The relationship between TSH levels and clinical pregnancy outcomes for patients who undergo in vitro fertilization/intracytoplasmic sperm injection: a retrospective study

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Background: Thyroid dysfunction is linked with adverse pregnancy outcomes, an upper limit of a normal thyroid-stimulating hormone (TSH) threshold of 4.12–4.5 mIU/L should be considered for subclinical hypothyroidism in the infertile female population. Whereas, it's controversial whether or not the infertility thresholds for upper limit of TSH threshold of 2.5 mIU/L. In our study examines the correlation of optimal TSH levels and clinical pregnancy outcomes after fresh in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) embryo transfer cycles.

Methods: Patients who underwent fresh IVF/ICSI embryo transfer cycles for the first time who presented between January 1, 2015 and December 31, 2017 at the Chongqing Institute of Reproductive and Genetic, Chongqing Health Center for Women and Children were enrolled. We excluded patients with ≥40 years, body mass index (BMI) ≤18 or ≥28 kg/m², the man with severe oligoasthenospermia, women with poor ovarian reserve, and presence of endocrine disorders, uterine anomaly, sactosalpinx, abnormal thyroid function, preimplantation genetic diagnosis, and chromosomal abnormality or polymorphism. Baseline characteristics and clinical pregnancy outcomes were observed in our study. We detected between TSH levels and clinical pregnancy outcomes in patients undergoing IVF/ICSI by Receiver operating characteristic (ROC) curves and logical regression.

Results: A total of 6,088 patients who undergo IVF/ICSI were included. We first detected that the live birth rate had a statistically significant difference when the TSH level was 3 mIU/L. With the TSH ≤3 mIU/L group having a higher live birth rate than the TSH >3 mIU/L group (51.79% vs. 47.89%, P=0.024), meanwhile no significant difference were revealed between the early miscarriage rate (12.54% vs. 14.97%, P=0.091) and early clinical pregnancy rate (59.21% vs. 56.32%, P=0.114). There were no differences in pregnancy outcomes when the TSH threshold was at 3.5 or 4 mIU/L and no association was detected between TSH levels and clinical pregnancy outcomes in patients undergoing IVF/ICSI by ROC curves and logical regression.

Conclusions: Patients undergoing IVF/ICSI with a serum TSH level ≤3 mIU/L may have a higher live birth rate rather than ≤2.5 or ≤4 mIU/L.

Keywords: Thyroid-stimulating hormone (TSH); live birth rate; pregnancy outcomes; miscarriage rate; in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI)
Introduction

Thyroid-stimulating hormone (TSH) has been proposed as playing a role in reproductive difficulties over several decades (1), including ovulatory dysfunction, infertility, miscarriage, and adverse maternal complications. Several researches have linked the thyroid function to ovarian function and the physiology of reproduction. Thyroid hormone may influence the folliculogenesis, estrogen and androgen metabolism, the menstrual cycle (2,3), and endometrial receptivity (4).

TSH levels prior to pregnancy are between 2.5 and 4 mIU/L, and management options include either monitoring levels and treatment when TSH >4 mIU/L, or treating with levothyroxine to maintain TSH less than 2.5 mIU/L according to Grade C evidence based on international guidelines from the Practice Committee of the American Society for Reproductive Medicine (5). In an iodine sufficient area, an upper limit of a normal TSH threshold of 4.12 mIU/L should be considered. According to the Chinese Society for Reproductive Medicine consensus for subclinical hypothyroidism in the infertile female population, a TSH threshold of 4–4.5 mIU/L for infertile women and women attempting pregnancy should be considered (6).

