Clinics in Surgery

Research Article
Published: 17 May, 2019

# Parecoxib Prevents Postoperative Pain after Radiofrequency Ablation for Liver Cancer: A Propensity Score Matching Analysis

*Jian-Cong Chen[#], Jun-Cheng Wang[#], Yao-Jun Zhang*, Li Xu, Jin-Bin Chen, Yang-Xun Pan, Ying-Qin Zhu, Min-Shan Chen and Zhong-Guo Zhou**

*Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, China*

*[#]Both authors contributed equally to this work*

## Abstract

**Background:** Pain is one of the most dominating adverse effects in radiofrequency ablation therapy. The purpose of this study is to evaluate the role of parecoxib sodium on pain management in patients with liver cancer undergoing radiofrequency ablation.

**Methods:** A total of 186 patients diagnosed as liver cancer (including primary cancer 122 cases and metastasis lesion 64 cases) and treated with radiofrequency ablation at Sun Yat-sen University Cancer Center between April 2015 and January 2016 were retrospectively reviewed. About 111 patients achieved the inclusion criteria and were divided into the parecoxib group (experimental group; n=56) and the non-parecoxib group (control group, receiving 0.9% sodium chloride; n=55), according to whether or not the medication was applied. Post-operative pain, vomiting, body temperature, changes in hepatic function, and duration of postoperative hospitalization time were compared between the two groups.

**Results:** After the propensity score matching analysis, the parecoxib group had suffered less severe pain on postoperative day 0, day 1 and day 2 (with P<0.000, 0.001 and 0.0041, respectively), compared with the non-parecoxib one, along with a lower ALT and CRP levels (177.0 ± 88.0 *vs.* 327.7 ± 387.1 U/L, P<0.016, and 20.0 ± 29.0 *vs.* 49.7 ± 44.1 mg/L, P<0.001, respectively), and an insignificant shorter postoperative hospitalization time was witnessed, though not significantly (2.4 ± 0.7 *vs.* 2.6 ± 0.6 days, P=0.186).

**Conclusion:** This research illustrated that the preemptive application of parecoxib can remarkably relieve postoperative discomfort, especially controlling post-operative pain, reducing hepatic inflammation, and shortening post-operative hospital stay after radiofrequency ablation for liver cancer.

**Keywords: Parecoxib; Postoperative complication control; Pain management; Radiofrequency ablation**

OPEN ACCESS

***Correspondence:***
*Zhong-Guo Zhou, Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, China, Tel: +86-20-87343828; Fax: +86-20-87343585; E-mail: zhouzhg@sysucc.org.cn*
*Yao-Jun Zhang, Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, China,*

**Received Date**: *05 Apr 2019*
**Accepted Date:** *13 May 2019*
**Published Date:** *17 May 2019*

***Citation:***
*Chen J-C, Wang J-C, Zhang Y-J, Xu L, Chen J-B, Pan Y-X, et al. Parecoxib Prevents Postoperative Pain after Radiofrequency Ablation for Liver Cancer: A Propensity Score Matching Analysis. Clin Surg. 2019; 4: 2438.*



## Abbreviations

AFP: α-Fetoprotein; ALB: Serum Albumin; ALT: Alanine Aminotransferase; APTT: Activated Partial Thromboplastin Time; AST: Aspartate Aminotransferase; HBG: Hemoglobin; HBV: Hepatitis B Virus; PLT: Platelet; PT: Prothrombin Time; TBIL: Total Bilirubin; WBC: White Blood Cell; VAS: Visual Analog Scale; ALB: Albumin; CRP: C-Reactive Protein; RFA: Radiofrequency Ablation; PSM: Propensity Score Matching

## Significance Statement

Radiofrequency ablation is an increasingly used therapeutic option. We analyzed the effects of preemptive administration of parecoxib and found that the use of parecoxib was associated with significantly less pain, lower C-reactive protein levels, and shorter hospital stays, suggesting that parecoxib is beneficial and helpful in speeding recovery.

