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Investigating the Association Between Cesarean Section, Endometriosis, Infertility, and Elevated CA-125 Levels

Hanan J. Kadhim [1], Sahar Mohammad Zaki[2], Mohsin H. Shekh Mohammed[3], Hamdia M. Ahmed[4], Edrees M Ameen[5]

[1] Subspecialty in infertility and IVF, Kurdistan Higher Council of Medical Specialties, Erbil, Kurdistan Region, Iraq.

[2] College of Health Sciences, Hawler Medical University, Erbil, Kurdistan Region, Iraq

[3]Reproductive physiology, Kurdistan Higher Council of Medical Specialties, Erbil, Kurdistan Region, Iraq

[4]Maternity Nursing, College of Health Sciences, Hawler Medical University, Erbil, Kurdistan Region, Iraq

[5]Reproductive physiology, Salahaddin University-College of Science-Biology Department, Erbil-Iraq.

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Corresponding author E mail: Hananjawad0750@gmail.com

ABSTRACT

Background: The emergence of endometriosis-related symptoms following cesarean section that accompanied by secondary infertility, has drawn the attention of clinicians. This study aimed to investigate the association between Cesarean section and the development of endometriosis, as well as its subsequent impact on infertility and the presence of elevated CA-125 levels.

Methods: A cross-sectional study was conducted on women attending an obstetrics and gynecology department in the Kurdistan region (Erbil, Sulaymaniyah, Duhok, Halabja) between February 2023 and August 2025, using convenience sampling. Participants presented with symptoms suggestive of primary or iatrogenic endometriosis and were assessed through history, examination, and investigations, including imaging, laparoscopy, and histopathology. Serum CA-125 levels supported the diagnosis and follow-up, and the data were analyzed using SPSS with both descriptive and inferential statistics.
Most of the study sample aged between 18 and 45 years old. Twelve complaints were recorded by the sample, with the three highest rates: infertility (75.12%), dysmenorrhea (31%), and menorrhagia (23.5%).

Result: There was a highly significant association between endometriosis and cesarean section, infertility, and abnormal CA-125 marker level. Also, there was a highly significant association between infertility (high rate of secondary infertility) and undergoing cesarean section previously ($p=<0.001$).
Cesarean section is associated with an increased risk of iatrogenic endometriosis. This form of endometriosis may contribute to the development of secondary infertility in affected individuals. While observational studies support this association, the evidence remains inconclusive regarding a direct causal link. Therefore, further research employing robust methodological designs is essential to clarify the relationship and guide clinical practice.

INTRODUCTION

Endometriosis is a chronic inflammatory condition frequently characterized by pelvic pain, defined by the ectopic growth of endometrial-like tissue outside the uterine cavity—histological verification [9][21]. The exact pathogenesis of endometriosis is not fully understood; however, proposed mechanisms involve retrograde menstruation, hereditary predisposition, and aberrant immune responses [20][44].

Ongoing research is investigating whether surgical interventions, notably cesarean deliveries, may predispose women to endometriosis. Research has demonstrated that endometrial cells can occasionally colonize surgical incisions, including cesarean section scars, which may lead to localized scar endometriosis or more extensive pelvic disease [1].

A large experimental result linking the locations of abdominal wall lesions (adipose vs. muscle layers) denotes that cesarean scar endometriosis (CSE) progresses months to years after the cesarean, typically about 40 months later, and can be discovered by symptoms and biomarker levels (e.g., CA-125) [54].

Surgical disruption of the uterine lining, especially at the endometrium-myometrium boundary, can facilitate the ectopic spread of endometrial tissue, potentially elevating the likelihood of later complications such as impaired fertility [47][58].

The significance of biomarkers, including CA-125, a glycoprotein frequently increased in individuals with endometriosis, has been extensively investigated [5]. Although CA-125 lacks specificity for endometriosis, it remains useful in monitoring disease progression, particularly in moderate to severe presentations [60]. Ongoing investigations are focused on identifying additional promising biomarkers that may facilitate earlier or more precise detection of endometriosis [28].

Considering the continuing amplification in cesarean section rates worldwide, including Iraq, a thorough understanding of the potential reproductive implications is essential [12].

