Prognostic value of total tumor volume in patients with nasopharyngeal carcinoma treated with intensity-modulated radiotherapy

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Abstract

Background: Few studies have evaluated the prognostic value of total tumor volume (TTV), which reflects both the primary tumor volume and nodal tumor volume, in NPC. Furthermore, the relationship between TTV and survival remains unknown. The purpose of this study was to evaluate the prognostic value of TTV in patients with NPC treated with intensity-modulated radiation therapy (IMRT).

Methods: TTV was retrospectively assessed in 455 patients with newly diagnosed, non-metastatic NPC. All patients were treated using IMRT; 91.1% (288/316) of patients with stage III-IVb also received cisplatin-based chemotherapy. Receiver operating characteristic (ROC) curves were used to identify the optimal TTV cut-off point and examine the prognostic value of combined TTV with current clinical stage.

Results: Mean TTV was 11.1 cm³ (range, 0.3–27.9 cm³) in stage I, 22.5 cm³ (1.3–92.4 cm³) in stage II, 40.6 cm³ in stage III (3.2–129.2 cm³), and 77.5 cm³ in stage IVa-b (7.1–284.1 cm³). For all patients, the 4-year estimated FFS, OS, DMFS, and LRRFS rates for patients with a TTV ≤ 28 vs. > 28 cm³ were 93 vs. 71.4% (P < 0.001), 95.1 vs. 75.4% (P < 0.001), 94.5 vs. 79.4% (P < 0.001), and 96.2 vs. 88% (P = 0.001). TTV was an independent prognostic factor for FFS, OS, DMFS and LRRFS in all patients. In stage III-IVb, 4-year estimated FFS, OS, DMFS, and LRRFS for a TTV ≤28 vs. >28 cm³ were 88.9 vs. 70.5% (P = 0.001), 96.2 vs. 72.7% (P < 0.001), 91.2 vs. 78.3% (P = 0.008), and 93.8 vs. 87.6% (P = 0.063). TTV was an independent prognostic factor for FFS, OS and DMFS in stage III-IVb. Receiver operating characteristic (ROC) curve analysis curves revealed adding TTV to clinical stage had superior prognostic value for treatment failure compared to clinical stage alone (P = 0.016).

Conclusions: TTV is an important prognosticator for treatment outcome and significantly improves the prognostic value of the current staging system for patients with NPC treated with IMRT.

Keywords: Nasopharyngeal carcinoma, Intensity-modulated radiotherapy, Tumor volume, Treatment failure, Staging system
Background

Based on GLOBOCAN estimates, there were an estimated 86,700 new cases of nasopharyngeal carcinoma (NPC) and 50,800 associated deaths worldwide in 2012 [1]. The geographic distribution of NPC is extremely unbalanced, with a very low incidence in most regions of the world and high incidence in China and other countries in Southeastern Asia [1, 2]. Radical radiotherapy (RT) is the first treatment choice for non-metastatic NPC and the addition of concomitant chemotherapy to RT provides a significant survival benefit in locoregionally advanced NPC [3].

The overall survival (OS) of patients with NPC has significantly improved in recent years due to widespread application of magnetic resonance imaging (MRI), improvements in RT techniques and the combination of RT with concomitant chemotherapy [4–6]. The 5-year estimated OS rate is currently about 80%, while treatment failure remains the predominant cause of death; 5-year local control ranges from 86 to 95%, 5-year nodal control from 92 to 97% and 5-year distant control from 82 to 85% [7–12].

Accurate prognostication is critical when deciding treatment strategies. Tumor volume is a significant independent prognostic factor in most cancers, including oral carcinoma, B-cell lymphoma and rhabdomyosarcoma [13–15]. Several studies have confirmed the primary tumor volume (PTV) has high prognostic value for survival in NPC [16, 17]. However, few studies have evaluated the prognostic value of the total tumor volume (TTV), which incorporates both the PTV and nodal tumor volume (NTV), in NPC and the relationship between the TTV and survival remains unknown.

Therefore, we initiated a retrospective, large cohort study to evaluate the prognostic value of TTV in patients with NPC treated with intensity-modulated radiation therapy (IMRT), and assessed whether the prognostic validity of the current staging system for NPC could be improved by incorporating assessment of the TTV. We hope this information may help to further clarify the biological characteristics of NPC and guide the design of individual treatment strategies.

