Pregnancy- and Lactation-associated Osteoporosis with Vertebral Fractures: A Systematic Review

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Abstract

Backgroud: To review, analyze and characterize the pregnancy and lactation-related osteoporosis (PLO) with vertebral fractures based on the extraction data in the previous studies.

Methods: A comprehensive literature search of electronic databases including the PubMed, Embase and Web of Science was conducted from January 1st,1990 to December 1st, 2020. The enrolled data were pooled to analyze the baseline characteristics, clinical features, risk factors and treatment options.

Results: A total of 65 articles with 338 cases were enrolled for data extraction. The enrolled cases aged from 19 to 47 years, with a mean value of 35.7 years old. The average body mass index (BMI) was 22.2kg/m^2 ranged from 16.0 to 39.0 kg/m^2. Of the 173 cases, 149 cases with vertebral fractures occurred in the first pregnancy, 19 cases in the second pregnancy, four cases in the third pregnancy and one case in the fourth pregnancy. Up to 91.5% of the back pain occurred within the last three months of pregnancy and the first three months after delivery. The most involved vertebral levels were L2, L1 and T12 accounting for 32.6% of all the fractures. The average fracture numbers were 4.4 levels per patient. The lumbar Z-scores were mostly recorded with a mean value of -3.2 ranged from -7.8 to 0.

Conclusions: PLO with vertebral fractures is a rare clinical entity, which is more likely to occur in older and thinner pregnant women. Back pain is the clinical complaint and mostly occurs in the late pregnancy and early lactation periods. Most vertebral fractures appear in the first pregnancy but it can occur in any time of pregnancy. Thoracolumbar region is the mostly involved region. As compared with postmenopausal osteoporotic fractures, PLO usually has multiple levels fractures. Bisphosphonates are the most widely used treatment so far, but teriparatide has become an effective alternative to bisphosphonates.

Background

Pregnancy- and lactation-associated osteoporosis (PLO) is a rare type of osteoporosis that often occurred during the late pregnancy and early lactation [1–4]. Epidemiological data on PLO are limited although previous study has estimated that the prevalence was 4–8 patients per million of population [5]. Back pain is one of the most common clinical manifestation and many patients may suffer from vertebral fractures or even kyphosis. PLO carries great physiological and psychological burdens to patients and has positive effects on quality of life and working ability. It was reported that the mean time for the PLO patients returned to work was more than three years [6].

Since the first report in 1955 by Nordin, many studies have reported this clinical entity [1–4, 6–19]. Because of the relatively low incidence, most of the studies were case reports and case series, and the clinical features were systematically varied. The patients had experienced back pain differently. Pain can vary from mild to severe and the manifestations of PLO can be present in different trimester of pregnancy. Certain PLO cases occur in the first pregnancy and some occurred in the fourth pregnancy[20]. The patients may have modifiable risk factors like prior fractures history[21, 22], taking drugs affecting bone metabolism[23–25] and smoking, and non-modifiable risk factors like having family history of osteoporosis [6, 17, 26], and have no risk factors. There is no specific department for PLO. Patients may have attended the Department of Endocrinology, Orthopedics or Obstetrics and Gynecology, however, due to the study limitations and poor awareness, many clinicians have imposing appropriate diagnostic delay and may result in poor prognosis.

In order to enhance the knowledge on PLO with vertebral fractures, a systematic review was conducted. We aimed to characterize the clinical manifestation, risk factors, fracture sites and treatment options of PLO based on a data extraction file.

Methods

Search Terms

A comprehensive literature search of electronic databases including the PubMed, Embase and Web of Science was conducted on December 1st, 2020 to retrieve all articles reporting PLO. The search strategy utilized the following key terms: “Pregnancy OR pregnant OR lactation OR breastfeeding”, “Osteoporosis OR osteoporotic”, “Vertebra OR spine OR spinal OR lumbar OR thoracic OR thoracolumbar”, “Fracture OR fractures”. The search terms were simply contained in the words of the title and abstract of the Pubmed and Embase and in topic terms in the Web of Science. The cases reported in the early literature were seldom diagnosed by using MRI for vertebral fractures, therefore we only included studies published after January 1st, 1990.

Inclusion and Exclusion Criteria

The inclusion criteria included all articles on PLO published in English. Exclusion criteria were: 1) basic research; 2) editorials, letters or meeting abstract; 3) studies that could not found full-text; 4) inadequate information; 5) vertebral fractures that had no direct connection with pregnancy; 6) vertebral fractures occurring during pregnancy or lactation but having underlying diseases that led to osteoporosis.

Data Extraction

The retrieved articles were examined and reviewed independently by two researchers. Duplicates were removed automatically by EndNote X8.1 and manually by comparing authors, titles and date of the publications. After the removal of duplicates, title, abstract and full text of articles were screened. Articles reporting the same cohort were also excluded. Then, the supplement search of the references in all the enrolled articles was performed. Data extraction of the selected articles was conducted by two authors using a standard table based on the Cochrane Handbook. For those articles reporting case series, data

extractions were performed only in those cases with vertebral fractures. Any disagreements were resolved by a third researcher. In order to unify the standard, the age at onset of symptoms and the height before pregnancy were recorded.

