

# Perioperative Outcomes of Endoscopic versus Open Operation in the Treatment of Hyperparathyroidism: A Systematic Review and Meta-analysis

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## ABSTRACT

**Objective:** Hyperthyroidism can cause multiple organs damage, which is characterized by diversity and systemic. At present, there are mainly drug treatment and surgical treatment, among which surgical treatment has the highest cure rate. Surgical treatment mainly includes endoscopic and open surgery in clinical. This article systematically reviews previously published trials on the two surgical methods, and provides an updated meta-analysis of the perioperative outcomes of different surgical methods on hyperthyroidism.

**Methods:** We searched 7 online databases home and abroad retrieval time till 3 February, 2021. We studied the influence of endoscopic and open surgery on the perioperative outcome of HPT. Data were processed with RevMan 5.3 and Stata 12.0. The methodological quality assessment of non-randomized clinical trials used risk of bias in non-randomised studies of interventions. The cochrane collaboration's tool for assessing bias risk was used to assess the quality of the included randomized controlled studies. The operation time, intraoperative blood loss, postoperative drainage volume and hospital stay were examined. Two authors exchanged and checked the extraction tables, and resolved any inconsistencies by discussing.

**Results:** A total of 4 studies were included, including 124 patients and 246 controls. The combined results of random-effect model: WMD (95% CI)=-12.96 minutes (-43.47, 17.54), P=0.40. Similarly, intraoperative blood loss, postoperative drainage volume and hospital stay also showed significant heterogeneity (I<sup>2</sup>>50%), but the combined results were statistically significant. Meta-analysis results of the three indicators (WMD (95%CI)) were as follows: -10.59 (-15.64, -5.54) mL, P<0.001; -11.69 (-19.65, -3.73) mL, P=0.004; -1.02 (-1.88, -0.16) days, P=0.02. In addition to the operation time, intraoperative blood loss, postoperative drainage volume and hospital stay of the intervention group were significantly lower than the control group.

**Conclusions:** This paper concluded that endoscopic surgery showed certain advantages over open surgery in the treatment of hyperparathyroidism by performed the meta-analysis of clinical studies on the treatment of HPT with EPTX and OPTX, which the finding could provide theoretical guidance for clinical practice.

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## INTRODUCTION

Hyperparathyroidism (HPT) is the general term of a group of clinical symptoms caused by excessive secretion of parathyroid hormone (PTH) from the parathyroid glands acting on bone, kidney and small intestine. According to the causes, it can be divided into: i) primary hyperparathyroidism (PHPT), the parathyroid gland has pathological changes, such as hyperplasia, neoplasia, carcinogenesis. ii) Secondary hyperparathyroidism (SHPT), due to the presence of other body's diseases, such as vitamin D chronic deficiency, small intestinal malabsorption or renal insufficiency, if serum calcium is lower than normal level, the parathyroid gland increased the blood calcium level by secreting parathyroid hormone; iii) Tertiary hyperparathyroidism (THPT), parathyroid gland neoplastic is based on chronic secondary hyperparathyroidism.

**Associated Data:** Data Availability Statement All data generated or analysed during this study are included in this published article or are available from the corresponding author on reasonable request

### KEYWORDS:

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Patients with PHPT should be treated surgically, because the damage of the type of hyperparathyroidism have the characteristics of long-term and progressive generally, and may even lead to coma and cardiac arrest when serum calcium levels are high. SHPT is common in patients with long-term hemodialysis and is a risk factor for cardiovascular adverse events of the hemodialysis patients. Parathyroidectomy is an effective treatment for refractory SHPT patients who are responded poorly to drug therapy.

Mandel first performed parathyroidectomy on patients with HPT in 1925.<sup>1</sup> In 1960, Stanbury reported that subtotal parathyroidectomy (SPTX) treated SHPT.<sup>2</sup> In 1968, total parathyroidectomy (TPTX) was applied in clinical practice.<sup>3</sup> However, the traditional open parathyroidectomy (OPTX) affects the social life of the patients seriously, because it has features of great trauma, many complications and obvious postoperative scar on the neck. In 1996, Gagner performed the first endoscopic parathyroidectomy successfully.<sup>4</sup> Some single-arm studies of small samples have shown that endoscopic total parathyroidectomy (EPTX) has good curative effect and acceptability in the treatment of primary/secondary hyperparathyroidism.<sup>5-8</sup> Recently, clinical studies have compared the perioperative outcomes between EPTX and OPTX for HPT.<sup>9,10</sup> In order to obtain more comprehensive and objective results, we have conducted a meta-analysis of clinical studies EPTX vs OPTX in the treatment of HPT.