Methods

Patient characteristics

The Institutional Review Board of First People’s Hospital of Foshan Affiliated to Sun Yat-sen University approved this retrospective study; as this was an analysis of routine clinical data, an exemption from requiring written informed consent was granted. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2017000217. A total of 455 patients with newly diagnosed, non-metastatic NPC treated by IMRT at First People’s Hospital of Foshan Affiliated to Sun Yat-sen University from April 2010 to March 2014 were enrolled in this study [18]. The patients included 347 (76.3%) males and 108 (23.7%) females. The median age was 45 years (17–80 years). All cases had the non-keratinizing pathological type.

Pretreatment examinations included a medical history, physical examination, hematologic and biochemistry profiles, electrocardiogram, chest X-ray, abdominal ultrasound, nasal endoscopy and biopsy, pathological examination of the primary tumor, bone scan, and MRI of the nasopharynx and neck. All patients were restaged using the 7th edition of the American Joint Commission on Cancer staging system (AJCC) [19]. The stage/category distribution for the entire cohort was as follows: 127/455 (27.9%) in T1, 59 (13.0%) in T2, 157 (34.5%) in T3 and 112 (24.6%) in T4; 58 (12.7%) in N0, 255 (56.0%) in N1, 119 (26.2%) in N2 and 23 (5.1%) in N3; 29 (6.4%) in stage I, 110 (24.2%) in stage II, 184 (40.4%) in stage III and 132 (29.0%) in stage IVa-b.

Tumor volume measurement

The patients were immobilized in a supine position using a thermoplastic mask extending from the head to shoulders. CT simulation (Brilliance Big Bore, Phillips, Amsterdam, Netherlands) was performed at a slice thickness of 3 mm from the head to 2 cm below the sternoclavicular joint. The control CT and contrast-enhanced CT images were transferred to the inverse IMRT planning system (Version 8.6, Eclipse, Varian, CA, USA). Tumor volumes were delineated by a radiation oncologist, and verified by another radiation oncologist who specializes in NPC treatment.

The PTV and NTV were both delineated on the planning system according to the pretreatment MRI. The PTV included the primary tumor and retropharyngeal lymph node (RLN) involvement as these anatomic sites are so close that it remains difficult to distinguish between them (Fig. 1a–b) [16, 20, 21]. The NTV included metastatic cervical lymph nodes (CLN) and nodal extracapsular spread (Fig. 1c–d). The metastatic lymph nodes were diagnosed based on the criteria recommended by Van et al. and Mao et al. [22, 23]. The diagnostic criteria for nodal extracapsular spread included blurred margins or irregular capsular enhancement of lymph nodes, or tumor invasion into adjacent fat and muscle (Fig. 1c). The PTV and NTV were automatically calculated using a shape-based interpretation algorithm, which is obtained by tri-linear interpolation of a stack of two-dimensional distance transforms of transaxial shapes. The TTV was obtained by summing the PTV and NTV.
Treatment
All patients were treated using IMRT. Target volumes were delineated according to the RTOG IMRT protocols [18]. The planning target volume of the clinical target volume (CTV)70 received 70 Gy in 33 fractions at 2.12 Gy per fraction. Small-volume lymph nodes received 63 Gy in 33 fractions at 1.9 Gy per fraction. The planning target volume of the CTV59.4 received 59.4 Gy in 33 fractions at 1.8 Gy per fraction. The planning target volume of the CTV50.4 received 50.4 Gy in 28 fractions at 1.8 Gy per fraction. RT was delivered over one fraction daily, 5 days per week.

Based on the treatment guidelines for NPC at our hospital, concurrent chemotherapy was recommended to patients with stage T1–2N1M0 and concurrent chemotherapy +/- induction chemotherapy or adjuvant chemotherapy to patients with stage III-IVb NPC. In total, 82 (82/107, 76.6%) patients with clinical stage T1–2N1M0 and 288 (288/316, 91.1%) patients with stage III-IVb received chemotherapy. Induction chemotherapy or adjuvant chemotherapy was consisted of cisplatin (80 mg/m²) and fluorouracil (1000 mg/m² daily for 4 days); docetaxel (75 mg/m²) and cisplatin (75 mg/m²); or a triplet of docetaxel (60 mg/m²), cisplatin (60 mg/m²) and fluorouracil (800 mg/m² daily for 4 days) every 3 weeks for 2–3 cycles. Concurrent chemotherapy was consisted of cisplatin given every 3 weeks (100 mg/m²) or weekly (40 mg/m²) during RT. In the event of documented relapse, salvage treatments including RT, surgery or chemotherapy were provided when appropriate.

