

## Peer Review File

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Reviewer A:

*The intracytoplasmic sperm injection (ICSI) has been well used as a simple, non-invasive method to retrieve spermatozoa from patients with anejaculation, yet its clinical outcomes have not been well evaluated. This study reports the clinical outcome from a relatively big cohort of 96 patients with 41 orgasmic dysfunction patients and 55 anejaculation patients. With a total of 56 fresh transplantation cycles, they achieved a favorable clinical pregnancy rate and live birth rate, which is 57.1% and 51.8%, respectively. The authors further show that the sperm frozen process has no impact on clinical outcomes. Overall this is an important study that provides useful insight for urologists in the field.*

*Few minor suggestions include:*

*1. While the ages of patients are within a relatively narrow range (30.15+-4.75), still it will be interesting to analyze whether there is any correlation between the clinical outcome and age of the patients.*

Reply: Thank for your useful suggestions. There is indeed negative correlation between the clinical outcome and the age of the **famale patients**, especially when women are over 35. Due to the small number of cases, we did not make a sub-classification to analyze the impact of age on pregnancy rate. We only counted the age difference between the two groups.

*2. Some writing is confusing, for example in their abstract the authors overstated that “there were 28 cases (50.9%) caused by diabetes”. At this level of study, this overstatement should be corrected to “there were 28 cases (50.9%) have diabetes”.*

Reply: We have corrected it as your suggestion. Changes in the text in Line 27.

**Reviewer B:**

*The authors conducted a retrospective study of 41 orgasmic dysfunction patients and 55 anejaculation patients who underwent epididymal /testicular sperm aspiration for ICSI. The percutaneous epididymal sperm aspiration was the first choice, and if failed, testicular sperm aspiration was performed instead. ICSI outcomes, clinical pregnancy (per embryo transfer), live birth rate] were recorded. Based on the results, the authors concluded that epididymal sperm aspiration for ICSI can achieve favorable results, and caudal epididymis puncture for sperm aspiration is preferred in patients with orgasmic dysfunction and anejaculation. Meanwhile, the frozen epididymal sperm for ICSI can be obtained a good clinical outcome as well as using fresh sperm. Well, after reading this manuscript carefully, this reviewer cannot find what is new information for the field. Those kinds of results have been reported from many papers published. In another word, the objective or purpose of this study is not clear. The authors cannot just perform a retrospective analysis to record the pregnancy outcomes. From the results, it should be drawn solid conclusion, which will be new or important information for the field, but it is not the case. Therefore, this reviewer cannot recommend the paper to be accepted for publication in this journal.*

Reply: We admitted that this paper have some shortcomings and carefully revised our paper according yours and other reviewers suggestions. We hope you can comment again.

**Reviewer C:**

Major comments

*- I miss the knowledge gap in the Introduction. What is currently unknown, why is this important and how are the authors going to solve this knowledge gap?*

Reply: Thank you for your useful suggestions. Based your suggestions we carefully revised the Introudction. Changes in the text in Line 55-57.

***- The endpoint of the study is unclear. In the introduction, it seems as if it is a single center series of the ICSI outcome, but the Tables are set up as; Orgasmic dysfunction vs. anejaculation; Fresh vs. Frozen; and Diabetes mellitus vs. Unexplained reason. If the authors would like to compare certain groups, please state so in the Introduction (with reasons) and Methods.***

Reply: This is a descriptive retrospective single center study. The author mainly summarized the ICSI results in 91 patients with orgasmic dysfunction and anejaculation by epididymitis sperm acquired by PESA. The results were compared with those of CBAVD patients who underwent ICSI with sperm from epididymis puncture at the same time. The clinical pregnancy rate and live rate were similar between the two groups. Furthermore, we compared ICSI results between orgasmic dysfunction and anejaculation, frozen and fresh epididymis sperm, and diabetic and non-diabetic patients with anejaculation. Similar results were obtained between these groups. Changes in the text in Line 57-63.

***- The results of this study are not discussed in the Discussion. They are repeated but they are not compared to what has been found in other studies. In addition, several important references are missing.***

Reply: Based your suggestions, We compared our results with other ICSI studies with several other obtaining sperm measures in treatments of ejaculatory dysfunction, and add some important references according to you recommendation.