Therefore, the suggested TSH threshold before women undergo in vitro fertilization (IVF) and embryo transfer should be 4 mIU/L. Infertile patients with untreated TSH >2.5 mIU/L before IVF/intracytoplasmic sperm injection (ICSI) have been examined in retrospective studies, and reported better pregnancy outcomes when TSH is <2.5 mIU/L compared with women with TSH <2.5 mIU/L (7,8). Both the Endocrine Society and the American Thyroid Association guidelines recommend TSH ranges from 0.1–2.5 mIU/L in the first trimester of pregnancy; 0.2–3.0 mIU/L in the second trimester; and 0.3–3.5 mIU/L in the third trimester (9,10). Some studies suggest the upper reference range of TSH may be approximately 2.5–3.1 mIU/L based on normative data of healthy pregnant women (11-13). Therefore, what the TSH threshold should be before women undergo IVF and embryo transfer remains controversial. We present the following article in accordance with the STARD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-79/rc).

Methods

Study design

Patients undergoing fresh IVF/ICSI embryo transfer cycles for the first time who presented between January 1, 2015 and December 31, 2017 at the Chongqing Institute of Reproductive and Genetic, Chongqing Health Center for Women and Children were recruited into this retrospective cohort study. The center is the largest reproductive medicine center in southwestern China.

Study participants

All TSH and hormone levels were measured before patients underwent IVF/ICSI within 1 year. Patients with advanced reproductive age (≥40 years), severe underweight or obese status [body mass index (BMI) ≤18 or ≥28 kg/m²], the man with severe oligoasthenospermia, women with poor ovarian reserve, and presence of endocrine disorders (diabetes mellitus, hyperprolactinemia, congenital adrenal hyperplasia, or Cushing syndrome), uterine anomaly confirmed by either hysterosalpingography or hysteroscopy, sactosalpinx diagnosed by gynecological ultrasound, hystersalpingography or pelvic surgery, untreated hyperthyroidism (TSH <0.35 mIU/L), hypothyroidism (TSH >4.94 mIU/L) or abnormal serum FT3 and FT4 level, preimplantation genetic diagnosis, and chromosomal abnormality or polymorphism were excluded.

IVF/ICSI procedure

Patients underwent controlled ovarian stimulation accomplished with an individualized GnRH-agonist/GnRH-antagonist protocol. All patients underwent first fresh embryo transfers which were performed 3 days after oocyte retrieval.

Laboratory analysis

Serum TSH levels was measured by Chemiluminescent Microparticle ImmunoAssay, CMIA (Abbott Architect TSH, Abbott Architect i2000SR, South Kraemer Boulevard, CA). A normal range was allocated as 0.35–4.94 mIU/L,
and the intra- and inter-assay coefficient of variation (CV) was ≤10%.

**Statistical analysis**

Statistical analysis was performed using SPSS 13.0 statistical software (Chicago, IL, USA). Data are presented as mean ± SD. An independent-sample t-test was used for continuous variables where appropriate, and Chi-square or Fisher exact tests were used for categorical variables. Receiver operating characteristic (ROC) curves were generated by plotting the sensitivity and 1-specificity of TSH values for all variables, while logical regression was used to reveal the predictors of clinical pregnancy outcome. All analyses of significance were two-sided and tested at the 5% level, and P<0.05 was considered statistically significant.

**Ethical statement**

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Chongqing Health Center for Women and Children Ethics Committee (No. 2022-RGI-02). Individual consent for this retrospective analysis was waived.

**Results**

We recruited 6,088 first time fresh transfer cycles, and the overall clinical pregnancy rate, live birth rate, and miscarriage rate were 58.65%, 51.15% and 12.95%, respectively. The area under the ROC curves for live birth was 0.496 (95% CI: 0.481–0.510), for clinical pregnancy 0.503 (95% CI: 0.488–0.517), and for miscarriage 0.523 (95% CI: 0.496–0.552) (Figure 1). All three ROC curves approached the line of no discrimination, indicating there was no value of TSH within the normal range that could predict clinical pregnancy, live birth, or miscarriage in patients who underwent IVF/ICSI.