## Introduction

Liver cancer is one of the most prevalent malignant tumors globally, and it is now the second dominating cause of cancer-related death in China [1]. In 2011, there were estimated 782,000 new

diagnosed cases in China and 746,000 deaths related to this disease [2,3].

The therapeutic modalities commonly used for liver cancer include surgical resection, local ablation treatment, liver transplantation, Transcatheter Arterial Chemoembolization (TACE), and Radiotherapy (RT). Image-mediated local ablation treatment, in particular, Radiofrequency Ablation (RFA), is regarded as one of the most effective curative therapy for liver cancer secondary to surgical resection and hepatic transplantation [4]. It is increasingly considered the preferred therapy to patients diagnosed as early-phase cancer or recurrence who are not eligible to proceed surgical resection or hepatic transplantation [5,6]. The minimally invasive treatment should be RFA; however, it frequently goes along with common complications of pain, vomiting, and fever and hepatic inflammation. The proper prevention and treatment of these adverse effects are of great importance to accelerate patients' recovery.

As a selective Cyclooxygenase-2 (COX-2) inhibitor, parecoxib is the first agent that can be administered intravenously or intramuscularly and thereby favorable to patients experiencing nausea or vomiting other than oral NSAIDs [7]. Moreover, as parecoxib does not interact with platelet aggregation, it will not increase excessive bleeding risks during surgical procedures [7,8]. Many clinical trials have demonstrated that parecoxib has an excellent analgesic role in postoperative pain management after nasal orthopedic procedures, endoscopy, gastrointestinal and prostate surgery [9-12]. It is also reported that parecoxib may alleviate fever and the inflammation in our previous study [13]. To the best of our knowledge, little is known about its short term usage in preemptive analgesia. Thereby, we aimed to address this issue and conducted the retrospective investigation to study the preemptive analgesia effect of parecoxib after RFA of liver cancer.

## Patients and Methods

### Patient enrollment

This retrospective investigation was approved by the Institutional Review Board (IRB) at the Sun Yat-sen University Cancer Center and carried out in accordance with approved guidelines. The patients enrolled within this research were diagnosed as liver cancer on the basis of the criteria established by the European Association for the Study of the Liver who aged between 18 and 65 years old, Karnofsky Performance Status (KPS) score greater than 70, a confirmed imaging diagnostic lesion located in the liver, received no other treatment prior to the RFA for the liver tumor, and a Child-Pugh class A or B status (class B patients should have scored no larger than 7). Besides, the results of basic lab finding had to meet the criteria as follow: leukocyte count ≥ $2.0 \times 10^9$/L, thrombocyte ≥ $50 \times 10^9$/L, hemoglobin ≥ 80 g/L, Alanine Transaminase (ALT) and Aspartate Transaminase (AST) ≤ 2 × the Upper Limit of Normal (ULN), Serum Albumin (ALB) ≥ 30 g/L, Total Bilirubin (TBIL) ≤ 34 mmol/L, an international normalized ratio <1.5 or prothrombin time ≤ 3 second above the ULN, and serum creatinine ≤ 1.5 × ULN. Patients would be eliminated if they had an allergy to COX-2 inhibitors, severe cardiopulmonary insufficiency, significant pain or fever before the procedure or continuous use of NSAIDs in the last three months.

### Process for radiofrequency ablation therapy

All RFA therapy was implemented as described in the previous study [14]. Every patient was performed under conscious sedation. 5 mL to 10 mL of 1% lidocaine was injected percutaneously to achieve local anesthesia. An additional analgesic such as pentazocine and/or sufentanil would be administered whenever it was supposed necessary by the anesthetist in the course of ablation or patients complained of intolerable pain.

