregnancy *vs.* missed abortion, CM *vs.* missed abortion, PM *vs.* missed abortion).

2.3 Statistical analysis

Descriptive analysis: Categorical data were described using frequencies and percentages. Continuous variables with normal distribution were presented as means \pm standard deviations. Median values and ranges were used to describe variables that did not distribute normally.

In an inferential analysis, categorical variables were compared between the groups with the Chi square test or Fisher's exact tests (when expectancy <5). Continuous variables were compared between the groups using the independent *t*-test or the Mann-Whitney test (if normal distribution was found, the independent *t*-test was used). The distribution shape was determined mainly by a histogram. $p < 0.05$ was considered to be significant.

Multivariable linear regression models were performed to examine correlations of molar pregnancy versus missed abortion with the inflammation measures: neutrophils, lymphocytes, PLR, NLR and WBC. These measures were the dependent variables, while lymphocytes and gestational age were independent variables in the models, in addition to molar pregnancy and missed abortion.

IBM SPSS Statistics software, version 25.0 (IBM, Armonk, New York, USA) was used for the statistical analysis.

3. Results

We included 104 women with confirmed molar pregnancies from January 2010 to December 2020: 35 (33.7%) with a CM and 69 (66.3%) with a PM. In addition, we established a group of 110 women with confirmed missed abor-

tions of similar gestational ages, treated during the same period.

Table 1 compares maternal and pregnancy characteristics, and laboratory parameters between women with molar pregnancy and women with missed abortions. Compared to the missed abortion group, for the molar pregnancy group, the mean absolute neutrophil level was higher (5.67 ± 1.92 vs. 5.02 ± 1.65 , $p = 0.013$) and the proportion of smokers was lower (9.6% vs. 26.4%, $p = 0.002$). Five (4.8%) women in the molar pregnancy group and none in the missed abortion group had a previous molar pregnancy ($p = 0.026$). Statistically significant differences were not found between the molar pregnancy and the missed abortion group with respect to age, parity, the number of previous abortions, intrauterine fetal death, *in vitro* fertilization (IVF) or gestational age. Differences between the groups in PLT, WBC, NLR and PLR were not statistically significant.

Table 2 compares characteristics of women with PM to women with missed abortions. Compared to women with missed abortions, for women with PM, the mean absolute neutrophil level was higher (5.65 ± 1.73 vs. 5.02 ± 1.65 , $p = 0.024$) and the proportion of smokers lower (11.6% vs. 26.4%, $p = 0.022$). Statistically significant differences were not found between the PM and missed abortion groups in age, parity, gravidity, previous abortions, intrauterine fetal death, IVF or gestational age; nor in platelets, WBC, absolute lymphocytes, NLR and PLR.

Table 3 compares characteristics of women with CM and missed abortions. Compared to women with missed abortions, for women with CM, the proportion of smokers, and the median numbers of pregnancies and deliveries were lower (5.7% vs. 26.4%, $p = 0.016$; 3 vs. 3.5, $p = 0.006$; and 1 vs. 2, $p = 0.010$, respectively). Statistically significant differences were not found between the groups in platelets, WBC, absolute lymphocytes, absolute neutrophils, NLR and PLR.

A multivariable linear model was adapted to examine the correlation between molar pregnancy and neutrophils. The dependent variable was neutrophil count. In addition to the molar pregnancy and abortion variable, lymphocytes and gestational age were included in the multivariable model as independent variables since they were found to be significant in univariable analysis and according to theoretical considerations. The model was found to be significant ($p < 0.001$). Women with molar pregnancy were more likely to have higher neutrophil values than women with missed abortion ($p = 0.0230$). Moreover, lymphocyte levels were related to neutrophil values ($p < 0.001$); as the level of lymphocytes increased, the level of neutrophils increased. Additionally, gestational age was not correlated to the neutrophil values ($p = 0.168$).

4. Discussion

During the 11-year study period, 104 women were confirmed to have molar pregnancy in our institute; one-

third had a CM and two-thirds had a PM. This distribution is similar to that reported in the United Kingdom and other developed countries in which the incidence of CM was about 1 per 1000 pregnancies compared to 3 per 1000 pregnancies for PM [24,25]. Furthermore, the pre-evacuation diagnosis of molar pregnancy in our cohort was 56.7% of the women with a final histology of molar pregnancy, which is consistent with previous studies [13,14].

