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RESEARCH ARTICLE

Landscape of *IDH1/2* mutations in Chinese patients with solid tumors: A pan-cancer analysis

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Abstract

Background: Isocitrate dehydrogenase (IDH) is an enzyme family involved in cell aerobic metabolism of tricarboxylic acid cycle. However, the landscape of *IDH* mutations in pan-cancer has not been fully characterized.

Methods: Tissue or blood samples were subjected to next-generation sequencing (NGS) for detection the *IDH* mutation.

Results: A total of 28.868 patients from more than 20 solid tumor species were analyzed. A total of 374 cases (1.30%) with *IDH* mutations were identified. Among all the *IDH* mutations cases, 80 (21.4%) were biliary tract cancer (BTC), 80 (21.4%) were lung cancer, 57 (15.2%) were liver cancer, and 42 (11.2%) were colorectal cancer. The most common *IDH* variant were *IDH1* and *IDH2* which were discovered in 0.81% cases and 0.47% cases, respectively. However, there were significant differences in *IDH1* and *IDH2* mutation frequency among different tumor species ($p = 0.0003$). Of the patients with *IDH1* mutations, about 53.0% of these mutations occur in codons 132. Codons 172 (25.4%) was high-frequency mutation subtypes in *IDH2* mutation. *TP53*, *PBRM1*, and *BAP1* were the most significantly mutated genes in BTC which were different from others cancer. Moreover, TMB were significantly higher in lung cancer, colorectal cancer, and gastric cancer than BTC ($p = 0.0164$, $p < 0.0001$, $p = 0.0067$, respectively) and BTC patients with *IDH* mutation had lower TMB compared with wild-type *IDH*.

Conclusion: Somatic *IDH* mutation was found in multiple solid tumors and *IDH* would be a driver gene in BTC.

KEYWORDS
IDH mutation, next-generation sequencing, pan-cancer, TMB

Dong Shen and Junling Zhang contributed equally to this work.

1 | INTRODUCTION

Isocitrate dehydrogenase (IDH) is a family of enzymes involved in cell aerobic metabolism of tricarboxylic acid cycle, among which *IDH1* and *IDH2* are common mutated metabolic genes in human cancers such as glioma and hematologic malignancies (Norsworthy et al., 2019; Yang et al., 2012). Since 2008, when *IDH1* missense mutation was first identified in progressive glioblastoma (Parsons et al., 2008), numerous studies have been conducted to describe this gene mutation and understand its biological impact on tumors (Turkalp et al., 2014). And it has been confirmed that *IDH1/2* mutation as a biomarker was associated with tumor prognosis and predictive value (Mondesir et al., 2016).

The understanding of the role of *IDH1/2* mutations in tumorigenesis and early occurrence has led to the development of *IDH1/2* mutation inhibitors. With the clinical development of IDH inhibitors and the entry into phase I trials, IDH inhibitors have shown promising efficacy not only in hematologic malignancies but also in patients with unresectable or metastatic *IDH1/2* mutant biliary tract cancer (BTC). In patients with BTC, ivosidenib has been approved in patients with mutant *IDH1*-BTC according to NCT02073994 study (Lowery et al., 2019). A recent phase III ClaridHY trial showed that ivosidenib showed a greater advantage over placebo in median PFS and OS in patients with advanced *IDH1*-mutated BTC (2.7 vs. 1.4 months, HR 0.37, 95% CI 0.25.0.54, $p < 0.0001$; Lamarca et al., 2020; Abou-Alfa et al., 2020). AG-221 (Enasidenib) and other IDH1/2 inhibitors are currently being assessed in multiple phases I/II clinical trials in subjects with advanced solid tumors, including BTC, who harbor an *IDH2* mutation (NCT02273739, NCT02273739, NCT02381886, and NCT02481154). Therefore, the application of IDH inhibitors in BTC looks promising.

However, the landscape of *IDH1/2* mutations in pan-cancer has not been fully characterized. In this study, we invested the *IDH1/2* pathologic or likely pathologic mutations landscape in pan-cancer.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was conducted under the approval of the ethics committees of the hospitals and informed consents were obtained from patients.