## METHODS

### Literature search strategy

According to the pre-established retrieval strategy, we collected a comprehensive literature search from the PubMed ([https://](https://www.ncbi.nlm.nih.gov/pubmed/)

[www.ncbi.nlm.nih.gov/pubmed/](https://www.ncbi.nlm.nih.gov/pubmed/)), Cochrane Central Register of Controlled Trials (<https://www.cochranelibrary.com/central>), Embase (<https://www.elsevier.com/solutions/embase-bio-medical-research>), China Biology Medicine disc (<http://www.sinomed.ac.cn/>), China National Knowledge Infrastructure (<http://www.cnki.net/>), WANFANG data (<http://www.wanfangdata.com.cn/index.html>), China Science and technology journal database (<http://en.cqvip.com/cstj.html>) and other databases. The following keywords was included, (“Endoscopic Parathyroidectomy” or “EPTX”) and (“open parathyroidectomy” or “OPTX”) and (“hyperparathyroidism” or “hyperparathyroid”). The keywords of the same categories are jointed with “or”, the different keywords of the different categories are grouped together with “and”. Combining search of subject words and free words, the retrieval mode was adjusted according to the characteristics of the databases (The detailed retrieval steps of the PubMed database are showed in Table1). Articles were searched until February 3, 2021. The search strategy was no language restrictions. In addition, the study also carried out a manual search on the paper version, and screened the relevant reviews and references of the included literature, we hoped to obtain more studies that can be used for meta-analysis.

### Selection criteria

Eligible studies were included when the following criteria were met: 1) research object were primary or secondary hyperparathyroidism patients; 2) the intervention group received endoscopic total parathyroidectomy (ETP) or combined parathyroid tissue autotransplantation (PTA). The control group was open parathyroidectomy or combined with PTA; 3) randomized controlled trials, (RCT), prospective/retrospective clinical control study can be incorporated; 4) literature reported one or more of the following outcomes: operation time (minute), intraoperative blood loss (mL), postoperative drainage curve (mL), days of Hospital stay, recurrent laryngeal nerve injury, incisional infection, recurrence, subcutaneous hematomas, skin ecchymosis on the neck, etc.

Exclusion criteria: 1) reviews, conference abstracts, comments and other non-treatise research; 2) incomplete data and lack of sufficient data for meta-analysis study were excluded; 3) for repeated publications or the same data used by multiple papers, only one paper with the most complete research information was included, and the rest were excluded.

### Data Extraction and Quality Assessment

Two authors finished screening literatures according to the above inclusion and exclusion criteria. When determined incorporated literatures, the extraction was confirmed independently on the basis of a standardized data extraction form. The following data were sought: the basic information of included research, including the first author’s name, publication year, the basic characteristics of the study object (the crowd type, sample size, age, gender, etc.), intervention plan and outcome indicators, etc. After the above data extraction work is completed, the two authors exchanged and checked the extraction tables, and resolved any inconsistencies by discussing.

The methodological quality assessment of non-randomized clinical trials used risk of bias in non-randomised studies of

**Table1:** Retrieval steps and results in PubMed  
(The retrieval time: 20210203)

Search	Query	Items found
#1	("endoscope s"[All Fields] OR "endoscoped"[All Fields] OR "endoscopes"[MeSH Terms] OR "endoscopes"[All Fields] OR "endoscope"[All Fields] OR "endoscopical"[All Fields] OR "endoscopically"[All Fields] OR "endoscopy"[MeSH Terms] OR "endoscopy"[All Fields] OR "endoscopic"[All Fields]) AND ("parathyroidectomy"[MeSH Terms] OR "parathyroidectomy"[All Fields] OR "parathyroidectomies"[All Fields])	435
#2	"EPTX"[All Fields]	11
#3	#1 OR #2	446
#4	"open"[All Fields] AND ("parathyroidectomy"[MeSH Terms] OR "parathyroidectomy"[All Fields] OR "parathyroidectomies"[All Fields])	235
#5	"OPTX"[All Fields]	35
#6	#1 OR #2	268
#7	"hyperparathyroid"[All Fields] OR "hyperparathyroidism"[MeSH Terms] OR "hyperparathyroidism"[All Fields] OR "hyperparathyroidisms"[All Fields]	32043
#8	#3 AND #6 AND #7	62