Results

Studies selection process

At the initial, 458 articles were retrieved from the database searching, 307 of which remained after duplicates removed. After removing meeting abstract, editorial material and letters, 292 articles were obtained. Of these, 209 were excluded since they did not meet the inclusion criteria. After full text articles assessed for eligibility, another 18 articles were excluded. Finally, 65 articles with 338 cases were enrolled in this systematic review for further data extraction. The flow chart shown in Figure.1 demonstrates the selection process in detail.

Study characteristics

Baseline characteristics are showed in Table 1. All the enrolled studies were case report and case series with the case number ranged from 1 to 107 patients. Kyvernitakis[1] reported the most cases numbered at 107 based on the German reference center for PLO and Laroche[2] reported the subsequent most cases numbered at 52 based on the French Society of Rheumatology. The number of articles published increased year by year, with 9 articles from 1991 to 2000, 13 articles from 2001 to 2010, and 43 articles from 2011 to 2020. The enrolled studies distributed globally with 34 studies in Europe, 17 studies in Asia, 5 studies in Australia, 5 studies in South America, 3 studies in North America and one study in Africa. Turkey had the highest number of PLO articles which 11 articles were recorded, followed by Germany with 8 articles and Italy (n = 7) and South Korea (n = 7).

Table 1

The enrolled studies and baseline characteristics of the enrolled cases

Number	First author	Location	Published year	Journal	No of Cases	Race	Age at onset(years)	Height(cm)	Weight(kg)	BM
1	Tuna	Turkey	2020	Gynecol Endocrinol	9/14		31			21
2	Hardcastle	UK	2019	Osteoporos Int	10	1Moroccan	33			23
3	Scott	Australia	2019	Osteoporos Int	1	Caucasian	33	162	74	28
4	Ozturk	Turkey	2019	Gynecol Endocrinol	2		33,28			27
5	Gehlen	Germany	2019	Clin Rheumatol	20		33.9□27-42□			23
6	Zhu	Australia	2018	Osteoporos Int	2		29			
7	Li	China	2018	Clin Rheumatol	10/12	9Han,1Manchu	31			21
8	Hong	Korea	2018	Clin Endocrinol	32		31.3 ± 2.6			20
9	Butscheidt	Germany	2018	Osteoporos Int	5/7		35			22
10	Taraktas	Italy	2018	Turk J Endocrinol Metab	1		22			
11	Yun	Korea	2017	Obstet Gynecol Sci	6		32	164	57	21
12	Kyvernitakis	Germany	2017	Osteoporos Int	107		39.5+-6.0	165.9+/-6.3;	63.5+/-11.1	23
13	Zhang	China	2017	Medicine	1		23			21
14	Laroche	France	2017	Osteoporos Int	52		27			
15	Ljuin	Japan	2017	Taiwan J Obstet Gynecol	1		27	163	45	17
16	Pola	Italy	2016	J Biol Regul Homeost Agents	1	Caucasian	33	167	60	21
17	Krishnakumar	India	2016	J Craniovert Jun Spine	2		27,31			
18	Sánchez	Argentina	2016	Clin Cases Miner Bone Metab	2		35,33	162157		
19	Grana	Italy	2016	Pain Med	1	Caucasian	31			
20	Gaudio	Italy	2016	Clin Cases Miner Bone Metab	1		38	167	54	19
21	Ekim	Turkey	2016	J Clin Anal Med	1		35	165	54	19
22	Polat	Turkey	2015	Gynecol Endocrinol	1		23			24
23	Hadgaonkar	India	2015	Asian Spine J	1		24			
24	Ozdemir	Turkey	2015	Osteoporos Int	2		34,36	168, 162	62,59	21
25	Kovacs	Canada	2015	Osteoporos Int	1/2		35	151	46	20
26	Grizzo	Brazil	2015	Calcif Tissue Int	1	Caucasian	31	165	55	20
27	Zarattini	Italy	2014	Clin Cases	1	Caucasian	27	165	63	23