To the best of our knowledge, this is the first study that specifically evaluated WBC, neutrophil and lymphocyte counts, PLT, NLR and PLR in women with molar pregnancies; and that compared values to those of women with missed abortions. We found no significant differences between these two groups in WBC, lymphocyte count, PLT, NLR and PLR levels. However, for the molar pregnancy group, the mean neutrophil level was significantly higher; this difference was driven mainly by the PM group. Additionally, a multivariable linear model demonstrated higher neutrophil values in women with molar pregnancies than in women with missed abortions ($p = 0.0230$). Moreover, the level of neutrophils increased in parallel to an increase in lymphocyte levels. However, despite the statistically significant difference, the clinical difference was relatively small and cannot be applied in clinical practices. Nevertheless, the finding may serve as a basis for future studies that attempt to increase the sensitivity of molar pregnancy diagnosis. We also observed a trend for higher values of WBC in women with molar pregnancy, but this was not statistically or clinically significant. Nonetheless, these findings may help elucidate the physiology of the disease as discussed below.

Notably, we observed a higher proportion of smokers among the women with missed abortions than among those with molar pregnancies ((10) 9.6% – (29) 26.4%, $p = 0.002$). Although smoking may increase the WBC count [26], we report a higher mean level of neutrophils among women with molar pregnancies than among women with missed abortions, despite a smaller proportion of smokers. This may strengthen our findings.

Our results contrast with two studies [15,16] that described decreased absolute and relative lymphocyte levels, and also the WBC count in molar pregnancy. However, those studies compared between women with molar pregnancy and women with a sustainable pregnancy. We believe that comparing molar pregnancy and missed abortion is more relevant because the embryo is not alive in both situations. We presume that the lower WBC count described in molar pregnancy compared to normal viable pregnancy was driven by the physiological leukocytosis in the latter [27].

The pathophysiologic mechanism underlying molar pregnancies is still unclear. In CM, defective placentation due to lack of villous trophoblast development and endovascular trophoblastic invasion may lead to incomplete development of the placenta decidual interface. However, in PM,

Table 1. Maternal and pregnancy characteristics, and laboratory parameters - molar pregnancy vs. missed abortion.

Item	Molar pregnancy N = 104	Missed abortion N = 110	2-sided*, 1-sided+
Age, years mean (SD)	31.84 (7.59)	32.18 (6.10)	0.715*
Age, years (range)	19–53	19–44	Independent <i>t</i> -test
Comorbidities (N)%	(30) 28.8%	(24) 21.8%	0.272*
Pre-evacuation of a suspected mole (N)%	(59) 56.7%	(2) 1.8%	Chi-square exact $p < 0.001$
Smoking (N)%	(10) 9.6%	(29) 26.4%	Chi-square test 0.002*
Pregnancy age, mean (SD)	9.60 (2.35)	9.30 (2.06)	Chi-square exact 0.318*
range, weeks	3–16.3	5–17	Independent <i>t</i> -test 2-sided 0.011*
Gravidity, range (median)	1–10 (3)	1–14 (3.5)	Mann-Whitney test 0.053 +
Parity, range (median)	0–7 (2)	0–11 (2)	0.105* Mann-Whitney test 0.047+
Abortion, range (median)	0–5 (0.00)	0–5 (0.00)	0.094* Mann-Whitney test 0.697*
TOP, range (median)	0–2 (0.00)	0–3 (0.00)	Mann-Whitney test 0.370*
EUP (N)%	(1) 1 %	(4) 3.6%	Fisher's exact test 0.026*
Previous molar pregnancy (N)%	(5) 4.8%	0	Mann-Whitney test 0.235*
IUFD (N)%	(2) 1.9%	0	Fisher's exact test 0.247*
IVF (N)%	0	(3) 2.7%	Fisher's exact test 0.104*
WBC, mean (SD)	8.35 (2.36)	7.81 (2.19)	0.052+ Independent <i>t</i> -test 0.850
PLT, mean (SD)	247.7 (54.4)	249.34 (65.3)	Independent <i>t</i> -test 0.013*
Neutrophils, mean (SD)	5.67 (1.92)	5.02 (1.65)	Independent <i>t</i> -test 0.263*
Lymphocytes, mean (SD)	2.03 (0.63)	1.93 (0.59)	Independent <i>t</i> -test
NLR, range (median)	0.93–9.5 (2.66)	0.94–5.21 (2.64)	0.447* Mann-Whitney test
NLR, mean (SD)	3.01 (1.4)	2.72 (0.94)	
PLR, range (median)	49.85–130.98 (121.5)	59.52–501.45 (127.73)	0.364* Mann-Whitney test
PLR mean (SD)	133.09 (50.13)	137.47 (54.41)	

SD, standard deviation; N, number; TOP, termination of pregnancy; EUP, ectopic pregnancy; IUFD, intrauterine fetal death; IVF, *in vitro* fertilization; WBC, white blood cells; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; *, 2-sided; +, 1-sided.