***Other (major and minor) comments per section:***

***Abstract***

***- It is stated that most patients are diagnosed with unknown causes. But this conclusion can't be made based on this study. This was a retrospective study; thus, it is more likely that the cause of orgasmic dysfunction was not properly recorded.***

Reply: The etiology of anejaculation in our group is mostly clear, but the etiology of orgasmic dysfunction in our group is mostly unclear. We lack some psychological evaluation, such as anxiety and depression. However, according to our observation,

most of the patients with orgasmic desfunction have less speech and introverted personality, but this information are not reflected in our article. Changes in the text in Abstract part.

### ***Introduction***

***- Line 36-39 (Premature ... patients): Please add reference.***

Reply: We have revised it.

***- Line 46: First report the term, then the abbreviation.***

Reply: We have revised it.

***- The readability of the Introduction would be greatly improved if the different parts are divided in separate paragraphs.***

Reply: We accept your suggestion and divided it into two sections. Changes in the text in Introduction.

***- There is no knowledge gap identified in the Introduction. What is it that the authors want to investigate? Why is this important and has it been done before? What is unknown?***

Reply: We agree it and rewrited the section of Introduction.Changes in the text in Line 55-58.

### ***Materials and methods***

#### ***Patients***

***- Please give more detail about the setting of the study. Were all consecutive patients who had orgasmic dysfunction or anejaculation included in the study? What kind of hospital is it? A tertiary referral center? A local hospital? How were patients referred? By a medical specialist in another hospital or by a general practitioner?***

Reply: The layout and logic of our manuscript are not ideal indeed. We have tried our best to make revisions and hope that our work can be recognized by our peers. Our hospital is the teaching hospital and the First Affiliated Hospital of Nanjing Medical University. Dr. Yang is a medical specialist who only works in this hospital.

Many of our patients are transferred from local hospitals. Our study included all patients with orgasmic dysfunction or anejaculation requiring epididymis or testicular puncture for ICSI during January 2013 and December 2018 (defined by the date of oocyte retrieval). Changes in the text in Line 66-82.

***- It is stated that only the first ICSI cycle is included. Was also only the first embryo transfer per couple included? Or were more transfers per couple possible? If so, state this in the Methods and report this also in the Results.***

Reply: The clinical pregnancy rate and live birth rate only counted the fresh transfer cycle, and other data such as fertilization rate and high-quality embryo were calculated according to the ovulation / oocyte collection cycle. Perhaps what we have described is misleading and has been revised in the revised manuscript. Changes in the text in Line 70-72.

#### ***Retrieval techniques***

***- Line 62: Explain abbreviations PESA/TESA.***

Reply: We have explained it in the manuscript.

***- Line 71: "some liquid like semen" please rephrase.***

Reply: We have rephrased it. Changes in the text in Line 91.

***- Who examined the specimen? An embryologist?***

Reply: The andrologist will place the liquid obtained from the puncture into a test tube containing the culture liquid and send it to the embryo laboratory. The embryologist will evaluate, process, freeze and select the sperm for ICSI.

***- When was the retrieval sperm deemed favorable? Was there a cutoff value of number of spermatozoa alive? Or was the presence of only 1 sperm cell enough?***

Reply: Under 400 times phase-contrast microscope, 10 ul of epididymal fluid (0.5-1 ml) containing culture were dropped into slides for analysis. If more than one forward motile sperm can be observed in 10 visual fields, it would meet the freezing standard; if one forward motile sperm with relatively normal morphology can be seen in the whole slide, it would meet the ICSI standard. Changes in the text in Line 94-98.

***- When was fresh and when was frozen embryo transfer performed? This should be added to the Methods section.***

Reply: Whole embryo cryopreservation will carry out when too much follicle development and too high estrogen level led to the risk of ovarian hyperstimulation, and when the endometrium does not meet the transplantation standards (thickness less than 7mm). Changes in the text in Line 104-107.

#### ***Statistical analysis***

***- Why was paired samples t-test used? Why not independent samples?***

Reply: We are very sorry for this mistake and revised it. Changes in the text in Line 113-116.

#### ***Results***

***- How many causes of orgasmic dysfunction were unexplained and how many were explained?***

Reply: There were 41 cases of orgasmic disorder, 36 cases of primary and 5 cases of secondary. Most of the causes are unknown, only one case may be clear. He has secondary orgasmic disorder after severe brain injury. Changes in the text in Line 118-122.