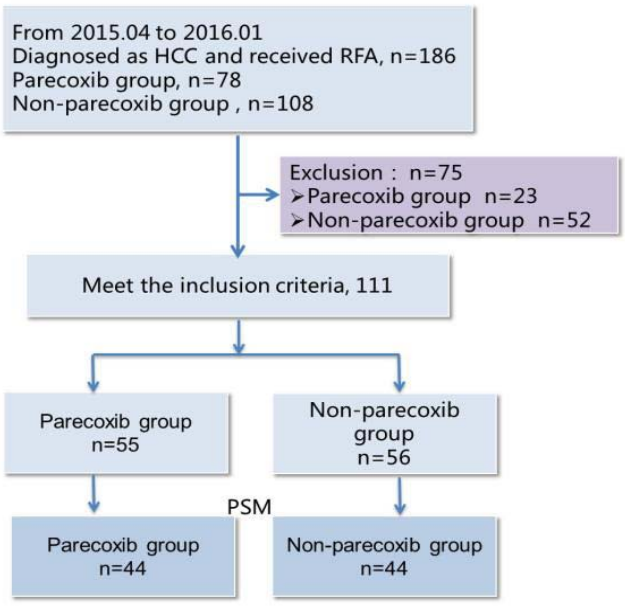


**Figure 1:** Flow chart patients who underwent radiofrequency ablation for hepatocellular carcinoma.

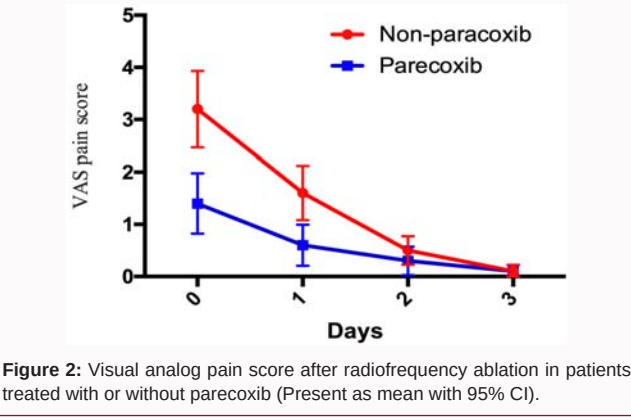


**Figure 2:** Visual analog pain score after radiofrequency ablation in patients treated with or without parecoxib (Present as mean with 95% CI).

In brief, the claw-shaped needle of MedSphere (Medsphere International, Silicon Valley, USA) with 8 sub-needles was stick into the tumor under ultrasonographic guidance. The needle was linked to a 480 kHz output power radiofrequency generator (Medsphere International, Silicon Valley, USA). The 8 sub needle can uphold as an umbrella once the electrode was inserted into the lesion, then the ablation would start from 60 W, and power can be adjusted during operation and kept between 90°C to 110°C according to temperature feedback. The power was increased gradually to 150 W until the entire tumor was completely ablated. If tumor located adjacent to the diaphragm, the intrapleural or intraperitoneal infusion technique would be employed to protect surrounding organs [15].

### Patient grouping

Between April 2015 and January 2016, 186 patients were diagnosed to be liver cancer and implemented RFA at the Sun Yat-sen University Cancer Center. Among them, 78 patients were assigned

**Table 1:** Comparison of complications, liver function, and hospital stay after radiofrequency ablation for hepatocellular carcinoma.