Table 2. Maternal and pregnancy characteristics, and laboratory parameters – partial mole vs. missed abortion.

Item	Partial mole N = 69	Missed abortion N = 110	2-sided*, 1-sided+
Age, years mean (SD)	32.19 (6.8)	32.18 (6.1)	0.995* Independent <i>t</i> -test
Age, years (range)	20–46	19–44	
Comorbidities (N)%	(21) 30.4%	(24) 21.8%	0.218* Chi-square test
Pre-evacuation of a suspected mole (N)%	(30) 43.5%	(2) 1.8%	$p < 0.001^*$ Chi-square test
Smoking (N)%	(8) 11.6%	(29) 26.4%	0.022* Chi-square test
Pregnancy age, mean (SD)	9.88 (2.54)	9.30 (2.06)	0.099* Independent <i>t</i> -test
Gravidity, range (median)	1–10 (3)	1–14 (3.5)	0.049+ Mann-Whitney test
Parity, range (median)	0–7 (2)	0–11 (2)	0.584* Mann-Whitney test
Abortion, range (median)	0–4 (0.00)	0–5 (0.00)	0.099* Mann-Whitney test
TOP, range (median)	0–2 (0.00)	0–3 (0.00)	0.049+ Mann-Whitney test
EUP (N)%	(1) 1.4%	(4) 3.6%	0.876 Mann-Whitney test
Previous molar pregnancy (N)%	(1) 1.4%	0	0.065* Fisher's exact test
IUFD (N)%	(2) 2.9%	0	0.147* Fisher's exact test
IVF (N)%	0	(3) 2.7%	0.147* Fisher's exact test
WBC, mean (SD)	8.37 (2.10)	7.81 (2.19)	0.285* Fisher's exact test
PLT Mean (SD)	243.65 (50.42)	249.34 (65.36)	0.120* Independent <i>t</i> -test
Neutrophils, mean (SD)	5.65 (1.73)	5.02 (1.65)	0.535* Independent <i>t</i> -test
Lymphocytes, mean (SD)	2.08 (0.63)	1.93 (0.59)	0.024* Independent <i>t</i> -test
NLR, range (median)	0.93–9.50 (2.62)	0.94–5.21 (2.64)	0.138* Independent <i>t</i> -test
NLR, mean (SD)	2.96 (1.44)	2.72 (0.94)	0.069+ Independent <i>t</i> -test
PLR, range (median)	68.36–310.98 (121.5)	59.52–501.45 (127.73)	0.727* Mann-Whitney test
PLR, mean (SD)	125.59 (41.18)	137.47 (54.41)	0.143* Mann-Whitney test
			0.071+ Mann-Whitney test

SD, standard deviation; N, number; TOP, termination of pregnancy; EUP, ectopic pregnancy; IUFD, intrauterine fetal death; IVF, *in vitro* fertilization; WBC, white blood cells; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; *, 2-sided; +, 1-sided.

Table 3. Maternal and pregnancy characteristics, and laboratory parameters – complete mole vs. missed abortion.