Research has expanded into proteomic and inflammatory biomarkers, including cytokines, chemokines, and growth factors such as interleukins, tumor necrosis factor-α, and vascular endothelial growth factor [6]. Although individual markers often lack sufficient sensitivity or specificity, recent evidence suggests that biomarker panels, rather than single analyses, may significantly improve diagnostic performance, particularly for early-stage disease [45].

Advances in molecular diagnostic have propelled metabolomics and extra-cellular vesicle-associated biomarkers to the forefront of contemporary precision medicine. Metabolic phenotyping has demonstrated diseases-specific modifications in lipid metabolism, oxidative stress pathways, and amino acid replacement in women with endometriosis [4]. Furthermore, exosomes liberated from ectopic endometrial lesions transporters disease-specific proteins and nucleic acids that could consider lesion activity and severity, donation another path for non-invasive identification and disease monitoring [11][34].

This study represents the first comprehensive investigation in Iraq to explore the interrelationship between the cesarean section history, endometriosis, infertility, and circulating biomarkers such

as CA-125. Whereas previous Iraqi studies have addressed these conditions in isolation, the present research integrates them within a unified analytical framework for the first time [38]. Given that cesarean section is increasingly prevalent in Iraq, the prospective seeding of endometrial cells leads to an assessment of both current and clinically relevant [16][22].

The objective of this research is to evaluate the prospective links between Cesarean section (C-section) and the development of endometriosis, as well as its subsequent impact on infertility and the presence of increased CA-125 levels.

MATERAILS AND METHODS

STUDY DESIGN AND SAMPLING

A cross-sectional study was implemented to evaluate the statistical association among cesarean section, endometriosis, infertility and CA-125 marker levels. Data were documented at a single point in time from target population, enabling the estimation it possible to estimate of the prevalence of outcomes and their relationships with selected variables. The 250 cases were taken through convenience sampling.

SAMPLE SIZE CALCULATION

According to an expected prevalence (P), a 95% statistical certainty Z= 1.96), and a 5% margin of error (d=0.05), the single-proportion formula was used to establish the minimum necessary sample size. To improve the study's statistical power, 250 women were selected overall, though this calculation confirmed the bare minimum of participants needed to fulfil sufficient precision.

THE CRITERIA OF SAMPLE SELECTION

1. Inclusion criteria
    - Women who have been permanent residents of Kurdistan region (Erbil, Sulaymaniyah, Duhok and Halabja)
    - Women with documented history of cesarean section and/or vaginal delivery, allowing comparison between exposure groups.
    - Women within the age range relevant to the study objective (18-45 years)
    - Complete obstetrics and gynecological records available from public and private healthcare facilities in the Kurdistan region including delivery mode and infertility evaluation.
2. Exclusion criteria
    - Women with Current pregnancy or lactation because its physiologically alter the CA125 level and fertility status
    - Women with History of malignancy including ovarian and endometrial cancer
    - Pelvic inflammatory disease such as active tuberculosis or sever adhesions of non-endometriotic origin
    - Infertility confirmed due to non-gynecological factors as sever male factor or genetic infertility disorder

PROTOCOL

The research included 249 cases; all participants were between the ages of 18 - 45 years old. Data were collected through interviews and filling the structured questionnaire written in Kurdish and Arabic languages, including address, sociodemographic, obstetrical, and gynecological history, including age, parity, and having abortion, cesarean section (CS), number of CS, infertility,

duration of infertility, and chief complain/s. Endometriosis diagnosis was through clinical history, physical examination, radiological examination, laparoscopy, and histopathology according to the chief complaints and the site of possible endometriosis. Samples were sent to the laboratory for measuring CA-125.

SETTING

The participants in the study were invited to contribute after being informed about the purpose, and they were free to withdraw at any time. The Data collected during attending to the obstetric and gynecologic public and private departments, during February 2024 and Aug 2025, in the Kurdistan region, Iraq.

STATISTICAL ANALYSIS

By utilizing the Statistical Package for the Social Sciences (SPSS), Data were managed and statistical analyzed. Frequencies and percentages were used to describe categorical variables and mean ± standard deviation (SD) with corresponding descriptive measures applied to continuous variables, as appropriate. Associations between categorical variables were assessed using the chi-square (x^2) test. A p-value of < 0.05 was considered statistically significant.

