Abstract. In the present study, the efficacy and safety of tenofovir disoproxil fumarate (TDF) switch therapy were assessed in patients with chronic hepatitis B exhibiting a suboptimal response to adefovir (ADV)-based combination therapy. First, the efficacy of the TDF switch therapy was retrospectively evaluated in 50 patients with chronic hepatitis B who failed to respond to ADV-based combination treatment. Among those, 48 patients with a median age of 35 years were hepatitis B e antigen (HBeAg)-positive and 17, 14 and 19 patients were previously treated with lamivudine (LAM) plus ADV, telbivudine plus ADV and entecavir (ETV) plus ADV, respectively. A total of 41 patients were treated with TDF alone and 9 with TDF plus ETV. The median time of follow-up was 102 weeks. The primary end-point was the cumulative probability of achieving a complete virologic response (CVR). The secondary end-points were the rate of alanine aminotransferase (ALT) normalization, HBeAg seroconversion in HBeAg-positive patients, and the plasma levels of creatinine and creatine kinase. The mean serum hepatitis B virus DNA levels prior to initiation of the TDF switch therapy were 4.8±1.6 log_{10} IU/ml. The cumulative probability of achieving a VR at 24, 48, 96 and 108 weeks was 52.0, 76.0, 89.8 and 94.9%, respectively. The cumulative probability of normalization of ALT at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 and 132 weeks was 34, 44, 50, 58, 66, 70, 74, 80, 90, 92 and 94%, respectively. HBeAg seroconversion was achieved in 5 patients. During the follow-up, 6 patients suffered from a virologic breakthrough, 3 patients failed to respond to the TDF treatment and the remaining patients were able to obtain VR following the continuation of TDF treatment. Slightly elevated serum levels of creatinine were observed in one patient, whereas creatine kinase activity did not increase in any of the subjects. In conclusion, TDF switch therapy is efficient and safe for patients with chronic hepatitis B with a suboptimal response to ADV-based combination therapy.

Introduction

Nucleoside/nucleotide analogues (NAs) are widely used for treating chronic hepatitis B virus (HBV) infection as the first-line antiviral drugs. NAs are prescribed to effectively suppress HBV DNA to achieve low or undetectable levels, prevent the progression of the disease to liver cirrhosis or hepatocellular carcinoma, and improve the quality of life and survival of affected patients (1). However, a major limitation of NAs is the development of drug resistance. Successful treatment of chronic HBV infection necessitates long-term suppression of the virus, which must be coupled with the prevention of the selection of drug-resistant mutants (2). Poor compliance and economic disadvantage directly contribute to a suboptimal response and may engender resistance to multiple NAs. Numerous patients do not respond to anti-virus medications even if treated with adefovir (ADV)-based combination therapies, including ADV plus lamivudine (LAM), ADV plus telbivudine or ADV plus entecavir (ETV). Thus, the development of an alternative treatment for patients with chronic hepatitis B with a suboptimal response to ADV-based combination therapy is crucial.

Tenofovir disoproxil fumarate (TDF) is an oral pro-drug of tenofovir, a nucleotide analogue that is one of the most potent...
HBV inhibitors (1) and is characterized by a high genetic barrier to resistance (2-4). It not only exhibited high efficacy in NA-naïve chronic hepatitis B patients but also produced a viral suppression response in patients with a history NA treatment (5-7). However, in these previous studies, the majority of patients that were switched to TDF had received previous monotherapy with LAM, ADV or ETV, or sequential therapy. In clinical practice, due to poor patient compliance and unsuitable initial drug selection, numerous patients require treatment with ADV-based combination therapy, which frequently produces suboptimal responses (8). The currently available data on the efficacy of the switch of chronic hepatitis B patients with a suboptimal response to ADV-based combination therapy to TDF therapy are limited. This paucity of clinically relevant information necessitates the further analysis of the clinical records of patients with chronic hepatitis B whose treatment involved a switch to TDF. Therefore, the major objective of the present study was to retrospectively evaluate the efficacy and safety of TDF switch therapy in chronic hepatitis B patients after a suboptimal response to ADV-based combination therapy.