| | Non-parecoxib (n=44) | Parecoxib (n=44) | P Value |
|---|---|---|---|
| VAS pain score | | | |
| D0 | 3.2 ± 2.4 | 1.4 ± 1.9 | <0.001 |
| D1 | 1.6 ± 1.7 | 0.6 ± 1.3 | 0.001 |
| D2 | 0.5 ± 0.9 | 0.3 ± 0.9 | 0.041 |
| D3 | 0.1 ± 0.4 | 0.1 ± 0.4 | 0.443 |
| Temperature | | | |
| D0 | 36.9 ± 0.3 | 36.8 ± 0.3 | 0.429 |
| D1 | 37.2 ± 0.5 | 37.1 ± 0.4 | 0.244 |
| D2 | 37.1 ± 0.6 | 37.1 ± 0.5 | 0.985 |
| D3 | 36.9 ± 0.3 | 36.9 ± 0.4 | 0.647 |
| Vomiting | | | |
| D0 | 0.7 ± 1.3 | 0.2 ± 0.6 | 0.067 |
| D1 | 0.3 ± 0.9 | 0.1 ± 0.3 | 0.093 |
| D2 | 0.1 ± 0.3 | 0 ± 0.0 | 0.341 |
| D3 | 0 ± 0.0 | 0 ± 0.0 | 1 |
| ALT (U/L) | 327.7 ± 387.1 | 177.0 ± 88.0 | 0.016 |
| AST (U/L) | 235.4 ± 266.7 | 170.9 ± 73.1 | 0.133 |
| ALB (g/L) | 39.1 ± 6.2 | 38.5 ± 3.9 | 0.549 |
| TBIL (μmol/L)* | 27.1 ± 28.9 | 27.9 ± 11.6 | 0.873 |
| CRP (mg/L) | 49.7 ± 44.1 | 20 ± 29.0 | 0.001 |
| Post operative hospital stay (days) | 2.6 ± 0.6 | 2.4 ± 0.7 | 0.186 |

to the experimental group and intravenously received 40 mg of parecoxib one hour before RFA and every 12 h on the following days. Patients assigned into the control group (n=108) received 5 mL 0.9% sodium chloride instead. If patients complained of unbearable pain, they received 5 mg of morphine as a rescue treatment.

Among them, 75 patients were excluded based on the inclusion criteria. So the total of 111 patients was enrolled for eligible assessment, including 56 patients in the parecoxib group and 55 cases in the non-parecoxib group. To minimize bias, propensity score matching analysis, which matches the patients by their age, gender, lesion diameter, tumor numbers, ablation time, preoperative pain scores, temperature and vomiting grade? Finally, 44 pairs of patients were involved after the propensity score matching (Table 1).

### Measurements and outcomes

The recorded values were evaluated at following time points: Dx, D0, D1, D2 and/or D3, which represent all variables, were respectively measured at the preoperative period, two hours after the RFA surgery, and the following postoperative days. The maximum Visual Analog Scale (VAS) pain score, highest daily body temperature and vomiting grade were recorded for each day. The results of serum biochemistry examinations acquired on D2 or D3, and the length of hospitalization time was also recorded. Furthermore, the painful feeling was evaluated by Visual Analog Score (VAS) pain chart under the help of our physician. It contains four levels of pain, 0 (no pain), 2 (least pain), 4 (mild pain), 6 (moderate pain), 8 (severe pain), and 10 (worst pain possible). We also adopted a score list with a five-score form sheet to evaluate vomiting grades. Scoring was set at III (severe vomiting: more than five times per day), II (moderate vomiting: three to five times per day, I (slightly vomiting: one to two times per day), and 0 (absence of vomiting). Hepatic inflammatory status was assessed according to the serum biochemistry examinations, including Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin (TBIL), Albumin (ALB), and the level of C-Reactive Protein (CRP).

**Statistical analysis:** Data were analyzed using IBM SPSS Statistics 22.0 software. Student t-tests and Mann-Whitney U test was implemented in the statistical analysis. The results are presented as the mean ± the standard deviation. P value <0.05 was considered statistically significant.

## Results

### Patients recruitment and clinical baseline

The records of 111 patients satisfied the inclusion standard and were enrolled in the analysis. Comparison of baseline clinicopathologic characteristics between the parecoxib and non-parecoxib groups demonstrated that most indexes were consistent (Table 2 and Figure 1). Gender, age, liver function, AFP level, and coagulation function presented no remarkable difference between the two groups.