As a cutoff value of TSH was not identified for clinical pregnancy outcomes in the ROC analysis, we divided patients into the following groups according to the serum TSH levels: 0.35 to ≤1, 1 to ≤1.5, 1.5 to ≤2, 2 to ≤2.5, 2.5 to ≤3, 3 to ≤3.5, 3.5 to ≤4, 4 to ≤4.5, and 4.5 to ≤4.94 mIU/L (Table 1). The live birth rate, clinical pregnancy rate and miscarriage rate were then evaluated among the groups, and the results showed there was a general downward trend in live birth rate and clinical pregnancy rate and an upward trend in the miscarriage rate at the cutoff value of TSH >3 mIU/L (Figure 2). As a cutoff value of TSH was not identified for clinical pregnancy outcomes in the ROC analysis, we divided patients into the following groups according to the serum TSH levels: 0.35 to ≤1, 1 to ≤1.5, 1.5 to ≤2, 2 to ≤2.5, 2.5 to ≤3, 3 to ≤3.5, 3.5 to ≤4, 4 to ≤4.5, and 4.5 to ≤4.94 mIU/L (Table 1). The live birth rate, clinical pregnancy rate and miscarriage rate were then evaluated among the groups, and the results showed there was a general downward trend in live birth rate and clinical pregnancy rate and an upward trend in the miscarriage rate at the cutoff value of TSH >3 mIU/L (Figure 2). However, as guidelines dictate a TSH level >4 mIU/L during pregnancy is associated with miscarriage, we analyzed the clinical pregnancy outcomes and general characteristics at the upper range of TSH at 3, 3.5, and 4 mIU/L (Tables 2-4).

This showed that when the cutoff value of TSH was 3 mIU/L, there was no difference in the general characteristics of patients with TSH ≤3 mIU/L (5,092 cycles) vs. >3 mIU/L (996 cycles). In addition, women were similar with regards to age, duration of infertility, body
mass index (BMI), basal follicle-stimulating hormone (FSH) and estradiol (E2), and anti-Mullerian hormone (AMH) (Table 2). There was no difference in FT3 and FT4 levels, duration of Gn, total Gn dose, number of oocytes retrieved, number of usable embryos, and endometrial thickness on day of embryo transfer. While at the 3 mIU/L threshold of TSH level, the TSH ≤3 mIU/L group had a higher clinical pregnancy rate and live birth rate and a lower miscarriage rate than the TSH >3 mIU/L group, only the live birth rate had a statistically significant difference between the TSH ≤3 and >3 mIU/L groups.

When the cutoff value of TSH was 3.5 mIU/L, there was no difference in the general characteristics of patients with TSH ≤3.5 mIU/L (5,552 cycles) vs. >3.5 mIU/L (536 cycles), and at the threshold, the TSH ≤3.5 mIU/L group had a higher clinical pregnancy rate and live birth rate, and lower miscarriage rate. However, there was no statistical difference among groups (Table 3).

When the cutoff value of TSH was 4 mIU/L, there was no difference in general characteristics of patients with TSH ≤4 mIU/L (5,813 cycles) vs. >4 mIU/L (275 cycles), and at the threshold, the TSH ≤4 mIU/L group had a higher clinical pregnancy rate and live birth rate, and a lower miscarriage rate, with no statistical difference among the groups (Table 4).

We then performed a stratified analysis of the relationship between age, duration of infertility, BMI, serum AMH, basal FSH level, TSH level, and clinical pregnancy outcomes by logical regression. The results indicated logical regression for interactions was not statistically significant between serum TSH level, duration of infertility, BMI, serum AMH, basal FSH level, and clinical pregnancy outcomes (Tables 5-7). However, significant interactions were detected between the age of women among live-birth rate and clinical pregnancy rate (OR 0.943, P=0.000; and OR 0.946, P=0.000, respectively).

Discussion

While the role of TSH in pregnancy outcomes in the case of IVF/ICSI is widely debated, the link between the
thyroid and hypothalamic-pituitary-ovarian axis is well established (14). TSH and thyroid hormone (FT3, FT4) act by binding to specific G protein-coupled TSH receptors (TSHRs) and nuclear thyroid hormone receptors (THRs) (15). TSHRs are not only present on the surface of thyroid epithelial cells, but are also found on adipose tissue, fibroblasts, and reproductive tissues, including the ovaries and endometrium (4,14,16). TSH is critical for substance metabolism, folliculogenesis, ovine preimplantation embryo, placental formation, adverse pregnancy outcomes and neurological development (17-19). Hyperthyroidism and hypothyroidism during pregnancy have a well-established detrimental impact on menstrual irregularities (irregular or absent menstrual bleeding) and pregnancy complications, including pregnant and obstetric complications, adverse obstetric outcomes (19), and adverse neurological development of offspring (20).