2.2 | Clinical specimens

Formalin-fixed paraffin-embedded (FFPE) tumor sample or biopsy ($n = 28{,}868$) of pan-cancer patients between January 2017 and January 2020 was enrolled in this study, including biliary carcinoma (1377 cases), liver cancer (2148 cases), lung cancer (11614 cases), colorectal cancer (4056 cases), etc. Tumor tissue samples (self-blood negative control) of pan-cancer were subjected to NGS for detection the *IDH1/2* mutation with a well-designed 733 cancer gene panel on Illumina HiSeq sequencer (Illumina) with 800× sequencing depth in a College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory (3D Medicine Inc.; Wang et al., 2019)]. The details of *IDH1/2* genes, such as the locations and the meaning of the mutations, were showed in supplement. Somatic alterations were identified and clinical information including age, gender, and tumor histology was collected. In addition, the TMB was defined as the number of nonsynonymous somatic SNVs and indels in examined coding regions, with driver mutations excluded. All SNVs and indels in the coding region of targeted genes, including missense, silent, stop gain, stop loss, in-frame, and frameshift mutations, were considered.

2.3 | DNA extraction

FFPE tissue sections were evaluated for tumor cell content using hematoxylin and eosin (H&E) staining. Only samples with a tumor content of ≥20% were eligible for subsequent analyses. FFPE tissue sections were placed in a 1.5

TABLE 1 Clinical characteristics of patients

Characteristics	Total ($n = 28.868$)	*IDH* mutated (n, %)
Gender		
Male	17140 (59.37)	234 (1.37%)
Female	11728 (40.63)	140 (1.19%)
Age		
<60	13938 (48.28)	186 (1.33%)
≥60	14930 (51.72)	188 (1.26%)
Tumor		
Lung cancer	11614 (40.23%)	80 (0.69%)
Colorectal cancer	4056 (14.05%)	42 (1.04%)
Liver cancer	2148 (7.44%)	57 (2.65%)
Gastric cancer	1418 (4.91%)	16 (1.13%)
Biliary tract cancer	1377 (4.77%)	80 (5.81%)
Intestinal cancer	1117 (3.87%)	12 (1.07%)
Pancreatic cancer	987 (3.42%)	7 (0.71%)
Kidney cancer	981 (3.40%)	5 (0.51%)
Breast cancer	662 (2.29%)	5 (0.76%)
Ovarian cancer	545 (1.89%)	7 (1.28%)
Prostate cancer	321 (1.11%)	9 (2.80%)
Endometrial carcinoma	276 (0.96%)	6 (2.17%)
Other	270 (0.94%)	43 (15.93%)
Melanoma	232 (0.8%)	5 (2.16%)

microcentrifuge tube and deparaffinized with mineral oil. Samples were incubated with lysis buffer and proteinase K at 56℃ overnight until the tissue was completely digested. The lysate was subsequently incubated at 80 ℃ for 4 hours to reverse formaldehyde crosslinks. Genomic DNA was isolated from tissue samples using the ReliaPrep™ FFPE gDNA Miniprep System (Promega) and quantified using the Qubit™ dsDNA HS Assay Kit (Thermo Fisher Scientific) following the manufacturer's instructions.

2.4 | Library preparation and DNA sequencing

DNA extracts (30–200 ng) were sheared to 250 bp fragments using an S220 focused ultrasonicator (Covaris). Libraries were prepared using the KAPA Hyper Prep Kit (KAPA Biosystems) following the manufacturer's protocol. The concentration and size distribution of each library were determined using a Qubit 3.0 fluorometer (Thermo Fisher Scientific) and a LabChip GX Touch HT Analyzer (PerkinElmer), respectively. Single nucleotide variation (SNV), insertions/deletions, copy number variations (CNV), and gene fusions were assessed and the corresponding criteria are the same as our previous study (Yang et al., 2018). Germline alterations were excluded.