### Propensity score matching

For all the 111 patients enrolled in the analysis, 44 pairs of them were generated after the propensity score matching, based on the tumor diameter, tumor number, ablation time, preoperative pain scores, and temperature and vomiting grade. These factors could have effects on the postoperative physical variables of patients. Table 3 shows the pre-match and post-match characteristics of patients from two groups with or without parecoxib usage. The tumor numbers differed significantly between the two groups before matching (1.5 ± 1.2 *vs.* 1.2 ± 0.5, P=0.087), but this difference was well balanced after the propensity score matching (1.3 ± 0.5 *vs.* 1.3 ± 0.7, P=0.859). None of the other factors differed significantly by Student t-test.

**Table 2:** Baseline characteristics of patients who underwent radiofrequency ablation for hepatocellular carcinoma.

| Characteristics | Non-parecoxib (n=55) | Parecoxib (n=56) | P Value |
|---|---|---|---|
| Gender (Male:Female) | 48:7 | 49:7 | 0.971 |
| Age (years) | 57.4 ± 13.4 | 55 ± 12.0 | 0.316 |
| WBC (× $10^9$/L) | 5.1 ± 1.6 | 5.9 ± 1.8 | 0.015 |
| HBG (× $10^9$/L) | 138.4 ± 17.7 | 135 ± 30.5 | 0.469 |
| PLT (× $10^9$/L) | 135.7 ± 57.9 | 161 ± 73.3 | 0.047 |
| ALT (U/L) | 44.2 ± 43.0 | 42.9 ± 35.2 | 0.865 |
| AST (U/L) | 40.7 ± 35.7 | 37.3 ± 27.3 | 0.575 |
| ALB (g/L) | 42.1 ± 3.6 | 42.2 ± 4.4 | 0.856 |
| TBIL (μmol/L) | 15.7 ± 6.8 | 13.4 ± 6.8 | 0.08 |
| AFP( ng/mL) | 182.7 ± 499.5 | 346.8 ± 813.1 | 0.207 |
| PT (s) | 11.5 ± 0.8 | 11.3 ± 0.8 | 0.364 |
| APTT (s) | 30.1 ± 5.0 | 29.7 ± 5.0 | 0.712 |
| HBV-DNA (lg IU/mL) | 0.6 ± 1.0 | 0.7 ± 1.1 | 0.686 |

**Table 3:** Covariates in patients with and without parecoxib before and after propensity score matching.

| | Pre-matching | | | Post-matching | | |
|---|---|---|---|---|---|---|
| | Non-parecoxib (n=55) | Parecoxib (n=56) | P Value | Non-parecoxib (n=44) | Parecoxib (n=44) | P Value |
| Number (%) | 55 (49.5) | 56 (50.5) | | 44 (50) | 44 (50) | |
| Age | 57.4 ± 13.4 | 55 ± 12.0 | 0.322 | 55.1 ± 11.4 | 55.5 ± 12.8 | 0.888 |
| Gender (Male:Female) | 47:7 | 49:7 | 0.942 | 37:7 | 37:7 | 1.000 |
| Diameter (mm) | 24.6 ± 8.6 | 22.6 ± 10.4 | 0.275 | 24.2 ± 8.2 | 23.7 ± 10.8 | 0.801 |
| Tumor number | 1.5 ± 1.2 | 1.2 ± 0.5 | 0.087 | 1.3 ± 0.5 | 1.3 ± 0.7 | 0.859 |
| Ablation time (min) | 14.7 ± 8.1 | 12.2 ± 7.6 | 0.087 | 14.1 ± 6.1 | 12.6 ± 8.1 | 0.320 |
| Pain score (Dx) | 0.3 ± 1.3 | 0.1 ± 0.3 | 0.421 | 0.0 ± 0.0 | 0.1 ± 0.3 | 0.317 |
| Temperature (Dx, °C) | 36.6 ± 0.3 | 36.7 ± 0.3 | 0.094 | 36.7 ± 0.2 | 36.6 ± 0.3 | 0.206 |
| Vomiting† (Dx) | 0.1 ± 0.4 | 0 ± 0.1 | 0.99 | 0.1 ± 0.5 | 0 ± 0.2 | 0.987 |

†The vomiting grades were grade 0 with no vomiting; grade I with mild vomiting (one to two times per day); grade II with moderate vomiting (three to five times per day); and grade III with severe vomiting (more than five times per day).