Item	Complete mole N = 35	Missed abortions N = 110	2-sided*, 1-sided+
Age, years, mean (SD)	31.14 (9.02)	32.18 (6.10)	0.528*
Age, years, (range)	19–53	19–44	Independent <i>t</i> -test
Comorbidities (N)%	(9) 25.7%	(24) 21.8%	0.648*
Pre-evacuation of a suspected mole (N)%	(29) 82.9%	(2) 1.8%	Chi-square exact <i>p</i> < 0.001*
Smoking (N)%	(2) 5.7%	(29) 26.4%	Chi-square exact 0.016*
Pregnancy age, mean (SD)	9.08 (1.86)	9.30 (2.06)	0.579*
Gravidity, range (median)	1–8 (3)	1–14 (3.50)	Independent <i>t</i> -test 0.006*
Parity, range (median)	0–5 (1)	0–11 (2)	Mann-Whitney test 0.010*
Abortion, range (median)	0–5 (0.00)	0–5 (0.00)	Mann-Whitney test 0.374*
TOP, range (median)	0–2 (0.00)	0–3 (0.00)	Mann-Whitney test 0.670*
EUP (N)%	0	(4) 3.6%	Mann-Whitney test 0.572*
Previous molar pregnancy (N)%	(3) 8.6%	0	Fisher exact test 0.013*
IUFD (N)%	0	0	Fisher exact test
IVF (N)%	0	(3) 2.7%	<i>p</i> = 1.000 Fisher exact test
WBC, mean (SD)	8.31 (2.79)	7.81 (2.19)	0.282*
PLT, mean (SD)	254.69 (60.75)	249.34 (65.3)	Independent <i>t</i> -test 0.671*
Neutrophils, mean (SD)	5.697 (2.230)	5.025 (1.657)	Independent <i>t</i> -test 0.130*
Lymphocytes, mean (SD)	1.945 (0.639)	1.931 (0.597)	0.065+ Independent <i>t</i> -test 0.911*
NLR, range (median)	1.44–8.0 (2.76)	0.94–5.21 (2.64)	0.321* Mann-Whitney test
NLR, mean (SD)	3.087 (1.361)	2.727 (0.943)	
PLR, range (median)	49.85–277.04 (125.18)	59.52–501.45 (127.73)	0.773* Mann-Whitney test
PLR, mean (SD)	145.90 (61.11)	137.47 (54.41)	

SD, standard deviation; N, number; TOP, termination of pregnancy; EUP, ectopic pregnancy; IUFD, intrauterine fetal death; IVF, *in vitro* fertilization; WBC, white blood cells; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; *, 2-sided; +, 1-sided.

normal endovascular decidual trophoblastic invasion is not reduced. Hence, PMs are thought to be commonly polypoid. Therefore, the different expression of additional maternal genetic components of PM compared to CM may be a reason for the sufficient interaction between trophoblasts and the decidual layer [28].

As noted above, a physiological increase in WBC count occurs during pregnancy [27]. Leukocytosis results from an inflammatory process that is induced during the

implantation phase [29]. Leukocyte activation and the expression of various adhesion molecules on activated leukocytes occur at the beginning of pregnancy, during the implantation phase [30]. These cells secrete granulocyte-macrophage colony-stimulating factor, which enhances trophoblastic invasion. The large granular lymphocyte count is also elevated; this is thought to originate from bone marrow in the mid-luteal phase in which implantation occurs. Other studies found that WBC count was lower in molar

pregnancy than in healthy pregnancy [15,16]. They explained that this relation between WBC and GTD might be due to inadequate placentation in molar pregnancy, especially in CM, due to the absence of villous development and cytotrophoblastic invasiveness [28]. Our findings support this proposition, as the neutrophil level was not elevated in the CM compared to the missed abortion group.

In contrast to the above, in normal pregnancy, the conceptus after the demise of the embryo is most often dropped out as spontaneous abortion, due to the cessation of trophoblast activity. This leads to suppression of the inflammatory and implantation processes, and to a decrease in WBC to normal levels. Compared to molar pregnancy, after the demise of the embryo or without the embryo, the trophoblast continues to grow, and the implantation process continues. We believe that this may explain the significantly higher neutrophil level in PM compared to missed abortion.

The increased neutrophil count demonstrated in molar pregnancy, especially in PM compared to missed abortion, may prompt studies aimed to better understand the physiology of molar pregnancy. Limitations of our research include the relatively small sample size and the retrospective design.

5. Conclusions

Among women with molar pregnancy compared to missed abortion, neutrophils were significantly increased; this could be due to continued trophoblastic growth. However, the magnitude of the difference was small and not helpful in establishing a diagnosis. Differences between women with molar pregnancy and missed abortion were not observed in the other hematologic parameters examined, NLR and PLR.

Author contributions

AA, KN, IZ, AS, JB and LL designed the research study. AA and LL performed the research. AA, KN and LL analyzed the data. AA and LL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board (Helsinki Committee) of Galilee Medical Center (authorization number 0158-20-NHT on October 2020).

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Conflict of interest

The authors declare no conflict of interest.

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