				Miner Bone Metab						
28	Takahashi	Japan	2014	Fukushima J Med Sci	1		22	163	60	22
29	Obando	Netherlands	2014	J Clin Endocrinol Metab	1	Caucasian	27	158	53	21
30	Raffaetà	Italy	2014	Clin Cases Miner Bone Metab	2		42,21	167	66	23
31	Ozturk	Turkey	2014	J Obstet Gynaecol	2		22,34			
32	Baldane	Turkey	2014	Turk Fiz Tip Rehabil Derg	1		35	155	45	18
33	Winarno	Germany	2014	Z Geburtsh Neonatol	1		29	158	46	18
34	Terzi	Turkey	2014	BioMed Res Int	1		32			
35	Cook	USA	2014	J Bone Miner Res	1	Caucasian	26	161	68	26
36	Scozzari	Italy	2014	Acta Medica Mediterranea	1		19			
37	Lee	Korea	2013	J Bone Metab	1		39	156	50	20
38	Bonacker	Germany	2013	Arch Orthop Trauma Surg	1		40			
39	Lwamoto	Japan	2012	Ther Clin Risk Manag	1		32	155	57	23
40	Adamidou	Greece	2012	Horm-Int J Endocrinol Metab	1	Caucasian	40	158	56	22
41	Choe	Korea	2012	J Bone Miner Metab	3		36,32,30			20
42	Stupar	Serbia	2012	Rheumatol Int	1		30	152	52	22
43	Lee	Korea	2011	J Back Musculoskelet Rehabil	1		31	157	50	20
44	Mastaglia	Argentina	2010	Osteoporos Int	1		20			
45	Kim	Korea	2010	J Korean Neurosurg Soc	1		35	150	42	18
46	Hellmeyer	Germany	2010	Gynecol Endocrinol	1		40	171	62	21
47	Tanriover	Turkey	2009	Spine J	1	Caucasian	23	169	65	22
48	Jang	Korea	2009	Rheumatol Int	1		30	163	52	19
49	Ofluoglu	Turkey	2008	Rheumatol Int	1		30	162	50	19
50	Stumpf	Germany	2007	Adv Med Sci	2		32,41			19
51	Hellmeyer	Germany	2007	Exp Clin Endocrinol Diabet	1		28	158	46	18
52	O'Sullivan	New Zealand	2006	Osteoporos Int	10	9Caucasian,1Fijian	31			22
53	Bayram	Turkey	2006	Joint Bone Spine	1		37			
54	Allali	Morocco	2005	Clin Rheumatol	1		38			
55	Tran	Australia	2002	Intern Med J	3	2Caucasian	23.22,36	157, 170, 160	47,48,47	19
56	Peris	Spain	2002	Clin Exp Rheumatol	5		31	155	54	22

57	Yamaga	Japan	2000	Eur J Obstet Gynecol Reprod Biol	1		25			
58	Gregorio	Argentina	2000	Nutrition	3	3Caucasian	38,33,30	155151	56,47	23
59	Anai	Japan	1999	J Obstet Gynaecol Res	2		24,30	161 155	44,47	17
60	Babbitt	USA	1998	J Clin Densitom	1		46	175	71	23
61	Smith	England	1995	QJM-Mon J Assoc Physicians	16		28			
62	Yamamoto	Japan	1994	Calcif Tissue Int	5		30	153	57	24
63	Rillo	Argentina	1994	Clin Rheumatol	1		25			
64	Blanch	England	1994	Br J Rheumatol	2	2Caucasian	31,28			
65	Reid	New Zealand	1992	Clin Endocrinol	1	Caucasian	31			

Baseline characteristics of enrolled cases

All the enrolled PLO patients aged 19 to 47 years. A total of 191 cases documented the detailed age information with a mean age of 35.7 years. Of the 191 cases, 6 cases over 40 years old accounting for 3.1%, 109 cases over 30 years old accounting for 57.1%, 29 cases under 26 years old accounting for 15.2%. The age distributions are illustrated in Figure.2. The average height of the included cases is 164.2cm, ranged from 144cm to 175cm. The body mass index (BMI) of 46 studies was calculated and documented with a mean value of 22.2kg/m^2 ranged from 16.0 kg/m^2 to 39.0 kg/m^2. The BMI distributions of 98 individuals are showed in Figure.3. The observed data showed that few PLO patients were obese and overweight. Furthermore, race information of 38 cases was documented, which was Caucasians (n = 26), Hans (n = 9), Manchu (n = 1), Fijian (n = 1) and Moroccan (n = 1).

Clinical features

A total of 173 cases had the information on number of pregnancy when vertebral fractures occurred, in whom 149 cases were in primiparity, 19 cases were in the second pregnancy, 4 cases were in the third pregnancy and one case was in the fourth pregnancy. There were 108 cases clearly defined feeding manner, with 102 cases breast-feeding accounting for 94.4%. Up to date, not much literature described the delivery way, in which there were vaginal delivery (n = 11) and cesarean delivery (n = 5).

All the included PLO patients with vertebral fractures were symptomized with back pain. The visual analogue score (VAS) were documented in 17 cases, of which all suffered from mild to severe pain and eight cases (47.1%) complained of severe pain. The earliest time of symptom onset was determined at the 5th month pregnancy, while the latest was at nine months postpartum. Of the 82 cases with definite symptom onset time, 75 cases (91.5%) with back pain occurred during the last three months of pregnancy and the first three months after delivery. The details of distributions are shown in Figure.4.