### Results of parecoxib on pain score and hepatic inflammation

On Dx before surgery, the VAS pain scores did not differ remarkably between the experimental and control group (P=0.317; Table 3), but after RFA, the parecoxib group illustrated a significantly lower pain scores than the non-parecoxib group on both D0 (P<0.000), D1 (P=0.001) and D2 (P<0.05) (Table 1 and Figure 2). Hepatic inflammation was evident after RFA in an early stage for both groups, but only the levels of ALT (177.0 ± 88.0 *vs.* 327.7 ± 387.1 U/L, P<0.016) and CRP (20.0 ± 29.0 *vs.* 49.7 ± 44.1 mg/L, P<0.001) were significantly lower in the parecoxib group. As for liver function indicators of AST, ABL, and TBIL, they didn't have any statistical differences (P=0.133, 0.549 and 0.873).

### Postoperative vomiting, body temperature and postoperative hospitalization time

As showed in Table 1, vomiting demonstrated no statistical difference between the two groups at any time points. With regard to the body temperature, interestingly, the parecoxib group presented a relatively lower level without obvious differences significantly. In addition, after RFA, patients in the parecoxib group indicated a slightly shorter postoperative hospital stay (2.4 ± 0.7 *vs.* 2.6 ± 0.6 days, P=0.186) than the non-parecoxib group, but no significant differences as well (Table 1).

## Discussion and Conclusion

Radiofrequency ablation, as a minimally invasive therapy for a solid tumor, has the superiorities of less damage, lower costs, and shortened hospitalization time compared with surgical resection. It could destroy the target tumor tissues by inducing a high temperature, causing cell membrane destruction, protein denaturation, and a region of tissue necrosis surrounding the electrode [5,6]. Inflammatory induced by the tumor necrosis would bring obvious pain for patients, which is the most common symptom [12,16]. However, a limited study focusing on pain control after RFA is reported until now. Hinshaw JL et al., [17] reported a case-control study evaluating the application of the peritoneal infusion of 5% dextrose in water (D5W) could reduce postoperative pain and morphine consumption during the RFA treatment of peripheric liver cancer. The results from his team demonstrated that the patients in the experimental group demonstrated significantly less pain in the first operation day (2.3 *vs* 6.3, p=0.003).

Generally, the duration of RFA procedure is approximately 0.5 h to 1 h, and the incidence of moderate to severe pain on movement (an NRS value equal to or greater than 4) was 11.6% [18]. It is reported that 50% to 60% of patients would require additional analgesic therapy during the first day after the treatment [14]. With intraperitoneal instillation of D5W being technically inconvenient

and short-acting analgesic agents being repeatedly given, a long-acting analgesic should be employed to control postoperative pain imperatively. In this propensity-scored matched retrospective observational research, we selected parecoxib sodium, an injection form of analgesic, which is the first injectable and selective COX-2 inhibitor used in pain management. The results proved that it can effectively reduce postoperative pain because the mean VAS pain scores were significantly lower in the parecoxib group than control at several time points after RFA. Interestingly, however, parecoxib had no evident effect on fever or vomiting at several time points as our previous study, it might be for the reason that these complications may be less common after RFA, inducing the difference undetectable between the two groups [19].

Moreover, a hepatic inflammatory marker, especially serum ALT and CRP, presented a significantly lower level in the parecoxib group, which may be the result of parecoxib's selective inhibition of COX-2. This suggests that parecoxib protected the liver postoperatively. Although we found another difference of shorter hospital stay for the parecoxib group was no statistical differences, we think the further studies with larger number of enrollment patients may indicate further that parecoxib might help to reduce patients' discomfort and accelerate postoperative recovery.