2.5 | Statistical analysis

The paired-end reads were mapped by BWA (Li & Durbin, 2010) MEM algorithm. SNVs were called by MuTect (Cibulskis et al., 2013) with default parameters. Small insertions and deletions were called from the union of Varscan 2 (Koboldt et al., 2012) and Pindel (Ye et al., 2009) with default parameters. Fusions were called by self-developed scripts with at least 5 pairs of reads spanned over the breakpoints between two partner genes. The CNVs of

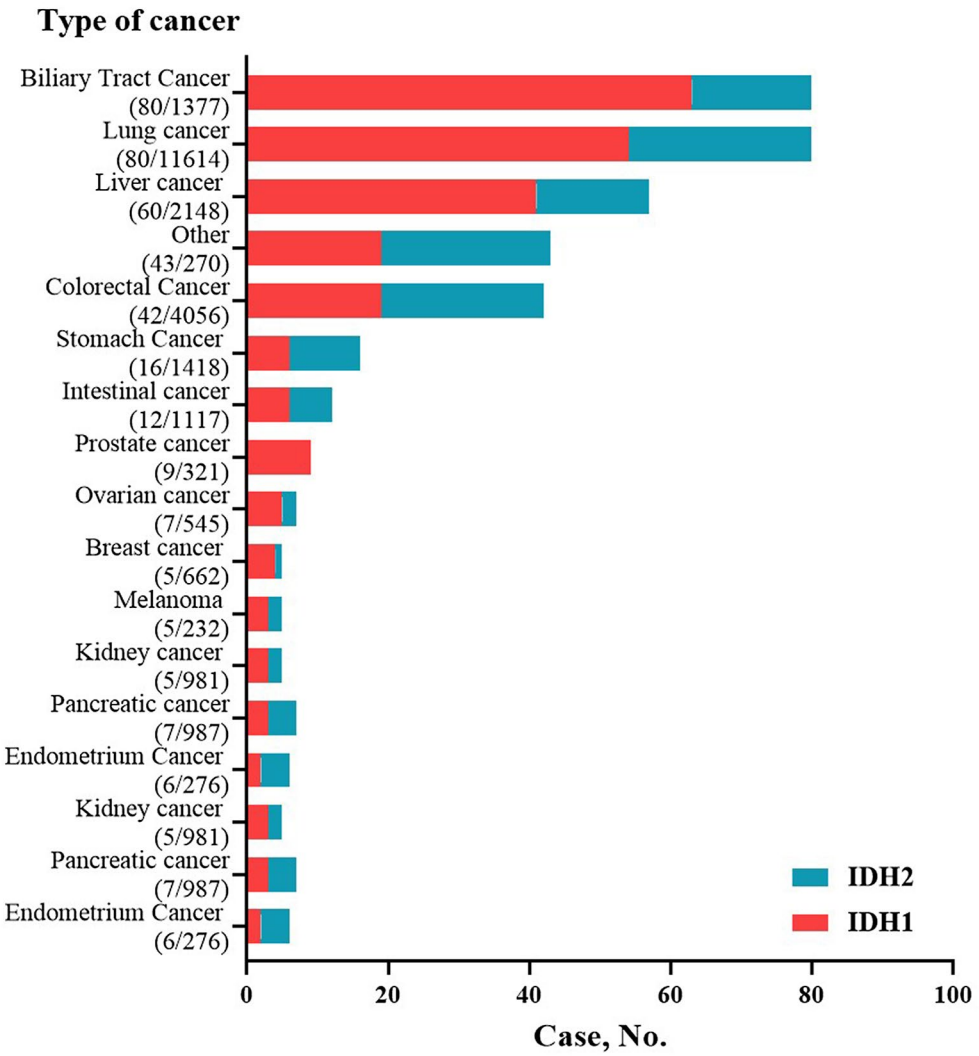

FIGURE 1 Prevalence of *IDH1/IDH2* mutations in 28,868 patients with pan-cancer

tumor tissues were calculated by BIC-seq2 (Xi et al., 2016) with default parameters, and the CNVs of ctDNA samples were called by a method reported by Chabon et al. (2016). All mutations were manually reviewed using integrative genomics viewer (IGV; Robinson et al., 2011) to further eliminate false-positive results. The probability density distributions of mutant and wild-type fragments were calculated by Gaussian kernel smoothing using StatsModels 0.8.0.

Categorical variables were described as number and proportions. Categorical relationships were examined by using Pearson's chi-square test with the Yates continuity correction when applicable and p value <0.05 was considered statistically significant. The SPSS22.0 software (SPSS, Inc.) was carried out for statistical analysis.