interventions (Robins-I). The cochrane collaboration’s tool for assessing bias risk was used to assess the quality of the included randomized controlled studies.<sup>11</sup>

### Statistical Analysis

WMD (weighted mean difference) and its 95% confidence interval (CI) were used to combine the continuous variables. For categorical variables, OR (odd ratio) and 95% CI were used as effect-size indicators. The heterogeneity between studies was evaluated using the Cochran’s Q test and the I<sup>2</sup> test.<sup>12</sup> A P-value <0.05 and/or I<sup>2</sup>>50% are considered significant heterogeneity, and then a random-effect model is used to meta-analysis. A fixed-effects model was applied when there was no or low heterogeneity (P≥0.05 and I<sup>2</sup><50%). Sensitivity analysis was conducted by omitting one study by turn to test the robustness of the outcomes. The above statistical analysis was performed by using Review Manager, version 5.3 (RevMan 5.3, Nordic Cochrane Center, Oxford, England) and Stata 12.0 (StataCorp, College Station, Tex).

## RESULTS

### Literature search

The results and screening process of literature are presented (Figure 1). A total of 689 articles were collected, 62 from Pubmed, 353 from Embase, 7 from Cochrane library, 133 from CNKI, 27 from CQVIP, 31 from CBM and 76 from WANGFANG. After discarding the duplicate literatures, 558 literatures were remained. After reading the titles and abstracts, 550 literatures were excluded that don’t met the inclusion criteria obviously. Finally, after reading the full text, 4 of the 8 literatures were eliminated. A manual search failed to find any studies that could be included in the analysis, and four articles[9,10,13,14] were included to meta-analysis in the final analysis.

### Study Characteristics and Quality assessments

As shown in Table2, A total of 4 papers (1 RCT, 1 PCCS, and 2 RCCs) were included in the meta-analysis. The study was published between 2000 and 2020 and was distributed in China and Australia. With the exception of Delbridge LW’s

study included primary hyperparathyroidism (PHPT), while the rest studies included secondary hyperparathyroidism (SHPT). The sample size ranged from 47 to 185 cases. A total of 370 (124 patients, 246 controls) subjects were included. The mean age of the subjects ranged from 42.24 to 66 years, and there was no statistically significant difference in the ratio of males to females between the two groups. Except for Qin JY’s study did not introduce the surgical team, other studies reported that the two surgical methods were performed by the same surgeon or team.

Quality evaluation results are shown in supplementary Table3 and Table4. The included studies showed a moderate amount of bias or uncertain risk bias in different evaluation items. Overall, the methodological quality of the included studies was moderate.