The risk factors associated with PLO were examined such as drug affecting bone metabolism, pre-partum fractures history, family history of osteoporosis, smoking and abnormal menstruation. A total of 59 patients had provided accurate medication history, of which 17 patients (28.8%) had a history of oral anticoagulants such as heparin, low molecular weight heparin (LMWH) and four patients had a corticosteroids history. Of the 68 cases with pre-partum fractures history documented, 17 (25%) cases were suffered from bone fractures before pregnancy. Regarding to family history of osteoporosis, of all the 172 cases with definite documentation, 57 patients (33.1%) had positive family history of osteoporosis. Smoking status was recorded for 111 cases, in which 24 cases (21.6%) were smokers and ex-smokers. There are less menstruation records in the studies, 4 of 25 cases presenting irregular menses.

The studied articles have indicated variable rates of vertebral fractures. Fracture sites were described in 155 cases with 684 vertebral fractures and the average fracture was 4.4 vertebrae per patient. Most cases were suffered from multiple vertebral fractures with only 14 single segment vertebral fractures. As for specific fracture locations, the three most frequently involved vertebral fractures were L2, L1 and T12 (32.6% of all the fractures). The number and site of fractured vertebrae are shown in Figure.5.

Another important factor is Body mineral density (BMD). BMD values of the enrolled cases were analyzed. *Z*-scores have been preferable used in the studies as compared to *T*-scores. The lumbar *Z*-scores were recorded in 123 cases in mean value of -3.2 ranged from -7.8 to 0, while the hip *Z*-score were recorded in 122 cases with an average of -2.2 ranged from -5.5 to 0.9. The lumbar *T*-scores were recorded in 51 cases with an average of -3.6 ranged from -6.5 to -1.3, while the average of the hip T-scores of 47 cases was -2.5 (ranged from -6.5 to -0.2).

Treatment options

Different therapies that have been used in the management of PLO were documented in 108 cases. These therapies included Calcium and vitamin D therapy (n = 7), bisphosphonates (n = 58), teriparatide (n = 24), denosumab (n = 10), calcitonin (n = 6), strontium ranelate (n = 2), simple rehabilitation without medication (n = 2, with mild symptoms) and vertebroplasty (n = 4, with severe symptoms).

Discussion

The current study demonstrated that PLO is a rare clinical entity and distributed worldwide. To date, although more and more reports are available, the documentation of PLO is still very limited and its mechanism remains unclear. The pooled data revealed PLO is more likely appeared in those pregnant women of advanced maternal age. PLO is an age-related disease. Pregnant women in more than half of the cases were over 30 years. Therefore, wide age range of the enrolled pregnant or postpartum women with acute back pain should be excluded from the study.

Similar to postmenopausal osteoporosis, BMI may contribute to increasing risk of PLO. People who are obese or overweight have relatively higher risk of getting PLO.

In general, pregnant women experience calcium loss during the late pregnancy and postpartum lactation. BMD of pregnant women might be associated with pregnancy. In the study of Martina et al (2010), the prospective changes of BMD with an ultrasonometry measurement in 59 pregnant women were observed. The results showed that BMD was reduced significantly in the second and third trimester of pregnancy [27]. This study indicated that osteopenia is a common condition in pregnant women. However, it is difficult and unethical to measure BMD of pregnant women by X-ray or CT. Contrarily, Lebel et al (2014) studied the T-scores and Z-scores of the first 2 days after delivery in 132 pregnant women and found that both scores were within the normal limits regardless of age [28]. These findings indicated that the exact bone metabolism would be more sophisticated in pregnant women.

The pooled data also revealed that PLO may not appear in the first pregnancy. It might be occurred in the second, third or even fourth pregnancy. For patients with multiple pregnancies, PLO might appear in one of them, while other pregnancies were normal [20].

Fracture sites were analyzed in the present study. As compared with other osteoporotic vertebral fractures, PLO had more vertebrae involved. Only a few patients had a single level vertebral fracture. Thoracolumbar region is remained as the most affected area. Magnetic resonance imaging (MRI) should be recommended to detect the conditions of thoracic and lumbar vertebrae if cases of missed diagnosis of the fractured vertebrae for the patients with suspected PLO occurred.

Despite its common occurrence, there is no standard clinical guideline for the treatment of PLO. The current review exhibited various drugs have been used in clinical practice for the treatment of PLO such as bisphosphonates, teriparatide, denosumab and calcitonin. Among the drugs, bisphosphonates are the mostly used. The safety of PLO therapy always is the major concern of clinicians and patients because of its long-term calcium deposits to the bone. The use of bisphosphonates may develop adverse effects on both the fetus and the mother. However, so far, no adverse effects of bisphosphonates on the pregnancy were reported. Due to unforeseen circumstances of bisphosphonates, teriparatide, which helps to regulate calcium metabolism, has been used more frequently for PLO.