***- As stated before, it can't be stated that most causes were unexplained. They were probably not recorded. This was a retrospective study.***

Reply: The etiology of anejaculation in our group is mostly clear, but the etiology of orgasmic dysfunction in our group is mostly unclear. We lack some psychological evaluation, such as anxiety and depression. However, according to our observation, most of the patients with orgasmic dysfunction have less speech and introverted personality, but these information are not reflected in our article. Changes in the text in Result part.

***- The two patients with surgery for right-sided cryptorchidism, did they have surgery before or after diagnosis of orgasmic dysfunction?***

Reply: We listed two cases of right cryptorchidism at preadolescence with primary orgasmic disorder, and the PRL and testosterone levels were normal. We

don't think there is a causal relationship. It may just be coincidence. Changes in the text in Line 120-122.

*- Was PESA/TESA successful in all patients? I find this hard to believe. This gives the impression that only patients with successful sperm retrieval were included (96 pts). However, this is not stated in the inclusion and exclusion criteria. It would be better to include all patients in whom PESA/TESA was performed and also report the number of patients in whom PESA/TESA was unsuccessful.*

Reply: In fact, some patients with IHH and klinefilter syndrome also show ejaculation disorder because of low testosterone, but we did not include in the group. That is to say, the ejaculatory disorder patients we enrolled actually have a enrollment standard, which is the normal range of sexual hormone levels, especially T, PRL and FSH.

#### *ICSI outcomes*

*- What happened with the 40 couples in whom no fresh embryo transfer was performed? As stated before, it seems that sperm retrieval was successful, so was oocyte puncture unsuccessful? Or was ICSI unsuccessful? The authors seem to skip a few steps here.*

Reply: Almost all of these patients developed transplantable embryos and high-quality embryos, but 40 couples were carried out with whole embryo cryopreservation, because too much follicle development and too high estrogen level led to the risk of ovarian hyperstimulation, and sometimes the endometrium did not meet the transplantation standards. Changes in the text in Line 104-107.

*- Why was one embryo not transferable?*

Reply: Almost all of these patients developed transplantable embryos and high-quality embryos.

*- Line 111: Number of oocytes for ICSI has nothing to do with spermatozoa quality, thus is unrelated with azoospermia cause. This can be omitted from the text.*

Reply: We listed the number of mature oocytes to express that there is no significant difference in the background of women in different groups, so that we can further compare the results between groups.

*- Line 113: Rephrase the part about spontaneous abortion rate. Although not statistically significant, I would say that the difference is quite big (zero vs. one-fifth). Same for live birth rate. The lack of significance might be due to the small sample size.*

Reply: We agree with you and revised it. Changes in the text in Line 108-110.

*- Line 111-114: Report all P-values separately. It is insufficient to simply state  $P > 0.05$ .*

*- Line 117-119: Same comment.*

*- Line 123-125: Same comment.*

Reply: We added the P values separately. Changes in the text in Result part.

*- The Results section is a repetition of the Tables. Try to use different phrases, otherwise it becomes quite "listing".*

Reply: We rewrote this part in the revised manuscript. Changes in the text in Result part.

*- Depending on the journal guidelines, percentages can be truncated at one decimal.*

Reply: We revised it according to the journal guidelines.

### ***Discussion***

*- The paragraphs are too long. To make a clear point, the maximum should be four to five sentences per paragraph.*

Reply: We divided it into suitable paragraphs as your suggestion. Changes in the text in Discussion part.

*- The Discussion is more like an essay; the results of the study are not compared to what has been found in other studies.*



Reply: We compared our results with other ICSI studies with several other obtaining sperm measures in treatments of ejaculatory dysfunction, and add some important references according to you recommendation.

**- *The limitations and strengths of the study are missing.***

Reply: We add the limitations and strengths of the study in Discussion part. Changes in the text in line 210-213.

**- *Line 129-130 (Treatment ... father): I don't understand this sentence.***

Reply: This sentence is indeed subjective and arbitrary. It has been revised as follows: It is very important to explore the cause of ejaculation disorder, but the cause of orgasmic dysfunction, especially the cause of orgasm disorder, is not clear. This presents a great challenge to the treatment. Changes in the text in line 160-162.