Patients and methods

Study population. The present retrospective study enrolled patients with chronic hepatitis B who received TDF therapy after a suboptimal response to ADV-based combination therapy. The subjects were selected from patients treated at the Department of Infectious Diseases, The Third Affiliated Hospital, Sun Yat-sen University (Guangzhou, China); the samples were obtained between June 2012 and December 2015. The suboptimal response to ADV-based combination therapy was defined as either a nonresponse (decreased serum HBV DNA <2 log₁₀ IU/ml after 6 months of treatment) or an incomplete response (a decrease in HBV DNA of ≥1 log₁₀ IU/ml but detectable HBV DNA after at least 6 months of therapy in compliant patients). The inclusion criterion was the presence of serum HBV DNA at levels of ≥10⁷ IU/ml at the time of initiation of the TDF switch therapy. Patients with either human immunodeficiency virus or other hepatitis virus infections, or evidence of liver decompensation, as well as pregnant and breast-feeding women were excluded from the study. A virologic breakthrough was defined as an increase in HBV DNA of >1 log₁₀ IU/ml in comparison with the baseline at any time during treatment.

Clinical indexes and measurement methods. Subjects received TDF monotherapy (300 mg/day) or of TDF (300 mg/day) combined with ETV (0.5 mg/day). A 2-ml blood sample was collected at the baseline and every 12 weeks thereafter and stored at -80°C for future assessment. The assays included hematological analysis, biochemical indices in liver parameters, HBV DNA, serological analysis, hepatic synthetic function, creatine kinase (CK), blood urea nitrogen and creatinine levels. The measurements were performed using automated techniques. Blood was centrifuged for 5 min at 3,000 x g and 25°C to obtain the serum. The serum HBV DNA levels were measured by the HBV nucleic acid quantitative detection kit (cat. no. LANBORUI0001; DAAN Gene Co., Ltd., Guangzhou, China), with a minimum detection limit of 100 IU/ml. Hepatitis B s antigen (HBsAg; cat. no. 11820532122), HBeAg (cat. no. 11820583122) and the respective antibodies anti-HBs (cat. no. 11820524122) and anti-HBe (cat. no. 11820613122) antibodies were determined using commercially available chemiluminescence assay kits (Roche Diagnostic Systems, Basel, Switzerland). An ultrasound examination of the liver was also performed. The patients were thoroughly examined at each follow-up visit every 12 weeks over 144 weeks and requested to report any incidence of adverse events.

End-points. The primary end-point was the cumulative probability of patients achieving VR (undetectable HBV DNA, i.e. <100 IU/ml) during TDF treatment. The secondary end-points were the rate of HBeAg seroconversion in HBeAg-positive patients, alanine aminotransferase (ALT) normalization and the percentage of cases with elevated creatinine and CK.

Statistical analysis. Data were analyzed using the SPSS software package version 13.0 (SPSS Inc., Chicago, IL, USA). Quantitative data are expressed as the mean ± standard deviation. The categorical data are presented as counts and percentages. HBV DNA levels are presented in the log-transformed format. Student's t-test was used to evaluate the statistical significance of quantitative data with a normal distribution, including the liver and kidney indexes. The cumulative probability of achieving undetectable HBV DNA was assessed using the Kaplan-Meier method. The difference between the cumulative curves was estimated using the log-rank test. A two-tailed P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. The baseline characteristics of the study subjects are presented in Table I. In the cohort of 50 patients, 41 (82%) were treated with TDF alone and 9 (18%) were treated with TDF plus ETV. The median age was 35 years (range, 23-51 years), and 43 patients (86%) were males. A total of 48 patients were HBeAg-positive (96%), 3 (6%) suffered from cirrhosis and 1 (2%) had liver cancer diagnosed as small hepatocellular carcinoma by magnetic resonance imaging and computed tomography examination. In this patient, the ADV-based combination therapy was immediately discontinued and was replaced by TDF combined with ETV, while small hepectomy was performed to treat the liver cancer. Additionally, in this patient, no recurrence of hepatocellular carcinoma was identified at the follow-up at the week 144 and the mean serum HBV DNA level was 4.8±1.6 log₁₀ IU/ml. The number of patients previously treated with LAM plus ADV, telbivudine (LdT) plus ADV and ETV plus ADV was 17 (34%), 14 (28%) and 19 (38%), respectively. The median follow-up duration during TDF treatment with or without ETV was 102 weeks (range, 24-192 weeks).