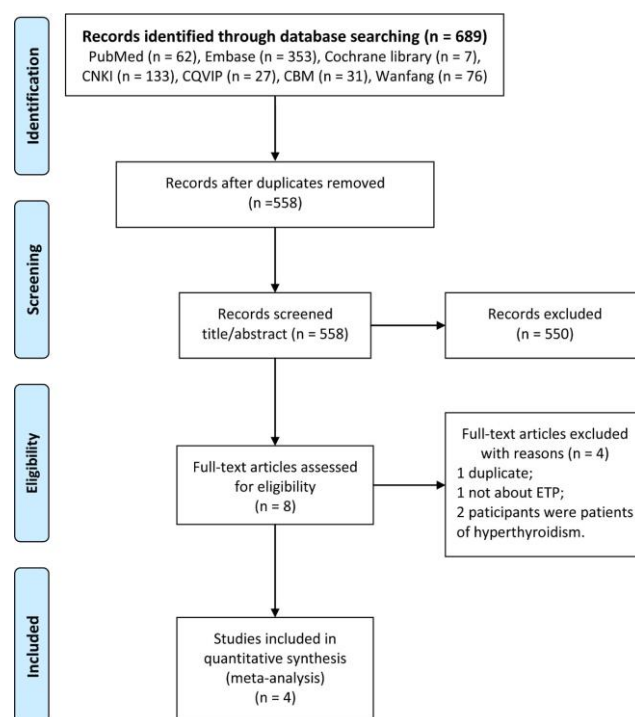


Fig. 1: Flow diagram of the selection of included studies

Table 2: Characteristics of 4 included studies in this meta-analysis

Study	Country	Duration	Design of study	Participants	Intervention	n, M/F	Age, years	Surgical team	Outcomes
Cui, HF 2014	China	2009.04- 2012.06	RCCS	SHPT from CRF	ETP+PTA OP+PTA	22, 13/9 25, 15/10	45.2 (30-69) 46.5 (32-65)	The same group	a, b, d, e, f, l
Delbridge, LW 2000	Australia	1998.05- 1999.10	PCCS	PHPT	ETP OP	35, NR/NR 150, 32/118	66 (27-87) 65 (20-90)	Performed by, or under the supervision of, one surgeon (LWD)	a, d, f, g, l
Jin, CG 2018	China	2014.06- 2016.05	RCCS	SHPT from CRF	ETP/ETP+PTA OP/OP+PTA	26, 11/15 30, 12/18	42.24±9.45 45.43±10.54	The same group	a, b, c, d, e, f, g, h, l
Qin, JY 2020	China	2018.07- 2019.10	RCT	SHPT	ETP OP	41, 19/22 41, 18/23	43.7±3.4 43.3±3.6	NR	a, b, c, d, e, f, g, h

CRF, chronic renal failure; NR, not reported; ETP, endoscopic total parathyroidectomy; SHPT, secondary hyperparathyroidism; PHPT, primary hyperparathyroidism; OP, open parathyroidectomy; PTA, parathyroid tissue autotransplantation; RCCS, retrospective clinical control study; RCT, randomized controlled trial.

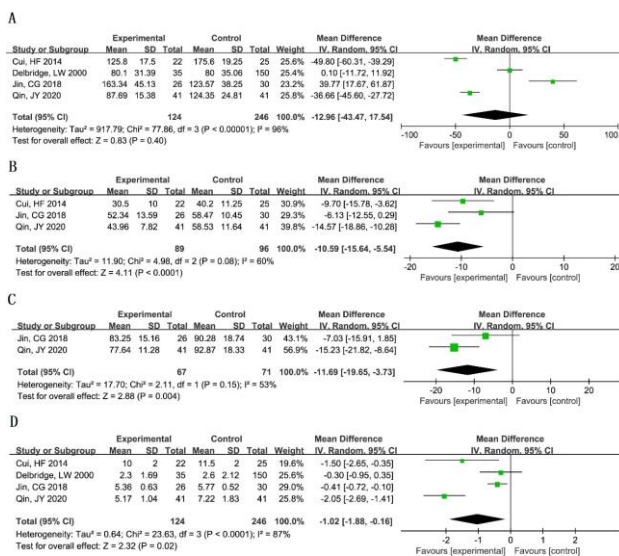
a, Operation time (minute); b, Intraoperative blood loss (mL); c, Postoperative drainage (mL); d, Days of Hospital stay; e, Recurrent nerve injury; f, Wound infection; g, Subcutaneous haematomas; h, Skin ecchymosis; i, Persistent hyperparathyroidism.