**- *Line 153-162: This can be omitted. This paper is not about Diabetes mellitus.***

Reply: Diabetes mellitus is the most common cause of anejaculation. We think it is important to this part. Based your suggestion, we rewrite this part in line 189-196.

**- *Line 180-191: This section doesn't have a single reference! Please add references!***

Reply: Sorry, this section should have reference and we add reference in this paragraph.

**- *Some important references are missing:***

***Soeterik et al. Electroejaculation in psychogenic anejaculation. Fertil Steril. 2014 (PMID: 24726223) >> Important paper in patients with anejaculation.***

***Soeterik et al. Electroejaculation in patients with spinal cord injuries: A 21-year, single-center experience. Int J Urol 2017 (PMID: 27862365) >> Shows the results of electroejaculation***

***Blok et al. Open epididymal spermatozoa aspiration for obstructive azoospermia. Andrologia 2019 (PMID: 30575065) >> Results of OESA, which is a modification of PESA and a large sample of couples who have underwent ICSI.***

*Shih et al. Testicular versus percutaneous epididymal sperm aspiration for patients with obstructive azoospermia: a systematic review and meta-analysis. TAU 2019 (PMID: 32038959) >> Review on TESA vs PESA*

*Esteves et al. Reproductive potential of men with obstructive azoospermia undergoing percutaneous sperm retrieval and intracytoplasmic sperm injection according to the cause of obstruction. Journal of Urology 2013 (PMID 23174251) >> Large series on PESA, important to compare your results with*

*Bromage et al. Sperm retrieval rates in subgroups of primary azoospermic males. Eur Urol 2007 (PMID: 16997455) >> Large series*

Reply: We add these important references in the revised manuscript.

*- I believe it is not possible to make strong conclusions based on this study. The lack of statistical significance is probably due to the small sample size. This should be added to the Discussion.*

Reply: Through a small sample size and retrospective study, we really should not arbitrarily and rashly conclude that epididymal sperm extraction is better than testicular sperm extraction or as a preferred treatment. What we want to express is that the epididymal puncture is relatively simple and the embryo laboratory may think that the epididymal sperm is simpler to process and easier to choose for ICSI than the testicular sperm in the laboratory.

*- Line 190-191 (Caudal ... technology): This is not based on the results.*

Reply: We add this into the Result part. Changes in the text in line 129-130.

#### **Tables**

*- How is early pregnancy loss defined? Add this to the Results section.*

Reply: We add it in Result section. Changes in the text in line 109-110.

*- Table 1: This is set up as orgasmic dysfunction vs anejaculation. Why? Was this an end-point of the study? To investigate the difference between these groups? If so, this should be added to the Introduction (aim) and Methods section. Please also give the overall results (add extra column).*

Reply: This is a descriptive retrospective single center study. The author mainly summarized the ICSI results in 91 patients with orgasmic dysfunction and anejaculation by epididymitis sperm acquired by PESA. The results were compared with those of CBAVD patients who underwent ICSI with sperm from epididymis puncture at the same time. The clinical pregnancy rate and live rate were similar between the two groups. Furthermore, we compared ICSI results between orgasmic dysfunction and anejaculation, frozen and fresh epididymis sperm, and between diabetic and non-diabetic patients with anejaculation. Similar results were obtained between these groups. We have improved the sections of Introduction, Methods and Results in the manuscript.

***- Table 2: Same comment as above, but this is set up as Fresh vs Frozen. Also, add overall results.***

Reply: Furthermore, we compared ICSI results between frozen and fresh epididymis sperm. Similar results were obtained between two groups. We have improved the sections of Methods and Results in the manuscript.

***- Table 3: The same comment as above, but this is set up as Diabetes mellitus vs Unexplained reason.***

Reply: Furthermore, we compared ICSI results between diabetic and non-diabetic patients with anejaculation. Similar results were obtained between two groups. We have improved the sections of Methods and Results in the manuscript.

***- Table 2: Title: fresh vs frozen sperm? I think a frozen embryo is meant.***

Reply: It means ICSI using fresh and frozen epididymal spermatozoa, we changed the table name.

***- Table 2: There are 51 frozen embryos transferred, but what is meant by 27 fresh embryo transfer cycle??? 27 of 51 frozen embryos turned out to be fresh after all???***

Reply: We are so sorry to mislead you and revised the table to make it more clearly.