3 | RESULTS

3.1 | Patient characteristics

From January 01, 2017, to October 30, 2019, a total of 28,868 cases of Chinese solid tumor types were included in this study, including biliary carcinoma (4.77%), liver cancer (7.44%), lung cancer (40.23%), and colorectal cancer (14.05%). A total of 374 cases (1.30%) with *IDH* mutations were identified. Patients with *IDH* mutation <60 years old were 49.7% (n=186). Among all the *IDH* mutations cases, 80 (21.4%) were BTC, 80 (21.4%) were lung cancer, 57 (15.2%) were liver cancer, and 42 (11.2%) were colorectal cancer (Table 1).

TABLE 2 Clinicopathological characteristics of *IDH* mutant tumor

	***IDH1* mut (n = 236)**	***IDH2* mut (n = 138)**	***p***
Age			
≥60	123	64	0.2839
<60	113	74	
Sex			
Male	149	84	0.6603
Female	87	54	
Tumor location			
Lung cancer	53	27	0.0003
Colorectal cancer	19	23	
Liver cancer	41	16	
Gastric cancer	6	10	
Biliary tract cancer	63	17	
Intestinal cancer	6	6	
Pancreatic cancer	3	4	
Kidney cancer	3	2	
Breast cancer	4	1	
Ovarian cancer	5	2	
Prostate cancer	9	0	
Endometrial carcinoma	2	4	
Other	19	24	
Melanoma	3	2	

3.2 | IDH mutation of pan-cancer

The prevalence of *IDH1/IDH2* mutations in 28.868 patients with different cancer types is summarized in Figure 1, with BTC patients having the highest levels of *IDH1/IDH2* mutations (80/1377). Across all 28,868 patients, the mutational frequencies of *IDH1* and *IDH2* were 0.81% and 0.47%, respectively. Furthermore, we analyzed the differences between *IDH1* and *IDH2* in different tumor species. There was no significant difference in age and sex between the two groups. However, we found that there were significant differences in *IDH1* and *IDH2* mutation frequency among different tumor species ($p = 0.0003$, Table 2).

Of the patients with *IDH1* mutations, about 53.0% of these mutations occur in codons 132 (Figure 2A). The proportions of the major other *IDH1* mutation were as follows: copy number variations (CNV) loss (3.0%), *Y208C* (3.0%), *R20Q* (1.3%), and *R49C* (1.3%). Codons 172 (25.4%) was high-frequency mutation subtypes in *IDH2* mutation, followed by CNV gain (5.4%), CNV loss (3.9%), and *T146Lfs*15* (3.1%; Figure 2B).

We further investigated the genetic variation spectrum of *IDH*-mutated patients (Figure 2). Targeted therapies have been successfully developed to treat lung cancer harboring driver gene mutations. In lung cancer, driver gene mutations *EGFR* and *KRAS* were the most significantly mutated genes, whereas *TP53*, *PBRM1*, and *BAP1* were more frequently observed in BTC (Figure 3a,c). In addition, *TP53*, *PBRM1*, and *BAP1* were high-frequency mutated gene in liver cancer (Figure 3b). *APC*, *TP53*, and *KRAS* were among the top mutated genes in colorectal cancer, while *TP53*, *SPTA1*, and *ACVR2A* were more in *IDH*-mutated gastric cancer (Figure 3d,e).

3.3 | Associate with TMB and IDH mutation

We also analyzed the association between *IDH1/IDH2* mutations and TMB in five type of cancer. As shown in Figure 3f, the TMB were significantly higher in lung cancer, colorectal cancer, and gastric cancer than biliary tract cancer ($p = 0.0164$, $p < 0.0001$, $p = 0.0067$, respectively). In addition, we also analyzed the relationship between IDH mutation