Pain management is becoming more and more important in cancer treatment [20]. Defined as preoperative pain management that prevents the exaggeration and extension of postoperative pain, the notion of preemptive analgesia was first introduced in the early 20$^{th}$ century and experienced a thriving development ever since [21]. Our study showed that preemptive therapy with 40 mg of parecoxib before RFA treatment can provide sufficient antinociceptive protection against postoperative pain significantly.

As a selective COX-2 inhibitor, parecoxib can relieve inflammatory response *in vivo* by reducing the synthesis of prostaglandin, which would lead to leukocyte aggregation and formation of bradykinin [22]. After the RFA, treatment-induced high temperature can cause cytomembrane destruction, protein denaturalization, and tissue necrosis, these can all aggravated local inflammation and damage [23,24]. By early and selectively inhibiting COX-2, prophylactic administration of parecoxib demonstrated a significantly lower level of ALT and CRP but not on AST, ALB, or TBIL, suggesting that parecoxib can affect the level of the satisfying anti-inflammatory and prevent complications after the RFA surgery. Fever and vomiting are considered to be other main common adverse effects of RFA, but this research did not find any obvious effects on them. However, more studies are still warranted to explore whether prophylactic use of antipyretics or antanacathartic is necessary to optimize the perioperative quality of life.

To the best of our knowledge, this study is the first observational research using a parenteral analgesic to control pain during RFA for liver cancer and it demonstrates that preemptive treatment of parecoxib in RFA has the ability to provide antinociceptive protection against postoperative pain and reduce systemic inflammatory. What's more, to overcome selection bias as far as possible, propensity score matching was employed in our study. Although a randomized controlled trial can provide most unbiased evidence for clinical science, it is unlikely to recruit patients and obtain consent when patients have to choose not being given preemptive analgesia. A propensity score model is closest to reality and decreases the variance of an estimated exposure effect without increasing the bias. This method could overcome observed differences between treatment and comparison.

In summary, our research gives evidence that the prophylactically application of parecoxib can dramatically improve postoperative analgesia for patients undergoing RFA. The preemptive analgesia should be highly recommended in the clinical practice for further clinical practices. As for the further validation pain management after RFA, large-scale prospective controlled studies might be required.

## Author Contributions

Jian-Cong Chen and Zhong-Guo Zhou conceived and designed the project. Jun-Cheng Wang, Jin-Bin Chen, Yang-Xun Pan and Ying-Qin Zhu collected the data. Xu li, Yao-Jun Zhang and Min-Shan Chen analyzed and interpreted the data. Jian-Cong Chen and Jun-Cheng Wang drafted the manuscript.

## Funding

This work was supported by the National Natural Science Foundation of China [grant number 81602143] and Sun Yat-sen University Cancer Center physician-scientist funding [grant number 16zxqk04].

## References

1. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321-8.
2. Zuo TT, Zheng RS, Zhang SW, Zeng HM, Chen WQ. Incidence and mortality of liver cancer in China in 2011. Chin J Cancer. 2015;34(11):508-13.
3. Chen WQ, Zheng RS, Zhang SW. Liver cancer incidence and mortality in China, 2009. Chin J Cancer. 2013;32(4):162-9.
4. Peng ZW, Zhang YJ, Chen MS, Lin XJ, Liang HH, Shi M. Radiofrequency ablation as first-line treatment for small solitary hepatocellular carcinoma: long-term results. Eur J Surg Oncol. 2010;36(11):1054-60.
5. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. Ann Surg. 2009;249(1):20-5.
6. Zerbini A, Pilli M, Laccabue D, Pelosi G, Molinari A, Negri E, et al. Radiofrequency thermal ablation for hepatocellular carcinoma stimulates autologous NK-cell response. Gastroenterology. 2010;138(5):1931-42.
7. Zhu Y, Zhou C, Yang Y, Chen Y. Efficacy of parecoxib sodium on postoperative shivering: meta-analysis of clinical trials. J Int Med Res. 2018;46(1):3-10.
8. Cheng L, Long HT, Sun BH, Zhao SS, Zhu Y. The efficacy of a multimodal analgesia protocol in preventing heterotopic ossification after acetabular fractures surgery. Int J Clin Pharm. 2017;39(4):826-30.
9. Chen H, Luo A. Safety and Efficacy Study of the Cyclooxygenase-2 Inhibitor Parecoxib Sodium Applied for Postoperative Analgesia After Endo-Nasal Operation. Pain Pract. 2016;16(4):467-72.
10. Siribumrungwong K, Cheewakidakarn J, Tangtrakulwanich B, Nimmaanrat S. Comparing parecoxib and ketorolac as preemptive analgesia in patients undergoing posterior lumbar spinal fusion: a prospective randomized double-blinded placebo-controlled trial. BMC Musculoskelet Disord. 2015;16:59.
11. Dirkmann D, Groeben H, Farhan H, Stahl DL, Eikermann M. Effects of parecoxib on analgesia benefit and blood loss following open prostatectomy: a multicentre randomized trial. BMC Anesthesiol. 2015;15:31.
12. Zhu Y, Wang S, Wu H, Wu Y. Effect of perioperative parecoxib on