Conclusion

PLO is a rare clinical type of osteoporosis, which is more likely occur in older and thinner pregnant women. Back pain is a common clinical manifestation during the last three months of pregnancy and the first three months after delivery. Most PLO occurs in the first pregnancy but it may appear at different stages of pregnancy. Thoracolumbar region is the mostly affected region, however, as compared with postmenopausal osteoporotic fractures, PLO usually has multiple levels fractures. Presently, bisphosphonates are the most widely used treatment for PLO, however, due to the increased of clinical concern, teriparatide has been used as it is an effective alternative to bisphosphonates.

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Weimin Huang conceived the idea and contributed to design. Weimin Huang and Ying Qian ran the searches and extracted data. Weimin Huang and Lei Wang assessed the methodological quality. Weimin Huang and Lili Yu conducted the meta-analysis. Weimin Huang and Ying Qian wrote the manuscript. All authors

approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Figures

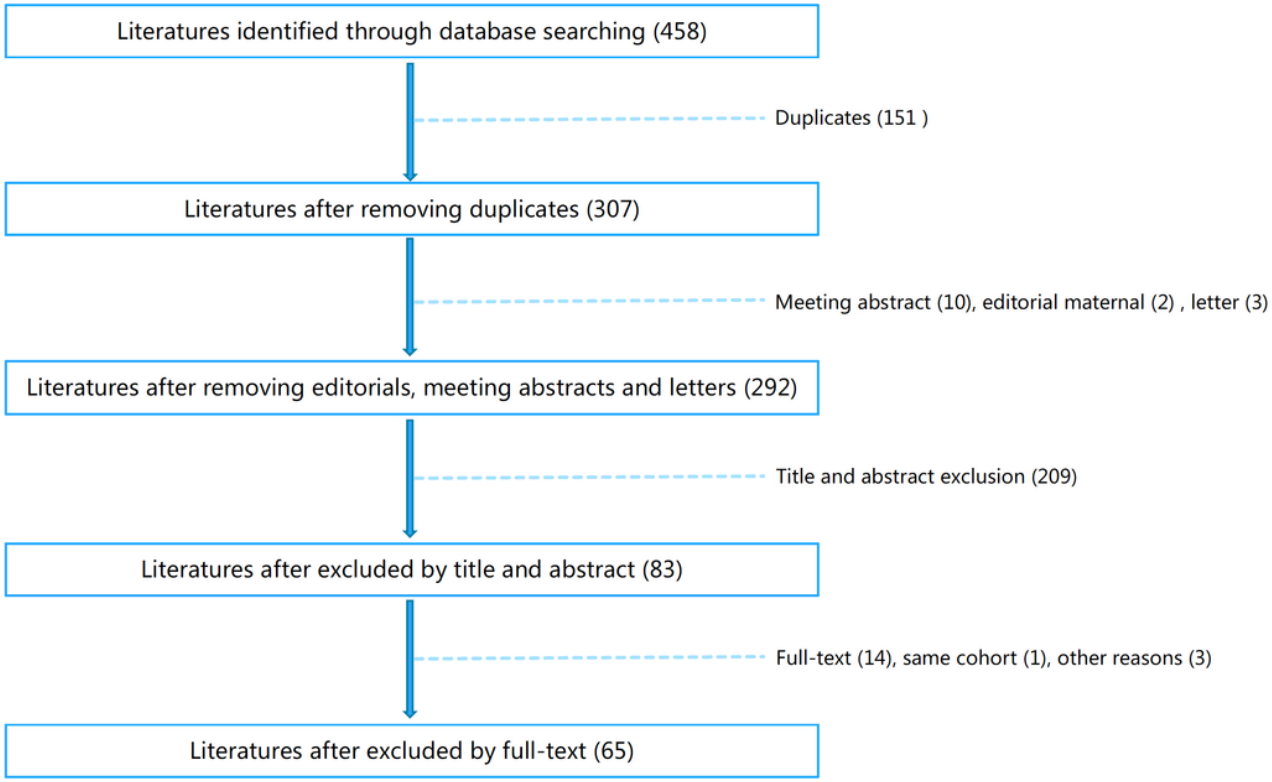

Figure 1

The flow diagram of included and excluded studies

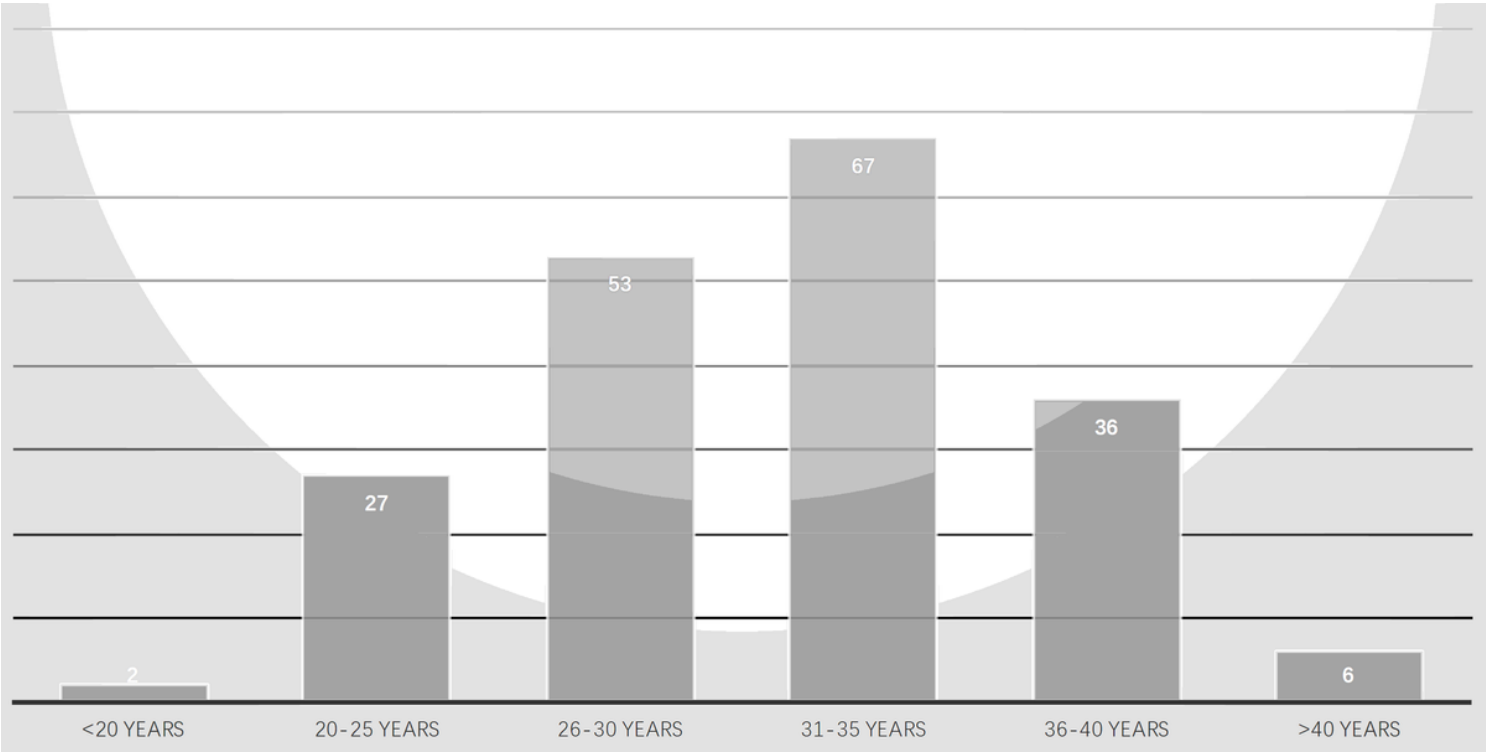