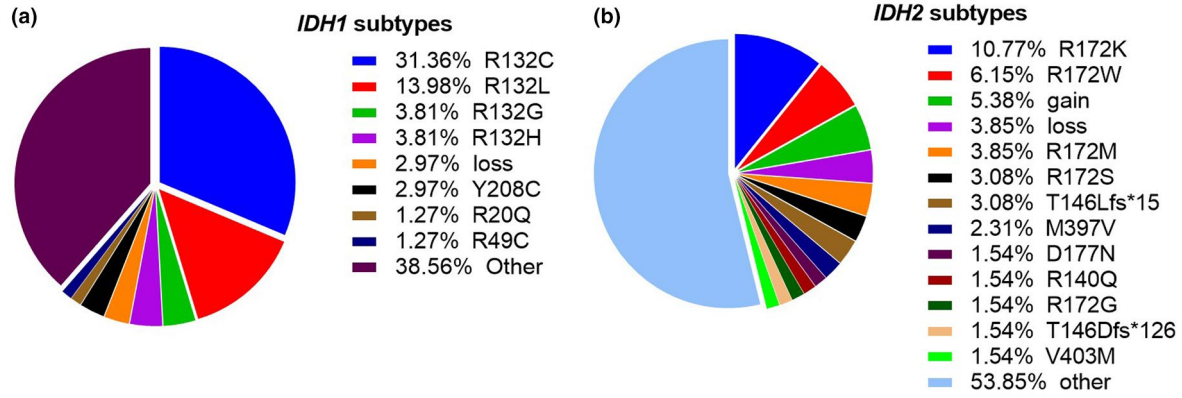

FIGURE 2 Pie charts of patients with *IDH* mutation. Pie charts showing the proportions of *IDH1* mutation (mut) subtypes (a) and the proportions of *IDH2* mutation subtypes (b)