postoperative pain and local inflammation factors PGE2 and IL-6 for total knee arthroplasty: a randomized, double-blind, placebo-controlled study. Eur J Orthop Surg Traumatol. 2014;24(3):395-401.

13. Chong SJ, Wong YC, Wu J, Tan MH, Lu J, Moochhala SM. Parecoxib reduces systemic inflammation and acute lung injury in burned animals with delayed fluid resuscitation. Int J inflammation. 2014;2014.

14. Hori M, Tanaka M, Suzuki Y, Fukao M, Shimizu H, Mikoshiba N, et al. Periprocedural pain of radiofrequency ablation for hepatocellular carcinoma. Gastroenterol Nurs. 2011;34(2):129-34.

15. Liu LN, Xu HX, Lu MD, Xie XY. Percutaneous ultrasound-guided thermal ablation for liver tumor with artificial pleural effusion or ascites. Chin J Cancer. 2010;29(9):830-5.

16. Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245(1):36-43.

17. Hinshaw JL, Laeseke PF, Winter TC 3rd, Kliewer MA, Fine JP, Lee FT Jr. Radiofrequency ablation of peripheral liver tumors: intraperitoneal 5% dextrose in water decreases post procedural pain. AJR Am J Roentgenol. 2006;186:S306-10.

18. Ongiem A, Siriussawakul A, Aungsumat Wangdee BNS W, Homsud S, Jaiyen T. Assessment of Pain Severity after Radiofrequency Ablation in Patients with Hepatocellular Carcinoma. J Med Assoc Thai. 2016;99(5):572-7.

19. Zhou ZG, Chen JB, Qiu HB, Wang RJ, Chen JC, Xu L, et al. Parecoxib prevents complications in hepatocellular carcinoma patients receiving hepatic transarterial chemoembolization: a prospective score-matched cohort study. Oncotarget. 2016;7(19):27938-45.

20. Yang YP, Ma YX, Huang Y, Zhao YY, Xu F, Tian Y, et al. The good pain management (GPM) ward program in China and its impact on Chinese cancer patients: the SYSUCC experience. Chin J Cancer. 2014;33(7):323-9.

21. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, et al. Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology. 1992;77(3):439-46.

22. Jiang Y, Huang Q, Chen M, Qian Z. Analysis and design of a new hot-striking igniter for HID lamp. IEEE. 2004;1.

23. Zhou ZG, Zheng XR, Zhou Q, Shi M, Zhang YJ, Guo RP, et al. Impact of oral anti-hepatitis B therapy on the survival of patients with hepatocellular carcinoma initially treated with chemoembolization. Chin J Cancer. 2015;34(5):205-16.

24. Ma C, Xu B, Jia Z, Chen M, Qian Z. A timing controllable and polarity tracked igniter for High Intensity Discharge lamp electronic ballast. IEEE. 2010:1018-21.