Follow up and statistical analysis
After RT, all patients were assessed every 3 months during the first 2 years, and every 6 months thereafter until death. The median follow-up for the entire cohort was
53 months (range, 2 to 83 months). Overall, 439 patients (439/455, 96.5%) received regular follow-up until death or latest scheduled assessment. Failure free survival (FFS) was calculated from assignment to the first failure at any site, OS to death from any cause, distant metastasis-free survival (DMFS) to first remote failure, and loco-regional relapse free survival (LRRFS) to first locoregional failure.

Stata Statistical Package (STATA 11; StataCorp LP, College Station, TX, USA) was used for all analysis. The Kruskal-Wallis test was used to examine the differences in TTV between stages. Actuarial rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses with the Cox proportional hazards model were used to test for significant independent prognostic factors using a backward elimination strategy. All patients were randomly allocated to a training set (n = 152) or test set (n = 303). Receiver operating characteristic (ROC) curve analysis was used to evaluate different cut-off points for TTV in the training set. Then, the test set and all patients were stratified according to the optimal cut-off point. The area under the ROC curve was used to assess the

![Fig. 2 Distribution of tumor volume by stage for all 455 patients. a Distribution of primary tumor volume by T category. b Distribution of nodal tumor volume by N category. c Distribution of total tumor volume by clinical stage.](image-url)

### Table 1 Clinical characteristics of 455 patients with TTV ≤ 28 and TTV > 28 cm³

| Characteristics | TTV ≤ 28 cm³ (N = 188) | TTV > 28 cm³ (N = 267) | P Value† |
|-----------------|-------------------------|-------------------------|----------|
| Sex (%)         |                          |                          | <0.001   |
| Male            | 127                     | 220                     |          |
| Female          | 61                      | 47                      |          |
| Age (years)     |                          |                          | 0.908    |
| ≤ 45 years      | 82                      | 115                     |          |
| > 45 years      | 106                     | 152                     |          |
| T-categorya (%) |                          |                          | <0.001   |
| T1              | 93                      | 34                      |          |
| T2              | 31                      | 28                      |          |
| T3              | 52                      | 105                     |          |
| T4              | 12                      | 100                     |          |
| N-categorya (%) |                          |                          | <0.001   |
| N0              | 43                      | 15                      |          |
| N1              | 116                     | 139                     |          |
| N2              | 26                      | 93                      |          |
| N3              | 3                       | 20                      |          |
| Stage-groupa (%)|                          |                          | <0.001   |
| I               | 29                      | 0                       |          |
| II              | 78                      | 32                      |          |
| III             | 66                      | 118                     |          |
| IVa–b           | 15                      | 117                     |          |
| Chemotherapy    |                          |                          | <0.001   |
| Yes             | 139                     | 245                     |          |
| No              | 49                      | 22                      |          |
| Additional boost|                          |                          | <0.025   |
| Yes             | 28                      | 22                      |          |
| No              | 160                     | 245                     |          |

TTV total tumor volume; †P values were calculated by the Chi-square test; aAccording to the 7th edition of the American Joint Commission on Cancer staging system.
prognostic validity of the TTV. The criterion for statistical significance was set at \( \alpha = 0.05 \); \( P \)-values were based on two-sided tests.