In this retrospective study, we compared the clinical pregnancy outcomes of first attempts of fresh IVF/ICSI cycles in infertile couples when the cutoff of TSH was 3, 3.5, and 4 mIU/L, and the relationship between TSH level and clinical pregnancy outcomes, before submission to assisted reproductive technology (ART) at the Chongqing Institute of Reproductive and Genetic. There are more than 10,000 fresh IVF cycles every year in our institute, which is the largest reproductive center in southwestern China, and our study utilized the largest sample size to date to analyze whether the TSH threshold before IVF affects the pregnancy outcomes. The main results demonstrated that the live birth rate of infertile couples decreased significantly when TSH levels were below 3 mIU/L, while levels of 3.5 and 4 mIU/L were not of clinical significance in pregnancy outcomes. This may be because raising TSH levels from 3 to 4 mIU/L would result in a nearly fourfold decrease in the number of patients in the higher TSH level group. Differences in the miscarriage rate were not statistically significant, which may be due to the smaller sample size.

| Characteristic                        | TSH ≤3 mIU/L | TSH >3 mIU/L | P value |
|--------------------------------------|--------------|--------------|---------|
| No. of cycles                        | 5,092        | 996          |         |
| Age (years)                          | 31.17±4.08   | 31.43±4.21   | 0.068   |
| Duration of infertility (years)      | 5.78±3.90    | 5.95±3.70    | 0.205   |
| BMI (kg/m\(^2\))                     | 21.88±2.29   | 22.03±2.26   | 0.053   |
| Basal FSH (IU/L)                     | 5.77±1.91    | 5.62±1.76    | 0.653   |
| Basal E\(_2\) (pg/mL)                | 41.39±130.43 | 45.39±202.03 | 0.495   |
| AMH (ng/mL)                          | 3.59±2.86    | 3.40±2.50    | 0.111   |
| TSH (mIU/L)                          | 1.73±0.62    | 3.70±0.53    | 0.000   |
| FT3 (pmol/L)                         | 4.39±0.46    | 4.41±0.47    | 0.659   |
| FT4 (pmol/L)                         | 13.51±1.50   | 13.32±1.52   | 0.594   |
| Duration of Gn (days)                | 11.26±1.42   | 11.31±1.47   | 0.280   |
| Total Gn dose (IU)                   | 2,525.12±800.38 | 2,540.75±829.40 | 0.575   |
| No. of oocytes retrieved             | 10.01±4.29   | 10.06±4.35   | 0.774   |
| No. of usable embryos (n)            | 3.59±2.56    | 3.99±2.59    | 0.631   |
| Endometrial thickness on day of ET (mm) | 10.09±1.62 | 10.09±1.62 | 0.973   |
| Clinical pregnancy rate (%)          | 3,015/5,092 (59.21%) | 561/996 (56.32%) | 0.091   |
| Miscarriage rate (%)                 | 378/3,015 (12.54%) | 84/561 (14.97%) | 0.114   |
| Live birth rate (%)                  | 2,637/5,092 (51.79%) | 477/996 (47.89%) | 0.024   |