***General minor comments***

*- There are quite some small spelling and grammar errors. For example, space before the comma (line 33). Singular form when plural is necessary (line 35). No space between the last word of sentence and reference (line 35 + 44). No space between word and abbreviation (line 45). Etc.*

Reply: We have revised these mistakes based your suggestions.

*- This report would greatly improve if checked by a native speaker of English.*

Reply: We asked a professional English editor to improve our manuscript comprehensively.

**Reviewer D:**

*Dear authors there are major flaws that impede the publication of the paper in its current format which is itemized as follows:*

*Introduction section*

*Premature ejaculation and delayed ejaculation usually have a little negative effect on fertility, and medical treatment or sperm retrieval from the urine could be used for assisted reproductive technology ART in retrograde ejaculation patients, you should not mention Premature ejaculation and delayed ejaculation in this statement to avoid any confusion to the readers?*

Reply: Premature ejaculation and delayed ejaculation usually do not affect fertility, except for extravaginal premature ejaculation or severe delayed ejaculation (most sexual life without ejaculation). Based your suggestion, we deleted this sentence to avoid confusion.

*Once again there is another confusing statement that needs clarification to me as anejaculation means anorgasmia while retrograde ejaculation means dry orgasm? " Orgasmic dysfunction is difficulty or absence of attaining orgasm after sufficient sexual stimulation, while anejaculation is completely absence of antegrade or retrograde ejaculation accompanying the presence of orgasm.*

Reply: EAU Guidelines on Ejaculatory Dysfunction(European Urology 46 (2004) 555–558) describe: Anejaculation is the complete absence of an antegrade or retrograde ejaculation. True anejaculation is usually associated with a normal

orgasmic sensation, and Anorgasmia is the inability to reach orgasm and this may give rise to anejaculation: its causes are usually psychological.

***As long as this is a retrospective study, its' aim should be modified into a comparison between the outcome of different sperm sources (PESA vs. TESA vs. EEJ) Which I think would be more interesting to the readers***

Reply: Among the 96 patients with ejaculation dysfunction, 91 cases got motile sperm from epididymis, and only 5 cases get sperm from testis. The number of testicular sperm samples is a little small, which is not proper for statistical comparison. We plan to carry out a prospective study in the future to compare the ICSI outcomes between PESA and TESA in patients with ejaculatory dysfunction. However, we cannot carry out a comparison between PESA and EEJ for lack of EEJ.

#### ***Methods section***

***Why TESA can cause irreversible testicular damage?***

Reply: What we want to express is that testicular puncture will remove some seminiferous tubules, which may be non renewable tissue. In the case of small testis, the testosterone level will decrease in a short period of time, but it will also recover in 6 months, because there are stem leydig cells in the testis to supplement more leydig cells and restore the secretion of testosterone. In fact, epididymis and testicular puncture have some slight side effects such as hematoma and pain. We have revised this sentence which is not very proper. Changes in the text in line 80-82.

***Another confusing point as long as these patients were suffering from ejaculatory dysfunction why you set TSEA as a second option in case of PESA failure as absence of sperm in PESA means most probably absence of sperm from TESA?***

Reply: In the absence of ejaculation, spermatozoa accumulate in the epididymides, then overflow into the urethra and are flushed out in urine (Cooper et al., 1993; De Jonge et al., 2004). What we want to express is that the epididymal puncture is relatively simple and the embryo laboratory may think that the epididymal sperm is

simpler to process and easier to choose for ICSI than the testicular sperm in the laboratory.

***How can circumcision cause ejaculatory dysfunction also do you think that there is a relationship between orchidectomy and orgasmic dysfunction?***

Reply: Orgasmic dysfunction is the inability to reach orgasm: its causes are usually psychological. It is often primary. In this case of secondary anorgasmia, the patient described orgasmic disorder after circumcision. The causal relationship can not be determined, which may be caused by psychological factors. We listed two cases of right cryptorchidism with primary orgasmic disorder, and the PRL and testosterone levels were normal. We also don't think there is a causal relationship. It may just be coincidence.