**Table 3:** Quality assessment of the clinical controlled studies.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Cui, HF 2014	Moderate	Low	Low	Low	Low	Low	Low
Delbridge, LW 2000	Low	Moderate	Low	Low	Low	Low	Moderate
Jin, CG 2018	Moderate	Moderate	Low	Low	Low	Low	Low

**Table 4:** Quality assessment of the randomized controlled trial

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Qin, JY 2020	Unclear	Unclear	Low	Unclear	Low	Low	Unclear

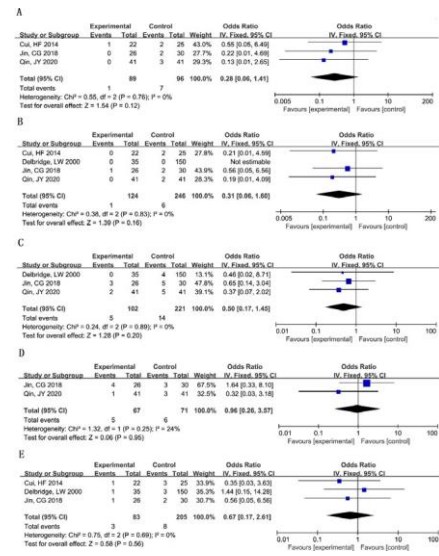


**Fig. 2:** The results of meta-analysis. (A) operative time between the experimental and the control. (B) intraoperative blood loss between the experimental and the control. (C) postoperative drainage volume between the experimental and the control. (D) hospital stay between the experimental and the control.

**Meta-analysis results**

As shown in Figure 2A, 4 studies reported the different operative time between the two types. Heterogeneity test:  $I^2=96\%$ ,  $P<0.00001$ . The combined results of random-effect model: WMD (95% CI)=-12.96 minutes (-43.47, 17.54),  $P=0.40$ . Similarly, intraoperative blood loss (Figure2B), postoperative drainage volume (Figure2C) and hospital stay (Figure2D) also showed significant heterogeneity ( $I^2>50\%$ ), but the combined results were statistically significant. Meta-analysis results of the three indicators (WMD (95%CI)) were as follows: -10.59 (-15.64, -5.54) mL,  $P<0.001$ ; -11.69 (-19.65, -3.73) mL,  $P=0.004$ ; -1.02 (-1.88, -0.16) days,  $P=0.02$ . In addition to the operation time, intraoperative blood loss, postoperative drainage volume and hospital stay of the intervention group were significantly lower than the control group.

The differences of complications were compared as shown in Figure3, and there was no significant heterogeneity among all



**Fig. 3:** The differences of complications between the experimental and the control. (A) recurrent laryngeal nerve injury between the experimental and the control. (B) incisional infection between the experimental and the control. (C) subcutaneous hematoma between the experimental and the control. (D) Skin ecchymosis on the neck between the experimental and the control. (E) recurrence between the experimental and the control

indicators ( $I^2<50\%$  and  $P>0.05$ ). A fixed-effect model was used for Meta-analysis. The combined results were as follows: recurrent-laryngeal nerve injury (OR=0.28, 95% CI=0.06-1.41,  $P=0.12$ , Figure3A); incisional infection (OR=0.31, 95% CI=0.06-1.60,  $P=0.16$ , Figure3B); subcutaneous hematoma (OR=0.50, 95% CI=0.17-1.45,  $P=0.20$ , Figure3C); Skin ecchymosis on the neck (OR=0.96, 95% CI=0.26-3.57,  $P=0.95$ , Figure3D); recurrence (OR=0.67, 95% CI=0.17-2.61,  $P=0.56$ , Figure3E). Although the risk of complications was lower in the experimental than the control, the difference was not statistically significant.

**Sensitivity analyses**

The sensitivity analysis results (Table 5) showed that the results of operation time and postoperative drainage were unstable. After ignoring the studies of Jin CG, the combined results of operation time indicated that there was significant differences between the two groups (WMD=-28.95, 95% CI=-55.84-2.06,  $P=0.03$ ). However, after ignoring the studies of Jin CG, there



**Table 5:** Outcomes of sensitivity analysis.

Outcomes	Number of studies	Change of Effect Size, WMD/OR (95%CI)	Robust, Yes or No
Operation time	4	-28.95 (-55.84, -2.06) to -0.09 (-38.42, 38.23)	No
Intraoperative blood loss	3	-12.63 (-17.30, -7.96) to -8.01 (-12.43, -3.60)	Yes
Postoperative drainage	2	-15.23 (-21.82, -8.64) to -7.03 (-15.91, 1.85)	No
Days of Hospital stay	4	-1.28 (-2.50, -0.07) to -0.52 (-0.99, -0.06)	Yes
Recurrent nerve injury	3	0.17 (0.02, 1.44) to 0.38 (0.06, 2.61)	Yes
Wound infection	4	0.20 (0.02, 1.76) to 0.38 (0.06, 2.62)	Yes
Subcutaneous haematomas	3	0.39 (0.09, 1.70) to 0.60 (0.15, 2.37)	Yes
Skin ecchymosis	2	0.32 (0.03, 3.18) to 1.64 (0.33, 8.10)	Yes
Persistent hyperparathyroidism	3	0.44 (0.08, 2.38) to 0.93 (0.17, 4.97)	Yes