**Results**

**Distribution of tumor volume by category/stage**

The distribution of PTV stratified by T category is presented in Fig. 2a. The mean PTV was 12.7 cm\(^3\) (range, 0.3–69.2 cm\(^3\)) in T1, 18.9 cm\(^3\) (3.2–40 cm\(^3\)) in T2, 30.7 cm\(^3\) in T3 (2.4–122.5 cm\(^3\)), and 68.7 cm\(^3\) in T4 (4.1–275.3 cm\(^3\)). The distribution of NTV by N category is presented in Fig. 2b. The mean NTV was 8.0 cm\(^3\) (0–72.9 cm\(^3\)) in N1, 18.4 cm\(^3\) in N2 (0.3–107.5 cm\(^3\)), and 44.7 cm\(^3\) in N3 (2.4–184.0 cm\(^3\)). The distribution of TTV by clinical stage is presented in Fig. 2c. The mean TTV was 11.1 cm\(^3\) (range, 0.3–27.9 cm\(^3\)) in stage I, 22.5 cm\(^3\) (1.3–92.4 cm\(^3\)) in stage II, 40.6 cm\(^3\) in stage III (3.2–129.2 cm\(^3\)), and 77.5 cm\(^3\) in stage IVa-b (7.1–284.1 cm\(^3\)).

**Identification and verification of TTV cut-off point**

With respect to FFS, the optimal cut-off point for the TTV was 28 cm\(^3\) in the training set (sensitivity 95.7%, specificity 50.4%; area under the ROC curve [AUC] = 0.73, \( P = 0.001 \)). Therefore, we selected 28 cm\(^3\) as a uniform cut-off point (\( \leq 28 \) vs. \( > 28 \) cm\(^3\)) in order to classify the test set and all patients into high and low TTV groups for survival analysis.

In the test set (\( n = 303 \)), the 4-year estimated FFS, OS, DMFS, and LRRFS rates for patients with a TTV \( \leq 28 \) cm\(^3\) are shown in Fig. 3. The survival rates are depicted in the following figures:
vs. > 28 cm³ were 90.9 vs. 69.8% (P < 0.001), 95.1 vs. 75.1% (P < 0.001), 93.4 vs. 77.8% (P < 0.001), and 95.8 vs. 88.1% (P = 0.005), respectively.

Prognostic significance of TTV in all patients
The clinical characteristics of the 455 patients with NPC stratified by TTV ≤ 28 cm³ and >28 cm³ are shown in Table 1. In all patients (n = 455), the 4-year estimated FFS, OS, DMFS, and LRRFS rates of the patients with a TTV ≤ 28 vs. > 28 cm³ were 93 vs. 71.4% (P < 0.001), 95.1 vs. 75.4% (P < 0.001), 94.5 vs. 79.4% (P < 0.001), and 96.2 vs. 88% (P = 0.001), respectively (Fig. 3).

The following parameters were included in the Cox proportional hazards model: age (≤ 45 vs. > 45 years), sex (male vs. female), T category (T1–2 vs. T3–4), N category (N0–1 vs. N2–3), chemotherapy (yes vs. no), additional boost (yes vs. no) and TTV (≤ 28 vs. > 28 cm³). TTV was an independent prognostic factor for FFS, OS, DMFS and LRRFS in all patients (all P < 0.05; Table 2).

Prognostic significance of TTV in stage III-IVb NPC
The 316 patients with stage IIIb–IVb were divided into two subgroups: patients with a TTV ≤ 28 cm³ (n = 81) and patients with a TTV > 28 cm³ (n = 235). The 4-year estimated FFS, OS, DMFS, and LRRFS rates of the patients with a TTV ≤ 28 cm³ and TTV > 28 cm³ were 88.9 vs. 70.5% (P = 0.001), 96.2 vs. 72.7% (P < 0.001), 91.2 vs. 78.3% (P = 0.008), and 93.8 vs. 87.6% (P = 0.063; Fig. 4).

The following parameters were included in the Cox proportional hazards model: age (≤ 45 vs. > 45 years), sex (male vs. female), T category (T1–2 vs. T3–4), N category (N0–1 vs. N2–3), chemotherapy (yes vs. no), additional boost (yes vs. no) and TTV (≤ 28 vs. > 28 cm³). TTV was an independent prognostic factor for FFS, OS and DMFS in stage III-IVb NPC (all P < 0.05; Table 3).