RESULTS

The analysis consisted of 249 women in total. Table 1 exhibits the geographical distribution of endometriosis by governorate, from which 199 (79.9%) had endometriosis. Erbil governorate had the largest proportion of cases (79.7%), ranked next by Duhok (82.1%) and Sulaymaniyah (81.1%), whereas Halabja had the lowest percentage (62.5%). Table 2 summarizes and highlights the sociodemographic and obstetrical characteristics of the study population. The plurality of participants was aged 31-40 years (40%), multiparous (59.6%), no abortion history (70.4%). These findings show that the study cohort comprised mainly of women in their reproductive age group with prior childbirth experience and a comparatively low rate of abortion history. Table 3 consolidates most chief complaints (signs and symptoms) of the study sample (201 cases with endometriosis). The most frequent complaints were infertility (75.12%), dysmenorrhea (31%), and menorrhagia (23.5%). Table 4 shows 201 participants diagnosed with endometriosis, and the clinical findings verified the strong predominance of endometrioma. The most common finding of endometrioma, was observed in 122 cases, constituting 60.7% of the total samples. Conversely, endometriosis found at surgical scars was the second prevalent category. Table 6 presents the highly significant associations between the presence of endometriosis with having a cesarean section, infertility, and abnormal levels of CA-125, and a significant association with parity. Table 7 presents a significant relationship between infertility and cesarean section history ($p < 0.001$). The occurrence of secondary infertility was markedly different between women with a previous cesarean section (58.4%) and those without (15.8%). Alternatively, primary infertility was more common among women without prior cesarean section (47.4%). When evaluated according to the number of cesarean section deliveries, the incidence of secondary infertility increased with the number of cesarean sections. By contrast, women without previous cesarean sections exhibited a higher prevalence of primary infertility ($p < 0.001$).

DISCUSSION

Analyzing the interaction among cesarean section (CS), endometriosis, infertility, and **high CA-125 levels** emphasize significant clinical collaboration that could impact diagnostic and management strategies. Endometriosis is a chronic inflammatory condition described by ectopic endometrial tissue that influences up to 10% of women of reproductive age and is essentially connected with infertility attributable to anatomical distortion, adhesion, and inflammatory factors diminishing gamete transport and implantation pathways [39].

Numerous clinical studies evidence that women with endometriosis have advanced rates of reproductive success, involving diminished pregnancy rates, raised miscarriage, and a higher probability of cesarean delivery. A substantial retrospective cohort established that endometriosis individually raised the risk of cesarean section, implying that disease-related factors-such as placental anomalies, pain pain evasion, or received history-could furnish to operative delivery decisions [27].

Also, observational research constantly reports an advanced prevalence of infertility in women with advanced endometriosis, emphasis the severity-dependent influence of ectopic lesions on reproductive function [52].

ENDOMETRIOSIS AND GEOGRAPHICAL DISTRIBUTION

The present study analyzed the geographic distribution of endometriosis cases in four governorates. The patterns of prevalence, however, varied clinically, with lower rates in Halabja and higher proportions in Duhok and Sulaymaniyah. The governorate and symptoms of endometriosis did not show a significant correlation. These findings support the hypothesis that the development of endometriosis in the studied group is unlikely to be independently influenced by geographic location [59].

The absence of statistical consequences may be explained by differences in healthcare availability and patients' referral between governorates could impact diagnosis rates rather than representing true differences in disease magnitude [30]. Additionally, endometriosis is etiologically diverse, impacted by genetic, hormonal, environmental, and reproductive factors, which could exceed the influence of geographic variations [14].

CESAREAN SECTION (CS) AND CA-125 LEVELS

CA-125 is a glyco-protein antigen expressed by coelomic epithelia, remnant one of the extremely studied biomarkers in endometriosis. Although, not adequately sensitive or specific to supplant surgical diagnostic, serum CA-125 incline to be lifted in women with moderate-to-severe endometriosis and relates with disease burden and inflammatory activity [43].