was no significant difference in the postoperative drainage between the two groups (WMD=-7.03, 95% CI=-15.91-1.85, P=0.12). The sensitivity analysis results of other indicators were consistent with the original combined results, and the results were stable.

### Publication Bias Test

Due to the relatively small number of included literatures, the number of studies on all indicators's outcome was less than 5. Whether qualitative (funnel plot) or quantitative test method (such as Egger test), the test efficiency is relatively low. Therefore, statistically significant publication bias was unlikely to occur in this meta-analysis.

## DISCUSSION

HPT is a rare disease in clinic, with a relatively high incidence in Europe and America, but there is no unified incidence data in China. Especially in PHPT patients, most of them were first diagnosed in orthopedics, urology or nephrology department with recurrent ostealgia, recurrent fracture, urolithiasis, renal colic and so on, few of them were first diagnosed in Thyroid specialist department. SHPT is common in patients with long-term hemodialysis, who are treated in hemodialysis rooms and oral treatment of Cinacalcet and Paricalcitol drugs[15]. Only for refractory SHPT patients with ineffective drug treatment, they are transferred to thyroid specialist for treatment. At present, open parathyroidectomy (OPTX) is the main surgical method used in clinical practice. Recently, there have been reports about Endoscopic surgery[16,17] and Endoscopic total parathyroidectomy (EPTX) of Da Vinci robotic surgery[18,19]. In this paper, we performed a meta-analysis to the clinical studies on the treatment of HPT with EPTX and OPTX.

We searched several Chinese and English databases and found that the number of studies eligible for inclusion was small and the sample size was small, which limited the extrapolation of the combined results. Meanwhile the combined results of some indicators are unstable and it need to be verified by more large sample studies. Among the included subjects, 3 articles were reported in Chinese and 1 article in English. SHPT was used as the surgical object in Chinese literature, and scarless in the neck method was adopted; PHPT was used as the surgical object in English literature, and a small incision surgical method was used. Therefore, there is no clear consensus on the operational specifications and indications

of EPTX surgical methods. Compared with EPTX, endoscopic thyroid surgery forms a relatively fixed surgical approach, including the anterior chest approach, the axillary approach, the postauricular hairline approach, the transoral vestibular approach and so on[20]. The application of these approaches in parathyroid surgery is mainly studied with single-arm studies with small samples now, which need to be verified by more high quality, multi-center large randomized controlled trials.

Among these approaches, we consider that endoscopic parathyroid surgery via the transoral vestibular approach may be a more desirable surgical approach. It provides patients with a "completely no scar" surgical option and better search for lower position parathyroid glands. Endoscopic surgery via transoral vestibular approach is at the cutting edge of thyroid surgery now. It can also be combined with Da Vinci robot to better complete the operation.

We searched several Chinese and English databases, and the possibility of missing detection was relatively small. In the study, the methodological quality of the included studies was medium, and the bias risk of performance bias, attrition bias and reporting bias was small. The heterogeneity of the binary variable indicator was small, and the stability of the combined results was good. Based on the current literature summary, we concluded that intraoperative blood loss, postoperative drainage volume and hospital stay of endoscopic parathyroid surgery were significantly lower than those of open surgery.

Through literature review, we also found that radiofrequency ablation (RFA) has been gradually applied in parathyroid surgery, which provides a therapeutic option for some the old and infirm patients who cannot tolerate general anesthesia surgery, especially for some PHPT patients. But its safety and reliability have yet to be verified.

## CONCLUSION

Endoscopic surgery and open surgery in the treatment of hyperparathyroidism, the former shows certain advantages. However, more high-quality large randomized controlled trials are needed to verify.

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