TSH, thyroid-stimulating hormone; BMI, body mass index; FSH, follicle-stimulating hormone; E\(_2\), estradiol; AMH, anti-Mullerian hormone; ET, embryo transfer.
recommend optimal preconception levels of TSH be <2.5 mIU/L for women before IVF or pregnancy (21). International guidelines from the Practice Committee of the American Society for Reproductive Medicine (Grade C evidence), state that if pre-pregnancy TSH levels were between 2.5 and 4 mIU/L, treatment measures should involve monitoring levels and treatment when TSH >4 mIU/L or treating with levothyroxine to maintain TSH <2.5 mIU/L (5). Some researchers observed no significant differences in pregnancy outcomes among women undergoing IVF or IUI with TSH levels at 2.5 mIU/L (22-25). Furthermore, we first detected that the live birth rate had a statistically significant difference when the TSH level was 3 mIU/L, and that the ≤3 mIU/L group had a higher live birth rate than the TSH >3 mIU/L group. Due to the small sample size, there was no statistically significant difference when the TSH level was 3.5 or 4 mIU/L, and no association was detected between TSH levels and clinical pregnancy outcomes in patients undergoing IVF/ICSI through ROC curves and logical regression. Therefore, additional data are needed to define the TSH cutoffs of women undergoing IVF.

Controversy remains regarding the TSH threshold before IVF in pregnancy. Recent studies have indicated the cut-offs are too low and may lead to over diagnosis and unnecessary treatment or even overtreatment. Based on our data, a TSH threshold of 3 mIU/L would result in a live birth rate that decreases in women with higher levels of TSH. Further research is required investigating infertile women who undergo IVF/ICSI to minimize the potential risks associated with lower live birth higher miscarriages rate.

| Characteristic                        | TSH ≤3.5 mIU/L | TSH >3.5 mIU/L | P value |
|---------------------------------------|----------------|----------------|---------|
| No. of cycles                         | 5,552          | 536            |         |
| Age (years)                           | 31.19±4.10     | 31.33±4.12     | 0.459   |
| Duration of infertility (years)       | 5.79±3.90      | 5.94±3.57      | 0.369   |
| BMI (kg/m²)                           | 21.79±2.71     | 21.90±2.77     | 0.353   |
| Basal FSH (IU/L)                      | 4.13±7.68      | 3.82±2.89      | 0.367   |
| Basal E₂ (pg/mL)                      | 30.42±113.24   | 33.67±210.13   | 0.562   |
| AMH (ng/mL)                           | 2.52±2.89      | 2.40±2.16      | 0.366   |
| TSH (mIU/L)                           | 1.86±0.73      | 4.32±0.53      | 0.000   |
| FT3 (pmol/L)                          | 4.38±0.45      | 4.42±0.47      | 0.820   |
| FT4 (pmol/L)                          | 13.52±1.47     | 13.35±1.55     | 0.781   |
| Duration of Gn (days)                 | 11.26±1.42     | 11.29±1.47     | 0.645   |
| Total Gn dose (IU)                    | 2,529.06±802.74| 2,509.23±830.38| 0.584   |
| No. of oocytes retrieved              | 10.02±4.31     | 9.97±4.23      | 0.789   |
| No. of usable embryos (n)             | 3.90±2.57      | 3.93±2.65      | 0.856   |
| Endometrial thickness on day of ET (mm)| 10.04±1.74   | 10.03±1.93     | 0.857   |
| Clinical pregnancy rate (%)           | 3,268/5,552 (58.86%) | 308/536 (57.46%) | 0.530   |
| Miscarriage rate (%)                  | 414/3,268 (12.67%) | 48/308 (15.58%) | 0.145   |
| Live birth rate (%)                   | 2,854/5,552 (51.40%) | 260/536 (48.51%) | 0.200   |

TSH, thyroid-stimulating hormone; BMI, body mass index; FSH, follicle-stimulating hormone; E₂, estradiol; AMH, anti-Mullerian hormone; ET, embryo transfer.
Table 4 Baseline characteristics and clinical pregnancy outcomes of patients with TSH levels of 4 mIU/L