The finding of this study indicates that delivery by cesarean section could increase the likelihood of endometriosis, which consequently is expected to promote secondary infertility. Furthermore, increased CA-125 levels can serve as an indicator of endometriosis, potentially affecting various anatomical sites. The studies cited further support and reinforce these conclusions [61]. Elevated CA-125 levels, although frequently associated with ovarian malignancy, could moreover be recorded in benign conditions, including endometriosis [7]. Rao et al. (2018) presented a case of stage IV endometriosis with bilateral ovarian endometrium and cyst leakage, where CA-125 levels were markedly high. Research-based evidence reinforces the importance of considering endometriosis in the differential diagnosis

to prevent unnecessary invasive procedures [49].

Cancer antigen-125 (CA-125) continues to be the most studied serological marker in endometriosis [19]. In spite of its limitations in diagnostic accuracy due to menstrual cycle variability and overlap with other gynecological conditions, it plays a crucial role in assessing disease severity, treatment response, and risk of malignant transformation [3][35]. Ongoing studies are evaluating its consolidation use with biomarkers such as HE4 to enhance diagnostic accuracy and guide targeted therapeutic strategies [13][56]. The cohort study conducted at Ain Shams University substantiated the level of CA-125 in preoperative decision-making for endometriosis, particularly in association with adhesion scoring, lesion dimensions, and disease staging [55].

There is a strong relationship between pre-surgical CA-125 levels and endometriosis stage, with levels declining post-surgery. This validates its role in staging and postoperative monitoring, while the full article was locally stored and not reachable through a public connection [31][40] . More confirmation from a cohort study demonstrated that CA-125 levels were significantly increased in patients with ovarian and mixed lesions, correlated with those with extra-ovarian foci. Whereas forcefully connected with disease severity, CA-125 levels did not impact fertility outcomes [46].

There was research conducted by Karimi-Zarchi et al. (2016), who measured CA-125 in 87 women and discovered a significant relationship with disease stage, lesion size, and adhesion score, but there was no connection with age, marital status, or pelvic pain. They recommended threshold values of 37 U/ mL for premenopausal and 37 U/ mL for postmenopausal women, corroborating CA-125's role in preoperative evaluation [32].

THE RELATIONSHIP BETWEEN CESAREAN SECTION AND (INFERTILITY, ENDOMETRIOSIS)

The results of the present study emphasize the consequence of obstetric history, particularly the number of preceding cesarean section, when evaluating infertility etiology. They similarly highlight the need for careful reflection of cesarean section indications, given its capability long-term reproductive consequences.

A latest cohort study discovered that women with cesarean scar syndrome showed remarkably increased rates of chronic endometritis and endometriosis, with raised pro-inflammatory markers (TNF-α, IL-1β) in the uterine cavity improved with controls [17]. These inflammatory changes were connected with secondary infertility because of implantation failure and chronic uterine pathology after cesarean section [43].

There was a retrospective study conducted by Karli's also reinforced CA-125 as a predictive marker, exhibiting a significant connection with chronic pelvic pain, dysmenorrhea, infertility, and endometriosis [33].

A review and retrospective clinical case series illustrated women with cwsarean secar defficiency and persistent hydrometra carrying with secondary infertility. Surgical repair of these defficiency was connected with restored fertility in the report cases, confirming the notion that structural defects from preceding cesarean section may provide directly to infertility [2].

Meta analysis and systematic review concentrating on isthmocel (cesarean scar niche) restore reported that women with reproductive issue connected to scar defficiency had enhanced pregnancy and

live birth rates surgical correction. These results further indicate that uterine niche pathologym, more abundant with numerous cesarean may defect endometrial receptivity, embryo impalntation, and final reproductive success [48][57].

Numerous studies indicate a moderate decrease in the following pregnancy and birth rates within women with previous cesarean section, compared to vaginal delivery [25].

Sima et al. found that a previous cesarean section was associated with lower fecundability and a higher risk of infertility. Surprisingly, women who took longer to conceive also had a higher chance of giving birth via cesarean section, indicating a reciprocal relationship that may be caused by similar etiologic factors [53].

A study conducted by Levy and Shiner showed the similarity related to prior cesarean section and increased infertility in later pregnancies [41].

In addition, a retrospective research done by Ahvaz Imam Hospital observed no significant difference regarding reproductive outcomes following vaginal delivery versus cesarean section, indicating there may be other primary causes of infertility after cesarean section [26]..