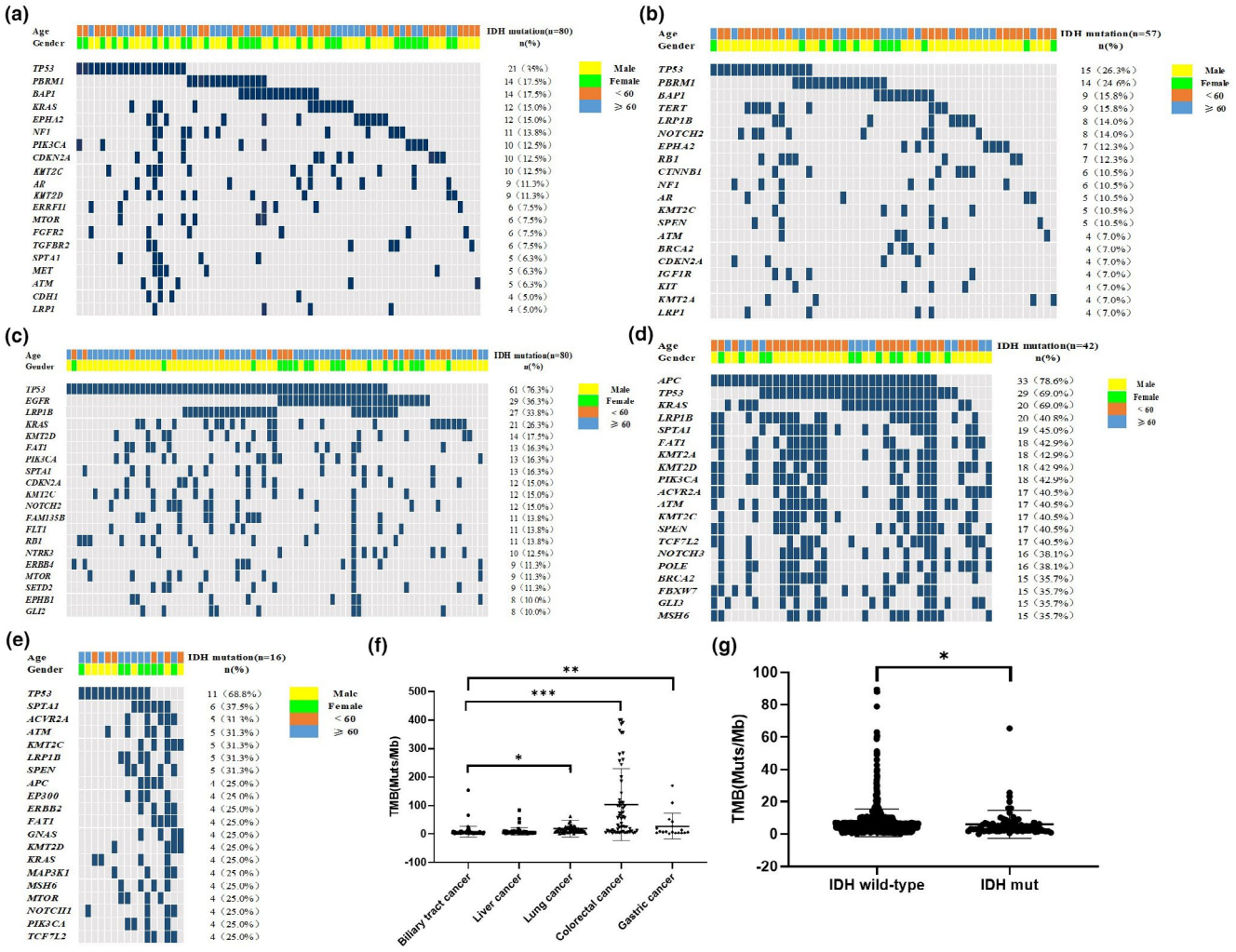

FIGURE 3 Top 20 significantly mutated genes in *IDH1/2*-mutated patients of biliary tract cancer (a), liver cancer (b), lung cancer (c), colorectal cancer (d), and gastric cancer (e). genes were ranked by mutation frequencies (right panel). Age and gender are annotated in the top panel. Tumor mutational load among *IDH1/2*-mutated pan-cancers (f) and in biliary tract cancer (g)

and wild-type with TMB in BTC (Figure 3G). Patients with *IDH* mutation had lower TMB compared with patients with wild-type *IDH* ($p = 0.0236$).

4 | DISCUSSION

From a cohort of 28.868 patients with different types of solid tumors, a high frequency of *IDH1/IDH2* mutations was observed not only in BTC but also in liver cancer, lung cancer, colorectal cancer, and others. The reprogramming of cellular metabolism is a fundamental characteristic of cancer, and *IDH1/2* mutations represent key therapeutic targets in this arena. Somatic *IDH1/2* mutations are found in multiple solid tumors, and mounting evidence indicates that they contribute to premalignant disorders as well as early and late cancers.

In addition, we found that TMB was higher in other gastrointestinal tumors. However, in BTC, *IDH* mutation accompanied by low TMB indicates that *IDH* would be a driver gene in BTC. With the continuous emergence of IDH inhibitors, a considerable number of patients with solid tumors carrying *IDH1/2* gene mutations may be more likely to benefit from IDH inhibitors, which is worth further expectation and exploration in clinical studies.

Since the heterogeneity of tumor poses a severe challenge to clinical management, it is an urgent need to understand the molecular classification of tumor. For example, although intrahepatic, perihilar, and extrahepatic BTC share the same morphological characteristics and are not subdivided in most clinical trials, there is currently available evidence that there are important biological and genetic differences between tumors at different anatomical sites (Chan-On et al., 2013). In addition to the *IDH1/2* gene, additional recurrent mutations and fusions have been reported in BTC. Therefore, further elucidation of the molecular alterations in these heterogeneous tumors and discovery of meaningful subtypes is a key step in the development of more rational, specific, and effective treatments (Kelley & Bardeesy, 2015). Therefore, we further studied the genetic variation spectrum of patients with *IDH* mutation. *IDH*-mutated lung cancer is accompanied by common co-mutations in the driver genes *EGFR* and *KRAS*. *TP53*, *PBRM1*, and *BAP1* were more common in *IDH*-mutated BTC and liver cancer. It can be seen that *IDH* is associated with different high-frequency mutation genes in different cancer types.

In summary, we revealed within the molecular landscape of *IDH1/2* pan-cancer that concurrent *IDH1/2* mutation was accompanied by low TMB in BTC.

CONFLICT OF INTEREST

Drs. Junling Zhang, Jing Zhao, Zhengyi Zhao, Longgang Cui, Yuzi Zhang, Guoqiang Wang, Shangli Cai, and Yuezong Bai are employees of 3D Medicines Inc. Other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Shen D, Zhang JL, Li W, and Huang X. Analysis and interpretation of data: Zhang JL. Drafting the article: All authors. Huang X accepts full responsibility for the work and/or the conduct of the study, had access to the data, and oversaw the decision to publish.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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