Figure 2

The age distributions of the enrolled cases

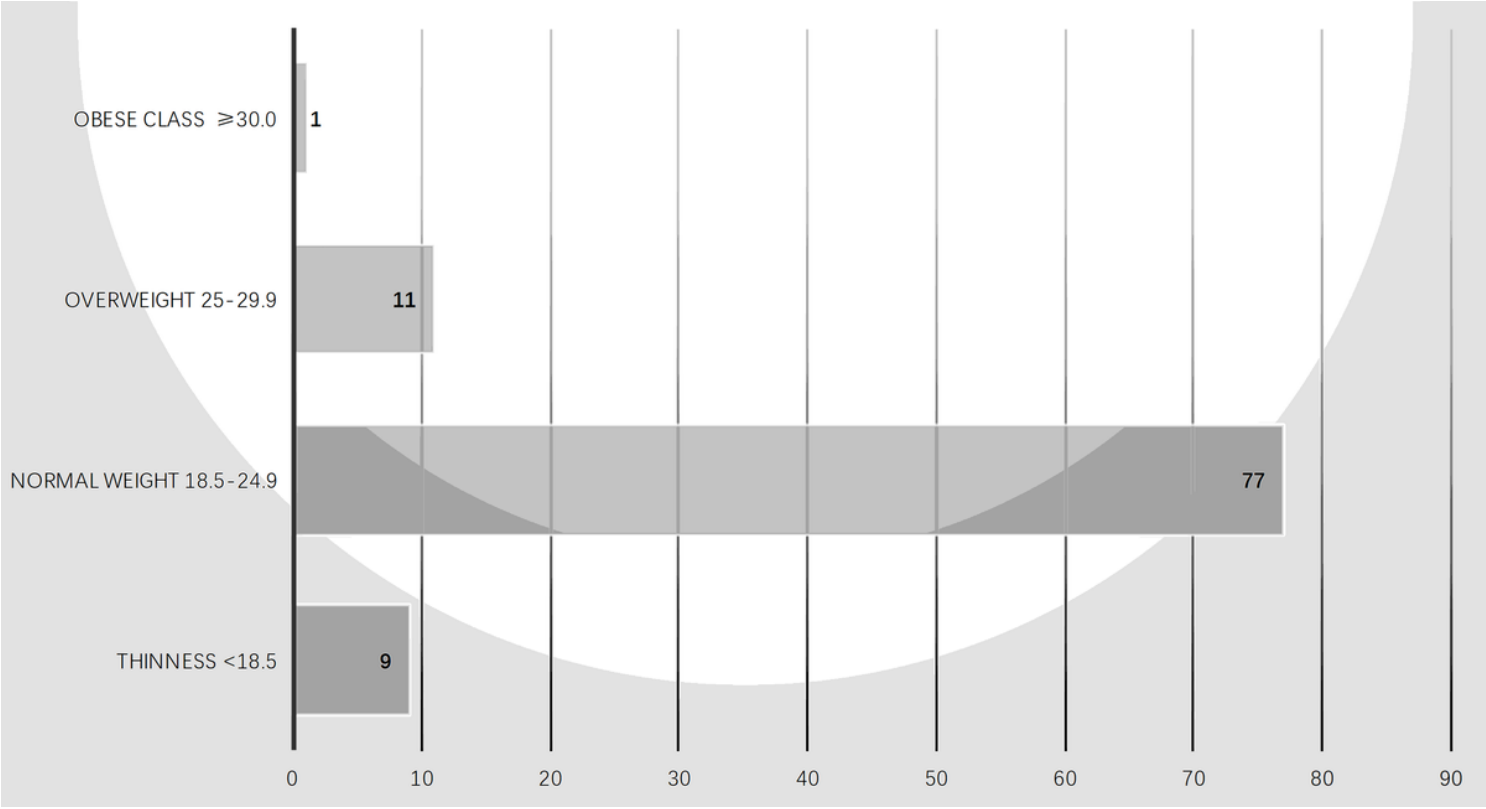

Figure 3

The BMI distributions of the included cases

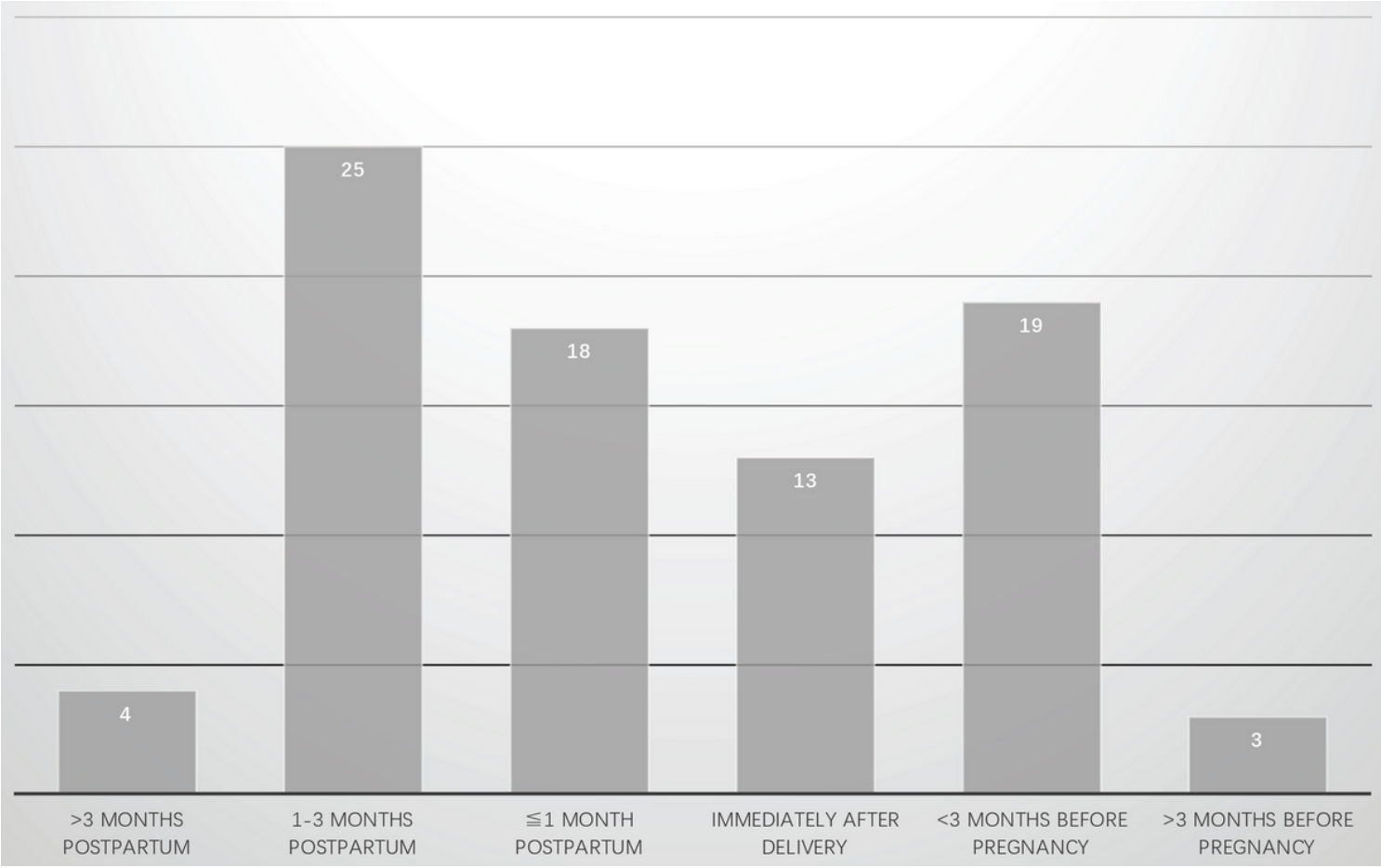

Figure 4

Symptom onset time of the enrolled patients

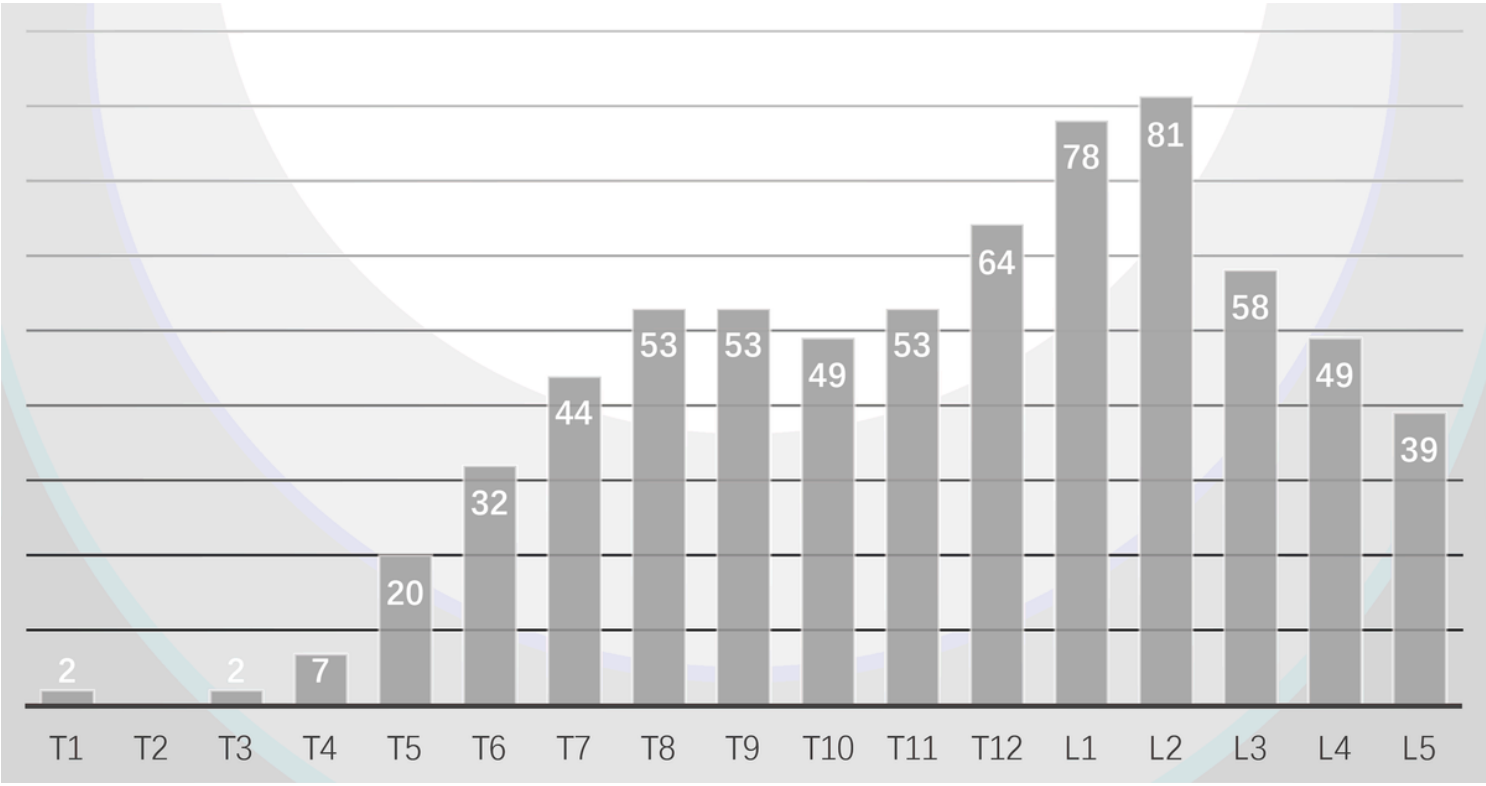

Figure 5

The fractured site of the enrolled cases

Supplementary Files

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- Rawdata.xlsx