Table 2 Multivariate analyses of prognostic factors in all 455 patients

| Endpoint | Variable | HR    | 95% CI          | P-value |
|----------|----------|-------|-----------------|---------|
| FFS      | TTV      | 4.523 | 2.482–8.241     | <0.001  |
|          | N stage⁴ | 1.567 | 1.027–2.391     | 0.037   |
| OS       | Sex      | 1.661 | 0.915–3.013     | 0.095   |
|          | Chemotherapy | 1.882 | 0.986–3.592     | 0.055   |
|          | T stage⁴ | 1.763 | 1.054–2.951     | 0.031   |
|          | N stage⁴ | 1.920 | 1.254–2.939     | 0.003   |
|          | TTV      | 3.231 | 1.776–5.878     | <0.001  |
| DMFS     | N stage⁴ | 1.764 | 1.064–2.925     | 0.028   |
|          | TTV      | 3.749 | 1.877–7.489     | <0.001  |
| LRRFS    | TTV      | 3.810 | 1.679–8.645     | 0.001   |

⁴According to the 7th edition of the American Joint Commission on Cancer staging system; HR hazard ratio, CI confidence interval, FFS failure free survival, OS overall survival, DMFS distant metastasis-free survival, LRRFS loco-regional relapse free survival, TTV total tumor volume

Prognostic validity of clinical stage combined with TTV vs. clinical stage alone for treatment failure
ROC curves were used to compare the prognostic validity of clinical stage combined with TTV vs. clinical stage alone for treatment failure. The AUC for clinical stage combined with TTV was 0.706 compared to 0.667 for clinical stage alone (P = 0.016; Fig. 5). Therefore, the addition of TTV to clinical stage was superior to clinical stage alone for predicting treatment failure.

Discussion
Tumor size is an important prognostic factor in cancer treatment and has been adopted in the staging systems for most carcinomas [19]. This NPC study demonstrated that patients with a TTV > 28 cm³ had significantly poorer survival outcomes compared to those with a TTV ≤ 28 cm³. Moreover, TTV was an independent prognostic factor in patients with NPC, and the addition of TTV to clinical stage was superior to clinical stage alone for predicting treatment failure.

Distribution and optimal cut-off point for TTV
High TTV values were more frequent in patients with advanced clinical stage. However, the distribution of the TTV values varied widely within the same clinical stage, and overlapped between different clinical stages. Moreover, TTV, PTV and NTV exhibited large variations between different T and N categories [20, 24]. Our previous studies demonstrated that the distribution of the maximum primary tumor diameter (MPTD), another index of tumor size, exhibits a similar trend [25, 26]. Therefore, the current staging system for NPC has the disadvantage of assessing tumor size poorly.

Previous studies have divided patients into 2–4 groups on the basis of tumor volume using different methods [16, 27, 28]. Standard cutoff points should be adopted to achieve optimal sensitivity and specificity. For cancer patients at high risk of treatment failure, it is reasonable to maximize sensitivity over specificity. Therefore, we defined the ideal cut-off point based on a sensitivity estimate of over 80%. A cut-off point of 28 cm³ for the TTV was selected to assess treatment failure, and this cut-off value was validated in the test set.

Prognostic value of the TTV in all patients with NPC
This study confirmed a large TTV was not only associated with poor FFS, DMFS and LRRFS, but also with poor OS in all patients with NPC. Chua et al. reported the 5-year FFS rates for patients with NPC treated by two-dimensional RT (2D–RT) with a TTV ≤ 20 cm³, > 20–40 cm³, > 40–60 cm³ and >60 cm³ were 89, 84, 76 and 55%, respectively (P < 0.001); and the corresponding 5-year DMFS rates were 84, 82, 73 and 61%, respectively (P < 0.001) [20]. Thus, it can be concluded that survival
rates decrease with increasing tumor volume in patients with NPC treated by 2D–RT or IMRT. Multivariate analyses showed TTV was an independent prognostic factor for FFS, OS, DMFS and LRRFS. In comparison, T category was an independent prognostic factor for OS, but not for FFS, DMFS or LRRFS. Furthermore, the only independent prognostic factor for LRRFS was TTV. Similar results were also observed in head and neck carcinomas: TTV was an independent variable, but T and N category were not independent prognostic variables unless the multivariate analyses did not include TTV [29]. In both this and the previous study, TTV appeared to be a more useful prognostic factor than the AJCC staging system. A large tumor volume may indicate a high potential for micro-metastasis, tumor hypoxia that promotes resistance to RT and chemotherapy, and an increased number of cancer clone cells to be killed [30, 31].