***pituitary adeoma was misspelled it should be adenoma. After ttt of pituitary adenoma why they were still suffering from ejaculatory dysfunction?***

Reply: We are also curious that these two cases of secondary anejaculation are all postoperative pituitary adenoma ( one case was PRL adenoma, one case was GH adenoma). Low dose bromocriptine was maintained after prolactinoma operation. Prolactin and testosterone have returned to normal for nearly one year, but ejaculation still cannot be resumed.

### ***Results***

***Why you mentioned that the live births were free from significant birth defects, ejaculatory dysfunction is not a congenital anomaly as long as not caused by CBAVD?***

Reply: Several healthy follow-up studies of ICSI offspring have suggested that the incidence of small malformations such as hypospadias in ICSI offspring is higher than that in infants born in natural pregnancy ( Fertil Steril 2013b;99:327–332. N Engl J Med 2012;366:1803-13. Hum Reprod 2007;22:506–515, etc). We are worried about the effect of ICSI on the teratogenesis of offspring.

### ***Conclusion***

***How did you reach such conclusion, as long as there were 91 cases epididymal sperm while only 5 cases testicular sperm?***

Reply: Through a small sample size and retrospective study, we really should not arbitrarily and rashly conclude that epididymal sperm extraction is better than testicular sperm extraction or as a preferred treatment. What we want to express is that the epididymal puncture is relatively simple and the embryo laboratory may think that the epididymal sperm is simpler to process and easier to choose for ICSI than the testicular sperm in the laboratory. Changes in the text in line 214-217.

**Reviewer E:**

*1) Epididymal and testicular sperm aspiration patients are different procedures which I do not believe should be grouped together. The epigenetic effects on sperm are very different within the epididymis and the testis, so this must be considered. Additionally, patients who utilized testicular sperm were patients who failed attempts at epididymal sperm. So, the testicular sperm patients were worse prognosis patients by design.*

Reply: Thank you for your suggestion. We mainly analyze and compare the ICSI outcomes of epididymal sperm in the revised manuscript.

*2) The combination of both testicular and epididymal as well as fresh and frozen sperm in the same analysis creates a significant problem with interpretation of results.*

Reply: We mainly analyze and compare the ICSI outcomes of fresh and frozen epididymal sperm in the revised manuscript.

*3) Is it true that all female patients received hCG trigger following ovarian stimulation? This seems unlikely in current practice with increased prevalence of GnRH-agonist triggers. I would make sure the authors double check this information.*

Reply: We are very sorry and revised in this section. For some patients with OHSS risk, we will use GnRH-agonist triggers for prevention. In our study, 12 of 91 in the PESA-ICSI cases with ejaculation dysfunction used GnRH-agonist triggers, 79 used HCG triggers. Changes in the text in line 101-102.

***Were medications considered as an underlying cause for ejaculatory dysfunction or anorgasmia? It seems like this would be a common cause but was not mentioned.***

Reply: The patients in our group strictly follow the diagnosis and treatment process of ejaculation dysfunction, and exclude drug factors: such as antipsychotics, antidepressants, antihypertensives, alpha1-adrenoceptor antagonist, etc. Changes in the text in line 75-77.

***4) Since testicular aspiration was only performed in 5 patients, I don't think it should be included in the analysis at all. These patients should be excluded and the research should focus only on epididymal sperm.***

Reply: Based your suggestion, we mainly analyze the ICSI outcomes of epididymal sperm in the revised manuscript.

***In the discussion, the authors make the claim that epididymal sperm aspiration is easier to perform than electroejaculation. I agree with this statement, but this study does not compare epididymal sperm to electroejaculation.***

Reply: PESA or TESA is easier to perform than electroejaculation, especially those patients who need anesthesia. Due to limited conditions, we did not compare epididymal sperm to electroejaculation sperm for lack of EEJ instrument in our hospital.

***7) Overall there is really no control or comparison group for this study. This is simply an observational study. If the authors wanted to make an impactful statement, they should compare rates to a control group (ejaculated sperm) or to electroejaculated sperm or epididymal to testicular sperm. As it stands, the paper lists percentages but it is difficult to infer any applicable meaning from the results.***

Reply: Because of the absence of bilateral vas deferens, CBAVD can only obtain spermatozoa from testis or epididymis, and ICSI can be used to give birth to the consanguineous offspring of husband. In order to compare the ICSI outcomes of epididymis sperm, we selected the CBAVD patients who performed PESA-ICSI in our center as the control group. Changes in the Table I.