Antiviral efficacy of TDF. The cumulative probability of achieving a VR at 12, 24, 48, 60, 72, 84, 96 and 108 weeks was 36.0, 52.0, 66, 76.0, 78.2, 89.8 and 94.9%, respectively (Fig. 1). The highest decrease in the levels of HBV DNA was detected at week 12 and the reduction continued with time to reach stable levels at 48 weeks (Fig. 2). According to three
distinct levels of HBV DNA at the baseline (<4, 4-6 and ≥6 log_{10} IU/ml), the patients were assigned to three groups. A HBV DNA level of ≥6 log_{10} IU/ml at the baseline was significantly associated with an increased VR rate among the patients (P=0.038; Fig. 3). According to the history of treatment, the patients were divided into three groups: LAM plus ADV, LdT plus ADV and ETV plus ADV. The cumulative VR rates of patients previously treated with LAM plus ADV were 41.2, 58.8, 70.6, 82.4, 88.2 and 94.1% at weeks 12, 24, 36, 48, 72 and 84, respectively, while those of patients previously treated with LdT plus ADV were 21.4, 42.9, 50.0, 57.1 and 78.6% at weeks 12, 24, 36, 48 and 72, respectively. In addition, in the group with a history of ETV plus ADV treatment, the response rates were 42.1, 52.6, 68.4, 84.2, 89.5 and 94.7% at weeks 12, 24, 36, 48, 72 and 96, respectively. However, the cumulative probability of VR among the three groups was not statistically different (P=0.229; Fig. 4). In the LdT plus ADV group, the probability of VR was lower compared with the other groups, however the size of the group (n=14; 28%) may be too small to be statistically significant. The efficacy of TDF monotherapy did not significantly differ from that of combined therapy with TDF and ETV (P=0.612; Fig. 5). During the follow-up, 6 patients suffered from a virologic breakthrough. Five of these cases received treatment with TDF and 1 was treated with TDF plus ETV. Among them, 3 patients (2 treated with TDF and 1 with TDF plus ETV) failed to achieve a VR.
obtained. In addition, 3 patients developed a virologic breakthrough during the course of TDF treatment. The genes were sequenced from the serum of 2 patients with poor efficacy and 3 patients with VR (Table III). A 204V mutation (HBV genotype, B) and 204I mutation (HBV genotype, C) were detected separately in 2 out of 5 patients who had a poor response to TDF within 24 weeks.
Safety. No severe adverse events were reported during the study. The baseline levels of CK were recorded for 50 patients, out of which 5 had values slightly higher than the normal reference range (24-194 IU/l) at week 132. Consistent with previous results (7), however, the activity of this enzyme returned to normal levels after these patients reduced their physical exercise. The remaining patients did not display any elevated CK concentration after 132 weeks of the follow-up. Normal ranges were as follows: CK, 24‑294 U/l (9); CR, 44‑133 µmol/l (10); Ca, 2.25‑2.75 mmol/l (11); P , 0.97‑1.61 mmol/l; AST, 8‑40 U/l) (12); ALT, 5‑40 U/l (13); ALB, 40‑55 G/l; TB, 1.71~17.1 µmol/l (14).

To assess the renal safety, the creatinine levels were analyzed in a subset of 50 patients, for which the baseline values were available. Only 1 patient, treated with TDF plus ETV , exhibited slightly elevated creatinine. This female patient was 38  years old and free of any renal disease. The serum creatinine was 130 µmol/l at baseline, fluctuated between 128 and 146 µmol/l during the treatment and was 130 µmol/l at 132 weeks, i.e., the last follow‑up. The blood phosphorus and calcium concentrations were also measured in all patients. The blood phosphorus content remained within the 0.95‑1.79 µmol/l range, and the blood calcium content was within the range of 2.03‑2.67 µmol/l. Only four patients had calcium concentrations below the normal range. Compared with TDF alone, the number of patients whose serum levels of CK, CR, P, Ca, AST, ALT, ALB and TB tended to be normal after TDF + EVT treatment was markedly improved (Table IV). No significant difference was identified in the mean CK, CR, P, Ca, AST, ALT, ALB and TB concentrations in the different treatment groups at the follow‑up time‑points (Table V).