Bar-EI et AL. (2021) reported that a rare case of diffuse peritoneal endometriosis, including a cesarean scar isthmocele, linked to secondary infertility and unsuccessful embryo transfers. This demonstrates that the means by which endometriosis could result in surgical scars connected to challenging reproductive issues [8]. A study was conducted for five patients with primary umbilical endometriosis who received successful surgical excision; no complications were observed, and no umbilical recurrence occurred during long-term follow-up [41]. An uncommon case of vaginal endometriosis arising at a typical site after repeated urogynaecological surgeries, presumably due to iatrogenic implantation of endometrial tissue. Surgical excision led to resolution, highlighting prior pelvic surgery as a possible risk factor and the significance of considering endometriosis in postoperative vaginal lesions [15].

In women who were at high risk of recurrent stress urine incontinence, retro pubic mid-urethral slings demonstrated higher objective and subjective cure rates than trans obturator slings[51]. On the other hand, retro pubic slings were associated with increased postoperative voiding dysfunction, while trans obturator slings showed a better safety profile [36] . In a cross-sectional NHANES analysis of 3,636 U.S. women, elevated serum lutein/zeaxanthin levels were significantly associated 4.with a lower incidence of endometriosis after controlling for covariates (highest vs. lowest quartile OR ≈ 0.54–0.62, P for trend = 0.001). No significant correlations were found with other carotenoids (α-carotene, β-carotene, β-cryptoxanthin, and trans-lycopene); the negative association between lutein and zeaxanthin was particularly evident in women under 40, smokers, and oral contraceptive users [29].

Current large-scale studies, containing a landmark investigation of over more one million low-risk first-time mothers, have notably clarified the association between cesarean sections and future fertility. Although, prior smaller studies frequently suggested a connction between cesarean section and reduced fertility, recent data exhibite that for most women, a cesarean section has tiny to no independent impact on the ability to conceive again [18].

The research conducted on massive population (such as those in Sweden, Denmark, and Norway) has exhibited that

after adjusting maternal age and the initial reason for surgery, the (fertility gap) mostly vanishs [37].

The least significant effect was seen after a breech elective C-section, which did not have a statistically significant effect on women under 30. This implies that the social and clinical context of the C-section, rather than the actual procedure, has an impact on subsequent fertility [23].

There is a study conducted on over one million women exhibited that those who had an elective cesarean section for breech baby, demonstrated no statistical differences in future birth rates compared to those who delivered vaginally [10] . If the surgery itself generated infertility, it could be seen as a drop across all cesarean section types. Since the drop is only seen in (emergency) or (maternal-indication)cesarean section, it indicates that maternal choice or underlying health conditions are the real operators [50].

CONCLUSION

Most cases that attend the obstetrics and gynecology department complain of gynecological signs and symptoms in the form of severe dysmenorrhea or abnormal vaginal bleeding and are diagnosed with endometriosis. The majority underwent cesarean section previously and currently complained of secondary infertility. These results suggested that cesarean section is associated with developing iatrogenic endometriosis leading to secondary infertility. Further rigorous study is necessary to confirm these relationships.

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AUTHOR CONTRIBUTIONS

The authors have contributed to conducting the research

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL COMMITTEE

The proposal of the research was approved by the Ethical Committee of the College of Health Sciences at Hawler Medical University (NO. M.E.C.3B).

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TABLES

Table 1. Geographical Distribution of Endometriosis by Governorate

Governorate	No Endometriosis n (%)	Endometriosis n (%)	Total	
Erbil	25(20.3)	98(79.7)	123	
Sulaymaniyah	17(18.9)	73(81.1)	90	
Duhok	5(17.9)	23(82.1)	28	
Halabja	3(37.5)	5(62.5)	8	
Total	50(20.1)	199(79.9)	249	

Table 2. Sociodemographic and Obstetrical History

Variables	F	%
Age		
- Less than 31	91	36.4
- 31 - 40	100	40.0
- More than 40	59	23.6
Parity		
- Nulliparous	10	4.0
- Prime Para	59	23.6
- Multipara	149	59.6
- Grand multi para	32	12.8
Abortion		
- No abortion	176	70.4
- One or more abortions	74	29.6

Table 3. Chief complains (signs and symptoms) of the study sample (201 cases with endometriosis)