| Characteristic                  | TSH ≤4 mIU/L | TSH >4 mIU/L | P value |
|--------------------------------|--------------|--------------|---------|
| No. of cycles                  | 5,813        | 275          |         |
| Age (years)                    | 31.20±4.10   | 31.42±4.08   | 0.377   |
| Duration of infertility (years)| 5.79±3.90    | 5.98±3.43    | 0.414   |
| BMI (kg/m²)                    | 21.80±2.71   | 21.89±2.90   | 0.581   |
| Basal FSH (IU/L)               | 4.12±7.53    | 3.83±2.96    | 0.524   |
| Basal E₂ (pg/mL)               | 30.23±110.86 | 40.49±289.92 | 0.178   |
| AMH (ng/mL)                    | 2.51±2.87    | 2.44±2.79    | 0.653   |
| TSH (mIU/L)                    | 1.94±0.81    | 4.86±2.89    | 0.000   |
| FT3 (pmol/L)                   | 4.42±0.48    | 4.51±0.41    | 0.998   |
| FT4 (pmol/L)                   | 13.61±1.49   | 13.45±1.53   | 0.958   |
| Duration of Gn (days)          | 11.24±1.41   | 11.35±1.48   | 0.385   |
| Total Gn dose (IU)             | 2,525.06±803.18 | 2,573.12±845.71 | 0.327   |
| No. of oocytes retrieved       | 10.02±4.30   | 9.84±4.32    | 0.484   |
| No. of usable embryos (n)      | 3.91±2.57    | 3.91±2.65    | 0.995   |
| Endometrial thickness on day of ET (mm) | 10.04±1.74 | 10.05±1.95 | 0.986 |
| Clinical pregnancy rate (%)    | 3,414/5,813 (58.73%) | 162/275 (58.91%) | 0.953 |
| Miscarriage rate (%)           | 435/3,414 (12.74%) | 27/162 (16.67%) | 0.146 |
| Live birth rate (%)            | 2,979/5,813 (51.24%) | 135/275 (49.10%) | 0.485 |

TSH, thyroid-stimulating hormone; BMI, body mass index; FSH, follicle-stimulating hormone; E₂, estradiol; AMH, anti-Mullerian hormone; ET, embryo transfer.

Table 5 Live birth logistic regression

| Variables                  | OR  | 95.0% CI     | P value |
|----------------------------|-----|--------------|---------|
| Age (years)                | 0.943 | 0.925–0.962  | 0.000   |
| Duration of infertility (years) | 0.991 | 0.971–1.011  | 0.367   |
| BMI (kg/m²)                | 0.997 | 0.965–1.029  | 0.830   |
| AMH (ng/mL)                | 1.022 | 0.994–1.048  | 0.137   |
| Basal FSH (IU/L)           | 0.984 | 0.945–1.025  | 0.463   |
| TSH (pmol/L)               | 1.010 | 0.952–1.072  | 0.741   |

BMI, body mass index; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone.
Table 6 Clinical pregnancy logical regression

| Variables                  | OR    | 95.0% CI       | P value |
|----------------------------|-------|----------------|---------|
| Age (years)                | 0.946 | 0.927–0.966    | 0.000   |
| Duration of infertility (years) | 0.988 | 0.968–1.008    | 0.228   |
| BMI (kg/m²)                | 0.999 | 0.968–1.032    | 0.972   |
| AMH (ng/mL)                | 1.027 | 0.999–1.056    | 0.061   |
| Basal FSH (IU/L)           | 0.964 | 0.925–1.005    | 0.084   |
| TSH (pmol/L)               | 1.022 | 0.961–1.088    | 0.484   |

OR, odds ratio; CI, confidence interval; BMI, body mass index; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone.

Table 7 Miscarriage logical regression

| Variables                  | OR    | 95.0% CI       | P value |
|----------------------------|-------|----------------|---------|
| Age (years)                | 0.989 | 0.950–1.029    | 0.572   |
| Duration of infertility (years) | 1.021 | 0.995–1.048    | 0.118   |
| BMI (kg/m²)                | 1.010 | 0.950–1.074    | 0.745   |
| AMH (ng/mL)                | 1.009 | 0.959–1.061    | 0.735   |
| Basal FSH (IU/L)           | 0.938 | 0.857–1.026    | 0.163   |
| TSH (pmol/L)               | 1.024 | 0.931–1.125    | 0.629   |

OR, odds ratio; CI, confidence interval; BMI, body mass index; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-79/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-79/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-79/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Chongqing Health Center for Women and Children Ethics Committee (No. 2022-RGI-02), Individual consent for this retrospective analysis was waived.

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