Discussion

The results of the present study demonstrate that long‑term treatment with TDF, applied in the cases chronic hepatitis B with a suboptimal response to ADV‑based combination treatment, provides a robust viral response and a high rate of ALT normalization. A gradual increase of the cumulative VR rate was observed with prolonged administration of TDF. The efficacy of the TDF therapy was associated with the baseline level of HBV: Patients with HBV DNA <6 log_{10} IU/ml at baseline displayed a significantly higher VR rate than those with HBV DNA ≥6 log_{10} IU/ml.

Previous studies have documented that TDF has a favorable tolerability profile and induces a rapid and sustained suppression of HBV DNA in patients with chronic hepatitis B, regardless of their previous treatment with NAs (15‑18). A prospective study from Germany has indicated that after 36 months of treatment with TDF, the HBV DNA became undetectable in 91% of previously TDF‑naïve patients and in 96% of patients with prior NA treatment (6). In a trial involving 252 chronic hepatitis B patients, the TDF switch therapy yielded a stable VR in 84.9% of subjects with previous NA treatment after 22 months (19).

| Case no. | Treatment history | Genotype | Baseline of rescue therapy | Suboptimal response at 24 weeks | Virologic breakthrough |
|----------|-------------------|----------|-----------------------------|--------------------------------|-----------------------|
| 9        | LdT → ADV → ADV+LdT → TDF | B        | 181V, 236T                  | -                              | 181V, 236T            |
| 10       | ADV → ADV+LAM → TDF | C        | 181V, 204V                  | -                              | 181V, 204V            |
| 18       | ADV → ADV+LAM → TDF | B        | 204V                        | 204V                           | -                     |
| 33       | LAM → ADV → ETV → ADV+ETV → TDF | B | 181V, 204I, 236T            | -                              | 181V, 204I, 236T      |
| 37       | LAM → ADV → ADV+ETV → TDF | C | 204I                        | 204I                           | -                     |

ADV, adefovir dipivoxil; LAM, lamivudine; LdT, telbivudine; ETV , entecavir; TDF, tenofovir disoproxil fumarate.
Table IV. Liver and kidney function of patients with chronic hepatitis B treated with TDF alone (n=41) or with TDF plus ETV (n=9).

| Index; Time (weeks) | CK (>194 U/l) | CR (>133 µmol/l) | Ca (<2.25 mmol/l) | P (<0.97 mmol/l) | P (>1.61 mmol/l) | AST (>40 U/l) | ALT (>40 U/l) | ALB (>55 G/l) | TB (>17.1 µmol/l) |
|---------------------|---------------|------------------|-------------------|-----------------|-----------------|----------------|----------------|---------------|------------------|
| 0                   | 7             | 0                | 1                 | 4               | 0               | 2              | 0              | 1             | 0                |
| 12                  | 5             | 3                | 0                 | 4               | 0               | 3              | 0              | 0             | 0                |
| 24                  | 9             | 3                | 0                 | 0               | 0               | 4              | 0              | 0             | 0                |
| 36                  | 7             | 3                | 0                 | 1               | 1               | 2              | 0              | 0             | 0                |
| 48                  | 11            | 3                | 0                 | 1               | 0               | 2              | 0              | 1             | 0                |
| 60                  | 6             | 3                | 0                 | 0               | 0               | 1              | 1              | 0             | 0                |
| 72                  | 7             | 1                | 0                 | 1               | 1               | 1              | 0              | 1             | 0                |
| 84                  | 6             | 1                | 0                 | 0               | 0               | 1              | 1              | 0             | 0                |
| 96                  | 5             | 0                | 0                 | 1               | 0               | 3              | 0              | 0             | 0                |
| 108                 | 4             | 3                | 0                 | 1               | 0               | 1              | 1              | 0             | 0                |
| 120                 | 5             | 1                | 0                 | 0               | 0               | 1              | 1              | 0             | 0                |
| 132                 | 3             | 2                | 0                 | 0               | 0               | 0              | 1              | 0             | 0                |
| 144                 | 0             | 0                | 0                 | 0               | 0               | 0              | 0              | 0             | 0                |