Chief complains*	F	%
Infertility	151	75.12
Dysmenorrhea	62	31
Menorrhagia	47	23.5
Hemorrhagic cyst	23	11.5
Chronic abdominal pain	11	5.5
Irregular menstrual cycle	10	5
Chronic pelvic pain	9	4.5
Acute abdominal pain	8	4
Severe abdominal pain	7	3.5
Dyspareunia	1	0.5
Oligo- menorrhea	1	0.5
Post- coital bleeding	1	0.5

Table 4. Site of endometriosis among study sample (total= 201)

Clinical Findings	F	% of 201
Endometrioma (general or unspecified)	122	60.7%
Scar endometriosis	8	4.0%
Cesarean scar endometriosis	7	3.5%
Bilateral endometrioma	4	2.0%
Subcutaneous endometriosis	4	2.0%
Rectus sheath endometriosis	4	2.0%
Right-sided endometrioma	3	1.5%
Kissing chocolate cyst	3	1.5%
Endometrioma + pelvic adhesion	3	1.5%
Bladder endometriosis	3	1.5%
Rectal endometriosis	3	1.5%
Hydrosalpinx	3	1.5%
Blocked fallopian tubes	3	1.5%
Peri tubal adhesion	3	1.5%
Bilateral tubal adhesion + hydrosalpinx	3	1.5%

Laparoscopic diagnosis of endometriosis	3	1.5%
Recurrent endometrioma	2	1.0%
Endometrioma + chronic abdominal pain	2	1.0%
Anterior abdominal wall endometriosis	2	1.0%
Pelvic endometriosis	2	1.0%
Dehiscent uterine scar	2	1.0%
Left-sided endometrioma	1	0.5%
Sub-bladder hematoma	1	0.5%
Bloody abdominal wall mass	1	0.5%
Adenomyosis	1	0.5%
Endometrial hyperplasia	1	0.5%
Intrauterine adhesion	1	0.5%
Multiple surgeries for endometrioma	1	0.5%
Vaginal fornix endometriosis	1	0.5%
Thoracic parenchymal endometriosis	1	0.5%

Table 5. History of CS, infertility, endometriosis, and level of CA-125 biomarker

Variables	**F**	**%**
Cesarean section (CS)		
- Yes	231	92.4
- No	19	7.6
No of CS		
- No CS	19	7.6
- 1 - 2 CS	155	61.8
- 3 CS and more	76	30.5
Infertility		
- No infertility	98	39.2
- Primary infertility	14	5.6
- Secondary infertility	138	55.2
Duration of infertility		
- No infertility	97	39.0
- less than 6 years of infertility	84	33.7
- 6 and more infertility	68	27.3
Endometriosis		
- Yes	201	62.2
- No	49	37.8
CA-125		
- Normal	98	39.2
- Abnormal	152	60.8

Table 6. Association between the presence of endometriosis with CS, infertility, and level of CA-125

Variables	**Endometriosis**		**p-value**
	Yes **F (%)**	**No** **F (%)**	
Cesarean section			
- Yes	153 (66.2)	78 (33.8)	< 0.001
- No	3 (15.8)	16 (84.2)	
Infertility			
- No infertility	39 (39.8)	59 (60.2)	< 0.001
- Primary infertility	6 (42.9)	8 (57.1)	
- Secondary infertility	111 (80.4)	27 (19.6)	
CA-125			
- Normal	37 (37.8)	61 (62.2)	< 0.001
- Abnormal	119 (78.3)	33 (21.7)	
Parity			
- Nulliparous	4 (40)	6 (60)	0.041
- Prime para			
- Multipara			

Grand multi para	44 (74.6) 91 (61.1) 17 (53.1)	15 (25.4) 58 (38.9) 15 (46.9)	

Table 7. Association between infertility with CS

Variables	Infertility			p-value
	No infertility F (%)	Primary infertility F (%)	Secondary infertility F (%)	
Cesarean section - Yes - No	91(39.4) 7(36.8)	5(2.2) 9(47.4)	135(58.4) 3(15.8)	< 0.001
No. of CS - No CS - 1-2 CS - 3 and more CS	7 (36.8) 51 (32.9) 4 (52.6)	9 (47.4) 2 (1.3) 3 (3.9)	3 (15.8) 102 (65.8) 33 (43.4)	< 0.001*