Prognostic significance of the TTV in loco-regionally advanced NPC
This study also demonstrated that a large TTV was associated with poor FFS, OS and DMFS in stage III–IVb NPC. The TTV was also an independent prognostic factor for FFS, OS and DMFS in this group of patients. Our previous studies confirmed that MPTD is an independent prognostic variable in stage T3–T4 NPC [25, 26]. These findings indicate that although loco-regionally advanced disease is usually associated with a high risk of
Table 3 Multivariate analyses of prognostic factors in 316 patients with stage III-IVb

| Endpoint  | Variable | HR   | 95% CI     | P-value |
|-----------|----------|------|------------|---------|
| FFS       | TTV      | 3.362| 1.677–6.738| 0.001   |
| OS        | Sex      | 1.735| 0.906–3.321| 0.096   |
|           | Additional boost | 1.860| 0.947–3.654| 0.072   |
|           | Chemotherapy | 2.384| 1.109–5.126| 0.026   |
|           | N stagea  | 1.551| 0.994–2.421| 0.053   |
|           | TTV      | 4.364| 2.125–8.964| <0.001  |
| DMFS      | TTV      | 2.923| 1.323–6.459| 0.008   |
| LRRFS     | TTV      | 2.464| 0.951–6.383| 0.063   |

*According to the 7th edition of the American Joint Commission on Cancer staging system; HR hazard ratio, CI confidence interval, FFS failure free survival, OS overall survival, DMFS distant metastasis-free survival, LRRFS loco-regional relapse free survival, TTV total tumor volume, RT radiotherapy.

Prognostic validity of adding TTV to clinical stage

The combination of TTV and clinical stage was superior to clinical stage alone for predicting treatment failure. Guo et al. reported prognostic assessment could be improved by combining the PTV with the current T classification criteria [21]. Our previous study also showed inclusion of the MPTD improved the prognostic value of the current T classification criteria [25]. Therefore, the current staging system for patients with NPC could be refined by incorporating tumor size.

In the clinic, the treatment strategy for NPC is mainly based on the name staging system, which lacks indexes related to tumor burden. TTV closely reflects tumor burden and is easily obtained from the IMRT planning system. As a large TTV was associated with a high incidence of treatment failure, patients with a large TTV may benefit from more aggressive treatment. For instance, adding induction chemotherapy, including cisplatin, fluorouracil, and docetaxel (TPF), to concurrent chemoradiotherapy could significantly improve FFS in locoregionally advanced NPC [32].

Conclusions

This is the first evaluation of the prognostic value of the TTV in NPC, and reveals the TTV is an important prognostic factor for treatment outcomes in patients treated with IMRT. Incorporation of the TTV could help to refine the prognostic validity of the current staging system for NPC. Patients with a large TTV had a poor prognosis and may benefit from more aggressive treatment. However, this was a retrospective study of consecutive patients who received different chemotherapy regimens, which may have affected the treatment outcomes. Furthermore, this analysis was based on single-institution data, and needs to be confirmed via large-cohort multicenter studies.

Abbreviations

AJCC: American Joint Commission on Cancer staging system; AUC: area under the curve; 2D: two-dimensional; CTV: clinical target volume; DMFS: distant metastasis-free survival; FFS: failure free survival; IMRT: intensity-modulated radiation therapy; LRRFS: loco-regional relapse free survival; MPTD: maximum primary tumor diameter; MRI: magnetic resonance imaging; NPC: nasopharyngeal carcinoma; NTV: nodal tumor volume; OS: overall survival; PTV: primary tumor volume; ROC: Receiver operating characteristic; RT: radiotherapy; TTV: total tumor volume.

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Availability of data and materials

The datasets used and analysed during the current study were available from the corresponding author on reasonable request.

Authors’ contributions

SBL and JJT contributed to the conception and design of the study, data acquisition, data analysis, data interpretation and the draft of the manuscript. XFH, XLY, ML and XNF carried out the acquisition and interpretation of data.
DSL performed the data analysis and data interpretation. YC and LWF contributed with the conception and design of the study, data acquisition, data interpretation and critical edit of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of First People’s Hospital of Foshan Affiliated to Sun Yat-sen University. It was a retrospective analysis of routine data and thus we were granted an exemption from requiring written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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