Normal ranges were as follows: CK, 24‑294 U/l; CR, 44‑133 µmol/l; Ca, 2.25‑2.75 mmol/l; P, 0.97‑1.61 mmol/l; AST, 8‑40 U/l; ALT, 5‑40 U/l; ALB, 40‑55 G/l; TB, 1.71~17.1 µmol/l. CK, creatine kinase; CR, creatinine; Ca, calcium; P, inorganic phosphate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; TB, total bilirubin; ETV, entecavir; TDF, tenofovir disoproxil fumarate.
Table V. Level of liver and kidney function (n=50).

| Treatment group; TDF TDF+ETV | Time-point (weeks) | CK     | CR     | Ca     | P      | ALB    | AST    | ALT    | TB     |
|------------------------------|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| TDF                         | 0                 | 173.60± | 95.70± | 2.37±  | 1.22±  | 46.55± | 58.94± | 99.53± | 12.19± |
| 12                           | 164.00±           | 97.75± | 0.12   | 0.18   | 0.69   | 12.91± | 29.04± | 0.65   |
| 24                           | 173.60±           | 95.70± | 2.37±  | 1.22±  | 46.55± | 58.94± | 99.53± | 12.19± |
| 36                           | 164.00±           | 97.75± | 0.12   | 0.18   | 0.69   | 12.91± | 29.04± | 0.65   |
| 48                           | 173.60±           | 95.70± | 2.37±  | 1.22±  | 46.55± | 58.94± | 99.53± | 12.19± |
| 60                           | 164.00±           | 97.75± | 0.12   | 0.18   | 0.69   | 12.91± | 29.04± | 0.65   |
| 72                           | 173.60±           | 95.70± | 2.37±  | 1.22±  | 46.55± | 58.94± | 99.53± | 12.19± |
| 84                           | 164.00±           | 97.75± | 0.12   | 0.18   | 0.69   | 12.91± | 29.04± | 0.65   |
| 96                           | 173.60±           | 95.70± | 2.37±  | 1.22±  | 46.55± | 58.94± | 99.53± | 12.19± |
| 108                          | 164.00±           | 97.75± | 0.12   | 0.18   | 0.69   | 12.91± | 29.04± | 0.65   |
| 120                          | 173.60±           | 95.70± | 2.37±  | 1.22±  | 46.55± | 58.94± | 99.53± | 12.19± |
| 132                          | 164.00±           | 97.75± | 0.12   | 0.18   | 0.69   | 12.91± | 29.04± | 0.65   |
| 144                          | 173.60±           | 95.70± | 2.37±  | 1.22±  | 46.55± | 58.94± | 99.53± | 12.19± |
| TDF+ETV                      | 0                 | 148.00± | 87.49± | 2.46±  | 1.15±  | 43.82± | 37.89± | 50.89± | 13.72± |
| 12                           | 174.00±           | 85.04± | 2.44±  | 1.19±  | 43.71± | 35.13± | 49.13± | 13.35± |
| 24                           | 66.91±            | 26.16± | 0.12   | 0.14   | 1.98±  | 4.29   | 6.23   |
| 36                           | 181.20±           | 83.24± | 2.41±  | 1.24±  | 43.46± | 39.11± | 69.44± | 13.7±  |
| 48                           | 63.02±            | 25.56± | 0.12   | 0.14   | 1.33±  | 5.87   | 22.33± | 1.25   |
| 60                           | 266.30±           | 87.13± | 2.45±  | 1.14±  | 45.25± | 35.00± | 40.88± | 17.36± |
| 72                           | 245.70±           | 72.62± | 0.07   | 0.16   | 1.85±  | 5.88   | 4.35   | 0.95   |
| 84                           | 149.70±           | 72.32± | 0.14   | 0.19   | 1.85±  | 4.48   | 5.15   | 1.13   |
| 96                           | 158.60±           | 80.48± | 2.49±  | 1.14±  | 45.78± | 30.20± | 34.04± | 12.05± |
| 108                          | 156.60±           | 80.90± | 2.49±  | 1.14±  | 45.78± | 30.20± | 34.04± | 12.05± |
| 120                          | 158.60±           | 80.90± | 2.49±  | 1.14±  | 45.78± | 30.20± | 34.04± | 12.05± |
| Values are expressed as the mean ± standard deviation. No significant difference was identified in any of the variables between the two treatment groups. |
with a suboptimal response to previous LAM monotherapy or sequential therapy with LAM and ETV, undetectable HBV DNA was achieved in >80% of cases after 18 months of TDF monotherapy (7). The effectiveness of tenofovir switch therapy in patients with prior NA treatment of chronic hepatitis B patients was further proven by a study which determined that introduction of tenofovir in subjects resistant to LAM, ADV or ETV achieved cumulative VR rates of 82.8, 81.4 and 84.1%, respectively (20).

In the present study, the efficiency of TDF switch therapy in chronic hepatitis B patients with a suboptimal response to ADV-based combination therapy was noteworthy. The cumulative probability rate of a VR reached 52.0, 76.0, 89.8 and 94.9% at week 24, 48, 96 and 108, respectively. Other studies indicated a similar kinetics of HBV DNA decline in patients exhibiting a suboptimal response to ADV or ADV resistance. Baran et al (21) reported that the rate of complete VR in patients with chronic hepatitis B with a suboptimal response or resistance to ADV-based combination therapy, respectively, was 75 and 58% at 12 months, 87 and 79% at 24 months and 94 and 79% at 36 months after switching to TDF. Similar rates of wild-type and rtN236T-mutant HBV DNA decline were noted following 4 weeks of treatment with TDF (22), despite the proportion of rtN236T mutant HBV DNA remaining unaltered during the therapeutic intervention. It has been demonstrated in vitro that HBV mutations selected by ADV confer a multi-drug resistance that also affects the efficacy of TDF (23).

However, van Bommel et al (24) observed that although ADV resistance mutations (rtN236T and/or rtA181V/T) remained detectable after TDF switch therapy, the level of HBV DNA in most of the patients decreased at 12 months, and 2 patients achieved a complete viral response after 72 weeks. This result demonstrates that ADV-resistant HBV variants may be further selected during TDF treatment; however, they only cause a mild decrease in the sensitivity to TDF. Of note, the switch to TDF rescue treatment due to a suboptimal response to ETV plus ADV combination therapy had a potent effect: The cumulative VR rate reached 52.6, 84.2 and 94.7% at week 24, 48 and 96, respectively (18). Simultaneously, the cumulative response rates among ADV plus LAM/LdT/ETV groups were not significantly different (P=0.229), suggesting that TDF may be employed as an efficient agent irrespective of the type of prior ADV-based combination therapy.

The present study revealed that the VR rates after switching to TDF treatment were associated with the baseline levels of HBV DNA. In this regard, Lo et al (19) evaluated the response of HBV to TDF switch therapy by Kaplan-Meier analysis. The patients were stratified into groups based on their HBV DNA levels during the switch to TDF (<200 IU/ml, 200-1999, and ≥20,000 IU/ml). The results indicated that, in a manner similar to that observed in the present study, a low HBV DNA level at the time of switching to TDF was an independent predictor of the treatment efficacy in NAs-experienced chronic hepatitis B patients. Another study also assessed the effect of TDF in 151 NAs-naïve subjects and revealed that the HBV DNA levels at baseline were significantly associated with a greater VR (3). Comparable conclusions were reached by Park et al (25), who determined that when patients are stratified according to their HBV DNA levels at baseline (2-3, 3-4, 4-5 and ≥6 log10 IU/ml), the increase in VR is highest for the group with the lowest.
108 weeks of TDF monotherapy, the HBV DNA was significantly reduced, but still detectable. In the other patient, the drug resistance mutation 204I was detected and TDF monotherapy was continued for 96 weeks, at which the VR was achieved. 204T/V is a common resistance mutation site for nucleoside analogues and, based on the above analysis, it may represent the mutation site associated with TDF resistance.

In conclusion, the present study demonstrated that TDF rescue treatment was efficient and safe for chronic hepatitis B patients with a suboptimal response to ADV-based combination therapy.

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Availability of data and materials

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

Authors’ contributions

XL, JL, YZ and XS conceived of and designed the study, performed the literature search, acquired and analyzed the data, and prepared the manuscript. CZ, YW, ZL and YJ assisted in acquiring and analyzing the data, and performing the statistical analysis. YZ, GL and XL performed the literature search, acquired the data, and edited the manuscript. All authors have read and approved the content of the manuscript.

Ethical approval and consent to participate

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). Informed consent from the patients regarding the use of their anonymized data was not required due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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